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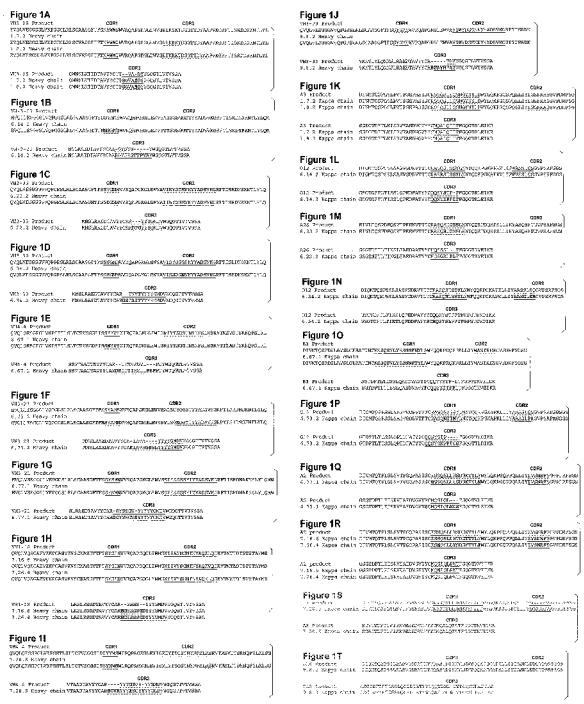

(57) Abstract: The present disclosure relates to antibodies including human antibodies and antigen- binding portions thereof that specifically bind to MAdCAM, preferably human MAdCAM and that function to inhibit MAdCAM. The disclosure also relates to human anti-MAdCAM antibodies and antigen-binding portions thereof. The disclosure also relates to antibodies that are chimeric, bispecific, derivatized, single chain antibodies or portions of fusion proteins. The disclosure also relates to isolated heavy and light chain immunoglobulins derived from human anti-MAdCAM antibodies and nucleic acid molecules encoding such immunoglobulins. The present disclosure also relates to methods of making human anti- MAdCAM antibodies, compositions comprising these antibodies and methods of using the antibodies and compositions for diagnosis and treatment. The disclosure also provides gene therapy methods using nucleic acid molecules encoding the heavy and/or light immunoglobulin molecules that comprise the human anti-MAdCAM antibodies. The disclosure also relates to transgenic animals or plants comprising nuclpeic acid molecules of the disclosure.

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ANTIBODIES TO MAdCAM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to U.S.S.N. 62/532,809 filed on July 14, 2017, the content of which is incorporated herein in its entirety.

INCORPORATION-BY-REFERENCE OF SEQUENCE LISTING

[0002] The content of the text file name "SHR-1258A_ST25.txt", which was created on July 14, 2017 and is 197 KB in size, is hereby incorporated-by-reference in its entirety.

BACKGROUND OF THE INVENTION

[0003] Mucosal addressin cell adhesion molecule (MAdCAM) is a member of the immunoglobulin superfamily of cell adhesion receptors. The selectivity of lymphocyte homing to specialized lymphoid tissue and mucosal sites of the gastrointestinal tract is determined by the endothelial expression of MAdCAM (Berlin, C. et al., *Cell*, 80:413-422(1994); Berlin, C., et al., *Cell*, 74:185-195 (1993); and Erle, D.J., et al., *J. Immunol.*, 153: 517-528 (1994)). MAdCAM is uniquely expressed on the cell surface of high endothelial venules of organized intestinal lymphoid tissue, such as Peyer's patches and mesenteric lymph nodes (Streeter et al., *Nature*, 331:41-6 (1988); Nakache et al., *Nature*, 337:179-81 (1989); Briskin et al. , *Am. J. Pathol.* 151-97-110 (1997)), but also in other lymphoid organs, such as pancreas, gall bladder and splenic venules and marginal sinus of the splenic white pulp (Briskin et al(1997), *supra*; Kraal et al. , *Am. J. Path.*, 147: 763-771 (1995)).

[0004] While MAdCAM plays a physiological role in gut immune surveillance, it appears to facilitate excessive lymphocyte extravasation in inflammatory bowel disease under conditions of chronic gastrointestinal tract inflammation. TNFα and other pro-inflammatory cytokines increase endothelial MAdCAM expression and, in biopsy specimens taken from patients with Crohn's disease and ulcerative colitis, there is an approximate 2-3 fold focal

increase in MAdCAM expression at sites of inflammation (Briskin et al. (1997), Souza et al., *Gut*, 45:856-63 (1999); Arihiro et al., *Pathol Int.*, 52:367-74 (2002)). Similar patterns of elevated expression have been observed in experimental models of colitis (Hesterberg et al. , *Gastroenterology*, 111:1373-1380 (1997); Picarella et al., *J. Immunol.*, 158: 2099-2106 (1997); Connor et al., *J Leukoc Biol.*, 65:349-55 (1999); Kato et al. , *J Pharmacol Exp Ther.*, 295:183-9 (2000); Hokari et al. , *Clin Exp Immunol.,* 26:259-65 (2001); Shigematsu et al., *Am J Physiol Gastrointest Liver Physiol.*, 281:G1309-15 (2001)). In other pre-clinical models for inflammatory conditions, such as insulin-dependent diabetes (Yang et al. *Diabetes*, 46:1542-7 (1997); Hänninen et al., *J Immunol.*, 160:6018-25 (1998)), graft versus host disease (Fujisaki et al., *Scand J Gastroenterol.*, 38:437-42 (2003), Murai et al. , *Nat Immunol.*, 4:154-60 (2003)), chronic liver disease (Hillan et al., *Liver*, 19:509-18 (1999); Grant et al., *Hepatology*, 33:1065-72 (2001)), inflammatory encephalopathy (Stalder et al., *Am J Pathol.*, 153:767-83 (1998); Kanawar et al. , *Immunol Cell Biol.*, 78:641-5 (2000)), and gastritis (Barrett et al. , *J Leukoc Biol.*, 67:169-73 (2000); Hatanaka et al., *Clin Exp Immunol.*, 130:183-9 (2002)), there is also reawakening of fetal MAdCAM expression and participation of activated $\alpha_4\beta_7^+$ lymphocytes in disease pathogenesis. In these inflammatory models as well as hapten-mediated (*e.g.,* TNBS, DSS, etc.) or adoptive transfer ($CD4^+CD45Rb^{high}$) mouse colitic models, the rat anti-mouse MAdCAM monoclonal antibody (mAb), MECA-367, which blocks the binding of $\alpha_4\beta_7^+$ lymphocytes to MAdCAM, reduces the lymphocyte recruitment, tissue extravasation, inflammation and disease severity. Mouse monoclonal antibodies (mAbs) against human MAdCAM also have been reported (see, *e.g.*, WO 96/24673 and WO 99/58573).

[0005] Given the role of MAdCAM in inflammatory bowel disease (IBD) and other inflammatory diseases associated with the gastrointestinal tract or other tissues, a means for inhibiting $\alpha_4\beta_7$ binding and MAdCAM-mediated leukocyte recruitment is desirable. It

further would be desirable to have such therapeutic means with advantageous properties including but not limited to the absence of unwanted interactions with other medications in patients and favorable physico-chemical properties such as pK/pD values in humans, solubility, stability, shelf-life and *in vivo* half-life. A therapeutic protein, such as an antibody, would advantageously be free of unwanted post-translational modifications or aggregate formation. Accordingly, there is a critical need for therapeutic anti-MAdCAM antibodies.

SUMMARY OF THE INVENTION

[0006] Provided herein is an isolated antibody that specifically binds MAdCAM, wherein at least the CDR sequences of said antibody are human CDR sequences, or an antigen-binding portion of said antibody. In embodiments the antibody is a human antibody, preferably an antibody that acts as a MAdCAM antagonist. Also provided are compositions comprising said antibodies or portions.

[0007] The disclosure also provides a composition comprising the heavy and/or light chain of said anti-MAdCAM antagonist antibody or the variable region or other antigen-binding portion thereof or nucleic acid molecules encoding any of the foregoing and a pharmaceutically acceptable carrier. Compositions of the invention may further comprise another component, such as a therapeutic agent or a diagnostic agent. Diagnostic and therapeutic methods are also provided by the invention.

[0008] The disclosure further provides an isolated cell line, that produces said anti-MAdCAM antibody or antigen-binding portion thereof.

[0009] The disclosure also provides nucleic acid molecules encoding the heavy and/or light chain of said anti-MAdCAM antibody or the variable region thereof or antigen-binding portion thereof.

[0010] The disclosure provides vectors and host cells comprising said nucleic acid molecules, as well as methods of recombinantly producing the polypeptides encoded by the nucleic acid molecules.

[0011] Non-human transgenic animals or plants that express the heavy and/or light chain of said anti-MAdCAM antibody, or antigen-binding portion thereof, are also provided.

[0012] In embodiments, a human monoclonal antibody or an antigen-binding portion thereof is provided that specifically binds to Mucosal Adressin Cell Adhesion Molecule (MAdCAM).

[0013] In embodiments, the human monoclonal antibody or antigen-binding portion possesses at least one of the following properties: (a) binds to human cells; (b) has a selectivity for MAdCAM over VCAM or fibronectin of at least 100 fold; (c) binds to human MAdCAM with a K_d of 3 x 10^{-10} M or less; or (d) inhibits the binding of $\alpha_4\beta_7$ expressing cells to human MAdCAM. (e) inhibits the recruitment of lymphocytes to gastrointestinal lymphoid tissue.

[0014] In embodiments, the human monoclonal antibody or antigen-binding portion binds human MAdCAM with a K_d of 3 x 10^{-10} M or less and inhibits α_4 β_7 binding to human MAdCAM.

[0015] In embodiments, the heavy chain comprises an amino acid sequence at least 80%, 85%, or 90% identical to SEQ ID NO: 148.

[0016] In embodiments, the heavy chain comprises an amino acid sequence identical to SEQ ID NO: 148.

[0017] In embodiments, heavy chain comprises between 1 and 25 amino acid substitutions as compared to SEQ ID NO: 148.

[0018] In embodiments, the heavy chain comprises between 1 and 10 amino acid substitutions as compared to SEQ ID NO: 148.

[0019] In embodiments, the light chain comprises an amino acid sequence at least 80%, 85%, or 90% identical to SEQ ID NO: 150.

[0020] In embodiments, the light chain comprises an amino acid sequence identical to SEQ ID NO: 150.

[0021] In embodiments, the light chain comprises between 1 and 25 amino acid substitutions as compared to SEQ ID NO: 150.

[0022] In embodiments, the light chain comprises between 1 and 10 amino acid substitutions as compared to SEQ I DNO: 150.

[0023] In embodiments, the heavy chain comprises an amino acid sequence at least 80%, 85%, or 90% identical to SEQ ID NO: 148, and the light chain comprises an amino acid sequence at least 80%, 85%, or 90% identical to SEQ ID NO: 150.

[0024] In embodiments, the heavy chain comprises an amino acid sequence identical to SEQ ID NO: 148, and the light chain comprises an amino acid sequence identical to SEQ ID NO: 150.

[0025] In embodiments, a nucleic acid sequence encoding the amino acid sequence of a MAdCAM antibody is provided.

[0026] In embodiments, a cell producing a human monoclonal antibody that binds MAdCAM is provided.

[0027] In embodiments, a cell comprising a nucleic acid sequence encoding a MAdCAM antibody is provided.

[0028] In embodiments, a hybridoma cell line that produces a human monoclonal MAdCAM antibody is provided. In embodiments, the hybridoma is selected from the group consisting of 1.7.2 (ECACC Accession No. 03090901), 1.8.2 (ECACC Accession No. 03090902), 6.14.2 (ECACC Accession No. 03090903), 6.22.2 (ECACC Accession No. 03090904), 6.34.2 (ECACC Accession No. 03090905), 6.67.1 (ECACC Accession No.

03090906), 6.73.2 (ECACC Accession No. 03090907), 6.77.1 (ECACC Accession No. 03090908), 7.16.6 (ECACC Accession No. 03090909), 7.20.5 (ECACC Accession No. 03090910), 7.26.4 (ECACC Accession No. 03090911), and 9.8.2 (ECACC Accession No. 03090912).

[0029] In embodiments, the human monoclonal antibody produced by the hybridoma cell line or an antigen-binding portion of said monoclonal antibody is provided.

[0030] In embodiments, the heavy chain C-terminal lysine is cleaved.

[0031] In embodiments, said antibody or antigen-binding portion inhibits binding of human MAdCAM to $\alpha_4\beta_7$, and wherein the antibody or portion thereof has at least one of the following properties: (a) cross-competes with a reference antibody for binding to MAdCAM; (b) competes with a reference antibody for binding to MAdCAM; (c) binds to the same epitope of MAdCAM as a reference antibody; (d) binds to MAdCAM with substantially the same K_d as a reference antibody; (e) binds to MAdCAM with substantially the same off rate as a reference antibody; wherein the reference antibody is selected from the group consisting of: monoclonal antibody 1.7.2, monoclonal antibody 1.8.2, monoclonal antibody 6.14.2, monoclonal antibody 6.22.2, monoclonal antibody 6.34.2, monoclonal antibody 6.67.1, monoclonal antibody 6.73.2, monoclonal antibody 6.77.1, monoclonal antibody 7.16.6, monoclonal antibody 7.20.5, monoclonal antibody 7.26.4, monoclonal antibody 9.8.2, X481.2 monoclonal antibody, monoclonal antibody 6.22.2-mod, monoclonal antibody 6.34.2-mod, monoclonal antibody 6.67.1-mod, monoclonal antibody 6.77.1-mod and monoclonal antibody 7.26.4-mod.

[0032] In embodiments, the antibody is selected from the group consisting of: (a) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 4, without the signal sequences; (b) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 6 and SEQ ID NO: 8, without the signal sequences; (c) an antibody

comprising the amino acid sequences set forth in SEQ ID NO: 10 and SEQ ID NO: 12, without the signal sequences; (d) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 14 and SEQ ID NO: 16, without the signal sequences; (e) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 18 and SEQ ID NO: 20, without the signal sequences; (f) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 22 and SEQ ID NO: 24, without the signal sequences; (g) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 26 and SEQ ID NO: 28, without the signal sequences; (h) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 30 and SEQ ID NO: 32, without the signal sequences; (i) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 34 and SEQ ID NO: 36, without the signal sequences; (j) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 38 and SEQ ID NO: 40, without the signal sequences; (k) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 42 and SEQ ID NO: 44, without the signal sequences; (l) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 46 and SEQ ID NO: 48, without the signal sequences; (m) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 52 and SEQ ID NO: 54, without the signal sequences; (n) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 56 and SEQ ID NO: 58, without the signal sequences; (o) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 60 and SEQ ID NO: 62, without the signal sequences; (p) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 64 and SEQ ID NO: 66, without the signal sequences; and (q) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 42 and SEQ ID NO: 68, without the signal sequences (r) an antibody comprising the amino acid sequences set forth in SEQ ID NO: 148 and SEQ ID NO: 150, without the signal sequence.

[0033] In embodiments, the heavy chain of said antibody or portion thereof comprises the heavy chain CDR1, CDR2 and CDR3 or wherein the light chain comprises the light chain CDR1, CDR2 and CDR3 of a monoclonal antibody selected from the group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod.

[0034] In embodiments, said antibody or portion comprises a heavy chain that utilizes a human VH 1-18 gene, a human VH 3-15 gene, a human VH 3-21 gene, a human VH 3-23 gene, a human VH 3-30 gene, a human VH 3-33 gene or a human VH 4-4 gene.

[0035] In embodiments, said antibody or portion comprises a light chain that utilizes a human V_K A2 gene, a human V_K A3 gene, a human V_K A26 gene, a human V_K B3 gene, a human V_K O12 gene or a human V_K O18 gene.

[0036] In embodiments, the heavy chain variable region, the light chain variable region or both are at least 90% identical in amino acid sequence to the corresponding region or regions of a monoclonal antibody selected from the group consisting of: monoclonal antibody 1.7.2, monoclonal antibody 1.8.2, monoclonal antibody 6.14.2, monoclonal antibody 6.22.2, monoclonal antibody 6.34.2, monoclonal antibody 6.67.1, monoclonal antibody 6.73.2, monoclonal antibody 6.77.1, monoclonal antibody 7.16.6, monoclonal antibody 7.20.5, monoclonal antibody 7.26.4, monoclonal antibody 9.8.2, monoclonal antibody X481.2, monoclonal antibody 6.22.2-mod, monoclonal antibody 6.34.2-mod, monoclonal antibody 6.67.1-mod, monoclonal antibody 6.77.1-mod and monoclonal antibody 7.26.4-mod.

[0037] In embodiments, a monoclonal antibody or an antigen-binding portion thereof is provided that specifically binds MAdCAM, wherein: (a) the heavy chain comprises the heavy chain CDR1, CDR2 and CDR3 amino acid sequences of a reference antibody selected from the group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-

mod (b) the light chain comprises the light chain CDR1, CDR2 and CDR3 amino acid sequences of a reference antibody selected from the group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod (c) the antibody comprises a heavy chain of (a) and a light chain of (b); and (d) the antibody of (c) wherein the heavy chain and light chain CDR amino acid sequences are selected from the same reference antibody.

[0038] In embodiments, the heavy chain, the light chain or both comprise the amino acid sequence from the beginning of the CDR1 through the end of the CDR3 of the heavy chain, the light chain or both, respectively, of the reference antibody.

[0039] In embodiments, said antibody comprises: (a) a heavy chain comprising the heavy chain variable region amino acid sequence of an antibody selected from the group consisting of: 1.7.2 (SEQ ID NO: 2); 1.8.2 (SEQ ID NO: 6); 6.14.2 (SEQ ID NO: 10); 6.22.2 (SEQ ID NO: 14); 6.34.2 (SEQ ID NO: 18); 6.67.1 (SEQ ID NO: 22); 6.73.2 (SEQ ID NO: 26); 6.77.1 (SEQ ID NO: 30); 7.16.6 (SEQ ID NO: 34); 7.20.5 (SEQ ID NO: 38); 7.26.4 (SEQ ID NO: 42); and 9.8.2 (SEQ ID NO: 46); X481.2 (SEQ ID NO: 148), 6.22.2-mod (SEQ ID NO: 52); 6.34.2-mod (SEQ ID NO: 56); 6.67.1-mod (SEQ ID NO: 60); 6.77.1-mod (SEQ ID NO: 64); and 7.26.4-mod (SEQ ID NO: 42); (b) a light chain comprising the light chain variable region amino acid sequence of an antibody selected from the group consisting of: 1.7.2 (SEQ ID NO: 4); 1.8.2 (SEQ ID NO: 8); 6.14.2 (SEQ ID NO: 12); 6.22.2 (SEQ ID NO: 16); 6.34.2 (SEQ ID NO: 20); 6.67.1 (SEQ ID NO: 24); 6.73.2 (SEQ ID NO: 28); 6.77.1 (SEQ ID NO: 32); 7.16.6 (SEQ ID NO: 36); 7.20.5 (SEQ ID NO: 40); 7.26.4 (SEQ ID NO: 44); and 9.8.2 (SEQ ID NO: 48); X481.2 (SEQ ID NO: 150), 6.22.2-mod (SEQ ID NO: 54); 6.34.2-mod (SEQ ID NO: 58); 6.67.1-mod (SEQ ID NO: 62); 6.77.1-mod (SEQ ID NO: 66); and 7.26.4-mod (SEQ ID NO: 68); or (c) the heavy chain of (a) and the light chain of (b).

[0040] In embodiments, the monoclonal antibody is an immunoglobulin G (IgG), an IgM, an IgE, and IgA or an IgD molecule, a humanized antibody, a chimeric antibody or a bispecific antibody.

[0041] In embodiments, the antigen-binding portion is an Fab fragment, an $F(ab')_2$ fragment, an F_V fragment or a single chain antibody.

[0042] In embodiments, a pharmaceutical composition is provided comprising an effective amount of the monoclonal antibody or antigen-binding portion thereof and a pharmaceutically acceptable carrier.

[0043] In embodiments, a method of treating inflammatory disease in a subject in need thereof is provided, comprising the step of administering to said subject the monoclonal antibody or antigen-binding portion thereof wherein said antibody or antigen-binding portion inhibits binding of MAdCAM to $\alpha_4\beta_7$.

[0044] In embodiments, the inflammatory disease is inflammatory disease of the gastrointestinal tract.

[0045] In embodiments, the inflammatory disease of the gastrointestinal tract is selected from the group consisting of inflammatory bowel disease, Crohn's disease, ulcerative colitis, diverticula disease, gastritis, liver disease, primary biliary sclerosis and sclerosing cholangitis.

[0046] In embodiments, the inflammatory bowel disease is Crohn's disease, ulcerative colitis or both.

[0047] In embodiments, the inflammatory diseases are insulin-dependent diabetes and graft versus host disease.

[0048] In embodiments, an isolated cell line is provided that produces the monoclonal antibody or antigen-binding portion or the heavy chain or light chain of said antibody or of said portion thereof. In embodiments, the cell line produces an antibody selected from the

group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, and X481.2 or an antibody comprising the amino acid sequences of one of said antibodies. In embodiments, the cell line produces a monoclonal antibody selected from the group consisting of: 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod, 7.26.4-mod, and X481.2 or an antibody comprising the amino acid sequences of one of said antibodies.

[0049] In embodiments, an isolated nucleic acid molecule is provided comprising a nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof or the light chain or an antigen-binding portion thereof of an antibody.

[0050] In embodiments, a vector is provided comprising a nucleic acid molecule, wherein the vector optionally comprises an expression control sequence operably linked to the nucleic acid molecule. In embodiments, a host cell is provided comprising the vector or the nucleic acid molecule.

[0051] In embodiments, a host cell is provided comprising a nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof and a nucleic acid molecule encoding the light chain or an antigen-binding portion thereof of an antibody or antigen-binding portion.

[0052] In embodiments, a method is provided for producing a human monoclonal antibody or antigen-binding portion thereof that specifically binds MAdCAM, comprising culturing the host cell or the cell line under suitable conditions and recovering said antibody or antigen-binding portion.

[0053] In embodiments, a non-human transgenic animal or transgenic plant is provided comprising (a) nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof; (b) a nucleic acid molecule encoding the light chain or an antigen-binding portion thereof; or (c) both (a) and (b) of an antibody, wherein the non-human transgenic animal or transgenic plant expresses said heavy chain or light chain or both.

[0054] In embodiments, a method is provided of isolating an antibody or antigen-binding portion thereof that specifically binds to MAdCAM, comprising the step of isolating the antibody from the non-human transgenic animal or transgenic plant.

[0055] In embodiments, a method is provided of treating a subject in need thereof with a human antibody or antigen-binding portion thereof that specifically binds to MAdCAM and inhibits binding to $\alpha_4\beta_7$ comprising the steps of: (a) administering an effective amount of an isolated nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof, an isolated nucleic acid molecule encoding the light chain or an antigen-binding portion thereof, or nucleic acid molecules encoding the light chain and the heavy chain or antigen-binding portions thereof; and (b) expressing the nucleic acid molecule.

[0056] In embodiments, a method for producing a human monoclonal antibody that specifically binds MAdCAM is provided, comprising the steps of: (a) immunizing a non-human transgenic animal that is capable of producing human antibodies with MAdCAM, with an immunogenic portion of MAdCAM or a with cell or tissue expressing MAdCAM; and (b) allowing the transgenic animal to mount an immune response to MAdCAM.

[0057] In embodiments, a human monoclonal antibody is produced as above.

[0058] In embodiments, a method is provided of inhibiting $\alpha_4\beta_7$ binding to cells expressing human MAdCAM comprising contacting the cells with the monoclonal antibody or an antigen-binding portion thereof.

[0059] In embodiments, a method for inhibiting MAdCAM-mediated leukocyte-endothelial cell adhesion is provided comprising contacting the endothelial cells with the monoclonal antibody or an antigen-binding portion thereof.

[0060] In embodiments, a method is provided for inhibiting MAdCAM-mediated leukocyte adhesion, migration and infiltration into tissues comprising the step of contacting the endothelial cells with the monoclonal antibody or an antigen-binding portion thereof.

[0061] In embodiments, a method is provided for inhibiting α_4 β_7 /MAdCAM-dependent cellular adhesion comprising the step of contacting cells expressing human MAdCAM with the monoclonal antibody or antigen-binding portion thereof.

[0062] In embodiments, a method is provided for inhibiting the MAdCAM-mediated recruitment of lymphocytes to gastrointestinal lymphoid tissue comprising the step of contacting cells expressing human MAdCAM with the monoclonal antibody or antigen-binding portion thereof.

[0063] In embodiments, a monoclonal antibody or an antigen-binding portion thereof is provided that specifically binds MAdCAM, wherein said antibody or portion thereof comprises one or more of an FR1, FR2, FR3 or FR4 amino acid sequence of a human monoclonal antibody selected from the group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod.

[0064] In embodiments, the human monoclonal antibody or antigen-binding portion comprises: (a) a heavy chain amino acid sequence that is at least 90% identical to the heavy chain amino acid sequence of a monoclonal antibody selected from the group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod; (b) a light chain amino acid sequence that is at least 90% identical to the light chain amino acid sequence of a monoclonal antibody selected from the group consisting of: 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod; (c) both (a) and (b); or (d) either (a), (b) or (c), with or without the signal sequence.

[0065] In embodiments, a method is provided for diagnosing a disorder characterized by circulating soluble human MAdCAM comprising the steps of: (1) contacting a biological sample with the monoclonal antibody or antigen-binding portion and (2) detecting binding.

[0066] In embodiments, a method is provided for detecting inflammation in a subject comprising the steps of: (1) administering to said subject the monoclonal antibody or antigen-binding portion wherein said antibody or portion thereof is detectably labeled and (2) detecting binding.

[0067] In embodiments, a diagnostic kit is provided comprising the monoclonal antibody or antigen-binding portion.

[0068] In embodiments, the pharmaceutical composition is provided further comprising one or more additional anti-inflammatory or immunomodulatory agents. In embodiments, the one or more additional anti-inflammatory or immunomodulatory agents are selected from the group consisting of: corticosteroids, aminosalicylates, azathioprine, methotrexate, cyclosporin, FK506, IL-10, GM-CSF, rapamycin, anti-TNFα agents and adhesion molecule antagonists.

[0069] In embodiments, a vaccine is provided comprising an effective amount of the human antibody thereof or antigen-binding portion and a pharmaceutically acceptable carrier. In embodiments, the vaccine is mucosal.

[0070] In embodiments, a method is provided of detecting the effect of administration of an inhibitory anti-MAdCAM antibody or antigen-binding portion thereof to a subject comprising the steps of: (a) administering to a subject a human monoclonal antibody that specifically binds to MAdCAM; and (b) determining whether there is an increase in the levels of circulating $\alpha_4\beta_7$-expressing leukocytes. In embodiments, said leukocytes are lymphocytes. In embodiments, said increase in the levels of circulating $\alpha_4\beta_7$-expressing leukocytes is determined by FACS analysis.

[0071] In embodiments, a monoclonal antibody, or antigen-binding portion thereof, is provided that binds MAdCAM comprising the variable region of the light chain of SEQ ID NO: 150 and the variable region of the heavy chain of SEQ ID NO: 148.

[0072] In embodiments, a monoclonal antibody, or antigen-binding fragment thereof, is provided that binds MAdCAM comprising a heavy chain variable region encoded by nucleotide SEQ ID NO: 149, and a light chain variable region encoded by nucleotide SEQ ID NO: 35.

BRIEF DESCRIPTION OF THE DRAWINGS

[0073] Figure 1 (i.e. Figure 1A - Figure 1T) is an alignment of the predicted amino acid sequences of the heavy and kappa light chain variable regions of twelve human anti-MAdCAM monoclonal antibodies with the germline amino acid sequences of the corresponding human genes.

[0074] Figure 1A shows an alignment of the predicted amino acid sequence of the heavy chain for antibodies 1.7.2 and 1.8.2 with the germline human VH 3-15 gene product.

[0075] Figure 1B shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 6.14.2 with the germline human VH 3-23 gene product.

[0076] Figure 1C shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 6.22.2 with the germline human VH 3-33 gene product.

[0077] Figure 1D shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 6.34.2 with the germline human VH 3-30 gene product.

[0078] Figure 1E shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 6.67.1 with the germline human VH 4-4 gene product.

[0079] Figure 1F shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 6.73.2 with the germline human VH 3-23 gene product.

[0080] Figure 1G shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 6.77.1 with the germline human VH 3-21 gene product.

[0081] Figure 1H shows an alignment of the predicted amino acid sequence of the heavy chain for antibodies 7.16.6 and 7.26.4 with the germline human VH 1-18 gene product.

[0082] Figure 1I shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 7.20.5 with the germline human VH 4-4 gene product.

[0083] Figure 1J shows an alignment of the predicted amino acid sequence of the heavy chain for antibody 9.8.2 with the germline human VH 3-33 gene product.

[0084] Figure 1K shows an alignment of the predicted amino acid sequence of the light kappa chain for antibodies 1.7.2 and 1.8.2 with the germline human A3 gene product.

[0085] Figure 1L shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 6.14.2 with the germline human O12 gene product.

[0086] Figure 1M shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 6.22.2 with the germline human A26 gene product.

[0087] Figure 1N shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 6.34.2 with the germline human O12 gene product.

[0088] Figure 1O shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 6.67.1 with the germline human B3 gene product.

[0089] Figure 1P shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 6.73.2 with the germline human O12 gene product.

[0090] Figure 1Q shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 6.77.1 with the germline human A2 gene product.

[0091] Figure 1R shows an alignment of the predicted amino acid sequence of the kappa light chain for antibodies 7.16.6 and 7.26.4 with the germline human A2 gene product.

[0092] Figure 1S shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 7.20.5 with the germline human A3 gene product.

[0093] Figure 1T shows an alignment of the predicted amino acid sequence of the kappa light chain for antibody 9.8.2 with the germline human O18 gene product.

[0094] Figure 2 (i.e. Figure 2A and Figure 2B) are CLUSTAL alignments of the predicted heavy and kappa light chain amino acid sequences of human anti-MAdCAM antibodies.

[0095] Figure 2A is a CLUSTAL alignment and radial tree of the predicted kappa light chain amino acid sequences, showing the degree of similarity between the anti-MAdCAM antibody kappa light chains.

[0096] Figure 2B is a CLUSTAL alignment and radial tree of the predicted heavy amino acid sequences, showing the degree of similarity between the anti-MAdCAM antibody heavy chains.

[0097] Figure 3 is an amino acid sequence CLUSTAL alignment of the 2 N-terminal domains of cynomolgus and human MAdCAM which form the $\alpha_4\beta_7$ binding domain. The β-strands are aligned according to Tan et al., Structure (1998) 6:793-801.

[0098] Figure 4 is a graph representing the dose effects of purified biotinylated 1.7.2 and 7.16.6 on the adhesion of human peripheral blood lymphocytes to sections of MAdCAM-expressing frozen human liver endothelium.

[0099] Figure 5 shows a two dimensional graphical representation based on the data captured in Table 7 of the diversity of MAdCAM epitopes to which the anti-MAdCAM antibodies, 1.7.2, 6.22.2, 6.34.2, 6.67.1, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2 bind. Anti-MAdCAM antibodies within the same circle show the same reactivity pattern, belong in the same epitope bin and are likely to recognize the same epitope on MAdCAM. Anti-MAdCAM antibody clones within overlapping circles are unable to bind simultaneously and

are, therefore, likely to recognize an overlapping epitope on MAdCAM. Non-integrating circles represent anti-MAdCAM antibody clones with distinct spatial epitope separation.

[0100] Figure 6 shows sandwich ELISA data with anti-MAdCAM antibodies 1.7.2 and an Alexa 488-labelled 7.16.6, showing that two antibodies that are able to detect different epitopes on MAdCAM could be used to detect soluble MAdCAM for diagnostic purposes.

[0101] Figure 7 shows the effect of an inhibitory anti-MAdCAM antibody (1 mg/kg) on the number of circulating peripheral $\alpha_4\beta_7^+$ lymphocytes, expressed as a fold increase over control IgG2a mAb or vehicle, using anti-MAdCAM mAb 7.16.6 in a cynomolgus monkey model.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Techniques

[0102] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure 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. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, *e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates (1992), and Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold

Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0103] The following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0104] The term "polypeptide" encompasses native or artificial proteins, protein fragments and polypeptide analogs of a protein sequence. A polypeptide may be monomeric or polymeric.

[0105] The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is free of other proteins from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

[0106] A protein or polypeptide is "substantially pure," "substantially homogeneous" or "substantially purified" when at least about 60 to 75% of a sample exhibits a single species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as

polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

[0107] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence. In some embodiments, fragments are at least 5, 6, 8 or 10 amino acids long. In other embodiments, the fragments are at least 14 amino acids long, more preferably at least 20 amino acids long, usually at least 50 amino acids long, even more preferably at least 70, 80, 90, 100, 150 or 200 amino acids long.

[0108] The term "polypeptide analog" as used herein refers to a polypeptide that comprises a segment of at least 25 amino acids that has substantial identity to a portion of an amino acid sequence and that has at least one of the following properties: (1) specific binding to MAdCAM under suitable binding conditions, (2) ability to inhibit $\alpha_4\beta_7$ integrin and/or L-selectin binding to MAdCAM, or (3) ability to reduce MAdCAM cell surface expression *in vitro* or *in vivo*. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally-occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50, 60, 70, 80, 90, 100, 150 or 200 amino acids long or longer, and can often be as long as a full-length naturally-occurring polypeptide.

[0109] Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, or (5) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various muteins of a sequence

other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally-occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al., *Nature*, 354:105 (1991), which are each incorporated herein by reference.

[0110] Non-peptide analogs are commonly used in the pharmaceutical industry as drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, *J. Adv. Drug Res.*, 15:29(1986); Veber and Freidinger, *TINS*, p.392(1985); and Evans et al., *J. Med. Chem.*, 30:1229(1987), which are incorporated herein by reference. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a desired biochemical property or pharmacological activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage such as: $–CH_2NH–$, $–CH_2S–$, $–CH_2-CH_2–$, –CH=CH– (cis and trans), $–COCH_2–$, $–CH(OH)CH_2–$, and $–CH_2SO–$, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino

acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* 61:387 (1992), incorporated herein by reference); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0111] An "immunoglobulin" is a tetrameric molecule. In a naturally-occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as κ and λ light chains. Heavy chains are classified as μ, δ, γ, α, or ε, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 or more amino acids. See generally, *Fundamental Immunology*, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

[0112] Immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions to form an epitope-specific binding site. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and

FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk, *J. Mol. Biol.*, 196:901-917(1987); Chothia et al., *Nature*, 342:878-883(1989), each of which is incorporated herein by reference in their entirety.

[0113] An "antibody" refers to an intact immunoglobulin or to an antigen-binding portion thereof that competes with the intact antibody for specific binding. In some embodiments, an antibody is an antigen-binding portion thereof. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen-binding portions include, *inter alia*, Fab, Fab', $F(ab')_2$, Fv, dAb, and complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. A Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a $F(ab)_2$ fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consists of the VH and CH1 domains; an Fv fragment consists of the VL and VH domains of a single arm of an antibody; and a dAb fragment (Ward et al., *Nature*, 341:544-546(1989)) consists of a VH domain.

[0114] As used herein, an antibody that is referred to as, *e.g.*, 1.7.2, 1.8.2, 6.14.2, 6.34.2, 6.67.1, 6.77.2, 7.16.6, 7.20.5, 7.26.4, 9.8.2 or X481.2 is a monoclonal antibody that is produced by the hybridoma of the same name. For example, antibody 1.7.2 is produced by hybridoma 1.7.2. An antibody that is referred to as 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod, 7.26.4-mod, or X481.2 is a monoclonal antibody whose sequence has been modified from its corresponding parent by site-directed mutagenesis.

[0115] A single-chain antibody (scFv) is an antibody in which VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain (Bird et al., *Science*, 242:423-426 (1988) and Huston et al., *Proc. Natl. Acad. Sci. USA*, 85:5879-5883 (1988)). Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see, *e.g.*, Holliger, P., et al., *Proc. Natl. Acad. Sci. USA*, 90: 6444-6448 (1993) and Poljak, R. J., et al., *Structure*, 2:1121-1123 (1994)). One or more CDRs from an antibody of the disclosure may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin that specifically binds to MAdCAM. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest.

[0116] An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally-occurring immunoglobulin has two identical binding sites, a single-chain antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody (diabody) has two different binding sites.

[0117] An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. Examples of isolated antibodies include an anti-MAdCAM antibody that has been affinity purified using MAdCAM, an anti-

MAdCAM antibody that has been produced by a hybridoma or other cell line *in vitro*, and a human anti-MAdCAM antibody derived from a transgenic mammal or plant.

[0118] As used herein, the term "human antibody" means an antibody in which the variable and constant region sequences are human sequences. The term encompasses antibodies with sequences derived from human genes, but which have been changed, *e.g.*, to decrease possible immunogenicity, increase affinity, eliminate cysteines or glycosylation sites that might cause undesirable folding, etc. The term encompasses such antibodies produced recombinantly in non-human cells which might impart glycosylation not typical of human cells. The term also emcompasses antibodies which have been raised in a transgenic mouse which comprises some or all of the human immunoglobulin heavy and light chain loci.

[0119] In one aspect, the disclosure provides a humanized antibody. In some embodiments, the humanized antibody is an antibody that is derived from a non-human species, in which certain amino acids in the framework and constant domains of the heavy and light chains have been mutated so as to avoid or abrogate an immune response in humans. In some embodiments, a humanized antibody may be produced by fusing the constant domains from a human antibody to the variable domains of a non-human species. Examples of how to make humanized antibodies may be found in United States Patent Nos. 6,054,297, 5,886,152 and 5,877,293. In some embodiments, a humanized anti-MAdCAM antibody of the disclosure comprises the amino acid sequence of one or more framework regions of one or more human anti-MAdCAM antibodies of the disclosure.

[0120] In another aspect, the disclosure provides a "chimeric antibody". In some embodiments the chimeric antibody refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In a preferred embodiment, one or more of the CDRs are derived from a human anti-MAdCAM antibody of the disclosure. In a more preferred embodiment, all of the CDRs are derived from a human

anti-MAdCAM antibody of the disclosure. In another preferred embodiment, the CDRs from more than one human anti-MAdCAM antibody of the disclosure are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-MAdCAM antibody may be combined with CDR2 and CDR3 from the light chain of a second human anti-MAdCAM antibody, and the CDRs from the heavy chain may be derived from a third anti-MAdCAM antibody. Further, the framework regions may be derived from one of the same anti-MAdCAM antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody.

[0121] A "neutralizing antibody," "an inhibitory antibody" or antagonist antibody is an antibody that inhibits the binding of $\alpha_4\beta_7$ or $\alpha_4\beta_7$-expressing cells, or any other cognate ligand or cognate ligand-expressing cells, to MAdCAM by at least about 20%. In a preferred embodiment, the antibody reduces and/or inhibits the binding of $\alpha_4\beta_7$ integrin or $\alpha_4\beta_7$-expressing cells to MAdCAM by at least 40%, more preferably by 60%, even more preferably by 80%, 85%, 90%, 95% or 100%. The binding reduction may be measured by any means known to one of ordinary skill in the art, for example, as measured in an *in vitro* competitive binding assay. An example of measuring the reduction in binding of $\alpha_4\beta_7$-expressing cells to MAdCAM is presented in Example I.

[0122] Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify

protein sequences that fold into a known three-dimensional structure are known (Bowie et al., *Science*, 253:164 (1991)).

[0123] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson, U., et al., *Ann. Biol. Clin.*, 51:19-26 (1993); Jonsson, U., et al., *Biotechniques*, 11:620-627 (1991); Johnsson, B., et al., *J. Mol. Recognit.*, 8:125-131 (1995); and Johnnson, B., et al., *Anal. Biochem.*, 198:268-277 (1991).

[0124] The term "k_{off}" refers to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

[0125] The term "K_d" refers to the dissociation constant of a particular antibody-antigen interaction. An antibody is said to bind an antigen when the dissociation constant is $\leq$ 1 μM, preferably $\leq$ 100 nM and most preferably $\leq$ 10 nM.

[0126] The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor or otherwise interacting with a molecule. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or carbohydrate side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. An epitope may be "linear" or "conformational." In a linear epitope, all of the points of interaction between the protein and the interacting molecule (such as an antibody) occur linearally along the primary amino acid sequence of the protein. In a conformational epitope, the points of interaction occur across amino acid residues on the protein that are separated from one another.

[0127] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See *Immunology - A Synthesis* (2nd Edition, E.S. Golub and D.R. Gren,

Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference. Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α-, α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present disclosure. Examples of unconventional amino acids include: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, s-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the amino terminal direction and the righthand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0128] The term "polynucleotide" as referred to herein means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

[0129] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

[0130] The term "oligonucleotide" referred to herein includes naturally occurring, and modified nucleotides linked together by naturally occurring, and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. Preferably oligonucleotides are 10 to 60 bases in length and

most preferably 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 bases in length. Oligonucleotides are usually single stranded, *e.g.*, for probes; although oligonucleotides may be double stranded, *e.g.*, for use in the construction of a gene mutant. Oligonucleotides of the disclosure can be either sense or antisense oligonucleotides.

[0131] The term "naturally occurring nucleotides" referred to herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" referred to herein includes oligonucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoroamidate, and the like. See, *e.g.*, LaPlanche et al., *Nucl. Acids Res.* 14:9081 (1986); Stec et al., *J. Am. Chem. Soc.* 106:6077(1984); Stein et al., *Nucl. Acids Res.*, 16:3209(1988); Zon et al., *Anti-Cancer Drug Design* 6:539(1991); Zon et al., *Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England(1991)); Stec et al., U.S. Patent No. 5,151,510; Uhlmann and Peyman, *Chemical Reviews*, 90:543(1990), the disclosures of which are hereby incorporated by reference. An oligonucleotide can include a label for detection, if desired.

[0132] "Operably linked" sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in *trans* or at a distance to control the gene of interest. The term "expression control sequence" as used herein refers to polynucleotide sequences which are necessary to effect the expression and processing of coding sequences to which they are ligated. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., Kozak

consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

[0133] The term "vector", as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the disclosure is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0134] The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

[0135] The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments thereof in accordance with the disclosure selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. "High stringency" or "highly stringent" conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. An example of "high stringency" or "highly stringent" conditions is a method of incubating a polynucleotide with another polynucleotide, wherein one polynucleotide may be affixed to a solid surface such as a membrane, in a hybridization buffer of 6X SSPE or SSC, 50% formamide, 5X Denhardt's reagent, 0.5% SDS, 100 μg/ml denatured, fragmented salmon sperm DNA at a hybridization temperature of 42°C for 12-16 hours, followed by twice washing at 55°C using a wash buffer of 1X SSC, 0.5% SDS. See also Sambrook et al., *supra*, pp. 9.50-9.55.

[0136] The term "percent sequence identity" in the context of nucleotide sequences refers to the residues in two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 18 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36, 48 or more nucleotides. There are a number of

different algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.3, Accelrys, San Diego, CA. FASTA, which includes, *e.g.*, the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.,* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.*, 132: 185-219 (2000); Pearson, *Methods Enzymol.*, 266: 227-258 (1996); Pearson, *J. Mol. Biol.*, 276: 71-84 (1998); herein incorporated by reference). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleotide sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in Wisconsin Package Version 10.3, herein incorporated by reference.

[0137] A reference to a nucleotide sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence.

[0138] In the molecular biology art, researchers use the terms "percent sequence identity", "percent sequence similarity" and "percent sequence homology" interchangeably. In this application, these terms shall have the same meaning with respect to nucleotide sequences only.

[0139] The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 85%, preferably at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide

bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

[0140] As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 75% or 80% sequence identity, preferably at least 90% or 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions that are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. See, *e.g.*, Pearson, *Methods Mol. Biol.*, 24: 307-31 (1994), herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; and 6) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine.

[0141] Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al., *Science*, 256: 1443-45 (1992),

herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0142] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG contains programs such as "Gap" and "Bestfit" which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, *e.g.*, Wisconsin package Version 10.3. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in Wisconsin package Version 10.3. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (1990); Pearson (2000)). Another preferred algorithm when comparing a sequence of the disclosure to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn, using default parameters. See, *e.g.*, Altschul et al., *J. Mol. Biol.* 215: 403-410 (1990); Altschul et al., *Nucleic Acids Res.* 25:3389-402 (1997); herein incorporated by reference.

[0143] The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of different organisms, it is preferable to compare amino acid sequences.

[0144] As used herein, the terms "label" or "labeled" refers to incorporation of another molecule in the antibody. In one embodiment, the label is a detectable marker, *e.g.*,

incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (*e.g.*, streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In another embodiment, the label or marker can be therapeutic, *e.g.*, a drug conjugate or toxin. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic labels (*e.g.*, horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent markers, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags), magnetic agents, such as gadolinium chelates, toxins such as pertussis toxin, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0145] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials. The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient. Other chemistry terms herein are used according to conventional usage in the art, as exemplified by *The McGraw-Hill Dictionary of Chemical Terms* (Parker, S., Ed., McGraw-Hill, San Francisco (1985)), incorporated herein by reference).

[0146] The term "anti-inflammatory" or "immuno-modulatory" agent is used herein to refer to agents that have the functional property of inhibiting inflammation, including inflammatory disease in a subject, including in a human. In various embodiments of this disclosure, the inflammatory disease may be, but is not limited to inflammatory diseases of the gastrointestinal tract including Crohn's disease, ulcerative colitis, diverticula disease, gastritis, liver disease, primary biliary sclerosis, sclerosing cholangitis. Inflammatory diseases also include but are not limited to abdominal disease (including peritonitis, appendicitis, biliary tract disease), acute transverse myelitis, allergic dermatitis (including allergic skin, allergic eczema, skin atopy, atopic eczema, atopic dermatitis, cutaneous inflammation, inflammatory eczema, inflammatory dermatitis, flea skin, miliary dermatitis, miliary eczema, house dust mite skin), ankylosing spondylitis (Reiters syndrome), asthma, airway inflammation, atherosclerosis, arteriosclerosis, biliary atresia, bladder inflammation, breast cancer, cardiovascular inflammation (including vasculitis, rheumatoid nail-fold infarcts, leg ulcers, polymyositis, chronic vascular inflammation, pericarditis, chronic obstructive pulmonary disease), chronic pancreatitis, perineural inflammation, colitis (including amoebic colitis, infective colitis, bacterial colitis, Crohn's colitis, ischemic colitis, ulcerative colitis, idiopathic proctocolitis, inflammatory bowel disease, pseudomembranous colitis), collagen vascular disorders (rheumatoid arthritis, SLE, progressive systemic sclerosis, mixed connective tissue disease, diabetes mellitus), Crohn's disease (regional enteritis, granulomatous ileitis, ileocolitis, digestive system inflammation), demyelinating disease (including myelitis, multiple sclerosis, disseminated sclerosis, acute disseminated encephalomyelitis, perivenous demyelination, vitamin B12 deficiency, Guillain-Barre syndrome, MS-associated retrovirus), dermatomyositis, diverticulitis, exudative diarrhea, gastritis, granulomatous hepatitis, granulomatous inflammation, cholecystitis, insulin-dependent diabetes mellitus, liver inflammatory diseases (liver fibrosis primary biliary

cirrhosis, hepatitis, sclerosing cholangitis), lung inflammation (idiopathic pulmonary fibrosis, eosinophilic granuloma of the lung, pulmonary histiocytosis X, peribronchiolar inflammation, acute bronchitis), lymphogranuloma venereum, malignant melanoma, mouth/tooth disease (including gingivitis, periodontal disease), mucositis, musculoskeletal system inflammation (myositis), nonalcoholic steatohepatitis (nonalcoholic fatty liver disease), ocular & orbital inflammation (including uveitis, optic neuritis, peripheral rheumatoid ulceration, peripheral corneal inflammation,), osteoarthritis, osteomyelitis, pharyngeal inflammation, polyarthritis, proctitis, psoriasis, radiation injury, sarcoidosis, sickle cell necropathy, superficial thrombophlebitis, systemic inflammatory response syndrome, thyroiditis, systemic lupus erythematosus, graft versus host disease, acute burn injury, Behçet's syndrome, Sjögren's syndrome.

[0147] The terms patient and subject include human and veterinary subjects.

Human Anti-MAdCAM Antibodies and Characterization Thereof

[0148] In one embodiment, the disclosure provides anti-MAdCAM antibodies comprising human CDR sequences. In a preferred embodiment, the disclosure provides human anti-MAdCAM antibodies. In some embodiments, human anti-MAdCAM antibodies are produced by immunizing a non-human transgenic animal, *e.g.*, a rodent, whose genome comprises human immunoglobulin genes so that the transgenic animal produces human antibodies. In some embodiments, the disclosure provides an anti-MAdCAM antibody that does not bind complement.

[0149] In a preferred embodiment, the anti-MAdCAM antibody is 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the anti-MAdCAM antibody comprises a light chain comprising an amino acid sequence selected from SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 66, , 68 or 150 (with

or without the signal sequence) or the variable region of any one of said amino acid sequences, or one or more CDRs from these amino acid sequences. In another preferred embodiment, the anti-MAdCAM antibody comprises a heavy chain comprising an amino acid sequence selected from SEQ ID NO: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64 or 148 (with or without the signal sequence) or the amino acid sequence of the variable region, or of one or more CDRs from said amino acid sequences. Also included in the disclosure are human anti-MAdCAM antibodies comprising the amino acid sequence from the beginning of the CDR1 to the end of the CDR3 of any one of the above-mentioned sequences. The disclosure further provides an anti-MAdCAM antibody comprising one or more FR regions of any of the above-mentioned sequences.

[0150] The disclosure further provides an anti-MAdCAM antibody comprising one of the afore-mentioned amino acid sequences in which one or more modifications have been made. In some embodiments, cysteines in the antibody, which may be chemically reactive, are substituted with another residue, such as, without limitation, alanine or serine. In one embodiment, the substitution is at a non-canonical cysteine. The substitution can be made in a CDR or framework region of a variable domain or in the constant domain of an antibody. In some embodiments, the cysteine is canonical.

[0151] In some embodiments, an amino acid substitution is made to eliminate potential proteolytic sites in the antibody. Such sites may occur in a CDR or framework region of a variable domain or in the constant domain of an antibody. Substitution of cysteine residues and removal of proteolytic sites may decrease the heterogeneity in the antibody product. In some embodiments, asparagine-glycine pairs, which form potential deamidation sites, are eliminated by altering one or both of the residues. In some embodiments, an amino acid substitution is made to add or to remove potential glycosylation sites in the variable region of an antibody of the disclosure.

[0152] In some embodiments, the C-terminal lysine of the heavy chain of the anti-MAdCAM antibody of the disclosure is cleaved. In various embodiments of the disclosure, the heavy and light chains of the anti-MAdCAM antibodies may optionally include a signal sequence.

[0153] In one aspect, the disclosure provides twelve inhibitory human anti-MAdCAM monoclonal antibodies and the hybridoma cell lines that produce them. Table 1 lists the sequence identifiers (SEQ ID NO:) of the nucleic acids encoding the full-length heavy and light chains (including signal sequence), and the corresponding full-length deduced amino acid sequences.

Table 1

HUMAN ANTI-MAdCAM ANTIBODIES				
Monoclonal Antibody	SEQUENCE IDENTIFIER (SEQ ID NO:)			
	Full Length			
	Heavy		Light	
	DNA	Protein	DNA	Protein
1.7.2	1	2	3	4
1.8.2	5	6	7	8
6.14.2	9	10	11	12
6.22.2	13	14	15	16
6.34.2	17	18	19	20
6.67.1	21	22	23	24
6.73.2	25	26	27	28
6.77.1	29	30	31	32
7.16.6	33	34	35	36
7.20.5	37	38	39	40
7.26.4	41	42	43	44
9.8.2	45	46	47	48
X481.2	149	148	35	150

[0154] In another aspect, the disclosure provides a modified version of certain of the above-identified human anti-MAdCAM monoclonal antibodies. Table 2 lists the sequence identifiers for the DNA and protein sequences of the modified antibodies.

Table 2

HUMAN ANTI-MAdCAM ANTIBODIES				
Modified Monoclonal Antibody	SEQUENCE IDENTIFIER (SEQ ID NO:)			
	Full Length			
	Heavy		Light	
	DNA	Protein	DNA	Protein
6.22.2-mod	51	52	53	54
6.34.2-mod	55	56	57	58
6.67.1-mod	59	60	61	62
6.77.1-mod	63	64	65	66
7.26.4-mod	41	42	67	68
X481.2	149	148	35	150

Class and Subclass of anti-MAdCAM Antibodies

[0155] The antibody may be an IgG, an IgM, an IgE, an IgA or an IgD molecule. In a preferred embodiment, the antibody is an IgG class and is an IgG_1, IgG_2, IgG_3 or IgG_4 subclass. In a more preferred embodiment, the anti-MAdCAM antibody is subclass IgG_2 or IgG_4. In another preferred embodiment, the anti-MAdCAM antibody is the same class and subclass as antibody 1.7.2, 1.8.2, 7.16.6, 7.20.5, 7.26.4, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod which is IgG_2, or 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1 or 9.8.2, which is IgG_4.

[0156] The class and subclass of anti-MAdCAM antibodies may be determined by any method known in the art. In general, the class and subclass of an antibody may be determined using antibodies that are specific for a particular class and subclass of antibody. Such antibodies are available commercially. ELISA, Western Blot as well as other techniques can determine the class and subclass. Alternatively, the class and subclass may be

determined by sequencing all or a portion of the constant domains of the heavy and/or light chains of the antibodies, comparing their amino acid sequences to the known amino acid sequences of various classes and subclasses of immunoglobulins, and determining the class and subclass of the antibodies as the class showing the highest sequence identity.

Species and Molecule Selectivity

[0157] In another aspect of the disclosure, the anti-MAdCAM antibody demonstrates both species and molecule selectivity. In one embodiment, the anti-MAdCAM antibody binds to human, cynomolgus or dog MAdCAM. In some embodiments, the anti-MAdCAM antibody does not bind to a New World monkey species such as a marmoset. Following the teachings of the specification, one may determine the species selectivity for the anti-MAdCAM antibody using methods well known in the art. For instance, one may determine species selectivity using Western blot, FACS, ELISA or immunohistochemistry. In a preferred embodiment, one may determine the species selectivity using immunohistochemistry.

[0158] In some embodiments, an anti-MAdCAM antibody that specifically binds MAdCAM has selectivity for MAdCAM over VCAM, fibronectin or any other antigen that is at least 10 fold, preferably at least 20, 30, 40, 50, 60, 70, 80 or 90 fold, most preferably at least 100 fold. In a preferred embodiment, the anti-MAdCAM antibody does not exhibit any appreciable binding to VCAM, fibronectin or any other antigen other than MAdCAM. One may determine the selectivity of the anti-MAdCAM antibody for MAdCAM using methods well known in the art following the teachings of the specification. For instance, one may determine the selectivity using Western blot, FACS, ELISA, or immunohistochemistry.

Binding Affinity of anti-MAdCAM antibodies to MAdCAM

[0159] In another aspect of the disclosure, the anti-MAdCAM antibodies specifically bind to MAdCAM with high affinity. In one embodiment, the anti-MAdCAM antibody specifically binds to MAdCAM with a K_d of 3×10^{-8} M or less, as measured by surface

plasmon resonance, such as BIAcore. In more preferred embodiments, the antibody specifically binds to MAdCAM with a K_d of 1 x 10^{-8} or less or 1 x 10^{-9} M or less. In an even more preferred embodiment, the antibody specifically binds to MAdCAM with a K_d or 1 x 10^{-10} M or less. In other preferred embodiments, an antibody of the disclosure specifically binds to MAdCAM with a K_d of 2.66 x 10^{-10}M or less, 2.35 x 10^{-11}M or less or 9 x 10^{-12}M or less. In another preferred embodiment, the antibody specifically binds to MAdCAM with a K_d or 1 x 10^{-11} M or less. In another preferred embodiment, the antibody specifically binds to MAdCAM with substantially the same K_d as an antibody selected from 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. An antibody with "substantially the same K_d" as a reference antibody has a K_d that is ± 100 pM, preferably ± 50 pM, more preferably ± 20 pM, still more preferably ± 10 pM, ± 5 pM or ± 2 pM, compared to the K_d of the reference antibody in the same experiment. In another preferred embodiment, the antibody binds to MAdCAM with substantially the same K_d as an antibody that comprises one or more variable domains or one or more CDRs from an antibody selected from 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In still another preferred embodiment, the antibody binds to MAdCAM with substantially the same K_d as an antibody that comprises one of the amino acid sequences selected from SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 48, 52, 54, 56, 58, 62, 64, 66, 68, 148 or 450 (with or without the signal sequence), or the variable domain thereof. In another preferred embodiment, the antibody binds to MAdCAM with substantially the same K_d as an antibody that comprises one or more CDRs from an antibody that comprises an amino acid sequence selected from SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 48, 52, 54, 56, 58, 62, 64, 66, 68, 148 or 450.

[0160] The binding affinity of an anti-MAdCAM antibody to MAdCAM may be determined by any method known in the art. In one embodiment, the binding affinity can be measured by competitive ELISAs, RIAs or surface plasmon resonance, such as BIAcore. In a more preferred embodiment, the binding affinity is measured by surface plasmon resonance. In an even more preferred embodiment, the binding affinity and dissociation rate is measured using a BIAcore. An example of determining binding affinity is described below in Example II.

Half-Life of Anti-MAdCAM Antibodies

[0161] According to another object of the disclosure, the anti-MAdCAM antibody has a half-life of at least one day *in vitro* or *in vivo*. In a preferred embodiment, the antibody or portion thereof has a half-life of at least three days. In a more preferred embodiment, the antibody or portion thereof has a half-life of four days or longer. In another embodiment, the antibody or portion thereof has a half-life of eight days or longer. In another embodiment, the antibody or antigen-binding portion thereof is derivatized or modified such that it has a longer half-life, as discussed below. In another preferred embodiment, the antibody may contain point mutations to increase serum half life, such as described WO 00/09560, published February 24, 2000.

[0162] The antibody half-life may be measured by any means known to one having ordinary skill in the art. For instance, the antibody half life may be measured by Western blot, ELISA or RIA over an appropriate period of time. The antibody half-life may be measured in any appropriate animal, such as a primate, *e.g.*, cynomolgus monkey, or a human.

Identification of MAdCAM Epitopes Recognized by Anti-MAdCAM Antibody

[0163] The disclosure also provides a human anti-MAdCAM antibody that binds the same antigen or epitope as a human anti-MAdCAM antibody provided herein. Further, the

disclosure provides a human anti-MAdCAM antibody that competes or cross-competes with a human anti-MAdCAM antibody. In a preferred embodiment, the human anti-MAdCAM antibody is 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the human anti-MAdCAM antibody comprises one or more variable domains or one or more CDRs from an antibody selected from 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In still another preferred embodiment, the human anti-MAdCAM antibody comprises one of the amino acid sequences selected from SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 48, 52, 54, 56, 58, 62, 64, 66, 68, 148 or 150 (with or without the signal sequence), or a variable domain thereof. In another preferred embodiment, the human anti-MAdCAM antibody comprises one or more CDRs from an antibody that comprises one of the amino acid sequences selected from SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 48, 52, 54, 56, 58, 62, 64, 66, 68, 148 or 150. In a highly preferred embodiment, the anti-MAdCAM antibody is another human antibody.

[0164] One may determine whether an anti-MAdCAM antibody binds to the same antigen as another anti-MAdCAM antibody using a variety of methods known in the art. For instance, one can use a known anti-MAdCAM antibody to capture the antigen, elute the antigen from the anti-MAdCAM antibody, and then determine whether the test antibody will bind to the eluted antigen. One may determine whether an antibody competes with an anti-MAdCAM antibody by binding the anti-MAdCAM antibody to MAdCAM under saturating conditions, and then measuring the ability of the test antibody to bind to MAdCAM. If the test antibody is able to bind to the MAdCAM at the same time as the anti-MAdCAM antibody, then the test antibody binds to a different epitope than the anti- MAdCAM

antibody. However, if the test antibody is not able to bind to the MAdCAM at the same time, then the test antibody competes with the human anti-MAdCAM antibody. This experiment may be performed using ELISA, or surface plasmon resonance or, preferably, BIAcore. To test whether an anti-MAdCAM antibody cross-competes with another anti-MAdCAM antibody, one may use the competition method described above in two directions, i.e. determining if the known antibody blocks the test antibody and vice versa.

Light and Heavy Chain Gene Usage

[0165] The disclosure also provides an anti-MAdCAM antibody that comprises a light chain variable region encoded by a human κ gene. In a preferred embodiment, the light chain variable region is encoded by a human Vκ A2, A3, A26, B3, O12 or O18 gene family. In various embodiments, the light chain comprises no more than eleven, no more than six or no more than three amino acid substitutions from the germline human Vκ A2, A3, A26, B3, O12 or O18 sequence. In a preferred embodiment, the amino acid substitutions are conservative substitutions.

[0166] SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 150 provide the amino acid sequences of the full-length kappa light chains of thirteen anti-MAdCAM antibodies, 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 and 9.8.2 and X481.2. Figures 1K-1T are alignments of the amino acid sequences of the light chain variable domains of twelve anti-MAdCAM antibodies with the germline sequences from which they are derived. Figure 2A shows an alignment of the amino acid sequences of the light chain variable domains of the kappa light chains of twelve anti-MAdCAM antibodies to each other. Following the teachings of this specification, one of ordinary skill in the art could determine the differences between the germline sequences and the antibody sequences of additional anti-MAdCAM antibodies. SEQ ID NOS: 54, 58, 62, 66 or 68 provide the amino acid sequences of the full length kappa light chains of five additional anti-MAdCAM

antibodies, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod, modified by amino acid substitution from their parent anti-MAdCAM antibodies, 6.22.2, 6.34.2, 6.67.1, 6.77.1 or 7.26.4, respectively.

[0167] In a preferred embodiment, the VL of the anti-MAdCAM antibody contains the same mutations, relative to the germline amino acid sequence, as any one or more of the VL of antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. The disclosure includes an anti-MAdCAM antibody that utilizes the same human Vκ and human Jk genes as an exemplified antibody. In some embodiments, the antibody comprises one or more of the same mutations from germline as one or more exemplified antibodies. In some embodiments, the antibody comprises different substitutions at one or more of the same positions as one or more of the exemplified antibodies. For example, the VL of the anti-MAdCAM antibody may contain one or more amino acid substitutions that are the same as those present in antibody 7.16.6, and another amino acid substitution that is the same as antibody 7.26.4. In this manner, one can mix and match different features of antibody binding in order to alter, *e.g.*, the affinity of the antibody for MAdCAM or its dissociation rate from the antigen. In another embodiment, the mutations are made in the same position as those found in any one or more of the VL of antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod, but conservative amino acid substitutions are made rather than using the same amino acid. For example, if the amino acid substitution compared to the germline in one of the antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod is glutamate, one may conservatively substitute aspartate. Similarly, if the amino acid substitution is serine, one may conservatively substitute threonine.

[0168] In another preferred embodiment, the light chain comprises an amino acid sequence that is the same as the amino acid sequence of the VL of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another highly preferred embodiment, the light chain comprises amino acid sequences that are the same as the CDR regions of the light chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the light chain comprises an amino acid sequence with at least one CDR region of the light chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the light chain comprises amino acid sequences with CDRs from different light chains that use the same Vκ and Jκ genes. In a more preferred embodiment, the CDRs from different light chains are obtained from 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the light chain comprises an amino acid sequence selected from SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 64, 66, 68, or 150 with or without the signal sequence. In another embodiment, the light chain comprises an amino acid sequence encoded by a nucleotide sequence selected from SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 53, 57, 61, 65 or 67 (with or without the signal sequence), or a nucleotide sequence that encodes an amino acid sequence having 1-11 amino acid insertions, deletions or substitutions therefrom. Preferably, the amino acid substitutions are conservative amino acid substitutions. In another embodiment, the antibody or portion thereof comprises a lambda light chain.

[0169] The present disclosure also provides an anti-MAdCAM antibody or portion thereof that comprises a human VH gene sequence or a sequence derived from a human VH gene. In one embodiment, the heavy chain amino acid sequence is derived from a human VH 1-18, 3-15, 3-21, 3-23, 3-30, 3-33 or 4-4 gene family. In various embodiments, the heavy chain comprises no more than fifteen, no more than six or no more than three amino acid changes from germline human VH 1-18, 3-15, 3-21, 3-23, 3-30, 3-33 or 4-4 gene sequence.

[0170] SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 148 provide the amino acid sequences of the full-length heavy chains of thirteen anti-MAdCAM antibodies. Figures 1A-1J are alignments of the amino acid sequences of the heavy chain variable regions of twelve anti-MAdCAM antibodies with the germline sequences from which they are derived. Figure 2B shows the alignments of the amino acid sequences of the heavy chain variable regions of twelve anti-MAdCAM antibodies to each other. Following the teachings of this specification and the nucleotide sequences of the disclosure, one of ordinary skill in the art could determine the encoded amino acid sequence of the twelve anti-MAdCAM heavy chains and the germline heavy chains and determine the differences between the germline sequences and the antibody sequences. SEQ ID NOS: 52, 56, 60 and 64 provide the amino acid sequences of the full length heavy chains of anti-MAdCAM antibodies, 6.22.2-mod, 6.34.2-mod and 6.67.1-mod, modified by amino acid substitution from their parent anti-MAdCAM antibodies, 6.22.2, 6.34.2 and 6.67.1 respectively. One further modified anti-MAdCAM antibody, 7.26.4-mod, has a full length heavy chain amino acid sequence which is SEQ ID NO: 42.

[0171] In a preferred embodiment, the VH of the anti-MAdCAM antibody contains the same mutations, relative to the germline amino acid sequence, as any one or more of the VH of antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. Similar to

that discussed above, the antibody comprises one or more of the same mutations from germline as one or more exemplified antibodies. In some embodiments, the antibody comprises different substitutions at one or more of the same positions as one or more of the exemplified antibodies. For example, the VH of the anti-MAdCAM antibody may contain one or more amino acid substitutions that are the same as those present in antibody 7.16.6, and another amino acid substitution that is the same as antibody 7.26.4. In this manner, one can mix and match different features of antibody binding in order to alter, *e.g.*, the affinity of the antibody for MAdCAM or its dissociation rate from the antigen. In another embodiment, an amino acid substitution compared to germline is made at the same position as a substitution from germline as found in any one or more of the VH of reference antibody 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod, but the position is substituted with a different residue, which is a conservative substitution compared to the reference antibody.

[0172] In another preferred embodiment, the heavy chain comprises an amino acid sequence that is the same as the amino acid sequence of the VH of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another highly preferred embodiment, the heavy chain comprises amino acid sequences that are the same as the CDR regions of the heavy chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the heavy chain comprises an amino acid sequence from at least one CDR region of the heavy chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.4, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the heavy chain comprises amino acid

sequences with CDRs from different heavy chains. In a more preferred embodiment, the CDRs from different heavy chains are obtained from 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the heavy chain comprises an amino acid sequence selected from SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64 or 148 with or without the signal sequence. In another embodiment, the heavy chain comprises an amino acid sequence encoded by a nucleotide sequence selected from SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 51, 55, 59, 63 or 149 or a nucleotide sequence that encodes an amino acid sequence having 1-15 amino acid insertions, deletions or substitutions therefrom. In another embodiment, the substitutions are conservative amino acid substitutions.

Methods of Producing Antibodies and Antibody-Producing Cell Lines

Immunization

[0173] In one embodiment of the instant disclosure, human antibodies are produced by immunizing a non-human animal comprising some or all of the human immunoglobulin heavy and light chain loci with an MAdCAM antigen. In a preferred embodiment, the non-human animal is a XENOMOUSE™ animal, which is an engineered mouse strain that comprises large fragments of the human immunoglobulin loci and is deficient in mouse antibody production. See, *e.g.*, Green et al., *Nature Genetics* 7:13-21 (1994) and United States Patents 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001, 6,114,598 and 6,130,364. See also WO 91/10741, WO 94/02602, WO 96/34096 and WO 96/33735, WO 98/16654, WO 98/24893, WO 98/50433, WO 99/45031, WO 99/53049, WO 00 09560 and WO 00/037504. The XENOMOUSE ™ animal produces an adult-like human repertoire of fully human antibodies and generates antigen-specific human mAbs. A second generation XENOMOUSE ™ animal contains approximately 80% of the human antibody V gene

repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and κ light chain loci. In other embodiments, XENOMOUSE ™mice contain approximately all of the human heavy chain and λ light chain locus. See Mendez et al., *Nature Genetics* 15:146-156 (1997), Green and Jakobovits, *J. Exp. Med.* 188:483-495 (1998), the disclosures of which are hereby incorporated by reference.

[0174] The disclosure also provides a method for making anti-MAdCAM antibodies from non-human, non-mouse animals by immunizing non-human transgenic animals that comprise human immunoglobulin loci. One may produce such animals using the methods described immediately above. The methods disclosed in these documents can be modified as described in U.S. Patent 5,994,619 (the "'619 patent"), which is here in incorporated by reference. The '619 patent describes methods for producing novel cultured inner cell mass (CICM) cells and cell lines, derived from pigs and cows, and transgenic CICM cells into which heterologous DNA has been inserted. CICM transgenic cells can be used to produce cloned transgenic embryos, fetuses, and offspring. The '619 patent also describes methods of producing transgenic animals that are capable of transmitting the heterologous DNA to their progeny. In a preferred embodiment, the non-human animals may be rats, sheep, pigs, goats, cattle or horses.

[0175] In another embodiment, the non-human animal comprising human immunoglobulin loci are animals that have a "minilocus" of human immunoglobulins. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of individual genes from the Ig locus. Thus, one or more VH genes, one or more DH genes, one or more JH genes, a μ constant domain(s), and a second constant domain(s) (preferably a gamma constant domain(s) are formed into a construct for insertion into an animal. This approach is described, *inter alia*, in U.S. Patent No. 5,545,807, 5,545,806, 5,625,126, 5,633,425,

5,661,016, 5,770,429, 5,789,650, 5,814,318, 5,591,669, 5,612,205, 5,721,367, 5,789,215, and 5,643,763, hereby incorporated by reference.

[0176] An advantage of the minilocus approach is the rapidity with which constructs including portions of the Ig locus can be generated and introduced into animals. However, a potential disadvantage of the minilocus approach is that there may not be sufficient immunoglobulin diversity to support full B-cell development, such that there may be lower antibody production.

[0177] To produce a human anti-MAdCAM antibody, a non-human animal comprising some or all of the human immunoglobulin loci is immunized with a MAdCAM antigen and an antibody or the antibody-producing cell is isolated from the animal. The MAdCAM antigen may be isolated and/or purified MAdCAM and is preferably a human MAdCAM. In another embodiment, the MAdCAM antigen is a fragment of MAdCAM, preferably the extracellular domain of MAdCAM. In another embodiment, the MAdCAM antigen is a fragment that comprises at least one epitope of MAdCAM. In another embodiment, the MAdCAM antigen is a cell that expresses MAdCAM on its cell surface, preferably a cell that overexpresses MAdCAM on its cell surface.

[0178] Immunization of animals may be done by any method known in the art. See, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor Press (1990). Methods for immunizing non-human animals such as mice, rats, sheep, goats, pigs, cattle and horses are well known in the art. See, *e.g.*, Harlow and Lane and United States Patent 5,994,619. In a preferred embodiment, the MAdCAM antigen is administered with an adjuvant to stimulate the immune response. Such adjuvants include complete or incomplete Freund's adjuvant, RIBI (muramyl dipeptides) or ISCOM (immunostimulating complexes). Such adjuvants may protect the polypeptide from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are

chemotactic for macrophages and other components of the immune system. Preferably, if a polypeptide is being administered, the immunization schedule will involve two or more administrations of the polypeptide, spread out over several weeks.

[0179] Example I provides a protocol for immunizing a XENOMOUSE™ animal with full-length human MAdCAM in phosphate-buffered saline.

Production of Antibodies and Antibody-Producing Cell Lines

[0180] After immunization of an animal with a MAdCAM antigen, antibodies and/or antibody-producing cells may be obtained from the animal. An anti-MAdCAM antibody-containing serum is obtained from the animal by bleeding or sacrificing the animal. The serum may be used as it is obtained from the animal, an immunoglobulin fraction may be obtained from the serum, or the anti-MAdCAM antibodies may be purified from the serum.

[0181] In another embodiment, antibody-producing immortalized cell lines may be prepared from the immunized animal. After immunization, the animal is sacrificed and B cells are immortalized using methods well-known in the art. Methods of immortalizing cells include, but are not limited to, transfecting them with oncogenes, infecting them with an oncogenic virus and cultivating them under conditions that select for immortalized cells, subjecting them to carcinogenic or mutating compounds, fusing them with an immortalized cell, *e.g.*, a myeloma cell, and inactivating a tumor suppressor gene. See, *e.g.*, Harlow and Lane, *supra*. In embodiments involving the myeloma cells, the myeloma cells do not secrete immunoglobulin polypeptides (a non-secretory cell line). After immortalization and antibiotic selection, the immortalized cells, or culture supernatants thereof, are screened using MAdCAM, a portion thereof, or a cell expressing MAdCAM. In a preferred embodiment, the initial screening is performed using an enzyme-linked immunoassay (ELISA) or a radioimmunoassay (RIA), preferably an ELISA. An example of ELISA screening is provided in PCT Publication No. WO 00/37504, herein incorporated by reference.

[0182] In another embodiment, antibody-producing cells may be prepared from a human who has an autoimmune disorder and who expresses anti-MAdCAM antibodies. Cells expressing the anti-MAdCAM antibodies may be isolated by isolating white blood cells and subjecting them to fluorescence-activated cell sorting (FACS) or by panning on plates coated with MAdCAM or a portion thereof. These cells may be fused with a human non-secretory myeloma to produce human hybridomas expressing human anti-MAdCAM antibodies. In general, this is a less preferred embodiment because it is likely that the anti-MAdCAM antibodies will have a low affinity for MAdCAM.

[0183] Anti-MAdCAM antibody-producing cells, *e.g.*, hybridomas are selected, cloned and further screened for desirable characteristics, including robust cell growth, high antibody production and desirable antibody characteristics, as discussed further below. Hybridomas may be cultured and expanded *in vivo* in syngeneic animals, in animals that lack an immune system, *e.g.*, nude mice, or in cell culture *in vitro*. Methods of selecting, cloning and expanding hybridomas are well known to those of ordinary skill in the art.

[0184] Preferably, the immunized animal is a non-human animal that expresses human immunoglobulin genes and the splenic B cells are fused to a myeloma derived from the same species as the non-human animal. More preferably, the immunized animal is a XENOMOUSE™ animal and the myeloma cell line is a non-secretory mouse myeloma, such as the myeloma cell line is P3-X63-AG8-653 (ATCC). See, *e.g.*, Example I.

[0185] Thus, in one embodiment, the disclosure provides methods for producing a cell line that produces a human monoclonal antibody or a fragment thereof directed to MAdCAM comprising (a) immunizing a non-human transgenic animal described herein with MAdCAM, a portion of MAdCAM or a cell or tissue expressing MAdCAM; (b) allowing the transgenic animal to mount an immune response to MAdCAM; (c) isolating antibody-producing cells from transgenic animal; (d) immortalizing the antibody-producing cells; (e)

creating individual monoclonal populations of the immortalized antibody-producing cells; and (f) screening the immortalized antibody-producing cells or culture supernatants thereof to identify an antibody directed to MAdCAM.

[0186] In one aspect, the disclosure provides hybridomas that produce human anti-MAdCAM antibodies. In a preferred embodiment, the hybridomas are mouse hybridomas, as described above. In another embodiment, the hybridomas are produced in a non-human, non-mouse species such as rats, sheep, pigs, goats, cattle or horses. In another embodiment, the hybridomas are human hybridomas, in which a human non-secretory myeloma is fused with a human cell expressing an anti-MAdCAM antibody.

Nucleic Acids, Vectors, Host Cells and Recombinant Methods of Making Antibodies

Nucleic Acids

[0187] Nucleic acid molecules encoding anti-MAdCAM antibodies of the disclosure are provided. In one embodiment, the nucleic acid molecule encodes a heavy and/or light chain of an anti-MAdCAM immunoglobulin. In a preferred embodiment, a single nucleic acid molecule encodes a heavy chain of an anti- MAdCAM immunoglobulin and another nucleic acid molecule encodes the light chain of an anti-MAdCAM immunoglobulin. In a more preferred embodiment, the encoded immunoglobulin is a human immunoglobulin, preferably a human IgG. The encoded light chain may be a λ chain or a κ chain, preferably a κ chain.

[0188] In a preferred embodiment the nucleic acid molecule encoding the variable region of the light chain comprises the germline sequence of a human Vκ the A2, A3, A26, B3, O12 or O18 gene or a variant of said sequence. In a preferred embodiment, the nucleic acid molecule encoding the light chain comprises a sequence derived from a human Jκ1, Jκ2, Jκ3, Jκ4 or Jκ5 gene. In a preferred embodiment, the nucleic acid molecule encoding the light chain encodes no more than eleven amino acid changes from the germline A2, A3, A26, B3, O12 or O18 Vκ gene, preferably no more than six amino acid changes, and even more

preferably no more than three amino acid changes. In a more preferred embodiment, the nucleic acid encoding the light chain is the germline sequence.

[0189] The disclosure provides a nucleic acid molecule that encodes a variable region of the light chain (VL) containing up to eleven amino acid changes compared to the germline sequence, wherein the amino acid changes are identical to amino acid changes from the germline sequence from the VL of one of the antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. The disclosure also provides a nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence of the variable region of the light chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. The disclosure also provides a nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence of one or more of the CDRs of any one of the light chains of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In a preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of all of the CDRs of any one of the light chains of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of one of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 66, 68, 150 or comprises a nucleotide sequence of one of SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 53, 57, 61, 65 or 67. In another preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of one or more of the CDRs of any one of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54,

58, 62, 66, 68, 150 or comprises a nucleotide sequence of one or more of the CDRs of any one of SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 53, 57, 61, 65, or 67. In a more preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of all of the CDRs of any one of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 66, 68, 150 or comprises a the nucleotide sequence of all the CDRs of any one of SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 53, 57, 61, 65, or 67.

[0190] The disclosure also provides a nucleic acid molecule that encodes an amino acid sequence of a VL that has an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a VL described above, particularly to a VL that comprises an amino acid sequence of one of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 66, , 68 or 150. The disclosure also provides a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of one of SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 53, 57, 61, 65 or 67.

[0191] In another embodiment, the disclosure provides a nucleic acid molecule that hybridizes under highly stringent conditions to a nucleic acid molecule encoding a VL as described above, particularly a nucleic acid molecule that comprises a nucleotide sequence encoding an amino acid sequence of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 66, 68, 150. The disclosure also provides a nucleic acid molecule that hybridizes under highly stringent conditions to a nucleic acid molecule comprising a nucleotide sequence of one of SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 53, 57, 61, 65 or 67.

[0192] The disclosure also provides a nucleic acid molecule encoding a heavy chain variable region (VH) that utilizes a human VH 1-18, 3-15, 3-21, 3-23, 3-30, 3-33 or 4-4 VH

gene. In some embodiments, the nucleic acid molecule encoding the VH gene further utilizes a human JH4 or JH6 family gene. In some embodiments, the nucleic acid molecule encoding the VH gene utilize the human JH4b or JH6b gene. In another embodiment, the nucleic acid molecule comprises a sequence derived from a human D 3-10, 4-23, 5-5, 6-6 or 6-19 gene. In an even more preferred embodiment, the nucleic acid molecule encoding the VH contains no more than fifteen amino acid changes from the germline VH 1-18, 3-15, 3-21, 3-23, 3-30, 3-33 or 4-4 genes, preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes. In a highly preferred embodiment, the nucleic acid molecule encoding the VH contains at least one amino acid change compared to the germline sequence, wherein the amino acid change is identical to an amino acid change from the germline sequence from the heavy chain of one of the antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In an even more preferred embodiment, the VH contains no more than fifteen amino acid changes compared to the germline sequences, wherein the changes are identical to those changes from the germline sequence from the VH of one of the antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod.

[0193] In one embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of the VH of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of one or more of the CDRs of the heavy chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In a

preferred embodiment, the nucleic acid molecule comprises nucleotide sequences that encode the amino acid sequences of all of the CDRs of the heavy chain of 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64 or 148 or that comprises a nucleotide sequence of one of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 51, 55, 59, 63, or 149. In another preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence of one or more of the CDRs of any one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64 or 148 or comprises a nucleotide sequence of one or more of the CDRs of any one of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 51, 55, 59,63 or 149. In a preferred embodiment, the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequences of all of the CDRs of any one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64, 148 or comprises a nucleotide sequence of all of the CDRs of any one of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41 45, 51, 55, 59, 63 or 149. In some embodiments the nucleic acid molecule comprises a nucleotide sequence encoding a contiguous region from the beginning of CDR1 to the end of CDR3 of a heavy or light chain of any of the above-mentioned anti-MAdCAM antibodies.

[0194] In another embodiment, the nucleic acid molecule encodes an amino acid sequence of a VH that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to one of the amino acid sequences encoding a VH as described immediately above, particularly to a VH that comprises an amino acid sequence of one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60 or 64. The disclosure also provides a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a

nucleotide sequence of one of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 51, 55, 59, 63 or 149.

[0195] In another embodiment, the nucleic acid molecule encoding a VH is one that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH as described above, particularly to a VH that comprises an amino acid sequence of one of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64 or 148. The disclosure also provides a nucleotide sequence encoding a VH that hybridizes under highly stringent conditions to a nucleic acid molecule comprising a nucleotide sequence of one of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 51, 55, 59, 63, 149.

[0196] The nucleotide sequence encoding either or both of the entire heavy and light chains of an anti-MAdCAM antibody or the variable regions thereof may be obtained from any source that produces an anti-MAdCAM antibody. Methods of isolating mRNA encoding an antibody are well-known in the art. See, *e.g.*, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989). The mRNA may be used to produce cDNA for use in the polymerase chain reaction (PCR) or cDNA cloning of antibody genes. In one embodiment of the disclosure, the nucleic acid molecules may be obtained from a hybridoma that expresses an anti-MAdCAM antibody, as described above, preferably a hybridoma that has as one of its fusion partners a transgenic animal cell that expresses human immunoglobulin genes, such as a XENOMOUSE™ animal, a non-human mouse transgenic animal or a non-human, non-mouse transgenic animal. In another embodiment, the hybridoma is derived from a non-human, non-transgenic animal, which may be used, *e.g.*, for humanized antibodies.

[0197] A nucleic acid molecule encoding the entire heavy chain of an anti-MAdCAM antibody may be constructed by fusing a nucleic acid molecule encoding the entire variable domain of a heavy chain or an antigen-binding domain thereof with a constant domain of a

heavy chain. Similarly, a nucleic acid molecule encoding the light chain of an anti-MAdCAM antibody may be constructed by fusing a nucleic acid molecule encoding the variable domain of a light chain or an antigen-binding domain thereof with a constant domain of a light chain. Nucleic acid molecules encoding the VH and VL regions may be converted to full-length antibody genes by inserting them into expression vectors already encoding heavy chain constant and light chain constant regions, respectively, such that the VH segment is operatively linked to the heavy chain constant region (CH) segment(s) within the vector and the VL segment is operatively linked to the light chain constant region (CL) segment within the vector. Alternatively, the nucleic acid molecules encoding the VH or VL chains are converted into full-length antibody genes by linking, *e.g.*, ligating, the nucleic acid molecule encoding a VH chain to a nucleic acid molecule encoding a CH chain using standard molecular biological techniques. The same may be achieved using nucleic acid molecules encoding VL and CL chains. The sequences of human heavy and light chain constant region genes are known in the art. See, *e.g.*, Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed., NIH Publ. No. 91-3242 (1991). Nucleic acid molecules encoding the full-length heavy and/or light chains may then be expressed from a cell into which they have been introduced and the anti-MAdCAM antibody isolated.

[0198] In a preferred embodiment, the nucleic acid encoding the variable region of the heavy chain encodes the variable region of amino acid sequences of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, 56, 60, 64 or 148, and the nucleic acid molecule encoding the variable region of the light chains encodes the variable region of amino acid sequence of SEQ ID NOS: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 54, 58, 62, 66, 68 or 150.

[0199] In one embodiment, a nucleic acid molecule encoding either the heavy chain of an anti-MAdCAM antibody or an antigen-binding portion thereof, or the light chain of an anti-

MAdCAM antibody or an antigen-binding portion thereof may be isolated from a non-human, non-mouse animal that expresses human immunoglobulin genes and has been immunized with a MAdCAM antigen. In other embodiment, the nucleic acid molecule may be isolated from an anti-MAdCAM antibody-producing cell derived from a non-transgenic animal or from a human patient who produces anti-MAdCAM antibodies. mRNA from the anti-MAdCAM antibody-producing cells may be isolated by standard techniques, cloned and/or amplified using PCR and library construction techniques, and screened using standard protocols to obtain nucleic acid molecules encoding anti-MAdCAM heavy and light chains.

[0200] The nucleic acid molecules may be used to recombinantly express large quantities of anti-MAdCAM antibodies, as described below. The nucleic acid molecules may also be used to produce chimeric antibodies, single chain antibodies, immunoadhesins, diabodies, mutated antibodies and antibody derivatives, as described further below. If the nucleic acid molecules are derived from a non-human, non-transgenic animal, the nucleic acid molecules may be used for antibody humanization, also as described below.

[0201] In another embodiment, the nucleic acid molecules of the disclosure may be used as probes or PCR primers for specific antibody sequences. For instance, a nucleic acid molecule probe may be used in diagnostic methods or a nucleic acid molecule PCR primer may be used to amplify regions of DNA that could be used, *inter alia*, to isolate nucleotide sequences for use in producing variable domains of anti-MAdCAM antibodies. In a preferred embodiment, the nucleic acid molecules are oligonucleotides. In a more preferred embodiment, the oligonucleotides are from highly variable regions of the heavy and light chains of the antibody of interest. In an even more preferred embodiment, the oligonucleotides encode all or a part of one or more of the CDRs.

Vectors

[0202] The disclosure provides vectors comprising the nucleic acid molecules of the disclosure that encode the heavy chain or the antigen-binding portion thereof. The disclosure also provides vectors comprising the nucleic acid molecules of the disclosure that encode the light chain or antigen-binding portion thereof. The disclosure also provides vectors comprising nucleic acid molecules encoding fusion proteins, modified antibodies, antibody fragments, and probes thereof.

[0203] To express the antibodies, or antibody portions of the disclosure, DNAs encoding partial or full-length light and heavy chains, obtained as described above, are inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. Expression vectors include plasmids, retroviruses, adenoviruses, adeno-associated viruses (AAV), plant viruses such as cauliflower mosaic virus, tobacco mosaic virus, cosmids, YACs, EBV derived episomes, and the like. The antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector. In a preferred embodiment, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (*e.g.*, ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present).

[0204] A convenient vector is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, as described above. In such vectors, splicing

usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The recombinant expression vector can also encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene may be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

[0205] In addition to the antibody chain genes, the recombinant expression vectors of the disclosure carry regulatory sequences that control the expression of the antibody chain genes in a host cell. It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from retroviral LTRs, cytomegalovirus (CMV) (such as the CMV promoter/enhancer), Simian Virus 40 (SV40) (such as the SV40 promoter/enhancer), adenovirus, (*e.g.*, the adenovirus major late promoter (AdMLP)), polyoma and strong mammalian promoters such as native immunoglobulin and actin promoters. For further description of viral regulatory elements, and sequences thereof, see *e.g.*, U.S. Pat. Nos. 5,168,062, 4,510,245, and 4,968,615, each of which is hereby incorporated by reference. Methods for expressing antibodies in plants, including a description of promoters and vectors, as well as transformation of plants are known in the art. See, *e.g*, United States Patent

6,517,529. Methods of expressing polypeptides in bacterial cells or fungal cells, *e.g.*, yeast cells, are also well known in the art.

[0206] In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors of the disclosure may carry additional sequences, such as sequences that regulate replication of the vector in host cells (*e.g.*, origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see, *e.g.*, U.S. Pat. Nos. 4,399,216, 4,634,665 and 5,179,017). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable marker genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr$^-$ host cells with methotrexate selection/amplification) and the neo gene (for G418 selection), and the glutamate synthetase gene.

Non-Hybridoma Host Cells and Methods of Recombinantly Producing Protein

[0207] Nucleic acid molecules encoding the heavy chain or an antigen-binding portion thereof and/or the light chain or an antigen-binding portion thereof of an anti-MAdCAM antibody, and vectors comprising these nucleic acid molecules, can be used for transformation of a suitable mammalian plant, bacterial or yeast host cell. Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors. Methods of transforming cells are well known in the art. See, *e.g.*, U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated

herein by reference). Methods of transforming plant cells are well known in the art, including, *e.g.*, Agrobacterium-mediated transformation, biolistic transformation, direct injection, electroporation and viral transformation. Methods of transforming bacterial and yeast cells are also well known in the art.

[0208] Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, *inter alia,* Chinese hamster ovary (CHO) cells, NS0, SP2 cells, HEK-293T cells, NIH-3T3 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and fungal cells. When recombinant expression vectors encoding the heavy chain or antigen-binding portion thereof, the light chain and/or antigen-binding portion thereof are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods. Plant host cells include, *e.g.*, Nicotiana, Arabidopsis, duckweed, corn, wheat, potato, etc. Bacterial host cells include *E. coli* and *Streptomyces* species. Yeast host cells include *Schizosaccharomyces pombe*, *Saccharomyces cerevisiae* and *Pichia pastoris*.

[0209] Further, expression of antibodies of the disclosure (or other moieties therefrom) from production cell lines can be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common

approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with European Patent Nos. 0 216 846, 0 256 055, 0 338 841 and 0 323 997.

[0210] It is likely that antibodies expressed by different cell lines or in transgenic animals will have different glycosylation from each other. However, all antibodies encoded by the nucleic acid molecules provided herein, or comprising the amino acid sequences provided herein are part of the instant disclosure, regardless of the glycosylation of the antibodies.

Transgenic Animals and Plants

[0211] The disclosure also provides transgenic non-human animals and transgenic plants comprising one or more nucleic acid molecules of the disclosure that may be used to produce antibodies of the disclosure. Antibodies can be produced in and recovered from tissue or bodily fluids, such as milk, blood or urine, of goats, cows, horses, pigs, rats, mice, rabbits, hamsters or other mammals. See, *e.g.*, U.S. Patent Nos. 5,827,690, 5,756,687, 5,750,172, and 5,741,957. As described above, non-human transgenic animals that comprise human immunoglobulin loci can be immunized with MAdCAM or a portion thereof. Methods for making antibodies in plants are described, *e.g.*, in U.S. Patents 6,046,037 and 5,959,177, incorporated herein by reference.

[0212] In another embodiment, non-human transgenic animals and transgenic plants are produced by introducing one or more nucleic acid molecules of the disclosure into the animal or plant by standard transgenic techniques. See Hogan, *supra*. The transgenic cells used for making the transgenic animal can be embryonic stem cells, somatic cells or fertilized egg cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. See, *e.g.*, Hogan et al.,, *Manipulating the Mouse Embryo: A Laboratory Manual 2ed.*, Cold Spring Harbor Press (1999); Jackson et al., *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press (2000); and Pinkert,

Transgenic Animal Technology: A Laboratory Handbook, Academic Press (1999). In another embodiment, the transgenic non-human organisms may have a targeted disruption and replacement that encodes a heavy chain and/or a light chain of interest. In a preferred embodiment, the transgenic animals or plants comprise and express nucleic acid molecules encoding heavy and light chains that combine to bind specifically to MAdCAM, preferably human MAdCAM. In another embodiment, the transgenic animals or plants comprise nucleic acid molecules encoding a modified antibody such as a single-chain antibody, a chimeric antibody or a humanized antibody. The anti-MAdCAM antibodies may be made in any transgenic animal. In a preferred embodiment, the non-human animals are mice, rats, sheep, pigs, goats, cattle or horses. The non-human transgenic animal expresses said encoded polypeptides in blood, milk, urine, saliva, tears, mucus and other bodily fluids.

Phage Display Libraries

[0213] The disclosure provides a method for producing an anti-MAdCAM antibody or antigen-binding portion thereof comprising the steps of synthesizing a library of human antibodies on phage, screening the library with a MAdCAM or a portion thereof, isolating phage that bind MAdCAM, and obtaining the antibody from the phage. One method to prepare the library of antibodies comprises the steps of immunizing a non-human host animal comprising a human immunoglobulin locus with MAdCAM or an antigenic portion thereof to create an immune response, extracting cells from the host animal the cells that are responsible for production of antibodies; isolating RNA from the extracted cells, reverse transcribing the RNA to produce cDNA, amplifying the cDNA using a primer, and inserting the cDNA into phage display vector such that antibodies are expressed on the phage. Recombinant anti-MAdCAM antibodies of the disclosure may be obtained in this way.

[0214] Recombinant anti-MAdCAM human antibodies of the disclosure in addition to the anti-MAdCAM antibodies disclosed herein can be isolated by screening of a recombinant

combinatorial antibody library, preferably a scFv phage display library, prepared using human VL and VH cDNAs prepared from mRNA isolated from human lymphocytes. Methodologies for preparing and screening such libraries are known in the art. There are commercially available kits for generating phage display libraries (*e.g.*, the Pharmacia Recombinant Phage Antibody System, catalog no. 27-9400-01; and the Stratagene SurfZAP™ phage display kit, catalog no. 240612). There are also other methods and reagents that can be used in generating and screening antibody display libraries (see, *e.g.*, U.S. Pat. No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; Fuchs et al. (1991), *Biotechnology*, 9:1369-1372; Hay et al., *Hum. Antibod. Hybridomas*, 3:81-85 (1992); Huse et al., *Science*, 246:1275-1281 (1989); McCafferty et al., *Nature*, 348:552-554 (1990); Griffiths et al., *EMBO J*, 12:725-734 (1993); Hawkins et al., *J. Mol. Biol.*, 226:889-896 (1992); Clackson et al., *Nature*, 352:624-628 (1991); Gram et al., *Proc. Natl. Acad. Sci. USA*, 89:3576-3580 (1992); Garrad et al., *Biotechnology*, 9:1373-1377 (1991); Hoogenboom et al., *Nuc Acid Res*, 19:4133-4137 (1991); and Barbas et al., *Proc. Natl. Acad. Sci. USA*, 88:7978-7982 (1991).

[0215] In a preferred embodiment, to isolate human anti-MAdCAM antibodies with the desired characteristics, a human anti-MAdCAM antibody as described herein is first used to select human heavy and light chain sequences having similar binding activity toward MAdCAM, using the epitope imprinting methods described in Hoogenboom et al., PCT Publication No. WO 93/06213. The antibody libraries used in this method are preferably scFv libraries prepared and screened as described in McCafferty et al., PCT Publication No. WO 92/01047, McCafferty et al., *Nature*, 348:552-554 (1990); and Griffiths et al., *EMBO J*,

12:725-734 (1993). The scFv antibody libraries preferably are screened using human MAdCAM as the antigen.

[0216] Once initial human VL and VH segments are selected, "mix and match" experiments, in which different pairs of the initially selected VL and VH segments are screened for MAdCAM binding, are performed to select preferred VL/VH pair combinations. Additionally, to further improve the quality of the antibody, the VL and VH segments of the preferred VL/VH pair(s) can be randomly mutated, preferably within the CDR3 region of VH and/or VL, in a process analogous to the *in vivo* somatic mutation process responsible for affinity maturation of antibodies during a natural immune response. This *in vitro* affinity maturation can be accomplished by amplifying VH and VL regions using PCR primers complimentary to the VH CDR3 or VL CDR3, respectively, which primers have been "spiked" with a random mixture of the four nucleotide bases at certain positions such that the resultant PCR products encode VH and VL segments into which random mutations have been introduced into the VH and/or VL CDR3 regions. These randomly mutated VH and VL segments can be rescreened for binding to MAdCAM.

[0217] Following screening and isolation of an anti-MAdCAM antibody of the disclosure from a recombinant immunoglobulin display library, nucleic acid encoding the selected antibody can be recovered from the display package (*e.g.*, from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. If desired, the nucleic acid can be further manipulated to create other antibody forms of the disclosure, as described below. To express a recombinant human antibody isolated by screening of a combinatorial library, the DNA encoding the antibody is cloned into a recombinant expression vector and introduced into a mammalian host cells, as described above.

Class Switching

[0218] Another aspect of the instant disclosure is to provide a mechanism by which the class of an anti-MAdCAM antibody may be switched with another. In one aspect of the disclosure, a nucleic acid molecule encoding VL or VH is isolated using methods well-known in the art such that it does not include any nucleotide sequences encoding CL or CH. The nucleic acid molecule encoding VL or VH is then operatively linked to a nucleotide sequence encoding a CL or CH from a different class of immunoglobulin molecule. This may be achieved using a vector or nucleic acid molecule that comprises a CL or CH encoding sequence, as described above. For example, an anti-MAdCAM antibody that was originally IgM may be class switched to an IgG. Further, the class switching may be used to convert one IgG subclass to another, *e.g.*, from IgG_4 to IgG_2. A preferred method for producing an antibody of the disclosure comprising a desired isotype or antibody subclass comprises the steps of isolating a nucleic acid encoding the heavy chain of an anti-MAdCAM antibody and a nucleic acid encoding the light chain of an anti-MAdCAM antibody, obtaining the variable region of the heavy chain, ligating the variable region of the heavy chain with the constant domain of a heavy chain of the desired isotype, expressing the light chain and the ligated heavy chain in a cell, and collecting the anti-MAdCAM antibody with the desired isotype.

Antibody Derivatives

[0219] One may use the nucleic acid molecules described above to generate antibody derivatives using techniques and methods known to one of ordinary skill in the art.

Humanized Antibodies

[0220] The immunogenicity of non-human antibodies can be reduced to some extent using techniques of humanization, potentially employing display techniques using appropriate libraries. It will be appreciated that murine antibodies or antibodies from other species can be humanized or primatized using techniques well known in the art. See, *e.g.*, Winter and

Harris, *Immunol Today*, 14:43-46 (1993) and Wright et al., *Crit. Reviews in Immunol.*, 12125-168 (1992). The antibody of interest may be engineered by recombinant DNA techniques to substitute the C_H1, C_H2, C_H3, hinge domains, and/or the framework domain with the corresponding human sequence (see WO 92/02190 and U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,761, 5,693,792, 5,714,350, and 5,777,085). In another embodiment, a non-human anti-MAdCAM antibody can be humanized by substituting the C_H1, hinge domain, C_H2, C_H3, and/or the framework domains with the corresponding human sequence of a anti-MAdCAM antibody of the disclosure.

Mutated Antibodies

[0221] In another embodiment, the nucleic acid molecules, vectors and host cells may be used to make mutated anti-MAdCAM antibodies. The antibodies may be mutated in the variable domains of the heavy and/or light chains to alter a binding property of the antibody. For example, a mutation may be made in one or more of the CDR regions to increase or decrease the K_d of the antibody for MAdCAM. Techniques in site-directed mutagenesis are well-known in the art. See, *e.g.*, Sambrook et al., and Ausubel et al., *supra*. In a preferred embodiment, mutations are made at an amino acid residue that is known to be changed compared to germline in a variable region of an anti-MAdCAM antibody. In a more preferred embodiment, one or more mutations are made at an amino acid residue that is known to be changed compared to the germline in a variable region or CDR region of one of the anti-MAdCAM antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another embodiment, one or more mutations are made at an amino acid residue that is known to be changed compared to the germline in a variable region or CDR region whose amino acid sequence is presented in SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 52, 54, 56, 58, 62, 64, 66, 68 148 or

150 or whose nucleotide sequence is presented in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 51, 53, 55, 57, 61, 63, 65, 67 or 149. In another embodiment, the nucleic acid molecules are mutated in one or more of the framework regions. A mutation may be made in a framework region or constant domain to increase the half-life of the anti-MAdCAM antibody. See, *e.g.*, WO 00/09560, published February 24, 2000, herein incorporated by reference. In one embodiment, there may be one, three or five or ten point mutations and no more than fifteen point mutations. A mutation in a framework region or constant domain may also be made to alter the immunogenicity of the antibody, to provide a site for covalent or non-covalent binding to another molecule, or to alter such properties as complement fixation. Mutations may be made in each of the framework regions, the constant domain and the variable regions in a single mutated antibody. Alternatively, mutations may be made in only one of the framework regions, the variable regions or the constant domain in a single mutated antibody.

[0222] In one embodiment, there are no greater than fifteen amino acid changes in either the VH or VL regions of the mutated anti-MAdCAM antibody compared to the anti-MAdCAM antibody prior to mutation. In a more preferred embodiment, there is no more than ten amino acid changes in either the VH or VL regions of the mutated anti-MAdCAM antibody, more preferably no more than five amino acid changes, or even more preferably no more than three amino acid changes. In another embodiment, there are no more than fifteen amino acid changes in the constant domains, more preferably, no more than ten amino acid changes, even more preferably, no more than five amino acid changes.

Modified Antibodies

[0223] In another embodiment, a fusion antibody or immunoadhesin may be made which comprises all or a portion of an anti-MAdCAM antibody linked to another polypeptide. In a preferred embodiment, only the variable regions of the anti-MAdCAM antibody are linked to

the polypeptide. In another preferred embodiment, the VH domain of an anti-MAdCAM antibody are linked to a first polypeptide, while the VL domain of an anti-MAdCAM antibody are linked to a second polypeptide that associates with the first polypeptide in a manner in which the VH and VL domains can interact with one another to form an antibody binding site. In another preferred embodiment, the VH domain is separated from the VL domain by a linker such that the VH and VL domains can interact with one another (see below under Single Chain Antibodies). The VH-linker-VL antibody is then linked to the polypeptide of interest. The fusion antibody is useful to directing a polypeptide to a MAdCAM-expressing cell or tissue. The polypeptide may be a therapeutic agent, such as a toxin, growth factor or other regulatory protein, or may be a diagnostic agent, such as an enzyme that may be easily visualized, such as horseradish peroxidase. In addition, fusion antibodies can be created in which two (or more) single-chain antibodies are linked to one another. This is useful if one wants to create a divalent or polyvalent antibody on a single polypeptide chain, or if one wants to create a bispecific antibody.

[0224] To create a single chain antibody, (scFv) the VH- and VL-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, *e.g.*, encoding the amino acid sequence $(Gly_4\text{-}Ser)_3$, such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (see, *e.g.*, Bird et al., *Science*, 242:423-426 (1988); Huston et al., *Proc. Natl. Acad. Sci. USA*, 85:5879-5883 (1988); McCafferty et al., *Nature*, 348:552-554 (1990)). The single chain antibody may be monovalent, if only a single VH and VL are used, bivalent, if two VH and VL are used, or polyvalent, if more than two VH and VL are used.

[0225] In another embodiment, other modified antibodies may be prepared using anti-MAdCAM-encoding nucleic acid molecules. For instance, "Kappa bodies" (Ill et al., *Protein Eng*, 10: 949-57(1997)), "Minibodies" (Martin et al., *EMBO J*, 13: 5303-9(1994)),

"Diabodies" (Holliger et al., *PNAS USA*, 90: 6444-6448(1993)), or "Janusins" (Traunecker et al., *EMBO J*, 10:3655-3659 (1991) and Traunecker et al., "Janusin: new molecular design for bispecific reagents," *Int J Cancer Suppl*, 7:51-52 (1992)) may be prepared using standard molecular biological techniques following the teachings of the specification.

[0226] In another aspect, chimeric and bispecific antibodies can be generated. A chimeric antibody may be made that comprises CDRs and framework regions from different antibodies. In a preferred embodiment, the CDRs of the chimeric antibody comprises all of the CDRs of the variable region of a light chain or heavy chain of a human anti-MAdCAM antibody, while the framework regions are derived from one or more different antibodies. In a more preferred embodiment, the CDRs of the chimeric antibody comprise all of the CDRs of the variable regions of the light chain and the heavy chain of a human anti-MAdCAM antibody. The framework regions may be from another species and may, in a preferred embodiment, be humanized. Alternatively, the framework regions may be from another human antibody.

[0227] A bispecific antibody can be generated that binds specifically to MAdCAM through one binding domain and to a second molecule through a second binding domain. The bispecific antibody can be produced through recombinant molecular biological techniques, or may be physically conjugated together. In addition, a single chain antibody containing more than one VH and VL may be generated that binds specifically to MAdCAM and to another molecule. Such bispecific antibodies can be generated using techniques that are well known for example, in connection with (i) and (ii) see, *e.g.*, Fanger et al., *Immunol Methods* 4: 72-81 (1994) and Wright and Harris, *supra.* and in connection with (iii) see, *e.g.*, Traunecker et al., *Int. J. Cancer (Suppl.)* 7: 51-52 (1992). In a preferred embodiment, the bispecific antibody binds to MAdCAM and to another molecule expressed at high level on endothelial cells. In a more preferred embodiment, the other molecule is VCAM, ICAM or L-selectin.

[0228] In various embodiments, the modified antibodies described above are prepared using one or more of the variable regions or one or more CDR regions from one of the antibodies selected from 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, X481.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod or 7.26.4-mod. In another embodiment, the modified antibodies are prepared using one or more of the variable regions or one or more CDR regions whose amino acid sequence is presented in SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 52, 54, 56, 58, 62, 64, 66, 68, 148 or 150 or whose nucleotide sequence is presented in SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 51, 53, 55, 57, 61, 63, 65, 67 or 149.

Derivatized and Labeled Antibodies

[0229] An antibody or antibody portion of the disclosure can be derivatized or linked to another molecule (*e.g.*, another peptide or protein). In general, the antibodies or portions thereof are derivatized such that the MAdCAM binding is not affected adversely by the derivatization or labeling. Accordingly, the antibodies and antibody portions of the disclosure are intended to include both intact and modified forms of the human anti-MAdCAM antibodies described herein. For example, an antibody or antibody portion of the disclosure can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detection agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

[0230] One type of derivatized antibody is produced by crosslinking two or more antibodies (of the same type or of different types, *e.g.*, to create bispecific antibodies). Suitable

crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (*e.g.*, m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (*e.g.*, disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

[0231] Another type of derivatized antibody is a labeled antibody. Useful detection agents with which an antibody or antibody portion of the disclosure may be derivatized include fluorescent compounds, including fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin, lanthanide phosphors and the like. An antibody may also be labeled with enzymes that are useful for detection, such as horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase, glucose oxidase and the like. When an antibody is labeled with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a reaction product that can be discerned. For example, when the agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody may also be labeled with biotin, and detected through indirect measurement of avidin or streptavidin binding. An antibody may be labeled with a magnetic agent, such as gadolinium. An antibody may also be labeled with a predetermined polypeptide epitope recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0232] An anti-MAdCAM antibody may also be labeled with a radiolabeled amino acid. The radiolabel may be used for both diagnostic and therapeutic purposes. For instance, the radiolabel may be used to detect MAdCAM-expressing tissues by x-ray or other diagnostic techniques. Further, the radiolabel may be used therapeutically as a toxin for diseased tissue or MAdCAM expressing tumors. Examples of labels for polypeptides include, but are not

limited to, the following radioisotopes or radionuclides -- ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I.

[0233] An anti-MAdCAM antibody may also be derivatized with a chemical group such as polyethylene glycol (PEG), a methyl or ethyl group, or a carbohydrate group. These groups may be useful to improve the biological characteristics of the antibody, *e.g.*, to increase serum half-life or to increase tissue binding. This methodology would also apply to any antigen-binding fragments or versions of anti-MAdCAM antibodies.

Pharmaceutical Compositions and Kits

[0234] In a further aspect, the disclosure provides compositions comprising an inhibitory human anti-MAdCAM antibody and methods for treating subjects with such compositions. In some embodiments, the subject of treatment is human. In other embodiments, the subject is a veterinary subject. In some embodiments, the veterinary subject is a dog or a non-human primate.

[0235] Treatment may involve administration of one or more inhibitory anti-MAdCAM monoclonal antibodies of the disclosure, or antigen-binding fragments thereof, alone or with a pharmaceutically acceptable carrier. Inhibitory anti-MAdCAM antibodies of the disclosure and compositions comprising them, can be administered in combination with one or more other therapeutic, diagnostic or prophylactic agents. Additional therapeutic agents include anti-inflammatory or immunomodulatory agents. These agents include, but are not limited to, the topical and oral corticosteroids such as prednisolone, methylprednisolone, NCX-1015 or budesonide; the aminosalicylates such as mesalazine, olsalazine, balsalazide or NCX-456; the class of immunomodulators such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporin, FK506, IL-10 (Ilodecakin), IL-11 (Oprelevkin), IL-12, MIF/CD74 antagonists, CD40 antagonists, such as TNX-100/5-D12, OX40L antagonists, GM-CSF, pimecrolimus or rapamycin; the class of anti-TNFα agents such as infliximab, adalimumab, CDP-870,

onercept, etanercept; the class of anti-inflammatory agents, such as PDE-4 inhibitors (roflumilast, etc), TACE inhibitors (DPC-333, RDP-58, etc) and ICE inhibitors (VX-740, etc) as well as IL-2 receptor antagonists, such as daclizumab, the class of selective adhesion molecule antagonists, such as natalizumab, MLN-02, or alicaforsen, classes of analgesic agents such as, but not limited to, COX-2 inhibitors, such as rofecoxib, valdecoxib, celecoxib, P/Q-type volatge senstize channel ($\alpha 2\delta$) modulators, such as gabapentin and pregabalin, NK-1 receptor antagonists, cannabinoid receptor modulators, and delta opioid receptor agonists, as well as anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agents Such additional agents may be included in the same composition or administered separately. In some embodiments, one or more inhibitory anti-MAdCAM antibodies of the disclosure can be used as a vaccine or as adjuvants to a vaccine. In particular, because MAdCAM is expressed in lymphoid tissue, vaccine antigens can be advantageously targeted to lymphoid tissue by conjugating the antigen to an anti-MAdCAM antibody of the disclosure.

[0236] As used herein, "pharmaceutically acceptable carrier" means any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption enhancing or delaying agents, and the like that are physiologically compatible. Some examples of pharmaceutically acceptable carriers are water, saline, phosphate buffered saline, acetate buffer with sodium chloride, dextrose, glycerol, Polyethylene glycol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Additional examples of pharmaceutically acceptable substances are surfectants, wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody.

[0237] The compositions of this disclosure may be in a variety of forms, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, lyophilized cake, dry powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular, intradermal). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular, intradermal or subcutaneous injection.

[0238] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, lyophilized cake, dry powder, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the anti-MAdCAM antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any any additional desired ingredient from a previously sterile solution thereof. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. The desired characteristics of a solution can be maintained, for example, by the use of surfactants and the required particle size in the case of dispersion by the use of surfactants, phospholipids and polymers. Prolonged absorption of injectable

compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts, polymeric materials, oils and gelatin.

[0239] The antibodies of the present disclosure can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is subcutaneous, intramuscular, intradermal or intravenous infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results.

[0240] In certain embodiments, the antibody compositions may be prepared with a carrier that will protect the antibody against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.*, *Sustained and Controlled Release Drug Delivery Systems* (J. R. Robinson, ed., Marcel Dekker, Inc., New York (1978)).

[0241] In certain embodiments, an anti-MAdCAM antibody of the disclosure can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) can also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the anti-MAdCAM antibodies can be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the disclosure by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

[0242] The compositions of the disclosure may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antigen-binding portion of the disclosure. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount may be less than the therapeutically effective amount.

[0243] Dosage regimens can be adjusted to provide the optimum desired response (*e.g.*, a therapeutic or prophylactic response). For example, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a pre-determined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on (a) the unique characteristics of the anti-MAdCAM antibody or portion thereof and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations

inherent in the art of compounding such an antibody for the treatment of sensitivity in individuals.

[0244] An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the disclosure is 0.025 to 50 mg/kg, more preferably 0.1 to 50 mg/kg, more preferably 0.1-25, 0.1 to 10 or 0.1 to 3 mg/kg. In some embodiments, a formulation contains 5 mg/mL of antibody in a buffer of 20 mM sodium acetate, pH 5.5, 140 mM NaCl, and 0.2 mg/mL polysorbate 80. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

[0245] Another aspect of the present disclosure provides kits comprising an anti-MAdCAM antibody or antibody portion of the disclosure or a composition comprising such an antibody. A kit may include, in addition to the antibody or composition, diagnostic or therapeutic agents. A kit can also include instructions for use in a diagnostic or therapeutic method. In a preferred embodiment, the kit includes the antibody or a composition comprising it and a diagnostic agent that can be used in a method described below. In another preferred embodiment, the kit includes the antibody or a composition comprising it and one or more therapeutic agents that can be used in a method described below.

Gene Therapy

[0246] The nucleic acid molecules of the instant disclosure can be administered to a patient in need thereof via gene therapy. The therapy may be either in vivo or ex vivo. In a preferred embodiment, nucleic acid molecules encoding both a heavy chain and a light chain

are administered to a patient. In a more preferred embodiment, the nucleic acid molecules are administered such that they are stably integrated into chromosomes of B cells because these cells are specialized for producing antibodies. In a preferred embodiment, precursor B cells are transfected or infected ex vivo and re-transplanted into a patient in need thereof. In another embodiment, precursor B cells or other cells are infected in vivo using a recombinant virus known to infect the cell type of interest. Typical vectors used for gene therapy include liposomes, plasmids and viral vectors. Exemplary viral vectors are retroviruses, adenoviruses and adeno-associated viruses. After infection either in vivo or ex vivo, levels of antibody expression can be monitored by taking a sample from the treated patient and using any immunoassay known in the art or discussed herein.

[0247] In a preferred embodiment, the gene therapy method comprises the steps of administering an isolated nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof of an anti-MAdCAM antibody and expressing the nucleic acid molecule. In another embodiment, the gene therapy method comprises the steps of administering an isolated nucleic acid molecule encoding the light chain or an antigen-binding portion thereof of an anti-MAdCAM antibody and expressing the nucleic acid molecule. In a more preferred method, the gene therapy method comprises the steps of administering of an isolated nucleic acid molecule encoding the heavy chain or an antigen-binding portion thereof and an isolated nucleic acid molecule encoding the light chain or the antigen-binding portion thereof of an anti-MAdCAM antibody of the disclosure and expressing the nucleic acid molecules. The gene therapy method may also comprise the step of administering another anti-inflammatory or immunomodulatory agent.

Diagnostic Methods of Use

[0248] The anti-MAdCAM antibodies may be used to detect MAdCAM in a biological sample *in vitro* or *in vivo*. The anti-MAdCAM antibodies may be used in a conventional

immunoassay, including, without limitation, an ELISA, an RIA, FACS, tissue immunohistochemistry, Western blot or immunoprecipitation. The anti-MAdCAM antibodies of the disclosure may be used to detect MAdCAM from humans. In another embodiment, the anti-MAdCAM antibodies may be used to detect MAdCAM from Old World primates such as cynomolgus and rhesus monkeys, chimpanzees and apes. The disclosure provides a method for detecting MAdCAM in a biological sample comprising contacting a biological sample with an anti-MAdCAM antibody of the disclosure and detecting the antibody bound to MAdCAM. In one embodiment, the anti-MAdCAM antibody is directlyderivatized with a detectable label. In another embodiment, the anti-MAdCAM antibody (the first antibody) is unlabeled and a second antibody or other molecule that can bind the anti-MAdCAM antibody is labeled. As is well known to one of skill in the art, a second antibody is chosen that is able to specifically bind the specific species and class of the first antibody. For example, if the anti-MAdCAM antibody is a human IgG, then the secondary antibody may be an anti-human-IgG. Other molecules that can bind to antibodies include, without limitation, Protein A and Protein G, both of which are available commercially, *e.g.*, from Pierce Chemical Co.

[0249] Suitable labels for the antibody or secondary have been disclosed *supra*, and include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, magnetic agents and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; an example of a

magnetic agent includes gadolinium; and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[0250] In an alternative embodiment, MAdCAM can be assayed in a biological sample by a competition immunoassay utilizing MAdCAM standards labeled with a detectable substance and an unlabeled anti-MAdCAM antibody. In this assay, the biological sample, the labeled MAdCAM standards and the anti-MAdCAM antibody are combined and the amount of labeled MAdCAM standard bound to the unlabeled antibody is determined. The amount of MAdCAM in the biological sample is inversely proportional to the amount of labeled MAdCAM standard bound to the anti-MAdCAM antibody.

[0251] One may use the immunoassays disclosed above for a number of purposes. In one embodiment, the anti-MAdCAM antibodies may be used to detect MAdCAM in cells in cell culture. In a preferred embodiment, the anti-MAdCAM antibodies may be used to determine the level of cell surface MAdCAM expression after treatment of the cells with various compounds. This method can be used to test compounds that may be used to activate or inhibit MAdCAM. In this method, one sample of cells is treated with a test compound for a period of time while another sample is left untreated, cell surface expression could then be determined by flow cytometry, immunohistochemistry, Western blot, ELISA or RIA. In addition, the immunoassays may be scaled up for high throughput screening in order to test a large number of compounds for either activation or inhibition of MAdCAM.

[0252] The anti-MAdCAM antibodies of the disclosure may also be used to determine the levels of MAdCAM on a tissue or in cells derived from the tissue. In a preferred embodiment, the tissue is a diseased tissue. In a more preferred embodiment, the tissue is inflamed gastrointestinal tract or a biopsy thereof. In a preferred embodiment of the method, a tissue or a biopsy thereof is excised from a patient. The tissue or biopsy is then used in an immunoassay to determine, *e.g.*, MAdCAM levels, cell surface levels of MAdCAM, or

localization of MAdCAM by the methods discussed above. The method can be used to determine if an inflamed tissue expresses MAdCAM at a high level.

[0253] The above-described diagnostic method can be used to determine whether a tissue expresses high levels of MAdCAM, which may be indicative that the tissue will respond well to treatment with anti-MAdCAM antibody. Further, the diagnostic method may also be used to determine whether treatment with anti-MAdCAM antibody (see below) is causing a tissue to express lower levels of MAdCAM and thus can be used to determine whether the treatment is successful.

[0254] The antibodies of the present disclosure may also be used *in vivo* to localize tissues and organs that express MAdCAM. In a preferred embodiment, the anti-MAdCAM antibodies can be used to localize inflamed tissue. The advantage of the anti-MAdCAM antibodies of the present disclosure is that they will not generate an immune response upon administration. The method comprises the steps of administering an anti-MAdCAM antibody or a pharmaceutical composition thereof to a patient in need of such a diagnostic test and subjecting the patient to imaging analysis determine the location of the MAdCAM-expressing tissues. Imaging analysis is well known in the medical art, and includes, without limitation, x-ray analysis, gamma scintigraphy, magnetic resonance imaging (MRI), positron emission tomography or computed tomography (CT). In another embodiment of the method, a biopsy is obtained from the patient to determine whether the tissue of interest expresses MAdCAM rather than subjecting the patient to imaging analysis. In a preferred embodiment, the anti-MAdCAM antibodies may be labeled with a detectable agent that can be imaged in a patient. For example, the antibody may be labeled with a contrast agent, such as barium, which can be used for x-ray analysis, or a magnetic contrast agent, such as a gadolinium chelate, which can be used for MRI or CT. Other labeling agents include, without limitation, radioisotopes, such as ^{99}Tc. In another embodiment, the anti-MAdCAM antibody will be unlabeled and will

be imaged by administering a second antibody or other molecule that is detectable and that can bind the anti-MAdCAM antibody.

[0255] The anti-MAdCAM antibodies of the disclosure may also be used to determine the levels of soluble MAdCAM present in donor blood, serum, plasma, or other biofluid, including, but not limited to, stool, urine, sputum or biopsy sample. In a preferred embodiment, the biofluid is plasma. The biofluid is then used in an immunoassay to determine levels of soluble MAdCAM. Soluble MAdCAM could be a surrogate marker for ongoing gastrointestinal inflammation and the method of detection could be used as a diagnostic marker to measure disease severity.

[0256] The above-described diagnostic method can be used to determine whether an individual expresses high levels of soluble MAdCAM, which may be indicative that the individual will respond well to treatment with an anti-MAdCAM antibody. Further, the diagnostic method may also be used to determine whether treatment with anti-MAdCAM antibody (see below) or other pharmaceutical agent of the disease is causing an individual to express lower levels of MAdCAM and thus can be used to determine whether the treatment is successful.

Inhibition of $\alpha_4\beta_7$/MAdCAM-dependent adhesion by anti-MAdCAM antibody:

[0257] In another embodiment, the disclosure provides an anti-MAdCAM antibody that binds MAdCAM and inhibits the binding and adhesion of $\alpha_4\beta_7$-integrin bearing cells to MAdCAM or other cognate ligands, such as L-selectin, to MAdCAM. In a preferred embodiment, the MAdCAM is human and is either a soluble form, or expressed on the surface of a cell. In another preferred embodiment, the anti-MAdCAM antibody is a human antibody. In another embodiment, the antibody or portion thereof inhibits binding between $\alpha_4\beta_7$ and MAdCAM with an IC_{50} value of no more than 50 nM. In a preferred embodiment, the IC_{50} value is no more than 5 nM. In a more preferred embodiment, the IC_{50} value is less

than 5 nM. In a more preferred embodiment, the IC_{50} value is less than 0.05 μg/mL, 0.04 μg/mL or 0.03 μg/mL. In another preferred embodiment the IC_{50} value is less than 0.5 μg/mL, 0.4 μg/mL or 0.3 μg/mL. The IC_{50} value can be measured by any method known in the art. Typically, an IC_{50} value can be measured by ELISA or adhesion assay. In a preferred embodiment, the IC_{50} value is measured by adhesion assay using either cells or tissue which natively express MAdCAM or cells or tissue which have been engineered to express MAdCAM.

Inhibition of lymphocyte recruitment to gut-associated lymphoid tissue by anti-MAdCAM antibodies

[0258] In another embodiment, the disclosure provides an anti-MAdCAM antibody that binds natively expressed MAdCAM and inhibits the binding of lymphocytes to specialised gastrointestinal lymphoid tissue. In a preferred embodiment, the natively-expressed MAdCAM is human or primate MAdCAM and is either a soluble form, or expressed on the surface of a cell. In another preferred embodiment, the anti-MAdCAM antibody is a human antibody. In another embodiment, the antibody or portion thereof inhibits the recruitment of gut-trophic $\alpha_4\beta_7^+$ lymphocytes to tissues expressing MAdCAM with an IC_{50} value of no more than 5 mg/kg. In a preferred embodiment, the IC_{50} value is no more than 1 mg/kg. In a more preferred embodiment, the IC_{50} value is less than 0.1 mg/kg. In one embodiment, the IC_{50} value can be determined by measuring the dose effect relationship of recruitment of technetium-labeled peripheral blood lymphocytes to the gastrointestinal tract using gamma scintigraphy or single photon emission computed tomography. In an another embodiment, the IC_{50} value can be determined by measuring the increase in gut-trophic $\alpha_4\beta_7^+$ lymphocytes, such as, but not limited to, $CD4^+$ $\alpha_4\beta_7^+$ memory T-cells, in the peripheral circulation using flow cytometry as a function of the dose of anti-MAdCAM antibody.

[0259] In order that this disclosure may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the disclosure in any manner.

EXAMPLE 1:

Generation of anti-MAdCAM producing hybridomas

[0260] Antibodies of the disclosure were prepared, assayed and selected in accordance with the present Example

Primary Immunogen Preparation:

[0261] Two immunogens were prepared for immunisation of the XenoMouse™ mice: (i) a MAdCAM-IgG_1 Fc fusion protein and (ii) cell membranes prepared from cells stably transfected with MAdCAM.

(i) MAdCAM-IgG_1 Fc Fusion Protein

Expression vector construction:

[0262] An EcoRI/BglII cDNA fragment encoding the mature extracellular, immunoglobulin-like domain of MAdCAM was excised from a pINCY Incyte clone (3279276) and cloned into EcoRI/BamHI sites of the pIG1 vector (Simmons, D. L. (1993) in *Cellular Interactions in Development: A Practical Approach*, ed. Hartley, D. A. (Oxford Univ. Press, Oxford), pp. 93-127.)) to generate an in frame IgG_1 Fc fusion. The resulting insert was excised with EcoRI/NotI and cloned into pCDNA3.1+ (Invitrogen). The MAdCAM-IgG_1 Fc cDNA in the vector was sequence confirmed. The amino acid sequence of the MAdCAM-IgG_1 Fc fusion protein is shown below:

MAdCAM-IgG_1 Fc Fusion Protein:

MDFGLALLLAGLLGLLLGQSLQVKPLQVEPPEPVVAVALGASRQLTCRLACADRGASVQWRG
LDTSLGAVQSDTGRSVLTVRNASLSAAGTRVCVGSCGGRTFQHTVQLLVYAFPDQLTVSPAA
LVPGDPEVACTAHKVTPVDPNALSFSLLVGGQELEGAQALGPEVQEEEEEPQGDEDVLFRVT
ERWRLPPLGTPVPPALYCQATMRLPGLELSHRQAIPVLHSPTSPEPPDTTSPESPDTTSPES
PDTTSQEPPDTTSQEPPDTTSQEPPDTTSPEPPDKTSPEPAPQQGSTHTPRSPGSTRTRRPE

IQPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKATPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
107)

Underlined: signal peptide
Bold: MAdCAM extracellular domain

Recombinant Protein Expression/Purification:

[0263] CHO-DHFR cells were transfected with pCDNA3.1+ vector containing MAdCAM-IgG_1 Fc fusion protein cDNA and stable clones expressing MAdCAM-IgG_1 Fc fusion protein selected in Iscove's media containing 600 μg/mL G418 and 100 ng/mL methotrexate. For protein expression, a hollow fibre bioreactor was seeded with stably expressing MAdCAM-IgG_1 Fc CHO cells in Iscove's media containing 10% low IgG fetal bovine serum (Gibco), non essential amino acids (Gibco), 2 mM glutamine (Gibco), sodium pyruvate (Gibco), 100 μg/mL G418 and 100 ng/mL methotrexate, and used to generate concentrated media supernatant. The MAdCAM-IgG_1 Fc fusion protein was purified from the harvested supernatant by affinity chromatography. Briefly, supernatant was applied to a HiTrap Protein G Sepharose (5 mL, Pharmacia) column (2 mL/min), washed with 25 mM Tris pH 8, 150 mM NaCl (5 column volumes) and eluted with 100 mM glycine pH 2.5 (1 mL/min), immediately neutralising fractions to pH 7.5 with 1M Tris pH 8. Fractions containing MAdCAM-IgG_1 Fc fusion protein were identified by SDS-PAGE, pooled together and applied to a Sephacryl S100 column (Pharmacia), pre-equilibrated with 35 mM BisTris pH 6.5, 150 mM NaCl. The gel filtration was performed at 0.35 mL/min, collecting a peak of MAdCAM-IgG_1 Fc fusion protein in *ca.* 3 x 5 mL fractions. These samples were pooled and applied to a Resource Q (6 mL, Pharmacia) column, pre-equilibrated in 35 mM BisTris pH6.5. The column was washed with 5 column volumes of 35 mM Bis Tris pH 6.5, 150 mM NaCl (6 mL/min) and MAdCAM-IgG_1 Fc fusion protein eluted into a 4-6 mL fraction with 35 mM Bis Tris pH 6.5, 400 mM NaCl. At this stage the protein was 90% pure and

migrating as a single band at approximately 68 kD by SDS-PAGE. For use as an immunogen and all subsequent assays, the material was buffer exchanged into 25 mM HEPES pH 7.5, 1 mM EDTA, 1 mM DTT, 100 mM NaCl, 50% glycerol and stored as aliquots at -80°C.

(ii) Cell membranes stably expressing MAdCAM

[0264] A SacI/NotI fragment comprising nucleotides 645-1222 of the published MAdCAM sequence (Shyjan AM, et al., *J Immunol.*, 156, 2851-7 (1996)) was PCR amplified from a colon cDNA library and cloned into SacI/NotI sites of pIND-Hygro vector (Invitrogen). A SacI fragment, comprising the additional 5' coding sequence was sub-cloned into this construct from pCDNA3.1 MAdCAM-IgG_1 Fc, to generate the full length MAdCAM cDNA. A KpnI/NotI fragment containing the MAdCAM cDNA was then cloned into corresponding sites in a pEF5FRTV5GWCAT vector (Invitrogen) and replacing the CAT coding sequence. The cDNA insert was sequence verified and used in transfections to generate single stably expressing clones in FlpIn NIH 3T3 cells (Invitrogen) by Flp recombinase technology, according to the manufacturer's instructions. Stably expressing clones were selected by their ability to support the binding of a $\alpha_4\beta_7^+$ JY human B lymphoblastoid cell line (Chan BM, et al, *J. Biol. Chem.*, 267:8366-70 (1992)), outlined below. Stable clones of CHO cells expressing MAdCAM were prepared in the same way, using FlpIn CHO cells (Invitrogen).

[0265] MAdCAM-expressing FlpIn NIH-3T3 cells were grown in Dulbecco's modified Eagles Medium (Gibco), containing 2 mM L-glutamine, 10% Donor calf serum (Gibco) and 200 μg/mL Hygromycin B (Invitrogen) and expanded in roller bottles. MAdCAM-expressing FlpIn CHO cells were grown in Ham's F12/Dulbecco's modified Eagles Medium (Gibco), containing 2 mM L-glutamine, 10% Donor calf serum (Gibco) and 350 μg/mL Hygromycin B (Invitrogen) and expanded in roller bottles. Cells were harvested by use of a non-enzymatic cell dissociation solution (Sigma) and scraping, washing in phosphate buffered

saline by centrifugation. Cell membranes were prepared from the cell pellet by two rounds of polytron homogenization in 25 mM Bis Tris pH 8, 10 mM $MgCl_2$, 0.015% (w/v) aprotinin, 100 U/mL bacitracin and centrifugation. The final pellet was resuspended in the same buffer, and $50x10^6$ cell equivalents aliquoted into thick-walled eppendorfs and spun at >100,000*g* to generate cell membrane pellets for XenoMouse mice immunisations. Supernatant was decanted and membranes were stored in eppendorfs at -80°C until required. Confirmation of protein expression in the cell membranes was determined by SDS-PAGE and Western blotting with a rabbit anti-peptide antibody raised against the N-terminal residues of MAdCAM ([C]-KPLQVEPPEP).

Immunization and hybridoma generation:

[0266] Eight to ten week old XENOMOUSE™ mice were immunized intraperitoneally or in their hind footpads with either the purified recombinant MAdCAM-IgG_1 Fc fusion protein (10 μg/dose/mouse), or cell membranes prepared from either stably expressing MAdCAM-CHO or NIH 3T3 cells ($10x10^6$ cells/dose/mouse). This dose was repeated five to seven times over a three to eight week period. Four days before fusion, the mice received a final injection of the extracellular domain of human MAdCAM in PBS. Spleen and lymph node lymphocytes from immunized mice were fused with the non-secretory myeloma P3-X63-Ag8.653 cell line and were subjected to HAT selection as previously described (Galfre and Milstein, *Methods Enzymol.* 73:3-46 (1981)). A panel of hybridomas all secreting MAdCAM specific human $IgG_2κ$ and $IgG_4κ$ antibodies were recovered and sub-cloned. Twelve hybridoma sub-clones, 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 and 9.8.2, producing monoclonal antibodies specific for MAdCAM were recovered and detected with assays described below. The parental lines 1.7, 1.8, 6.14, 6.22, 6.34, 6.67, 6.73, 6.77, 7.16, 7.20, 7.26 and 9.8, from which the sub-clone hybridoma lines,

1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 and 9.8.2, were derived all had anti-MAdCAM activity.

X481.2

[0267] A selected clone was further engineered to remove an inadvertent splicing event in the final protein. The inadvertent splicing event resulted in the production of an extended protein. It was discovered that the extension was the result of a read-through that led to the inadvertent splicing event. Without wishing to be bound by theory, it is believed that the inadvertent splicing event brought together the end of the heavy chain with a region 4244bp downstream (in the SV40 Derived Sequence Region). A new vector was designed to eliminate this observed extension. The heavy chain region was engineered to replace a nucleotide at the 3'end of the heavy chain (a change from T to A) resulting in the removal of the splice donor sight. The resulting MAdCAM antibody from this reengineered clone is X481.2.

ELISA assays:

[0268] Detection of antigen-specific antibodies in mouse serum and hybridoma supernatant was determined by ELISA as described (Coligan et al., Unit 2.1 "Enzyme-linked immunosorbent assays," in *Current ProtocolsIinImmunology* (1994)) using MAdCAM-IgG_1 Fc fusion protein to capture the antibodies. For animals that were immunised with MAdCAM-IgG_1 Fc fusion protein, antibodies were screened for non-specific reactivity against human IgG_1 and for the ability to bind to FlpIn CHO MAdCAM cells by flow cytometry.

[0269] In a preferred ELISA assay, the following techniques are used:

[0270] ELISA plates were coated overnight at 4°C with 100 μL/well of MAdCAM-IgG_1 Fc fusion (4.5 μg/mL) in plate containing buffer (100 mM sodium carbonate/bicarbonate buffer

pH 9.6). After incubation, coating buffer was removed and the plate blocked with 200 μL/well blocking buffer (5% BSA, 0.1% Tween 20, in phosphate buffered saline) and incubated at room temperature for 1 hour. Blocking buffer was removed and 50 μL/well of hybridoma supernatant or other serum or supernatant (*e.g.*, positive control) added for 2 hours at room temperature. After incubation the plate was washed with PBS (3 x 100 μL/well) and the binding of the hybridoma mAb detected with HRP-conjugated secondary antibodies (*i.e.* 1:1000 mouse anti-human IgG_2-HRP (SB Cat. No. 9060-05) for IgG_2 antibodies or 1:1000 mouse anti-human IgG_4-HRP (Zymed Cat. No. 3840) for IgG_4 antibodies) diluted in PBS. The plates were incubated at room temperature for 1 hour, washed in PBS (3 x 100 μL/well) and finally developed with 100 μL OPD (o-phenylenediamine (DAKO S2405) + 5 μL 30% H_2O_2/12 mL). The plates were allowed to develop 10-20 mins, stopping the reaction with 100 μL 2M H_2SO_4. The plates were read at 490 nm.

Adhesion assays:

[0271] Antibodies that demonstrated binding to MAdCAM-IgG1 Fc fusion protein by ELISA, were assessed for antagonist activity in an adhesion assays with $\alpha_4\beta_7^+$ JY cells and either (i) MAdCAM-IgG_1 Fc fusion protein or (ii) MAdCAM-CHO cells.

(i) MAdCAM-IgG_1 Fc fusion assay

[0272] 100μL of a 4.5μg/mL solution of purified MAdCAM-IgG_1 Fc fusion protein in Dulbecco's PBS was adsorbed to 96 well Black Microfluor "B" u-bottom (Dynex #7805) plates overnight at 4°C. The MAdCAM coated plates were then inverted and excess liquid blotted off, prior to blocking at 37°C for at least 1 hour in 10% BSA/ PBS. During this time cultured JY cells were counted using tryptan blue exclusion (should be approximately $8x10^5$ cells/mL) and $20x10^6$ cells/assay plate pipetted into a 50 mL centrifuge tube. JY cells were cultured in RPMI1640 media (Gibco), containing 2 mM L-glutamine and 10% heat-

inactivated fetal bovine serum (Life Technologies #10108-165) and seeded at 1-2x10^5/mL every 2-3 days to prevent the culture from differentiating. The cells were washed twice with RPMI 1640 media (Gibco) containing 2 mM L-glutamine (Gibco) by centrifugation (240*g*), resuspending the final cell pellet at 2x10^6 cells/mL in RPMI 1640 for Calcein AM loading. Calcein AM (Molecular Probes #C-3099) was added to the cells as a 1:200 dilution in DMSO (*ca.* final concentration 5 μM) and the cells protected from light during the course of the incubation (37°C for 30 min). During this cell incubation step the antibodies to be tested, were diluted as follows: for single dose testing, the antibodies were made up to 3 μg/mL (1 μg/mL final) in 0.1 mg/mL BSA (Sigma#A3059) in PBS; for full IC_{50} curves, the antibodies were diluted in 0.1 mg/mL BSA/ PBS, with 3 μg/mL (1 μg/mL final) being the top concentration, then doubling dilutions (1:2 ratio) across the plate. The final well of the row was used for determining total binding, so 0.1mg/ml BSA in PBS was used.

[0273] After blocking, the plate contents were flicked out and 50 μL of antibodies/controls were added to each well and the plate incubated at 37°C for 20 min. During this time, Calcein-loaded JY cells were washed once with RPMI 1640 media containing 10% fetal bovine serum and once with 1 mg/mL BSA/PBS by centrifugation, resuspending the final cell pellet to 1x10^6/mL in 1 mg/mL BSA/PBS. 100 μL of cells were added to each well of the U bottomed plate, the plate sealed, briefly centrifuged (1000 rpm for 2 min) and the plate then incubated at 37°C for 45 min. At the end of this time, the plates were washed with a Skatron plate washer and fluorescence measured using a Wallac Victor^2 1420 Multilabel Reader (excitation λ 485nm, emission λ 535nm count from top, 8 mm from bottom of plate, for 0.1 sec with normal emission aperture). For each antibody concentration, percent adhesion was expressed as a percentage of maximal fluorescence response in the absence of any antibody minus fluorescence associated with non-specific binding. The IC_{50} value is defined as the anti-MAdCAM antibody concentration at which the adhesion response is decreased to 50%

of the response in the absence of anti-MAdCAM antibody. Antibodies that were able to inhibit the binding of JY cells to MAdCAM-IgG_1 Fc fusion with an IC_{50} value <0.1 μg/mL, were considered to have potent antagonist activity and were progressed to the MAdCAM-CHO adhesion assay. All twelve of the tested Abs showed potent antagonist activity (Table 3). Monoclonal antibodies 1.7.2, 1.8.2, 7.16.6, 7.20.5 and 7.26.4 were derived from $IgG_2\kappa$ lineages, and monoclonal antibodies 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1 and 9.8.2 were derived from $IgG_4\kappa$ lineages.

(ii) MAdCAM-CHO cell adhesion assay.

[0274] JY cells were cultured as above. MAdCAM-expressing CHO cells were generated with the pEF5FRT MAdCAM cDNA construct and using the Flp recombinase technology (Invitrogen) as described above. Single stable clones of MAdCAM-expressing CHO cells were selected based on their ability to support the adhesion of JY cells and the binding, by flow cytometry, of the rabbit anti-peptide antibody, raised against the N-terminus of MAdCAM and described above. MAdCAM-expressing CHO cells were cultured in a DMEM/F12 media (Gibco # 21331-020) containing 2 mM L-glutamine, 10% fetal bovine serum (Gibco) and 350 μg/mL Hygromycin B (Invitrogen), splitting 1:5 every 2/3 days. For the adhesion assay, MAdCAM-expressing CHO cells were seeded at $4x10^4$ cells/well in 96 well black plates–clear bottom (Costar # 3904) in 200 μL culture medium and cultured overnight at 37°C/5% CO_2.

[0275] The following day, hybridoma supernatant or purified monoclonal antibody was diluted from a starting concentration of 30 μg/mL (equivalent to a final concentration of 10 μg/mL) in 1 mg/mL BSA/PBS, as described above. For the MAdCAM CHO plates, the plate contents were flicked out and 50 μL of antibodies/controls were added to each well and the plate incubated at 37°C for 20 min. The final well of the row was used for determining total

binding, so 0.1 mg/mL BSA in PBS was used. Calcein AM-loaded JY cells, to a final concentration of $1x10^6$/mL in 1 mg/mL BSA/PBS, were prepared as above, then 100 µL added to the plate after the 20 min incubation period with the antibody. The plate was then incubated at 37°C for 45 min, then washed on a Tecan plate washer (PW 384) and fluorescence measured using the Wallac plate reader as described above. For each antibody concentration, percent adhesion was expressed as a percentage of maximal fluorescence response in the absence of any antibody minus fluorescence associated with non-specific binding. Antibodies that were able to inhibit the binding of JY cells to MAdCAM CHO cells with an IC_{50} value <1 µg/mL were considered to have potent antagonist activity. As before, the IC_{50} value is defined as the anti-MAdCAM antibody concentration at which the adhesion response had decreased to 50% of the response in the absence of anti-MAdCAM antibody. The IC_{50} potencies for 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 and 9.8.2 in this assay are described below in Table 3.

Table 3. IC_{50} values of exemplified anti-MAdCAM antibodies

Clone	MAdCAM IgG $_1$ Fc fusion Mean IC50 (µg/mL)	n	MAdCAM FlpIn CHO Assay Mean IC50 (µg/mL)	n
1.7.2	0.030 ± 0.011	6	0.502 ± 0.280	9
1.8.2	0.027 ± 0.011	4	0.424 ± 0.107	8
7.16.6	0.019 ± 0.009	7	0.389 ± 0.093	16
7.20.5	0.025 ± 0.027	7	0.387 ± 0.202	9
7.26.4	0.021 ± 0.040	4	0.574 ± 0.099	15
6.14.2	0.011 ± 0.005	4	0.291 ± 0.096	6
6.22.2	0.018 ± 0.011	4	0.573 ± 0.168	7
6.34.2	0.013 ± 0.008	4	0.285 ± 0.073	7
6.67.1	0.013 ± 0.070	4	0.298 ± 0.115	8
6.73.2	0.020 ± 0.010	4	0.369 ± 0.103	8
6.77.1	0.022 ± 0.004	4	0.520 ± 0.100	4
9.8.2	0.020 ± 0.050	4	0.440 ± 0.342	8

IgG2
IgG4

[0276] To measure the antagonist potency of anti-MAdCAM mAbs in flow-based assays, under sheer stress conditions that are designed to mimic the microvascular environment on the high endothelial venules which serve the gut associated lymphoid tissue, CHO cells expressing MAdCAM were plated in glass microslides (50 x 4 mm) and allowed to adhere to form a confluent monolayer (*ca.* 2.5 x 10^5 cells). The cells were then incubated with affinity-purified mAb over a range of concentrations (0.1-10 μg/mL) for 20 mins at 37°C, before being connected to the flow assay system. An isotype matched IgG_2 or IgG_4 mAb (10 μg/mL) was used as a negative control. Normal donor peripheral blood lymphocytes (PBLs) were perfused over the cell monolayer at a constant shear stress of 0.05 Pa. Experiments were videoed and total adhesion of lymphocytes (rolling + firm adhesion) was calculated. All of the tested monoclonal antibodies were shown to be potent antagonists under the conditions described.

(iii) Stamper-Woodruff assays

[0277] To visualise $MAdCAM^+$ vessels, biotinylated anti-MAdCAM mAb was generated on 1-2 mg of affinity-purified protein, using a 20 molar excess of biotin-NHS (Pierce) in phosphate buffer saline, according to manufacturer's instructions. The reaction was allowed to sit at room temperature (30 min), and desalted with a PD-10 (Pharmacia) column and the protein concentration determined.

[0278] Normal liver lymph node was removed from a donor organ, snap-frozen in liquid nitrogen and stored at -70°C until use. 10 μm cryostat sections were cut, air-dried on poly-L lysine coated slides, and fixed in acetone prior to the assay. Sections were blocked using an avidin-biotin blocking system (DAKO), and then incubated with biotinylated anti-MAdCAM mAb over a range of concentrations (1-50 μg/mL) at room temperature (2 hrs). An isotype matched IgG_2 or IgG_4 mAb (50 μg/mL) was used as a negative control and a blocking anti-β_7 antibody (50 μg/mL) as a positive control.

[0279] Peripheral blood lymphocytes, taken from normal donors, were labeled with a mouse anti-human CD2 mAb (DAKO) to allow subsequent visualisation of adherent cells. $5x10^5$ PBLs were added to each lymph node section and incubated for 30 mins before being gently rinsed off to avoid detachment of adherent cells. Sections were then re-fixed in acetone, and re-incubated with biotinylated anti-MAdCAM mAb (10 μg/mL), followed by biotinylated goat-anti-mouse mAb (to recognise CD2 labeled PBLs and unstained $MAdCAM^+$ vessels) and then streptABcomplex/HRP (DAKO). Finally $MAdCAM^+$ vessels & CD2 labeled PBLs were visualised by addition of DAB substrate (DAKO) to the sections, with a brown reaction product showing areas of positive staining. Lymphocyte adhesion was quantified by counting the number of lymphocytes adhering to 50 MAdCAM-1^+ vessels of portal tracts, veins or sinusoids. Data, expressed as mean values, were then normalised to percent adhesion, using the adhesion of PBLs in the absence of any antibody taken as 100%. The data were compiled on the basis of n=3 different PBL donors and for different liver lymph node donors. Representative data for biotinylated purified monoclonal antibodies 1.7.2 and 7.16.6 are depicted in Figure 4 compared to a blocking anti-β_7 antibody control.

Selectivity assays:

[0280] VCAM and fibronectin are close structural and sequence homologues to MAdCAM. Affinity-purified anti-MAdCAM mAbs were assessed for MAdCAM-specificity by determining their ability to block the binding of $\alpha_4\beta_1^+/\alpha_5\beta_1^+$ Jurkat T-cells (ATCC) to their cognate cell adhesion molecule. 100μL of a 4.5μg/mL solution of Fibronectin cell binding fragment (110 Kd, Europa Bioproducts Ltd, Cat. No. UBF4215-18) or VCAM (Panvera) in Dulbecco's PBS was adsorbed to 96 well Black Microfluor "B" u-bottom (Dynex #7805) plates overnight at 4°C. The coated plates were then inverted and excess liquid blotted off, prior to blocking at 37°C for at least 1 hour in 10% BSA/ PBS. During this time cultured Jurkat T cells were counted using tryptan blue exclusion and loaded with Calcein AM dye as

previously described for JY cells above. The antibodies to be tested, were diluted from a top concentration of 10 μg/mL in 0.1 mg/ml BSA in PBS. The final well of the row was used for determining total binding, so 0.1mg/ml BSA in PBS was used. Echistatin (Bachem, Cat. No. H-9010) prepared in PBS was used at a top concentration of 100 nM to block the $\alpha_5\beta_1$/Fibronectin interaction. An anti-CD106 mAb (Clone 51-10C9, BD Pharmingen Cat. No. 555645) at a top concentration of 1 μg/mL was used to block the $\alpha_4\beta_1$/VCAM interaction.

[0281] After blocking, the plate contents were flicked out and 50 μL of antibodies/controls were added to each well and the plate incubated at 37°C for 20 min. Calcein-loaded Jurkat T cells were washed once as before, resuspending the final cell pellet to $1x10^6$/mL in 1 mg/mL BSA/PBS. 100 μL of cells were added to each well of the U bottomed plate, the plate sealed, briefly centrifuged (1000 rpm for 2 min) and the plate then incubated at 37°C for 45 min. At the end of this time, the plates were washed with a Skatron plate washer and fluorescence measured using a Wallac Victor^2 1420 Multilabel Reader (excitation λ485nm, emission λ535nm count from top, 8 mm from bottom of plate, for 0.1 sec with normal emission aperture). For each antibody, the degree of inhibition is expressed below pictorially, in Table 4 (- negligible inhibition of adhesion, *** complete inhibition of adhesion). All mAbs exemplified are potent and selective anti-MAdCAM antagonists, demonstrating substantially greater than 100 fold selectivity for MAdCAM over VCAM and fibronectin.

Table 4. Comparative selectivity of anti-MAdCAM antibody for MAdCAM over other cell adhesion molecules, Fibronectin and VCAM

Clone	Inhibition in α5β1/Fibronectin assay (10 μg/mL)	Inhibition in α4β1/VCAM assay (10 μg/mL)	Inhibition in α4β7/MAdCAM assay (0.1 μg/mL)
1.7.2	-	-	***
1.8.2	-	-	***
7.16.6	-	-	***
7.20.5	-	-	***
7.26.4	-	-	***
6.14.2	-	-	***
6.22.2	-	-	***
6.34.2	-	-	***
6.67.1	-	-	***
6.73.2	-	-	***
6.77.1	-	-	***
9.8.2	-	-	***

IgG2
IgG4

[0282] Hybridomas were deposited in the European Collection of Cell Cultures (ECACC), H.P.A at CAMR, Porton Down, Salisbury, Wiltshire SP4 0JG on 9th September 2003 with the following deposit numbers:

Hybridoma	Deposit No.
1.7.2	03090901
1.8.2	03090902
6.14.2	03090903
6.22.2	03090904
6.34.2	03090905

6.67.1	03090906
6.73.2	03090907
6.77.1	03090908
7.16.6	03090909
7.20.5	03090910
7.26.4	03090911
9.8.2	03090912

EXAMPLE II:

Determination of Affinity Constants (K_d) of Fully Human Anti-MAdCAM Monoclonal Antibodies by BIAcore

[0283] We performed affinity measures of purified antibodies by surface plasmon resonance using the BIAcore 3000 instrument, following the manufacturer's protocols.

Protocol 1

[0284] To perform kinetic analyses, a high density mouse anti-human (IgG_2 and IgG_4) antibody surface over a CM5 BIAcore sensor chip was prepared using routine amine coupling. Hybridoma supernatants were diluted 10, 5, 2-fold in HBS-P (10 mM HEPES pH 7.4, 150 mM NaCl, 0.005% Surfactant P20) running buffer containing 100 μg/mL BSA and 10 mg/mL carboxymethyldextran or used neat. Each mAb was captured onto a separate surface using a 1 min contact time and a 5 min wash for stabilization of the mAb baseline. MAdCAM-IgG_1 Fc (141 nM) fusion protein was then injected at over all surfaces for one minute, followed by a 3 min dissociation. The data were normalized for the amount of antibody captured on each surface and evaluated with global fit Langmuir 1:1, using baseline drift models available on the BIAevaluation software provided by BIAcore.

Protocol 2

[0285] Affinity-purified mAb were immobilized onto the dextran layer of a CM5 biosensor chip using amine coupling. Chips were prepared using pH 4.5 acetate buffer as the immobilization buffer and protein densities of 2.5-5.5 kRU were achieved. Samples of MAdCAM-IgG_1 Fc fusion protein in running buffer were prepared at concentrations ranging

from 0.2-55 nM (a 0 nM solution comprising running buffer alone was included as a zero reference). Samples were randomized and injected in duplicate for 3 min each across 4 flow cells using HBS-EP (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.005% Surfactant P20) as running buffer. A flow rate of 100 μL/min was used to minimize mass transport limitations. Dissociation of MAdCAM-IgG_1 Fc fusion protein was monitored for 180 mins, the surface regenerated by a 6 sec injection of 25 mM H_3PO_4 (50 μL/min), or 10 mM (6.22.2), 20 mM (6.67.1, 6.73.2, 6.77.1) to 25 mM (6.34.2) and 45 mM NaOH (6.14.2) and the data analysed using the BIAevaluation (v3.1) software package.

[0286] Table 5 lists affinity measurements for representative anti-MAdCAM antibodies of the present disclosure:

Table 5. Determination of affinity constant, K_d, by surface plasmon resonance (BIAcore)

	Protocol 1			Protocol 2		
CLONE	k_{on} (1/Ms)	k_{off} (1/s)	$K_{D\ (pM)}$	k_{on} (1/Ms)	k_{off} (1/s)	$K_{D\ (pM)}$
1.7.2	2.4×10^5	1×10^{-5}	42	5.5×10^3	1.3×10^{-7}	23.6
1.8.2	2.9×10^5	1×10^{-5}	35	1.8×10^5	2.3×10^{-5}	128
7.16.6	1.5×10^6	2.2×10^{-6}	1.5	2.9×10^5	1.4×10^{-6}	4.8
7.20.5	4.5×10^5	1.9×10^{-5}	42.2	1.6×10^5	1.2×10^{-5}	75
7.26.4	9.6×10^5	2.6×10^{-4}	271	1.5×10^5	1.2×10^{-5}	80
6.14.2	1.3×10^5	1×10^{-5}	7.7	5×10^5	$< 5 \times 10^{-6}$	< 10
6.22.2	1.5×10^6	1.4×10^{-5}	9.3	2.3×10^5	8.7×10^{-7}	3.8
6.34.2	1.2×10^6	1.9×10^{-5}	15.8	3.3×10^5	$< 5 \times 10^{-6}$	<15
6.67.1	5.9×10^5	1×10^{-5}	17	2.4×10^5	$< 5 \times 10^{-6}$	<20
6.73.2	1.4×10^5	1.3×10^{-4}	93			
6.77.1	1.5×10^5	1×10^{-5}	6.7			
9.8.2	2.3×10^6	2.3×10^{-4}	100	4.4×10^5	1.4×10^{-5}	32.5

IgG2
IgG4

[0287] The kinetic analyses indicate that the antibodies prepared in accordance with the disclosure possess high affinities and strong binding constants for the extracellular domain of MAdCAM.

EXAMPLE III:

Identification of epitope selectivity and species cross-reactivity of anti-MAdCAM mAbs

[0288] Antibodies recognize surface-exposed epitopes on antigens as regions of linear (primary) sequence or structural (secondary) sequence. Luminex epitope binning, BIAcore binning and species immunohistochemical analysis were used in concert, in order to define the functional epitope landscape of the anti-MAdCAM antibodies.

Luminex-based Epitope Binning:

[0289] MxhlgG 2,3.4-conjugated beads (Calbiochem Ml 1427) were coupled to the primary unknown anti-MAdCAM antibody. We added 150 μL of primary unknown antibody dilution (0.1 μg/mL diluted in hybridoma medium) to the well of a 96-well tissue culture plate. The bead stock was gently vortexed and diluted in supernatant to a concentration of 0.5×10^5 beads/mL. The beads were incubated in the supernatant on a shaker overnight in the dark at 4°C.

[0290] Each well of a 96-well microtiter filter plate (Millipore # MABVN1250) was pre-wetted by adding 200 μL wash buffer (PBS containing 0.05% Tween20) and removed by aspiration. Next, 50 μL/well of the 0.5×10^5 beads/mL stock was added to the filter plate, and the wells washed with wash buffer (2 x100 μL/well). 60 μL/well of MAdCAM-IgG_1 Fc antigen diluted in hybridoma medium (0.1 μg/mL) was added. The plates were covered and incubated at room temperature with gentle shaking for one hour. The wells were washed twice by addition of 100 μL/well wash buffer followed by aspiration. Next, we added 60

μL/well of secondary unknown anti-MAdCAM antibody diluted in hybridoma medium (0.1 μg/mL). The plates were shaken at room temperature in the dark for two hours. Next, the wells were washed twice by addition of 100 μL/well wash buffer followed by aspiration. Next, 60 μL/well of biotinylated MxhIgG 2,3,4 (0.5 μg/mL) was added. The plates were shaken at room temperature in the dark for one hour. The wells were washed twice by addition of 100 μL/well wash buffer followed by aspiration. To each well, 60 μL of 1 μg/mL MxhIgG 2,3,4 Streptavidin-PE (Pharmacia #554061) diluted in hydridoma medium was added. The plates were shaken at room temperature in the dark for twenty minutes. The wells were washed twice by addition of 100 μL/well wash buffer followed by aspiration. Next, each well was resuspended in 80 μL blocking buffer (PBS with 0.5% bovine serum albumin, 0.1% TWEEN and 0.01% Thimerosal) carefully pipetted up and down to resuspend the beads.

[0291] Using Luminex 100 and its accompanying software (Luminex® Corporation) the plates were read to determine luminescence readings. Based on the luminescence data obtained for the various anti-MAdCAM antibodies tested, the anti-MAdCAM antibodies were grouped according to their binding specificities. The anti-MAdCAM antibodies that were tested fall into a series of epitope bins, represented in Table 8.

BIAcore binning:

[0292] In a similar method to that described above, BIAcore can also be used to determine the epitope exclusivity of the anti-MAdCAM antibodies exemplified by this disclosure. Nine anti-MAdCAM antibody clones, 6.22.2, 6.34.2, 6.67.1, 6.77.1, 7.20.5, 9.8.2, 1.7.2, 7.26.4 and 7.16.6, were immobilized onto the dextran layer of separate flow cells of a CM5 biosensor chip using amine coupling. The immobilization buffer was either 10 mM acetate buffer pH 4.5 (clones 6.22.2, 6.34.2, 7.20.5, 9.8.2, 1.7.2, 7.26.4 and 7.16.6) or 10 mM acetate buffer pH 5.5 (clones 6.67.1 and 6.77.1). A protein density of approximately 3750 RU was achieved in

all cases. Deactivation of unreacted N-hydroxysuccinimide esters was performed using 1 M ethanolamine hydrochloride, pH 8.5.

[0293] MAdCAM-IgG1 Fc fusion protein was diluted to a concentration of 1.5 µg/mL (approximately 25 nM) in HBS-EP running buffer (0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% Polysorbate 20). It was then injected across the first flow cell, in a volume of 50 µL at a rate of 5 µL/min. After the injection was complete, the first antibody probe was added to the same flow cell. All test antibodies were diluted to a concentration of approximately 20 µg/mL in HBS-EP, and also injected in a volume of 50 µL at a flow rate of 5 µL/min. When no binding of the test antibody was observed, the next test clone was injected immediately afterwards. When binding did occur, the sensor surface was regenerated to remove both the MAdCAM-IgG1 Fc fusion protein and the test antibody. A variety of regeneration solutions were useddepending upon the immobilized antibody and the test antibody present. A summary of the regeneration conditions used is depicted in Table 6.

Table 6. Summary of regeneration conditions used to perform BIAcore epiope mapping

Immobilised antibody	Antibody probe to be removed	Regeneration solution	Injection volume
7.16.6	6.22.2	40 mM Phosphoric Acid	20 µL
	6.34.2	40 mM Phosphoric Acid	40 µL
	7.20.5	40 mM Phosphoric Acid	20 µL
6.77.1	9.8.2	40 mM Phosphoric Acid	10 µL
	1.7.2	40 mM Phosphoric Acid	5 µL
	7.16.6	40 mM Phosphoric Acid	10 µL
1.7.2	6.77.1	25 mM Phosphoric Acid	5 µL
	9.8.2	25 mM Phosphoric Acid	5 µL
	7.20.5	25 mM Phosphoric Acid	5 µL
	6.22.2	25 mM Phosphoric Acid	5 µL
	6.34.2	25 mM Sodium Hydroxide	5 µL
	6.67.1	25 mM Sodium Hydroxide	5 µL
6.22.2	9.8.2	25 mM Sodium Hydroxide	20 µL
	7.26.4	25 mM Sodium Hydroxide	5 µL
6.34.2	9.8.2	25 mM Sodium Hydroxide	70 µL
	1.7.2	40 mM Sodium Hydroxide	5 µL
	7.26.4	40 mM Sodium Hydroxide	5 µL

6.67.1	9.8.2	40 mM Sodium Hydroxide	5 µL
	1.7.2	40 mM Sodium Hydroxide	5 µL
7.20.5	9.8.2	25 mM Phosphoric Acid	5 µL
	1.7.2	25 mM Phosphoric Acid	5 µL
	7.26.4	25 mM Phosphoric Acid	5 µL
7.26.4	9.8.2	40 mM Sodium Hydroxide	20 µL
	6.22.2	75 mM Phosphoric Acid	20 µL
	7.20.5	75 mM Phosphoric Acid	20 µL
	7.16.6	75 mM Phosphoric Acid	20 µL
9.8.2	9.8.2	25 mM Phosphoric Acid	15 µL
	6.22.2	25 mM Phosphoric Acid	10 µL
	7.20.5	25 mM Phosphoric Acid	20 µL
	7.16.6	25 mM Phosphoric Acid	10 µL

(Flow rate was 50 µL/min during all regeneration procedures)

[0294] After regeneration, MAdCAM-IgG$_1$ Fc fusion protein was bound again and further test antibodies were injected. These procedures were carried out until the entire panel of clones had been injected over the surface of the immobilised antibody, with bound MAdCAM-IgG$_1$ Fc fusion protein. A new flow cell with a different immobilised antibody and bound MAdCAM was then used for probing with the nine test clones. Anti-MAdCAM antibodies 1.7.2 and 1.8.2 were expected to recognise the same MAdCAM epitope, based on the close primary amino acid sequence homology of their heavy and kappa light chains, SEQ ID NOS: 2, 4, 6, 8 respectively. Accordingly, only 1.7.2 was assessed though the BIAcore response matrix. Antibodies 6.14.2 and 6.73.2 were omitted from this analysis, but all other combinations of anti-MAdCAM antibody pairs were tested in this way. An arbitrary level of 100 RU was chosen as the threshold between binding/non-binding and a response matrix, (Table 7), was created based on whether binding was observed.

Table 7. BIAcore epitope binning response matrix

Immobilised antibody	**Secondary antibody**								
	6.22.2	**6.34.2**	**6.67.1**	**6.77.1**	**7.20.5**	**9.8.2**	**1.7.2**	**7.26.4**	**7.16.6**
6.22.2	-	-	-	-	-	x	x	x	x
6.34.2	-	-	-	-	-	x	x	x	x
6.67.1	-	-	-	-	-	x	x	-	-
6.77.1	-	-	-	-	-	x	x	-	x

7.20.5	-	-	-	-	-	x	x	x	x
9.8.2	x	x	x	x	x	x	-	-	x
1.7.2	x	x	x	x	x	x	-	-	x
7.26.4	x	x	-	-	x	x	-	-	x
7.16.6	x	x	-	-	x	-	-	-	x

Response matrix for all combinations of antibody pairs. - indicates no binding of the antibody probe, x indicates binding was observed (above a chosen threshold level of 100 RU).

[0295] The matrix diagonal in Table 7 (shaded grey) holds the binding data for identical probe pairs. In all instances, except for the two clones 7.16.6 and 9.8.2, the antibodies were self-blocking. Antibodies 7.16.6 and 9.8.2 do not cross compete. The lack of self-blocking could be due to a mAb-induced conformational change in the fusion protein that permits additional binding of the mAb to a second site on MAdCAM-IgFc. Grouping the clones that show the same reactivity pattern gives rise to at least six different epitope bins, as shown in the graphical representation, Figure 5).

[0296] Further precise identification of the MAdCAM epitope sequences with which an anti-MAdCAM antibody interacts can be determined by any of a number of methods, including, but not limited to, Western analysis of spotted peptide library arrays (Reineke et al., *Curr. Topics in Microbiol. and Immunol* 243: 23-36 (1999), M. Famulok, E-L Winnacker, C-H Wong eds., Springer-Verlag , Berlin), phage or bacterial flagellin/*fliC* expression library display, or simple MALDI-TOF analysis of bound protein fragments following limited proteolysis.

Immunohistochemical assays:

[0297] OCT or sucrose-embedded frozen tissue specimens of ileum (Peyer's patches), mesenteric lymph node, spleen, stomach, duodenum, jejunum and colon were used as a positive staining controls for the anti-MAdCAM mAbs. For staining human sections with human IgG_2 mAbs, biotinylated derivatives of the anti-MAdCAM mAbs were generated. 10 μm frozen tissue sections were cut onto poly L-lysine coated slides, placed directly into

100% acetone 4°C (10 min), then 3% hydrogen peroxide in methanol (10 min), washing between steps with PBS. The slides were blocked with Biotin Blocking System (DAKO Cat. No. X0590), prior to incubation with the primary antibody (1:100 - 1:1000) in PBS (1 hr), washed with PBS-Tween 20 (0.05%) and then binding developed with HRP-Streptavidin (BD Bioscience Cat. No.550946, 30 min) and DAB substrate (Sigma Cat. No. D5905). For IgG_4 mAbs, an HRP-conjugated, mouse anti-human IgG_4 (Zymed Cat. No. 3840) secondary was used. The slides were counterstained with Mayer's Haemalum (1 min), washed and then mounted in DPX.

[0298] Binding affinity was compared for a number of species (mouse, rat, rabbit, dog, pig, cynomolgus and human tissue). There was no reactivity for rat, rabbit and pig tissue by immunohistochemistry and no cross-reactivity of the anti-MAdCAM antibodies for recombinant mouse MAdCAM, when analyzed by ELISA. The data for human, cynomolgus and dog tissue are presented in table form, Table 8 below:

Table 8. Pattern of cross reactivity of anti-MAdCAM antibodies to MAdCAM species orthologues

		IHC cross-reactivity			
	Luminex	human	cyno	marmoset	dog
CLONE	BIN	ileum	ileum	ileum	ileum
1.7.2	3a				
1.8.2	3a				
7.16.6	3b				
7.20.5	2b			n.d	
7.26.4	3b			n.d	
6.14.2	2			n.d	
6.22.2	2			n.d	
6.34.2	6			n.d	
6.67.1	5			n.d	
6.73.2	3		n.d	n.d	
6.77.1	1			n.d	
9.8.2	3a		n.d		

IgG2
IgG4

No Binding
Binding

n.d: not determined

[0299] Anti-MAdCAM binding to specialised endothelial structures and lymphoid tissue is indicated by the shading, according to the key. The epitope bin based on Luminex epitope analysis and the pattern of MAdCAM cross-reactivity are indicated for each antibody. Luminex epitope binning data for anti-MAdCAM antibodies 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.3 and 6.77.1 (italics) were derived from separate experiments than that for 1.7.2, 1.8.2, 7.16.6, 7.20.5, 7.26.4 and 9.8.2 (bold type), as indicated by the difference in font character.

[0300] All anti-MAdCAM antibodies tested had the ability to recognize a human MAdCAM epitope expressed on vascular endothelial compartments of the gastrointestinal tract. Apart from 1.7.2 and 1.8.2, all other anti-MAdCAM antibodies tested were able to specifically bind the vascular endothelial compartments of the cynomolgus gastrointestinal tract Certain other anti-MAdCAM antibodies, namely 6.14.2 and 6.67.1 also had the ability to specifically recognize the dog MAdCAM orthologue as well as cynomolgus MAdCAM.

Generation of a functionally active chimeric cynomolgus/human MAdCAM-expressing CHO cell line:

[0301] The differences in binding affinity of certain anti-MAdCAM antibodies for human and cynomolgus MAdCAM led us to determine whether a structural basis for this observation could be made.

[0302] Based on the published amino acid sequence for Macaque MAdCAM (Shyjan AM, et al., *J Immunol.*, 156, 2851-7 (1996)), primers were designed to PCR amplify the cynomolgus MAdCAM $\alpha_4\beta_7$ binding domain sequence. Total RNA was prepared from frozen excised cynomolgus mesenteric lymph node (*ca.* 200 mg) using the Trizol method (Invitrogen) according to the manufacturer's instructions. 1-2 μg was oligo-dT primed and reverse transcribed with AMV reverse transcriptase (Promega). A proportion of the reverse transcribed product was subjected to PCR with forward 5'-AGC ATG GAT CGG GGC CTG GCC-3' (SEQ ID NO: 67) and reverse 5'-GTG CAG GAC CGG GAT GGC CTG-3' (SEQ

ID NO: 68) primers with GC-2 polymerase in 1M GC melt (Clontech) and at an annealing temperature of 62°C. An RT-PCR product of the appropriate size was excised and purified from a 1% agarose gel after electrophoresis, then TOPO-TA cloned (Invitrogen) between EcoRI sites of pCR2.1. The insert was sequence confirmed. The nucleotide and predicted translated amino acid sequences are shown in SEQ ID NOS 49 and 50, respectively.

[0303] The predicted human and cynomolgus MAdCAM amino acid sequences for the $\alpha_4\beta_7$ binding domain show a high degree of sequence identity (90.8%) when aligned (Figure 3 provides this sequence alignment). To generate a functionally active cynomolgus MAdCAM-expressing cell line, which mimicked the anti-MAdCAM binding pattern represented by Table 8, a SacI fragment corresponding to the cynomolgus $\alpha_4\beta_7$ binding domain sequence in pCR2.1, was subcloned directly into the C-terminal human MAdCAM pIND-Hygro construct containing carboxyl-terminal mucin stalk and transmembrane domain, described above. The sequence and orientation was verified, then a KpnI/NotI fragment was cloned into pEF5FRTV5GWCAT vector (Invitrogen), replacing the CAT coding sequence and used in transfections to generate single stably expressing clones in Flp In CHO cells (Invitrogen), according to the manufacturer's instructions.

[0304] The binding of anti-MAdCAM antibody clones to the CHO cells expressing cynomolgus/human MAdCAM chimera was assessed by flow cytometry and the functional activity of anti-MAdCAM antibodies was determined using a very similar JY cell adhesion assay as that described above. The binding and functional activity of anti-MAdCAM antibodies areexpressed in Table 9.

[0305] Table 9. Correlation between the functional activity in the cynomolgus/human MAdCAM-CHO/JY adhesion assay and human and cynomolgus/human MAdCAM CHO cell binding, as measured by FACS, for a range of anti-MAdCAM antibodies.

CLONE	Functional IC_{50} (μg/mL)	FACS binding	
		human	cyno/human
1.7.2	inactive		
1.8.2	inactive		
7.16.6	0.72		
7.20.5	0.62		
7.26.4	0.96		
6.14.2	0.53		
6.22.2	0.83		
6.34.2	0.47		
6.67.1	0.75		
6.73.2	inactive		
6.77.1	0.64		
9.8.2	0.83		

IgG2	No Binding
IgG4	Binding

[0306] Taken together, there is a good correlation between the ability of a given anti-MAdCAM antibody to bind human or cynomolgus MAdCAM, as detected by immunohistochemistry (Table 8), with recombinant cell-based binding and functional activity (Table 9). Anti-MAdCAM antibodies 1.7.2, 1.8.2 and 6.73.2, for instance, demonstrated a consistent lack of binding to cynomolgus tissue and cells expressing a chimeric cynomolgus/human MAdCAM protein. Anti-MAdCAM antibodies 1.7.2, 1.8.2 and 6.73.2 also did not have the ability to detect functional blocking activity in the cynomolgus/human MAdCAM/JY adhesion assay.

[0307] Similar approaches could be used to define the epitope of the anti-MAdCAM antibodies 6.14.2 and 6.67.1 that recognise dog MAdCAM.

EXAMPLE IV:

Use of anti-MAdCAM mAbs
in the detection of circulating soluble MAdCAM as a method of disease diagnosis

[0308] Anti-MAdCAM antibodies can be used for the detection of circulating soluble MAdCAM (sMAdCAM). Detection of sMAdCAM in clinical plasma, serum samples or other biofluid, such as, but not limited to, stool, urine, sputum. is likely to be a useful surrogate disease biomarker for underlying disease, including, but not limited to, inflammatory bowel disease.

[0309] Based on the epitope binning data (Tables 7 and 8), anti-MAdCAM antibodies 1.7.2 and 7.16.6 appear to recognise different epitopes on human MAdCAM. ELISA plates were coated overnight at 4°C with 100 µL/well of a 50 µg/mL solution of 1.7.2 in phosphate buffered saline (PBS). After incubation the plate was blocked for 1.5 hours with a PBS blocking buffer containing 10% milk (200 µL/well). After incubation the plate was washed with PBS (2 x 100 µL/well) and serial dilutions of MAdCAM-IgG1-Fc fusion protein, from a top concentration of 50 µg/mL down to approximately 5 ng/mL in PBS, to a final volume of 100 µL, were added to the plate for incubation of 2 hours at room temperature. In a similar approach the MAdCAM-IgG1-Fc protein can be diluted in plasma or serum, or some other such relevant biofluid and used to determine the expression of soluble MAdCAM in a clinical sample, as described below. As a negative control, only buffer was added to the wells containing the primary anti-MAdCAM antibody. After this time, the plate was washed with PBS (3 x 100 µL/well) and the plate then incubated in the dark with an Alexa488-labelled 7.16.6 (100 µL, 5 µg/mL). The Alexa488-labelled 7.16.6 was generated using a commercially available kit (Molecular Probes, A-20181), following Manufacturer's protocols.

[0310] The plate was washed with PBS containing 0.05% Tween-20, and binding of labeled 7.16.6 to captured soluble MAdCAM determined by measuring the fluorescence (Wallac Victor^2 1420 Multilabel Reader, excitation λ485nm, emission λ535nm count from top, 3 mm from bottom of plate, for 0.1 sec with normal emission aperture). When fluorescence is plotted as a function of the concentration of MAdCAM-IgG1-Fc fusion protein, Figure 6, it indicates that 1.7.2 and a labeled 7.16.6 can be used for diagnostic purposes to determine the level of circulating soluble MAdCAM expressed in a biofluid or clinical sample. This sandwich ELISA approach is not restricted to the use of 1.7.2 and 7.16.6, but any combination of anti-MAdCAM antibodies that recognise different epitopes on MAdCAM, as outlined by the data and interpretation of table 7 and Figure 5. Similar strategies could be applied to the development of similar assays, such as immunohistochemistry and Western Blot, with the other anti-MAdCAM antibodies described, using different partners, variants, labels, etc.

EXAMPLE V:

Amino acid structure of anti-MAdCAM mAbs prepared in accordance to the disclosure

[0311] In the following discussion, structural information related to the anti-MAdCAM mAbs prepared in accordance with the disclosure is provided.

[0312] To analyze structures of mAbs produced in accordance with the disclosure, we cloned the genes encoding the heavy and light chain fragments out of the specific hybridoma clone. Gene cloning and sequencing was accomplished as follows:

[0313] Poly(A)+ mRNA was isolated from approximately 2x10^5 hybridoma cells derived from immunized XenoMouse mice using Fast-Track kit (Invitrogen). The generation of random primed cDNA was followed by PCR. Human VH or Vκ family specific primers (Marks et al., 'Oligonucleotide primers for polymerase chain reaction amplification of human

immunoglobulin variable genese and design of family-specific oligonucleotide probes'; *Eur. J. Immunol.*, 21, 985-991 (1991)) or a universal human VH primer, MG-30 (5'-CAG GTG CAG CTG GAG CAG TCI GG-3 (SEQ ID NO: 108) was used in conjunction with primers specific for the human Cγ2, MG40-d (5'-GCT GAG GGA GTA GAG TCC TGA GGA-**3** (SEQ ID NO: 109) or Cγ4 constant region, MG-40d (5'GCT GAG GGA GTA GAG TCC TGA GGA CTG T -3 (SEQ ID NO: 110), or Cκ constant region (hκP2; as previously described in Green et al., 1994). Sequences of the human mAb-derived heavy and kappa chain transcripts from hybridomas were obtained by direct sequencing of PCR products generated from poly (A+) RNA using the primers described above. PCR products were cloned into pCR2.1 using a TOPO-TA cloning kit (Invitrogen) and both strands were sequenced using Prism dye terminator sequencing kits and an ABI 377 sequencing machine. All sequences were analysed by alignments to the 'V BASE sequence directory' (Tomlinson, et al, *J. Mol. Biol.*, 227, 776–798 (1992); *Hum. Mol. Genet.*, 3, 853–860 (1994); *EMBO J.*, 14, 4628–4638 (1995).)

[0314] Further each of the antibodies, 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4, 9.8.2, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod, were subjected to full length DNA sequencing. For such, total RNA was isolated from approximately 3-6x10^6 hybridoma cells using an RNeasy kit (Qiagen). The mRNA was reverse transcribed using oligo-dT and an AMV-based reverse transcriptase system (Promega). V BASE was used to design 5' specific amplification primers, containing an optimal Kozak sequence and ATG start codon (underlined) and 3' reverse primers for the specific heavy and kappa chains as depicted in Table 10.

Table 10: PCR primer pairs for cDNA amplification from anti-MAdCAM mAb-expressing hybridomas and primers used in the construction of modified versions of anti-MAdCAM antibodies.

	Oligo sequence
VH1-18	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGGACTGGACCTGGAGCATCCTT 3′ (SEQ ID NO: 70)
VH3-15	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGGAGTTTGGGCTGAGCTGGATT 3′ (SEQ ID NO: 71)
VH3-21	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGGAACTGGGGCTCCGCTGGGTT 3′ (SEQ ID NO: 72)
VH3-23	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGGAGTTTGGGCTGAGCTGGCTT 3′ (SEQ ID NO: 73)
VH3-30	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGGAGTTTGGGCTGAGCTGGGTT 3′ (SEQ ID NO: 74)
VH3-33	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGGAGTTTGGGCTGAGCTGGGTT 3′ (SEQ ID NO: 75)
VH4-4	5′ TATCTAAGCTTCTAGACTCGAGCGCCACCATGAAACACCTGTGGTTCTTCCTC 3′ (SEQ ID NO: 76)
A2/A3	5′ TATCTAAGCTTCTAGACCCGGGCGCCACCATGAGGCTCCCTGCTCAGCTCCTG 3′ (SEQ ID NO: 77)
A26	5′ TATCTAAGCTTCTAGACCCGGGCGCCACCATGTTGCCATCACAACTCATTGGG 3′ (SEQ ID NO: 78)
B3	5′ TATCTAAGCTTCTAGACCCGGGCGCCACCATGGTGTTGCAGACCCAGGTCTTC 3′ (SEQ ID NO: 79)
O12	5′ TATCTAAGCTTCTAGACCCGGGCGCCACCATGGACATGAGGGTCCCCGCTCAG 3′ (SEQ ID NO: 80)
O18	5′ TATCTAAGCTTCTAGACCCGGGCGCCACCATGGACATGAGGGTCCCTGCTCAG 3′ (SEQ ID NO: 81)
RevIgG2	5′ TTCTCTGATCAGAATTCCTATCATTTACCCGGAGACAGGGAGAG 3′ (SEQ ID NO: 82)
RevIgG4	5′ TTCTTTGATCAGAATTCTCACTAACACTCTCCCCTGTTGAAGC 3′ (SEQ ID NO: 83)
RevKappa	5′ TTCTCTGATCAGAATTCCTATCATTTACCCAGAGACAGGGAGAG 3′ (SEQ ID NO: 84)
6.22.2VK_F1	5′-GGA TCT GGG ACA GAT TTC ACC CTC ACC ATC AAT AGC CTG GAA GC-3′(SEQ ID NO: 85)
6.22.2VK_R1	5′-GCT TCC AGG CTA TTG ATG GTG AGG GTG AAA TCT GTC CCA GAT CC-3′(SEQ ID NO: 86)
6.22.2VH_F1	5′-GCA GCG TCT GGA TTC ACC TTC AGT AGC-3′(SEQ ID NO: 87)
6.22.2VH_R1	5′-GCT ACT GAA GGT GAA TCC AGA CGC TGC-3′(SEQ ID NO: 88)
6.22.2VH_CS*	5′-CGG AGG TGC TTC TAG AGC AGG GCG-3′(SEQ ID NO: 89)
6.34.2VK_F1	5′-GCA AGT CAG AGT ATT AGT AGC TAT TTA AAT TGG TAT CAG CAG AAA CC-3′(SEQ ID NO: 90)
6.34.2VK_R1	5′-GGT TTC TGC TGA TAC CAA TTT AAA TAG CTA CTA ATA CTC TGA CTT GC-3′(SEQ ID NO: 91)
6.34.2VK_F2	5′-CCA TCA GTT CTC TGC AAC CTG AGG ATT TTG CAA CTT ACT ACT GTC ACC-3′(SEQ ID NO: 92)
6.34.2VK_R3	5′-GGT GAC AGT AGT AAG TTG CAA AAT CCT CAG GTT GCA GAG AAC TGA TGG-3′(SEQ ID NO: 93)
6.34.2VH_F16.34	5′-GCA AAT GAA CAG CCT GCG CGC TGA GGA CAC G-3′(SEQ ID NO: 94)
.2VH_R1	5′-CGT GTC CTC AGC GCG CAG GCT GTT CAT TTG C-3′(SEQ ID NO: 95)
6.67.1VK_F1	5′-CAA TAA GAA CTA CTT AGC TTG GTA CCA ACA GAA ACC AGG ACA GCC-3′(SEQ ID NO: 96)
6.67.1VK_R1	5′-GGC TGT CCT GGT TTC TGT TGG TAC CAA GCT AAG TAG TTC TTA TTG-3′(SEQ ID NO: 97)
6.67.1VH_F1	5′-CCC TCA GGG GTC GAG TCA CCA TGT CAG TAG ACA CGT CCA AGA ACC-3′(SEQ ID NO: 98)
6.67.1VH_R1	5′-GGT TCT TGG ACG TGT CTA CTG ACA TGG TGA CTC GAC CCC TGA GGG-3′(SEQ ID NO: 99)
6.67.1VH_CS*	5′-ATT CTA GAG CAG GGC GCC AGG-3′(SEQ ID NO: 100)
6.77.1VK_F1	5′-CCA TCT CCT GCA AGT CTA GTC AGA GCC TCC-3′(SEQ ID NO: 101)
6.77.1VK_R1	5′-GGA GGC TCT GAC TAG ACT TGC AGG AGA TGG-3′(SEQ ID NO: 102)
6.77.1VK_F2	5′-GGT TTA TTA CTG CAT GCA AAG TAT ACA GCT TAT GTC CAG TTT TGG CC -

	Oligo sequence
6.77.1VK_R2	3'(SEQ ID NO: 103) 5'-GGC CAA AAC TGG ACA TAA GCT GTA TAC TTT GCA TGC AGT AAT AAA CC - 3'(SEQ ID NO: 104)
7.26.4K_F1	5'-CCT GCA AGT CTA GTC AGA GCC TCC-3'(SEQ ID NO: 105)
7.26.4K_R1	5'-GGA GGC TCT GAC TAG ACT TGC AGG-3'(SEQ ID NO: 106)

[0315] The primers pairs were used to amplify the cDNAs using Expand High Fidelity Taq polymerase (Roche), and the PCR products cloned into pCR2.1 TOPO-TA (Invitrogen) for subsequent sequencing. Heavy and kappa light chain sequence verified clones were then cloned into pEE6.1 and pEE12.1 vectors (LONZA) using XbaI/EcoRI and HindIII/EcoRI sites respectively.

Gene Utilization Analysis

[0316] Table 11 displays the heavy and kappa light chain gene utilization for each hybridoma outlined in the disclosure.

	Heavy Chain			Kappa light Chain	
CLONE	VH	D	JH	Vκ	Jκ
1.7.2	VH3-15	D6-19	JH4b	A3	JK5
1.8.2	VH3-15	D6-19	JH4b	A3	JK5
7.16.6	VH1-18	D6-6	JH6b	A2	JK1
7.20.5	VH4-4	D3-10	JH6b	A3	JK4
7.26.4	VH1-18	D6-6	JH6b	A2	JK1
6.14.2	VH3-23	D5-5	JH4b	O12	JK5
6.22.2	VH3-33	D5-12	JH6b	A26	JK4
6.34.2	VH3-30	D4-23	JH6b	O12	JK3
6.67.1	VH4-4	D3-10	JH4b	B3	JK4
6.73.2	VH3-23	D6-19	JH6b	O12	JK2
6.77.1	VH3-21	D6-19	JH6b	A2	JK2
9.8.2	VH3-33	D3-10 or D3-16	JH4b	O18	JK5

IgG2
IgG4

Table 11: Heavy and Kappa light chain Gene Utilization

Sequence Analysis

[0317] To further examine antibody structure predicted amino acid sequences of the antibodies were obtained from the cDNAs obtained from the clones.

[0318] Sequence identifier numbers (SEQ ID NO:) 1-48 and 51-68 provide the nucleotide and amino acid sequences of the heavy and kappa light chains of the anti-MAdCAM antibodies 1.7.2 (SEQ ID NOS 1-4), 1.8.2 (SEQ ID NOS 5-8), 6.14.2 (SEQ ID NOS 9-12), 6.22.2 (SEQ ID NOS 13-16), 6.34.2 (SEQ ID NOS 17-20), 6.67.1 (SEQ ID NOS 21-24), 6.73.2 (SEQ ID NOS 25-28), 6.77.1 (SEQ ID NOS 29-32), 7.16.6 (SEQ ID NOS 33-36), 7.20.5 (SEQ ID NOS 37-40), 7.26.4 (SEQ ID NOS 41-44), 9.8.2 (SEQ ID NOS 45-48) and the modified anti-MAdCAM antibodies 6.22.2-mod (SEQ ID NOS 51-54), 6.34.2-mod (SEQ ID NOS 55-58), 6.67.1-mod (SEQ ID NOS 59-62) and 6.77.1-mod (SEQ ID NOS 63-66) and 7.26.4-mod (SEQ ID NOS 41-42, 67-68). For each anti-MAdCAM antibody sequence cloned, the sequences of the signal peptide sequence (or the bases encoding the same) are indicated in lower case and underlined.

[0319] Figures 1A-1J provide sequence alignments between the predicted heavy chain amino acid sequences of antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 and 9.8.2 and the amino acid sequence of the respective germline gene products. The positions of the CDR1, CDR2 and CDR3 sequences of the antibodies are underlined, differences between the expressed sequence the corresponding germline sequence are indicated in bold and where there are additions in the expressed sequence compared to the germline these are indicated as a (-) in the germline sequence.

[0320] Figures 1K-1T provide sequence alignments between the predicted kappa light chain amino acid sequences of the antibodies 1.7.2, 1.8.2, 6.14.2, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.16.6, 7.20.5, 7.26.4 and 9.8.2 and the amino acid sequence of the respective germline gene products. The positions of the CDR1, CDR2 and CDR3 sequences of the

antibodies are underlined, differences between the expressed sequence the corresponding germline they are indicated in bold and where there are additions in the expressed sequence compared to the germline these are indicated as a (-) in the germline sequence.

Presence of post-translational modification: glycosylation and deamidation:

[0321] The effect of some of the changes in the expressed anti-MAdCAM antibody sequence, compared with the derived germline sequence, is to introduce residues that potentially could be subject to N-linked glycosylation (Asn-X-Ser/Thr) and/or deamidation (Asn-Gly) (see Table 12). The nucleic acid sequences encoding the kappa light chain variable domain amino acid sequences of the anti-MAdCAM antibodies 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.26.4 and 9.8.2, (SEQ ID NOS: 16, 20, 24, 28, 32, 44 and 48) and the heavy chain variable domain of antibody 6.14.2, (SEQ ID NO: 10), predict the presence of N-linked glycosylation. The presence of this post-translational modification was investigated using a combination of SDS-PAGE and Pro-Q® Emerald 488 Glycoprotein (Molecular Probes) staining with mAbs 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.26.4 and 9.8.2.

[0322] Briefly, approximately 2 μg of reduced anti-MAdCAM antibody was loaded onto a 4-12% SDS-polyacrylamide gel using a MOPS buffer. Following electrophoresis, the gel was fixed in 50% MeOH, 5% acetic acid and washed in 3% acetic acid. Any carbohydrates on the gel were then oxidised with periodic acid and stained using Pro-Q® Emerald 488 Glycoprotein Stain Kit (Molecular Probes). After a final wash step, glycoprotein staining was visualised using a fluorescence scanner set at a wavelength of 473 nm.

[0323] After glycoprotein staining, the gel was stained for total protein using SYPRO Ruby protein gel stain and analysed using a fluorescence scanner set at a wavelength of 473 nm. The kappa light chains of anti-MAdCAM antibodies, 6.22.2, 6.34.2, 6.67.1, 6.73.2, 6.77.1, 7.26.4 and 9.8.2, all stained positively for the presence of glycosylation. As an additional confirmation, anti-MAdCAM antibody 7.26.4, was subjected to tryptic/chymotrypic

digestion, the LC-MS/MS analysis confirmed the presence of a modified tryptic peptide and provided additional confirmation of kappa light chain glycosylation.

[0324] Specific Asn-Gly sequences in the CDR1 regions of anti-MAdCAM antibodies, 1.7.2, 1.8.2, 6.22.2 and 7.20.5, render these regions sensitive to deamidation. Deamidation at neutral pH introduces a negative charge and can also lead to β-isomerisation, which could affect the properties of an antibody. For anti-MAdCAM antibodies 1.7.2, 1.8.2 and 7.20.5, the presence of deamidated Asn-isoaspartate residues was assessed by mass spectroscopy following trapping the isoaspartate side chain with MeOH.

[0325] In brief, for the anti-MAdCAM antibody 1.7.2, the status of the tryptic/Asp-N peptide SSQSLLQSNGYNYL (SEQ ID NO: 69) (1573.7 Da) was selected for monitoring by LC-MS/MS. Anti-MAdCAM antibody 1.7.2 was reduced in 10 mM DTT, alkylated in 5 mM Na iodoacetate and subsequently buffer exchanged into trypsin digestion buffer (50mM Tris-HCl, 1mM $CaCl_2$, pH 7.6). The antibody was then mixed with sequencing grade modified trypsin (Promega) in a protease:protein ratio of 1:20. Protein was digested in trypsin for 15 hours at 30°C, and the resulting peptides separated by HPLC using a C-18 RPC on an Ettan LC system. The ^{33}Asn-containing peptide (4032 Da) was collected from the column and diluted in Asp-N digestion buffer (50 mM sodium phosphate buffer, pH 8.0). Endoproteinase Asp-N (Roche) was then added at an approximate peptide:enzyme ratio of 10:1.

[0326] Acetyl chloride (100 µL) was added to a sample of methanol (1 mL, -20°C), the mixture warmed to room temperature. The tryptic+Asp-N digest was dried in a Speed-Vac and then 5 µL of the methanol/acetyl chloride was added (45 min, room temp), then dried again in a Speed-Vac. The resulting residue was re-constituted in 0.1% TFA and peptides were analysed initially on the Voyager-DE STR MALDI-TOF mass spectrometer using either the nitrocellulose thin layer sample preparation method or reverse phase purification using C18 ZipTips (Millipore) followed by droplet mixing with α-cyano matrix. The methylated

peptide mixture was also analysed using LC-MS/MS on a Deca XP Plus Ion Trap Mass Spectrometer as above. The elution was plumbed straight into the Ion Trap MS and peptides were subsequently analysed by MS and MS/MS. The MS was set to analyse all ions between 300 and 2000 Da. The strongest ion in any particular scan was then subjected to MS/MS analysis.

Table 12. Post-translational modification of anti-MAdCAM antibodies

	Heavy Chain		Kappa light chain			
CLONE	Glycosylation (NXS/T)	Confirmed	Glycosylation (NXS/T)	Confirmed	Deamidation (NG)	Confirmed
1.7.2					LQS**NG**YN	MS
1.8.2					LQS**NG**YN	MS
7.16.6						
7.20.5					HG**NG**YNY	MS
7.26.4			CKS**NQS**LLY	MS/PAGE		
6.14.2	TF**NNS**AMT	N.D				
6.22.2			SGT**NFT**LTI	PAGE	LTI**NG**LEA	N.D
6.34.2			ASQ**NIS**SYL	PAGE		
6.67.1			SSN**NKT**YLA	PAGE		
6.73.2			RASQ**NIT**N	PAGE		
6.77.1			SC**NSS**QSL	PAGE		
9.8.2			HSD**NLS**IT	PAGE		

IgG2
IgG4

Mutagenesis studies:

[0327] The primary amino acid sequence of the anti-MAdCAM antibodies exemplified in this disclosure can be modified, by site-directed mutagenesis, to remove potential sites of post-translational modification (*e.g.*, glycosylation, de-amidation) or to alter the isotype background, or to engineer other changes which may improve the therapeutic utility. As an example, PCR was used to engineer changes to the anti-MAdCAM antibodies 6.22.2, 6.34.2, 6.67.1, 6.77.1 and 7.26.4, to revert certain framework sequences to germline, to remove potential glycosylation sites and/or to change the isotype background to a human IgG_2. pCR2.1 TOPO-TA cloned cDNAs (100 ng), corresponding to heavy chain nucleotide SEQ ID NOS: 13, 17, 21 and 29, and kappa light nucleotide SEQ ID NOS: 15, 19, 23, 31 and 43,

were used as a template in a series of PCRs using overlap-extension and a panel of primer sets described in Table 10.

[0328] 6.22.2 Heavy chain: PCR primer sets 6.22.2_VH_F1 and 6.22.2VH_CS* (1) and VH3-33 and 6.22.2_VH_R1 (2) were used to generate separate PCR products (1) and (2), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 13 . Products (1) and (2) were purified and combined in a third PCR step (*ca.* 50 ng each) along with VH3-33 and VK6.22.2_CS* primers, to generate the modified 6.22.2 heavy chain V-domain. This modified version contains a His/Phe mutation in FR1 and introduces an XbaI restriction site to enable in frame cloning into a pEE6.1 derived vector, termed pEE6.1CH, which contains the corresponding human IgG_2 constant domain. The final PCR fragment was cloned into the XbaI site of pEE6.1CH, checked for orientation and the insert full sequence verified. The nucleotide sequence for the modified 6.22.2 heavy chain is found in SEQ ID NO: 51 and the corresponding amino acid sequence in SEQ ID NO: 52. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0329] 6.22.2 kappa light chain: PCR primer sets 6.22.2_VK_F1 and revKappa (1), and A26 and 6.22.2_VK_R1 (2) were used to generate separate PCR products (1) and (2), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 15. Products (1) and (2) were purified and combined in a third PCR step (*ca.* 50 ng each) along with A26 and revKappa primers, to generate the modified 6.22.2 kappa light chain V-domain. This modified version contains Asn/Asp and Gly/Ser changes to the FR3 sequence. The resultant PCR product was cloned into pEE12.1 using HindIII/EcoR1 sites and fully sequence verified. The nucleotide sequence for the modified 6.22.2 kappa light chain is found in SEQ ID NO: 53 and the corresponding amino

acid sequence in SEQ ID NO: 54. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0330] 6.34.2 Heavy chain: PCR primer sets 6.34.2_VH_F1 and 6.22.2VH_CS* (1) and VH3-30 and 6.34.2_VH_R1 (2) were used to generate separate PCR products (1) and (2), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 17. Products (1) and (2) were purified and combined in a third PCR step (*ca.* 50 ng each) along with VH3-30 and VK6.22.2_CS* primers, to generate the modified 6.34.2 heavy chain V-domain. This modified version contains a Ser/Arg mutation in FR3 and introduces an XbaI restriction site to enable in frame cloning into a pEE6.1 derived vector, termed pEE6.1CH, which contains the corresponding human IgG2 constant domain. The final PCR fragment was cloned into the XbaI site of pEE6.1CH, checked for orientation and the insert full sequence verified. The nucleotide sequence for the modified 6.34.2 heavy chain is found in SEQ ID NO: 55 and the corresponding amino acid sequence in SEQ ID NO: 56. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0331] 6.34.2 kappa light chain: PCR primer sets O12 and 6.34.2_VK_R1 (1), 6.34.2_VK_F1 and 6.34.2_VK_R2 (2), as well as 6.34.2_VK_F2 and revKappa (3) were used to generate separate PCR products (1), (2) and (3), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 19. Products (1), (2) and (3) were purified and (1) and (2) were combined in a third PCR step (*ca.* 50 ng each), along with O12 and 6.34.2_VK_R2 primers, to generate the PCR product (4). PCR products (2) and (3) were combined in a fourth PCR step (*ca.* 50 ng each), along with 6.34.2_VK_F1 and revKappa, to generate the PCR product (5). PCR products (4) and (5) were purified and combined together (*ca.*50 ng each) with primers O12 and revKappa to generate the modified 6.34.2 kappa light chain V-domain. This modified version contains

an Asn/Ser change in CDR1, a Phe/Tyr change in FR2 and Arg-Thr/Ser-Ser, Asp/Glu and Ser/Tyr changes to the FR3 sequence. The resultant PCR product was cloned into pEE12.1 using HindIII/EcoR1 sites and fully sequence verified. The nucleotide sequence for the modified 6.34.2 kappa light chain is found in SEQ ID NO: 57 and the corresponding amino acid sequence in SEQ ID NO: 58. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0332] 6.67.1 Heavy chain: PCR primer sets 6.67.1_VH_F1 and 6.67.1VH_CS* (1) and VH4-4 and 6.67.1_VH_R1 (2) were used to generate separate PCR products (1) and (2), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 21. Products (1) and (2) were purified and combined in a third PCR step (*ca.* 50 ng each) along with VH4-4 and VK6.67.1_CS* primers, to generate the modified 6.67.1 heavy chain V-domain. This modified version contains an Ile-Leu-Ala/Met-Ser-Val conversion in FR3 and introduces an XbaI restriction site to enable in frame cloning into a pEE6.1 derived vector, termed pEE6.1CH, which contains the corresponding human IgG2 constant domain. The final PCR fragment was cloned into the XbaI site of pEE6.1CH, checked for orientation and the insert full sequence verified. The nucleotide sequence for the modified 6.67.1 heavy chain is found in SEQ ID NO: 59 and the corresponding amino acid sequence in SEQ ID NO: 60. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0333] 6.67.1 kappa light chain: PCR primer sets 6.67.1_VK_F1 and revKappa (1), and B3 and 6.67.1_VK_R1 (2) were used to generate separate PCR products (1) and (2), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 23. Products (1) and (2) were purified and combined in a third PCR step (*ca.* 50 ng each) along with B3 and revKappa primers, to generate the modified 6.67.1 kappa light chain V-domain. This modified version contains a Thr/Asn

change in CDR1 and an Arg/Gly change in FR2. The resultant PCR product was cloned into pEE12.1 using HindIII/EcoR1 sites and fully sequence verified. The nucleotide sequence for the modified 6.67.1 kappa light chain is found in SEQ ID NO: 61 and the corresponding amino acid sequence in SEQ ID NO: 62. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0334] 6.77.1 Heavy chain: PCR primer sets VH 3-21 and 6.22.2VH_CS* were used to generate a single PCR product using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 29. The PCR products were digested with XbaI, gel purified and cloned into the XbaI site of pEE6.1CH, checking for orientation. The insert was fullly sequence verified. The nucleotide sequence for the modified 6.77.1 heavy chain is found in SEQ ID NO: 63 and the corresponding amino acid sequence in SEQ ID NO: 64. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0335] 6.77.1 kappa light chain: PCR primer sets A2 and 6.77.1_VK_R1 (1), 6.77.1_VK_VK_F1 and 6.77.1_R2 (2), as well as 6.77.1_VK_F2 and revKappa (3) were used to generate separate PCR products (1), (2) and (3), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 31. Products (1), (2) and (3) were purified and, (1) and (2) were combined in a third PCR step (*ca.* 50 ng each) along with A2 and 6.77.1_VK_R2 primers, to generate PCR product (4). PCR product (2) and (3) were combined in a fourth PCR step (*ca.* 50 ng each) along with 6.77.1_VK_F1 and revKappa primers, to generate PCR product (5). PCR products (4) and (5) were purified and combined together (*ca.*50 ng each) with primers A2 and JK2 to generate the modified 6.77.1 kappa light chain V-domain. This modified version contains an Asn/Lys change in CDR1, a Ser/Tyr change in FR3 and a Cys/Ser residue change in CDR3 sequence. The resultant PCR product was cloned into pEE12.1 using

HindIII/EcoR1 sites and fully sequence verified. The nucleotide sequence for the modified 6.77.1 kappa light chain is found in SEQ ID NO: 65 and the corresponding amino acid sequence in SEQ ID NO: 66. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0336] 7.26.4 kappa light chain: PCR primer sets 7.26.4_VK_F1 and revKappa (1), and A2 and 7.26.4_VK_R1 (2) were used to generate separate PCR products (1) and (2), using an Expand *Taq* polymerase and a pCR2.1 TOPO-TA cDNA template (100 ng) represented by nucleotide sequence SEQ ID NO: 43. Products (1) and (2) were purified and combined in a third PCR step (*ca.* 50 ng each) along with A2 and revKappa primers, to generate the modified 7.26.4 kappa light chain V-domain. This modified version contains an Asn/Ser change in CDR1. The resultant PCR product was cloned into pEE12.1 using HindIII/EcoR1 sites and fully sequence verified. The nucleotide sequence for the modified 7.26.4 kappa light chain is found in SEQ ID NO: 67 and the corresponding amino acid sequence in SEQ ID NO: 68. The changes in the nucleotide and amino acid sequences compared with the parent are indicated.

[0337] A functional eukaryotic expression vector for each of the modified versions of 6.22.2, 6.34.2, 6.67.1, 6.77.1 and 7.26.4, referred to as 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod, and representing respectively the heavy chain nucleotide sequences SEQ ID NOS: 51, 55, 59, 63 and 41, and corresponding amino acid sequences SEQ ID NOS: 52, 56, 60, 64 and 42, as well as the kappa light chain nucleotide sequences SEQ ID NOS: 53, 57, 61, 65 and 67, and the corresponding amino acid sequences SEQ ID NOS: 54, 58, 62, 66 and 68 were assembled as follows: The heavy chain cDNA inserts corresponding to 6.22.2-mod, 6.34.2-mod, 6.67.1-mod and 6.77.1-mod were excised from the pEE6.1CH vector with NotI/SalI, the parental version of the heavy chains of 7.26.4 was excised from the pEE6.1 vector with NotI/SalI, and the purified fragments were cloned into

identical sites into the corresponding pEE12.1 vector containing the modified versions of the kappa light chain sequences 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod. The sequences of the vectors were confirmed, and purified amounts used in transient transfections with HEK 293T cells. Briefly, $9x10^6$ HEK 293T cells, seeded in a T165 flask the day before transfection and washed into Optimem, were transiently transfected with vector cDNAs corresponding to 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod (40 μg) using Lipofectamine PLUS (Invitrogen) according to manufacturer's instructions. The cells were incubated for 3 hrs, then the transfection media replaced with DMEM (Invitrogen 21969-035) media containing 10% ultra-low IgG fetal calf serum (Invitrogen 16250-078) and L-Glutamine (50 mL). The media supernatant was harvested 5 days later, filter sterilised and the anti-MAdCAM antibody purified using protein G sepharose affinity chromatography, in a similar manner as to that described above. The amount of antibody recovered (20-100 μg) was quantified by a Bradford assay.

[0338] The anti-MAdCAM activity of affinity purified antibody corresponding to 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod was assessed in the MAdCAM-IgG1-Fc fusion assay as described previously. The IC_{50} values of these anti-MADCAM antibodies compared with the parental anti-MAdCAM antibodies from which they were derived are presented in Table 13. There was minimal effect of the amino acid substitutions described above on the activity of the modified anti-MAdCAM antibodies compared with their parents was minimal. The antibodies also maintained their binding to CHO cells expressing recombinant human MAdCAM or the cynomolgus/human MAdCAM chimera.

Table 13. Activity of modified versions of anti-MAdCAM antibodies, 6.22.2-mod, 6.34.2-mod, 6.67.1-mod, 6.77.1-mod and 7.26.4-mod compared with their parents.

CLONE	MAdCAM IgG1 Fc fusion Assay Mean IC50 (μg/mL)	
	Parent	Modified
6.22.2	0.018	0.058
6.34.2	0.013	0.049
6.67.1	0.013	0.037
6.77.1	0.022	0.077
7.26.4	0.021	0.033

EXAMPLE VI

Increase in β_7^+ lymphocytes in the peripheral circulation by blocking anti-MAdCAM antibodies

[0339] An assay was developed to identify and correlate a mechanistic effect of an anti-MAdCAM antibody and its circulating level in blood. An inhibitory anti-MAdCAM antibody should have the effect of inhibiting the recruitment of leukocytes expressing the $\alpha_4\beta_7$ integrin to the gastrointestinal tract. Classes of $\alpha_4\beta_7$ integrin-bearing leukocytes should, therefore, be restricted to the peripheral circulation.

[0340] This was demonstrated with a fully human anti-human MAdCAM mAb 7.16.6, in cynomolgus.

[0341] Purified anti-human MAdCAM mAb 7.16.6 (1 mg/kg) or vehicle (20 mM NaAcetate, 0.2 mg/mL polysorbate 80, 45 mg/mL mannitol, and 0.02 mg/mL EDTA at pH 5.5) were assessed in a similar manner by intravenous administration via the saphenous vein to two groups of cynomolgus monkeys (n=4/group). At day 3 post-dosing blood samples were collected in EDTA tubes by femoral venipuncture. LPAM specifc antibodies, which crossreact with the cynomolgus $\alpha_4\beta_7$ integrin, are not commercially available, so an anti-β_7 antibody (recognising $\alpha_4\beta_7$ and $\alpha_E\beta_7$ integrin) was used instead. Antibodies (30 μL), according to the following table, table 15, were added to tubes containing 100 μL of cynomolgus blood, mixed by gentle vortexing and incubated for 20-30 mins at 4^0C.

Table 15. Antibodies (BD Pharmingen) used in immunophenotyping of cynomologus blood

Catalogue Number	Antibody or Isotype
555748	mIgG1, k-FITC
555844	mIgG2a, k-PE
559425	mIgG1 - PerCP
555751	mIgG1, k-APC
555728	CD 28-FITC
555945	β7-PE
558814	CD 95-APC
550631	CD 4-PerCP

[0342] To each tube, 1 mL of 1:10 FACSlyse solution (BD # 349202) was added, mixed by gentle vortex and incubated at room temperature for approximately 12 minutes in the dark until red blood cell lysis was complete. Then 2 mL of BD stain buffer (# 554656) was added to each tube, mixed and centrifuged at 250 x *g* for 6-7 mins at room temperature. The supernatant was decanted and the pellet resuspended in 3 mL of stain buffer, mixed again and centrifuged at 250 x *g* for 6-7 mins at room temperature. Cytofix buffer (BD # 554655), containing w/v paraformaldehyde (100 µL) was added to the cell pellets from monkey peripheral blood and mixed thoroughly by low/moderate speed of vortexer. The samples were kept at 4^0C in the dark until they acquired on the FACSCalibur. Just prior to acquisition, PBS (100 µL) was added to all tubes immediately before acquisition. The absolute cell numbers of $CD4^+\beta_7^+CD95loCD28^+$ (naïve), $CD4^+\beta_7^+CD95hiCD28^+$ (central memory), $CD4^+\beta_7$-$CD95hiCD28^+$ (central memory), $CD4^+\beta_7^+CD95hiCD28^-$ (effector memory) were acquired by appropriate gating and quandrant analyses. Other T cell subsets for example, $CD8^+$ T central memory cell ($\beta_7^+CD8^+CD28^+CD95^+$) and any other leukocytes bearing a MAdCAM ligand, may also be analyzed by this method with the appropriate antibodies. Compared with the vehicle control, anti-MAdCAM mAb 7.16.6 caused an approximate 3 fold increase in the levels of circulating $CD4^+\beta_7^+CD95hiCD28^+$ central memory T cells, as shown in Figure 7. There were no effects on the population of circulating

$CD4^{+}\beta_7$-CD95hiCD28^{+} central memory T cells, indicating that the effect of anti-MAdCAM mAb 7.16.6 is specific for gut homing T cells. The effects of anti-MAdCAM mAb 7.16.6, in cynomolgus, on populations of circulating $(\alpha_4)\beta_7^{+}$ lymphocytes indicates that this is a robust surrogate proof of mechanism biomarker, particularly in the context of practical application in a clinical setting.

Sequences

[0343] SEQ ID NO: 1-48,51-68 and 148-150 provide nucleotide and amino acid sequences of the heavy and kappa light chains for thirteen human anti-MAdCAM antibodies, nucleotide and amino acid sequences of cynomolgus MAdCAM $\alpha_4\beta_7$ binding domain sequences and nucleotide and amino acid sequences of five modified human anti-MAdCAM antibodies.

[0344] SEQ ID NO: 1-48 and 148-150 provide the heavy and kappa light chain nucleotide and amino acid sequences of thirteen human monoclonal anti-MAdCAM antibodies: 1.7.2 (SEQ ID NO: 1-4), 1.8.2 (SEQ ID NO: 5-8), 6.14.2 (SEQ ID NO: 9-12), 6.22.2 (SEQ ID NO: 13-16), 6.34.2 (SEQ ID NO: 17-20), 6.67.1 (SEQ ID NO: 21-24), 6.73.2 (SEQ ID NO: 25-28), 6.77.1 (SEQ ID NO: 29-32), 7.16.6 (SEQ ID NO: 33-36), 7.20.5 (SEQ ID NO: 37-40), 7.26.4 (SEQ ID NO: 41-44), 9.8.2 (SEQ ID NO: 45-48), X481.2 (SEQ ID NO: 35, 148-150).

[0345] SEQ ID NO: 49-50 provide the nucleotide and amino acid sequences of a cynomolgus MAdCAM $\alpha_4\beta_7$ binding domain.

0346] SEQ ID NO: 51-68 provide the heavy and kappa light chain nucleotide and amino acid sequences for the modified monoclonal anti-MAdCAM antibodies: 6.22.2 (SEQ ID NO: 51-54), modified 6.34.2 (SEQ ID NO: 55-58), modified 6.67.1 (SEQ ID NO: 59-62), modified 6.77.1 (SEQ ID NO: 63-66) and the kappa light chain nucleotide and amino acid sequences of modified monoclonal anti-MAdCAM antibody: modified 7.26.4 (SEQ ID NO: 67-68).

SEQ ID NOS: 70-106 and 108-110 provide various primer sequences.

Key:
Signal sequence: underlined lower case

Amino acid changes in modified anti-MAdCAM antibodies sequence compared to parent: underlined upper case

SEQ ID NO. 1
1.7.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg gattttcctt gctgctattt taaaaggtgt
  51  ccagtgtGAG GTGCAGCTGG TGGAGTCTGG GGGAGGCTTG GTGAAGCCTG
 101  GGGGGTCCCT TAGACTCTCC TGTGTAGCCT CTGGATTCAC TTTCACTAAC
 151  GCCTGGATGA TCTGGGTCCG CCAGGCTCCA GGGAAGGGGC TGGAGTGGGT
 201  TGGCCGTATT AAAAGGAAAA CTGATGGTGG GACAACAGAC TACGCTGCAC
 251  CCGTGAAAGG CAGATTCACC ATCTCAAGAG ATGATTCAAA AAACACGCTG
 301  TATCTGCAAA TGAACAGCCT GAAAACCGAG GACACAGCCG TGTATTACTG
 351  TACCACAGGG GGAGTGGCTG AGGACTACTG GGGCCAGGGA ACCCTGGTCA
 401  CCGTCTCCTC AGCCTCCACC AAGGGCCCAT CGGTCTTCCC CCTGGCGCCC
 451  TGCTCCAGGA GCACCTCCGA GAGCACAGCG GCCCTGGGCT GCCTGGTCAA
 501  GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACTCA GGCGCTCTGA
 551  CCAGCGGCGT GCACACCTTC CCAGCTGTCC TACAGTCCTC AGGACTCTAC
 601  TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAACTTCG GCACCCAGAC
 651  CTACACCTGC AACGTAGATC ACAAGCCCAG CAACACCAAG GTGGACAAGA
 701  CAGTTGAGCG CAAATGTTGT GTCGAGTGCC CACCGTGCCC AGCACCACCT
 751  GTGGCAGGAC CGTCAGTCTT CCTCTTCCCC CCAAAACCCA AGGACACCCT
 801  CATGATCTCC CGGACCCCTG AGGTCACGTG CGTGGTGGTG GACGTGAGCC
 851  ACGAAGACCC CGAGGTCCAG TTCAACTGGT ACGTGGACGG CGTGGAGGTG
 901  CATAATGCCA AGACAAAGCC ACGGGAGGAG CAGTTCAACA GCACGTTCCG
 951  TGTGGTCAGC GTCCTCACCG TTGTGCACCA GGACTGGCTG AACGGCAAGG
1001  AGTACAAGTG CAAGGTCTCC AACAAAGGCC TCCCAGCCCC CATCGAGAAA
1051  ACCATCTCCA AAACCAAAGG GCAGCCCCGA GAACCACAGG TGTACACCCT
1101  GCCCCCATCC CGGGAGGAGA TGACCAAGAA CCAGGTCAGC CTGACCTGCC
1151  TGGTCAAAGG CTTCTACCCC AGCGACATCG CCGTGGAGTG GGAGAGCAAT
1201  GGGCAGCCGG AGAACAACTA CAAGACCACA CCTCCCATGC TGGACTCCGA
1251  CGGCTCCTTC TTCCTCTACA GCAAGCTCAC CGTGGACAAG AGCAGGTGGC
1301  AGCAGGGGAA CGTCTTCTCA TGCTCCGTGA TGCATGAGGC TCTGCACAAC
1351  CACTACACGC AGAAGAGCCT CTCCCTGTCT CCGGGTAAAT GA
```

SEQ ID NO. 2
1.7.2 Predicted Heavy Chain Protein Sequence

```
  1   mefglswifl aailkgvqcE VQLVESGGGL VKPGGSLRLS CVASGFTFTN
 51   AWMIWVRQAP GKGLEWVGRI KRKTDGGTTD YAAPVKGRFT ISRDDSKNTL
101   YLQMNSLKTE DTAVYYCTTG GVAEDYWGQG TLVTVSSAST KGPSVFPLAP
151   CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY
201   SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP
251   VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ FNWYVDGVEV
301   HNAKTKPREE QFNSTFRVVS VLTVVHQDWL NGKEYKCKVS NKGLPAPIEK
351   TISKTKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN
401   GQPENNYKTT PPMLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN
451   HYTQKSLSLS PGK
```

SEQ ID NO. 3
1.7.2 Kappa Light Chain Nucleotide Sequence

```
  1   atgaggctcc ctgctcagct cctggggctg ctaatgctct gggtctctgg
 51   atccagtggg GATATTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA
101   CCCCTGGAGA GCCGGCCTCC ATCTCCTGCA GGTCTAGTCA GAGCCTCCTG
151   CAAAGTAATG GATACAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA
201   GTCTCCACAG CTCCTGATCT ATTTGGGTTC TAATCGGGCC TCCGGGGTCC
251   CTGACAGGTT CAGTGGCAGT GGATCAGGCA CAGATTTTAC ACTGAAAATC
301   AGCAGAGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAGCTCT
351   ACAAACTATC ACCTTCGGCC AAGGGACACG ACTGGAGATT AAACGAACTG
401   TGGCTGCACC ATCTGTCTTC ATCTTCCCGC CATCTGATGA GCAGTTGAAA
451   TCTGGAACTG CCTCTGTTGT GTGCCTGCTG AATAACTTCT ATCCCAGAGA
501   GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC
551   AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC
601   AGCACCCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC
651   CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA
701   ACAGGGGAGA GTGTTAGTGA
```

SEQ ID NO. 4
1.7.2 Predicted Kappa Light Chain Protein Sequence

```
  1   mrlpaqllgl lmlwvsgssg DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL
 51   QSNGYNYLDW YLQKPGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI
101   SRVEAEDVGV YYCMQALQTI TFGQGTRLEI KRTVAAPSVF IFPPSDEQLK
151   SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS
202   STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
```

SEQ ID NO. 5
1.8.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg gattttcctt gctgctattt taaaaggtgt
  51  ccagtgtGAG GTGCAGCTGG TGGAGTCTGG GGGAGGCTTG GTGAAGCCTG
 101  GGGGGTCCCT TAGACTCTCC TGTGTAGTCT CTGGATTCAC TTTCACTAAC
 151  GCCTGGATGA TCTGGGTCCG CCAGGCTCCA GGGAAGGGGC TGGAGTGGGT
 201  TGGCCGTATT AAAAGGAAAA CTGATGGTGG GACAACAGAC TACGCTGCAC
 251  CCGTGAAAGG CAGATTCACC ATCTCAAGAG ATGATTCAAA AAACACGCTG
 301  TATCTGCAAA TGAACAGCCT GAAAACCGAG GACACAGCCG TGTATTACTG
 351  TACCACAGGG GGAGTGGCTG AGGACTACTG GGGCCAGGGA ACCCTGGTCA
 401  CCGTCTCCTC AGCCTCCACC AAGGGCCCAT CGGTCTTCCC CCTGGCGCCC
 451  TGCTCCAGGA GCACCTCCGA GAGCACAGCG GCCCTGGGCT GCCTGGTCAA
 501  GGACTACTTC CCCGAACCGG TGACGGTGTC GTGGAACTCA GGCGCTCTGA
 551  CCAGCGGCGT GCACACCTTC CCAGCTGTCC TACAGTCCTC AGGACTCTAC
 601  TCCCTCAGCA GCGTGGTGAC CGTGCCCTCC AGCAACTTCG GCACCCAGAC
 651  CTACACCTGC AACGTAGATC ACAAGCCCAG CAACACCAAG GTGGACAAGA
 701  CAGTTGAGCG CAAATGTTGT GTCGAGTGCC CACCGTGCCC AGCACCACCT
 751  GTGGCAGGAC CGTCAGTCTT CCTCTTCCCC CCAAAACCCA AGGACACCCT
 801  CATGATCTCC CGGACCCCTG AGGTCACGTG CGTGGTGGTG GACGTGAGCC
 851  ACGAAGACCC CGAGGTCCAG TTCAACTGGT ACGTGGACGG CGTGGAGGTG
 901  CATAATGCCA AGACAAAGCC ACGGGAGGAG CAGTTCAACA GCACGTTCCG
 951  TGTGGTCAGC GTCCTCACCG TTGTGCACCA GGACTGGCTG AACGGCAAGG
1001  AGTACAAGTG CAAGGTCTCC AACAAAGGCC TCCCAGCCCC CATCGAGAAA
1051  ACCATCTCCA AAACCAAAGG GCAGCCCCGA GAACCACAGG TGTACACCCT
1101  GCCCCCATCC CGGGAGGAGA TGACCAAGAA CCAGGTCAGC CTGACCTGCC
1151  TGGTCAAAGG CTTCTACCCC AGCGACATCG CCGTGGAGTG GGAGAGCAAT
1201  GGGCAGCCGG AGAACAACTA CAAGACCACA CCTCCCATGC TGGACTCCGA
1251  CGGCTCCTTC TTCCTCTACA GCAAGCTCAC CGTGGACAAG AGCAGGTGGC
1301  AGCAGGGGAA CGTCTTCTCA TGCTCCGTGA TGCATGAGGC TCTGCACAAC
1351  CACTACACGC AGAAGAGCCT CTCCCTGTCT CCGGGTAAAT GA
```

SEQ ID NO. 6
1.8.2 Predicted Heavy Chain Protein Sequence

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   1  mefglswifl aailkgvqcE VQLVESGGGL VKPGGSLRLS CVVSGFTFTN
  51  AWMIWVRQAP GKGLEWVGRI KRKTDGGTTD YAAPVKGRFT ISRDDSKNTL
 101  YLQMNSLKTE DTAVYYCTTG GVAEDYWGQG TLVTVSSAST KGPSVFPLAP
 151  CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY
 201  SLSSVVTVPS SNFGTQTYTC NVDHKPSNTK VDKTVERKCC VECPPCPAPP
 251  VAGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVQ FNWYVDGVEV
 301  HNAKTKPREE QFNSTFRVVS VLTVVHQDWL NGKEYKCKVS NKGLPAPIEK
 351  TISKTKGQPR EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN
 401  GQPENNYKTT PPMLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN
 451  HYTQKSLSLS PGK
```

SEQ ID NO. 7
1.8.2 Kappa Light Chain Nucleotide Sequence

```
   1   atgaggctcc ctgctcagct cctggggctg ctaatgctct gggtctctgg
  51   atccagtggg GATATTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA
 101   CCCCTGGAGA GCCGGCCTCC ATCTCCTGCA GGTCTAGTCA GAGCCTCCTG
 151   CAAAGTAATG GATTCAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA
 201   GTCTCCACAG CTCCTGATCT ATTTGGGTTC TAATCGGGCC TCCGGGGTCC
 251   CTGACAGGTT CAGTGGCAGT GGGTCAGGCA CAGATTTTAC ACTGAAAATC
 301   AGCAGAGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAGCTCT
 351   ACAAACTATC ACCTTCGGCC AAGGGACACG ACTGGAGATT AAACGAACTG
 401   TGGCTGCACC ATCTGTCTTC ATCTTCCCGC CATCTGATGA GCAGTTGAAA
 451   TCTGGAACTG CCTCTGTTGT GTGCCTGCTG AATAACTTCT ATCCCAGAGA
 501   GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC
 551   AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC
 601   AGCACCCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC
 651   CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA
 701   ACAGGGGAGA GTGTTAGTGA
```

SEQ ID NO. 8
1.8.2 Predicted Kappa Light Chain Protein Sequence

```
   1   mrlpaqllgl lmlwvsgssg DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL
  51   QSNGFNYLDW YLQKPGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI
 101   SRVEAEDVGV YYCMQALQTI TFGQGTRLEI KRTVAAPSVF IFPPSDEQLK
 151   SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS
 202   STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
```

SEQ ID NO. 9
6.14.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg gctttttctt gtggctattt taaaaggtgt
  51  ccagtgtGAG GTGCAGCTGT TGGAGTCTGG GGGAGGCTTG GTACAGCCTG
 101  GGGGGTCCCT GAGACTCTCC TGTGCAGCCT CTGGACTCAC CTTTAACAAT
 151  TCTGCCATGA CCTGGGTCCG CCAGGCTCCA GGGAAGGGGC TGGAGTGGGT
 201  CTCAACTACT AGTGGAAGTG GTGGTACCAC ATACTACGCA GACTCCGTGA
 251  AGGGCCGGTT CACCATCTCC AGAGACTCTC CCAAGAACAC GCTCTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACACG GCCGTATATT ACTGTGCGGC
 351  CCGTGGATAC AGCTATGGTA CGACCCCCTA TGAGTACTGG GGCCAGGGAA
 401  CCCTGGTCAC CGTCTCCTCA GCTTCCACCA AGGGCCCATC CGTCTTCCCC
 451  CTGGCGCCCT GTTCCAGGAG CACCTCCGAG AGCACAGCCG CCCTGGGCTG
 501  CCTGGTCAAG GACTACTTCC CCGAACCGGT GACGGTGTCG TGGAACTCAG
 551  GCGCCCTGAC CAGCGGCGTG CACACCTTCC CGGCTGTCCT ACAGTCCTCA
 601  GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA GCAGCTTGGG
 651  CACGAAGACC TACACCTGCA ACGTAGATCA CAAGCCCAGC AACACCAAGG
 701  TGGACAAGAG AGTTGAGTCC AAATATGGTC CCCCATGCCC ATCATGCCCA
 751  GCACCTGAGT TCCTGGGGGG ACCATCAGTC TTCCTGTTCC CCCCAAAACC
 801  CAAGGACACT CTCATGATCT CCCGGACCCC TGAGGTCACG TGCGTGGTGG
 851  TGGACGTGAG CCAGGAAGAC CCCGAGGTCC AGTTCAACTG GTACGTGGAT
 901  GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG AGCAGTTCAA
 951  CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC
1001  TGAACGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGG CCTCCCGTCC
1051  TCCATCGAGA AAACCATCTC CAAAGCCAAA GGGCAGCCCC GAGAGCCACA
1101  GGTGTACACC CTGCCCCCAT CCCAGGAGGA GATGACCAAG AACCAGGTCA
1151  GCCTGACCTG CCTGGTCAAA GGCTTCTACC CCAGCGACAT CGCCGTGGAG
1201  TGGGAGAGCA ATGGGCAGCC GGAGAACAAC TACAAGACCA CGCCTCCCGT
1251  GCTGGACTCC GACGGCTCCT TCTTCCTCTA CAGCAGGCTA ACCGTGGACA
1301  AGAGCAGGTG GCAGGAGGGG AATGTCTTCT CATGCTCCGT GATGCATGAG
1351  GCTCTGCACA ACCACTACAC ACAGAAGAGC CTCTCCCTGT CTCTGGGTAA
1401  ATGA
```

SEQ ID NO. 10
6.14.2 Predicted Heavy Chain Protein Sequence

```
   1  mefglswlfl vailkgvqcE VQLLESGGGL VQPGGSLRLS CAASGLTFNN
  51  SAMTWVRQAP GKGLEWVSTT SGSGGTTYYA DSVKGRFTIS RDSPKNTLYL
 101  QMNSLRAEDT AVYYCAARGY SYGTTPYEYW GQGTLVTVSS ASTKGPSVFP
 151  LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS
 201  GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPSCP
 251  APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD
 301  GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS
 351  SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE
 401  WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE
 451  ALHNHYTQKS LSLSLGK
```

SEQ ID NO. 11
6.14.2 Kappa Light Chain Nucleotide Sequence

```
   1   atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct
  51   ccgaggggcc agatgtGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTGT
 101   CTGCATCTGT AGGAGACAGA GTCACCATCA CTTGCCGGGC AAGTCGGAGC
 151   ATTAGCAGCT ATTTAAATTG GTATCAGCAG AAACCAGGGA AAGCCCCTAA
 201   AGTCCTGATC TTTTTTGTGT CCAGTTTGCA AAGTGGGGTC CCATCAAGGT
 251   TCAGTGGCAG TGGCTCTGGG ACAGATTTCA CTCTCACCAT CAGCAGTCTG
 301   CAACCTGAAG ATTTTGCAAC TTACTACTGT CAACAGAATT ACATTCCCCC
 351   TATTACCTTC GGCCAGGGGA CACGACTGGA GATCAGACGA ACTGTGGCTG
 401   CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA
 451   ACTGCCTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA
 501   AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA
 551   GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
 601   CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA
 651   AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG
 701   GAGAGTGTTA G
```

SEQ ID NO. 12
6.14.2 Predicted Kappa Light Chain Protein Sequence

```
   1   mdmrvpaqll glllwlrga rcDIQMTQSP SSLSASVGDR VTITCRASRS
  51   ISSYLNWYQQ KPGKAPKVLI FFVSSLQSGV PSRFSGSGSG TDFTLTISSL
 101   QPEDFATYYC QQNYIPPITF GQGTRLEIRR TVAAPSVFIF PPSDEQLKSG
 151   TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
 202   LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

SEQ ID NO. 13
6.22.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt
  51  ccagtgtCAG GTGCAGCTGG TGGAGTCTGG GGGAGGCGTG GTCCAGCCTG
 101  GGAGGTCCCT GAGACTCTCC TGTGCAGCGT CTGGACACAC CTTCAGTAGC
 151  GATGGCATGC ACTGGGTCCG CCAGGCTCCA GGCAAGGGGC TGGAGTGGGT
 201  GGCAATTATA TGGTATGATG GAAGTAATAA ATATTATGCA GACTCCGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAATT CCAAGAACAC GCTGTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACACG GCTGTATATT ACTGTGCGAG
 351  AGATCCCGGC TACTATTACG GTATGGACGT CTGGGGCCAA GGGACCACGG
 401  TCACCGTCTC CTCAGCTTCC ACCAAGGGCC CATCCGTCTT CCCCCTGGCG
 451  CCCTGCTCCA GGAGCACCTC CGAGAGCACA GCCGCCCTGG GCTGCCTGGT
 501  CAAGGACTAC TTCCCCGAAC CGGTGACGGT GTCGTGGAAC TCAGGCGCCC
 551  TGACCAGCGG CGTGCACACC TTCCCGGCTG TCCTACAGTC CTCAGGACTC
 601  TACTCCCTCA GCAGCGTGGT GACCGTGCCC TCCAGCAGCT TGGGCACGAA
 651  GACCTACACC TGCAACGTAG ATCACAAGCC CAGCAACACC AAGGTGGACA
 701  AGAGAGTTGA GTCCAAATAT GGTCCCCCAT GCCCATCATG CCCAGCACCT
 751  GAGTTCCTGG GGGGACCATC AGTCTTCCTG TTCCCCCCAA AACCCAAGGA
 801  CACTCTCATG ATCTCCCGGA CCCCTGAGGT CACGTGCGTG GTGGTGGACG
 851  TGAGCCAGGA AGACCCCGAG GTCCAGTTCA ACTGGTACGT GGATGGCGTG
 901  GAGGTGCATA ATGCCAAGAC AAAGCCGCGG GAGGAGCAGT TCAACAGCAC
 951  GTACCGTGTG GTCAGCGTCC TCACCGTCCT GCACCAGGAC TGGCTGAACG
1001  GCAAGGAGTA CAAGTGCAAG GTCTCCAACA AAGGCCTCCC GTCCTCCATC
1051  GAGAAAACCA TCTCCAAAGC CAAAGGGCAG CCCCGAGAGC CACAGGTGTA
1101  CACCCTGCCC CCATCCCAGG AGGAGATGAC CAAGAACCAG GTCAGCCTGA
1151  CCTGCCTGGT CAAAGGCTTC TACCCCAGCG ACATCGCCGT GGAGTGGGAG
1201  AGCAATGGGC AGCCGGAGAA CAACTACAAG ACCGCGCCTC CCGTGCTGGA
1251  CTCCGACGGC TCCTTCTTCC TCTACAGCAG GCTAACCGTG GACAAGAGCA
1301  GGTGGCAGGA GGGGAATGTC TTCTCATGCT CCGTGATGCA TGAGGCTCTG
1351  CACAACCACT ACACACAGAA GAGCCTCTCC CTGTCTCTGG GTAAATGA
```

SEQ ID NO. 14
6.22.2 Predicted Heavy Chain Protein Sequence

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   1  mefglswvfl vallrgvqcQ VQLVESGGGV VQPGRSLRLS CAASGHTFSS
  51  DGMHWVRQAP GKGLEWVAII WYDGSNKYYA DSVKGRFTIS RDNSKNTLYL
 101  QMNSLRAEDT AVYYCARDPG YYYGMDVWGQ GTTVTVSSAS TKGPSVFPLA
 151  PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 201  YSLSSVVTVP SSSLGTKTYT CNVDHKPSNT KVDKRVESKY GPPCPSCPAP
 251  EFLGGPSVFL FPPKPKDTLM ISRTPEVTCV VVDVSQEDPE VQFNWYVDGV
 301  EVHNAKTKPR EEQFNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKGLPSSI
 351  EKTISKAKGQ PREPQVYTLP PSQEEMTKNQ VSLTCLVKGF YPSDIAVEWE
 401  SNGQPENNYK TAPPVLDSDG SFFLYSRLTV DKSRWQEGNV FSCSVMHEAL
 451  HNHYTQKSLS LSLGK
```

SEQ ID NO. 15
6.22.2 Kappa Light Chain Nucleotide Sequence

```
   1   atgttgccat cacaactcat tgggtttctg ctgctctggg ttccagcttc
  51   caggggtGAA ATTGTGCTGA CTCAGTCTCC AGACTTTCAG TCTGTGACTC
 101   CAAAAGAGAA AGTCACCATC ACCTGCCGGG CCAGTCAGAG AATTGGTAGT
 151   AGCTTACACT GGTACCAGCA GAAACCAGAT CAGTCTCCAA AACTCCTCAT
 201   CAAGTATGCT TCCCAGTCCT TCTCAGGGGT CCCCTCGAGG TTCAGTGGCA
 251   GTGGATCTGG GACAAATTTC ACCCTCACCA TCAATGGCCT GGAAGCTGAA
 301   GATGCTGCAA CTTATTACTG TCATCAGAGT GGTCGTTTAC CGCTCACTTT
 351   CGGCGGAGGG ACCAAGGTGG AGATCAAACG AACTGTGGCT GCACCATCTG
 401   TCTTCATCTT CCCGCCATCT GATGAGCAGT TGAAATCTGG AACTGCCTCT
 451   GTTGTGTGCC TGCTGAATAA CTTCTATCCC AGAGAGGCCA AAGTACAGTG
 501   GAAGGTGGAT AACGCCCTCC AATCGGGTAA CTCCCAGGAG AGTGTCACAG
 551   AGCAGGACAG CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG
 601   AGCAAAGCAG ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCCA
 651   TCAGGGCCTG AGCTCGCCCG TCACAAAGAG CTTCAACAGG GGAGAGTGTT
 701   AGTGA
```

SEQ ID NO. 16
6.22.2 Predicted Kappa Light Chain Protein Sequence

```
   1   mlpsqligfl llwvpasrgE IVLTQSPDFQ SVTPKEKVTI TCRASQRIGS
  51   SLHWYQQKPD QSPKLLIKYA SQSFSGVPSR FSGSGSGTNF TLTINGLEAE
 101   DAATYYCHQS GRLPLTFGGG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS
 151   VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
 201   SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
```

SEQ ID NO. 17
6.34.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt
  51  ccagtgtCAG GTGCAGCTGG TGGAGTCTGG GGGAGGCGTG GTCCAGCCTG
 101  GGAGGTCCCT GAGACTCTCC TGTGCAGCCT CTGGATTCAC CTTCAGTAGC
 151  TATGGCATGC ACTGGGTCCG CCAGGCTCCA GGCAAGGGGC TGGAGTGGGT
 201  GGCAGTTATA TCAAATGATG GAAATAATAA ATACTATGCA GACTCCGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAATT CCAAAAACAC GCTGTATCTG
 301  CAAATGAACA GCCTGAGCGC TGAGGACACG GCTGTGTATT ACTGTGCGAG
 351  AGATAGTACG GCGATAACCT ACTACTACTA CGGAATGGAC GTCTGGGGCC
 401  AAGGGACCAC GGTCACCGTC TCCTCAGCTT CCACCAAGGG CCCATCCGTC
 451  TTCCCCCTGG CGCCCTGCTC CAGGAGCACC TCCGAGAGCA CAGCCGCCCT
 501  GGGCTGCCTG GTCAAGGACT ACTTCCCCGA ACCGGTGACG GTGTCGTGGA
 551  ACTCAGGCGC CCTGACCAGC GGCGTGCACA CCTTCCCGGC TGTCCTACAG
 601  TCCTCAGGAC TCTACTCCCT CAGCAGCGTG GTGACCGTGC CCTCCAGCAG
 651  CTTGGGCACG AAGACCTACA CCTGCAACGT AGATCACAAG CCCAGCAACA
 701  CCAAGGTGGA CAAGAGAGTT GAGTCCAAAT ATGGTCCCCC ATGCCCATCA
 751  TGCCCAGCAC CTGAGTTCCT GGGGGGGACCA TCAGTCTTCC TGTTCCCCCC
 801  AAAACCCAAG GACACTCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG
 851  TGGTGGTGGA CGTGAGCCAG GAAGACCCCG AGGTCCAGTT CAACTGGTAC
 901  GTGGATGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCGC GGGAGGAGCA
 951  GTTCAACAGC ACGTACCGTG TGGTCAGCGT CCTCACCGTC CTGCACCAGG
1001  ACTGGCTGAA CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC
1051  CCGTCCTCCA TCGAGAAAAC CATCTCCAAA GCCAAAGGGC AGCCCCGAGA
1101  GCCACAGGTG TACACCCTGC CCCCATCCCA GGAGGAGATG ACCAAGAACC
1151  AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTACCCCAG CGACATCGCC
1201  GTGGAGTGGG AGAGCAATGG ACAGCCGGAG AACAACTACA AGACCACGCC
1251  TCCCGTGCTG GACTCCGACG GCTCCTTCTT CCTCTACAGC AGGCTAACCG
1301  TGGACAAGAG CAGGTGGCAG GAGGGGAATG TCTTCTCATG CTCCGTGATG
1351  CATGAGGCTC TGCACAACCA CTACACACAG AAGAGCCTCT CCCTGTCTCT
1401  GGGTAAATGA
```

SEQ ID NO. 18
6.34.2 Predicted Heavy Chain Protein Sequence

```
   1  mefglswvfl vallrgvqcQ VQLVESGGGV VQPGRSLRLS CAASGFTFSS
  51  YGMHWVRQAP GKGLEWVAVI SNDGNNKYYA DSVKGRFTIS RDNSKNTLYL
 101  QMNSLSAEDT AVYYCARDST AITYYYYGMD VWGQGTTVTV SSASTKGPSV
 151  FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ
 201  SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK PSNTKVDKRV ESKYGPPCPS
 251  CPAPEFLGGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY
 301  VDGVEVHNAK TKPREEQFNS TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL
 351  PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA
 401  VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM
 451  HEALHNHYTQ KSLSLSLGK
```

SEQ ID NO. 19
6.34.2 Kappa Light Chain Nucleotide Sequence

```
   1   atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct
  51   ccgaggtgcc agatgtGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTGT
 101   CTGCATCTGT CGGAGACAGA GTCACCATCA CTTGCCGGGC AAGTCAGAAT
 151   ATTAGTAGCT ATTTAAATTG GTTTCAGCAG AAACCAGGGA AAGCCCCTAA
 201   GCTCCTGATC TATGCTGCAT CCGGTTTGAA GCGTGGGGTC CCATCACGGT
 251   TCAGTGGTAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGGACTCTG
 301   CAACCTGATG ATTTTGCAAC TTACTCCTGT CACCAGAGTT ACAGTCTCCC
 351   ATTCACTTTC GGCCCTGGGA CCAAAGTGGA TATCAAACGA ACTGTGGCTG
 401   CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA
 451   ACTGCCTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA
 501   AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA
 551   GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
 601   CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA
 651   AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG
 701   GAGAGTGTTA GTGA
```

SEQ ID NO. 20
6.34.2 Predicted Kappa Light Chain Protein Sequence

```
   1   mdmrvpaqll glllwlrga rcDIQMTQSP SSLSASVGDR VTITCRASQN
  51   ISSYLNWFQQ KPGKAPKLLI YAASGLKRGV PSRFSGSGSG TDFTLTIRTL
 101   QPDDFATYSC HQSYSLPFTF GPGTKVDIKR TVAAPSVFIF PPSDEQLKSG
 151   TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
 201   LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

SEQ ID NO. 21
6.67.1 Heavy Chain Nucleotide Sequence

```
   1  atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt
  51  cctgtccCAG GTGCAGCTGC AGGAGTCGGG CCCAGGACTG GTGAAGCCTT
 101  CGGAGACCCT GTCCCTCACC TGCACTGTCT CTGGTGACTC CATCAGTAGT
 151  AACTATTGGA GCTGGATCCG GCAGCCCGCC GGGAAGGGAC TGGAGTGGAT
 201  TGGGCGTATC TATACCAGTG GGGGCACCAA CTCCAACCCC TCCCTCAGGG
 251  GTCGAGTCAC CATTTTAGCA GACACGTCCA AGAACCAGTT CTCTCTGAAA
 301  CTGAGTTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGAGA
 351  TCGTATTACT ATAATTCGGG GACTTATTCC ATCCTTCTTT GACTACTGGG
 401  GCCAGGGAAC CCTGGTCACC GTCTCCTCAG CTTCCACCAA GGGCCCATCC
 451  GTCTTCCCCC TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCCGC
 501  CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT
 551  GGAACTCAGG CGCCCTGACC AGCGGCGTGC ACACCTTCCC GGCTGTCCTA
 601  CAGTCCTCAG GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG
 651  CAGCTTGGGC ACGAAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA
 701  ACACCAAGGT GGACAAGAGA GTTGAGTCCA AATATGGTCC CCCATGCCCA
 751  TCATGCCCAG CACCTGAGTT CCTGGGGGGA CCATCAGTCT TCCTGTTCCC
 801  CCCAAAACCC AAGGACACTC TCATGATCTC CCGGACCCCT GAGGTCACGT
 851  GCGTGGTGGT GGACGTGAGC CAGGAAGACC CCGAGGTCCA GTTCAACTGG
 901  TACGTGGATG GCGTGGAGGT GCATAATGCC AAGACAAAGC CGCGGGAGGA
 951  GCAGTTCAAC AGCACGTACC GTGTGGTCAG CGTCCTCACC GTCCTGCACC
1001  AGGACTGGCT GAACGGCAAG GAGTACAAGT GCAAGGTCTC CAACAAAGGC
1051  CTCCCGTCCT CCATCGAGAA AACCATCTCC AAAGCCAAAG GGCAGCCCCG
1101  AGAGCCACAG GTGTACACCC TGCCCCCATC CCAGGAGGAG ATGACCAAGA
1151  ACCAGGTCAG CCTGACCTGC CTGGTCAAAG GCTTCTACCC CAGCGACATC
1201  GCCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACAACT ACAAGACCAC
1251  GCCTCCCGTG CTGGACTCCG ACGGCTCCTT CTTCCTCTAC AGCAGGCTAA
1301  CCGTGGACAA GAGCAGGTGG CAGGAGGGGA ATGTCTTCTC ATGCTCCGTG
1351  ATGCATGAGG CTCTGCACAA CCACTACACA CAGAAGAGCC TCTCCCTGTC
1401  TCTGGGTAAA TGA
```

SEQ ID NO. 22
6.67.1 Predicted Heavy Chain Protein Sequence

```
   1  mkhlwfflll vaaprwvlsQ VQLQESGPGL VKPSETLSLT CTVSGDSISS
  51  NYWSWIRQPA GKGLEWIGRI YTSGGTNSNP SLRGRVTILA DTSKNQFSLK
 101  LSSVTAADTA VYYCARDRIT IIRGLIPSFF DYWGQGTLVT VSSASTKGPS
 151  VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL
 201  QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP
 251  SCPAPEFLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS QEDPEVQFNW
 301  YVDGVEVHNA KTKPREEQFN STYRVVSVLT VLHQDWLNGK EYKCKVSNKG
 351  LPSSIEKTIS KAKGQPREPQ VYTLPPSQEE MTKNQVSLTC LVKGFYPSDI
 401  AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SRLTVDKSRW QEGNVFSCSV
 451  MHEALHNHYT QKSLSLSLGK
```

SEQ ID NO. 23
6.67.1 Kappa Light Chain Nucleotide Sequence

```
   1   atggtgttgc agacccaggt cttcatttct ctgttgctct ggatctctgg
  51   tgcctacggg GACATCGTGA TGACCCAGTC TCCAGACTCC CTGGCTGTGT
 101   CTCTGGGCGA GAGGGCCACC ATCAACTGCA AGTCCAGCCA GAGTGTTTTA
 151   TACAGCTCCA ACAATAAGAC CTACTTAGCT TGGTACCAAC AGAAACCAAG
 201   ACAGCCTCCT AAATTGCTCA TTTACTGGGC ATCTATACGG GAATATGGGG
 251   TCCCTGACCG ATTCAGTGGC AGCGGGTCTG GGACAGATTT CACTCTCACC
 301   ATCAGCAGCC TGCAGGCTGA AGATGTGGCA GTTTATTTCT GTCAACAATA
 351   TTATAGTATT CCTCCCCTCA CTTTCGGCGG AGGGACCAAG GTGGAGATCA
 401   AACGAACTGT GGCTGCACCA TCTGTCTTCA TCTTCCCGCC ATCTGATGAG
 451   CAGTTGAAAT CTGGAACTGC CTCTGTTGTG TGCCTGCTGA ATAACTTCTA
 501   TCCCAGAGAG GCCAAAGTAC AGTGGAAGGT GGATAACGCC CTCCAATCGG
 551   GTAACTCCCA GGAGAGTGTC ACAGAGCAGG ACAGCAAGGA CAGCACCTAC
 601   AGCCTCAGCA GCACCCTGAC GCTGAGCAAA GCAGACTACG AGAAACACAA
 651   AGTCTACGCC TGCGAAGTCA CCCATCAGGG CCTGAGCTCG CCCGTCACAA
 701   AGAGCTTCAA CAGGGGAGAG TGTTAGTGA
```

SEQ ID NO. 24
6.67.1 Predicted Kappa Light Chain Protein Sequence

```
   1   mvlqtqvfis lllwisgayg DIVMTQSPDS LAVSLGERAT INCKSSQSVL
  51   YSSNNKTYLA WYQQKPRQPP KLLIYWASIR EYGVPDRFSG SGSGTDFTLT
 101   ISSLQAEDVA VYFCQQYYSI PPLTFGGGTK VEIKRTVAAP SVFIFPPSDE
 151   QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY
 201   SLSSTLTLSK ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE C
```

SEQ ID NO. 25
6.73.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg gctttttctt gtggctattt taaaaggtgt
  51  ccagtgtGAG GTGCAGCTGT TGGAGTCTGG GGGAGACTTG GTCCAGCCTG
 101  GGGGGTCCCT GAGACTCTCC TGTGCAGCCT CTGGATTCAC CTTTAGAAGT
 151  TATGCCATGA ACTGGGTCCG ACAGGCTCCA GGGAAGGGGC TGGAGTGGGT
 201  CTCAGTTATT AGTGGTCGTG GTGGTACTAC ATACTACGCA GACTCCGTGA
 251  AGGGCCGGTT CACCATCTCC AGAGACAATT CCAAGAACAC GCTGTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACGCG GCCGTATATT ACTGTGCGAA
 351  GATAGCAGTG GCTGGAGAGG GGCTCTACTA CTACTACGGT ATGGACGTCT
 401  GGGGCCAAGG GACCACGGTC ACCGTCTCCT CAGCTTCCAC CAAGGGCCCA
 451  TCCGTCTTCC CCCTGGCGCC CTGCTCCAGG AGCACCTCCG AGAACACAGC
 501  CGCCCTGGGC TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTGT
 551  CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT CCCGGCTGTC
 601  CTACAGTCCT CAGGACTCTA CTCCCTCAGC AGCGTGGTGA CCGTGCCCTC
 651  TAGCAGCTTG GGCACGAAGA CCTACACCTG CAACGTAGAT CACAAGCCCA
 701  GCAACACCAA GGTGGACAAG AGAGTTGAGT CCAAATATGG TCCCCCATGC
 751  CCATCATGCC CAGCACCTGA GTTCCTGGGG GGACCATCAG TCTTCCTGTT
 801  CCCCCCAAAA CCCAAGGACA CTCTCATGAT CTCCCGGACC CCTGAGGTCA
 851  CGTGCGTGGT GGTGGACGTG AGCCAGGAAG ACCCCGAGGT CCAGTTCAAC
 901  TGGTACGTGG ATGGCGTGGA GGTGCATAAT GCCAAGACAA AGCCGCGGGA
 951  GGAGCAGTTC AACAGCACGT ACCGTGTGGT CAGCGTCCTC ACCGTCCTGC
1001  ACCAGGACTG GCTGAACGGC AAGGAGTACA AGTGCAAGGT CTCCAACAAA
1051  GGCCTCCCGT CCTCCATCGA GAAAACCATC TCCAAAGCCA AAGGGCAGCC
1101  CCGAGAGCCA CAGGTGTACA CCCTGCCCCC ATCCCAGGAG GAGATGACCA
1151  AGAACCAGGT CAGCCTGACC TGCCTGGTCA AAGGCTTCTA CCCCAGCGAC
1201  ATCGCCGTGG AGTGGGAGAG CAATGGGCAG CCGGAGAACA ACTACAAGAC
1251  CACGCCTCCC GTGCTGGACT CCGACGGCTC CTTCTTCCTC TACAGCAGGC
1301  TAACCGTGGA CAAGAGCAGG TGGCAGGAGG GGAATGTCTT CTCATGCTCC
1351  GTGATGCATG AGGCTCTGCA CAACCACTAC ACACAGAAGA GCCTCTCCCT
1401  GTCTCTGGGT AAATGATAG
```

SEQ ID NO. 26
6.73.2 Predicted Heavy Chain Protein Sequence

```
   1  mefglswlfl vailkgvqcE VQLLESGGDL VQPGGSLRLS CAASGFTFRS
  51  YAMNWVRQAP GKGLEWVSVI SGRGGTTYYA DSVKGRFTIS RDNSKNTLYL
 101  QMNSLRAEDA AVYYCAKIAV AGEGLYYYYG MDVWGQGTTV TVSSASTKGP
 151  SVFPLAPCSR STSENTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV
 201  LQSSGLYSLS SVVTVPSSSL GTKTYTCNVD HKPSNTKVDK RVESKYGPPC
 251  PSCPAPEFLG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SQEDPEVQFN
 301  WYVDGVEVHN AKTKPREEQF NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK
 351  GLPSSIEKTI SKAKGQPREP QVYTLPPSQE EMTKNQVSLT CLVKGFYPSD
 401  IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSRLTVDKSR WQEGNVFSCS
 451  VMHEALHNHY TQKSLSLSLG K
```

SEQ ID NO. 27
6.73.2 Kappa Light Chain Nucleotide Sequence

```
   1   atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct
  51   ccgaggtgcc agatgtGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTGT
 101   CTGCATCTGT AGGTGACAGA GTCACCTTCA CTTGCCGGGC AAGTCAGAAC
 151   ATTACCAACT ATTTAAATTG GTATCAGCAG AAACCAGGGA AGGCCCCTAA
 201   GCTCCTGATC TATGCTGCGT CCAGTTTGCC AAGAGGGGTC CCATCAAGGT
 251   TCCGTGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCAGTCTG
 301   CAACCTGAAG ATTTTGCAAC TTACTACTGT CAACAGAGTT ACAGTAATCC
 351   TCCGGAGTGC GGTTTTGGCC AGGGGACCAC GCTGGATATC AAACGAACTG
 401   TGGCTGCACC ATCTGTCTTC ATCTTCCCGC CATCTGATGA GCAGTTGAAA
 451   TCTGGAACTG CCTCTGTTGT GTGCCTGCTG AATAACTTCT ATCCCAGAGA
 501   GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC
 551   AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC
 601   AGCACCCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC
 651   CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA
 701   ACAGGGGAGA GTGTTAGTGA
```

SEQ ID NO. 28
6.73.2 Predicted Kappa Light Chain Protein Sequence

```
   1   mdmrvpaqll glllwlrga rcDIQMTQSP SSLSASVGDR VTFTCRASQN
  51   ITNYLNWYQQ KPGKAPKLLI YAASSLPRGV PSRFRGSGSG TDFTLTISSL
 101   QPEDFATYYC QQSYSNPPEC GFGQGTTLDI KRTVAAPSVF IFPPSDEQLK
 151   SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS
 201   STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
```

SEQ ID NO. 29
6.77.1 Heavy Chain Nucleotide Sequence

```
   1  atggaactgg ggctccgctg ggttttcctt gttgctattt tagaaggtgt
  51  ccagtgtGAG GTGCAGCTGG TGGAGTCTGG GGGAGGCCTG GTCAAGCCTG
 101  GGGGGTCCCT GAGACTCTCC TGTGCAGCCT CTGGATTCAC CTTCAGTAGC
 151  TATAGCATGA ACTGGGTCCG CCAGGCTCCA GGGAAGGGGC TGGAGTGGGT
 201  CTCATCCATT AGTAGTAGTA GTAGTTACAT ATACTACGCA GACTCAGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAACG CCAAGAACTC ACTGTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACACG GCTGTGTATT ACTGTGCGAG
 351  AGATGGGTAT AGCAGTGGCT GGTCCTACTA CTACTACTAC GGTATGGACG
 401  TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAGCTTC CACCAAGGGC
 451  CCATCCGTCT TCCCCCTGGC GCCCTGCTCC AGGAGCACCT CCGAGAGCAC
 501  AGCCGCCCTG GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG
 551  TGTCGTGGAA CTCAGGCGCC CTGACCAGCG GCGTGCACAC CTTCCCGGCT
 601  GTCCTACAGT CCTCAGGACT CTACTCCCTC AGCAGCGTGG TGACCGTGCC
 651  CTCCAGCAGC TTGGGCACGA AGACCTACAC CTGCAACGTA GATCACAAGC
 701  CCAGCAACAC CAAGGTGGAC AAGAGAGTTG AGTCCAAATA TGGTCCCCCA
 751  TGCCCATCAT GCCCAGCACC TGAGTTCCTG GGGGGACCAT CAGTCTTCCT
 801  GTTCCCCCCA AAACCCAAGG ACACTCTCAT GATCTCCCGG ACCCCTGAGG
 851  TCACGTGCGT GGTGGTGGAC GTGAGCCAGG AAGACCCCGA GGTCCAGTTC
 901  AACTGGTACG TGGATGGCGT GGAGGTGCAT AATGCCAAGA CAAAGCCGCG
 951  GGAGGAGCAG TTCAACAGCA CGTACCGTGT GGTCAGCGTC CTCACCGTCC
1001  TGCACCAGGA CTGGCTGAAC GGCAAGGAGT ACAAGTGCAA GGTCTCCAAC
1051  AAAGGCCTCC CGTCCTCCAT CGAGAAAACC ATCTCCAAAG CCAAAGGGCA
1101  GCCCCGAGAG CCACAGGTGT ACACCCTGCC CCCATCCCAG GAGGAGATGA
1151  CCAAGAACCA GGTCAGCCTG ACCTGCCTGG TCAAAGGCTT CTACCCCAGC
1201  GACATCGCCG TGGAGTGGGA GAGCAATGGG CAGCCGGAGA ACAACTACAA
1251  GACCACGCCT CCCGTGCTGG ACTCCGACGG CTCCTTCTTC CTCTACAGCA
1301  GGCTAACCGT GGACAAGAGC AGGTGGCAGG AGGGGAATGT CTTTTCACGC
1351  TCCGTGATGC ATGAGGCTCT GCACAACCAC TACACACAGA AGAGCCTCTC
1401  CCTGTCTCTG GGTAAATGAT AGGAATTCTG ATGA
```

SEQ ID NO. 30
6.77.1 Predicted Heavy Chain Protein Sequence

```
   1  melglrwvfl vailegvqcE VQLVESGGGL VKPGGSLRLS CAASGFTFSS
  51  YSMNWVRQAP GKGLEWVSSI SSSSSYIYYA DSVKGRFTIS RDNAKNSLYL
 101  QMNSLRAEDT AVYYCARDGY SSGWSYYYYY GMDVWGQGTT VTVSSASTKG
 151  PSVFPLAPCS RSTSESTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA
 201  VLQSSGLYSL SSVVTVPSSS LGTKTYTCNV DHKPSNTKVD KRVESKYGPP
 251  CPSCPAPEFL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSQEDPEVQF
 301  NWYVDGVEVH NAKTKPREEQ FNSTYRVVSV LTVLHQDWLN GKEYKCKVSN
 351  KGLPSSIEKT ISKAKGQPRE PQVYTLPPSQ EEMTKNQVSL TCLVKGFYPS
 401  DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSRLTVDKS RWQEGNVFSR
 451  SVMHEALHNH YTQKSLSLSL GK
```

SEQ ID NO. 31
6.77.1 Kappa Light Chain Nucleotide Sequence

```
   1   atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg
  51   atccagtgca GATATTGTGA TGACCCAGAC TCCACTCTCT CTGTCCGTCA
 101   CTCCTGGACA GCCGGCCTCC ATCTCCTGCA ACTCTAGTCA GAGCCTCCTG
 151   CTTAGTGATG GAAAGACCTA TTTGAATTGG TACCTGCAGA AGCCCGGCCA
 201   GCCTCCACAG CTCCTGATCT ATGAAGTTTC CAACCGGTTC TCTGGAGTGC
 251   CAGACAGGTT CAGTGGCAGC GGGTCAGGGA CAGATTTCAC ACTGAAAATC
 301   AGCCGGGTGG AGGCTGAGGA TGTTGGGGTT TATTCCTGCA TGCAAAGTAT
 351   ACAGCTTATG TGCAGTTTTG GCCAGGGGAC CAAGCTGGAG ATCAAACGAA
 401   CTGTGGCTGC ACCATCTGTC TTCATCTTCC CGCCATCTGA TGAGCAGTTG
 451   AAATCTGGAA CTGCCTCTGT TGTGTGCCTG CTGAATAACT TCTATCCCAG
 501   AGAGGCCAAA GTACAGTGGA AGGTGGATAA CGCCCTCCAA TCGGGTAACT
 551   CCCAGGAGAG TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC
 601   AGCAGCACCC TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA
 651   CGCCTGCGAA GTCACCCATC AGGGCCTGAG CTCGCCCGTC ACAAAGAGCT
 701   TCAACAGGGG AGAGTGTTAG TGA
```

SEQ ID NO. 32
6.77.1 Predicted Kappa Light Chain Protein Sequence

```
   1   mrlpaqllgl lmlwipgssa DIVMTQTPLS LSVTPGQPAS ISCNSSQSLL
  51   LSDGKTYLNW YLQKPGQPPQ LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI
 101   SRVEAEDVGV YSCMQSIQLM CSFGQGTKLE IKRTVAAPSV FIFPPSDEQL
 151   KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
 201   SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
```

SEQ ID NO. 33
7.16.6 Heavy Chain Nucleotide Sequence

```
   1  atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc
  51  ccactccCAG GTTCAGCTGG TGCAGTCTGG AGCTGAGGTG AAGAAGCCTG
 101  GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGGTTACAC CTTTACCAGC
 151  TATGGTATCA ACTGGGTGCG ACAGGCCCCT GGACAAGGGC TTGAGTGGAT
 201  GGGATGGATC AGCGTTTACA GTGGTAACAC AAACTATGCA CAGAAGGTCC
 251  AGGGCAGAGT CACCATGACC GCAGACACAT CCACGAGCAC AGCCTACATG
 301  GACCTGAGGA GCCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
 351  AGAGGGTAGC AGCTCGTCCG GAGACTACTA TTACGGTATG GACGTCTGGG
 401  GCCAAGGGAC CACGGTCACC GTCTCCTCAG CCTCCACCAA GGGCCCATCG
 451  GTCTTCCCCC TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCGGC
 501  CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT
 551  GGAACTCAGG CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA
 601  CAGTCCTCAG GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG
 651  CAACTTCGGC ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA
 701  ACACCAAGGT GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA
 751  CCGTGCCCAG CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCCC
 801  AAAACCCAAG GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG
 851  TGGTGGTGGA CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC
 901  GTGGACGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCAC GGGAGGAGCA
 951  GTTCAACAGC ACGTTCCGTG TGGTCAGCGT CCTCACCGTT GTGCACCAGG
1001  ACTGGCTGAA CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC
1051  CCAGCCCCCA TCGAGAAAAC CATCTCCAAA ACCAAAGGGC AGCCCCGAGA
1101  ACCACAGGTG TACACCCTGC CCCCATCCCG GGAGGAGATG ACCAAGAACC
1151  AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTACCCCAG CGACATCGCC
1201  GTGGAGTGGG AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACACC
1251  TCCCATGCTG GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG
1301  TGGACAAGAG CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG
1351  CATGAGGCTC TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC
1401  GGGTAAATGA
```

SEQ ID NO. 34
7.16.6 Predicted Heavy Chain Protein Sequence

```
   1  mdwtwsilfl vaaatgahsQ VQLVQSGAEV KKPGASVKVS CKASGYTFTS
  51  YGINWVRQAP GQGLEWMGWI SVYSGNTNYA QKVQGRVTMT ADTSTSTAYM
 101  DLRSLRSDDT AVYYCAREGS SSSGDYYYGM DVWGQGTTVT VSSASTKGPS
 151  VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL
 201  QSSGLYSLSS VVTVPSSNFG TQTYTCNVDH KPSNTKVDKT VERKCCVECP
 251  PCPAPPVAGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVQFNWY
 301  VDGVEVHNAK TKPREEQFNS TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL
 351  PAPIEKTISK TKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA
 401  VEWESNGQPE NNYKTTPPML DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM
 451  HEALHNHYTQ KSLSLSPGK
```

SEQ ID NO. 35
7.16.6 Kappa Light Chain Nucleotide Sequence and X481.2 Kappa Light Chain Nucleotide Sequence

```
   1   atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg
  51   atccagtgca GATATTGTGA TGACCCAGAC TCCACTCTCT CTGTCCGTCA
 101   CCCCTGGACA GCCGGCCTCC ATCTCCTGCA AGTCTAGTCA GAGCCTCCTG
 151   CATACTGATG GAACGACCTA TTTGTATTGG TACCTGCAGA AGCCAGGCCA
 201   GCCTCCACAG CTCCTGATCT ATGAAGTTTC CAACCGGTTC TCTGGAGTGC
 251   CAGATAGGTT CAGTGGCAGC GGGTCAGGGA CAGATTTCAC ACTGAAAATC
 301   AGCCGGGTGG AGGCTGAGGA TGTTGGGATT TATTACTGCA TGCAAAATAT
 351   ACAGCTTCCG TGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGAA
 401   CTGTGGCTGC ACCATCTGTC TTCATCTTCC CGCCATCTGA TGAGCAGTTG
 451   AAATCTGGAA CTGCCTCTGT TGTGTGCCTG CTGAATAACT TCTATCCCAG
 501   AGAGGCCAAA GTACAGTGGA AGGTGGATAA CGCCCTCCAA TCGGGTAACT
 551   CCCAGGAGAG TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC
 601   AGCAGCACCC TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA
 651   CGCCTGCGAA GTCACCCATC AGGGCCTGAG CTCGCCCGTC ACAAAGAGCT
 701   TCAACAGGGG AGAGTGTTAG TGA
```

SEQ ID NO. 36
7.16.6 Kappa Light Chain Protein Sequence

```
   1   mrlpaqllgl lmlwipgssa DIVMTQTPLS LSVTPGQPAS ISCKSSQSLL
  51   HTDGTTYLYW YLQKPGQPPQ LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI
 101   SRVEAEDVGI YYCMQNIQLP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL
 151   KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
 201   SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
```

SEQ ID NO. 37
7.20.5 Heavy Chain Nucleotide Sequence

```
   1  atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt
  51  cctgtccCAG GTGCAGCTGC AGGAGTCGGG CCCAGGACTG GTGAAGCCTT
 101  CGGAGACCCT GTCCCTCACC TGCACTGTCT CTGGTAGCTC CATCAGTAGT
 151  TACCACTGGA ACTGGATCCG GCAGCCCGCC GGGAAGGGAC TGGAGTGGAT
 201  TGGGCGTATC TATACCAGTG GGAGCACCAA CTACAACCCC TCCCTCAAGA
 251  GTCGAGTCAC CATGTCACTA GACACGTCCA AGAACCAGTT CTCCCTGAAG
 301  CTGAGCTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGAGA
 351  GGGGGTCAGG TATTACTATG CTTCGGGGAG TTATTACTAC GGTCTGGACG
 401  TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAGCCTC CACCAAGGGC
 451  CCATCGGTCT TCCCCCTGGC GCCCTGCTCC AGGAGCACCT CCGAGAGCAC
 501  AGCGGCCCTG GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG
 551  TGTCGTGGAA CTCAGGCGCT CTGACCAGCG GCGTGCACAC CTTCCCAGCT
 601  GTCCTACAGT CCTCAGGACT CTACTCCCTC AGCAGCGTGG TGACCGTGCC
 651  CTCCAGCAAC TTCGGCACCC AGACCTACAC CTGCAACGTA GATCACAAGC
 701  CCAGCAACAC CAAGGTGGAC AAGACAGTTG AGCGCAAATG TTGTGTCGAG
 751  TGCCCACCGT GCCCAGCACC ACCTGTGGCA GGACCGTCAG TCTTCCTCTT
 801  CCCCCCAAAA CCCAAGGACA CCCTCATGAT CTCCCGGACC CCTGAGGTCA
 851  CGTGCGTGGT GGTGGACGTG AGCCACGAAG ACCCCGAGGT CCAGTTCAAC
 901  TGGTACGTGG ACGGCGTGGA GGTGCATAAT GCCAAGACAA AGCCACGGGA
 951  GGAGCAGTTC AACAGCACGT TCCGTGTGGT CAGCGTCCTC ACCGTTGTGC
1001  ACCAGGACTG GCTGAACGGC AAGGAGTACA AGTGCAAGGT CTCCAACAAA
1051  GGCCTCCCAG CCCCCATCGA GAAAACCATC TCCAAAACCA AAGGGCAGCC
1101  CCGAGAACCA CAGGTGTACA CCCTGCCCCC ATCCCGGGAG GAGATGACCA
1151  AGAACCAGGT CAGCCTGACC TGCCTGGTCA AAGGCTTCTA CCCCAGCGAC
1201  ATCGCCGTGG AGTGGGAGAG CAATGGGCAG CCGGAGAACA ACTACAAGAC
1251  CACACCTCCC ATGCTGGACT CCGACGGCTC CTTCTTCCTC TACAGCAAGC
1301  TCACCGTGGA CAAGAGCAGG TGGCAGCAGG GGAACGTCTT CTCATGCTCC
1351  GTGATGCATG AGGCTCTGCA CAACCACTAC ACGCAGAAGA GCCTCTCCCT
1401  GTCTCCGGGT AAATGA
```

SEQ ID NO. 38
7.20.5 Predicted Heavy Chain Protein Sequence

```
   1  mkhlwfflll vaaprwvlsQ VQLQESGPGL VKPSETLSLT CTVSGSSISS
  51  YHWNWIRQPA GKGLEWIGRI YTSGSTNYNP SLKSRVTMSL DTSKNQFSLK
 101  LSSVTAADTA VYYCAREGVR YYYASGSYYY GLDVWGQGTT VTVSSASTKG
 151  PSVFPLAPCS RSTSESTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA
 201  VLQSSGLYSL SSVVTVPSSN FGTQTYTCNV DHKPSNTKVD KTVERKCCVE
 251  CPPCPAPPVA GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVQFN
 301  WYVDGVEVHN AKTKPREEQF NSTFRVVSVL TVVHQDWLNG KEYKCKVSNK
 351  GLPAPIEKTI SKTKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD
 401  IAVEWESNGQ PENNYKTTPP MLDSDGSFFL YSKLTVDKSR WQQGNVFSCS
 451  VMHEALHNHY TQKSLSLSPG K
```

SEQ ID NO. 39
7.20.5 Kappa Light Chain Nucleotide Sequence

```
   1   atgaggctcc ctgctcagct cctggggctg ctaatgctct gggtctctgg
  51   atccagtggg GATATTGTGA TGACTCAGTC TCCACTCTCC CTGCCCGTCA
 101   CCCCTGGAGA GCCGGCCTCC ATCTCCTGCA GGTCTAGTCA GAGCCTCCTG
 151   CATGGTAATG GATACAACTA TTTGGATTGG TACCTGCAGA AGCCAGGGCA
 201   GTCTCCACAG CTCCTGATCT ATTTGGGTTC TAATCGGGCC TCCGGGGTCC
 251   CTGACAGGTT CAGTGGCAGT GGATCAGGCA CAGATTTTAC ACTGAAAATC
 301   AGCAGAGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAGCTCT
 351   ACAAACTCTC ACTTTCGGCG GAGGGACCAA GGTGGAGATC AAACGAACTG
 401   TGGCTGCACC ATCTGTCTTC ATCTTCCCGC CATCTGATGA GCAGTTGAAA
 451   TCTGGAACTG CCTCTGTTGT GTGCCTGCTG AATAACTTCT ATCCCAGAGA
 501   GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC
 551   AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC
 601   AGCACCCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC
 651   CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA
 701   ACAGGGGAGA GTGTTAGTGA
```

SEQ ID NO. 40
7.20.5 Predicted Kappa Light Chain Protein Sequence

```
   1   mrlpaqllgl lmlwvsgssg DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL
  51   HGNGYNYLDW YLQKPGQSPQ LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI
 101   SRVEAEDVGV YYCMQALQTL TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK
 151   SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS
 201   STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
```

SEQ ID NO. 41
7.26.4 Heavy Chain Nucleotide Sequence

```
   1  atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc
  51  ccactccCAG GTTCAGCTGG TGCAGTCTGG AGCTGAGGTG AAGAAGCCTG
 101  GGGCCTCAGT GAAGGTCTCC TGCGAGGCTT CTGGTTACAC CTTTACCAGC
 151  TATGGTATCG ACTGGGTGCG ACAGGCCCCT GGACAAGGGC TTGAGTGGAT
 201  GGGATGGATC AGCGTTTACA GTGGTAACAC AAACTATGCA CAGAAGCTCC
 251  AGGGCAGAGT CACCATGTCC ACAGACACAT CCACGAGCAC AGCCTACATG
 301  GAGCTGAGGA GCCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
 351  AGAGGGTAGC AGCTCGTCCG GAGACTACTA CTACGGTATG GACGTCTGGG
 401  GCCAAGGGAC CACGGTCACC GTCTCCTCAG CCTCCACCAA GGGCCCATCG
 451  GTCTTCCCCC TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCGGC
 501  CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT
 551  GGAACTCAGG CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA
 601  CAGTCCTCAG GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG
 651  CAACTTCGGC ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA
 701  ACACCAAGGT GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA
 751  CCGTGCCCAG CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCCC
 801  AAAACCCAAG GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG
 851  TGGTGGTGGA CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC
 901  GTGGACGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCAC GGGAGGAGCA
 951  GTTCAACAGC ACGTTCCGTG TGGTCAGCGT CCTCACCGTT GTGCACCAGG
1001  ACTGGCTGAA CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC
1051  CCAGCCCCCA TTGAGAAAAC CATCTCCAAA ACCAAAGGGC AGCCCCGAGA
1101  ACCACAGGTG TACACCCTGC CCCCATCCCG GGAGGAGATG ACCAAGAACC
1151  AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTACCCCAG CGACATCGCC
1201  GTGGAGTGGG AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACACC
1251  TCCCATGCTG GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG
1301  TGGACAAGAG CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG
1351  CATGAGGCTC TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC
1402  GGGTAAATGA
```

SEQ ID NO. 42
7.26.4 Predicted Heavy Chain Protein Sequence

```
   1  mdwtwsilfl vaaatgahsQ VQLVQSGAEV KKPGASVKVS CEASGYTFTS
  51  YGIDWVRQAP GQGLEWMGWI SVYSGNTNYA QKLQGRVTMS TDTSTSTAYM
 101  ELRSLRSDDT AVYYCAREGS SSSGDYYYGM DVWGQGTTVT VSSASTKGPS
 151  VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL
 201  QSSGLYSLSS VVTVPSSNFG TQTYTCNVDH KPSNTKVDKT VERKCCVECP
 251  PCPAPPVAGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVQFNWY
 301  VDGVEVHNAK TKPREEQFNS TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL
 351  PAPIEKTISK TKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA
 401  VEWESNGQPE NNYKTTPPML DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM
 451  HEALHNHYTQ KSLSLSPGK
```

SEQ ID NO. 43
7.26.4 Kappa Light Chain Nucleotide Sequence

```
   1   atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg
  51   atccagtgcg GATATTGTGA TGACCCAGAC TCCACTCTCT CTGTCCGTCA
 101   CCCCTGGACA GCCGGCCTCC ATCTCCTGCA AGTCTAATCA GAGCCTCCTG
 151   TATAGTGATG GAAAGACCTA TTTGTTTTGG TACCTGCAGA AGCCAGGCCA
 201   GCCTCCACAG CTCCTGATCT ATGAAGTTTC CAACCGATTC TCTGGAGTGC
 251   CAGATAGGTT CAGTGGCAGC GGGTCAGGGA CAGATTTCAC ACTGAAAATC
 301   AGCCGGGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAAGTAT
 351   ACAGCTTCCG TGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGAA
 401   CTGTGGCTGC ACCATCTGTC TTCATCTTCC CGCCATCTGA TGAGCAGTTG
 451   AAATCTGGAA CTGCCTCTGT TGTGTGCCTG CTGAATAACT TCTATCCCAG
 501   AGAGGCCAAA GTACAGTGGA AGGTGGATAA CGCCCTCCAA TCGGGTAACT
 551   CCCAGGAGAG TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC
 601   AGCAGCACCC TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA
 651   CGCCTGCGAA GTCACCCATC AGGGCCTGAG CTCGCCCGTC ACAAAGAGCT
 701   TCAACAGGGG AGAGTGTTAG TGA
```

SEQ ID NO. 44
7.26.4 Predicted Kappa Light Chain Protein Sequence

```
   1   mrlpaqllgl lmlwipgssa DIVMTQTPLS LSVTPGQPAS ISCKSNQSLL
  51   YSDGKTYLFW YLQKPGQPPQ LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI
 101   SRVEAEDVGV YYCMQSIQLP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL
 151   KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
 201   SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
```

SEQ ID NO. 45
9.8.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt
  51  ccagtgtCAG GTGCAGCTGG TGGAGTCTGG GGGAGGCGTG GTCCAGCCTG
 101  GGAGGTCCCT GAGACTCTCC TGTGCAGCGT CTGGATTCAC CTTCAGTAGC
 151  TATGGCATGC ACTGGGTCCG CCAGGCTCCA GGCAAGGGGC TGGAGTGGGT
 201  GGCAGTTATA TGGTATGATG GAAGTAATGA ATACTATGCA GACTCCGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAATT CCAAGAACAC GCTGTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACACG GCTGTGTATT ACTGTGCGAG
 351  GGGGGCGTAC CACTTTGCCT ACTGGGGCCA GGGAACCCTG GTCACCGTCT
 401  CCTCAGCTTC CACCAAGGGC CCATCCGTCT TCCCCCTGGC GCCCTGCTCC
 451  AGGAGCACCT CCGAGAGCAC AGCCGCCCTG GGCTGCCTGG TCAAGGACTA
 501  CTTCCCCGAA CCGGTGACGG TGTCGTGGAA CTCAGGCGCC CTGACCAGCG
 551  GCGTGCACAC CTTCCCGGCT GTCCTACAGT CCTCAGGACT CTACTCCCTC
 601  AGCAGCGTGG TGACCGTGCC CTCCAGCAGC TTGGGCACGA AGACCTACAC
 651  CTGCAACGTA GATCACAAGC CCAGCAACAC CAAGGTGGAC AAGAGAGTTG
 701  AGTCCAAATA TGGTCCCCCA TGCCCATCAT GCCCAGCACC TGAGTTCCTG
 751  GGGGGACCAT CAGTCTTCCT GTTCCCCCCA AAACCCAAGG ACACTCTCAT
 801  GATCTCCCGG ACCCCTGAGG TCACGTGCGT GGTGGTGGAC GTGAGCCAGG
 851  AAGACCCCGA GGTCCAGTTC AACTGGTACG TGGATGGCGT GGAGGTGCAT
 901  AATGCCAAGA CAAAGCCGCG GGAGGAGCAG TTCAACAGCA CGTACCGTGT
 951  GGTCAGCGTC CTCACCGTCC TGCACCAGGA CTGGCTGAAC GGCAAGGAGT
1001  ACAAGTGCAA GGTCTCCAAC AAAGGCCTCC CGTCCTCCAT CGAGAAAACC
1051  ATCTCCAAAG CCAAAGGGCA GCCCCGAGAG CCACAGGTGT ACACCCTGCC
1101  CCCATCCCAG GAGGAGATGA CCAAGAACCA GGTCAGCCTG ACCTGCCTGG
1151  TCAAAGGCTT CTACCCCAGC GACATCGCCG TGGAGTGGGA GAGCAATGGG
1201  CAGCCGGAGA ACAACTACAA GACCACGCCT CCCGTGCTGG ACTCCGACGG
1251  CTCCTTCTTC CTCTACAGCA GGCTAACCGT GGACAAGAGC AGGTGGCAGG
1301  AGGGGAATGT CTTCTCATGC TCCGTGATGC ATGAGGCTCT GCACAACCAC
1351  TACACACAGA AGAGCCTCTC CCTGTCTCTG GGTAAATGA
```

SEQ ID NO. 46
9.8.2 Predicted Heavy Chain Chain Protein Sequence

```
   1  mefglswvfl vallrgvqcQ VQLVESGGGV VQPGRSLRLS CAASGFTFSS
  51  YGMHWVRQAP GKGLEWVAVI WYDGSNEYYA DSVKGRFTIS RDNSKNTLYL
 101  QMNSLRAEDT AVYYCARGAY HFAYWGQGTL VTVSSASTKG PSVFPLAPCS
 151  RSTSESTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
 201  SSVVTVPSSS LGTKTYTCNV DHKPSNTKVD KRVESKYGPP CPSCPAPEFL
 251  GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH
 301  NAKTKPREEQ FNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT
 351  ISKAKGQPRE PQVYTLPPSQ EEMTKNQVSL TCLVKGFYPS DIAVEWESNG
 401  QPENNYKTTP PVLDSDGSFF LYSRLTVDKS RWQEGNVFSC SVMHEALHNH
 451  YTQKSLSLSL GK
```

SEQ ID NO. 47
9.8.2 Kappa Light Chain Nucleotide Sequence

```
   1   atggacatga gggtccctgc tcagctcctg gggctcctgc tgctctggct
  51   ctcagtcgca ggtgccagat gtGACATCCA GATGACCCAG TCTCCATCCT
 101   CCCTGTCTGC ATCTGTAGGA GACAGAGTCA CCATCACTTG CCAGGCGAGT
 151   CAGGACATTA GCAACTATTT AAATTGGTAT CAGCAGAAAC CAGGGAAAGC
 201   CCCTAAGCTC CTGATCTACG ATGCATCCAA TTTGGAAACA GGGGTCCCAT
 251   CAAGGTTCAG TGGAAGTGGA TCTGGGACAG ATTTTACTTT CACCATCAGC
 301   AGCCTGCAGC CTGAAGATAT TGCAACATAT TCCTGTCAAC ACTCTGATAA
 351   TCTCTCGATC ACCTTCGGCC AGGGGACACG ACTGGAGATT AAACGAACTG
 401   TGGCTGCACC ATCTGTCTTC ATCTTCCCGC CATCTGATGA GCAGTTGAAA
 451   TCTGGAACTG CCTCTGTTGT GTGCCTGCTG AATAACTTCT ACCCCAGAGA
 501   GGCCAAAGTA CAGTGGAAGG TGGATAACGC CCTCCAATCG GGTAACTCCC
 551   AGGAGAGTGT CACAGAGCAG GACAGCAAGG ACAGCACCTA CAGCCTCAGC
 601   AGCACCCTGA CGCTGAGCAA AGCAGACTAC GAGAAACACA AAGTCTACGC
 651   CTGCGAAGTC ACCCATCAGG GCCTGAGCTC GCCCGTCACA AAGAGCTTCA
 701   ACAGGGGAGA GTGTTAGTGA
```

SEQ ID NO. 48
9.8.2 Predicted Kappa Light Chain Protein Sequence

```
   1   mdmrvpaqll glllwlsva garcDIQMTQ SPSSLSASVG DRVTITCQAS
  51   QDISNYLNWY QQKPGKAPKL LIYDASNLET GVPSRFSGSG SGTDFTFTIS
 101   SLQPEDIATY SCQHSDNLSI TFGQGTRLEI KRTVAAPSVF IFPPSDEQLK
 151   SGTASVVCLL NNFYPREAKV QWKVDNALQS GNSQESVTEQ DSKDSTYSLS
 201   STLTLSKADY EKHKVYACEV THQGLSSPVT KSFNRGEC
```

SEQ ID NO. 49
Nucleotide Sequence of cynomolgus MAdCAM $\alpha_4\beta_7$ binding domain

```
   1   ATGGATCGGG GCCTGGCCCT CCTGCTGGCG GGGCTTCTGG GGCTCCTCCA
  51   GCCGGGCTGC GGCCAGTCCC TCCAGGTGAA GCCCCTGCAG GTGGAGCCCC
 101   CGGAGCCGGT GGTGGCCGTG GCCCTGGGCG CCTCTCGCCA GCTCACCTGC
 151   CGCCTGGACT GCGCGGACGG CGGGGCCACG GTGCAGTGGC GGGGCCTGGA
 201   CACCAGCCTG GGCGCGGTGC AGTCGGACGC GGGCCGCAGC GTCCTCACCG
 251   TGCGCAACGC CTCGCTGTCG GCGGCCGGGA CCCGTGTGTG CGTGGGCTCC
 301   TGCGGGGGCC GCACCTTCCA GCACACCGTG CGGCTCCTTG TGTACGCCTT
 351   CCCGGACCAG CTGACCATCT CCCCGGCAGC CCTGGTGCCT GGTGACCCGG
 401   AGGTGGCCTG TACGGCTCAC AAAGTCACGC CTGTGGACCC CAATGCGCTC
 451   TCCTTCTCCC TGCTCCTGGG GGACCAGGAA CTGGAGGGGG CCCAGGCTCT
 501   GGGCCCGGAG GTGGAGGAGG AGGAGGAGCC CCAGGAGGAG GAGGACGTGC
 551   TGTTCAGGGT GACAGAGCGC TGGCGGCTGC CGACCCTGGC AACCCCTGTC
 601   CTGCCCGCGC TCTACTGCCA GGCCACGATG AGGCTGCCTG GCTTGGAGCT
 651   CAGCCACCGC CAGGCCATCC CGGTCCTGCA C
```

SEQ ID NO. 50
Amino acid sequence of cynomolgus MAdCAM $\alpha_4\beta_7$ binding domain

```
   1   MDRGLALLLA GLLGLLQPGC GQSLQVKPLQ VEPPEPVVAV ALGASRQLTC
  51   RLDCADGGAT VQWRGLDTSL GAVQSDAGRS VLTVRNASLS AAGTRVCVGS
 101   CGGRTFQHTV RLLVYAFPDQ LTISPAALVP GDPEVACTAH KVTPVDPNAL
 151   SFSLLLGDQE LEGAQALGPE VEEEEEPQEE EDVLFRVTER WRLPTLATPV
 201   LPALYCQATM RLPGLELSHR QAIPVLH
```

SEQ ID NO. 51
Modified 6.22.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt
  51  ccagtgtCAG GTGCAGCTGG TGGAGTCTGG GGGAGGCGTG GTCCAGCCTG
 101  GGAGGTCCCT GAGACTCTCC TGTGCAGCGT CTGGATTCAC CTTCAGTAGC
 151  GATGGCATGC ACTGGGTCCG CCAGGCTCCA GGCAAGGGGC TGGAGTGGGT
 201  GGCAATTATA TGGTATGATG GAAGTAATAA ATATTATGCA GACTCCGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAATT CCAAGAACAC GCTGTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACACG GCTGTATATT ACTGTGCGAG
 351  AGATCCCGGC TACTATTACG GTATGGACGT CTGGGGCCAA GGGACCACGG
 401  TCACCGTCTC CTCAGCTTCC ACCAAGGGCC CATCCGTCTT CCCCCTGGCG
 451  CCCTGCTCTA GAAGCACCTC CGAGAGCACA GCGGCCCTGG GCTGCCTGGT
 501  CAAGGACTAC TTCCCCGAAC CGGTGACGGT GTCGTGGAAC TCAGGCGCTC
 551  TGACCAGCGG CGTGCACACC TTCCCAGCTG TCCTACAGTC CTCAGGACTC
 601  TACTCCCTCA GCAGCGTGGT GACCGTGCCC TCCAGCAACT TCGGCACCCA
 651  GACCTACACC TGCAACGTAG ATCACAAGCC CAGCAACACC AAGGTGGACA
 701  AGACAGTTGA GCGCAAATGT TGTGTCGAGT GCCCACCGTG CCCAGCACCA
 751  CCTGTGGCAG GACCGTCAGT CTTCCTCTTC CCCCCAAAAC CCAAGGACAC
 801  CCTCATGATC TCCCGGACCC CTGAGGTCAC GTGCGTGGTG GTGGACGTGA
 851  GCCACGAAGA CCCCGAGGTC CAGTTCAACT GGTACGTGGA CGGCGTGGAG
 901  GTGCATAATG CCAAGACAAA GCCACGGGAG GAGCAGTTCA ACAGCACGTT
 951  CCGTGTGGTC AGCGTCCTCA CCGTTGTGCA CCAGGACTGG CTGAACGGCA
1001  AGGAGTACAA GTGCAAGGTC TCCAACAAAG GCCTCCCAGC CCCCATCGAG
1051  AAAACCATCT CCAAAACCAA AGGGCAGCCC CGAGAACCAC AGGTGTACAC
1101  CCTGCCCCCA TCCCGGGAGG AGATGACCAA GAACCAGGTC AGCCTGACCT
1151  GCCTGGTCAA AGGCTTCTAC CCCAGCGACA TCGCCGTGGA GTGGGAGAGC
1201  AATGGGCAGC CGGAGAACAA CTACAAGACC ACACCTCCCA TGCTGGACTC
1251  CGACGGCTCC TTCTTCCTCT ACAGCAAGCT CACCGTGGAC AAGAGCAGGT
1301  GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC
1351  AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA AATGATAG
```

SEQ ID NO. 52
Modified 6.22.2 Heavy Chain Amino Acid Sequence

```
   1  mefglswvfl vallrgvqcQ VQLVESGGGV VQPGRSLRLS CAASGFTFSS
  51  DGMHWVRQAP GKGLEWVAII WYDGSNKYYA DSVKGRFTIS RDNSKNTLYL
 101  QMNSLRAEDT AVYYCARDPG YYYGMDVWGQ GTTVTVSSAS TKGPSVFPLA
 151  PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
 201  YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVECPPCPAP
 251  PVAGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV QFNWYVDGVE
 301  VHNAKTKPRE EQFNSTFRVV SVLTVVHQDW LNGKEYKCKV SNKGLPAPIE
 351  KTISKTKGQP REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES
 401  NGQPENNYKT TPPMLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH
 451  NHYTQKSLSL SPGK
```

SEQ ID NO. 53
Modified 6.22.2 Kappa Light Chain Nucleotide Sequence

```
   1  atgttgccat cacaactcat tgggtttctg ctgctctggg ttccagcttc
  51  caggggtGAA ATTGTGCTGA CTCAGTCTCC AGACTTTCAG TCTGTGACTC
 101  CAAAAGAGAA AGTCACCATC ACCTGCCGGG CCAGTCAGAG AATTGGTAGT
 151  AGCTTACACT GGTACCAGCA GAAACCAGAT CAGTCTCCAA AACTCCTCAT
 201  CAAGTATGCT TCCCAGTCCT TCTCAGGGGT CCCCTCGAGG TTCAGTGGCA
 251  GTGGATCTGG GACAGATTTC ACCCTCACCA TCAATAGCCT GGAAGCTGAA
 301  GATGCTGCAA CTTATTACTG TCATCAGAGT GGTCGTTTAC CGCTCACTTT
 351  CGGCGGAGGG ACCAAGGTGG AGATCAAACG AACTGTGGCT GCACCATCTG
 401  TCTTCATCTT CCCGCCATCT GATGAGCAGT TGAAATCTGG AACTGCCTCT
 451  GTTGTGTGCC TGCTGAATAA CTTCTATCCC AGAGAGGCCA AAGTACAGTG
 501  GAAGGTGGAT AACGCCCTCC AATCGGGTAA CTCCCAGGAG AGTGTCACAG
 551  AGCAGGACAG CAAGGACAGC ACCTACAGCC TCAGCAGCAC CCTGACGCTG
 601  AGCAAAGCAG ACTACGAGAA ACACAAAGTC TACGCCTGCG AAGTCACCCA
 651  TCAGGGCCTG AGCTCGCCCG TCACAAAGAG CTTCAACAGG GGAGAGTGTT
 701  AGTGA
```

SEQ ID NO. 54
Modified 6.22.2 Kappa Light Chain Amino Acid Sequence

```
   1  mlpsqligfl llwvpasrgE IVLTQSPDFQ SVTPKEKVTI TCRASQRIGS
  51  SLHWYQQKPD QSPKLLIKYA SQSFSGVPSR FSGSGSGTDF TLTINSLEAE
 101  DAATYYCHQS GRLPLTFGGG TKVEIKRTVA APSVFIFPPS DEQLKSGTAS
 151  VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
 201  SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC
```

SEQ ID NO. 55

Modified 6.34.2 Heavy Chain Nucleotide Sequence

```
   1  atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt
  51  ccagtgtCAG GTGCAGCTGG TGGAGTCTGG GGGAGGCGTG GTCCAGCCTG
 101  GGAGGTCCCT GAGACTCTCC TGTGCAGCCT CTGGATTCAC CTTCAGTAGC
 151  TATGGCATGC ACTGGGTCCG CCAGGCTCCA GGCAAGGGGC TGGAGTGGGT
 201  GGCAGTTATA TCAAATGATG GAAATAATAA ATACTATGCA GACTCCGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAATT CCAAAAACAC GCTGTATCTG
 301  CAAATGAACA GCCTGCGCGC TGAGGACACG GCTGTGTATT ACTGTGCGAG
 351  AGATAGTACG GCGATAACCT ACTACTACTA CGGAATGGAC GTCTGGGGCC
 401  AAGGGACCAC GGTCACCGTC TCCTCAGCTT CCACCAAGGG CCCATCCGTC
 451  TTCCCCCTGG CGCCCTGCTC TAGAAGCACC TCCGAGAGCA CAGCGGCCCT
 501  GGGCTGCCTG GTCAAGGACT ACTTCCCCGA ACCGGTGACG GTGTCGTGGA
 551  ACTCAGGCGC TCTGACCAGC GGCGTGCACA CCTTCCCAGC TGTCCTACAG
 601  TCCTCAGGAC TCTACTCCCT CAGCAGCGTG GTGACCGTGC CCTCCAGCAA
 651  CTTCGGCACC CAGACCTACA CCTGCAACGT AGATCACAAG CCCAGCAACA
 701  CCAAGGTGGA CAAGACAGTT GAGCGCAAAT GTTGTGTCGA GTGCCCACCG
 751  TGCCCAGCAC CACCTGTGGC AGGACCGTCA GTCTTCCTCT TCCCCCCAAA
 801  ACCCAAGGAC ACCCTCATGA TCTCCCGGAC CCCTGAGGTC ACGTGCGTGG
 851  TGGTGGACGT GAGCCACGAA GACCCCGAGG TCCAGTTCAA CTGGTACGTG
 901  GACGGCGTGG AGGTGCATAA TGCCAAGACA AAGCCACGGG AGGAGCAGTT
 951  CAACAGCACG TTCCGTGTGG TCAGCGTCCT CACCGTTGTG CACCAGGACT
1001  GGCTGAACGG CAAGGAGTAC AAGTGCAAGG TCTCCAACAA AGGCCTCCCA
1051  GCCCCCATCG AGAAAACCAT CTCCAAAACC AAAGGGCAGC CCCGAGAACC
1101  ACAGGTGTAC ACCCTGCCCC CATCCCGGGA GGAGATGACC AAGAACCAGG
1151  TCAGCCTGAC CTGCCTGGTC AAAGGCTTCT ACCCCAGCGA CATCGCCGTG
1201  GAGTGGGAGA GCAATGGGCA GCCGGAGAAC AACTACAAGA CCACACCTCC
1251  CATGCTGGAC TCCGACGGCT CCTTCTTCCT CTACAGCAAG CTCACCGTGG
1301  ACAAGAGCAG GTGGCAGCAG GGGAACGTCT TCTCATGCTC CGTGATGCAT
1351  GAGGCTCTGC ACAACCACTA CACGCAGAAG AGCCTCTCCC TGTCTCCGGG
1401  TAAATGATAG
```

SEQ ID NO. 56
Modified 6.34.2 Heavy Chain Amino Acid Sequence

```
   1  mefglswvfl vallrgvqcQ VQLVESGGGV VQPGRSLRLS CAASGFTFSS
  51  YGMHWVRQAP GKGLEWVAVI SNDGNNKYYA DSVKGRFTIS RDNSKNTLYL
 101  QMNSLRAEDT AVYYCARDST AITYYYYGMD VWGQGTTVTV SSASTKGPSV
 151  FPLAPCSRST SESTAALGCL VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ
 201  SSGLYSLSSV VTVPSSNFGT QTYTCNVDHK PSNTKVDKTV ERKCCVECPP
 251  CPAPPVAGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVQFNWYV
 301  DGVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP
 351  APIEKTISKT KGQPREPQVY TLPPSREEMT KNQVSLTCLV KGFYPSDIAV
 401  EWESNGQPEN NYKTTPPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH
 451  EALHNHYTQK SLSLSPGK
```

SEQ ID NO. 57
Modified 6.34.2 Kappa Light Chain Nucleotide Sequence

```
   1  atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct
  51  ccgaggtgcc agatgtGACA TCCAGATGAC CCAGTCTCCA TCCTCCCTGT
 101  CTGCATCTGT CGGAGACAGA GTCACCATCA CTTGCCGGGC AAGTCAGAGT
 151  ATTAGTAGCT ATTTAAATTG GTATCAGCAG AAACCAGGGA AAGCCCCTAA
 201  GCTCCTGATC TATGCTGCAT CCGGTTTGAA GCGTGGGGTC CCATCACGGT
 251  TCAGTGGTAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGTTCTCTG
 301  CAACCTGAGG ATTTTGCAAC TTACTACTGT CACCAGAGTT ACAGTCTCCC
 351  ATTCACTTTC GGCCCTGGGA CCAAAGTGGA TATCAAACGA ACTGTGGCTG
 401  CACCATCTGT CTTCATCTTC CCGCCATCTG ATGAGCAGTT GAAATCTGGA
 451  ACTGCCTCTG TTGTGTGCCT GCTGAATAAC TTCTATCCCA GAGAGGCCAA
 501  AGTACAGTGG AAGGTGGATA ACGCCCTCCA ATCGGGTAAC TCCCAGGAGA
 551  GTGTCACAGA GCAGGACAGC AAGGACAGCA CCTACAGCCT CAGCAGCACC
 601  CTGACGCTGA GCAAAGCAGA CTACGAGAAA CACAAAGTCT ACGCCTGCGA
 651  AGTCACCCAT CAGGGCCTGA GCTCGCCCGT CACAAAGAGC TTCAACAGGG
 701  GAGAGTGTTA GTGA
```

SEQ ID NO. 58
Modified 6.34.2 Kappa Light Chain Amino Acid Sequence

```
   1  mdmrvpaqll glllwlrga rcDIQMTQSP SSLSASVGDR VTITCRASQS
  51  ISSYLNWYQQ KPGKAPKLLI YAASGLKRGV PSRFSGSGSG TDFTLTISSL
 101  QPEDFATYYC HQSYSLPFTF GPGTKVDIKR TVAAPSVFIF PPSDEQLKSG
 151  TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST
 201  LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC
```

SEQ ID NO. 59

Modified 6.67.1 Heavy Chain Nucleotide Sequence

```
   1  atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt
  51  cctgtccCAG GTGCAGCTGC AGGAGTCGGG CCCAGGACTG GTGAAGCCTT
 101  CGGAGACCCT GTCCCTCACC TGCACTGTCT CTGGTGACTC CATCAGTAGT
 151  AACTATTGGA GCTGGATCCG GCAGCCCGCC GGGAAGGGAC TGGAGTGGAT
 201  TGGGCGTATC TATACCAGTG GGGGCACCAA CTCCAACCCC TCCCTCAGGG
 251  GTCGAGTCAC CATGTCAGTA GACACGTCCA AGAACCAGTT CTCTCTGAAA
 301  CTGAGTTCTG TGACCGCCGC GGACACGGCC GTGTATTACT GTGCGAGAGA
 351  TCGTATTACT ATAATTCGGG GACTTATTCC ATCCTTCTTT GACTACTGGG
 401  GCCAGGGAAC CCTGGTCACC GTCTCCTCAG CTTCCACCAA GGGCCCATCC
 451  GTCTTCCCCC TGGCGCCCTG CTCTAGAAGC ACCTCCGAGA GCACAGCGGC
 501  CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT
 551  GGAACTCAGG CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA
 601  CAGTCCTCAG GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG
 651  CAACTTCGGC ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA
 701  ACACCAAGGT GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA
 751  CCGTGCCCAG CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCCC
 801  AAAACCCAAG GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG
 851  TGGTGGTGGA CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC
 901  GTGGACGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCAC GGGAGGAGCA
 951  GTTCAACAGC ACGTTCCGTG TGGTCAGCGT CCTCACCGTT GTGCACCAGG
1001  ACTGGCTGAA CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC
1051  CCAGCCCCCA TCGAGAAAAC CATCTCCAAA ACCAAAGGGC AGCCCCGAGA
1101  ACCACAGGTG TACACCCTGC CCCCATCCCG GGAGGAGATG ACCAAGAACC
1151  AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTACCCCAG CGACATCGCC
1201  GTGGAGTGGG AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACACC
1251  TCCCATGCTG GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG
1301  TGGACAAGAG CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG
1351  CATGAGGCTC TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC
1401  GGGTAAATGA TAG
```

SEQ ID NO. 60
Modified 6.67.1 Heavy Chain Amino Acid Sequence

```
   1  mkhlwfflll vaaprwvlsQ VQLQESGPGL VKPSETLSLT CTVSGDSISS
  51  NYWSWIRQPA GKGLEWIGRI YTSGGTNSNP SLRGRVTMSV DTSKNQFSLK
 101  LSSVTAADTA VYYCARDRIT IIRGLIPSFF DYWGQGTLVT VSSASTKGPS
 151  VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL
 201  QSSGLYSLSS VVTVPSSNFG TQTYTCNVDH KPSNTKVDKT VERKCCVECP
 251  PCPAPPVAGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSH EDPEVQFNWY
 301  VDGVEVHNAK TKPREEQFNS TFRVVSVLTV VHQDWLNGKE YKCKVSNKGL
 351  PAPIEKTISK TKGQPREPQV YTLPPSREEM TKNQVSLTCL VKGFYPSDIA
 401  VEWESNGQPE NNYKTTPPML DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM
 451  HEALHNHYTQ KSLSLSPGK
```

SEQ ID NO. 61
Modified 6.67.1 Kappa Light Chain Nucleotide Sequence

```
   1   atggtgttgc agacccaggt cttcatttct ctgttgctct ggatctctgg
  51   tgcctacggg GACATCGTGA TGACCCAGTC TCCAGACTCC CTGGCTGTGT
 101   CTCTGGGCGA GAGGGCCACC ATCAACTGCA AGTCCAGCCA GAGTGTTTTA
 151   TACAGCTCCA ACAATAAGAA CTACTTAGCT TGGTACCAAC AGAAACCAGG
 201   ACAGCCTCCT AAATTGCTCA TTTACTGGGC ATCTATACGG GAATATGGGG
 251   TCCCTGACCG ATTCAGTGGC AGCGGGTCTG GGACAGATTT CACTCTCACC
 301   ATCAGCAGCC TGCAGGCTGA AGATGTGGCA GTTTATTTCT GTCAACAATA
 351   TTATAGTATT CCTCCCCTCA CTTTCGGCGG AGGGACCAAG GTGGAGATCA
 401   AACGAACTGT GGCTGCACCA TCTGTCTTCA TCTTCCCGCC ATCTGATGAG
 451   CAGTTGAAAT CTGGAACTGC CTCTGTTGTG TGCCTGCTGA ATAACTTCTA
 501   TCCCAGAGAG GCCAAAGTAC AGTGGAAGGT GGATAACGCC CTCCAATCGG
 551   GTAACTCCCA GGAGAGTGTC ACAGAGCAGG ACAGCAAGGA CAGCACCTAC
 601   AGCCTCAGCA GCACCCTGAC GCTGAGCAAA GCAGACTACG AGAAACACAA
 651   AGTCTACGCC TGCGAAGTCA CCCATCAGGG CCTGAGCTCG CCCGTCACAA
 701   AGAGCTTCAA CAGGGGAGAG TGTTAGTGA
```

SEQ ID NO. 62
Modified 6.67.1 Kappa Light Chain Amino Acid Sequence

```
   1   mvlqtqvfis lllwisgayg DIVMTQSPDS LAVSLGERAT INCKSSQSVL
  51   YSSNNKNYLA WYQQKPGQPP KLLIYWASIR EYGVPDRFSG SGSGTDFTLT
 101   ISSLQAEDVA VYFCQQYYSI PPLTFGGGTK VEIKRTVAAP SVFIFPPSDE
 151   QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY
 201   SLSSTLTLSK ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE C
```

SEQ ID NO. 63
Modified 6.77.1 Heavy Chain Nucleotide Sequence

```
   1  atggaactgg ggctccgctg ggttttcctt gttgctattt tagaaggtgt
  51  ccagtgtGAG GTGCAGCTGG TGGAGTCTGG GGGAGGCCTG GTCAAGCCTG
 101  GGGGGTCCCT GAGACTCTCC TGTGCAGCCT CTGGATTCAC CTTCAGTAGC
 151  TATAGCATGA ACTGGGTCCG CCAGGCTCCA GGGAAGGGGC TGGAGTGGGT
 201  CTCATCCATT AGTAGTAGTA GTAGTTACAT ATACTACGCA GACTCAGTGA
 251  AGGGCCGATT CACCATCTCC AGAGACAACG CCAAGAACTC ACTGTATCTG
 301  CAAATGAACA GCCTGAGAGC CGAGGACACG GCTGTGTATT ACTGTGCGAG
 351  AGATGGGTAT AGCAGTGGCT GGTCCTACTA CTACTACTAC GGTATGGACG
 401  TCTGGGGCCA AGGGACCACG GTCACCGTCT CCTCAGCTTC CACCAAGGGC
 451  CCATCCGTCT TCCCCCTGGC GCCCTGCTCT AGAAGCACCT CCGAGAGCAC
 501  AGCGGCCCTG GGCTGCCTGG TCAAGGACTA CTTCCCCGAA CCGGTGACGG
 551  TGTCGTGGAA CTCAGGCGCT CTGACCAGCG GCGTGCACAC CTTCCCAGCT
 601  GTCCTACAGT CCTCAGGACT CTACTCCCTC AGCAGCGTGG TGACCGTGCC
 651  CTCCAGCAAC TTCGGCACCC AGACCTACAC CTGCAACGTA GATCACAAGC
 701  CCAGCAACAC CAAGGTGGAC AAGACAGTTG AGCGCAAATG TTGTGTCGAG
 751  TGCCCACCGT GCCCAGCACC ACCTGTGGCA GGACCGTCAG TCTTCCTCTT
 801  CCCCCCAAAA CCCAAGGACA CCCTCATGAT CTCCCGGACC CCTGAGGTCA
 851  CGTGCGTGGT GGTGGACGTG AGCCACGAAG ACCCCGAGGT CCAGTTCAAC
 901  TGGTACGTGG ACGGCGTGGA GGTGCATAAT GCCAAGACAA AGCCACGGGA
 951  GGAGCAGTTC AACAGCACGT TCCGTGTGGT CAGCGTCCTC ACCGTTGTGC
1001  ACCAGGACTG GCTGAACGGC AAGGAGTACA AGTGCAAGGT CTCCAACAAA
1051  GGCCTCCCAG CCCCCATCGA GAAAACCATC TCCAAAACCA AAGGGCAGCC
1101  CCGAGAACCA CAGGTGTACA CCCTGCCCCC ATCCCGGGAG GAGATGACCA
1151  AGAACCAGGT CAGCCTGACC TGCCTGGTCA AAGGCTTCTA CCCCAGCGAC
1201  ATCGCCGTGG AGTGGGAGAG CAATGGGCAG CCGGAGAACA ACTACAAGAC
1251  CACACCTCCC ATGCTGGACT CCGACGGCTC CTTCTTCCTC TACAGCAAGC
1301  TCACCGTGGA CAAGAGCAGG TGGCAGCAGG GGAACGTCTT CTCATGCTCC
1351  GTGATGCATG AGGCTCTGCA CAACCACTAC ACGCAGAAGA GCCTCTCCCT
1401  GTCTCCGGGT AAATGATAG
```

SEQ ID NO. 64
Modified 6.77.1 Heavy Chain Protein Sequence

```
   1  melglrwvfl vailegvqcE VQLVESGGGL VKPGGSLRLS CAASGFTFSS
  51  YSMNWVRQAP GKGLEWVSSI SSSSSYIYYA DSVKGRFTIS RDNAKNSLYL
 101  QMNSLRAEDT AVYYCARDGY SSGWSYYYYY GMDVWGQGTT VTVSSASTKG
 151  PSVFPLAPCS RSTSESTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA
 201  VLQSSGLYSL SSVVTVPSSN FGTQTYTCNV DHKPSNTKVD KTVERKCCVE
 251  CPPCPAPPVA GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVQFN
 301  WYVDGVEVHN AKTKPREEQF NSTFRVVSVL TVVHQDWLNG KEYKCKVSNK
 351  GLPAPIEKTI SKTKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD
 401  IAVEWESNGQ PENNYKTTPP MLDSDGSFFL YSKLTVDKSR WQQGNVFSCS
 451  VMHEALHNHY TQKSLSLSPG K
```

SEQ ID NO. 65
Modified 6.77.1 Kappa Light Chain Nucleotide Sequence

```
   1  atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg
  51  atccagtgca GATATTGTGA TGACCCAGAC TCCACTCTCT CTGTCCGTCA
 101  CTCCTGGACA GCCGGCCTCC ATCTCCTGCA AGTCTAGTCA GAGCCTCCTG
 151  CTTAGTGATG GAAAGACCTA TTTGAATTGG TACCTGCAGA AGCCCGGCCA
 201  GCCTCCACAG CTCCTGATCT ATGAAGTTTC CAACCGGTTC TCTGGAGTGC
 251  CAGACAGGTT CAGTGGCAGC GGGTCAGGGA CAGATTTCAC ACTGAAAATC
 301  AGCCGGGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAAGTAT
 351  ACAGCTTATG TGCAGTTTTG GCCAGGGGAC CAAGCTGGAG ATCAAACGAA
 401  CTGTGGCTGC ACCATCTGTC TTCATCTTCC CGCCATCTGA TGAGCAGTTG
 451  AAATCTGGAA CTGCCTCTGT TGTGTGCCTG CTGAATAACT TCTATCCCAG
 501  AGAGGCCAAA GTACAGTGGA AGGTGGATAA CGCCCTCCAA TCGGGTAACT
 551  CCCAGGAGAG TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC
 601  AGCAGCACCC TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA
 651  CGCCTGCGAA GTCACCCATC AGGGCCTGAG CTCGCCCGTC ACAAAGAGCT
 701  TCAACAGGGG AGAGTGTTAG TGA
```

SEQ ID NO. 66
Modified 6.77.1 Kappa Light Chain Amino Acid Sequence

```
   1  mrlpaqllgl lmlwipgssa DIVMTQTPLS LSVTPGQPAS ISCKSSQSLL
  51  LSDGKTYLNW YLQKPGQPPQ LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI
 101  SRVEAEDVGV YSCMQSIQLM SSFGQGTKLE IKRTVAAPSV FIFPPSDEQL
 151  KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
 201  SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
```

SEQ ID NO. 67
Modified 7.26.4 Kappa Light Chain Nucleotide Sequence

```
   1   atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg
  51   atccagtgcg GATATTGTGA TGACCCAGAC TCCACTCTCT CTGTCCGTCA
 101   CCCCTGGACA GCCGGCCTCC ATCTCCTGCA AGTCTAGTCA GAGCCTCCTG
 151   TATAGTGATG GAAAGACCTA TTTGTTTTGG TACCTGCAGA AGCCAGGCCA
 201   GCCTCCACAG CTCCTGATCT ATGAAGTTTC CAACCGATTC TCTGGAGTGC
 251   CAGATAGGTT CAGTGGCAGC GGGTCAGGGA CAGATTTCAC ACTGAAAATC
 301   AGCCGGGTGG AGGCTGAGGA TGTTGGGGTT TATTACTGCA TGCAAAGTAT
 351   ACAGCTTCCG TGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGAA
 401   CTGTGGCTGC ACCATCTGTC TTCATCTTCC CGCCATCTGA TGAGCAGTTG
 451   AAATCTGGAA CTGCCTCTGT TGTGTGCCTG CTGAATAACT TCTATCCCAG
 501   AGAGGCCAAA GTACAGTGGA AGGTGGATAA CGCCCTCCAA TCGGGTAACT
 551   CCCAGGAGAG TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC
 601   AGCAGCACCC TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA
 651   CGCCTGCGAA GTCACCCATC AGGGCCTGAG CTCGCCCGTC ACAAAGAGCT
 701   TCAACAGGGG AGAGTGTTAG TGA
```

SEQ ID NO. 68
Modified 7.26.4 Kappa Light Chain Amino Acid Sequence

```
   1   mrlpaqllgl lmlwipgssa DIVMTQTPLS LSVTPGQPAS ISCKSSQSLL
  51   YSDGKTYLFW YLQKPGQPPQ LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI
 101   SRVEAEDVGV YYCMQSIQLP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL
 151   KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
 201   SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
```

SEQ ID NO: 148
X481.2 Heavy Chain Amino Acid Sequence

```
  1   QVQLVQSGAE VKKPGASVKV SCKASGYTFT SYGINWVRQA PGQGLEWMGW
 51   ISVYSGNTNY AQKVQGRVTM TADTSTSTAY MDLRSLRSDD TAVYYCAREG
101   SSSSGDYYYG MDVWGQGTTV TVSSASTKGP SVFPLAPCSR STSESTAALG
151   CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSNF
201   GTQTYTCNVD HKPSNTKVDK TVERKCCVEC PPCPAPPVAG PSVFLFPPKP
251   KDTLMISRTP EVTCVVVDVS HEDPEVQFNW YVDGVEVHNA KTKPREEQFN
300   STFRVVSVLT VVHQDWLNGK EYKCKVSNKG LPAPIEKTIS KTKGQPREPQ
351   VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPM
401   LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK
```

SEQ ID NO: 149
X481.2 Heavy Chain Nucleotide Sequence

```
1     ATGGACTGGA CCTGGAGCAT CCTTTTCTTG GTGGCAGCAG CAACAGGTGC
```

```
51    CCACTCCCAG GTTCAGCTGG TGCAGTCTGG AGCTGAGGTG AAGAAGCCTG
101   GGGCCTCAGT GAAGGTCTCC TGCAAGGCTT CTGGTTACAC CTTTACCAGC
151   TATGGTATCA ACTGGGTGCG ACAGGCCCCT GGACAAGGGC TTGAGTGGAT
201   GGGATGGATC AGCGTTTACA GTGGTAACAC AAACTATGCA CAGAAGGTCC
251   AGGGCAGAGT CACCATGACC GCAGACACAT CCACGAGCAC AGCCTACATG
301   GACCTGAGGA GCCTGAGATC TGACGACACG GCCGTGTATT ACTGTGCGAG
351   AGAGGGTAGC AGCTCGTCCG GAGACTACTA TTACGGTATG GACGTCTGGG
401   GCCAAGGGAC CACGGTCACC GTCTCCTCAG CCTCCACCAA GGGCCCATCG
451   GTCTTCCCCC TGGCGCCCTG CTCCAGGAGC ACCTCCGAGA GCACAGCGGC
501   CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT
551   GGAACTCAGG CGCTCTGACC AGCGGCGTGC ACACCTTCCC AGCTGTCCTA
601   CAGTCCTCAG GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG
651   CAACTTCGGC ACCCAGACCT ACACCTGCAA CGTAGATCAC AAGCCCAGCA
701   ACACCAAGGT GGACAAGACA GTTGAGCGCA AATGTTGTGT CGAGTGCCCA
751   CCGTGCCCAG CACCACCTGT GGCAGGACCG TCAGTCTTCC TCTTCCCCCC
801   AAAACCCAAG GACACCCTCA TGATCTCCCG GACCCCTGAG GTCACGTGCG
851   TGGTGGTGGA CGTGAGCCAC GAAGACCCCG AGGTCCAGTT CAACTGGTAC
901   GTGGACGGCG TGGAGGTGCA TAATGCCAAG ACAAAGCCAC GGGAGGAGCA
951   GTTCAACAGC ACGTTCCGTG TGGTCAGCGT CCTCACCGTT GTGCACCAGG
1001  ACTGGCTGAA CGGCAAGGAG TACAAGTGCA AGGTCTCCAA CAAAGGCCTC
1051  CCAGCCCCCA TCGAGAAAAC CATCTCCAAA ACCAAAGGGC AGCCCCGAGA
1101  ACCACAGGTG TACACCCTGC CCCCATCCCG GGAGGAGATG ACCAAGAACC
1151  AGGTCAGCCT GACCTGCCTG GTCAAAGGCT TCTACCCCAG CGACATCGCC
1201  GTGGAGTGGG AGAGCAATGG GCAGCCGGAG AACAACTACA AGACCACACC
1251  TCCCATGCTG GACTCCGACG GCTCCTTCTT CCTCTACAGC AAGCTCACCG
1301  TGGACAAGAG CAGGTGGCAG CAGGGGAACG TCTTCTCATG CTCCGTGATG
1351  CATGAGGCTC TGCACAACCA CTACACGCAG AAGAGCCTCT CCCTGTCTCC
1401  GGGAAAATGA TAG
```

SEQ ID NO: 150
X481.2 Light Chain Amino Acid Sequence

```
1    DIVMTQTPLS LSVTPGQPAS ISCKSSQSLL HTDGTTYLYW YLQKPGQPPQ
51   LLIYEVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGI YYCMQNIQLP
101  WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
151  VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
201  VTHQGLSSPV TKSFNRGEC
```

[0347] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a state integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0348] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

[0349] Definitions of the specific embodiments of the invention as claimed herein follow.

[0340] In a first aspect, the invention relates to an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain, or an antigen-binding portion thereof, and a light chain, or an antigen-binding portion thereof, of a human monoclonal antibody that specifically binds to Mucosal Adressin Cell Adhesion Molecule (MAdCAM), wherein the nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof comprises SEQ ID NO: 149 and the nucleotide sequence that encodes the light chain or an antigen-binding portion thereof comprises SEQ ID NO: 35.

[0341] In a second aspect, the invention relates to a vector comprising the nucleic acid molecule according to the first aspect.

[0342] In a third aspect, the invention relates to a host cell comprising the vector according to the second aspect.

[0343] In a fourth aspect, the invention relates to a host cell comprising a first nucleic acid sequence encoding a heavy chain, or an antigen-binding portion thereof, and a second nucleic acid sequence encoding a light chain, or an antigen-binding portion thereof, of a monoclonal antibody that binds to human MAdCAM, wherein said first nucleic acid has a sequence of SEQ ID NO: 149, and the second nucleic acid has a sequence of SEQ ID NO: 35.

[0344] In a fifth aspect, the invention relates to a method for producing a human monoclonal antibody or antigen-binding portion thereof that specifically binds MAdCAM,

comprising culturing the host cell according to the third aspect of the fourth aspect under suitable conditions and recovering said antibody or antigen-binding portion.

[0345] In a sixth aspect, the invention relates to a method of manufacturing a human monoclonal antibody or an antigen-binding fragment portion thereof that specifically binds to Mucosal Adressin Cell Adhesion Molecule (MAdCAM), wherein the nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof comprises SEQ ID NO: 149 and the nucleotide sequence that encodes the light chain or an antigen-binding portion thereof comprises SEQ ID NO: 35.

[0346] In a seventh aspect, the invention relates to a non-human transgenic animal or transgenic plant comprising a first nucleic acid sequence encoding a heavy chain, or an antigen-binding portion thereof; and a second nucleic acid sequence encoding a light chain, or an antigen-binding portion thereof, of a monoclonal antibody that binds to human MAdCAM, wherein said first nucleic acid has a sequence of SEQ ID NO: 149, and the second nucleic acid has a sequence of SEQ ID NO: 35.

Claims

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain, or an antigen-binding portion thereof, and a light chain, or an antigen-binding portion thereof, of a human monoclonal antibody that specifically binds to Mucosal Adressin Cell Adhesion Molecule (MAdCAM), wherein the nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof comprises SEQ ID NO: 149 and the nucleotide sequence that encodes the light chain or an antigen-binding portion thereof comprises SEQ ID NO: 35.

2. The isolated nucleic acid molecule of claim 1, wherein the nucleotides defined by SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence; or

wherein the nucleotides defined by SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.

3. A vector comprising the nucleic acid molecule of claim 1 or 2.

4. The vector of claim 3 comprising an expression control sequence operably linked to the nucleic acid molecule.

5. A host cell comprising the vector of claim 3 or 4 or the nucleic acid molecule of claim 1 or 2.

6. A host cell comprising a first nucleic acid sequence encoding a heavy chain, or an antigen-binding portion thereof, and a second nucleic acid sequence encoding a light chain, or an antigen-binding portion thereof, of a monoclonal antibody that binds to human MAdCAM, wherein said first nucleic acid has a sequence of SEQ ID NO: 149, and the second nucleic acid has a sequence of SEQ ID NO: 35.

7. The host cell of claim 6, wherein the sequence of SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence; or

wherein the sequence of SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.

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8. A method for producing a human monoclonal antibody or antigen-binding portion thereof that specifically binds MAdCAM, comprising culturing the host cell according to any one of claims 5-7 under suitable conditions and recovering said antibody or antigen-binding portion.

9. A method of manufacturing a human monoclonal antibody or an antigen-binding fragment portion thereof that specifically binds to Mucosal Adressin Cell Adhesion Molecule (MAdCAM), wherein the nucleotide sequence that encodes the heavy chain or an antigen-binding portion thereof comprises SEQ ID NO: 149 and the nucleotide sequence that encodes the light chain or an antigen-binding portion thereof comprises SEQ ID NO: 35.

10. The method of claim 9, wherein nucleotide sequence defined by SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence; or

wherein the nucleotide sequence defined by SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.

11. A non-human transgenic animal or transgenic plant comprising a first nucleic acid sequence encoding a heavy chain, or an antigen-binding portion thereof; and a second nucleic acid sequence encoding a light chain, or an antigen-binding portion thereof, of a monoclonal antibody that binds to human MAdCAM, wherein said first nucleic acid has a sequence of SEQ ID NO: 149, and the second nucleic acid has a sequence of SEQ ID NO: 35.

12. The non-human transgenic animal or transgenic plant of claim 11, wherein the sequence of SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence; or

wherein the sequence of SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.

Figure 1A

```
                                CDR1                    CDR2
VH3-15 Product          EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYL
1.7.2 Heavy chain       EVQLVESGGGLVKPGGSLRLSCVASGFTFTNAWMIWVRQAPGKGLEWVGRIKRKTDGGTTDYAAPVKGRFTISRDDSKNTLYL
1.8.2 Heavy chain       EVQLVESGGGLVKPGGSLRLSCVVSGFTFTNAWMIWVRQAPGKGLEWVGRIKRKTDGGTTDYAAPVKGRFTISRDDSKNTLYL

                                                CDR3
VH3-15 Product          QMNSLKTEDTAVYYCTT--VA-DYWGQGTLVTVSSA
1.7.2 Heavy chain       QMNSLKTEDTAVYYCTTGGVAEDYWGQGTLVTVSSA
1.8.2 Heavy chain       QMNSLKTEDTAVYYCTTGGVAEDYWGQGTLVTVSSA
```

Figure 1B

```
                                CDR1                    CDR2
VH-3-23 Product         EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQM
6.14.2 Heavy chain      EVQLLESGGGLVQPGGSLRLSCAASGLTFNNSAMTWVRQAPGKGLEWVSTTSGSGGTTYYADSVKGRFTISRDSPKNTLYLQM

                                                CDR3
VH-3-23 Product         NSLRAEDTAVYYCAA-GYSYG-----YWGQGTLVTVSSA
6.14.2 Heavy chain NSLRAEDTAVYYCAARGYSYGTTPYEYWGQGTLVTVSSA
```

Figure 1C

```
                                    CDR1                                CDR2
VH3-33 Product
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ
6.22.2 Heavy chain
QVQLVESGGGVVQPGRSLRLSCAASGHTFSSDGMHWVRQAPGKGLEWVAIIWYDGSNKYYADSVKGRFTISRDNSKNTLYLQ

                                    CDR3
VH3-33 Product          MNSLRAEDTAVYYCAR---YYYGMDVWGQGTTVTVSSA
6.22.2 Heavy chain      MNSLRAEDTAVYYCARDPGYYYGMDVWGQGTTVTVSSA
```

Figure 1D

```
                                    CDR1                                CDR2
VH3-30 Product
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVKGRFTISRDNSKNTLYLQ
6.34.2 Heavy chain
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISNDGNNKYYADSVKGRFTISRDNSKNTLYLQ

                                    CDR3
VH3-30 Product          MNSLRAEDTAVYYCAR--TVVTYYYYGMDVWGQGTTVTVSSA
6.34.2 Heavy chain      MNSLSAEDTAVYYCARDSTAITYYYYGMDVWGQGTTVTVSSA
```

Figure 1E

```
VH4-4 Product                    CDR1                CDR2
QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMSVDTSKNQFSLKL
6.67.1 Heavy chain
QVQLQESGPGLVKPSETLSLTCTVSGDSISSNYWSWIRQPAGKGLEWIGRIYTSGGTNSNPSLRGRVTILADTSKNQFSLKL

                                 CDR3
VH4-4 Product       SSVTAADTAVYYCAR--ITMVRGVI---FDYWGQGTLVTVSSA
6.67.1 Heavy chain SSVTAADTAVYYCARDRITIIRGLIPSFFDYWGQGTLVTVSSA
```

Figure 1F

```
VH3-23 Product                   CDR1                CDR2
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQ
6.73.2 Heavy chain
EVQLLESGGDLVQPGGSLRLSCAASGFTFRSYAMNWVRQAPGKGLEWVSVISGRGGTTYYADSVKGRFTISRDNSKNTLYLQ

                                 CDR3
VH3-23 Product       MNSLRAEDTAVYYCA-IAVA----YYYYGMDVWGQGTTVTVSSA
6.73.2 Heavy chain   MNSLRAEDAAVYYCAKIAVAGEGLYYYYGMDVWGQGTTVTVSSA
```

Figure 1G

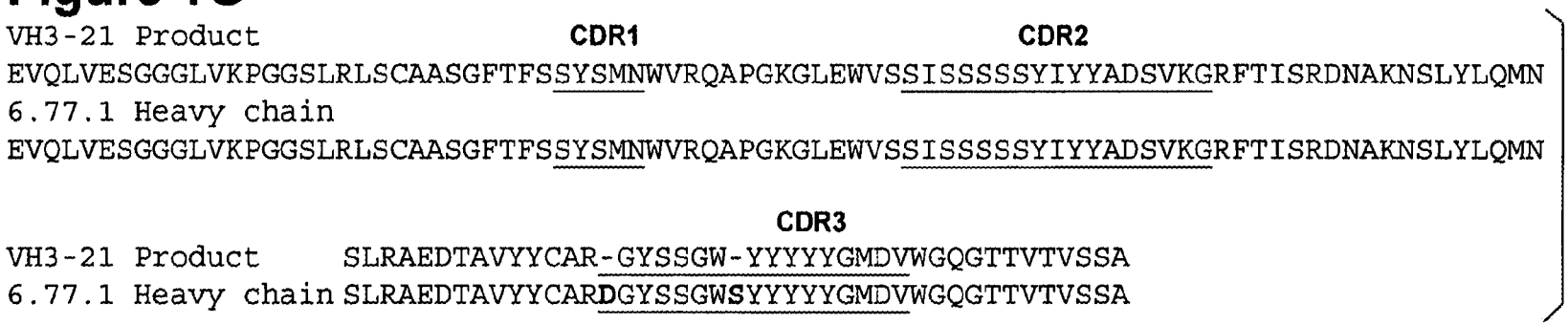

Figure 1H

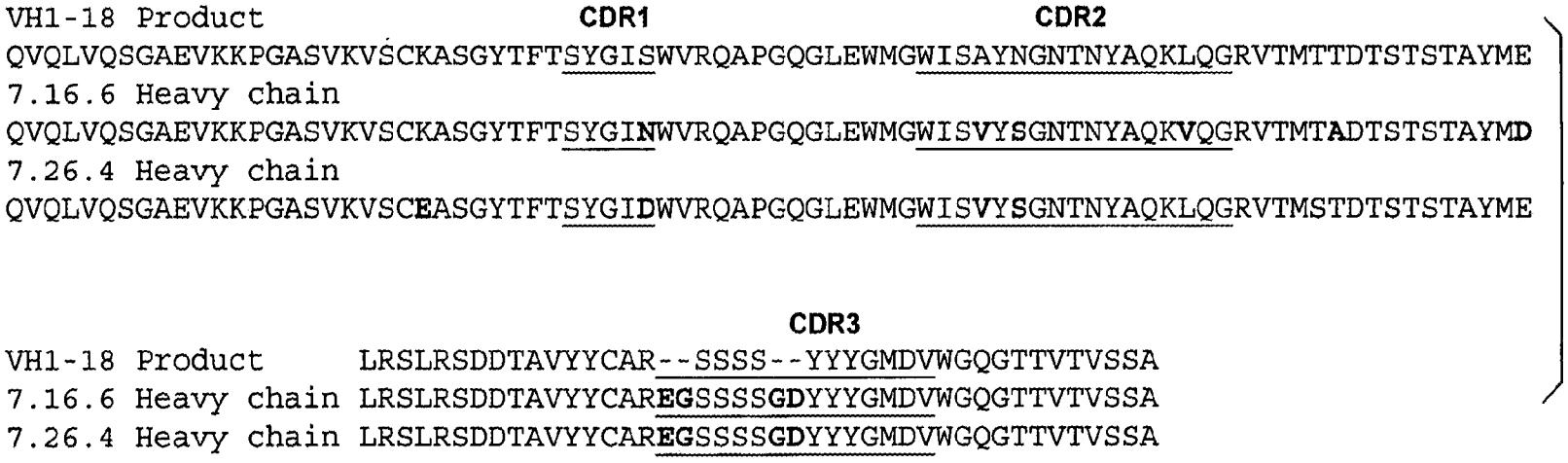

Figure 1I

```
VH4-4 Product                    CDR1                CDR2
QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMSVDTSKNQFSLKLSS
7.20.5 Heavy chain
QVQLQESGPGLVKPSETLSLTCTVSGSSISSYHWNWIRQPAGKGLEWIGRIYTSGSTNYNPSLKSRVTMSLDTSKNQFSLKLSS

                                 CDR3
VH4-4 Product      VTAADTAVYYCAR----YYYGSGS-YYGMDVWGQGTTVTVSSA
7.20.5 Heavy chain VTAADTAVYYCAREGVRYYYASGSYYYGLDVWGQGTTVTVSSA
```

Figure 1J

```
VH3-33 Product                   CDR1                CDR2
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNKYYADSVKGRFTISRDN
9.8.2 Heavy chain
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNEYYADSVKGRFTISRDN

                                 CDR3
VH3-33 Product     SKNTLYLQMNSLRAEDTAVYYCA-----FDYWGQGTLVTVSSA
9.8.2 Heavy chain  SKNTLYLQMNSLRAEDTAVYYCARGAYHFAYWGQGTLVTVSSA
```

Figure 1K

```
                                  CDR1                                CDR2
A3 Product          DIVMTQSPLSLPVTPGEPASISCRSSQSLLQSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSG
1.7.2 Kappa chain   DIVMTQSPLSLPVTPGEPASISCRSSQSLLQSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSG
1.8.2 Kappa chain   DIVMTQSPLSLPVTPGEPASISCRSSQSLLQSNGFNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSG

                                  CDR3
A3 Product          SGSGTDFTLKISRVEAEDVGVYYCMQALQTITFGQGTRLEIKR
1.7.2 Kappa chain   SGSGTDFTLKISRVEAEDVGVYYCMQALQTITFGQGTRLEIKR
1.8.2 Kappa chain   SGSGTDFTLKISRVEAEDVGVYYCMQALQTITFGQGTRLEIKR
```

Figure 1L

```
                                  CDR1                                CDR2
O12 Product         DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKVLIFAASSLQSGVPSRFSGS
6.14.2 Kappa chain  DIQMTQSPSSLSASVGDRVTITCRASRSISSYLNWYQQKPGKAPKVLIFFVSSLQSGVPSRFSGS

                                  CDR3
O12 Product         GSGTDFTLTISSLQPEDFATYYCQQSYSTP-TFGQGTRLEIKR
6.14.2 Kappa chain  GSGTDFTLTISSLQPEDFATYYCQQNYIPPTTFGQGTRLEIRR
```

Figure 1M

```
                                  CDR1                                CDR2
A26 Product         EIVLTQSPDFQSVTPKEKVTITCRASQSIGSSLHWYQQKPDQSPKLLIKYASQSFTGVPSRFSGS
6.22.2 Kappa chain  EIVLTQSPDFQSVTPKEKVTITCRASQRIGSSLHWYQQKPDQSPKLLIKYASQSFSGVPSRFSGS

                                  CDR3
A26 Product         GSGTDFTLTINSLEAEDAATYYCHQSSSL--TFGGGTKVEIKR
6.22.2 Kappa chain  GSGTNFTLTINGLEAEDAATYYCHQSGRLPLTFGGGTKVEIKR
```

Figure 1N

```
                                              CDR1                       CDR2
O12 Product         DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLSQGVPSRFSGS
6.34.2 Kappa chain  DIQMTQSPSSLSASVGDRVTITCRASQNISSYLNWFQQKPGKAPKLLIYAASGLKRGVPSRFSGS

                                              CDR3
O12 Product         GSGTDFTLTISSLQPEDFATYYCQQSYSTPFTFGPGTKVDIKR
6.34.2 Kappa chain  GSGTDFTLTIRTLQPDDFATYSCHQSYSLPFTFGPGTKVDIKR
```

Figure 1O

```
B3 Product                        CDR1                   CDR2
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSG
6.67.1 Kappa chain
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKTYLAWYQQKPRQPPKLLIYWASIREYGVPDRFSGSG

                                            CDR3
B3 Product          SGTDFTLTISSLQAEDVAVYYCQQYYSTP-LTFGGGTKVEIKR
6.67.1 Kappa chain  SGTDFTLTISSLQAEDVAVYFCQQYYSIPPLTFGGGTKVEIKR
```

Figure 1P

```
                                CDR1                CDR2
012 Product          DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
6.73.2 Kappa chain   DIQMTQSPSSLSASVGDRVTFTCRASQNITNYLNWYQQKPGKAPKLLIYAASSLPRGVPSRFRGSGS

                                CDR3
012 Product          GTDFTLTISSLQPEDFATYYCQQSYSTP----FGQGTTLDIKR
6.73.2 Kappa chain   GTDFTLTISSLQPEDFATYYCQQSYSNPPECGFGQGTTLDIKR
```

Figure 1Q

```
                                CDR1                CDR2
A2 Product           DIVMTQTPLSLSVTPGQPASISCKSSQSLLHSDGKTYLYWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGS
6.77.1 Kappa chain   DIVMTQTPLSLSVTPGQPASISCNSSQSLLLSDGKTYLNWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGS

                                CDR3
A2 Product           GSGTDFTLKISRVEAEDVGVYYCMQSIQL----FGQGTKLEIKR
6.77.1 Kappa chain   GSGTDFTLKISRVEAEDVGVYSCMQSIQLMCSFGQGTKLEIKR
```

Figure 1R

```
                                CDR1                CDR2
A2 product           DIVMTQTPLSLSVTPGQPASISCKSSQSLLHSDGKTYLYWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGS
7.16.6 Kappa chain   DIVMTQTPLSLSVTPGQPASISCKSSQSLLHTDGTTYLYWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGS
7.26.4 Kappa chain   DIVMTQTPLSLSVTPGQPASISCKSNQSLLYSDGKTYLFWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGS

                                CDR3
A2 product           GSGTDFTLKISRVEAEDVGVYYCMQSIQLPWTFGQGTKVEIKR
7.16.6 Kappa chain   GSGTDFTLKISRVEAEDVGIYYCMQNIQLPWTFGQGTKVEIKR
7.26.4 Kappa chain   GSGTDFTLKISRVEAEDVGVYYCMQSIQLPWTFGQGTKVEIKR
```

Figure 1S

```
                                  CDR1                                CDR2
A3 Product          DIVMTQSPLSLPVTPGEPASISCRSSQSLLHGNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSG
7.20.5 Kappa chain  DIVMTQSPLSLPVTPGEPASISCRSSQSLLHGNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSG

                                  CDR3
A3 Product          SGSGTDFTLKISRVEAEDVGVYYCMQALQTLTFGGGTKVEIKR
7.20.5 Kappa chain  SGSGTDFTLKISRVEAEDVGVYYCMQALQTLTFGGGTKVEIKR
```

Figure 1T

```
                                  CDR1                                CDR2
O18 Product         DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGS
9.8.2 Kappa chain   DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPSRFSGS

                                  CDR3
O18 Product         GSGTDFTFTISSLQPEDIATYYCQQYDNL-ITFGQGTRLEIKR
9.8.2 Kappa chain   GSGTDFTFTISSLQPEDIATYSCQHSDNLSITFGQGTRLEIKR
```

Figure 2A

```
1.7.2      --MRLPAQLLGLLMLWVS--GSSGDIVMTQSPLSLPVTPGEPASISCRSSQSLLQS-NGY
1.8.2      --MRLPAQLLGLLMLWVS--GSSGDIVMTQSPLSLPVTPGEPASISCRSSQSLLQS-NGF
7.20.5     --MRLPAQLLGLLMLWVS--GSSGDIVMTQSPLSLPVTPGEPASISCRSSQSLLHG-NGY
7.16.6     --MRLPAQLLGLLMLWIP--GSSADIVMTQTPLSLSVTPGQPASISCKSSQSLLHT-DGT
7.26.4     --MRLPAQLLGLLMLWIP--GSSADIVMTQTPLSLSVTPGQPASISCKSNQSLLYS-DGK
6.77.1     --MRLPAQLLGLLMLWIP--GSSADIVMTQTPLSLSVTPGQPASISCNSSQSLLLS-DGK
6.67.1     --MVLQTQVFISLLLWIS--GAYGDIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNK
6.34.2     MDMRVPAQLLGLLLLWLR--GARCDIQMTQSPSSLSASVGDRVTITCRASQNISSY----
6.73.2     MDMRVPAQLLGLLLLWLR--GARCDIQMTQSPSSLSASVGDRVTFTCRASQNITNY----
6.14.2     MDMRVPAQLLGLLLLWLR--GARCDIQMTQSPSSLSASVGDRVTITCRASRSISSY----
9.8.2      MDMRVPAQLLGLLLLWLSVAGARCDIQMTQSPSSLSASVGDRVTITCQASQDISNY----
6.22.2     ---MLPSQLIGFLLLWVP--ASRGEIVLTQSPDFQSVTPKEKVTITCRASQRIGSS----
                  : :*:::  *:**:  .:  :* :**:*   ..:  : .:::.*.:.: :

1.7.2      NYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ
1.8.2      NYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ
7.20.5     NYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ
7.16.6     TYLYWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQ
7.26.4     TYLFWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQ
6.77.1     TYLNWYLQKPGQPPQLLIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYSCMQ
6.67.1     TYLAWYQQKPRQPPKLLIYWASIREYGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCQQ
```

Figure 2A (cont.)

```
6.34.2      --LNWFQQKPGKAPKLLIYAASGLKRGVPSRFSGSGSGTDFTLTIRTLQPDDFATYSCHQ
6.73.2      --LNWYQQKPGKAPKLLIYAASSLPRGVPSRFRGSGSGTDFTLTISSLQPEDFATYYCQQ
6.14.2      --LNWYQQKPGKAPKVLIFFVSSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ
9.8.2       --LNWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYSCQH
6.22.2      --LHWYQQKPDQSPKLLIKYASQSFSGVPSRFSGSGSGTNFTLTINGLEAEDAATYYCHQ
              * *: *** :.*::**   *    ***.** ******:**:.*  :::.:* . * * :

1.7.2       ALQT---ITFGQGTRLEIKR
1.8.2       ALQT---ITFGQGTRLEIKR
7.20.5      ALQT---LTFGGGTKVEIKR
7.16.6      NIQLP--WTFGQGTKVEIKR
7.26.4      SIQLP--WTFGQGTKVEIKR
6.77.1      SIQLM--CSFGQGTKLEIKR
6.67.1      YYSIPP-LTFGGGTKVEIKR
6.34.2      SYSLP--FTFGPGTKVDIKR
6.73.2      SYSNPPECGFGQGTTLDIKR
6.14.2      NYIPP--ITFGQGTRLEIRR
9.8.2       SDNLS--ITFGQGTRLEIKR
6.22.2      SGRLP--LTFGGGTKVEIKR
                    ** ** ::*:*
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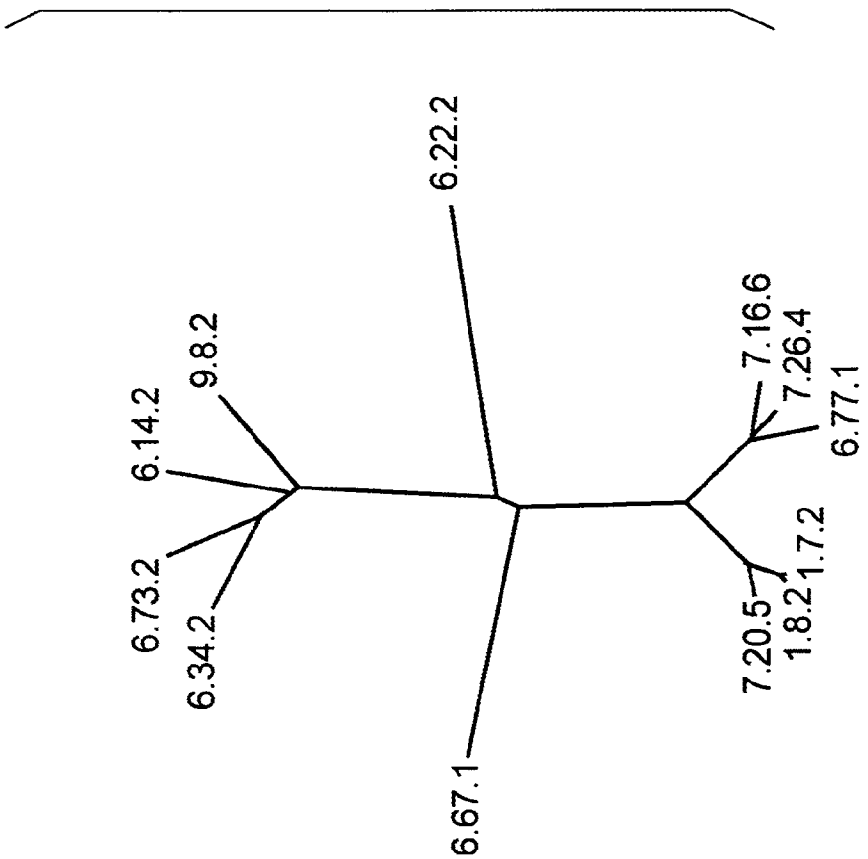

Figure 2A (cont.)

Figure 2B

```
7.16.6    QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGINWVRQAPGQGLEWMGWIS--VYSGNT
7.26.4    QVQLVQSGAEVKKPGASVKVSCEASGYTFTSYGIDWVRQAPGQGLEWMGWIS--VYSGNT
1.7.2     EVQLVESGGGLVKPGGSLRLSCVASGFTFTNAWMIWVRQAPGKGLEWVGRIKRKTDGGTT
1.8.2     EVQLVESGGGLVKPGGSLRLSCVVSGFTFTNAWMIWVRQAPGKGLEWVGRIKRKTDGGTT
6.14.2    EVQLLESGGGLVQPGGSLRLSCAASGLTFNNSAMTWVRQAPGKGLEWVSTTS--GSGGTT
6.73.2    EVQLLESGGDLVQPGGSLRLSCAASGFTFRSYAMNWVRQAPGKGLEWVSVIS--GRGGTT
6.77.1    EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSIS--SSSSYI
6.22.2    QVQLVESGGGVVQPGRSLRLSCAASGHTFSSDGMHWVRQAPGKGLEWVAIIW--YDGSNK
6.34.2    QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIS--NDGNNK
9.8.2     QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIW--YDGSNE
7.20.5    QVQLQESGPGLVKPSETLSLTCTVSGSSISSYHWNWIRQPAGKGLEWIGRIY---TSGST
6.67.1    QVQLQESGPGLVKPSETLSLTCTVSGDSISSNYWSWIRQPAGKGLEWIGRIY---TSGGT
          :*** :**  : :*. :: ::* .** :: .     *:**..*:****:.      ..

7.16.6    NYAQKVQGRVTMTADTSTSTAYMDLRSLRSDDTAVYYCAREG-SS--SSGDYYYGMDVWG
7.26.4    NYAQKLQGRVTMSTDTSTSTAFFLLRSLRSDDTAVYYCAREG-SS--SSGDYYYGMDVWG
1.7.2     DYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTGG-------VAEDY-----WG
1.8.2     DYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTGG-------VAEDY-----WG
6.14.2    YYADSVKGRFTISRDSPKNTLYLQMNSLRAEDTAVYYCAARG-YSYGTTPYEY-----WG
6.73.2    YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDAAVYYCAKIA-VAGEGLYYYYG-MDVWG
6.77.1    YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDG-YSSGWSYYYYYGMDVWG
6.22.2    YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARD--------PGYYYG-MDVWG
6.34.2    YYADSVKGRFTISRDNSKNTLYLQMNSLSAEDTAVYYCARDS-TA--ITYYYYG-MDVWG
9.8.2     YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARG----------AYH-FAYWG
7.20.5    NYNPSLKSRVTMSLDTSKNQFSLKLSSVTAADTAVYYCAREGVRYYYASGSYYYGLDVWG
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Figure 2B (cont.)

```
6.67.1      NSNPSLRGRVTILADTSKNQFSLKLSSVTAADTAVYYCARD--RITIIRGLIPSFFDYWG
                 ::.*.*:  * ...  : : *: : *:******:          **

7.16.6      QGTTVTVSSA
7.26.4      QGTTVTVSSA
1.7.2       QGTLVTVSSA
1.8.2       QGTLVTVSSA
6.14.2      QGTLVTVSSA
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6.77.1      QGTTVTVSSA
6.22.2      QGTTVTVSSA
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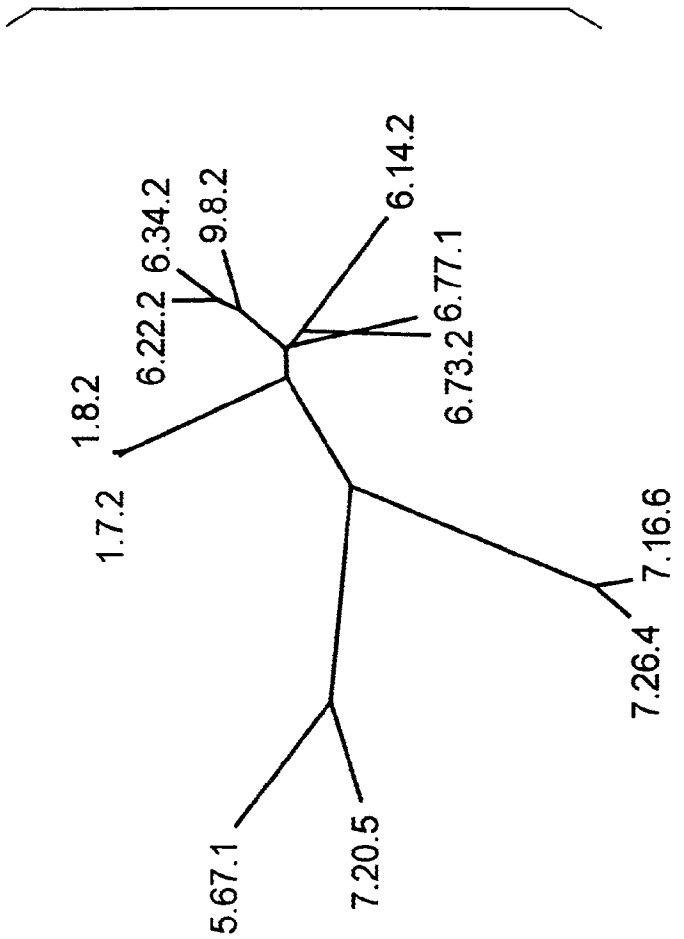

Figure 2B (cont.)

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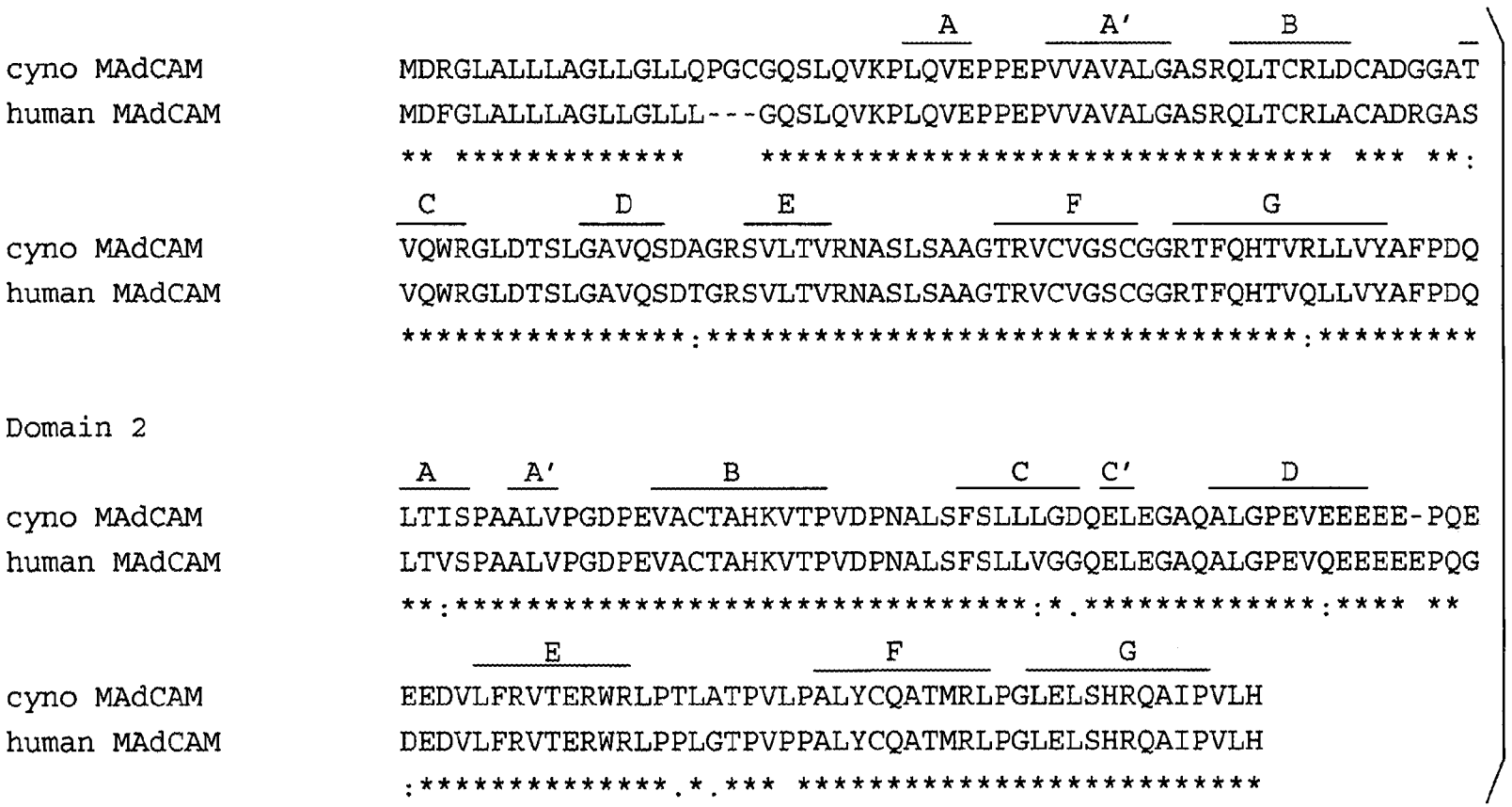

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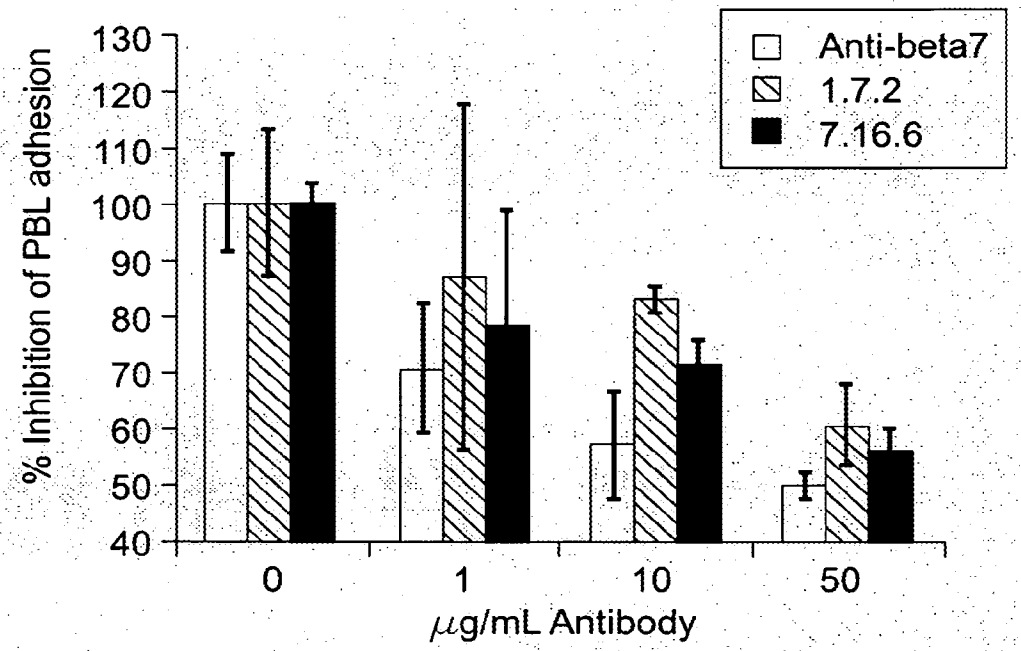

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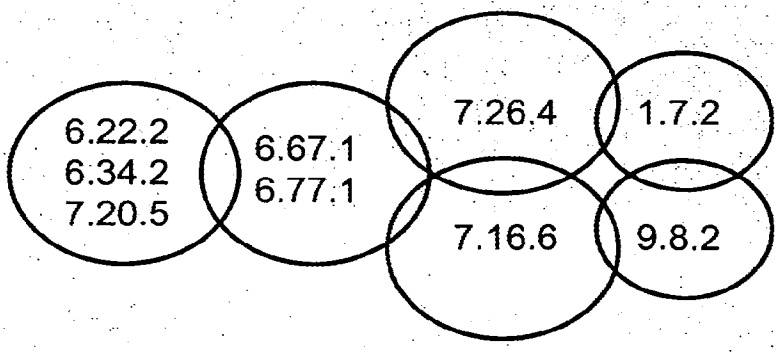

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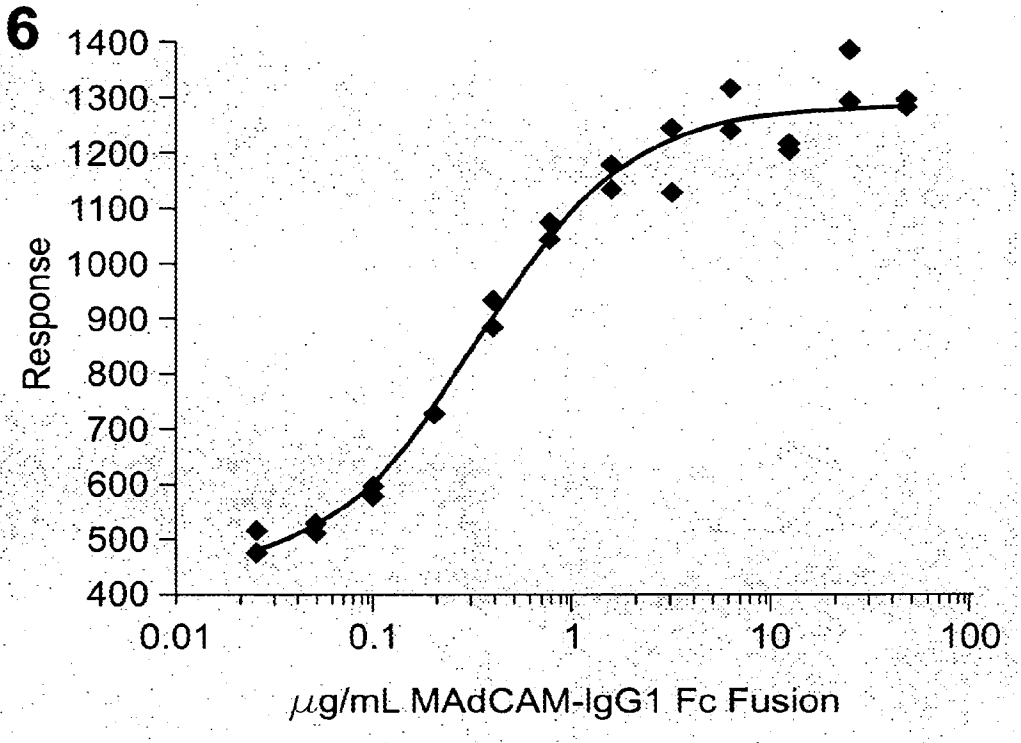

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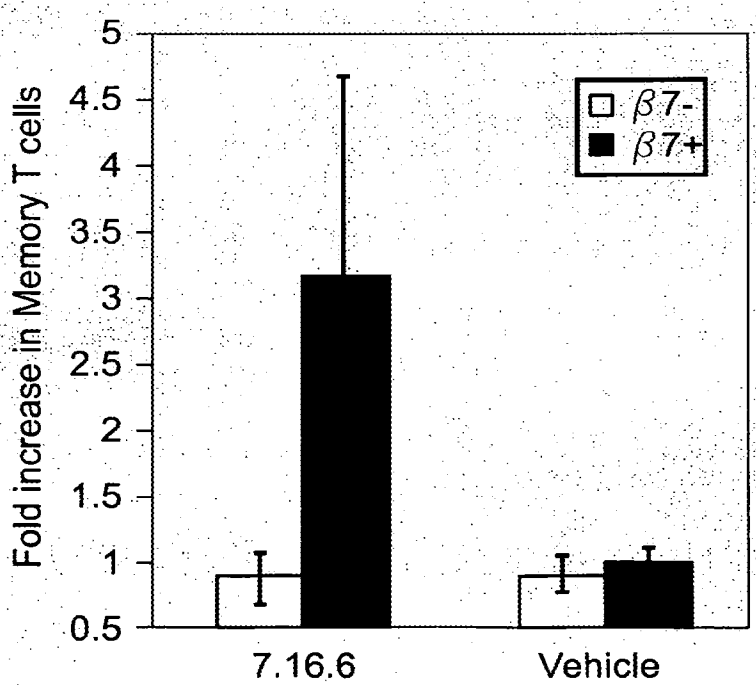

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Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr
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Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
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Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
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Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
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Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
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Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
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Cys Met Gln Ala Leu Gln Thr Ile Thr Phe Gly Gln Gly Thr Arg Leu
        115                 120                 125

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
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Glu Trp Val Gly Arg Ile Lys Arg Lys Thr Asp Gly Gly Thr Thr Asp
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Tyr Ala Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
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Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr
100 105 110

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Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
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Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
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Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
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Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
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Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His
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Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys
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Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
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Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
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Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile
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Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
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Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
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Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser
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Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
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Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
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Cys Met Gln Ala Leu Gln Thr Ile Thr Phe Gly Gln Gly Thr Arg Leu
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Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
    130                 135                 140

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
145                 150                 155                 160

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
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Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
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Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
        195                 200                 205

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


Asn Asn Ser Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60


Glu Trp Val Ser Thr Thr Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala
65                  70                  75                  80


Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Pro Lys Asn
                85                  90                  95


Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Ala Arg Gly Tyr Ser Tyr Gly Thr Thr Pro Tyr Glu
        115                 120                 125


Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140


Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160
```

```
Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
225                 230                 235                 240

Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
        275                 280                 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
            340                 345                 350
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365


Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
            420                 425                 430


Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460


Leu Gly Lys
465


<210>  11
<211>  711
<212>  DNA
<213>  Homo sapiens

<400>  11
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggggcc       60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggagacaga      120

gtcaccatca cttgccgggc aagtcggagc attagcagct atttaaattg gtatcagcag      180

aaaccaggga aagcccctaa agtcctgatc ttttttgtgt ccagtttgca aagtggggtc      240

ccatcaaggt tcagtggcag tggctctggg acagatttca ctctcaccat cagcagtctg      300
```

caacctgaag attttgcaac ttactactgt caacagaatt acattccccc tattaccttc 360

ggccagggga cacgactgga gatcagacga actgtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta g 711

<210> 12
<211> 236
<212> PRT
<213> Homo sapiens

<400> 12

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Arg Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Val Leu Ile Phe Phe Val Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

```
Asn Tyr Ile Pro Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile
        115                 120                 125

Arg Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 13
<211> 1398
<212> DNA
<213> Homo sapiens

<400> 13

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atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag       60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc      120

tgtgcagcgt ctggacacac cttcagtagc gatggcatgc actgggtccg ccaggctcca      180

ggcaaggggc tggagtgggt ggcaattata tggtatgatg gaagtaataa atattatgca      240
```

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtatatt actgtgcgag agatcccggc 360

tactattacg gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctcagcttcc 420

accaagggcc catccgtctt ccccctggcg ccctgctcca ggagcacctc cgagagcaca 480

gccgccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 540

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc 600

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcacgaa gacctacacc 660

tgcaacgtag atcacaagcc cagcaacacc aaggtggaca agagagttga gtccaaatat 720

ggtcccccat gcccatcatg cccagcacct gagttcctgg ggggaccatc agtcttcctg 780

ttcccccaa aacccaagga cactctcatg atctcccgga cccctgaggt cacgtgcgtg 840

gtggtggacg tgagccagga agaccccgag gtccagttca actggtacgt ggatggcgtg 900

gaggtgcata atgccaagac aaagccgcgg gaggagcagt tcaacagcac gtaccgtgtg 960

gtcagcgtcc tcaccgtcct gcaccaggac tggctgaacg gcaaggagta caagtgcaag 1020

gtctccaaca aaggcctccc gtcctccatc gagaaaacca tctccaaagc caaagggcag 1080

ccccgagagc cacaggtgta caccctgccc ccatcccagg aggagatgac caagaaccag 1140

gtcagcctga cctgcctggt caaaggcttc taccccagcg acatcgccgt ggagtgggag 1200

agcaatgggc agccggagaa caactacaag accgcgcctc ccgtgctgga ctccgacggc 1260

tccttcttcc tctacagcag gctaaccgtg gacaagagca ggtggcagga ggggaatgtc 1320

ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacacagaa gagcctctcc 1380

ctgtctctgg gtaaatga 1398

<210> 14
<211> 465
<212> PRT
<213> Homo sapiens

<400> 14

```
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                  10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly His Thr Phe
        35                  40                  45

Ser Ser Asp Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Ile Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asp Pro Gly Tyr Tyr Tyr Gly Met Asp Val Trp
        115                 120                 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
    130                 135                 140

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190
```

```
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
225                 230                 235                 240

Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
                245                 250                 255

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
            260                 265                 270

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
        275                 280                 285

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
    290                 295                 300

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
305                 310                 315                 320

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
                325                 330                 335

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
            340                 345                 350

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
        355                 360                 365

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
    370                 375                 380
```

```
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
385                 390                 395                 400


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Ala Pro Pro Val Leu
                405                 410                 415


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
            420                 425                 430


Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
        435                 440                 445


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
    450                 455                 460


Lys
465


<210>  15
<211>  705
<212>  DNA
<213>  Homo sapiens

<400>  15
atgttgccat cacaactcat tgggtttctg ctgctctggg ttccagcttc caggggtgaa       60

attgtgctga ctcagtctcc agactttcag tctgtgactc caaaagagaa agtcaccatc      120

acctgccggg ccagtcagag aattggtagt agcttacact ggtaccagca gaaaccagat      180

cagtctccaa aactcctcat caagtatgct tcccagtcct tctcaggggt cccctcgagg      240

ttcagtggca gtggatctgg gacaaatttc accctcacca tcaatggcct ggaagctgaa      300

gatgctgcaa cttattactg tcatcagagt ggtcgtttac cgctcacttt cggcggaggg      360

accaaggtgg agatcaaacg aactgtggct gcaccatctg tcttcatctt cccgccatct      420

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc      480

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag      540
```

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 600

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 660

agctcgcccg tcacaaagag cttcaacagg ggagagtgtt agtga 705

<210> 16
<211> 233
<212> PRT
<213> Homo sapiens

<400> 16

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

Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val
20 25 30

Thr Pro Lys Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Arg Ile
35 40 45

Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys
50 55 60

Leu Leu Ile Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asn Phe Thr Leu Thr Ile Asn Gly
85 90 95

Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Ser Gly Arg
100 105 110

Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
115 120 125

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
130 135 140

```
Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145                 150                 155                 160


Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
                165                 170                 175


Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
            180                 185                 190


Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
        195                 200                 205


Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
    210                 215                 220


Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  17
<211>  1410
<212>  DNA
<213>  Homo sapiens

<400>  17
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag       60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc      120

tgtgcagcct ctggattcac cttcagtagc tatggcatgc actgggtccg ccaggctcca      180

ggcaaggggc tggagtgggt ggcagttata tcaaatgatg gaaataataa atactatgca      240

gactccgtga agggccgatt caccatctcc agagacaatt ccaaaaacac gctgtatctg      300

caaatgaaca gcctgagcgc tgaggacacg gctgtgtatt actgtgcgag agatagtacg      360

gcgataacct actactacta cggaatggac gtctggggcc aagggaccac ggtcaccgtc      420

tcctcagctt ccaccaaggg cccatccgtc ttcccctgg cgccctgctc caggagcacc      480
```

tccgagagca cagccgccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacg 660

aagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagagagtt 720

gagtccaaat atggtccccc atgcccatca tgcccagcac ctgagttcct gggggggacca 780

tcagtcttcc tgttcccccc aaaacccaag gacactctca tgatctcccg gacccctgag 840

gtcacgtgcg tggtggtgga cgtgagccag gaagaccccg aggtccagtt caactggtac 900

gtggatggcg tggaggtgca taatgccaag acaaagccgc gggaggagca gttcaacagc 960

acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccgtcctcca tcgagaaaac catctccaaa 1080

gccaaagggc agccccgaga gccacaggtg tacaccctgc ccccatccca ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

gtggagtggg agagcaatgg acagccggag aacaactaca agaccacgcc tcccgtgctg 1260

gactccgacg gctccttctt cctctacagc aggctaaccg tggacaagag caggtggcag 1320

gaggggaatg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacacag 1380

aagagcctct ccctgtctct gggtaaatga 1410

<210> 18
<211> 469
<212> PRT
<213> Homo sapiens

<400> 18

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

```
Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Ser Asn Asp Gly Asn Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Ser Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asp Ser Thr Ala Ile Thr Tyr Tyr Tyr Tyr Gly
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145                 150                 155                 160

Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
    210                 215                 220
```

```
Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
225                 230                 235                 240


Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe
                245                 250                 255


Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            260                 265                 270


Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        275                 280                 285


Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    290                 295                 300


Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
305                 310                 315                 320


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                325                 330                 335


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            340                 345                 350


Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        355                 360                 365


Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    370                 375                 380


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                405                 410                 415
```

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
420 425 430

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
435 440 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
450 455 460

Leu Ser Leu Gly Lys
465

<210> 19
<211> 714
<212> DNA
<213> Homo sapiens

<400> 19
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt cggagacaga 120

gtcaccatca cttgccgggc aagtcagaat attagtagct atttaaattg gtttcagcag 180

aaaccaggga aagcccctaa gctcctgatc tatgctgcat ccggtttgaa gcgtggggtc 240

ccatcacggt tcagtggtag tggatctggg acagatttca ctctcaccat caggactctg 300

caacctgatg attttgcaac ttactcctgt caccagagtt acagtctccc attcactttc 360

ggccctggga ccaaagtgga tatcaaacga actgtggctg caccatctgt cttcatcttc 420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 480

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta gtga 714

<210> 20

<211> 236
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

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

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Gly Leu Lys Arg Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Arg Thr Leu Gln Pro Asp Asp Phe Ala Thr Tyr Ser Cys His Gln
            100                 105                 110

Ser Tyr Ser Leu Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175
```

```
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  21
<211>  1413
<212>  DNA
<213>  Homo sapiens

<400>  21
atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt cctgtcccag       60

gtgcagctgc aggagtcggg cccaggactg gtgaagcctt cggagaccct gtccctcacc      120

tgcactgtct ctggtgactc catcagtagt aactattgga gctggatccg gcagcccgcc      180

gggaagggac tggagtggat tgggcgtatc tataccagtg ggggcaccaa ctccaacccc      240

tccctcaggg gtcgagtcac cattttagca gacacgtcca agaaccagtt ctctctgaaa      300

ctgagttctg tgaccgccgc ggacacggcc gtgtattact gtgcgagaga tcgtattact      360

ataattcggg gacttattcc atccttcttt gactactggg gccagggaac cctggtcacc      420

gtctcctcag cttccaccaa gggcccatcc gtcttccccc tggcgccctg ctccaggagc      480

acctccgaga gcacagccgc cctgggctgc ctggtcaagg actacttccc cgaaccggtg      540

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta      600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc      660

acgaagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaga      720
```

gttgagtcca aatatggtcc cccatgccca tcatgcccag cacctgagtt cctgggggga 780

ccatcagtct tcctgttccc cccaaaaccc aaggacactc tcatgatctc ccggacccct 840

gaggtcacgt gcgtggtggt ggacgtgagc caggaagacc ccgaggtcca gttcaactgg 900

tacgtggatg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagttcaac 960

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaacggcaag 1020

gagtacaagt gcaaggtctc caacaaaggc ctcccgtcct ccatcgagaa aaccatctcc 1080

aaagccaaag ggcagccccg agagccacag gtgtacaccc tgcccccatc ccaggaggag 1140

atgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctaccc cagcgacatc 1200

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 1260

ctggactccg acggctcctt cttcctctac agcaggctaa ccgtggacaa gagcaggtgg 1320

caggagggga atgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacaca 1380

cagaagagcc tctccctgtc tctgggtaaa tga 1413

<210> 22
<211> 470
<212> PRT
<213> Homo sapiens

<400> 22

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile
35 40 45

Ser Ser Asn Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu
50 55 60

```
Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly Gly Thr Asn Ser Asn Pro
65                  70                  75                  80

Ser Leu Arg Gly Arg Val Thr Ile Leu Ala Asp Thr Ser Lys Asn Gln
                85                  90                  95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

Tyr Cys Ala Arg Asp Arg Ile Thr Ile Ile Arg Gly Leu Ile Pro Ser
        115                 120                 125

Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145                 150                 155                 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        195                 200                 205

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr
    210                 215                 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
225                 230                 235                 240

Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu
                245                 250                 255
```

```
Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
            260                 265                 270


Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
        275                 280                 285


Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
    290                 295                 300


Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
305                 310                 315                 320


Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
                325                 330                 335


Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
            340                 345                 350


Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
        355                 360                 365


Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
    370                 375                 380


Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
385                 390                 395                 400


Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
                405                 410                 415


Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
            420                 425                 430


Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
        435                 440                 445
```

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
450 455 460

Ser Leu Ser Leu Gly Lys
465 470

<210> 23
<211> 729
<212> DNA
<213> Homo sapiens

<400> 23
atggtgttgc agacccaggt cttcatttct ctgttgctct ggatctctgg tgcctacggg 60

gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 120

atcaactgca agtccagcca gagtgtttta tacagctcca acaataagac ctacttagct 180

tggtaccaac agaaaccaag acagcctcct aaattgctca tttactgggc atctatacgg 240

gaatatgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 300

atcagcagcc tgcaggctga agatgtggca gtttatttct gtcaacaata ttatagtatt 360

cctcccctca ctttcggcgg agggaccaag gtggagatca aacgaactgt ggctgcacca 420

tctgtcttca tcttcccgcc atctgatgag cagttgaaat ctggaactgc ctctgttgtg 480

tgcctgctga ataacttcta tcccagagag gccaaagtac agtggaaggt ggataacgcc 540

ctccaatcgg gtaactccca ggagagtgtc acagagcagg acagcaagga cagcacctac 600

agcctcagca gcaccctgac gctgagcaaa gcagactacg agaaacacaa agtctacgcc 660

tgcgaagtca cccatcaggg cctgagctcg cccgtcacaa agagcttcaa caggggagag 720

tgttagtga 729

<210> 24
<211> 241
<212> PRT
<213> Homo sapiens

<400> 24

```
Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1               5                  10                  15

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
        35                  40                  45

Val Leu Tyr Ser Ser Asn Asn Lys Thr Tyr Leu Ala Trp Tyr Gln Gln
    50                  55                  60

Lys Pro Arg Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ile Arg
65                  70                  75                  80

Glu Tyr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
                85                  90                  95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
            100                 105                 110

Phe Cys Gln Gln Tyr Tyr Ser Ile Pro Pro Leu Thr Phe Gly Gly Gly
        115                 120                 125

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175

Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu
            180                 185                 190
```

```
Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205


Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220


His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240


Cys
```

<210> 25
<211> 1419
<212> DNA
<213> Homo sapiens

<400> 25

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atggagtttg ggctgagctg gctttttctt gtggctattt taaaaggtgt ccagtgtgag       60

gtgcagctgt tggagtctgg gggagacttg gtccagcctg gggggtccct gagactctcc      120

tgtgcagcct ctggattcac ctttagaagt tatgccatga actgggtccg acaggctcca      180

gggaaggggc tggagtgggt ctcagttatt agtggtcgtg gtggtactac atactacgca      240

gactccgtga agggccggtt caccatctcc agagacaatt ccaagaacac gctgtatctg      300

caaatgaaca gcctgagagc cgaggacgcg gccgtatatt actgtgcgaa gatagcagtg      360

gctggagagg ggctctacta ctactacggt atggacgtct ggggccaagg gaccacggtc      420

accgtctcct cagcttccac caagggccca tccgtcttcc ccctggcgcc ctgctccagg      480

agcacctccg agaacacagc cgccctgggc tgcctggtca aggactactt ccccgaaccg      540

gtgacggtgt cgtggaactc aggcgccctg accagcggcg tgcacacctt cccggctgtc      600

ctacagtcct caggactcta ctccctcagc agcgtggtga ccgtgccctc tagcagcttg      660

ggcacgaaga cctacacctg caacgtagat cacaagccca gcaacaccaa ggtggacaag      720

agagttgagt ccaaatatgg tcccccatgc ccatcatgcc cagcacctga gttcctgggg      780
```

ggaccatcag tcttcctgtt ccccccaaaa cccaaggaca ctctcatgat ctcccggacc 840

cctgaggtca cgtgcgtggt ggtggacgtg agccaggaag accccgaggt ccagttcaac 900

tggtacgtgg atggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagttc 960

aacagcacgt accgtgtggt cagcgtcctc accgtcctgc accaggactg gctgaacggc 1020

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccgt cctccatcga gaaaaccatc 1080

tccaaagcca aggggcagcc ccgagagcca caggtgtaca ccctgccccc atcccaggag 1140

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac 1200

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc 1260

gtgctggact ccgacggctc cttcttcctc tacagcaggc taaccgtgga caagagcagg 1320

tggcaggagg ggaatgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1380

acacagaaga gcctctccct gtctctgggt aaatgatag 1419

<210> 26
<211> 471
<212> PRT
<213> Homo sapiens

<400> 26

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Asp Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Arg Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Val Ile Ser Gly Arg Gly Gly Thr Thr Tyr Tyr Ala
65 70 75 80

```
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ala Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Lys Ile Ala Val Ala Gly Glu Gly Leu Tyr Tyr Tyr
        115                 120                 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
    130                 135                 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145                 150                 155                 160

Ser Thr Ser Glu Asn Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
                165                 170                 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
            180                 185                 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
        195                 200                 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
    210                 215                 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225                 230                 235                 240

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
                245                 250                 255

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270
```

```
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    290                 295                 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
305                 310                 315                 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
                325                 330                 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            340                 345                 350

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
        355                 360                 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
    370                 375                 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            420                 425                 430

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
        435                 440                 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    450                 455                 460
```

Leu Ser Leu Ser Leu Gly Lys
465 470

<210> 27
<211> 720
<212> DNA
<213> Homo sapiens

<400> 27
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc 60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt aggtgacaga 120

gtcaccttca cttgccgggc aagtcagaac attaccaact atttaaattg gtatcagcag 180

aaaccaggga aggcccctaa gctcctgatc tatgctgcgt ccagtttgcc aagaggggtc 240

ccatcaaggt tccgtggcag tggatctggg acagatttca ctctcaccat cagcagtctg 300

caacctgaag attttgcaac ttactactgt caacagagtt acagtaatcc tccggagtgc 360

ggttttggcc aggggaccac gctggatatc aaacgaactg tggctgcacc atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttagtga 720

<210> 28
<211> 238
<212> PRT
<213> Homo sapiens

<400> 28

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

```
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Phe Thr Cys Arg Ala Ser
        35                  40                  45

Gln Asn Ile Thr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Pro Arg Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Ser Tyr Ser Asn Pro Pro Glu Cys Gly Phe Gly Gln Gly Thr Thr Leu
        115                 120                 125

Asp Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
    130                 135                 140

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
145                 150                 155                 160

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
            180                 185                 190

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
        195                 200                 205
```

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 29
<211> 1434
<212> DNA
<213> Homo sapiens

<400> 29
atggaactgg ggctccgctg ggttttcctt gttgctattt tagaaggtgt ccagtgtgag 60

gtgcagctgg tggagtctgg gggaggcctg gtcaagcctg gggggtccct gagactctcc 120

tgtgcagcct ctggattcac cttcagtagc tatagcatga actgggtccg ccaggctcca 180

gggaaggggc tggagtgggt ctcatccatt agtagtagta gtagttacat atactacgca 240

gactcagtga agggccgatt caccatctcc agagacaacg ccaagaactc actgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agatgggtat 360

agcagtggct ggtcctacta ctactactac ggtatggacg tctggggcca agggaccacg 420

gtcaccgtct cctcagcttc caccaagggc ccatccgtct tccccctggc gccctgctcc 480

aggagcacct ccgagagcac agccgccctg ggctgcctgg tcaaggacta cttccccgaa 540

ccggtgacgg tgtcgtggaa ctcaggcgcc ctgaccagcg gcgtgcacac cttcccggct 600

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcagc 660

ttgggcacga agacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac 720

aagagagttg agtccaaata tggtccccca tgcccatcat gcccagcacc tgagttcctg 780

gggggaccat cagtcttcct gttcccccca aaacccaagg acactctcat gatctcccgg 840

acccctgagg tcacgtgcgt ggtggtggac gtgagccagg aagaccccga ggtccagttc 900

aactggtacg tggatggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 960

ttcaacagca cgtaccgtgt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaac 1020

ggcaaggagt acaagtgcaa ggtctccaac aaaggcctcc cgtcctccat cgagaaaacc 1080

atctccaaag ccaaagggca gccccgagag ccacaggtgt acaccctgcc cccatcccag 1140

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctaccccagc 1200

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1260

cccgtgctgg actccgacgg ctccttcttc ctctacagca ggctaaccgt ggacaagagc 1320

aggtggcagg aggggaatgt cttttcacgc tccgtgatgc atgaggctct gcacaaccac 1380

tacacacaga agagcctctc cctgtctctg ggtaaatgat aggaattctg atga 1434

<210> 30
<211> 472
<212> PRT
<213> Homo sapiens

<400> 30

Met Glu Leu Gly Leu Arg Trp Val Phe Leu Val Ala Ile Leu Glu Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

```
Tyr Tyr Cys Ala Arg Asp Gly Tyr Ser Ser Gly Trp Ser Tyr Tyr Tyr
        115                 120                 125

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
    130                 135                 140

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
145                 150                 155                 160

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                165                 170                 175

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
            180                 185                 190

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
        195                 200                 205

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
    210                 215                 220

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
225                 230                 235                 240

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala
                245                 250                 255

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            260                 265                 270

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        275                 280                 285

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
    290                 295                 300
```

```
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
305                 310                 315                 320

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                325                 330                 335

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
            340                 345                 350

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        355                 360                 365

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
    370                 375                 380

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
385                 390                 395                 400

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                405                 410                 415

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            420                 425                 430

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
        435                 440                 445

Ser Arg Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    450                 455                 460

Ser Leu Ser Leu Ser Leu Gly Lys
465                 470
```

<210> 31
<211> 723

<212> DNA
<213> Homo sapiens

<400> 31
atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg atccagtgca 60

gatattgtga tgacccagac tccactctct ctgtccgtca ctcctggaca gccggcctcc 120

atctcctgca actctagtca gagcctcctg cttagtgatg gaaagaccta tttgaattgg 180

tacctgcaga agcccggcca gcctccacag ctcctgatct atgaagtttc caaccggttc 240

tctggagtgc cagacaggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 300

agccgggtgg aggctgagga tgttggggtt tattcctgca tgcaaagtat acagcttatg 360

tgcagttttg gccaggggac caagctggag atcaaacgaa ctgtggctgc accatctgtc 420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 720

tga 723

<210> 32
<211> 239
<212> PRT
<213> Homo sapiens

<400> 32

Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Ile Pro
1 5 10 15

Gly Ser Ser Ala Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
20 25 30

Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Asn Ser Ser Gln Ser
35 40 45

```
Leu Leu Leu Ser Asp Gly Lys Thr Tyr Leu Asn Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Ser
            100                 105                 110

Cys Met Gln Ser Ile Gln Leu Met Cys Ser Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 33
<211> 1410
<212> DNA
<213> Homo sapiens

<400> 33
atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc ccactcccag 60

gttcagctgg tgcagtctgg agctgaggtg aagaagcctg gggcctcagt gaaggtctcc 120

tgcaaggctt ctggttacac ctttaccagc tatggtatca actgggtgcg acaggcccct 180

ggacaagggc ttgagtggat gggatggatc agcgtttaca gtggtaacac aaactatgca 240

cagaaggtcc agggcagagt caccatgacc gcagacacat ccacgagcac agcctacatg 300

gacctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agagggtagc 360

agctcgtccg gagactacta ttacggtatg gacgtctggg gccaagggac cacggtcacc 420

gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcgccctg ctccaggagc 480

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 660

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 720

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 780

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gacccctgag 840

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 900

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 960

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1080

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1260

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1320

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1380

aagagcctct ccctgtctcc gggtaaatga 1410

<210> 34
<211> 469
<212> PRT
<213> Homo sapiens

<400> 34

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

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Trp Ile Ser Val Tyr Ser Gly Asn Thr Asn Tyr Ala
65 70 75 80

Gln Lys Val Gln Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser
85 90 95

Thr Ala Tyr Met Asp Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Glu Gly Ser Ser Ser Ser Gly Asp Tyr Tyr Tyr
115 120 125

```
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145                 150                 155                 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        195                 200                 205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
    210                 215                 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
225                 230                 235                 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
                245                 250                 255

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            260                 265                 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    290                 295                 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
305                 310                 315                 320
```

```
Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
                325                 330                 335

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
            340                 345                 350

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
        355                 360                 365

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                405                 410                 415

Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460

Leu Ser Pro Gly Lys
465
```

<210> 35
<211> 723
<212> DNA
<213> Homo sapiens

<400> 35
atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg atccagtgca 60

gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 120

atctcctgca agtctagtca gagcctcctg catactgatg gaacgaccta tttgtattgg 180

tacctgcaga agccaggcca gcctccacag ctcctgatct atgaagtttc caaccggttc 240

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 300

agccgggtgg aggctgagga tgttgggatt tattactgca tgcaaaatat acagcttccg 360

tggacgttcg gccaagggac caaggtggaa atcaaacgaa ctgtggctgc accatctgtc 420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 720

tga 723

<210> 36
<211> 239
<212> PRT
<213> Homo sapiens

<400> 36

Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Ile Pro
1 5 10 15

Gly Ser Ser Ala Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
20 25 30

Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser
35 40 45

Leu Leu His Thr Asp Gly Thr Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys
50 55 60

```
Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe
65                  70                  75                  80


Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95


Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr
            100                 105                 110


Cys Met Gln Asn Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125


Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140


Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160


Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175


Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190


Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205


Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220


Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  37
<211>  1416
<212>  DNA
<213>  Homo sapiens
```

<400> 37
atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt cctgtcccag 60

gtgcagctgc aggagtcggg cccaggactg gtgaagcctt cggagaccct gtccctcacc 120

tgcactgtct ctggtagctc catcagtagt taccactgga actggatccg gcagcccgcc 180

gggaagggac tggagtggat tgggcgtatc tataccagtg ggagcaccaa ctacaacccc 240

tccctcaaga gtcgagtcac catgtcacta gacacgtcca agaaccagtt ctccctgaag 300

ctgagctctg tgaccgccgc ggacacggcc gtgtattact gtgcgagaga gggggtcagg 360

tattactatg cttcggggag ttattactac ggtctggacg tctggggcca agggaccacg 420

gtcaccgtct cctcagcctc caccaagggc ccatcggtct tccccctggc gccctgctcc 480

aggagcacct ccgagagcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 540

ccggtgacgg tgtcgtggaa ctcaggcgct ctgaccagcg gcgtgcacac cttcccagct 600

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac 660

ttcggcaccc agacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac 720

aagacagttg agcgcaaatg ttgtgtcgag tgcccaccgt gcccagcacc acctgtggca 780

ggaccgtcag tcttcctctt cccccaaaa cccaaggaca ccctcatgat ctcccggacc 840

cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac 900

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccacggga ggagcagttc 960

aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc 1020

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag cccccatcga gaaaaccatc 1080

tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1140

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac 1200

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc 1260

atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1320

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1380

acgcagaaga gcctctccct gtctccgggt aaatga 1416

<210> 38
<211> 471
<212> PRT
<213> Homo sapiens

<400> 38

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Ser Ile
35 40 45

Ser Ser Tyr His Trp Asn Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu
50 55 60

Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro
65 70 75 80

Ser Leu Lys Ser Arg Val Thr Met Ser Leu Asp Thr Ser Lys Asn Gln
85 90 95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Glu Gly Val Arg Tyr Tyr Tyr Ala Ser Gly Ser Tyr
115 120 125

Tyr Tyr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
130 135 140

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
145 150 155 160

```
Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                165                 170                 175

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
            180                 185                 190

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
        195                 200                 205

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
    210                 215                 220

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
225                 230                 235                 240

Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    290                 295                 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
305                 310                 315                 320

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
                325                 330                 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            340                 345                 350
```

```
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
        355                 360                 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    370                 375                 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            420                 425                 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        435                 440                 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    450                 455                 460

Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 39
<211> 720
<212> DNA
<213> Homo sapiens

<400> 39

```
atgaggctcc ctgctcagct cctggggctg ctaatgctct gggtctctgg atccagtggg       60

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc      120

atctcctgca ggtctagtca gagcctcctg catggtaatg gatacaacta tttggattgg      180

tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc      240
```

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 300

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactctc 360

actttcggcg gagggaccaa ggtggagatc aaacgaactg tggctgcacc atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttagtga 720

<210> 40
<211> 238
<212> PRT
<213> Homo sapiens

<400> 40

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

Gly Ser Ser Gly Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro
20 25 30

Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
35 40 45

Leu Leu His Gly Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys
50 55 60

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

```
Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
            100                 105                 110


Cys Met Gln Ala Leu Gln Thr Leu Thr Phe Gly Gly Gly Thr Lys Val
        115                 120                 125


Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
    130                 135                 140


Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
145                 150                 155                 160


Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175


Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
            180                 185                 190


Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
        195                 200                 205


Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
    210                 215                 220


Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  41
<211>  1410
<212>  DNA
<213>  Homo sapiens

<400>  41
atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc ccactcccag       60

gttcagctgg tgcagtctgg agctgaggtg aagaagcctg gggcctcagt gaaggtctcc      120

tgcgaggctt ctggttacac ctttaccagc tatggtatcg actgggtgcg acaggcccct      180
```

ggacaagggc ttgagtggat gggatggatc agcgtttaca gtggtaacac aaactatgca 240

cagaagctcc agggcagagt caccatgtcc acagacacat ccacgagcac agcctacatg 300

gagctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agagggtagc 360

agctcgtccg gagactacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 420

gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcgccctg ctccaggagc 480

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 660

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 720

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 780

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 840

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 900

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 960

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccagccccca ttgagaaaac catctccaaa 1080

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1260

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1320

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1380

aagagcctct ccctgtctcc gggtaaatga 1410

<210> 42
<211> 469
<212> PRT
<213> Homo sapiens

<400> 42

```
Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Glu Ala Ser Gly Tyr Thr Phe
        35                  40                  45

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

Glu Trp Met Gly Trp Ile Ser Val Tyr Ser Gly Asn Thr Asn Tyr Ala
65                  70                  75                  80

Gln Lys Leu Gln Gly Arg Val Thr Met Ser Thr Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Ser Ser Ser Ser Gly Asp Tyr Tyr Tyr
        115                 120                 125

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145                 150                 155                 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190
```

```
Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        195                 200                 205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
    210                 215                 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
225                 230                 235                 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
                245                 250                 255

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            260                 265                 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    290                 295                 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
305                 310                 315                 320

Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
                325                 330                 335

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
            340                 345                 350

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
        355                 360                 365

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
    370                 375                 380
```

```
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                405                 410                 415


Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460


Leu Ser Pro Gly Lys
465


<210>  43
<211>  723
<212>  DNA
<213>  Homo sapiens

<400>  43
atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg atccagtgcg       60

gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc      120

atctcctgca agtctaatca gagcctcctg tatagtgatg gaaagaccta tttgttttgg      180

tacctgcaga agccaggcca gcctccacag ctcctgatct atgaagtttc caaccgattc      240

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc      300

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaagtat acagcttccg      360

tggacgttcg gccaagggac caaggtggaa atcaaacgaa ctgtggctgc accatctgtc      420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg      480
```

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 720

tga 723

<210> 44
<211> 239
<212> PRT
<213> Homo sapiens

<400> 44

Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Ile Pro
1 5 10 15

Gly Ser Ser Ala Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
20 25 30

Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Asn Gln Ser
35 40 45

Leu Leu Tyr Ser Asp Gly Lys Thr Tyr Leu Phe Trp Tyr Leu Gln Lys
50 55 60

Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
100 105 110

Cys Met Gln Ser Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys
115 120 125

```
Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235
```

<210> 45
<211> 1389
<212> DNA
<213> Homo sapiens

<400> 45

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atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag       60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc      120

tgtgcagcgt ctggattcac cttcagtagc tatggcatgc actgggtccg ccaggctcca      180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg gaagtaatga atactatgca      240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg      300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag gggggcgtac      360
```

cactttgcct actggggcca gggaaccctg gtcaccgtct cctcagcttc caccaagggc 420

ccatccgtct tccccctggc gccctgctcc aggagcacct ccgagagcac agccgccctg 480

ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgcc 540

ctgaccagcg gcgtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 600

agcagcgtgg tgaccgtgcc ctccagcagc ttgggcacga agacctacac ctgcaacgta 660

gatcacaagc ccagcaacac caaggtggac aagagagttg agtccaaata tggtccccca 720

tgcccatcat gcccagcacc tgagttcctg gggggaccat cagtcttcct gttcccccca 780

aaacccaagg acactctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac 840

gtgagccagg aagaccccga ggtccagttc aactggtacg tggatggcgt ggaggtgcat 900

aatgccaaga caaagccgcg ggaggagcag ttcaacagca cgtaccgtgt ggtcagcgtc 960

ctcaccgtcc tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 1020

aaaggcctcc cgtcctccat cgagaaaacc atctccaaag ccaaagggca gccccgagag 1080

ccacaggtgt acaccctgcc cccatcccag gaggagatga ccaagaacca ggtcagcctg 1140

acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg 1200

cagccggaga acaactacaa gaccacgcct cccgtgctgg actccgacgg ctccttcttc 1260

ctctacagca ggctaaccgt ggacaagagc aggtggcagg aggggaatgt cttctcatgc 1320

tccgtgatgc atgaggctct gcacaaccac tacacacaga agagcctctc cctgtctctg 1380

ggtaaatga 1389

<210> 46
<211> 462
<212> PRT
<213> Homo sapiens

<400> 46

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

```
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Ala Tyr His Phe Ala Tyr Trp Gly Gln Gly
        115                 120                 125

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
    130                 135                 140

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
145                 150                 155                 160

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
                165                 170                 175

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
            180                 185                 190

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
        195                 200                 205
```

```
Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
    210                 215                 220

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
225                 230                 235                 240

Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270

Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
        275                 280                 285

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400
```

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
405 410 415

Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
420 425 430

Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
450 455 460

<210> 47
<211> 720
<212> DNA
<213> Homo sapiens

<400> 47
atggacatga gggtccctgc tcagctcctg gggctcctgc tgctctggct ctcagtcgca 60

ggtgccagat gtgacatcca gatgacccag tctccatcct ccctgtctgc atctgtagga 120

gacagagtca ccatcacttg ccaggcgagt caggacatta gcaactattt aaattggtat 180

cagcagaaac cagggaaagc ccctaagctc ctgatctacg atgcatccaa tttggaaaca 240

ggggtcccat caaggttcag tggaagtgga tctgggacag attttacttt caccatcagc 300

agcctgcagc ctgaagatat tgcaacatat tcctgtcaac actctgataa tctctcgatc 360

accttcggcc aggggacacg actggagatt aaacgaactg tggctgcacc atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct accccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttagtga 720

<210> 48

<211> 238
<212> PRT
<213> Homo sapiens

<400> 48

```
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Leu Ser Val Ala Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro
            20                  25                  30

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln
        35                  40                  45

Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro
    50                  55                  60

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr
65                  70                  75                  80

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
                85                  90                  95

Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Ser Cys
            100                 105                 110

Gln His Ser Asp Asn Leu Ser Ile Thr Phe Gly Gln Gly Thr Arg Leu
        115                 120                 125

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
    130                 135                 140

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
145                 150                 155                 160

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
                165                 170                 175
```

```
Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
            180                 185                 190


Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
        195                 200                 205


Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
    210                 215                 220


Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  49
<211>  681
<212>  DNA
<213>  Macaca fascicularis

<400>  49
atggatcggg gcctggccct cctgctggcg gggcttctgg ggctcctcca gccgggctgc       60

ggccagtccc tccaggtgaa gcccctgcag gtggagcccc cggagccggt ggtggccgtg      120

gccctgggcg cctctcgcca gctcacctgc cgcctggact gcgcggacgg cggggccacg      180

gtgcagtggc ggggcctgga caccagcctg ggcgcggtgc agtcggacgc gggccgcagc      240

gtcctcaccg tgcgcaacgc ctcgctgtcg gcggccggga cccgtgtgtg cgtgggctcc      300

tgcgggggcc gcaccttcca gcacaccgtg cggctccttg tgtacgcctt cccggaccag      360

ctgaccatct ccccggcagc cctggtgcct ggtgacccgg aggtggcctg tacggctcac      420

aaagtcacgc ctgtggaccc caatgcgctc tccttctccc tgctcctggg ggaccaggaa      480

ctggaggggg cccaggctct gggcccggag gtggaggagg aggaggagcc ccaggaggag      540

gaggacgtgc tgttcagggt gacagagcgc tggcggctgc cgaccctggc aacccctgtc      600

ctgcccgcgc tctactgcca ggccacgatg aggctgcctg gcttggagct cagccaccgc      660

caggccatcc cggtcctgca c                                                 681
```

<210> 50
<211> 227
<212> PRT
<213> Macaca fascicularis

<400> 50

```
Met Asp Arg Gly Leu Ala Leu Leu Leu Ala Gly Leu Leu Gly Leu Leu
1               5                  10                  15


Gln Pro Gly Cys Gly Gln Ser Leu Gln Val Lys Pro Leu Gln Val Glu
            20                  25                  30


Pro Pro Glu Pro Val Val Ala Val Ala Leu Gly Ala Ser Arg Gln Leu
        35                  40                  45


Thr Cys Arg Leu Asp Cys Ala Asp Gly Gly Ala Thr Val Gln Trp Arg
    50                  55                  60


Gly Leu Asp Thr Ser Leu Gly Ala Val Gln Ser Asp Ala Gly Arg Ser
65                  70                  75                  80


Val Leu Thr Val Arg Asn Ala Ser Leu Ser Ala Ala Gly Thr Arg Val
                85                  90                  95


Cys Val Gly Ser Cys Gly Gly Arg Thr Phe Gln His Thr Val Arg Leu
            100                 105                 110


Leu Val Tyr Ala Phe Pro Asp Gln Leu Thr Ile Ser Pro Ala Ala Leu
        115                 120                 125


Val Pro Gly Asp Pro Glu Val Ala Cys Thr Ala His Lys Val Thr Pro
    130                 135                 140


Val Asp Pro Asn Ala Leu Ser Phe Ser Leu Leu Leu Gly Asp Gln Glu
145                 150                 155                 160
```

Leu Glu Gly Ala Gln Ala Leu Gly Pro Glu Val Glu Glu Glu Glu Glu
165 170 175

Pro Gln Glu Glu Glu Asp Val Leu Phe Arg Val Thr Glu Arg Trp Arg
180 185 190

Leu Pro Thr Leu Ala Thr Pro Val Leu Pro Ala Leu Tyr Cys Gln Ala
195 200 205

Thr Met Arg Leu Pro Gly Leu Glu Leu Ser His Arg Gln Ala Ile Pro
210 215 220

Val Leu His
225

<210> 51
<211> 1398
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody heavy chain nucleotide sequence

<400> 51
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag 60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcgt ctggattcac cttcagtagc gatggcatgc actgggtccg ccaggctcca 180

ggcaaggggc tggagtgggt ggcaattata tggtatgatg gaagtaataa atattatgca 240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtatatt actgtgcgag agatcccggc 360

tactattacg gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctcagcttcc 420

accaagggcc catccgtctt ccccctggcg ccctgctcta gaagcacctc cgagagcaca 480

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac 540

tcaggcgctc tgaccagcgg cgtgcacacc ttcccagctg tcctacagtc ctcaggactc 600

tactccctca gcagcgtggt gaccgtgccc tccagcaact tcggcaccca gacctacacc 660

tgcaacgtag atcacaagcc cagcaacacc aaggtggaca agacagttga gcgcaaatgt 720

tgtgtcgagt gcccaccgtg cccagcacca cctgtggcag gaccgtcagt cttcctcttc 780

cccccaaaac ccaaggacac cctcatgatc tcccggaccc ctgaggtcac gtgcgtggtg 840

gtggacgtga gccacgaaga ccccgaggtc cagttcaact ggtacgtgga cggcgtggag 900

gtgcataatg ccaagacaaa gccacgggag gagcagttca acagcacgtt ccgtgtggtc 960

agcgtcctca ccgttgtgca ccaggactgg ctgaacggca aggagtacaa gtgcaaggtc 1020

tccaacaaag gcctcccagc ccccatcgag aaaaccatct ccaaaaccaa agggcagccc 1080

cgagaaccac aggtgtacac cctgccccca tcccgggagg agatgaccaa gaaccaggtc 1140

agcctgacct gcctggtcaa aggcttctac cccagcgaca tcgccgtgga gtgggagagc 1200

aatgggcagc cggagaacaa ctacaagacc acacctccca tgctggactc cgacggctcc 1260

ttcttcctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc 1320

tcatgctccg tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg 1380

tctccgggta aatgatag 1398

<210> 52
<211> 464
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody heavy chain amino acid sequence

<400> 52

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

```
Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Asp Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Ile Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asp Pro Gly Tyr Tyr Tyr Gly Met Asp Val Trp
        115                 120                 125

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
    130                 135                 140

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
    210                 215                 220
```

```
His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
225                 230                 235                 240

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
                245                 250                 255

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
            260                 265                 270

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
        275                 280                 285

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
    290                 295                 300

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
305                 310                 315                 320

Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
                325                 330                 335

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
            340                 345                 350

Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
        355                 360                 365

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
    370                 375                 380

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
385                 390                 395                 400

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
                405                 410                 415
```

```
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
            420                 425                 430


Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
        435                 440                 445


Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210>  53
<211>  705
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Modified human monoclonal
       antibody light chain nucleotide sequence

<400>  53
atgttgccat cacaactcat tgggtttctg ctgctctggg ttccagcttc caggggtgaa       60

attgtgctga ctcagtctcc agactttcag tctgtgactc caaaagagaa agtcaccatc      120

acctgccggg ccagtcagag aattggtagt agcttacact ggtaccagca gaaaccagat      180

cagtctccaa aactcctcat caagtatgct tcccagtcct tctcaggggt cccctcgagg      240

ttcagtggca gtggatctgg gacagatttc accctcacca tcaatagcct ggaagctgaa      300

gatgctgcaa cttattactg tcatcagagt ggtcgtttac cgctcacttt cggcggaggg      360

accaaggtgg agatcaaacg aactgtggct gcaccatctg tcttcatctt cccgccatct      420

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc      480

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag      540

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg      600

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg      660

agctcgcccg tcacaaagag cttcaacagg ggagagtgtt agtga                      705
```

<210> 54
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain amino acid sequence

<400> 54

```
Met Leu Pro Ser Gln Leu Ile Gly Phe Leu Leu Leu Trp Val Pro Ala
1               5                  10                  15


Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val
            20                  25                  30


Thr Pro Lys Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Arg Ile
        35                  40                  45


Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys
    50                  55                  60


Leu Leu Ile Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg
65                  70                  75                  80


Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser
                85                  90                  95


Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Ser Gly Arg
            100                 105                 110


Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
        115                 120                 125


Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
    130                 135                 140
```

```
Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
145                 150                 155                 160


Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
                165                 170                 175


Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
            180                 185                 190


Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
        195                 200                 205


Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
    210                 215                 220


Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210>  55
<211>  1410
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Modified human monoclonal
       antibody heavy chain nucleotide sequence

<400>  55
atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag       60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc      120

tgtgcagcct ctggattcac cttcagtagc tatggcatgc actgggtccg ccaggctcca      180

ggcaaggggc tggagtgggt ggcagttata tcaaatgatg gaaataataa atactatgca      240

gactccgtga agggccgatt caccatctcc agagacaatt ccaaaaacac gctgtatctg      300

caaatgaaca gcctgcgcgc tgaggacacg gctgtgtatt actgtgcgag agatagtacg      360

gcgataacct actactacta cggaatggac gtctggggcc aagggaccac ggtcaccgtc      420
```

tcctcagctt ccaccaaggg cccatccgtc ttccccctgg cgccctgctc tagaagcacc 480

tccgagagca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 540

gtgtcgtgga actcaggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctacag 600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcaa cttcggcacc 660

cagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagacagtt 720

gagcgcaaat gttgtgtcga gtgcccaccg tgcccagcac cacctgtggc aggaccgtca 780

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc 840

acgtgcgtgg tggtggacgt gagccacgaa gaccccgagg tccagttcaa ctggtacgtg 900

gacggcgtgg aggtgcataa tgccaagaca aagccacggg aggagcagtt caacagcacg 960

ttccgtgtgg tcagcgtcct caccgttgtg caccaggact ggctgaacgg caaggagtac 1020

aagtgcaagg tctccaacaa aggcctccca gcccccatcg agaaaaccat ctccaaaacc 1080

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc 1140

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct accccagcga catcgccgtg 1200

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacacctcc catgctggac 1260

tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag 1320

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag 1380

agcctctccc tgtctccggg taaatgatag 1410

<210> 56
<211> 468
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody heavy chain amino acid sequence

<400> 56

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

```
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Ser Asn Asp Gly Asn Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asp Ser Thr Ala Ile Thr Tyr Tyr Tyr Tyr Gly
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145                 150                 155                 160

Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205
```

```
Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
    210                 215                 220

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225                 230                 235                 240

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
                245                 250                 255

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415


Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460


Ser Pro Gly Lys
465


<210>  57
<211>  714
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Modified human monoclonal
       antibody light chain nucleotide sequence

<400>  57
atggacatga gggtccccgc tcagctcctg gggctcctgc tactctggct ccgaggtgcc       60

agatgtgaca tccagatgac ccagtctcca tcctccctgt ctgcatctgt cggagacaga      120

gtcaccatca cttgccgggc aagtcagagt attagtagct atttaaattg gtatcagcag      180

aaaccaggga aagcccctaa gctcctgatc tatgctgcat ccggtttgaa gcgtggggtc      240

ccatcacggt tcagtggtag tggatctggg acagatttca ctctcaccat cagttctctg      300

caacctgagg attttgcaac ttactactgt caccagagtt acagtctccc attcactttc      360

ggccctggga ccaaagtgga tatcaaacga actgtggctg caccatctgt cttcatcttc      420

ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac      480
```

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 540

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 600

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 660

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta gtga 714

<210> 58
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain amino acid sequence

<400> 58

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Gly Leu Lys Arg Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln
100 105 110

```
Ser Tyr Ser Leu Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
        115                 120                 125


Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140


Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160


Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175


Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190


Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  59
<211>  1413
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Modified human monoclonal
       antibody heavy chain nucleotide sequence

<400>  59
atgaaacacc tgtggttctt cctcctgctg gtggcagctc ccagatgggt cctgtcccag       60

gtgcagctgc aggagtcggg cccaggactg gtgaagcctt cggagaccct gtccctcacc      120

tgcactgtct ctggtgactc catcagtagt aactattgga gctggatccg gcagcccgcc      180
```

gggaagggac tggagtggat tgggcgtatc tataccagtg ggggcaccaa ctccaacccc 240

tccctcaggg gtcgagtcac catgtcagta gacacgtcca agaaccagtt ctctctgaaa 300

ctgagttctg tgaccgccgc ggacacggcc gtgtattact gtgcgagaga tcgtattact 360

ataattcggg gacttattcc atccttcttt gactactggg gccagggaac cctggtcacc 420

gtctcctcag cttccaccaa gggcccatcc gtcttccccc tggcgccctg ctctagaagc 480

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 660

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 720

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 780

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 840

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 900

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 960

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1080

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1260

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1320

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1380

aagagcctct ccctgtctcc gggtaaatga tag 1413

<210> 60
<211> 469
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody heavy chain amino acid sequence

<400> 60

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1 5 10 15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile
35 40 45

Ser Ser Asn Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu
50 55 60

Glu Trp Ile Gly Arg Ile Tyr Thr Ser Gly Gly Thr Asn Ser Asn Pro
65 70 75 80

Ser Leu Arg Gly Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln
85 90 95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
100 105 110

Tyr Cys Ala Arg Asp Arg Ile Thr Ile Ile Arg Gly Leu Ile Pro Ser
115 120 125

Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
145 150 155 160

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

```
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
        195                 200                 205

Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr
    210                 215                 220

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
225                 230                 235                 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro
                245                 250                 255

Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            260                 265                 270

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    290                 295                 300

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
305                 310                 315                 320

Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
                325                 330                 335

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala
            340                 345                 350

Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro
        355                 360                 365
```

```
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
385                 390                 395                 400

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                405                 410                 415

Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
            420                 425                 430

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
        435                 440                 445

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    450                 455                 460

Leu Ser Pro Gly Lys
465
```

<210> 61
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain nucleotide sequence

<400> 61

```
atggtgttgc agacccaggt cttcatttct ctgttgctct ggatctctgg tgcctacggg       60

gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc      120

atcaactgca agtccagcca gagtgtttta tacagctcca acaataagaa ctacttagct      180

tggtaccaac agaaaccagg acagcctcct aaattgctca tttactgggc atctatacgg      240
```

gaatatgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 300

atcagcagcc tgcaggctga agatgtggca gtttatttct gtcaacaata ttatagtatt 360

cctcccctca ctttcggcgg agggaccaag gtggagatca aacgaactgt ggctgcacca 420

tctgtcttca tcttcccgcc atctgatgag cagttgaaat ctggaactgc ctctgttgtg 480

tgcctgctga ataacttcta tcccagagag gccaaagtac agtggaaggt ggataacgcc 540

ctccaatcgg gtaactccca ggagagtgtc acagagcagg acagcaagga cagcacctac 600

agcctcagca gcaccctgac gctgagcaaa gcagactacg agaaacacaa agtctacgcc 660

tgcgaagtca cccatcaggg cctgagctcg cccgtcacaa agagcttcaa caggggagag 720

tgttagtga 729

<210> 62
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain amino acid sequence

<400> 62

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

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
20 25 30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
35 40 45

Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ile Arg
65 70 75 80

```
Glu Tyr Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
                85                  90                  95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
            100                 105                 110

Phe Cys Gln Gln Tyr Tyr Ser Ile Pro Pro Leu Thr Phe Gly Gly Gly
        115                 120                 125

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
    130                 135                 140

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
145                 150                 155                 160

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
                165                 170                 175

Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu
            180                 185                 190

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
        195                 200                 205

Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
    210                 215                 220

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
225                 230                 235                 240

Cys
```

<210> 63
<211> 1419

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody heavy chain nucleotide sequence

<400> 63
atggaactgg ggctccgctg ggttttcctt gttgctattt tagaaggtgt ccagtgtgag 60

gtgcagctgg tggagtctgg gggaggcctg gtcaagcctg gggggtccct gagactctcc 120

tgtgcagcct ctggattcac cttcagtagc tatagcatga actgggtccg ccaggctcca 180

gggaaggggc tggagtgggt ctcatccatt agtagtagta gtagttacat atactacgca 240

gactcagtga agggccgatt caccatctcc agagacaacg ccaagaactc actgtatctg 300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agatgggtat 360

agcagtggct ggtcctacta ctactactac ggtatggacg tctggggcca agggaccacg 420

gtcaccgtct cctcagcttc caccaagggc ccatccgtct tccccctggc gccctgctct 480

agaagcacct ccgagagcac agcggccctg ggctgcctgg tcaaggacta cttccccgaa 540

ccggtgacgg tgtcgtggaa ctcaggcgct ctgaccagcg gcgtgcacac cttcccagct 600

gtcctacagt cctcaggact ctactccctc agcagcgtgg tgaccgtgcc ctccagcaac 660

ttcggcaccc agacctacac ctgcaacgta gatcacaagc ccagcaacac caaggtggac 720

aagacagttg agcgcaaatg ttgtgtcgag tgcccaccgt gcccagcacc acctgtggca 780

ggaccgtcag tcttcctctt ccccccaaaa cccaaggaca ccctcatgat ctcccggacc 840

cctgaggtca cgtgcgtggt ggtggacgtg agccacgaag accccgaggt ccagttcaac 900

tggtacgtgg acggcgtgga ggtgcataat gccaagacaa agccacggga ggagcagttc 960

aacagcacgt tccgtgtggt cagcgtcctc accgttgtgc accaggactg gctgaacggc 1020

aaggagtaca agtgcaaggt ctccaacaaa ggcctcccag cccccatcga gaaaaccatc 1080

tccaaaacca aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag 1140

gagatgacca agaaccaggt cagcctgacc tgcctggtca aaggcttcta ccccagcgac 1200

atcgccgtgg agtgggagag caatgggcag ccggagaaca actacaagac cacacctccc 1260

atgctggact ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg 1320

tggcagcagg ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac 1380

acgcagaaga gcctctccct gtctccgggt aaatgatag 1419

<210> 64
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody heavy chain amino acid sequence

<400> 64

Met Glu Leu Gly Leu Arg Trp Val Phe Leu Val Ala Ile Leu Glu Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

```
Tyr Tyr Cys Ala Arg Asp Gly Tyr Ser Ser Gly Trp Ser Tyr Tyr Tyr
        115                 120                 125

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
    130                 135                 140

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
145                 150                 155                 160

Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                165                 170                 175

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
            180                 185                 190

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
        195                 200                 205

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
    210                 215                 220

Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
225                 230                 235                 240

Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
                245                 250                 255

Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        275                 280                 285

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    290                 295                 300
```

```
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
305                 310                 315                 320


Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
                325                 330                 335


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            340                 345                 350


Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
        355                 360                 365


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    370                 375                 380


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385                 390                 395                 400


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                405                 410                 415


Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            420                 425                 430


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        435                 440                 445


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    450                 455                 460


Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> 65
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain nucleotide sequence

<400> 65
atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg atccagtgca 60

gatattgtga tgacccagac tccactctct ctgtccgtca ctcctggaca gccggcctcc 120

atctcctgca agtctagtca gagcctcctg cttagtgatg gaaagaccta tttgaattgg 180

tacctgcaga agcccggcca gcctccacag ctcctgatct atgaagtttc caaccggttc 240

tctggagtgc cagacaggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 300

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaagtat acagcttatg 360

tgcagttttg gccaggggac caagctggag atcaaacgaa ctgtggctgc accatctgtc 420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 720

tga 723

<210> 66
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain amino acid sequence

<400> 66

Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Ile Pro
1 5 10 15

```
Gly Ser Ser Ala Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
            20                  25                  30

Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser
        35                  40                  45

Leu Leu Leu Ser Asp Gly Lys Thr Tyr Leu Asn Trp Tyr Leu Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Ser
            100                 105                 110

Cys Met Gln Ser Ile Gln Leu Met Ser Ser Phe Gly Gln Gly Thr Lys
        115                 120                 125

Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205
```

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 67
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain nucleotide sequence

<400> 67
atgaggctcc ctgctcagct cctggggctg ctaatgctct ggatacctgg atccagtgcg 60

gatattgtga tgacccagac tccactctct ctgtccgtca cccctggaca gccggcctcc 120

atctcctgca agtctagtca gagcctcctg tatagtgatg gaaagaccta tttgttttgg 180

tacctgcaga agccaggcca gcctccacag ctcctgatct atgaagtttc caaccgattc 240

tctggagtgc cagataggtt cagtggcagc gggtcaggga cagatttcac actgaaaatc 300

agccgggtgg aggctgagga tgttggggtt tattactgca tgcaaagtat acagcttccg 360

tggacgttcg gccaagggac caaggtggaa atcaaacgaa ctgtggctgc accatctgtc 420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 720

tga 723

<210> 68
<211> 239
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Modified human monoclonal antibody light chain amino acid sequence

<400> 68

```
Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Ile Pro
1               5                  10                  15


Gly Ser Ser Ala Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser
            20                  25                  30


Val Thr Pro Gly Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser
        35                  40                  45


Leu Leu Tyr Ser Asp Gly Lys Thr Tyr Leu Phe Trp Tyr Leu Gln Lys
    50                  55                  60


Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe
65                  70                  75                  80


Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95


Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
            100                 105                 110


Cys Met Gln Ser Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys
        115                 120                 125


Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140


Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160
```

```
Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175


Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190


Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205


Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220


Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235


<210>  69
<211>  14
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic peptide

<400>  69

Ser Ser Gln Ser Leu Leu Gln Ser Asn Gly Tyr Asn Tyr Leu
1               5                   10


<210>  70
<211>  53
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic primer

<400>  70
tatctaagct tctagactcg agcgccacca tggactggac ctggagcatc ctt              53


<210>  71
<211>  53
```

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 71
tatctaagct tctagactcg agcgccacca tggagtttgg gctgagctgg att 53

<210> 72
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 72
tatctaagct tctagactcg agcgccacca tggaactggg gctccgctgg gtt 53

<210> 73
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 73
tatctaagct tctagactcg agcgccacca tggagtttgg gctgagctgg ctt 53

<210> 74
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 74
tatctaagct tctagactcg agcgccacca tggagtttgg gctgagctgg gtt 53

<210> 75
<211> 53

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 75
tatctaagct tctagactcg agcgccacca tggagtttgg gctgagctgg gtt 53

<210> 76
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 76
tatctaagct tctagactcg agcgccacca tgaaacacct gtggttcttc ctc 53

<210> 77
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 77
tatctaagct tctagacccg ggcgccacca tgaggctccc tgctcagctc ctg 53

<210> 78
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 78
tatctaagct tctagacccg ggcgccacca tgttgccatc acaactcatt ggg 53

<210> 79
<211> 53

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 79
tatctaagct tctagacccg ggcgccacca tggtgttgca gacccaggtc ttc 53

<210> 80
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 80
tatctaagct tctagacccg ggcgccacca tggacatgag ggtccccgct cag 53

<210> 81
<211> 53
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 81
tatctaagct tctagacccg ggcgccacca tggacatgag ggtccctgct cag 53

<210> 82
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 82
ttctctgatc agaattccta tcatttaccc ggagacaggg agag 44

<210> 83
<211> 43

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 83
ttctttgatc agaattctca ctaacactct cccctgttga agc 43

<210> 84
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 84
ttctctgatc agaattccta tcatttaccc agagacaggg agag 44

<210> 85
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 85
ggatctggga cagatttcac cctcaccatc aatagcctgg aagc 44

<210> 86
<211> 44
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 86
gcttccaggc tattgatggt gagggtgaaa tctgtcccag atcc 44

<210> 87
<211> 27

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 87
gcagcgtctg gattcacctt cagtagc 27

<210> 88
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 88
gctactgaag gtgaatccag acgctgc 27

<210> 89
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 89
cggaggtgct tctagagcag ggcg 24

<210> 90
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 90
gcaagtcaga gtattagtag ctatttaaat tggtatcagc agaaacc 47

<210> 91
<211> 47

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 91
ggtttctgct gataccaatt taaatagcta ctaatactct gacttgc 47

<210> 92
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 92
ccatcagttc tctgcaacct gaggattttg caacttacta ctgtcacc 48

<210> 93
<211> 48
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 93
ggtgacagta gtaagttgca aaatcctcag gttgcagaga actgatgg 48

<210> 94
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 94
gcaaatgaac agcctgcgcg ctgaggacac g 31

<210> 95
<211> 31

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 95
cgtgtcctca gcgcgcaggc tgttcatttg c 31

<210> 96
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 96
caataagaac tacttagctt ggtaccaaca gaaaccagga cagcc 45

<210> 97
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 97
ggctgtcctg gtttctgttg gtaccaagct aagtagttct tattg 45

<210> 98
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 98
ccctcagggg tcgagtcacc atgtcagtag acacgtccaa gaacc 45

<210> 99
<211> 45

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 99
ggttcttgga cgtgtctact gacatggtga ctcgacccct gaggg 45

<210> 100
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 100
attctagagc agggcgccag g 21

<210> 101
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 101
ccatctcctg caagtctagt cagagcctcc 30

<210> 102
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 102
ggaggctctg actagacttg caggagatgg 30

<210> 103
<211> 47

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 103
ggtttattac tgcatgcaaa gtatacagct tatgtccagt tttggcc 47

<210> 104
<211> 47
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 104
ggccaaaact ggacataagc tgtatacttt gcatgcagta ataaacc 47

<210> 105
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 105
cctgcaagtc tagtcagagc ctcc 24

<210> 106
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 106
ggaggctctg actagacttg cagg 24

<210> 107
<211> 543

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 107

```
Met Asp Phe Gly Leu Ala Leu Leu Leu Ala Gly Leu Leu Gly Leu Leu
1               5                  10                  15


Leu Gly Gln Ser Leu Gln Val Lys Pro Leu Gln Val Glu Pro Pro Glu
            20                  25                  30


Pro Val Val Ala Val Ala Leu Gly Ala Ser Arg Gln Leu Thr Cys Arg
        35                  40                  45


Leu Ala Cys Ala Asp Arg Gly Ala Ser Val Gln Trp Arg Gly Leu Asp
    50                  55                  60


Thr Ser Leu Gly Ala Val Gln Ser Asp Thr Gly Arg Ser Val Leu Thr
65                  70                  75                  80


Val Arg Asn Ala Ser Leu Ser Ala Ala Gly Thr Arg Val Cys Val Gly
                85                  90                  95


Ser Cys Gly Gly Arg Thr Phe Gln His Thr Val Gln Leu Leu Val Tyr
            100                 105                 110


Ala Phe Pro Asp Gln Leu Thr Val Ser Pro Ala Ala Leu Val Pro Gly
        115                 120                 125


Asp Pro Glu Val Ala Cys Thr Ala His Lys Val Thr Pro Val Asp Pro
    130                 135                 140


Asn Ala Leu Ser Phe Ser Leu Leu Val Gly Gly Gln Glu Leu Glu Gly
145                 150                 155                 160
```

```
Ala Gln Ala Leu Gly Pro Glu Val Gln Glu Glu Glu Glu Glu Pro Gln
                165                 170                 175

Gly Asp Glu Asp Val Leu Phe Arg Val Thr Glu Arg Trp Arg Leu Pro
            180                 185                 190

Pro Leu Gly Thr Pro Val Pro Pro Ala Leu Tyr Cys Gln Ala Thr Met
        195                 200                 205

Arg Leu Pro Gly Leu Glu Leu Ser His Arg Gln Ala Ile Pro Val Leu
    210                 215                 220

His Ser Pro Thr Ser Pro Glu Pro Pro Asp Thr Thr Ser Pro Glu Ser
225                 230                 235                 240

Pro Asp Thr Thr Ser Pro Glu Ser Pro Asp Thr Thr Ser Gln Glu Pro
                245                 250                 255

Pro Asp Thr Thr Ser Gln Glu Pro Pro Asp Thr Thr Ser Gln Glu Pro
            260                 265                 270

Pro Asp Thr Thr Ser Pro Glu Pro Pro Asp Lys Thr Ser Pro Glu Pro
        275                 280                 285

Ala Pro Gln Gln Gly Ser Thr His Thr Pro Arg Ser Pro Gly Ser Thr
    290                 295                 300

Arg Thr Arg Arg Pro Glu Ile Gln Pro Lys Ser Cys Asp Lys Thr His
305                 310                 315                 320

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
                325                 330                 335

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            340                 345                 350
```

```
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        355                 360                 365

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    370                 375                 380

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
385                 390                 395                 400

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                405                 410                 415

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
            420                 425                 430

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        435                 440                 445

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    450                 455                 460

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
465                 470                 475                 480

Gly Gln Pro Glu Asn Asn Tyr Lys Ala Thr Pro Pro Val Leu Asp Ser
                485                 490                 495

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            500                 505                 510

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        515                 520                 525

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    530                 535                 540
```

<210> 108
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<220>
<221> modified_base
<222> (21)..(21)
<223> Inosine

<220>
<221> misc_feature
<222> (21)..(21)
<223> n is a, c, g, or t

<400> 108
caggtgcagc tggagcagtc ngg 23

<210> 109
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 109
gctgagggag tagagtcctg agga 24

<210> 110
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 110
gctgagggag tagagtcctg aggactgt 28

<210> 111

<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 111
agcatggatc ggggcctggc c 21

<210> 112
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 112
gtgcaggacc gggatggcct g 21

<210> 113
<211> 116
<212> PRT
<213> Homo sapiens

<400> 113

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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


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


Val Ser Ser Ala
        115


<210>  114
<211>  116
<212>  PRT
<213>  Homo sapiens

<400>  114

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 Ser Tyr
            20                  25                  30


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


Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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

```
Val Ser Ser Ala
        115


<210>  115
<211>  117
<212>  PRT
<213>  Homo sapiens

<400>  115

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


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


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly 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 Arg Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
            100                 105                 110


Thr Val Ser Ser Ala
        115


<210>  116
<211>  122
<212>  PRT
<213>  Homo sapiens
```

<400> 116

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly 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 Arg Thr Val Val Thr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala
115 120

<210> 117
<211> 120
<212> PRT
<213> Homo sapiens

<400> 117

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

```
Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

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

Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

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

Arg Ile Thr Met Val Arg Gly Val Ile Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala
        115                 120
```

<210> 118
<211> 121
<212> PRT
<213> Homo sapiens

<400> 118

```
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 Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

```
Lys Gly 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 Ile Ala Val Ala Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Thr Val Thr Val Ser Ser Ala
        115                 120


<210>  119
<211>  125
<212>  PRT
<213>  Homo sapiens

<400>  119

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


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


Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg Gly Tyr Ser Ser Gly Trp Tyr Tyr Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
115 120 125

<210> 120
<211> 121
<212> PRT
<213> Homo sapiens

<400> 120

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

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

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln 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 Ser Ser Ser Ser Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala
115 120

<210> 121

<211> 122
<212> PRT
<213> Homo sapiens

<400> 121

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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

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

Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

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

Arg Tyr Tyr Tyr Gly Ser Gly Ser Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala
115 120

<210> 122
<211> 112
<212> PRT
<213> Homo sapiens

<400> 122

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

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


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


Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


<210>  123
<211>  112
<212>  PRT
<213>  Homo sapiens

<400>  123

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


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Gln Ser
            20                  25                  30


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


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60
```

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


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
            100                 105                 110


<210>  124
<211>  107
<212>  PRT
<213>  Homo sapiens

<400>  124

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 Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


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


Phe Ala Ala Ser Ser Leu Gln 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 Ser Tyr Ser Thr Pro Thr
                85                  90                  95


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


<210>  125
```

<211> 106
<212> PRT
<213> Homo sapiens

<400> 125

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 Arg Ala Ser Gln Ser Ile Gly Ser Ser
20 25 30

Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
35 40 45

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

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

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

Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 126
<211> 108
<212> PRT
<213> Homo sapiens

<400> 126

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 Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

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


Tyr Ala Ala Ser Ser Leu Ser Gln 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 Ser Tyr Ser Thr Pro Phe
                85                  90                  95


Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
            100                 105


<210>  127
<211>  114
<212>  PRT
<213>  Homo sapiens

<400>  127

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 Lys Ser Ser Gln Ser Val Leu Tyr Ser
            20                  25                  30


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


Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60


Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80
```

```
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95


Tyr Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
            100                 105                 110


Lys Arg



<210>  128
<211>  106
<212>  PRT
<213>  Homo sapiens

<400>  128

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 Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


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


Tyr Ala Ala Ser Ser Leu Gln 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 Ser Tyr Ser Thr Pro Phe
                85                  90                  95


Gly Gln Gly Thr Thr Leu Asp Ile Lys Arg
            100                 105


<210>  129
```

<211> 110
<212> PRT
<213> Homo sapiens

<400> 129

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser
85 90 95

Ile Gln Leu Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

<210> 130
<211> 113
<212> PRT
<213> Homo sapiens

<400> 130

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

```
Asp Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser
                85                  90                  95

Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg
```

<210> 131
<211> 112
<212> PRT
<213> Homo sapiens

<400> 131

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Gly
            20                  25                  30

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

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60
```

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


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
            100                 105                 110


<210>  132
<211>  107
<212>  PRT
<213>  Homo sapiens

<400>  132

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 Gln Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30


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


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


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


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


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


<210>  133
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<211> 125
<212> PRT
<213> Homo sapiens

<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 Glu Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

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

Gly Trp Ile Ser Val Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Ser Thr Asp Thr Ser Thr Ser Thr Ala Phe
65 70 75 80

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

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

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
115 120 125

<210> 134
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 134

Cys Lys Pro Leu Gln Val Glu Pro Pro Glu Pro
1 5 10

<210> 135
<211> 8
<212> PRT
<213> Homo sapiens

<400> 135

Thr Phe Asn Asn Ser Ala Met Thr
1 5

<210> 136
<211> 9
<212> PRT
<213> Homo sapiens

<400> 136

Cys Lys Ser Asn Gln Ser Leu Leu Tyr
1 5

<210> 137
<211> 9
<212> PRT
<213> Homo sapiens

<400> 137

Ser Gly Thr Asn Phe Thr Leu Thr Ile
1 5

<210> 138
<211> 9
<212> PRT
<213> Homo sapiens

<400> 138

Ala Ser Gln Asn Ile Ser Ser Tyr Leu
1 5

<210> 139
<211> 9
<212> PRT
<213> Homo sapiens

<400> 139

Ser Ser Asn Asn Lys Thr Tyr Leu Ala
1 5

<210> 140
<211> 8
<212> PRT
<213> Homo sapiens

<400> 140

Arg Ala Ser Gln Asn Ile Thr Asn
1 5

<210> 141
<211> 8
<212> PRT
<213> Homo sapiens

<400> 141

Ser Cys Asn Ser Ser Gln Ser Leu
1 5

<210> 142
<211> 8
<212> PRT
<213> Homo sapiens

<400> 142

His Ser Asp Asn Leu Ser Ile Thr
1 5

<210> 143
<211> 7
<212> PRT
<213> Homo sapiens

<400> 143

Leu Gln Ser Asn Gly Tyr Asn
1 5

<210> 144
<211> 7
<212> PRT
<213> Homo sapiens

<400> 144

Leu Gln Ser Asn Gly Tyr Asn
1 5

<210> 145
<211> 7
<212> PRT
<213> Homo sapiens

<400> 145

His Gly Asn Gly Tyr Asn Tyr
1 5

<210> 146
<211> 8
<212> PRT
<213> Homo sapiens

<400> 146

Leu Thr Ile Asn Gly Leu Glu Ala
1 5

<210> 147
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic linker peptide

<400> 147

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 148
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 148

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

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

Gly Trp Ile Ser Val Tyr Ser Gly Asn Thr Asn Tyr Ala Gln Lys Val
50 55 60

Gln Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

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

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

```
Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
    130                 135                 140

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
        195                 200                 205

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
    210                 215                 220

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210>  149
<211>  1413
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  Synthetic Polypeptide

<400>  149
atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc ccactcccag       60

gttcagctgg tgcagtctgg agctgaggtg aagaagcctg gggcctcagt gaaggtctcc      120
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tgcaaggctt ctggttacac ctttaccagc tatggtatca actgggtgcg acaggcccct 180

ggacaagggc ttgagtggat gggatggatc agcgtttaca gtggtaacac aaactatgca 240

cagaaggtcc agggcagagt caccatgacc gcagacacat ccacgagcac agcctacatg 300

gacctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agagggtagc 360

agctcgtccg gagactacta ttacggtatg gacgtctggg gccaagggac cacggtcacc 420

gtctcctcag cctccaccaa gggcccatcg gtcttccccc tggcgccctg ctccaggagc 480

acctccgaga gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg 540

acggtgtcgt ggaactcagg cgctctgacc agcggcgtgc acaccttccc agctgtccta 600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag caacttcggc 660

acccagacct acacctgcaa cgtagatcac aagcccagca acaccaaggt ggacaagaca 720

gttgagcgca aatgttgtgt cgagtgccca ccgtgcccag caccacctgt ggcaggaccg 780

tcagtcttcc tcttcccccc aaaacccaag gacaccctca tgatctcccg gaccctgag 840

gtcacgtgcg tggtggtgga cgtgagccac gaagaccccg aggtccagtt caactggtac 900

gtggacggcg tggaggtgca taatgccaag acaaagccac gggaggagca gttcaacagc 960

acgttccgtg tggtcagcgt cctcaccgtt gtgcaccagg actggctgaa cggcaaggag 1020

tacaagtgca aggtctccaa caaaggcctc ccagccccca tcgagaaaac catctccaaa 1080

accaaagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggaggagatg 1140

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctaccccag cgacatcgcc 1200

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacacc tcccatgctg 1260

gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1320

caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag 1380

aagagcctct ccctgtctcc gggaaaatga tag 1413

<210> 150
<211> 219

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Polypeptide

<400> 150

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


Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Thr
            20                  25                  30


Asp Gly Thr Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


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


Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Asn
                85                  90                  95


Ile Gln Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125


Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160
```

```
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175


Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190


Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```