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 one aspect, the present invention provides 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 for use in inhibiting at least one activity of alpha4beta7, wherein the antigen binding protein partially or fully inhibit adhesion of the cell to MAdCAM-1. In another aspect, the present invention provides 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 for use in inhibiting trafficking of cells expressing alpha4beta7 to tissues comprising cells that express MAdCAM-1, wherein the antigen binding protein partially or fully inhibit adhesion of the cells to MAdCAM-1. In another aspect, the present invention provides 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

for use in treating an individual afflicted with a condition characterized by inappropriate trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1, wherein the antigen binding protein is in an amount sufficient to inhibit the trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1. In another aspect, the present invention provides 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 for use in inhibiting at least one activity of alpha4beta7, wherein the antigen binding protein partially or fully inhibit adhesion of the cell to MAdCAM-1. In another aspect, the present invention provides 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 for use in inhibiting trafficking of cells expressing alpha4beta7 to tissues comprising cells that express MAdCAM-1, wherein the antigen binding protein partially or fully inhibit adhesion of the cells to MAdCAM-1. In another aspect, the present invention provides 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 for use in treating an individual afflicted with a condition characterized by inappropriate trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1, wherein the antigen binding protein is in an amount sufficient to inhibit the trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1. Also disclosed is an isolated antigen binding protein that specifically binds to human alpha4beta7 (i.e., an alpha4beta7 heterodimer specific antigen binding protein). In some examples, 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 examples, 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, the isolated antigen binding protein comprises a heavy chain constant region from one of the aforementioned antibodies; in another example, 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 afore-mentioned polypeptides which incorporates one or more post-translational modifications. In one example, the isolated antigen binding protein comprises a kappa light chain constant region, in another it comprises a lambda light chain region. In one 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 afore-mentioned polypeptides which incorporates one or more post-translational modifications

Also disclosed is 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, 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, 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 example, 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, the disclosure 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, the present disclosure 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, the heavy chain variable region comprises CDR1, CDR2 and CDR3 and the light chain variable region comprises CDR1, CDR2 and CDR3. In one example, 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 example, 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 example, 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, the disclosure 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.

Also disclosed is 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 example, 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 example, 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 example, 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, the disclosure 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 example, the heavy chain and light chain CDRs are identical to the respective CDRs of the recited SEQ ID NOs. In one example, 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 example, 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 example, 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 example, the heavy chain and light chain variable regions are identical to the respective variable regions of the recited SEQ ID NOs.

Also disclosed is 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 provides 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 example, the disclosure 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. Also disclosed is an

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

Also disclosed are provides nucleic acids encoding the aforementioned polypeptides. In another example the nucleic acid is a vector. In some example host cells transformed or transfected with the inventive nucleic acids. In another example, there is provided a method of preparing a polypeptide comprising incubating the host cells under conditions promoting expression of the polypeptides and harvesting the polypeptides.

In another example, the present disclosure provides an isolated cell that secretes an antigen binding protein that binds alpha4beta7. In another example, the cell is a hybridoma. In another example, the present disclosure 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 example, the present disclosure provides an isolated antigen binding protein that specifically binds to an alpha4beta7 heterodimer. In another example, the isolated antigen binding protein, when bound to a human alpha4beta7, inhibits binding of alpha4beta7 to MAdCAM-1. Accordingly, one example of the disclosure 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 aspect, such method is carried out in vivo. In one example, the isolated antigen binding protein inhibits adhesion of cells expressing alpha4beta7 to cells expressing MAdCAM-1. In yet another example, 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.

Also disclosed is a pharmaceutical composition comprising the antigen binding protein. In one example, the present disclosure 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 example, the subject is a human being. In another example, the condition is an inflammatory condition of the gastrointestinal system. Thus, there is provided 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, 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, 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, the method further comprises administering to the subject a second treatment. In another example, 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, the second treatment comprises an anti-inflammatory agent. In another example, 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, the method comprises administering to the subject a third treatment.

Also disclosed is a method of increasing the longevity of a subject comprising administering to the subject the pharmaceutical composition. Also disclosed is a method of decreasing alpha4beta7 activity in a subject in need thereof comprising administering to the subject the pharmaceutical composition. In another example, the present disclosure 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 and a carboxy terminus at the right; each single-stranded nucleic acid sequence, and the top strand of each double-stranded nucleic acid sequence has a 5' terminus at the left and a 3' terminus at the right. A particular polypeptide or polynucleotide sequence also can be described by explaining how it differs from a reference sequence.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific

What is claimed is:

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 for use in inhibiting at least one activity of alpha4beta7, wherein the antigen binding protein partially or fully inhibit adhesion of the cell to MAdCAM-1.

2. 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 for use in inhibiting trafficking of cells expressing alpha4beta7 to tissues comprising cells that express MAdCAM-1, wherein the antigen binding protein partially or fully inhibit adhesion of the cells to MAdCAM-1.

3. 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 for use in treating an individual afflicted with a condition characterized by inappropriate trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1, wherein the antigen binding protein is in an amount sufficient to inhibit the trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1.

4. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 3, wherein the condition is inflammatory bowel disease.

5. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 4, 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.

6. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 3 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.

7. The heterodimer specific antigen binding protein for use according to any one of the preceding claims, 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.

8. The heterodimer specific antigen binding protein for use according to claim 7, 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.

9. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to any one of the preceding claims, which further comprises a light chain constant region and a heavy chain constant region.

10. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 9 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.

11. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 9 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 one or more 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 one or more 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.

12. 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 for use in inhibiting at least one activity of alpha4beta7, wherein the antigen binding protein partially or fully inhibit adhesion of the cell to MAdCAM-1.

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 for use in inhibiting trafficking of cells

expressing alpha4beta7 to tissues comprising cells that express MAdCAM-1, wherein the antigen binding protein partially or fully inhibit adhesion of the cells to MAdCAM-1.

14. 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 for use in treating an individual afflicted with a condition characterized by inappropriate trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1, wherein the antigen binding protein is in an amount sufficient to inhibit the trafficking of cells expressing alpha4beta7 to tissues comprising cells expressing MAdCAM-1.

15. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 14, wherein the condition is inflammatory bowel disease.

16. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 15, 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.

17. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 14 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.

18. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to any one of claims 12 to 17 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.

19. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to any one of claims 12 to 17, 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.

20. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 19 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.

21. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 18, 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.

22. The isolated, alpha4beta7 heterodimer specific antigen binding protein for use according to claim 21 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.