

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

[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 examples 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 disclosure may further comprise another component, such as a therapeutic agent or a diagnostic agent. Diagnostic and therapeutic methods are also provided by the disclosure.

[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.

[0011a] In one aspect, the present disclosure provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain, or an antigen-binding portion thereof, or a light chain, or an antigen-binding portion thereof, of a human monoclonal antibody that specifically binds to Mucosal Addressin 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.

[0011b] In another aspect, the present disclosure provides a vector comprising the nucleic acid as described herein. In yet another aspect, the present disclosure provides a host cell comprising the vector as described herein. In yet another aspect, the present disclosure provides 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 the 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.

[0011c] In a further aspect, the present disclosure provides a method for producing a human monoclonal antibody or antigen-binding portion thereof that specifically binds MAdCAM, comprising culturing the host cell as described herein under suitable conditions and recovering said antibody or antigen-binding portion. In a further aspect, the present disclosure provides a method of manufacturing a human monoclonal antibody or an antigen-binding fragment portion thereof that specifically binds to Mucosal Addressin 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.

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

[0013] In examples, 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 3×10^{-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 examples, the human monoclonal antibody or antigen-binding portion binds human MAdCAM with a K_d of 3×10^{-10} M or less and inhibits $\alpha_4\beta_7$ binding to human MAdCAM.

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

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

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

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

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

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

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

[0022] In examples, the light chain comprises between 1 and 10 amino acid substitutions as compared to SEQ ID NO: 150.

[0023] In examples, 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 examples, 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 examples, a nucleic acid sequence encoding the amino acid sequence of a MAdCAM antibody is provided.

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

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

[0028] In examples, a hybridoma cell line that produces a human monoclonal MAdCAM antibody is provided. In examples, 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 examples, the human monoclonal antibody produced by the hybridoma cell line or an antigen-binding portion of said monoclonal antibody is provided.

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

[0031] In examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, the antigen-binding portion is an Fab fragment, an F(ab')₂ fragment, an Fv fragment or a single chain antibody.

[0042] In examples, 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 examples, 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 examples, the inflammatory disease is inflammatory disease of the gastrointestinal tract.

[0045] In examples, 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 examples, the inflammatory bowel disease is Crohn's disease, ulcerative colitis or both.

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

[0048] In examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, a host cell is provided comprising the vector or the nucleic acid molecule.

[0051] In examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, a human monoclonal antibody is produced as above.

[0058] In examples, 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 examples, 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 examples, 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 examples, a method is provided for inhibiting $\alpha_4 \beta_7$ /MAdCAM-dependent cellular adhesion comprising the step of contacting cells expressing human MAdCAM with the monoclonal antibody or antigen-binding portion thereof.

[0062] In examples, 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 examples, 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 examples, 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 examples, 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 examples, 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 examples, a diagnostic kit is provided comprising the monoclonal antibody or antigen-binding portion.

[0068] In examples, the pharmaceutical composition is provided further comprising one or more additional anti-inflammatory or immunomodulatory agents. In examples, 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-TNF α agents and adhesion molecule antagonists.

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

[0070] In examples, 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 examples, said leukocytes are lymphocytes. In examples, said increase in the levels of circulating $\alpha_4\beta_7$ -expressing leukocytes is determined by FACS analysis.

[0071] In examples, 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 examples, 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.

CLAIMS

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain, or an antigen-binding portion thereof, or a light chain, or an antigen-binding portion thereof, of a human monoclonal antibody that specifically binds to Mucosal Addressin 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 nucleotide sequence defined by SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence.
3. The isolated nucleic acid molecule of claim 1, wherein the nucleotide sequence defined by SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.
4. A vector comprising the nucleic acid of claim 1.
5. The vector of claim 4 comprising an expression control sequence operably linked to the nucleic acid.
6. A host cell comprising the vector of claim 5.
7. 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 the 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.
8. The host cell of claim 7, wherein the sequence of SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence.
9. The host cell of claim 7, wherein the sequence of SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.

10. A method for producing a human monoclonal antibody or antigen-binding portion thereof that specifically binds MAdCAM, comprising culturing the host cell according to claim 7 under suitable conditions and recovering said antibody or antigen-binding portion.
11. A method of manufacturing a human monoclonal antibody or an antigen-binding fragment portion thereof that specifically binds to Mucosal Addressin 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.
12. The method of claim 11, wherein nucleotide sequence defined by SEQ ID NO: 149 encodes amino acid sequence SEQ ID NO: 148 without the signal sequence.
13. The method of claim 11, wherein the nucleotide sequence defined by SEQ ID NO: 35 encodes amino acid SEQ ID NO: 150 without the signal sequence.