Antibodies that bind alpha4 and inhibit binding of alpha4beta1 to VCAM-1 and fibronection mapped to a 52-amino acid region of alpha4, between residues 152 and 203 (Schiffer et al., J. Biol. Chem. 270:14270; 1995). Tidswell et al. (J. Immuno 159:1497; 1997) identified domains of beta7 that are important in binding to MAdCAM-1, utilizing a panel of antibodies that bind beta7 in a mouse/human chimeric beta7 subunit approach. They found that six of seven antibodies that inhibited binding to MAdCAM-1 and E-cadherin mapped to a region comprising amino acids 176 through 250, which appears to have homology to the metal-ion dependent adhesion site (MIDAS) of other integrin subunits. One of the antibodies used by Tidswell et al. was an alpha4beta7 heterodimer specific antibody referred to as ACT-1.

The ACT-1 antibody was originally described by Lazarovitz et al. (J. Immunol. 133:1857; 1984) as an antibody developed by immunizing mice with human tetanus toxoid-specific T lymphocyte line from PBMC. Later it was shown that ACT-1 binds to the alpha4beta7 heterodimer specifically (Schweighoffer et al., J. Immunol. 151:717, 1993). While ACT-1 does not bind murine alpha4beta7, it does bind alpha4beta7 from least some non-human primate species, and has been shown to attenuate spontaneous colitis in captive cotton-top tamarins (Hesterberg et al., Gastroenterology 111:1373; 1996)

ACT-1 has been humanized and evaluated as a human therapeutic in ulcerative colitis (Feagan et al., N Engl J Med. 352:2499; 2005), and recently in Crohn's disease (Feagan et al, Clinical Gastroenterology and Hepatology, 6:1370, 2008). Humanized ACT-1, also known as vedolizumab, is described in WO 98/06248 and US patent 7,147,85, as well as WO 07/061679 and US 2007-0122404. Another humanized antibody, natalizumab (Tysabri®), has been used to treat Crohn's disease. Natalizumab is a humanized version of an alpha4-specific murine antibody. Vedolizumab has been shown to lead to a neutralizing anti-humanized antibody response in a portion of patients, and natalizumab has been associated with progressive multifocal leukoencephalopathy (PML), a neurological disorder that is associated with reactivation of prior infection with JC virus in immunocompromised individuals. Accordingly, there is a need for a therapeutic agent that ameliorates these disadvantages while disrupting the alpha4beta7/MAdCAM-1 pathway.

SUMMARY OF THE INVENTION

In a first aspect, the present invention refers to an isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 from SEQ ID NO:37, and a light chain variable region comprising CDR1, CDR2 and CDR3 from SEQ ID NO:9.

In a second aspect, the present invention refers to an isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region is encoded by a nucleic acid that encodes SEQ ID NO:37, and the light chain variable region is encoded by a nucleic acid that encodes SEQ ID NO:9.

In a third aspect, the present invention refers to a composition for treating inflammatory bowel disease, pancreatitis,

insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein as defined in anyone of claims 1 to 18 and a physiologically acceptable diluent, excipient or carrier.

In a fourth aspect, the present invention refers to an isolated nucleic acid that encodes the antigen binding protein of the present invention.

In a fifth aspect, the present invention refers to a vector comprising the nucleic acid of the present invention.

In a sixth aspect, the present invention refers to an isolated host cell transfected or transformed with the vector of the present invention.

In a seventh aspect, the present invention refers to a method for the production of an antigen binding protein comprising culturing the host cell of the present invention to express the protein and recovering the protein from the culture medium.

In one example, it is described~~aspect, the present invention provides~~ an isolated antigen binding protein that specifically binds to human alpha4beta7 (i.e., an alpha4beta7 heterodimer specific antigen binding protein). In another example~~aspect of the invention~~, the antigen binding protein specifically binds to the alpha4beta7 of a non-human primate, a cynomologous monkey, a chimpanzee, a non-primate mammal, a rodent, a mouse, a rat, a hamster, a guinea pig, a cat, or a dog. In another example~~embodiment~~, the isolated antigen binding protein comprises a human antibody; a chimeric antibody; a monoclonal antibody; a recombinant antibody; an antigen-binding antibody fragment; a single chain antibody; a diabody; a triabody; a tetrabody; a Fab fragment; a $F(ab')_2$ fragment; a domain antibody; an IgD antibody; an IgE antibody; an IgM antibody; an IgG1 antibody; an IgG2 antibody; an IgG3 antibody; an IgG4 antibody; or an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond. In another example~~aspect~~, the isolated antigen binding protein comprises a heavy chain constant region from one of the aforementioned antibodies; in another example~~aspect~~, the constant region is a polypeptide comprising SEQ ID NO:72; a polypeptide at least 90% identical to SEQ ID NO:72; a

polypeptide having an amino acid sequence as set forth in SEQ ID NO:72 from which one, two, three, four or five N-terminal and/or C-terminal amino acids have been removed; or one of the aforementioned polypeptides which incorporates one or more post-translational modifications. In one ~~embodiment~~example, the isolated antigen binding protein comprises a kappa light chain constant region, in another it comprises a lambda light chain region. In one ~~embodiment~~example, the light chain constant region is a polypeptide comprising SEQ ID NO:70; a polypeptide at least 90% identical to SEQ ID NO:70; a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five N-terminal and/or C-terminal amino acids have been removed; or one of the aforementioned polypeptides which incorporates one or more post-translational modifications

One example, it is described~~embodiment of the present invention provides~~ an alpha4beta7 heterodimer specific antigen binding protein having a heavy chain and a light chain, each of which comprise one or more complementarity determining regions, or CDRs. In another example~~aspect of the invention~~, the heavy chain variable region comprises CDR1, CDR2 and CDR3 and a light chain variable region comprises CDR1, CDR2 and CDR3, wherein each respective CDR is selected from the group consisting of the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:55, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:58; the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:56, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:59; and the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:57, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:60.

In another example~~aspect of the invention~~, the heavy chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4, and the light chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4. In one aspect, the FRs are selected from the same SEQ ID NO as the CDRs; in another, the FRs are selected from a different SEQ ID NO. In a further example, it is described~~embodiment, the invention provides~~ an alpha4beta7 heterodimer specific antigen binding protein wherein the light chain variable region comprises SEQ ID NO:55, and the heavy chain variable region comprises SEQ ID NO:58; the light chain variable region comprises SEQ ID NO:56, and the heavy chain variable region comprises SEQ ID NO:59; or the light chain variable region comprises SEQ ID NO:57, and the heavy chain variable region comprises SEQ ID NO:60.

In another example, it is described~~aspect of the invention, the present invention provides~~ an isolated alpha4beta7 heterodimer specific antigen binding protein, having a heavy chain and a light chain, each of which comprise one or more complementarity determining regions, or CDRs. In another example,~~aspect of the invention,~~ the heavy chain variable region comprises CDR1, CDR2 and CDR3 and the light chain variable region comprises CDR1, CDR2 and CDR3. In one example~~embodiment~~, the light chain CDRs are selected from the group consisting of a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 3; a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 5; a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 7; a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 22; and a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 24; and the heavy chain variable CDR1, CDR2 and CDR3 are from SEQ ID NO:58.

In another exampleaspect of the invention, the heavy chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4, and the light chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4. In one exampleaspect, the FRs are selected from the same SEQ ID NO as the CDRs; in another, the FRs are selected from a different SEQ ID NO. In a further example, it is describedembodiment, the invention provides an alpha4beta7 heterodimer specific antigen binding protein wherein the light chain variable region is selected from the group consisting of a light chain variable region at least 90% identical to SEQ ID NO:3; a light chain variable region at least 90% identical to SEQ ID NO:5; a light chain variable region at least 90% identical to SEQ ID NO:7; a light chain variable region at least 90% identical to SEQ ID NO:22; and a light chain variable region at least 90% identical to SEQ ID NO:24; and the heavy chain variable region comprises SEQ ID NO:58.

Another example describesaspect of the invention provides an isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 and a light chain variable region comprising CDR1, CDR2 and CDR3, wherein the light chain CDR1, CDR2 and CDR3 are selected from the group consisting of a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO:12; a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 25; and a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 26; and the heavy chain CDR1, CDR2 and CDR3 are selected from the group consisting of a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO:41; and a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO:54. In one exampleembodiment, the light chain variable region is selected from the group consisting of variable regions that are at least 90% identical to any one of SEQ ID NOs: 12, 25 and 26, and the heavy variable region is selected from the group consisting of variable regions that are at least 90% identical to any one of SEQ ID NOs:41 and 54. In another exampleaspect of the invention, the heavy chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4, and the light chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4. In one exampleaspect, the FRs are selected from the same SEQ ID NO as the CDRs; in another, the FRs are selected from a different SEQ ID NO.

In one example, it is describedembodiment, the invention provides an isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 and a light chain variable region comprising CDR1, CDR2 and CDR3, wherein each respective CDR is at least 90% identical to a CDR selected from the group consisting of a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:10, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:38; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:2, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:30; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:20, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:51; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:11, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:39; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:13, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:42; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:17, and a heavy chain CDR1, CDR2 and CDR3 from

SEQ ID NO:46; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:8, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:36; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:19, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:49; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:18, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:47; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:21, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:52; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:3, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:31; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:7, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:35; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:6, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:34; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:1, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:29; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:22, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:50; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:24, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:40; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:9, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:37; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:4, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:32; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:28, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:53; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:16, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:45; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:15, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:44; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:14, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:43; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:27, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:43; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:5, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:33; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:12, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:41; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:23, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:48; a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:25, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:54; and a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:26, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:54. In another exampleaspect, the heavy chain and light chain CDRs are identical to the respective CDRs of the recited SEQ ID NOs. In one exampleembodiment of the invention, the heavy chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4, and the light chain variable region further comprises four framework regions (FRs) designated FR1, FR2, FR3 andFR4. In one exampleaspect, the FRs are selected from the same SEQ ID NO as the CDRs; in another, the FRs are selected from a different SEQ ID NO.

In another exampleembodiment, an alpha4beta7 heterodimer specific antigen binding protein comprises a light chain variable region and a heavy chain variable region, wherein the light chain variable region is at least 90% identical to SEQ ID NO:10, and the heavy chain variable region is at least 90% identical to SEQ ID NO:38; the light chain variable region is at least 90% identical to SEQ ID NO:2, and the heavy chain variable region is at least 90% identical to SEQ ID NO:30; the light chain variable region is at least 90% identical to SEQ ID NO:20, and the heavy chain variable region is at least 90% identical to SEQ ID NO:51; the light chain variable region is at least 90% identical to SEQ

ID NO:11, and the heavy chain variable region is at least 90% identical to SEQ ID NO:39; the light chain variable region is at least 90% identical to SEQ ID NO:13, and the heavy chain variable region is at least 90% identical to SEQ ID NO:42; the light chain variable region is at least 90% identical to SEQ ID NO:17, and the heavy chain variable region is at least 90% identical to SEQ ID NO:46; the light chain variable region is at least 90% identical to SEQ ID NO:8, and the heavy chain variable region is at least 90% identical to SEQ ID NO:36; the light chain variable region is at least 90% identical to SEQ ID NO:19, and the heavy chain variable region is at least 90% identical to SEQ ID NO:49; the light chain variable region is at least 90% identical to SEQ ID NO:18, and the heavy chain variable region is at least 90% identical to SEQ ID NO:47; the light chain variable region is at least 90% identical to SEQ ID NO:21, and the heavy chain variable region is at least 90% identical to SEQ ID NO:52; the light chain variable region is at least 90% identical to SEQ ID NO:3, and the heavy chain variable region is at least 90% identical to SEQ ID NO:31; the light chain variable region is at least 90% identical to SEQ ID NO:7, and the heavy chain variable region is at least 90% identical to SEQ ID NO:35; the light chain variable region is at least 90% identical to SEQ ID NO:6, and the heavy chain variable region is at least 90% identical to SEQ ID NO:34; the light chain variable region is at least 90% identical to SEQ ID NO:1, and the heavy chain variable region is at least 90% identical to SEQ ID NO:29; the light chain variable region is at least 90% identical to SEQ ID NO:22, and the heavy chain variable region is at least 90% identical to SEQ ID NO:50; the light chain variable region is at least 90% identical to SEQ ID NO:24, and the heavy chain variable region is at least 90% identical to SEQ ID NO:40; the light chain variable region is at least 90% identical to SEQ ID NO:9, and the heavy chain variable region is at least 90% identical to SEQ ID NO:37; the light chain variable region is at least 90% identical to SEQ ID NO:4, and the heavy chain variable region is at least 90% identical to SEQ ID NO:32; the light chain variable region is at least 90% identical to SEQ ID NO:28, and the heavy chain variable region is at least 90% identical to SEQ ID NO:53; the light chain variable region is at least 90% identical to SEQ ID NO:16, and the heavy chain variable region is at least 90% identical to SEQ ID NO:45; the light chain variable region is at least 90% identical to SEQ ID NO:15, and the heavy chain variable region is at least 90% identical to SEQ ID NO:44; the light chain variable region is at least 90% identical to SEQ ID NO:14, and the heavy chain variable region is at least 90% identical to SEQ ID NO:43; the light chain variable region is at least 90% identical to SEQ ID NO:27, and the heavy chain variable region is at least 90% identical to SEQ ID NO:43; the light chain variable region is at least 90% identical to SEQ ID NO:5, and the heavy chain variable region is at least 90% identical to SEQ ID NO:33; the light chain variable region is at least 90% identical to SEQ ID NO:12, and the heavy chain variable region is at least 90% identical to SEQ ID NO:41; the light chain variable region is at least 90% identical to SEQ ID NO:23, and the heavy chain variable region is at least 90% identical to SEQ ID NO:48; the light chain variable region is at least 90% identical to SEQ ID NO:25, and the heavy chain variable region is at least 90% identical to SEQ ID NO:54; or the light chain variable region is at least 90% identical to SEQ ID NO:26, and the heavy chain variable region is at least 90% identical to SEQ ID NO:54. In another exampleaspect, the heavy chain and light chain variable regions are identical to the respective variable regions of the recited SEQ ID NOs.

One example describesaspect of the invention provides an isolated, alpha4beta7 heterodimer specific antigen binding protein having an EC50 of less than 35 ng/ml in a CD4+ memory T cell binding assay; another describesprovides an isolated, alpha4beta7 heterodimer specific antigen binding which has an EC50 of less than 10 ng/ml in a CD4+ memory T cell binding assay. In another exampleembodiment, it is describedthe invention provides an isolated, alpha4beta7 heterodimer specific antigen binding protein having an IC50 in a MAdCAM competition assay of less than 30 ng/m; in another is provided an isolated, alpha4beta7 heterodimer specific antigen binding which has an IC50 of less than 10 ng/ml in a MAdCAM competition assay. One example describesaspect of the invention provides an isolated, alpha4beta7 heterodimer specific antigen binding protein that binds an S250N mutant of alha4beta7.

In one exampleaspect of the invention, it is describedthe present invention provides nucleic acids encoding the aforementioned polypeptides. In another exampleaspect of the invention the nucleic acid is a vector. In another exampleembodiment of the invention, the invention provides host cells transformed or transfected with the inventive nucleic acids are described. In another exampleaspect of the invention, there is describedprovided a method of preparing a polypeptide comprising incubating the host cells under conditions promoting expression of the polypeptides and harvesting the polypeptides.

In another exampleaspect, it is describedthe present invention provides an isolated cell that secretes an antigen binding protein that binds alpha4beta7. In another exampleembodiment, the cell is a hybridoma. In another exampleembodiment, it is describedthe present invention provides a method of making an antigen binding protein that specifically binds alpha4beta7 (i.e., human alpha4beta7), comprising incubating said isolated cell under conditions that allow it to express said antigen binding protein.

In one exampleaspect, it is describedthe present invention provides an isolated antigen binding protein that specifically binds to an alpha4beta7 heterodimer. In another exampleembodiment, the isolated antigen binding protein, when bound to a human alpha4beta7, inhibits binding of alpha4beta7 to MAdCAM-1. Accordingly, one example describesembodiment of the invention provides a method of inhibiting at least one activity of alpha4beta7, comprising contacting a cell expressing alpha4beta7 with an alpha4beta7 heterodimer-specific antigen binding protein such that the activity is partially or fully inhibited. In one exampleaspect, such method is carried out in vivo. In one exampleaspect of the invention, the isolated antigen binding protein inhibits adhesion of cells expressing alpha4beta7 to cells expressing MAdCAM-1. In yet another exampleaspect of the invention, the isolated antigen binding protein inhibits trafficking of cells expressing alpha4beta7 to areas or tissues populated by cells expressing MAdCAM-1; in one example, of such an embodiment, the isolated antigen binding proteins inhibit trafficking of lymphocytes to the gut.

In another exampleaspect, it is describedthe present invention provides a pharmaceutical composition comprising the antigen binding protein. In one exampleembodiment, it is describedthe present invention provides a method of treating a condition in a subject comprising administering the pharmaceutical composition to the subject, wherein the condition is treatable by reducing the activity (partially or fully) of alpha4beta7 in the subject. In another exampleembodiment, the subject is a human being. In another exampleembodiment, the condition is an inflammatory condition of the gastrointestinal system. Thus, there is describedprovided a method of treating an individual afflicted with a condition characterized by inappropriate trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM, comprising administering to the individual an alpha4beta7 heterodimer specific antigen binding protein in am amount sufficient to

inhibit (partially or fully) the trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM. In one example~~embodiment~~, the condition is inflammatory bowel disease, for example, ulcerative colitis, Crohn's disease, Celiac disease (nontropical Sprue), enteropathy associated with seronegative arthropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy and ileoanal anastomosis. In another example~~embodiment~~, the condition is s pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma or graft versus host disease.

In another example~~embodiment~~, the method further comprises administering to the subject a second treatment. In another example~~embodiment~~, the second treatment is administered to the subject before and/or simultaneously with and/or after the pharmaceutical composition is administered to the subject. In another example~~embodiment~~, the second treatment comprises an anti-inflammatory agent. In another example~~embodiment~~, the second pharmaceutical composition comprises an agent selected from the group consisting of non-steroidal anti-inflammatory drugs, steroids, and immunomodulating agents. In another example~~embodiment~~, the method comprises administering to the subject a third treatment.

In another example~~aspect~~, it is described~~the present invention provides~~ a method of increasing the longevity of a subject comprising administering to the subject the pharmaceutical composition. In another example~~aspect, the~~ it is described~~present invention provides~~ a method of decreasing alpha4beta7 activity in a subject in need thereof comprising administering to the subject the pharmaceutical composition. In another example~~aspect, the present~~ it is described~~invention provides~~ a method of decreasing alpha4beta7-mediated trafficking (for example, alpha4beta7mediated gut homing) in a subject in need thereof comprising administering to the subject the pharmaceutical composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions, kits, and methods relating to molecules that bind to the integrin alpha4beta7 ("alpha4beta7"), including molecules that agonize or antagonize alpha4beta7, such as anti-alpha4beta7 antibodies, antibody fragments, and antibody derivatives, *e.g.*, antagonistic anti-alpha4beta7 antibodies, antibody fragments, or antibody derivatives. Also provided are nucleic acids, and derivatives and fragments thereof, comprising a sequence of nucleotides that encodes all or a portion of a polypeptide that binds to alpha4beta7, *e.g.*, a nucleic acid encoding all or part of an anti-alpha4beta7 antibody, antibody fragment, or antibody derivative, plasmids and vectors comprising such nucleic acids, and cells or cell lines comprising such nucleic acids and/or vectors and plasmids. The provided methods include, for example, methods of making, identifying, or isolating molecules that bind to alpha4beta7, such as anti-alpha4beta7 antibodies, methods of determining whether a molecule binds to alpha4beta7, methods of determining whether a molecule agonizes or antagonizes alpha4beta7, methods of making compositions, such as pharmaceutical compositions, comprising a molecule that binds to alpha4beta7, and methods for administering a molecule that binds alpha4beta7 to a subject, for example, methods for treating a condition mediated by alpha4beta7, and for agonizing or antagonizing a biological activity of alpha4beta7, *in vivo* or *in vitro*.

Polynucleotide and polypeptide sequences are indicated using standard one- or three-letter abbreviations. Unless otherwise indicated, each polypeptide sequence has amino terminus at the left

What is claimed is:

1. An isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 and a light chain variable region comprising CDR1, CDR2 and CDR3, wherein each respective CDR is selected from the group consisting of:

a) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:55, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:58;

b) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:56, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:59; and

c) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:57, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:60.

2. The alpha4beta7 heterodimer specific antigen binding protein of claim 1, selected from the group consisting of:

a) an antigen binding protein wherein the light chain variable region comprises SEQ ID NO:55, and the heavy chain variable region comprises SEQ ID NO:58;

b) an antigen binding protein wherein the light chain variable region comprises SEQ ID NO:55 wherein some, most or all of an N-terminal Glu is cyclized, and the heavy chain variable region comprises SEQ ID NO:58;

c) an antigen binding protein wherein the light chain variable region comprises SEQ ID NO:56, and the heavy chain variable region comprises SEQ ID NO:59; and

d) an antigen binding protein wherein the light chain variable region comprises SEQ ID NO:57, and the heavy chain variable region comprises SEQ ID NO:60;

3. An isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 and a light chain variable region comprising CDR1, CDR2 and CDR3, wherein the light chain CDR1, CDR2 and CDR3 are selected from the group consisting of:

a) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 3;

b) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 5;

c) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 7;

d) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 22; and

e) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 24;
and the heavy chain variable CDR1, CDR2 and CDR3 are from SEQ ID NO:58.

4. The alpha4beta7 heterodimer specific antigen binding protein of claim 3, wherein the light chain variable region is selected from the group consisting of:

a) a light chain variable region at least 90% identical to SEQ ID NO:3;

b) a light chain variable region at least 90% identical to SEQ ID NO:5;

c) a light chain variable region at least 90% identical to SEQ ID NO:7;

d) a light chain variable region at least 90% identical to SEQ ID NO:22; and

e) a light chain variable region at least 90% identical to SEQ ID NO:24;

and the heavy chain variable region comprises SEQ ID NO:58.

5. An isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 and a light chain variable region comprising CDR1, CDR2 and CDR3, wherein the light chain CDR1, CDR2 and CDR3 are selected from the group consisting of:

a) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO:12;

b) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 25; and

c) a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO: 26;

and the heavy chain CDR1, CDR2 and CDR3 are selected from the group consisting of:

a') a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO:41; and

b') a CDR1, CDR2 and CDR3 at least 90% identical to a CDR1, CDR2 and CDR3, respectively, of SEQ ID NO:54.

6. The alpha4beta7 heterodimer specific antigen binding protein of claim 5, wherein the light chain variable region is selected from the group consisting of variable regions that are at least 90% identical to any one of SEQ ID NOs: 12, 25 and 26, and the heavy chain variable region is selected from the group consisting of variable regions that are at least 90% identical to any one of SEQ ID NOs:41 and 54.

7. An isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 and a light chain variable region comprising CDR1,

CDR2 and CDR3, wherein each respective CDR is at least 90% identical to a CDR selected from the group consisting of:

a) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:10, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:38;

b) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:2, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:30;

c) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:20, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:51;

d) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:11, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:39;

e) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:13, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:42;

f) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:17, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:46;

g) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:8, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:36;

h) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:19, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:49;

i) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:18, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:47;

j) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:21, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:52;

k) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:3, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:31;

l) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:7, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:35;

m) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:6, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:34;

n) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:1, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:29;

o) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:22, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:50;

p) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:24, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:40;

q) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:9, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:37;

r) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:4, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:32;

s) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:28, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:53;

t) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:16, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:45;

u) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:15, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:44;

v) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:14, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:43;

w) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:27, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:43;

x) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:5, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:33;

y) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:12, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:41;

z) a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:23, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:48;

a') a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:25, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:54; and

b') a light chain CDR1, CDR2 and CDR3 from SEQ ID NO:26, and a heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:54.

8. The alpha4beta7 heterodimer specific antigen binding protein of claim 7, wherein each respective CDR is selected from the group consisting of:

a) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:10, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:38;

b) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:2, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:30;

c) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:20, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:51;

d) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:11, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:39;

e) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:13, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:42;

f) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:17, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:46;

g) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:8, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:36;

h) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:19, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:49;

i) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:18, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:47;

j) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:21, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:52;

k) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:3, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:31;

l) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:7, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:35;

m) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:6, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:34;

n) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:1, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:29;

o) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:22, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:50;

p) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:24, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:40;

q) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:9, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:37;

r) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:4, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:32;

s) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:28, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:56;

t) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:16, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:45;

u) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:15, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:44;

v) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:14, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:43;

w) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:27, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:43;

x) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:5, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:33;

y) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:12, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:41;

z) the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:23, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:48;

a') the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:25, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:54; and

b') the light chain CDR1, CDR2 and CDR3 from SEQ ID NO:26, and the heavy chain CDR1, CDR2 and CDR3 from SEQ ID NO:54.

9. The alpha4beta7 heterodimer specific antigen binding protein of claim 7, wherein

a) the light chain variable region is at least 90% identical to SEQ ID NO:10, and the heavy chain variable region is at least 90% identical to SEQ ID NO:38;

b) the light chain variable region is at least 90% identical to SEQ ID NO:2, and the heavy chain variable region is at least 90% identical to SEQ ID NO:30;

c) the light chain variable region is at least 90% identical to SEQ ID NO:20, and the heavy chain variable region is at least 90% identical to SEQ ID NO:51;

d) the light chain variable region is at least 90% identical to SEQ ID NO:11, and the heavy chain variable region is at least 90% identical to SEQ ID NO:39;

e) the light chain variable region is at least 90% identical to SEQ ID NO:13, and the heavy chain variable region is at least 90% identical to SEQ ID NO:42;

f) the light chain variable region is at least 90% identical to SEQ ID NO:17, and the heavy chain variable region is at least 90% identical to SEQ ID NO:46;

g) the light chain variable region is at least 90% identical to SEQ ID NO:8, and the heavy chain variable region is at least 90% identical to SEQ ID NO:36;

h) the light chain variable region is at least 90% identical to SEQ ID NO:19, and the heavy chain variable region is at least 90% identical to SEQ ID NO:49;

i) the light chain variable region is at least 90% identical to SEQ ID NO:18, and the heavy chain variable region is at least 90% identical to SEQ ID NO:47;

j) the light chain variable region is at least 90% identical to SEQ ID NO:21, and the heavy chain variable region is at least 90% identical to SEQ ID NO:52;

k) the light chain variable region is at least 90% identical to SEQ ID NO:3, and the heavy chain variable region is at least 90% identical to SEQ ID NO:31;

l) the light chain variable region is at least 90% identical to SEQ ID NO:7, and the heavy chain variable region is at least 90% identical to SEQ ID NO:35;

m) the light chain variable region is at least 90% identical to SEQ ID NO:6, and the heavy chain variable region is at least 90% identical to SEQ ID NO:34;

n) the light chain variable region is at least 90% identical to SEQ ID NO:1, and the heavy chain variable region is at least 90% identical to SEQ ID NO:29;

o) the light chain variable region is at least 90% identical to SEQ ID NO:22, and the heavy chain variable region is at least 90% identical to SEQ ID NO:50;

p) the light chain variable region is at least 90% identical to SEQ ID NO:24, and the heavy chain variable region is at least 90% identical to SEQ ID NO:40;

q) the light chain variable region is at least 90% identical to SEQ ID NO:9, and the heavy chain variable region is at least 90% identical to SEQ ID NO:37;

r) the light chain variable region is at least 90% identical to SEQ ID NO:4, and the heavy chain variable region is at least 90% identical to SEQ ID NO:32;

s) the light chain variable region is at least 90% identical to SEQ ID NO:28, and the heavy chain variable region is at least 90% identical to SEQ ID NO:53;

t) the light chain variable region is at least 90% identical to SEQ ID NO:16, and the heavy chain variable region is at least 90% identical to SEQ ID NO:45;

u) the light chain variable region is at least 90% identical to SEQ ID NO:15, and the heavy chain variable region is at least 90% identical to SEQ ID NO:44;

v) the light chain variable region is at least 90% identical to SEQ ID NO:14, and the heavy chain variable region is at least 90% identical to SEQ ID NO:43;

w) the light chain variable region is at least 90% identical to SEQ ID NO:27, and the heavy chain variable region is at least 90% identical to SEQ ID NO:43;

x) the light chain variable region is at least 90% identical to SEQ ID NO:5, and the heavy chain variable region is at least 90% identical to SEQ ID NO:33;

y) the light chain variable region is at least 90% identical to SEQ ID NO:12, and the heavy chain variable region is at least 90% identical to SEQ ID NO:41;

z) the light chain variable region is at least 90% identical to SEQ ID NO:23, and the heavy chain variable region is at least 90% identical to SEQ ID NO:48;

a') the light chain variable region is at least 90% identical to SEQ ID NO:25, and the heavy chain variable region is at least 90% identical to SEQ ID NO:54; and

b') the light chain variable region is at least 90% identical to SEQ ID NO:26, and the heavy chain variable region is at least 90% identical to SEQ ID NO:54.

10. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 9, wherein

a) the light chain variable region comprises SEQ ID NO:10, and the heavy chain variable region comprises SEQ ID NO:38;

b) the light chain variable region comprises SEQ ID NO:2, and the heavy chain variable region comprises SEQ ID NO:30;

c) the light chain variable region comprises SEQ ID NO:20, and the heavy chain variable region comprises SEQ ID NO:51;

d) the light chain variable region comprises SEQ ID NO:11, and the heavy chain variable region comprises SEQ ID NO:39;

e) the light chain variable region comprises SEQ ID NO:13, and the heavy chain variable region comprises SEQ ID NO:42;

f) the light chain variable region comprises SEQ ID NO:17, and the heavy chain variable region comprises SEQ ID NO:46;

g) the light chain variable region comprises SEQ ID NO:8, and the heavy chain variable region comprises SEQ ID NO:36;

h) the light chain variable region comprises SEQ ID NO:19, and the heavy chain variable region comprises SEQ ID NO:49;

i) the light chain variable region comprises SEQ ID NO:18, and the heavy chain variable region comprises SEQ ID NO:47;

j) the light chain variable region comprises SEQ ID NO:21, and the heavy chain variable region comprises SEQ ID NO:52;

k) the light chain variable region comprises SEQ ID NO:3, and the heavy chain variable region comprises SEQ ID NO:31;

l) the light chain variable region comprises SEQ ID NO:7, and the heavy chain variable region comprises SEQ ID NO:35;

m) the light chain variable region comprises SEQ ID NO:6, and the heavy chain variable region comprises SEQ ID NO:34;

n) the light chain variable region comprises SEQ ID NO:1, and the heavy chain variable region comprises SEQ ID NO:29;

o) the light chain variable region comprises SEQ ID NO:22, and the heavy chain variable region comprises SEQ ID NO:50;

p) the light chain variable region comprises SEQ ID NO:24, and the heavy chain variable region comprises SEQ ID NO:40;

q) the light chain variable region comprises SEQ ID NO:9, and the heavy chain variable region comprises SEQ ID NO:37;

r) the light chain variable region comprises SEQ ID NO:4, and the heavy chain variable region comprises SEQ ID NO:32;

s) the light chain variable region comprises SEQ ID NO:28, and the heavy chain variable region comprises SEQ ID NO:53;

t) the light chain variable region comprises SEQ ID NO:16, and the heavy chain variable region comprises SEQ ID NO:45;

u) the light chain variable region comprises SEQ ID NO:15, and the heavy chain variable region comprises SEQ ID NO:44;

v) the light chain variable region comprises SEQ ID NO:14, and the heavy chain variable region comprises SEQ ID NO:43;

w) the light chain variable region comprises SEQ ID NO:27, and the heavy chain variable region comprises SEQ ID NO:43;

x) the light chain variable region comprises SEQ ID NO:5, and the heavy chain variable region comprises SEQ ID NO:33;

y) the light chain variable region comprises SEQ ID NO:12, and the heavy chain variable region comprises SEQ ID NO:41;

z) the light chain variable region comprises SEQ ID NO:23, and the heavy chain variable region comprises SEQ ID NO:48;

a') the light chain variable region comprises SEQ ID NO:25, and the heavy chain variable region comprises SEQ ID NO:54;

b') the light chain variable region comprises SEQ ID NO:26, and the heavy chain variable region comprises SEQ ID NO:54.

11. The isolated, alpha4beta7 heterodimer specific antigen binding protein of any one of claims 1 through 10, which further comprises a light chain constant region and a heavy chain constant region.

12. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 11 wherein the light chain constant region is selected from the group consisting of:

a) a kappa-type light chain constant region; and

b) a lambda-type light chain constant region.

and the heavy chain constant region is selected from the group consisting of:

a') a constant region from an IgD antibody;

b') a constant region from an IgE antibody;

c') a constant region from an IgM antibody;

d') a constant region from an IgG1 antibody;

e') a constant region from an IgG2 antibody;

f') a constant region from an IgG3 antibody;

g') a constant region from an IgG4 antibody; and

h') a constant region from an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

13. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 12 wherein the light chain constant region is selected from the group consisting of:

a) a polypeptide comprising SEQ ID NO:70;

b) a polypeptide at least 90% identical to SEQ ID NO:70;

c) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five N-terminal and/or C-terminal amino acids have been removed; and

d) a polypeptide of a), b) or c) which incorporates one or more post-translational modifications;

and the heavy chain constant region is selected from the group consisting of:

a') a polypeptide comprising SEQ ID NO:72;

b') a polypeptide at least 90% identical to SEQ ID NO:72;

c' a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five N-terminal and/or C-terminal amino acids have been removed; and

d') a polypeptide of a'), b') or c') which incorporates one or more post-translational modifications.

14. An isolated, alpha4beta7 heterodimer specific antigen binding protein having an EC50 of less than 35 ng/ml in a CD4+ memory T cell binding assay.

15. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 14 which has an EC50 of less than 10 ng/ml in a CD4+ memory T cell binding assay.

16. An isolated, alpha4beta7 heterodimer specific antigen binding protein having an IC50 in a MAdCAM competition assay of less than 30 ng/ml.

17. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 16 which has an IC50 of less than 10 ng/ml in a MAdCAM competition assay.

18. An isolated, alpha4beta7 heterodimer specific antigen binding protein that binds an S250N mutant of alha4beta7.

19. An isolated nucleic acid that encodes the antigen binding protein of any one of claims 1 through 18.

20. A vector comprising the nucleic acid of claim 19.

21. An isolated host cell transfected or transformed with the vector of claim 20.

22. An *in vitro* method for the production of an antigen binding protein comprising culturing the host cell of claim 21 under conditions promoting expression and recovering the protein from the culture medium.

23. A composition comprising the polypeptide of any one of claims 1 through 18 and a physiologically acceptable diluent, excipient or carrier.

24. Use of the alpha4beta7 heterodimer-specific antigen binding protein according to any one of claims 1 through 18 in the manufacture of a medicament for inhibiting at least one activity of alpha4beta7, wherein the use comprises contacting a cell expressing alpha4beta7 with the alpha4beta7 heterodimer-specific antigen binding protein according to any one of claims 1 through 18 such that adhesion of the cell to MAdCAM-1 is partially or fully inhibited.

25. Use of the alpha4beta7 heterodimer-specific antigen binding protein according to any one of claims 1 through 18 in the manufacture of a medicament for inhibiting trafficking of cells expressing alpha4beta7 to tissues comprising cells that express MAdCAM-1, wherein the use comprises contacting a cell expressing alpha4beta7 to the alpha4beta7 heterodimer-specific antigen binding protein according to any one of claims 1 through 18 such that adhesion of the cell to MAdCAM-1 is partially or fully inhibited.

26. Use of the composition according to claim 23 treating an individual afflicted with a condition characterized by inappropriate trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1, wherein the use comprises administration to the individual the composition according to claim 23 in am amount sufficient to inhibit the trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1.

27. The use of claim 26 wherein the condition is inflammatory bowel disease

28. The use of claim 27 wherein the condition is selected from the group consisting of ulcerative colitis, Crohn's disease, Celiac disease (nontropical Sprue), enteropathy associated with seronegative arthropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, and pouchitis resulting after proctocolectomy and ileoanal anastomosis.

29. The use of claim 26 wherein the condition is selected from the group consisting of pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma and graft versus host disease.

30. An isolated polynucleotide sufficient for use as a hybridization probe, PCR primer or sequencing primer that is a fragment of the nucleic acid molecule of claim 19 or its complement.

CLAIMS :

1. An isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 from SEQ ID NO:37, and a light chain variable region comprising CDR1, CDR2 and CDR3 from SEQ ID NO:9.

2. The heterodimer specific antigen binding protein of claim 1, wherein the light chain variable region is at least 90% identical to SEQ ID NO:9 by containing substitutions in the framework regions set forth in SEQ ID NO:56, and the heavy chain variable region is at least 90% identical to SEQ ID NO:37 by containing substitutions in the framework regions set forth in SEQ ID NO:59.

3. The heterodimer specific antigen binding protein of claim 2, wherein the light chain variable region comprises SEQ ID NO:9, and the heavy chain variable region is selected from the group consisting of a polypeptide that comprises SEQ ID NO:37 and a polypeptide that comprises SEQ ID NO:37 wherein the N-terminal amino acid is converted to pyroglutamic acid.

4. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 1, which further comprises a light chain constant region and a heavy chain constant region.

5. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 4 wherein the light chain constant region is a kappa-type light chain constant region; and the heavy chain constant region is selected from the group consisting of:

a') a constant region from an IgD antibody;
b') a constant region from an IgE antibody;
c') a constant region from an IgM antibody;
d') a constant region from an IgG1 antibody;
e') a constant region from an IgG2 antibody;
f') a constant region from an IgG3 antibody;
g') a constant region from an IgG4 antibody; and
h') a constant region from an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

6. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 4 wherein the light chain constant region is selected from the group consisting of:

a) a polypeptide comprising SEQ ID NO:70;

b) a polypeptide at least 90% identical to SEQ ID NO:70;

c) a polypeptide of a) which incorporates a post-translational modification selected from the group consisting of conversion of glutamine to pyroglutamic acid, deamidation of an amino acid, isomerization of an amino acid, glycation of an amino acid, oxidation of an amino acid, N-linked glycosylation, and O-linked glycosylation;

d) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five N-terminal amino acids have been removed;

e) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five C-terminal amino acids have been removed; and

f) combinations of the above; and the heavy chain constant region is selected from the group consisting of:

a') a polypeptide comprising SEQ ID NO:72;

b') a polypeptide at least 90% identical to SEQ ID NO:72;

c') a polypeptide of a') which incorporates a post-translational modification selected from the group consisting of conversion of glutamine to pyroglutamic acid, deamidation of an amino acid, isomerization of an amino acid, glycation of an amino acid, oxidation of an amino acid, N-linked glycosylation, and O-linked glycosylation;

d') a polypeptide having an amino acid sequence as set forth in SEQ ID NO:72 from which one, two, three, four or five N-terminal amino acids have been removed;

e') a polypeptide having an amino acid sequence as set forth in SEQ ID NO:72 from which one, two, three, four or five C-terminal amino acids have been removed; and

f')combinations of the above.

7. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 2 which further comprises a light chain constant region and a heavy chain constant region.

8. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 7 wherein the light chain constant region is a kappa-type light chain constant region; and the heavy chain constant region is selected from the group consisting of:

a') a constant region from an IgD antibody;

b') a constant region from an IgE antibody;

c') a constant region from an IgM antibody;

d') a constant region from an IgG1 antibody;

e') a constant region from an IgG2 antibody;

f') a constant region from an IgG3 antibody;

g') a constant region from an IgG4 antibody; and

h') a constant region from an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

9. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 7 wherein the light chain constant region is selected from the group consisting of:

a) a polypeptide comprising SEQ ID NO:70;

b) a polypeptide at least 90% identical to SEQ ID NO:70;

c) a polypeptide of a) which incorporates a post-translational modification selected from the group consisting of conversion of glutamine to pyroglutamic acid, deamidation of an amino acid, isomerization of an amino acid, glycation of an amino acid, oxidation of an amino acid, N-linked glycosylation, and O-linked glycosylation; and

d) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five N-terminal amino acids have been removed;

e) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five C-terminal amino acids have been removed; and

f) combinations of the above; and the heavy chain constant region is selected from the group consisting of:

a') a polypeptide comprising SEQ ID NO:72;

b') a polypeptide at least 90% identical to SEQ ID NO:72;

c') a polypeptide of a') which incorporates a post-translational modification selected from the group consisting of conversion of glutamine to pyroglutamic acid, deamidation of an amino acid, isomerization of an amino acid, glycation of an amino acid, oxidation of an amino acid, N-linked glycosylation, and O-linked glycosylation; and

d') a polypeptide having an amino acid sequence as set forth in SEQ ID NO:72 from which one, two, three, four or five N-terminal amino acids have been removed;

e') a polypeptide having an amino acid sequence as set forth in SEQ ID NO:72 from which one, two, three, four or five C-terminal amino acids have been removed; and

f')combinations of the above.

10. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 3, which further comprises a light chain constant region and a heavy chain constant region.

11. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 10 wherein the light chain constant region is a kappa-type light chain constant region; and the heavy chain constant region is selected from the group consisting

of:

a') a constant region from an IgD antibody;
b') a constant region from an IgE antibody;
c') a constant region from an IgM antibody;
d') a constant region from an IgG1 antibody;
e') a constant region from an IgG2 antibody;
f') a constant region from an IgG3 antibody;
g') a constant region from an IgG4 antibody; and
h') a constant region from an IgG4 antibody having at least one mutation in a hinge region that alleviates a tendency to form intra-H chain disulfide bond.

12. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 10 wherein the light chain constant region is selected from the group consisting of:

a) a polypeptide comprising SEQ ID NO:70;
b) a polypeptide at least 90% identical to SEQ ID NO:70;
c) a polypeptide of a) which incorporates a post-translational modification selected from the group consisting of conversion of glutamine to pyroglutamic acid, deamidation of an amino acid, isomerization of an amino acid, glycation of an amino acid, oxidation of an amino acid, N-linked glycosylation, and O-linked glycosylation;
d) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five N-terminal amino acids have been removed;
e) a polypeptide having an amino acid sequence as set forth in SEQ ID NO:70 from which one, two, three, four or five C-terminal amino acids have been removed; and
f) combinations of the above; and the heavy chain constant region is selected from the group consisting of:

a') a polypeptide comprising SEQ ID NO:72;
b') a polypeptide at least 90% identical to SEQ ID NO:72;
c') a polypeptide of a') which incorporates a post-translational modification selected from the group consisting of conversion of glutamine to pyroglutamic acid, deamidation of an amino acid, isomerization of an amino acid, glycation of an amino acid, oxidation of an amino acid, N-linked glycosylation, and O-linked glycosylation; and
d') a polypeptide having an amino acid sequence as set forth in SEQ NO:72 from which one, two, three, four or five N-terminal amino acids have been removed;
e') a polypeptide having an amino acid sequence as set forth in SEQ ID NO:72 from which one, two, three, four or five C-terminal amino acids have been removed; and
f') combinations of the above.

13. An isolated, alpha4beta7 heterodimer specific antigen binding protein having a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region is encoded by a nucleic acid that encodes SEQ ID NO:37, and the light chain variable region is encoded by a nucleic acid that encodes SEQ ID NO:9.

14. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 13 wherein the nucleic acid that encodes the heavy chain variable region comprises SEQ ID NO:64, and the nucleic acid that encodes the light chain variable region comprises SEQ ID NO:63.

15. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 13, which further comprises a light chain constant region and a heavy china constant region, wherein the light chain constant region is encoded by a nucleic acid that encodes SEQ ID NO:70 and the heavy chain constant region is encoded by a nucleic acid that encodes SEQ ID NO:72.

16. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 15 wherein the light chain constant region is encoded by a nucleic acid that comprises SEQ ID NO:69, and the heavy chain constant region is encoded by a nucleic acid that comprises SEQ ID NO:71.

17. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 14, which further comprises a light chain constant region and a heavy china constant region, wherein the light chain constant region is encoded by a nucleic acid that encodes SEQ ID NO:70 and the heavy chain constant region is encoded by a nucleic acid that encodes SEQ ID NO:72.

18. The isolated, alpha4beta7 heterodimer specific antigen binding protein of claim 17 wherein the light chain constant region is encoded by a nucleic acid that comprises SEQ NO:69, and the heavy chain constant region is encoded by a nucleic acid that comprises SEQ ID NO:71.

19. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 1 and a physiologically acceptable diluent, excipient or carrier.

20. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 2 and a physiologically acceptable diluent, excipient or carrier.

21. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 3 and a physiologically acceptable diluent, excipient or carrier.

22. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 4 and a physiologically acceptable diluent, excipient or carrier.

23. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising protein of claim 5 and a physiologically acceptable diluent, excipient or carrier.

24. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 6 and a physiologically acceptable diluent, excipient or carrier.

25. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 7 and a physiologically acceptable diluent, excipient or carrier.

26. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 8 and a physiologically acceptable diluent, excipient or carrier.

27. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of Claim 9 and a physiologically acceptable diluent, excipient or carrier.

28. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 10 and a physiologically acceptable diluent, excipient or carrier.

29. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis,

chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 11 and a physiologically acceptable diluent, excipient or carrier.

30. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 12 and a physiologically acceptable diluent, excipient or carrier.

31. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 13 and a physiologically acceptable diluent, excipient or carrier.

32. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 14 and a physiologically acceptable diluent, excipient or carrier.

33. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 15 and a physiologically acceptable diluent, excipient or carrier.

34. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 16 and a physiologically acceptable diluent, excipient or carrier.

35. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 17 and a physiologically acceptable diluent, excipient or carrier.

36. A composition for treating inflammatory bowel disease, pancreatitis, insulin-dependent diabetes mellitus, mastitis, cholecystitis, cholangitis, pericholangitis, chronic bronchitis, chronic sinusitis, asthma, or graft versus host disease, comprising the protein of claim 18 and a physiologically acceptable diluent, excipient or carrier.

37. An isolated nucleic acid that encodes the antigen binding protein of any one of Claims 1 through 18.

38. A vector comprising the nucleic acid of Claim 37.

39. An isolated host cell transfected or transformed with the vector of Claim 38.

40. A method for the production of an antigen binding protein comprising culturing the host cell of Claim 39 to express the protein and recovering the protein from the culture medium.