ANTAGONISTIC HUMAN LIGHT-SPECIFIC HUMAN MONOCLONAL ANTIBODIES

INTRODUCTION

[0001] Provided herein are antibodies that immunospecifically bind to a human LIGHT (hLIGHT) (**l**ymphotoxin-like, exhibits **i**nducible expression and competes with HSV **g**lycoprotein D for **H**VEM, a receptor expressed by **T** lymphocytes) polypeptide, a hLIGHT polypeptide fragment or other hLIGHT epitope. In some embodiments the antibodies are fully human antibodies, preferably fully human monoclonal antibodies, that immunospecifically bind to a hLIGHT polypeptide, hLIGHT polypeptide fragment or hLIGHT epitope. Also provided are isolated nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide, hLIGHT polypeptide fragment, or hLIGHT epitope. The invention further provides vectors and host cells comprising nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide, hLIGHT polypeptide fragment, or hLIGHT epitope, as well as methods of making antibodies that immunospecifically bind to a hLIGHT polypeptide, hLIGHT polypeptide fragment, or hLIGHT epitope. Also provided are methods of using the anti-hLIGHT antibodies provided herein to inhibit hLIGHT biological activity *in vivo* and/or to treat or otherwise manage a hLIGHT-mediated disease in a patient.

BACKGROUND

[0002] LIGHT, (**l**ymphotoxin-like, exhibits **i**nducible expression and competes with HSV **g**lycoprotein D for **H**VEM, a receptor expressed by **T** lymphocytes) is one potential cytokine target that has been implicated in the processes of chronic inflammatory autoimmune diseases (Mauri *et al.* 1998 Immunity 8 21-30). As a member of the TNF superfamily (TNFSF) of ligands, LIGHT is also known as TNFSF14 or CD258. LIGHT is expressed on the surface of T cells upon activation in a tightly regulated manner appearing within 4 hours, peaking by 12-24 hours and disappearing by 48 hours (Castellano *et al.* 2002 J Biol Chem 277 42841-51). However, LIGHT is also present at detectable levels constitutively on the surface of immature dendritic cells (Tamada *et al.* 2000 J Immunol 164 4105-10) and on T cells and natural killer (NK) cells of the gut (Cohavy *et al.* 2005 J Immunol 174 646-53). LIGHT mediates its biologic effects by binding three TNF superfamily receptors including the lymphotoxin β receptor (LTβR) (Crowe *et al.* 1994 Science 264 707-10, Browning *et al.* 1997 J Immunol 159 3288-98), the herpes virus entry mediator

(HVEM) (Montgomery *et al.* 1996 Cell 87(3) 427-36), and decoy receptor 3 (DcR3) (Yu *et al.* 1999 J Biol Chem 274 13733-6).

[0003] Mice treated with an inhibitory LTβR-Fc fusion protein reduced the inflammatory symptoms in the CD4+CD45RB^{high} T cell transfer model of colitis, a CD4+ T cell-mediated pathology (Mackay *et al.* 1998 Gastroenterology 115 1464-75). Constitutive transgenic T cell specific expression of LIGHT also has been shown to lead to severe intestinal inflammation with autoimmune-like pathology resembling human inflammatory bowel disease (IBD) (Wang *et al.* 2005 J Immunol 174 8173-82, Shaikh *et al.* 2001 J Immunol 167 6330-7, Wang *et al.* 2001 J Immunol 167 5099-105, Wang *et al.* 2004 J Clin Invest 113 826-35). LIGHT-expressing lymphocytes can induce IBD-like symptoms (*e.g.*, cytokine profiles of human Crohn's disease, fissuring ulcers, ileitis, and increases in colonic IFN-γ and TNF) when mesenteric lymph node cells from LIGHT transgenic animals are transferred to RAG-/- (Wang *et al.* 2005 J Immunol 174 8173-82). In human disease, increases of LIGHT expression were observed in patients with active Crohn's disease (Cohavy *et al.* 2005 J Immunol 174 646-53, Wang *et al.* 2005 J Immunol 174 8173-82, Wang *et al.* 2004 J Clin Invest 113 826-35, Cohavy *et al.* 2004 J Immunol 173 251-8). LIGHT has also been demonstrated to be elevated in gut T cells of IBD patients (Cohavy *et al.* 2004 J Immunol 173 251-8). Genetic evidence also supports a role for LIGHT in IBD (Granger *et al.* 2001 J Immunol 167 5122-8); (Rioux *et al.* 2000 Am J Hum Genet 66 1863-70; Low *et al.* 2004 Inflamm Bowel Dis 10 173-81; Bonen and Cho 2003 Gastroenterology 124 521-36).

[0004] Moreover, CCL20-CCR6 signaling has been shown to be involved in IBD, and LIGHT induces CCL20 secretion from the human colonic epithelial cell line HT29.14s. In human studies, epithelial cells of the colon have been found to be a major source of CCL20 in IBD patients and CCL20 expression is increased in human IBD patients (Kwon *et al.* 2002 Gut 51 818-26; (Kaser *et al.* 2004 J Clin Immunol 24 74-85).

[0005] hLIGHT has also been implicated in graft-versus-host disease (GVHD). For example, LIGHT has been shown to provide potent costimulatory activity for T cells, enhancing proliferation an the production of Th1 cytokines independent of the B7-CD28 pathway (see, *e.g.*, Tamada *et al.* 2000 J. Immunol. 164 4105-4110). Blocking of LIGHT-HVEM costimulation by either anti-HVEM monoclonal antibodies, HVEM-Ig, or LTβR fusion protein inhibits allogeneic T cell responses (see, *e.g.*, Tamada *et al.*

2000 J. Immunol. 164 4105-4110., Harrop *et al.* 19998 J. Immunol. 161 1786). Furthermore, *in vivo* administration of LTβR-Ig or murine anti-LIGHT antibodies inhibits anti-host cytotoxic T lymphocyte (CTL) responses in a murine acute GVHD model (Tamada *et al.* 2000 Nat. Med. 6 283-289).

[0006] Although observations such as those discussed above indicate a role for LIGHT in inflammatory disorders, such as IBD or GVHD, to date no human anti-human LIGHT antibodies have been produced, nor have any human anti-hLIGHT antibodies or monoclonal anti-hLIGHT antibodies been shown to be antagonistic to hLIGHT biological activity. As such, a need continues to exist for identification of therapies, such as anti-LIGHT therapies, useful for treatment of inflammatory disorders in humans. Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

SUMMARY

[0007] Provided herein are antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided are isolated nucleic acids encoding antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Further provided are vectors and host cells comprising nucleic acids encoding antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided are methods of making antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided herein is a method of treating a hLIGHT-mediated disease comprising administering an antibody, such as a fully human antibody, that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. In preferred embodiments, anti-hLIGHT antibodies provided herein are antagonist antibodies that ameliorate, neutralize or otherwise inhibit hLIGHT biological activity *in vivo* (*e.g.*, the hLIGHT-mediated production or secretion of CCL20, IL-8 or RANTES from cells expressing a hLIGHT ligand, such as a hLIGHT receptor, (*e.g.*, HVEM, LTβR and/or DcR3)). An antibody of the disclosure can be a full-length antibody or an antigen-binding antibody fragment. The antibodies of the disclosure are also useful for detecting hLIGHT, as well as for ameliorating, neutralizing or otherwise inhibiting hLIGHT activity, *e.g.*, in a human subject suffering from a disorder in which hLIGHT activity is detrimental.

[0008] In one embodiment, provided herein is an isolated antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT polypeptide fragment, or a hLIGHT epitope. In some embodiments, the antibody immunospecifically binds to (a) a trimeric (or native) hLIGHT epitope, (b) a monomeric (or denatured) hLIGHT epitope, (c) both a trimeric hLIGHT epitope and a monomeric hLIGHT epitope, (d) a trimeric hLIGHT epitope but not a monomeric hLIGHT epitope, or (e) a monomeric hLIGHT epitope but not a trimeric hLIGHT epitope. In preferred embodiments, the antibody immunospecifically binds a trimeric hLIGHT epitope but not a human monomeric hLIGHT epitope. In preferred embodiments, the antibody is an E1 antibody, E13 antibody, E63 antibody, F19 antibody, or F23 antibody.

[0008a] In one aspect, there is provided an isolated antibody that is fully human and specifically binds to a hLIGHT epitope,wherein the antibody comprises:

(a) a VH CDR1, VH CDR2 and VH CDR3 of an antibody produced by a hybridoma having ATCC Accession NO. PTA-7819 and

(b) a VL CDR1, VL CDR2 and VL CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819.

[0008b] In one aspect, there is provided an isolated antibody that is fully human and specifically binds to a hLIGHT epitope, wherein the antibody comprises:

(a) a heavy chain variable region comprising

a VH CDR1 of SEQ ID NO:20,

a VH CDR2 of SEQ ID NO:21, and

a VH CDR3 of SEQ ID NO:22

and

(b) a light chain variable region comprising:

(1) a VL CDR1 of SEQ ID NO: 93, a VL CDR2 of SEQ ID NO: 96 and a VL CDR3 of SEQ ID NO: 99,

(2) a VL CDR1 of SEQ ID NO: 35, a VL CDR2 of SEQ ID NO: 36 and a VL CDR3 of SEQ ID NO: 37,

(3) a VL CDR1 of SEQ ID NO: 94, a VL CDR2 of SEQ ID NO: 97 and a VL CDR3 of SEQ ID NO: 100, or

(4) a VL CDR1 of SEQ ID NO: 95, a VL CDR2 of SEQ ID NO: 98 and a VL CDR3 of SEQ ID NO: 101.

[0009] Hybridomas that produce each of the E1, E13, E63, F19 and F23 antibodies were deposited under provisions of the Budapest Treaty with the American Type Culture Collection (ATCC, 10801 University Blvd., Manassas, VA 20110-2209) on July 12, 2006 (ATCC Accession Nos. PTA-7729 (hybridoma 124 E1) and PTA-7728 (hybridoma 124 F23), respectively), August 17, 2006 (ATCC Accession Nos. PTA-7818 (hybridoma 124 E63) and PTA-7819 (hybridoma 124 F19) and August 23, 2006 (ATCC Accession No. PTA-7842 (hybridoma 124 E13), and are herein incorporated by reference. Antibodies produced by each of hybridomas 124 E1, 124 E13, 124 E63, 124 F19 and 124 F23 may also be referred to herein as E1, E13, E63, F19, F23, respectively, and/or by the ATCC Accession Numbers. PTA-7729, PTA-7842, PTA-7818, PTA-7819, and PTA-7728, respectively.

[0010] These antibodies, hybridomas, methods of making these antibodies, and methods of using these antibodies are all included in the disclosure.

[0011] In specific embodiments, an antibody of the disclosure is one that is competitively blocked (*e.g.*, in a dose-dependent manner) by an E1 antibody, an E13 antibody, and/or an E63 antibody for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. In other embodiments, the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by an F19 antibody and/or an F23 antibody for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. In specific embodiments, the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by an E1 antibody, an E13 antibody and/or an E63 antibody, but is not competitively blocked (*e.g.*, in a dose-dependent manner) by an F19

antibody and/or an F23 antibody, for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. In other embodiments, the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by an F19 antibody and/or an F23 antibody, but is not competitively blocked (*e.g.*, in a dose-dependent manner) by an E1 antibody, an E13 antibody and/or an E63 antibody, for binding to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT fragment, or a hLIGHT epitope. Exemplary competitive blocking tests are provided in the Examples herein.

[0012] Provided herein are antibodies, or antigen binding antibody fragments thereof that immunospecifically bind to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the antibody or antigen-binding fragment comprises a VH chain, VL chain, VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of E1, E13, E63, F19 or F23.

[0013] In certain embodiments, the antibody or antigen binding fragment thereof comprises less than six CDRs. In some embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3. In specific embodiments, the antibody or antigen binding fragment thereof comprises or consists of one, two, three, four, or five CDRs selected from the group consisting of VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of E1, E13, E63, F19 or F23.

[0013a] In one aspect, there is provided a composition comprising the antibody as defined above.

[0014] Also provided herein are pharmaceutical compositions comprising an anti-hLIGHT antibody of the disclosure, such as E1, E13, E63, F19 or F23.

[0015] In specific embodiments, an antibody of the disclosure is a fully human antibody, a monoclonal antibody, a recombinant antibody, an antagonist antibody, or any combination thereof. In particular embodiments, the antibody is a fully human antibody, such as a fully human monoclonal antibody, or antigen binding fragment thereof, that immunospecifically binds to hLIGHT. In preferred embodiments, the antibody is an antagonist antibody.

[0016] In certain embodiments, the antibody competes (*e.g.*, in a dose dependent manner) with HVEM, LTβR, DcR3, or fusion proteins thereof (*e.g.*, Fc:HVEM, Fc:LTβR or Fc:DcR3), for binding to a hLIGHT polypeptide, such as a cell surface-expressed hLIGHT polypeptide or soluble hLIGHT polypeptide, a hLIGHT polypeptide

fragment, or a hLIGHT epitope. Exemplary competitive blocking tests are provided in the Examples herein.

[0017] In one embodiment, provided herein are isolated nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the nucleic acid encodes a VH chain, VL chain, VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of E1, E13, E63, F19 or F23.

[0017a] In one aspect, there is provided an isolated nucleic acid molecule

(i) comprising or consisting of a nucleic acid sequence that encodes (a) a VH amino acid sequence of an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819; and/or (b) a VL amino acid sequence of an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819, or

(ii) comprising a nucleic acid sequence that encodes (a) a VH CDR1, VH CDR2 and/or VH CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819, and/or (b) a VL CDR1, VL CDR2 and/or VL CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819, or a combination thereof, or

(iii) comprising or consisting of a nucleic acid sequence that encodes an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819,

(iv) comprising (a) a sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in SEQ ID NO: 44; and/or (b) a sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in any one of the SEQ ID NOS:49, 104, 105 or 106.

[0018] In one embodiment, provided herein are vectors and host cells comprising nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

[0018a] In one aspect, there is provided a vector comprising the nuclei acid molecule as defined above.

[0018b] In one aspect, there is provided a host cell comprising the vector as defined above.

[0018c] In one aspect, there is provided a method of producing the antibody as defined above, the method comprising culturing the host cell as defined above under conditions that promote production of the antibody.

[0019] In one embodiment, provided herein are methods of making antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the antibody immunospecifically binds to a single nucleotide polymorphism (SNP) variant of a hLIGHT polypeptide, such as 214E-32S, 214K-32S, 214E-32L and/or 214K-32L. Also provided herein are hybridomas that produce antibodies that immunospecifically bind to a hLIGHT polypeptide, or SNP variant thereof. In preferred embodiments, the hybridoma is the hybridoma that produces E1, E13, E63, F19 or F23.

[0019a] In one aspect, there is provided a hybridoma that produces an antibody as defined above, the hybridoma optionally having ATCC Accession No. PTA-7819.

[0019b] In one aspect, there is provided the composition as defined above

(i) for use in a method for alleviating one or more symptoms of inflammatory bowel disease (IBD) in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(ii) for use in a method for alleviating one or more symptoms of graft-versus-host disease (GVHD) in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(iii) for use in a method for decreasing or inhibiting binding of hLIGHT to HVEMLTβR, DcR3, or any combination thereof, in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(iv) for use in a method for decreasing or inhibiting the secretion of CCL20, IL-8, RANTES, or any combination thereof, in a human in need thereof, the method comprising administering to the human an effective amount of the composition.

[0020] In one embodiment, provided herein are methods of treating or otherwise alleviating one or more symptoms of a hLIGHT-mediated disease in a subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), wherein hLIGHT activity is inhibited by the antibody. In certain embodiments, the hLIGHT-mediated disease is an IBD, such as Crohn's disease or ulcerative colitis. In other embodiments, the hLIGHT mediated disease is GVHD.

[0021] In one embodiment, provided herein are methods for decreasing or inhibiting binding of hLIGHT to HVEM, LTβR and/or DcR3 in a subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT).

[0022] In one embodiment, provided herein are methods for decreasing or inhibiting a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a

subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed hLIGHT), wherein hLIGHT biological activity is decreased or inhibited by the antibody.

[0023] In one embodiment, provided herein are methods for decreasing or inhibiting binding of hLIGHT to HVEM, LTβR and/or DcR3 in a cell having cell surface-expressed hLIGHT, contacting the cell with an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), such as a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

[0024] In one embodiment, provided herein are methods for decreasing or inhibiting a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a cell having a cell surface-expressed hLIGHT receptor (such as, HVEM, LTβR and/or Dc3R), contacting the cell with an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT, or SNP variant thereof), wherein hLIGHT biological activity is decreased or inhibited by the antibody.

[0025] In one embodiment, provided herein is an antibody that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope, wherein said antibody further comprises a detectable tag. In certain embodiments, anti-hLIGHT antibodies that comprise a detectable tag are used in a method for the detection of hLIGHT in a sample, said method comprising contacting the sample with the anti-hLIGHT antibody. In specific embodiments, the sample comprises a cell expressing hLIGHT on the surface of the cell.

[0026] In one embodiment, provided herein are kits comprising an antibody that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

[0026a] In one aspect, there is provided a kit comprising the antibody as defined above, or the composition as defined above.

TERMINOLOGY

[0027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0028] The term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% (or 1% or less) of a given value or range.

[0029] As used herein, "administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (*e.g.*, an anti-hLIGHT antibody provided herein) into a patient, such as by mucosal, intradermal, intravenous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, or a symptom thereof, is being treated, administration of the substance typically occurs after the onset of the disease or symptoms thereof. When a disease, or symptoms thereof, are being prevented, administration of the substance typically occurs before the onset of the disease or symptoms thereof.

[0030] In the context of a polypeptide, the term "analog" as used herein refers to a polypeptide that possesses a similar or identical function as a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody but does not necessarily comprise a similar or identical amino acid sequence of a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody, or possess a similar or identical structure of a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody. A polypeptide that has a similar amino acid sequence refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide having an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, and preferably at least 90%, more preferably at least 95%, or most preferably at least 99% identical to the amino acid sequence of a hLIGHT polypeptide (*e.g.*, SEQ ID NO:52), a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody described herein; (b) a polypeptide encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody (or VH or VL region thereof) described herein of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues (see, *e.g.*, Sambrook *et al.* (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor

Laboratory Press, Cold Spring Harbor, NY; Maniatis *et al.* (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY); and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, and preferably at least 90%, more preferably at least 95%, or most preferably at least 99% identical to the nucleotide sequence encoding a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody (or VH or VL region thereof) described herein. A polypeptide with similar structure to a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an anti-hLIGHT antibody described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a hLIGHT polypeptide, a fragment of a hLIGHT, or a hLIGHT antibody described herein. The structure of a polypeptide can determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

[0031] To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = number of identical overlapping positions/total number of positions X 100%). In one embodiment, the two sequences are the same length.

[0032] The determination of percent identity between two sequences (*e.g.*, amino acid sequences or nucleic acid sequences) can also be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.*, 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.*, for score=100, wordlength=12 to obtain nucleotide

sequences homologous to a nucleic acid molecules of the present invention. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.*, to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule of the present invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, 1997, Nucleic Acids Res. 25:3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (see, *e.g.*, National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another preferred, non limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[0033] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

[0034] As used herein, an "antagonist" or "inhibitor" of hLIGHT refers to a molecule that is capable of inhibiting or otherwise decreasing one or more of the biological activities of hLIGHT, such as in a cell expressing hLIGHT or in a cell expressing a hLIGHT ligand, such as a hLIGHT receptor. For example, in certain embodiments, antibodies of the invention are antagonist antibodies that inhibit or otherwise decrease secretion of CCL20, IL-8 and/or RANTES from a cell having a cell surface-expressed hLIGHT receptor (*e.g.*, HVEM, LTβR and/or DcR3) when said antibody is contacted with said cell. In some embodiments, an antagonist of hLIGHT (*e.g.*, an antagonistic antibody of the invention) may, for example, act by inhibiting or otherwise decreasing the activation and/or cell signaling pathways of the cell expressing a hLIGHT receptor, thereby inhibiting a hLIGHT-mediated biological activity of the cell the relative to the hLIGHT-mediated biological activity in the absence of antagonist. In certain embodiments the antibodies provided herein are fully human, antagonistic anti-hLIGHT antibodies, preferably fully human, monoclonal, antagonistic anti-hLIGHT antibodies.

[0035] The term "antibody" and "immunoglobulin" or "Ig" may be used interchangeably herein. The terms "antibodies that immunospecifically bind to a hLIGHT antigen," "antibodies that immunospecifically bind to a hLIGHT epitope," "anti-hLIGHT antibodies" and analogous terms are also used interchangeably herein and refer to antibodies and fragments thereof, that specifically bind to a hLIGHT polypeptide, such as a hLIGHT antigen or epitope. An antibody or a fragment thereof that immunospecifically binds to a hLIGHT antigen may be cross-reactive with related antigens. Preferably, an antibody or a fragment thereof that immunospecifically binds to a hLIGHT antigen does not cross-react with other antigens. An antibody or a fragment thereof that immunospecifically binds to a hLIGHT antigen can be identified, for example, by immunoassays, BIAcore, or other techniques known to those of skill in the art. An antibody or a fragment thereof binds specifically to a hLIGHT antigen when it binds to a hLIGHT antigen with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). Typically a specific or selective reaction will be at least twice background signal or noise and more typically more than 10 times background. See, *e.g.*, Paul, ed., 1989, Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 for a discussion regarding antibody specificity.

[0036] Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (*e.g.*, including monospecific, bispecific, *etc.*), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. In particular, antibodies of the present invention include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, antigen binding domains or molecules that contain an antigen-binding site that immunospecifically binds to a hLIGHT antigen (*e.g.*, one or more complementarity determining regions (CDRs) of an anti-hLIGHT antibody). The antibodies of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (*e.g.*, IgG2a and IgG2b) of immunoglobulin molecule. In preferred embodiments, the hLIGHT antibodies are fully human, such as fully human monoclonal hLIGHT antibodies. In certain embodiments,

antibodies of the invention are IgG antibodies, or a class (*e.g.*, human IgG1 or IgG4) or subclass thereof.

[0037] The term "antigen binding domain," "antigen binding region," "antigen binding fragment," and similar terms refer to that portion of an antibody which comprises the amino acid residues that interact with an antigen and confer on the binding agent its specificity and affinity for the antigen (*e.g.*, the complementarity determining regions (CDR)). The antigen binding region can be derived from any animal species, such as rodents (*e.g.*, rabbit, rat or hamster) and humans. Preferably, the antigen binding region will be of human origin.

[0038] As used herein, the term "composition" is intended to encompass a product containing the specified ingredients (*e.g.*, an antibody of the invention) in, optionally, the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in, optionally, the specified amounts.

[0039] The term "constant region" or "constant domain" refers to a carboxy terminal portion of the light and heavy chain which is not directly involved in binding of the antibody to antigen but exhibits various effector function, such as interaction with the Fc receptor. The terms refer to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable domain, which contains the antigen binding site. The constant domain contains the CH1, CH2 and CH3 domains of the heavy chain and the CHL domain of the light chain.

[0040] In the context of a polypeptide, the term "derivative" as used herein refers to a polypeptide that comprises an amino acid sequence of a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an antibody that immunospecifically binds to a hLIGHT polypeptide which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or an antibody that immunospecifically binds to a hLIGHT polypeptide which has been chemically modified, *e.g.*, by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or a hLIGHT antibody may be chemically modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, *etc.* The derivatives are modified in a manner that is different from

naturally occurring or starting peptide or polypeptides, either in the type or location of the molecules attached. Derivatives further include deletion of one or more chemical groups which are naturally present on the peptide or polypeptide. A derivative of a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or a hLIGHT antibody may be chemically modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, *etc.* Further, a derivative of a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or a hLIGHT antibody may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a hLIGHT polypeptide, a fragment of a hLIGHT polypeptide, or a hLIGHT antibody described herein.

[0041] The term "effective amount" as used herein refers to the amount of a therapy (*e.g.*, an antibody or pharmaceutical composition provided herein) which is sufficient to reduce and/or ameliorate the severity and/or duration of a given disease and/or a symptom related thereto. This term also encompasses an amount necessary for the reduction or amelioration of the advancement or progression of a given disease, reduction or amelioration of the recurrence, development or onset of a given disease, and/or to improve or enhance the prophylactic or therapeutic effect(s) of another therapy (*e.g.*, a therapy other than anti-hLIGHT antibody provided herein). In some embodiments, the effective amount of an antibody of the invention is from about 0.1 mg/kg (mg of antibody per kg weight of the subject) to about 100 mg/kg. In certain embodiments, an effective amount of an antibody provided therein is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, 3 mg/kg, 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg about 90 mg/kg or about 100 mg/kg (or a range therein). In some embodiments, "effective amount" as used herein also refers to the amount of an antibody of the invention to achieve a specified result (*e.g.*, inhibition of a hLIGHT biological activity of a cell, such as inhibition of secretion of CCL20, IL-8 or RANTES from the cell).

[0042] The term "epitope" as used herein refers to a localized region on the surface of an antigen, such as hLIGHT polypeptide or hLIGHT polypeptide fragment, that is capable of being bound to one or more antigen binding regions of an antibody, and that has antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human, that is capable of eliciting an immune response. An epitope

having immunogenic activity is a portion of a polypeptide that elicits a antibody response in an animal. An epitope having antigenic activity is a portion of a polypeptide to which an antibody immunospecifically binds as determined by any method well known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three dimensional structural characteristics as well as specific charge characteristics. A region of a polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide The epitope may or may not be a three-dimensional surface feature of the antigen. In certain embodiments, a hLIGHT epitope is a three-dimensional surface feature of a hLIGHT polypeptide (*e.g.*, in a trimeric form of a hLIGHT polypeptide). In other embodiments, a hLIGHT epitope is linear feature of a hLIGHT polypeptide (*e.g.*, in a trimeric form or monomeric form of the hLIGHT polypeptide). Antibodies provided herein may immunospecifically bind to an epitope of the monomeric (denatured) form of hLIGHT, an epitope of the trimeric (native) form of hLIGHT, or both the monomeric (denatured) form and the trimeric (native) form of hLIGHT. In specific embodiments, the antibodies provided herein immunospecifically bind to an epitope of the trimeric form of hLIGHT but do not immunospecifically bind the monomeric form of hLIGHT.

[0043] The term "excipients" as used herein refers to inert substances which are commonly used as a diluent, vehicle, preservatives, binders, or stabilizing agent for drugs and includes, but not limited to, proteins (*e.g.*, serum albumin, *etc.*), amino acids (*e.g.*, aspartic acid, glutamic acid, lysine, arginine, glycine, histidine, *etc.*), fatty acids and phospholipids (*e.g.*, alkyl sulfonates, caprylate, *etc.*), surfactants (*e.g.*, SDS, polysorbate, nonionic surfactant, *etc.*), saccharides (*e.g.*, sucrose, maltose, trehalose, *etc.*) and polyols (*e.g.*, mannitol, sorbitol, *etc.*). See, also, Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA, which is hereby incorporated by reference in its entirety.

[0044] In the context of a peptide or polypeptide, the term "fragment" as used herein refers to a peptide or polypeptide that comprises less than the full length amino acid sequence. Such a fragment may arise, for example, from a truncation at the amino terminus, a truncation at the carboxy terminus, and/or an internal deletion of a residue(s) from the amino acid sequence. Fragments may, for example, result from alternative

RNA splicing or from *in vivo* protease activity. In certain embodiments, hLIGHT fragments include polypeptides comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least contiguous 100 amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, at least 200 contiguous amino acid residues, or at least 250 contiguous amino acid residues of the amino acid sequence of a hLIGHT polypeptide or an antibody that immunospecifically binds to a hLIGHT polypeptide. In a specific embodiment, a fragment of a hLIGHT polypeptide or an antibody that immunospecifically binds to a hLIGHT antigen retains at least 1, at least 2, or at least 3 functions of the polypeptide or antibody.

[0045] The terms "fully human antibody" or "human antibody" are used interchangeably herein and refer to an antibody that comprises a human variable region and, most preferably a human constant region. In specific embodiments, the terms refer to an antibody that comprises a variable region and constant region of human origin. "Fully human" anti-hLIGHT antibodies, in certain embodiments, can also encompass antibodies which bind hLIGHT polypeptides and are encoded by nucleic acid sequences which are naturally occurring somatic variants of human germline immunoglobulin nucleic acid sequence. In a specific embodiment, the anti-hLIGHT antibodies provided herein are fully human antibodies. The term "fully human antibody" includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat *et al.* (See Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Exemplary methods of producing fully human antibodies are provided, *e.g.*, in the Examples herein, but any method known in the art may be used.

[0046] The phrase "recombinant human antibody" includes human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated

from an animal (*e.g.*, a mouse or cow) that is transgenic and/or transchromosomal for human immunoglobulin genes (*see e.g.*, Taylor, L. D. *et al.* (1992) *Nucl. Acids Res.* 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies can have variable and constant regions derived from human germline immunoglobulin sequences (See Kabat, E. A. *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0047] The term "fusion protein" as used herein refers to a polypeptide that comprises an amino acid sequence of an antibody and an amino acid sequence of a heterologous polypeptide or protein (*i.e.*, a polypeptide or protein not normally a part of the antibody (*e.g.*, a non-anti-hLIGHT antigen antibody)). The term "fusion" when used in relation to hLIGHT or to a anti-hLIGHT antibody refers to the joining of a peptide or polypeptide, or fragment, variant and/or derivative thereof, with a heterologous peptide or polypeptide. Preferably, the fusion protein retains the biological activity of the hLIGHT or anti-hLIGHT antibody. In certain embodiments, the fusion protein comprises a hLIGHT antibody VH domain, VL domain, VH CDR (one, two or three VH CDRs), and/or VL CDR (one, two or three VL CDRs), wherein the fusion protein immunospecifically binds to a hLIGHT epitope.

[0048] The term "heavy chain" when used in reference to an antibody refers to five distinct types, called alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), based on the amino acid sequence of the heavy chain constant domain. These distinct types of heavy chains are well known and give rise to five classes of antibodies, IgA, IgD, IgE, IgG and IgM, respectively, including four subclasses of IgG, namely IgG1, IgG1, IgG3 and IgG4. Preferably the heavy chain is a human heavy chain.

[0049] The term "host" as used herein refers to an animal, preferably a mammal, and most preferably a human.

[0050] The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0051] The term "immunomodulatory agent" and variations thereof including, but not limited to, immunomodulatory agents, as used herein refer to an agent that modulates a host's immune system. In certain embodiments, an immunomodulatory agent is an immunosuppressant agent. In certain other embodiments, an immunomodulatory agent is an immunostimulatory agent. In accordance with the invention, an immunomodulatory agent used in the combination therapies of the invention does not include an anti-hLIGHT antibody or antigen-binding fragment. Immunomodulatory agents include, but are not limited to, small molecules, peptides, polypeptides, proteins, fusion proteins, antibodies, inorganic molecules, mimetic agents, and organic molecules.

[0052] As used herein, the term "in combination" in the context of the administration of other therapies refers to the use of more than one therapy. The use of the term "in combination" does not restrict the order in which therapies are administered to a subject with an infection. A first therapy can be administered before (*e.g.*, 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks), concurrently, or after (*e.g.*, 1 minute, 45 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks) the administration of a second therapy to a subject which had, has, or is susceptible to a hLIGHT-mediated disease. Any additional therapy can be administered in any order with the other additional therapies. In certain embodiments, the antibodies of the invention can be administered in combination with one or more therapies (*e.g.*, therapies that are not the antibodies of the invention that are currently administered to prevent, treat, manage, and/or ameliorate a hLIGHT-mediated disease. Non-limiting examples of therapies that can be administered in combination with an antibody of the invention include analgesic agents, anesthetic agents, antibiotics, or immunomodulatory

agents or any other agent listed in the U.S. Pharmacopoeia and/or Physician's Desk Reference.

[0053] The term "inorganic salt" as used herein refers to any compounds containing no carbon that result from replacement of part or all of the acid hydrogen or an acid by a metal or a group acting like a metal and are often used as a tonicity adjusting compound in pharmaceutical compositions and preparations of biological materials. The most common inorganic salts are NaCl, KCl, NaH_2PO_4, *etc.*

[0054] An "isolated" or "purified" antibody is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the antibody is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the antibody is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the antibody have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a preferred embodiment, antibodies of the invention are isolated or purified.

[0055] An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. In a specific embodiment, a nucleic acid molecule(s) encoding an antibody of the invention is isolated or purified.

[0056] The term "human LIGHT," "hLIGHT" or "hLIGHT polypeptide" and similar terms refers to the polypeptides ("polypeptides," "peptides" and "proteins" are used interchangeably herein) comprising the amino acid sequence of SEQ ID NO:52 and

related polypeptides, including SNP variants thereof. Related polypeptides include allelic variants (*e.g.*, SNP variants); splice variants; fragments; derivatives; substitution, deletion, and insertion variants; fusion polypeptides; and interspecies homologs, preferably, which retain hLIGHT activity and/or are sufficient to generate an anti-hLIGHT immune response. Exemplary non-synonymous SNP variants include, but are not limited to, hLIGHT polypeptides comprising 214E-32S (a glutamic acid at position 214 and serine at position 32 of a hLIGHT polypeptide (*e.g.*, the hLIGHT polypeptide depicted in SEQ ID NO:52)), 214K-32S, 214E-32L and 214E-32L. Also encompassed are soluble forms of hLIGHT which are sufficient to generate an anti-hLIGHT immunological response (*see, e.g.,* SEQ ID NO:53 and SEQ ID NO:54). As those skilled in the art will appreciate, an anti-hLIGHT antibody of the invention can bind to a hLIGHT polypeptide, polypeptide fragment, antigen, and/or epitope, as an epitope is part of the larger antigen, which is part of the larger polypeptide fragment, which, in turn, is part of the larger polypeptide. hLIGHT can exist in a trimeric (native) or monomeric (denatured) form.

[0057] The terms "Kabat numbering," and like terms are recognized in the art and refer to a system of numbering amino acid residues which are more variable (*i.e.* hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat *et al.* (1971) *Ann. NY Acad. Sci.* 190:382-391 and, Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region typically ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3. For the light chain variable region, the hypervariable region typically ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

[0058] The term "light chain" when used in reference to an antibody refers to two distinct types, called kappa (κ) of lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In preferred embodiments, the light chain is a human light chain.

[0059] As used herein, the terms "manage," "managing," and "management" refer to the beneficial effects that a subject derives from a therapy (*e.g.*, a prophylactic or therapeutic agent), which does not result in a cure of the infection. In certain

embodiments, a subject is administered one or more therapies (*e.g.*, prophylactic or therapeutic agents, such as an antibody of the invention) to "manage" a hLIGHT-mediated disease (*e.g.*, IBD or GVHD), one or more symptoms thereof, so as to prevent the progression or worsening of the disease.

[0060] The term "monoclonal antibody" refers to an antibody obtained from a population of homogenous or substantially homogeneous antibodies, and each monoclonal antibody will typically recognize a single epitope on the antigen. In preferred embodiments, a "monoclonal antibody," as used herein, is an antibody produced by a single hybridoma or other cell, wherein the antibody immunospecifically binds to only a hLIGHT epitope as determined, *e.g.*, by ELISA or other antigen-binding or competitive binding assay known in the art or in the Examples provided herein. The term "monoclonal" is not limited to any particular method for making the antibody. For example, monoclonal antibodies of the invention may be made by the hybridoma method as described in Kohler *et al.*; Nature, 256:495 (1975) or may be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel *et al.*, eds., John Wiley and Sons, New York). Other exemplary methods of producing other monoclonal antibodies are provided in the Examples herein.

[0061] The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to those which are found in nature and not manipulated by a human being.

[0062] The term "pharmaceutically acceptable" as used herein means being approved by a regulatory agency of the Federal or a state government, or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized Pharmacopeia for use in animals, and more particularly in humans.

[0063] "Polyclonal antibodies" as used herein refers to an antibody population generated in an immunogenic response to a protein having many epitopes and thus includes a variety of different antibodies directed to the same and to different epitopes within the protein. Methods for producing polyclonal antibodies are known in the art (See, *e.g.*, see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel *et al.*, eds., John Wiley and Sons, New York).

[0064] As used herein, the term "polynucleotide," "nucleotide," nucleic acid" "nucleic acid molecule" and other similar terms are used interchangeable and include DNA, RNA, mRNA and the like.

[0065] As used herein, the terms "prevent," "preventing," and "prevention" refer to the total or partial inhibition of the development, recurrence, onset or spread of a hLIGHT-mediated disease and/or symptom related thereto, resulting from the administration of a therapy or combination of therapies provided herein (*e.g.*, a combination of prophylactic or therapeutic agents, such as an antibody of the invention).

[0066] As used herein, the term "prophylactic agent" refers to any agent that can totally or partially inhibit the development, recurrence, onset or spread of a hLIGHT-mediated disease and/or symptom related thereto in a subject. In certain embodiments, the term "prophylactic agent" refers to an antibody of the invention. In certain other embodiments, the term "prophylactic agent" refers to an agent other than an antibody of the invention. Preferably, a prophylactic agent is an agent which is known to be useful to or has been or is currently being used to prevent a hLIGHT-mediated disease and/or a symptom related thereto or impede the onset, development, progression and/or severity of a hLIGHT-mediated disease and/or a symptom related thereto. In specific embodiments, the prophylactic agent is a fully human anti-hLIGHT antibody, such as a fully human anti-hLIGHT monoclonal antibody.

[0067] In certain embodiments of the invention, a "prophylactically effective serum titer" is the serum titer in a subject, preferably a human, that totally or partially inhibits the development, recurrence, onset or spread of a hLIGHT-mediated disease and/or symptom related thereto in said subject.

[0068] The term "hLIGHT antigen" refers to that portion of a hLIGHT polypeptide to which an antibody immunospecifically binds. A hLIGHT antigen also refers to an analog or derivative of a hLIGHT polypeptide or fragment thereof to which an antibody immunospecifically binds. In some embodiments, a hLIGHT antigen is a monomeric hLIGHT antigen or a trimeric hLIGHT antigen. A region of a hLIGHT polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide The epitope may or may not be a three-dimensional surface feature of the antigen. A localized region on the surface of a hLIGHT antigen that is capable of eliciting an immune response is a hLIGHT epitope. The epitope may or may not be a three-dimensional surface feature of the antigen.

[0069] A "hLIGHT-mediated disease" and "hLIGHT-mediated disorder" are used interchangeably and refer to any disease that is completely or partially caused by or is the result of hLIGHT. In certain embodiments, hLIGHT is aberrantly (*e.g.*, highly) expressed on the surface of a cell. In some embodiments, hLIGHT may be aberrantly upregulated on a particular cell type. In other embodiments, normal, aberrant or excessive cell signaling is caused by binding of hLIGHT to a hLIGHT ligand. In certain embodiments, the hLIGHT ligand is a hLIGHT receptor (*e.g.*, HVEM, LTβR, or DCR3), for example, that is expressed on the surface of a cell, such as a colonic epithelial cell. In certain embodiments, the hLIGHT-mediated disease is an inflammatory bowel disease (IBD), such as Crohn's disease (CD) or ulcerative colitis (UC). In other embodiments, the hLIGHT-mediated disease is graft-versus-host disease (GVHD).

[0070] A "hLIGHT ligand" refers to a molecule which binds or otherwise interacts with hLIGHT. In preferred embodiments, the hLIGHT ligand is a hLIGHT receptor.

[0071] The terms "hLIGHT receptor" or "hLIGHT binding receptor" are used interchangeably herein and refer to a receptor polypeptide that binds to hLIGHT. In specific embodiments, the hLIGHT receptor is HVEM, FcβR or DcR3. In some embodiments, the hLIGHT receptor is expressed on the surface of a cell, such as a colonic epithelial cell.

[0072] The term "saccharide" as used herein refers to a class of molecules that are derivatives of polyhydric alcohols. Saccharides are commonly referred to as carbohydrates and may contain different amounts of sugar (saccharide) units, *e.g.*, monosaccharides, disaccharides and polysaccharides.

[0073] The term "serum titer" as used herein refers to an average serum titer in a population of least 10, preferably at least 20, and most preferably at least 40 subjects up to about 100, 1000 or more.

[0074] As used herein, the term "side effects" encompasses unwanted and adverse effects of a therapy (*e.g.*, a prophylactic or therapeutic agent). Unwanted effects are not necessarily adverse. An adverse effect from a therapy (*e.g.*, a prophylactic or therapeutic agent) might be harmful or uncomfortable or risky. Examples of side effects include, diarrhea, cough, gastroenteritis, wheezing, nausea, vomiting, anorexia, abdominal cramping, fever, pain, loss of body weight, dehydration, alopecia, dyspenea, insomnia, dizziness, mucositis, nerve and muscle effects, fatigue, dry mouth, and loss of appetite, rashes or swellings at the site of administration, flu-like symptoms such as fever, chills and fatigue, digestive tract problems and allergic reactions. Additional

undesired effects experienced by patients are numerous and known in the art. Many are described in the Physician's Desk Reference (60^{th} ed., 2006).

[0075] The term "small molecule" and analogous terms include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogues, polynucleotides, polynucleotide analogues, nucleotides, nucleotide analogues, organic or inorganic compounds (*i.e.*, including heterorganic and/or ganometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

[0076] The terms "stability" and "stable" as used herein in the context of a liquid formulation comprising an antibody that immunospecifically binds to a hLIGHT antigen refer to the resistance of the antibody in the formulation to thermal and chemical unfolding, aggregation, degradation or fragmentation under given manufacture, preparation, transportation and storage conditions. The "stable" formulations of the invention retain biological activity equal to or more than 80%, 85%, 90%, 95%, 98%, 99%, or 99.5% under given manufacture, preparation, transportation and storage conditions. The stability of the antibody can be assessed by degrees of aggregation, degradation or fragmentation by methods known to those skilled in the art, including but not limited to reduced Capillary Gel Electrophoresis (rCGE), Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) and HPSEC, compared to a reference antibody. The overall stability of a formulation comprising an antibody that immunospecifically binds to a hLIGHT antigen can be assessed by various immunological assays including, for example, ELISA and radioimmunoassay using the specific epitope of hLIGHT.

[0077] As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, a subject is preferably a mammal such as a non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats, *etc.*) or a primate (*e.g.*, monkey and human), most preferably a human. In one embodiment, the subject is a mammal, preferably a human, having a hLIGHT-mediated disease. In another embodiment, the subject is a mammal, preferably a human, at risk of developing a hLIGHT-mediated disease.

[0078] As used herein "substantially all" refers to refers to at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or about 100%.

[0079] The term "substantially free of surfactant" as used herein refers to a formulation of an antibody that immunospecifically binds to a hLIGHT antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants and/or less than 0.0005%, less than 0.0003%, or less than 0.0001% of surfactants.

[0080] The term "substantially free of salt" as used herein refers to a formulation of an antibody that immunospecifically binds to a hLIGHT antigen, said formulation containing less than 0.0005%, less than 0.0003%, or less than 0.0001% of inorganic salts.

[0081] The term "surfactant" as used herein refers to organic substances having amphipathic structures; namely, they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic, and nonionic surfactants. Surfactants are often used as wetting, emulsifying, solubilizing, and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

[0082] As used herein, the term "tag" refers to any type of moiety that is attached to, *e.g.*, a polypeptide and/or a polynucleotide that encodes a hLIGHT or hLIGHT antibody or antigen binding fragment thereof. For example, a polynucleotide that encodes a hLIGHT, hLIGHT antibody or antigen binding fragment thereof can contain one or more additional tag-encoding nucleotide sequences that encode a, *e.g.*, a detectable moiety or a moiety that aids in affinity purification. When translated, the tag and the antibody can be in the form of a fusion protein. The term "detectable" or "detection" with reference to a tag refers to any tag that is capable of being visualized or wherein the presence of the tag is otherwise able to be determined and/or measured (*e.g.*, by quantitation). A non-limiting example of a detectable tag is a fluorescent tag.

[0083] As used herein, the term "therapeutic agent" refers to any agent that can be used in the treatment, management or amelioration of a hLIGHT-mediated disease and/or a symptom related thereto. In certain embodiments, the term "therapeutic agent" refers to an antibody of the invention. In certain other embodiments, the term "therapeutic agent" refers to an agent other than an antibody of the invention.

Preferably, a therapeutic agent is an agent which is known to be useful for, or has been or is currently being used for the treatment, management or amelioration of a hLIGHT-mediated disease or one or more symptoms related thereto. In specific embodiments, the therapeutic agent is a fully human anti-hLIGHT antibody, such as a fully human anti-hLIGHT monoclonal antibody.

[0084] The combination of therapies (*e.g.*, use of prophylactic or therapeutic agents) which is more effective than the additive effects of any two or more single therapy. For example, a synergistic effect of a combination of prophylactic and/or therapeutic agents permits the use of lower dosages of one or more of the agents and/or less frequent administration of said agents to a subject with a hLIGHT-mediated disease. The ability to utilize lower dosages of prophylactic or therapeutic therapies and/or to administer said therapies less frequently reduces the toxicity associated with the administration of said therapies to a subject without reducing the efficacy of said therapies in the prevention, management, treatment or amelioration of a hLIGHT-mediated disease. In addition, a synergistic effect can result in improved efficacy of therapies in the prevention, or in the management, treatment or amelioration of a hLIGHT-mediated disease. Finally, synergistic effect of a combination of therapies (*e.g.*, prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of any single therapy.

[0085] In certain embodiments of the invention, a "therapeutically effective serum titer" is the serum titer in a subject, preferably a human, that reduces the severity, the duration and/or the symptoms associated with a hLIGHT-mediated disease in said subject.

[0086] As used herein, the term "therapy" refers to any protocol, method and/or agent that can be used in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease (*e.g.*, IBD or GVHD). In certain embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies useful in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease known to one of skill in the art such as medical personnel.

[0087] As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of a hLIGHT-mediated disease (*e.g.*, IBD or GVHD) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents, such as an antibody of the invention). In specific embodiments, such

terms refer to the reduction or inhibition of the binding of hLIGHT to HVEM, the reduction or inhibition of the binding of hLIGHT to LTβR, the reduction or inhibition of the binding of hLIGHT to DcR3, the reduction or inhibition of the production or secretion of CCL20 from a cell expressing a hLIGHT receptor of a subject, the reduction or inhibition of the production or secretion of IL-8 from a cell expressing a hLIGHT receptor of a subject, the reduction or inhibition of the production or secretion of RANTES from a cell expressing a hLIGHT receptor of a subject, and/or the inhibition or reduction of one or more symptoms associated with a hLIGHT-mediated disease, such as an IBD or GVHD. In specific embodiments, a prophylactic agent is a fully human anti-hLIGHT antibody, such as a fully human anti-hLIGHT monoclonal antibody.

[0088] The term "variable region" or "variable domain" refers to a portion of the light and heavy chains, typically about the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino acids in the light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complimentarily determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). The CDRs of the light and heavy chains are primarily responsible for the interaction of the antibody with antigen. Numbering of amino acid positions used herein is according to the EU Index, as in Kabat *et al.* (1991) Sequences of proteins of immunological interest. (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed. ("Kabat *et al.*"). In preferred embodiments, the variable region is a human variable region.

[0089] The term "variant" when used in relation to hLIGHT or to a hLIGHT antibody refers to a peptide or polypeptide comprising one or more (such as, for example, about 1 to about 25, about 1 to about 20, and preferably about 1 to about 15, more preferably about 1 to about 10, and most preferably about 1 to about 5) amino acid sequence substitutions, deletions, and/or additions as compared to a native or unmodified sequence. For example, a hLIGHT variant may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, and preferably about 1 to about 15, more preferably about 1 to about 10, and most preferably about 1 to about 5) changes to an amino acid sequence of native hLIGHT. Also by way of example, a variant of an anti-hLIGHT antibody may result from one or more (such as, for example, about 1 to about 25, about 1 to about 20, and preferably about 1 to about 15, more

preferably about 1 to about 10, and most preferably about 1 to about 5) changes to an amino acid sequence of a native or previously unmodified anti-hLIGHT antibody. Variants may be naturally occurring, such as allelic or splice variants, or may be artificially constructed. Polypeptide variants may be prepared from the corresponding nucleic acid molecules encoding said variants. In preferred embodiments, the hLIGHT variant or hLIGHT antibody variant retains hLIGHT or hLIGHT antibody functional activity, respectively. In specific embodiments, a hLIGHT antibody variant immunospecifically binds hLIGHT and/or is antagonistic to hLIGHT activity. In certain embodiments, the variant is encoded by a single nucleotide polymorphism (SNP) variant of hLIGHT. An exemplary SNP variant of hLIGHT encodes either a glutamic acid (E) or an lysine (K) at amino acid position 214. Another exemplary SNP variant of hLIGHT encodes either a serine (S) or a leucine (L) at amino acid position 32.

BRIEF DESCRIPTION OF THE DRAWINGS

[0090] **FIG. 1A-1B** depicts a cytometric analysis of endogenously expressed hLIGHT with human anti-hLIGHT antibodies. **(A)** The human T cell line II23.D7 was activated with PMA and inonomycin overnight and stained for the activation marker CD69 in combination with various anti-hLIGHT antibodies. CD69 positive cells were gated and analyzed for hLIGHT staining (bold line) compared to control human anti-influenza IgG1 (dotted line) or staining of non-activated II23.D7 cells with anti-hLIGHT antibodies (grey line). Binding was detected with goat anti-human IgG-APC secondary antibody. **(B)** The staining of activated the human T cell line II-23.D7 with human anti-hLIGHT antibodies is saturable. Activated II-23.D7 cells were labeled with human anti-hLIGHT antibodies at various concentrations and detected with anti-human IgG-APC. Plots of the geometric mean fluorescence intensity data are shown along with non-linear regression.

[0091] **FIG. 2A-2B** depicts the staining of recombinant hLIGHT on EL4-hLIGHT cell line with human anti-hLIGHT antibodies. In **(A)** and **(B)**, graded amounts of anti-hLIGHT antibodies were used to stain EL4-hLIGHT cells, detected with anti-human IgG-APC and analyzed by flow cytometry. The geometric mean fluorescence intensity (MFI) was determined and non-linear regression analysis applied. In all experiments human anti-influenza protein M2 was used as a negative control. Data obtained from this analysis is represented in FIG. 3.

[0092] **FIG. 3** depicts characteristics of human anti-hLIGHT monoclonal antibodies.

[0093] **FIG. 4** depicts antibody cross-blocking by ELISA. This analysis defines two groups based on competition for binding to hLIGHT by ELISA. The individual antibodies were coated in the wells of a 96 well plate. Soluble FLAG-hLIGHT was pre-incubated with soluble anti-hLIGHT antibodies and then added to the coated wells. Binding of FLAG-hLIGHT to the coated antibody was detected with anti-FLAG IgG-HRP. The percent inhibition was determined using the OD of each sample in the following formula: % inhibition = (max – sample/max) x 100.

[0094] **FIG. 5A-5B** depicts the blockade of human HVEM:Fc binding to native hLIGHT on the cell surface by human anti-hLIGHT monoclonal antibodies. In **(A)** and **(B)**, graded amounts of antibodies were incubated with EL4-hLIGHT cells, biotinylated human HVEM:Fc was added at a sub-saturating concentration and detected with SA-APC. As shown in **(A)**, the human anti-influenza M2 antibody was used as a control.

[0095] **FIG. 6A-6B** depicts the blockade of human LTβR:Fc binding to native hLIGHT on the cell surface by human anti-hLIGHT monoclonal antibodies. In **(A)-(B)**, graded amounts of antibodies were incubated with EL4-hLIGHT cells, polyHis tagged human LTβR:Fc was added at a sub-saturating concentration and detected with anti-His-APC. As shown in **(A)**, the human anti-influenza M2 antibody was used as a control.

[0096] **FIG. 7** depicts hLIGHT-mediated CCL20 secretion from human colonic epithelial cells. Recombinant soluble hLIGHT was added to the growth medium of HT29.14s cells at increasing concentrations. Growth media was harvested at day 3 post treatment and levels of CCL20 were determined by ELISA. Error bars indicate two independent treatments.

[0097] **FIG. 8** depicts hLIGHT-mediated IL-8 and RANTES secretion from human colonic epithelial cells. Recombinant soluble hLIGHT, TNF, $LT\alpha_1\beta_2$ and FLAG-BAP (as a negative control) were added to the growth medium of HT29.14s cells. Growth media was harvested from different wells at days 1, 2 and 3 post-treatment. Levels of IL-8 and RANTES were determined by ELISA. FLAG tagged bacterial alkaline phosphatase (FLAG-BAP) was used as a tagged irrelevant protein negative control.

[0098] **FIG. 9A-9B** shows human anti-hLIGHT antibodies inhibit hLIGHT-mediated CCL20 secretion from human colonic epithelial cells. **(A)** Recombinant soluble hLIGHT (1 μg/ml) was pre-incubated with anti-hLIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells from each treatment at day 3. Levels of CCL20 were determined by ELISA. Media

alone, soluble hLIGHT alone, soluble hLIGHT incubated with anti-influenza M2 antibody and each anti-hLIGHT antibody alone were included as controls. **(B)** Nonlinear regression analysis of data represented in panel A.

[0099] **FIG. 10A-10B** shows human anti-hLIGHT antibodies inhibit cell surface expressed hLIGHT-mediated RANTES secretion from human colonic epithelial cells. **(A)** fixed EL4-hLIGHT cells were pre-incubated with anti-hLIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells for each treatment at day 3. Levels of RANTES were determined by ELISA. Media alone, EL4-hLIGHT cells alone, soluble hLIGHT alone, and each anti-hLIGHT antibody alone were included as controls. **(B)** Plot of data represented in **(A)**.

[00100] **FIG. 11** depicts the results of a competitive blocking experiment for binding to hLIGHT.

[0100] **FIG. 12** depicts the blocking activity of antibodies for HVEM:Fc binding to 293 hLIGHT cells. E1, E13 F19 human anti-hLIGHT monoclonal antibodies, the R&D mAb, and commercially available goat anti-hLIGHT polyclonal antibodies (R&D Systems), and rabbit anti-hLIGHT polyclonal antibodies (eBioscience) were tested for their ability to block binding of HVEM:Fc to 293 cells expressing hLIGHT.

[0101] **FIG. 13** depicts the blocking activity of antibodies for LTβR:Fc binding to 293 hLIGHT cells. E1 and E13 human anti-hLIGHT monoclonal antibodies, the R&D mAb, and commercially available goat anti-hLIGHT polyclonal antibodies (R&D Systems), and rabbit anti-hLIGHT polyclonal antibodies (eBioscience) were tested for their ability to block binding of LTβR:Fc to 293 cells expressing hLIGHT.

[0102] **FIG. 14** depicts the blocking activity of antibodies for **(A)** LTβR:Fc and **(B)** HVEM:Fc binding to 293 hLIGHT cells and is a graphical representation of the data shown in FIGS. 12 and 13.

[0103] **FIG. 15A-15B** depicts the binding of various anti-hLIGHT antibodies to native or denatured soluble hLIGHT. Five micrograms of soluble human LIGHT was either boiled in 2 x SDS sample buffer (denatured) or untreated (native), and then both were serially diluted in 6x increments. 5 μl of each hLIGHT dilution was spotted simultaneously onto hydrated 0.2 μm PVDF membranes (Invitrogen, Carlsbad, CA) using an 8 multi-channel pipette. The blots were allowed to air dry then re-hydrated, blocked (1 x TBST (Tris-buffered saline Tween-20) +2.5% skim milk + 0.02% sodium azide). Each blot was probed with 5 μg/ml of each primary antibody. The blots were

washed 3x in 1x TBST followed by biotinylated secondary Abs (Biotin-Goat αHuman (Vector Labs, Burlingame, CA), Biotin-Goat α mouse (Jackson labs, Bar Harbor, ME), Biotin-Mouse α goat (Sigma-Aldrich corp., St. Louis, MO)) at 5 μg/ml. The blots were washed 3x in 1x TBST followed by super SA-HRP (Amersham Biosciences, Piscataway, NJ). Chemiluminescence was used for detection using the ECL detection kit (Amersham Biosciences, Piscataway, NJ) and signal was visualized by exposure to X-OMAT AR imaging film (Kodak, Rochester, New York). **(A)** Dot blot results using E1, E13, E63, F19, F23 human anti-hLIGHT mAb, or two murine anti-hLIGHT monoclonal antibodies commercially available from R&D Systems ("R&D mouse mAb") and Abnova ("Abnova mouse mAb"). An anti-M2 (irrelevant antigen) antibody was used as a negative control. **(B)** Dot blot results using a commercial goat anti-hLIGHT polyclonal antibody preparation (R&D Systems "R&D goat pAb") or two commercial rabbit anti-hLIGHT polyclonal antibody preparations (eBioscience ("eBioscience rabbit pAb") and Peprotech ("Peprotech rabbit pAb")).

[0104] **FIG. 16** depicts the binding of various anti-hLIGHT antibodies to native or denatured soluble hLIGHT and summarizes the data presented in FIG. 15 in tabular form.

[0105] **FIG. 17** shows that human anti-LIGHT antibodies of the invention inhibit LIGHT-mediated CCL20 secretion from human colonic epithelial cells, whereas commercially available mouse anti-hLIGHT antibodies do not. Recombinant soluble human LIGHT (1 μg/ml) was pre-incubated with anti-LIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells from each treatment at day 3. Levels of CCL20 were determined by ELISA. Media alone, soluble LIGHT alone, soluble LIGHT incubated with anti-influenza M2 antibody, non-blocking anti-LIGHT Ab B12 and each anti-LIGHT antibody alone were included as controls. E1 and F19 are representatives of each cross-blocking epitope group.

[0106] **FIG. 18** shows that human anti-LIGHT antibodies of the invention inhibit LIGHT-mediated RANTES secretion from human colonic epithelial cells, whereas commercially available mouse anti-hLIGHT antibodies do not. Recombinant soluble human LIGHT (1 μg/ml) was pre-incubated with anti-LIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells from each treatment at day 3. Levels of RANTES were determined by ELISA. Media alone, soluble LIGHT alone, soluble LIGHT incubated with anti-influenza M2 antibody,

non-blocking anti-LIGHT Ab B12 and each anti-LIGHT antibody alone were included as controls. E1 and F19 are representatives of each cross-blocking epitope group

[0107] **FIGS. 19A-19B** depict a cytometric analysis of cell surface-expressed hLIGHT binding by human **(A)** E1 or **(B)** F19 anti-hLIGHT antibodies in comparison to their recombinant single kappa chain antibody counterparts. Stable hLIGHT expressing 293 cells were incubated with increasing amounts of anti-LIGHT antibodies indicated in the legend. Binding was detected with goat anti-human IgG-APC secondary antibody. Antibodies were purified from either hybridoma cultures or 293F cells transiently transfected with mammalian expression vectors encoding the different kappa chain cDNAs paired with the heavy chain gene. Plots of the geometric mean fluorescence intensity data are shown along with non-linear regression.

[0108] **FIG. 20** depicts antibody cross-blocking by ELISA comparing single kappa chain antibodies to their parental counterparts. This analysis defines two groups based on competition for binding to hLIGHT by ELISA. The individual antibodies were coated in the wells of a 96 well plate. Soluble FLAG-hLIGHT was pre-incubated with soluble anti-hLIGHT antibodies and then added to the coated wells. Binding of FLAG-hLIGHT to the coated antibody was detected with anti-FLAG IgG-HRP. The percent inhibition was determined using the OD of each sample in the following formula: % inhibition = (max – sample/max) x 100.

[0109] **FIGS. 21A-21B** depicts the blockade of **(A)** human HVEM:Fc or **(B)** human LTβR:Fc binding to native hLIGHT on the cell surface by human anti-hLIGHT monoclonal antibodies and their single kappa chain recombinant counterparts. Graded amounts of antibodies were incubated with EL4-hLIGHT cells, biotinylated human HVEM:Fc or polyHis labeled human LTβR:Fc added at a sub-saturating concentration, and then detected with SA-APC or anti-His-APC. Antibodies were purified from either hybridoma cultures or 293F cells transiently transfected with mammalian expression vectors encoding the different kappa chain cDNAs paired with the heavy chain gene.

[0110] **FIG. 22** depicts the inhibition of hLIGHT-mediated CCL20 secretion from human colonic epithelial cells by recombinant single kappa chain human anti-LIGHT antibodies compared to the parental hybridoma produced antibodies. Recombinant soluble human LIGHT (1 μg/ml) was pre-incubated with anti-LIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells from each treatment at day 3. Levels of CCL20 were determined by ELISA. Media alone, soluble LIGHT alone (SHL), soluble LIGHT incubated with anti-influenza

M2 antibody, or each antibody in the absence of soluble LIGHT were included as controls. Antibodies referred to as "E1k2" comprise E1kappa(B) and "F19k2" comprise F19kappa(B).

[0111] **FIG. 23** shows that human anti-LIGHT antibodies of the invention inhibit LIGHT -mediated CCL20 secretion from human colonic epithelial cells , whereas commercially available mouse anti-hLIGHT antibodies either do not inhibit (Abnova) or inhibit only at exceedingly high concentrations (100 μg/ml) (R&D). Recombinant soluble human LIGHT (1 μg/ml) was pre-incubated with anti-LIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells from each treatment at day 3. Levels of CCL20 were determined by ELISA. Media alone, soluble LIGHT alone (SHL), soluble LIGHT incubated with irrelevant anti-influenza M2 antibody, anti human serum albumin, or each antibody in the absence of soluble LIGHT were included as controls. E1 and F19 are representatives of each cross-blocking epitope group.

[0112] **FIGS. 24A-24B** depicts allelic frequency of certain non-synonymous single nucleotide polymorphism (SNP) hLIGHT variants **(A)** encoding a glutamic acid (E) or lysine (K) at amino acid position 214; or **(B)** encoding a leucine (L) or serine (S) at amino acid position 32) across various ethnic populations.

[0113] **FIG. 25A-25D.** FIGS. 25A-25C depict a dose titration of the staining of cell lines expressing non-synonymous SNP variants of human LIGHT with the human anti-hLIGHT antibodies 124F23 and 124E1kappa((B). Graded amounts of anti-hLIGHT antibodies were used to stain EL4-hLIGHT cells expressing either the SNP variant (A) 214E-32S **(B)** 214K-32S, or **(C)** 214E-32L, detected with anti-human IgG-APC and analyzed by flow cytometry. **(D)** depicts a dose titration of human anti-LIGHT antibody-mediated blockade of human HVEM:Fc (squares) or LTBR:Fc (triangles) binding to cell surface expressed 214K-32S LIGHT SNP variant performed as in FIG. 5. For (A)-(D) the geometric mean fluorescence intensity (MFI) was determined and non-linear regression analysis applied.

[0114] **FIGS. 26A-26B** depicts a flow cytometric analysis of cell lines expressing non-synonymous SNP variants with human anti-hLIGHT antibodies. (A) The EL4-LIGHT SNP 214E cell line and **(B)** the EL4 SNP 214K cell line were stained with one concentration (10 μg/ml) of each anti-hLIGHT antibody. Binding was detected with

goat anti-human IgG-APC secondary antibody. Isotype control human IgG was used as a negative control.

[0115] **FIG. 27** depicts human anti-hLIGHT antibody inhibition of cell surface-expressed hLIGHT SNP variant-mediated RANTES secretion from human colonic epithelial cells. Recombinant soluble hLIGHT (SHL) (1 μg/ml) or $5x10^5$ EL4-hLIGHT 214K or 214E SNP variant cells were preincubated with anti-hLIGHT antibodies and added to the growth medium of HT29.14s cells. Growth media was harvested from two wells from each treatment at day 3. Levels of RANTES were determined by ELISA. Media alone, EL4-hLIGHT cells alone, soluble hLIGHT alone and each anti-hLIGHT antibody alone were included as controls.

[0116] **FIG. 28** depicts a schematic representation of the acute xenogeneic GVHD model. SCID mice are injected with an IL2Rβ antibody (TM-β1) on day -2 to deplete NK cells. On day -1, the mice receive 2.5 Gy of sublethal irradiation. On day 0, the mice receive 10 million human PBMC by intraperitoneal injection followed immediately by intravenous injection of a human anti-human LIGHT or negative control antibody. Mice are weighed at 3-4 day intervals, and at day 12, the mice are sacrificed and assessed for gross pathology. Spleens are removed for flow cytometric analysis, cecums are removed for histology, and serum is collected for cytokine and antibody analyses.

[0117] **FIG. 29** depicts the gross pathology scores observed in the murine acute xenogeneic GVHD disease model. Pathology scores for no monoclonal antibody injection (circles), 124F23 anti-hLIGHT monoclonal antibody injection (triangles) and control human IgG1 monoclonal antibody (squares) are represented. Scores of 0, 1, 2, or 3 (none, mild, moderate, or severe, respectively) are assigned for each of three categories: diarrhea, peritoneal inflammation/ascites, and intestinal inflammation (maximum total score of 9).

[0118] **FIG. 30** depicts the histopathology scores observed in the murine acute xenogeneic GVHD disease model. Pathology scores for no MAb injection (circles), 124F23 anti-hLIGHT MAb injection (triangles) and control hIgG1 MAb (squares) are represented. Scores of 0, 1, 2, or 3 (none, mild, moderate, or severe, respectively) are assigned for each of four categories: inflammation severity, inflammation extent, villus damage/atrophy, and percent involvement (maximum total score of 12).

[0119] **FIGS. 31A-31B** depict representative histological hematoxylin and eosin (H&E) stained sections of the mouse cecum in the GVHD study. **(A)** Anti-LIGHT MAb treated mouse cecum section and **(B)** control human IgG treated mouse. Involution of

the sub-mucosa indicates ascites, dashed arrows indicate regions of blood and the solid arrow indicates a region of lymphocyte infiltrate.

[0120] **FIG. 32** depicts total T cell numbers in the spleen of mice in the xenogeneic GVHD study. Asterisks indicate student t-test values of less than 0.05 for the comparisons between anti-LIGHT MAb treated animals and controls.

DETAILED DESCRIPTION

[0121] Provided herein are antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided are isolated nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Further provided are vectors and host cells comprising nucleic acids encoding antibodies that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided are methods of making antibodies that that immunospecifically bind to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Also provided herein is a method of treating or managing a hLIGHT-mediated disease comprising administering an antibody that immunospecifically binds to a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope.

ANTIBODIES

[0122] Antibodies of the invention include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (*e.g.*, including monospecific, bispecific, *etc.*), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

[0123] In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds to a hLIGHT antigen. The immunoglobulin molecules provided herein can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In a specific embodiment, an antibody provided herein is an IgG antibody, preferably an IgG1 or IgG4.

[0124] Variants and derivatives of antibodies include antibody fragments that retain the ability to specifically bind to an epitope. Preferred fragments include Fab fragments (an antibody fragment that contains the antigen-binding domain and comprises a light chain and part of a heavy chain bridged by a disulfide bond); Fab' (an antibody fragment containing a single anti-binding domain comprising an Fab and an additional portion of the heavy chain through the hinge region); $F(ab')_2$ (two Fab' molecules joined by interchain disulfide bonds in the hinge regions of the heavy chains; the Fab' molecules may be directed toward the same or different epitopes); a bispecific Fab (a Fab molecule having two antigen binding domains, each of which may be directed to a different epitope); a single chain Fab chain comprising a variable region, also known as, a sFv (the variable, antigen-binding determinative region of a single light and heavy chain of an antibody linked together by a chain of 10-25 amino acids); a disulfide-linked Fv, or dsFv (the variable, antigen-binding determinative region of a single light and heavy chain of an antibody linked together by a disulfide bond); a camelized VH (the variable, antigen-binding determinative region of a single heavy chain of an antibody in which some amino acids at the VH interface are those found in the heavy chain of naturally occurring camel antibodies); a bispecific sFv (a sFv or a dsFv molecule having two antigen-binding domains, each of which may be directed to a different epitope); a diabody (a dimerized sFv formed when the VH domain of a first sFv assembles with the VL domain of a second sFv and the VL domain of the first sFv assembles with the VH domain of the second sFv; the two antigen-binding regions of the diabody may be directed towards the same or different epitopes); and a triabody (a trimerized sFv, formed in a manner similar to a diabody, but in which three antigen-binding domains are created in a single complex; the three antigen binding domains may be directed towards the same or different epitopes). Derivatives of antibodies also include one or more CDR sequences of an antibody combining site. The CDR sequences may be linked together on a scaffold when two or more CDR sequences are present. In certain embodiments, the antibody to be used with the invention comprises a single-chain Fv ("scFv"). scFvs are antibody fragments comprising the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFvs see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

[0125] The antibodies of the invention may be from any animal origin including birds and mammals (*e.g.*, human, murine, donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken). In certain embodiments, the antibodies of the invention are human or humanized monoclonal antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from mice that express antibodies from human genes.

[0126] In preferred embodiments, the antibodies of the invention are fully human antibodies, such as fully human antibodies that immunospecifically bind a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. Such fully human antibodies would be advantageous over fully mouse (or other full or partial non-human species antibodies), humanized antibodies, or chimeric antibodies to minimize the development of unwanted or unneeded side effects, such as immune responses directed toward non-fully human antibodies (*e.g.*, anti-hLIGHT antibodies derived from other species) when administered to the subject.

[0127] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a hLIGHT polypeptide or may be specific for both a hLIGHT polypeptide as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. In preferred embodiments, the antibodies provided herein are monospecific for a given epitope of a hLIGHT polypeptide and do not immunospecifically bind to other epitopes.

[0128] In preferred embodiments, antibodies of the compositions comprising the antibodies and methods of using the antibodies of the present invention include an E1, E13, E63, F19 or F23 antibody (ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728, respectively). Also provided herein are hybridomas that produce E1, E13, E63, F19 or F23 antibody (ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728, respectively) and/or other anti-hLIGHT monoclonal antibodies described herein.

[0129] In certain embodiments, an isolated antibody is provided herein that immunospecifically binds to a hLIGHT epitope wherein the binding to the hLIGHT epitope by the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by: (a) an E1 antibody, E13 antibody, or E63 antibody, or (b) an F19 antibody or F23 antibody; with the proviso that the binding to the hLIGHT epitope is not blocked by

both of: (a) the E1 antibody and the F19 antibody, (b) the E1 antibody and the F23 antibody, (c) the E13 antibody and the F19 antibody, (d) the E13 antibody and the F23 antibody, (e) the E63 antibody and the F19 antibody, or (f) the E63 antibody and the F23 antibody. The antibody may or may not be a fully human antibody. In preferred embodiments, the antibody is a fully human monoclonal anti-hLIGHT antibody, and even more preferably a fully human, monoclonal, antagonist anti-hLIGHT antibody. Exemplary competitive blocking tests that can be used are provided in the Examples herein.

[0130] In other embodiments, an isolated antibody, preferably a fully human antibody, is provided herein that immunospecifically binds to a hLIGHT epitope, wherein the binding to the hLIGHT epitope by the antibody is competitively blocked (*e.g.*, in a dose-dependent manner) by: (a) an E1 antibody, E13 antibody, or E63 antibody, or (b) an F19 antibody or F23 antibody. The antibody may or may not be a fully human antibody. In preferred embodiments, the antibody is a fully human monoclonal anti-hLIGHT antibody, and even more preferably a fully human, monoclonal, antagonist anti-hLIGHT antibody. Exemplary competitive blocking tests that can be used are provided in the Examples herein.

[0131] In some embodiments, the antibodies provided herein compete (*e.g.*, in a dose-dependent manner) with HVEM, LTβR and/or DcR3 (or fusion protein(s) thereof) for binding to cell surface-expressed hLIGHT. In other embodiments, the antibodies provided herein compete (*e.g.*, in a dose-dependent manner) with HVEM, LTβR and/or DcR3 (or fusion protein(s) thereof) for binding to soluble hLIGHT. Exemplary competitive binding assays that can be used are provided in the Examples herein. In one embodiment, the antibody partially or completely inhibits binding of HVEM, LTβR and/or DcR3 to cell surface-expressed hLIGHT, such as hLIGHT. In another embodiment, the antibody partially or completely inhibits binding of HVEM, LTβR and/or DcR3 to soluble hLIGHT. In some embodiments, the antibodies provided herein partially or completely inhibits the secretion of CCL20, IL-8, and/or RANTES from a cell having cell surface-expressed hLIGHT ligand, such as a hLIGHT receptor (*e.g.*, HVEM, LTβR and/or DcR3). In certain embodiments, the cell expressing the hLIGHT receptor is a colonic epithelial cell.

[0132] The antibodies of the present invention include those antibodies and antigen-binding fragments of the following antibodies: an E1 antibody (ATCC Accession No. PTA-7729), E13 antibody (ATCC Accession No. PTA-7842), or E63 antibody (ATCC

Accession No. PTA-7818), an F19 antibody (ATCC Accession No. PTA-7819) or F23 antibody (ATCC Accession No. PTA-7728) antibody, the Examples Section, and elsewhere in the application.. In a specific embodiment, an antibody of the present invention is E1, E13, E63, F19, or F23 antibody. In another embodiment, an antibody of the invention comprises an antigen-binding fragment (*e.g.*, a Fab fragment) of E1, E13, E63, F19, or F23.

[0133] Preferably, the antibodies of the invention are fully human, monoclonal antibodies, such as fully human, monoclonal antagonist antibodies, that immunospecifically bind to hLIGHT.

[0134] In some embodiments, the antibodies provided herein bind to a hLIGHT epitope that is a three-dimensional surface feature of a hLIGHT polypeptide (*e.g.*, in a trimeric form of a hLIGHT polypeptide). A region of a hLIGHT polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide A hLIGHT epitope may be present in (a) the trimeric form ("a trimeric hLIGHT epitope") of hLIGHT, (b) the monomeric form ("a monomeric hLIGHT epitope") of hLIGHT, (c) both the trimeric and monomeric form of hLIGHT, (d) the trimeric form, but not the monomeric form of hLIGHT, or (e) the monomeric form, but not the trimeric form of hLIGHT.

[0135] For example, in some embodiments, the epitope is only present or available for binding in the trimeric (native) form, but is not present or available for binding in the monomeric (denatured) form by an anti-hLIGHT antibody. In other embodiments, the hLIGHT epitope is linear feature of the hLIGHT polypeptide (*e.g.*, in a trimeric form or monomeric form of the hLIGHT polypeptide). Antibodies provided herein may immunospecifically bind to (a) an epitope of the monomeric form of hLIGHT, (b) an epitope of the trimeric form of hLIGHT, (c) an epitope of the monomeric but not the trimeric form of hLIGHT, (d) an epitope of the trimeric but not the monomeric form of hLIGHT, or (e) both the monomeric form and the trimeric form of hLIGHT. In preferred embodiments, the antibodies provided herein immunospecifically bind to an epitope of the trimeric form of hLIGHT but do not immunospecifically bind to an epitope the monomeric form of hLIGHT.

[0136] In a specific embodiment, the present invention provides for one or more antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a VH chain and/or VL chain having the amino acid sequence of a VH chain

and/or VL chain of an E1, E13, E63, F19, and/or F23 antibody; or of an antibody produced by a hybridoma having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728.

[0137] In another embodiment, the present invention provides for one or more antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a VH domain and/or VL domain having the amino acid sequence of a VH domain and/or VL domain of E1, E13, E63, F19, and/or F23 antibody; or of an antibody produced by a hybridoma having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728.

[0138] In another embodiment, the present invention provides for antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising one, two, three, or more CDRs having the amino acid sequence of one, two, three, or more CDRs of E1, E13, E63, F19, and/or F23 antibody; or of an antibody produced by a hybridoma having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728.

[0139] In one embodiment, the present invention provides for one or more antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a combination of VH CDRs and/or VL CDRs having the amino acid sequence of VH CDRs and/or VL CDRs of E1, E13, E63, F19, and/or F23; or of an antibody produced by a hybridoma having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728.

[0140] The present invention provides antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a VH chain and/or VL chain having an amino acid sequence of a VH chain and/or VL chain, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1, E13, or E63 antibody, or (b) an F19 or F23 antibody; with the proviso that the binding to the hLIGHT epitope is not blocked by both of: (a) the E1 and the F19 antibody, (b) the E1 and the F23 antibody, (c) the E13 and the F19 antibody, (d) the E13 and the F23 antibody, (e) the E63 and the F19 antibody, or (f) the E63 and the F23 antibody.

[0141] The present invention also provides fully human antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a VH chain and/or VL chain having an amino acid sequence of a VH chain and/or VL chain,

respectively, of an antibody that immunospecifically binds to a hLIGHT epitope, wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1 antibody, E13 antibody, or E63 antibody, or (b) an F19 antibody or F23 antibody. Preferably, the fully human antibody is a fully human monoclonal antibody and/or a hLIGHT antagonist antibody.

[0142] The present invention provides antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a VH domain and/or VL domain having an amino acid sequence of a VH domain and/or VL domain, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1, E13, or E63 antibody, or (b) an F19 or F23 antibody; with the proviso that the binding to the hLIGHT epitope is not blocked by both of: (a) the E1 and the F19 antibody, (b) the E1 and the F23 antibody, (c) the E13 and the F19 antibody, (d) the E13 and the F23 antibody, (e) the E63 and the F19 antibody, or (f) the E63 and the F23 antibody.

[0143] The present invention also provides fully human antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising a VH domain and/or VL domain having an amino acid sequence of a VH domain and/or VL domain, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope, wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1 antibody, E13 antibody, or E63 antibody, or (b) an F19 antibody or F23 antibody. Preferably, the fully human antibody is a fully human monoclonal antibody and/or a hLIGHT antagonist antibody.

[0144] The present invention provides antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising one, two or three VH CDRs (*i.e.*, VH CDR1, VH CDR2, and/or VH CDR3) having an amino acid sequence one, two or three VH CDRs, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1, E13, or E63 antibody, or (b) an F19 or F23 antibody; with the proviso that the binding to the hLIGHT epitope is not blocked by both of: (a) the E1 and the F19 antibody, (b) the E1 and the F23 antibody, (c) the E13 and the F19 antibody, (d) the E13 and the F23 antibody, (e) the E63 and the F19 antibody, or (f) the E63 and the F23 antibody.

[0145] The present invention also provides fully human antibodies that immunospecifically bind to a hLIGHT epitope, said comprising one, two or three VH CDRs (*i.e.*, VH CDR1, VH CDR2, and/or VH CDR3) having an amino acid sequence one, two or three VH CDRs, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope, wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1 antibody, E13 antibody, or E63 antibody, or (b) an F19 antibody or F23 antibody. Preferably, the fully human antibody is a fully human monoclonal antibody and/or a hLIGHT antagonist antibody.

[0146] The present invention provides antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising one, two or three VL CDRs (*i.e.*, VL CDR1, VL CDR2, and/or VL CDR3) having an amino acid sequence one, two or three VL CDRs, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1, E13, or E63 antibody, or (b) an F19 or F23 antibody; with the proviso that the binding to the hLIGHT epitope is not blocked by both of: (a) the E1 and the F19 antibody, (b) the E1 and the F23 antibody, (c) the E13 and the F19 antibody, (d) the E13 and the F23 antibody, (e) the E63 and the F19 antibody, or (f) the E63 and the F23 antibody.

[0147] The present invention also provides fully human antibodies that immunospecifically bind to a hLIGHT epitope, said comprising one, two or three VL CDRs (*i.e.*, VL CDR1, VL CDR2, and/or VL CDR3) having an amino acid sequence one, two or three VL CDRs, respectively, of an antibody that immunospecifically binds to a hLIGHT epitope, wherein the binding to the hLIGHT epitope by the antibody is competitively blocked in a dose-dependent manner by: (a) an E1 antibody, E13 antibody, or E63 antibody, or (b) an F19 antibody or F23 antibody. Preferably, the fully human antibody is a fully human monoclonal antibody and/or a hLIGHT antagonist antibody.

[0148] The present invention also provides antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising one or more VH CDRs (*i.e.*, VH CDR1, VH CDR2, and/or VH CDR3) having an amino acid sequence of any one of the VH CDRs (*i.e.*, VH CDR1, VH CDR2, and/or VH CDR3) of E1, E13, E63, F19, and/or F23; or of an antibody produced by a hybridoma having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728; or any combination thereof.

[0149] In one embodiment, antibodies that immunospecifically bind to a hLIGHT epitope comprise a VH domain having the amino acid sequence of the VH domain depicted in any one of SEQ ID NOS:1, 2, 3, 4 or 5 and/or a VL domain having the amino acid sequence of the VL domain depicted in any one of SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, or 10.

[0150] In certain embodiments, an antibody that immunospecifically binds to a hLIGHT epitope comprises (a) a VH domain having the amino acid sequence depicted in SEQ ID NO:1 and a VL domain having the amino acid sequence depicted in any one of SEQ ID NOS:82, 6 or 83; (b) a VH domain having the amino acid sequence depicted in SEQ ID NO:2 and a VL domain having the amino acid sequence depicted in SEQ ID NO:7; (c) a VH domain having the amino acid sequence depicted in SEQ ID NO:3 and a VL domain having the amino acid sequence depicted in SEQ ID NO:8; (d) a VH domain having the amino acid sequence depicted in SEQ ID NO:4 and a VL domain having the amino acid sequence depicted in any one of SEQ ID NOS:90, 9, 91 or 92; or (e) a VH domain having the amino acid sequence depicted in SEQ ID NO:5 and a VL domain having the amino acid sequence depicted in SEQ ID NO:10. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0151] In another embodiment, antibodies that immunospecifically bind to a hLIGHT epitope comprise a VH domain having the amino acid sequence of the VH domain of an antibody having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively) and/or a VL domain having the amino acid sequence of the VL domain of an antibody having ATCC Accession No. ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively).

[0152] In certain embodiments, an antibody that immunospecifically binds to a hLIGHT epitope comprises (a) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7729 (E1) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7729 (E1); (b) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7842 (E13) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7842 (E13); (c) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7818 (E63) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No.

PTA-7818 (E63); (d) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7819 (F19) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7819 (F19); or (e) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7728 (F23) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7728 (F23). Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0153] In some embodiments, antibodies of the invention comprise a VH CDR1 having the amino acid sequence of the VH CDR1 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In another embodiment, antibodies of the invention comprise a VH CDR2 having the amino acid sequence of the VH CDR2 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In another embodiment, antibodies of the invention comprise a VH CDR3 having the amino acid sequence of the VH CDR3 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In certain embodiments, antibodies of the invention comprise a VH CDR1 and/or a VH CDR2 and/or a VH CDR3 independently selected from a VH CDR1, VH CDR2, VH CDR3 as depicted in any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5.

[0154] The present invention also provides antibodies that immunospecifically bind to a hLIGHT epitope, said antibodies comprising one or more VL CDRs (*i.e.*, VL CDR1, VL CDR2, and/or VL CDR3) having an amino acid sequence of any one of the VL CDRs (*i.e.*, VL CDR1, VL CDR2 and/or VL: CDR3) of E1, E13, E63, F19, and/or F23; or of an antibody produced by a hybridoma having ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively); or any combination thereof.

[0155] In certain embodiments, an antibody that immunospecifically binds to an hLIGHT epitope comprises (1) a VH domain having (a) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:11, 12 and/or 13, respectively, (b) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:14, 15 and/or 16, respectively, (c) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:17, 18, and/or 19, respectively, (d) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:20, 21 and/or 22, respectively, or (e) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in

SEQ ID NOS:23, 24 and/or 24, respectively, and/or (2) a VL domain having (a) a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:84, 26 or 85; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:86, 27, or 87; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:88, 28, or 89, (b) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:29, 30 and/or 31, respectively, (c) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:32, 33 and/or 34, respectively, (d) a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:93, 35, 94, or 95; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98, or (e) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:38, 39 and/or 40, respectively. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0156] In some embodiments, an antibody that immunospecifically binds to an hLIGHT epitope comprises (1) a VH domain having (a) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1), (b) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13), (c) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63), (d) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19), or (e) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23), and/or (2) a VL domain having (a) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1), (b) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13), (c) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody

having ATCC Accession No. PTA-7818 (E63), (d) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19), or (e) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23). Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0157] In certain embodiments, an antibody that immunospecifically binds to an hLIGHT epitope comprises (1) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:11, 12 and/or 13, respectively, and (b) a VL domain having a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:84, 26 or 85; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:86, 27, or 87; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:88, 28, or 89; (2) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:14, 15 and/or 16, respectively, and (b) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:29, 30 and/or 31, respectively; (3) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:17, 18, and/or 19, respectively, and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:32, 33 and/or 34, respectively; (4) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:20, 21 and/or 22, respectively, and (b) a VL domain having a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:93, 35, 94, or 95; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98; or (5) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:23, 24 and/or 24, respectively, and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:38, 39 and/or 40, respectively. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0158] In some embodiments, an antibody that immunospecifically binds to an hLIGHT epitope comprises (1) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1), and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1); (2) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13) and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13); (3) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63) and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63); (4) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19) and a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19); or (5) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23) and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23). Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0159] In some embodiments, antibodies of the invention comprise a VL CDR1 having the amino acid sequence of the VL CDR1 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively). In another embodiment, antibodies of the invention comprise a VL CDR2 having the amino acid sequence of the

VL CDR2 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively). In another embodiment, antibodies of the invention comprise a VL CDR3 having the amino acid sequence of the VL CDR3 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively). In certain embodiments, antibodies of the invention comprise a VL CDR1 and/or a VL CDR2 and/or a VL CDR3 independently selected from the VL CDR1, VL CDR2, VL CDR3 as depicted in any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively).

[0160] In some embodiments, antibodies of the invention comprises a (1) VH domain or chain having one or more of (a) a VH CDR1 having the amino acid sequence of a VH CDR1 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), (b) a VH CDR2 having the amino acid sequence of a VH CDR2 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), or (c) a VH CDR3 having the amino acid sequence a VH CDR3 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively); and/or (2) a VL domain or chain having one of more of (a) a VL CDR1 having the amino acid sequence of the VL CDR1 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), (b) a VL CDR2 having the amino acid sequence of a VL CDR2 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), and/or (c) a VL CDR3

having the amino acid sequence of a VL CDR3 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively).

Table 1: Sequences of CDR regions of antibodies E1, E13, E63, F19, and F23 (SEQ ID NOS).

Ab	VH	VH CDR1	VH CDR2	VH CDR3	VL	VL CDR1	VL CDR2	VL CDR3
E1	(SEQ ID NO:1)	RFNMN (SEQ ID NO:11)	YISSSSYTIYYADSVKG (SEQ ID NO:12)	SIAAFDY (SEQ ID NO:13)	(SEQ ID NO:82, 6*, 83)	RASQGISSALA (SEQ ID NO:84) RASQSVSSSYLT (SEQ ID NO:26*) RASQSVSSSYLA (SEQ ID NO:85)	DASSLES (SEQ ID NO:86) GASSRAT (SEQ ID NO:27*) GASNRAT (SEQ ID NO:87)	QQFNSYRT (SEQ ID NO:88) QQYGSSMYT (SEQ ID NO:28*) QQYGSSPWT (SEQ ID NO:89)
E13	(SEQ ID NO:2)	NAWMS (SEQ ID NO:14)	RIKSKIDGGTTDYAAPVKG (SEQ ID NO:15)	AMAGAFGF (SEQ ID NO:16)	(SEQ ID NO:7)	RASQSVSSSYLA (SEQ ID NO:29)	GASSRAT (SEQ ID NO:30	QQYGSSPMYT (SEQ ID NO:31)
E63	(SEQ ID NO:3)	SGGYYWS (SEQ ID NO:17)	YIYYSGSTNYNPSLKS (SEQ ID NO:18)	WITMFRGVGFDP (SEQ ID NO:19)	(SEQ ID NO:8)	RASQSIGSSLH (SEQ ID NO:32)	YASQSFS (SEQ ID NO:33	HQSSSLPLT (SEQ ID NO:34)
F19	(SEQ ID NO:4)	GYNWH (SEQ ID NO:20)	EITHSGSTNYNPSLKS (SEQ ID NO:21)	EIAVAGTGYYGMDV (SEQ ID NO:22)	(SEQ ID NO:90, 9*, 91, 92)	RVSQGISSYLN (SEQ ID NO:93) RASQGINSAFA (SEQ ID NO:35*) RMSQGISSYLA (SEQ ID NO:94) RASQGVSSYLA (SEQ ID NO:95)	SASNLQS (SEQ ID NO:96) DASSLES (SEQ ID NO:36*) AASTLQS (SEQ ID NO:97) DASNRAT (SEQ ID NO:98)	QRTJNAPPT (SEQ ID NO:99) QQFNSYPLT (SEQ ID NO:37*) QQYYSFPYT (SEQ ID NO:100) QQRSNWHP (SEQ ID NO:101)
F23	(SEQ ID NO:5)	GYYWN (SEQ ID NO:23)	EINQYNPSLKS (SEQ ID NO:24)	EIATADKGYYGLDV (SEQ ID NO:25)	(SEQ ID NO:10)	RASQGISSALA (SEQ ID NO:38)	DASSLES (SEQ ID NO:39)	QQFNSYPLT SEQ ID NO:40)

* Preferred E1 and F19 VL and VL CDR1-3 sequences.

[0161] The present invention also provides antibodies comprising one or more VH CDRs and one or more VL CDRs listed in Table I. In particular, the invention provides for an antibody comprising a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH1 CDR1, a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29,

32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and

a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39), and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39), and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39), and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); or any combination thereof of the VH CDRs (SEQ ID NOS:11-25) and VL CDRs (SEQ ID NOS:26-40) listed in Table I. The corresponding VH CDRs and VL CDRs of ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), may also be used in any of the combinations listed above. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0162] The present invention also provides antibodies that immunospecifically bind to a hLIGHT epitope, the antibodies comprising derivatives of the VH domains, VH CDRs, VL domains, and VL CDRs described herein that immunospecifically bind to a hLIGHT antigen. The present invention also provides antibodies comprising derivatives of E1, E13, E63, F19, and/or F23, wherein said antibodies immunospecifically bind to a hLIGHT epitope. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In a preferred embodiment, the derivatives have conservative amino acid substitutions are made at one or more

predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

[0163] In another embodiment, an antibody that immunospecifically binds to a hLIGHT epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the amino acid sequence of E1, E13, E63, F19, and/or F23, or an antigen-binding fragment thereof, such as a VH domain, VL domain, VH chain, or VL chain. In one embodiment, an antibody that immunospecifically binds to a hLIGHT epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to an amino acid sequence depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In another embodiment, an antibody that immunospecifically binds to a hLIGHT epitope comprises an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to an amino acid sequence depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10. In yet another embodiment, an antibody that immunospecifically binds to a hLIGHT epitope comprises a VH CDR and/or a VL CDR amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a VH CDR amino acid sequence

depicted in SEQ ID NOS:11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 (VH CDRs) and/or a VL CDR amino acid sequence depicted in SEQ ID NOS:84, 26, 85, 86, 27, 87, 88, 28, 89, 2, 30, 31, 32, 33, 34, 93, 35, 94, 95, 96, 36, 97, 98, 99, 37, 100, 101, 38, 39, or 40.

[0164] In specific embodiments, the antibody is a fully human anti-human antibody, such as a fully human monoclonal antibody. Fully human antibodies may be produced by any method known in the art. Exemplary methods include immunization with a hLIGHT antigen (any hLIGHT polypeptide capable of eliciting an immune response, and optionally conjugated to a carrier) of transgenic animals (*e.g.*, mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production; *see, e.g.*, Jakobovits *et al.*, (1993) *Proc. Natl. Acad. Sci.*, 90:2551; Jakobovits *et al.*, (1993) *Nature*, 362:255 258 (1993); *Bruggermann et al.*, (1993) *Year in Immunol.*, 7:33. Other methods of producing fully human anti-hLIGHT antibodies can be found in the Examples provided herein.

[0165] Alternatively, fully human antibodies may be generated through the *in vitro* screening of phage display antibody libraries; see *e.g.*, Hoogenboom *et al.*, J. Mol. Biol., 227:381 (1991); Marks *et al.*, J. Mol. Biol., 222:581 (1991), incorporated herein by reference. Various antibody-containing phage display libraries have been described and may be readily prepared by one skilled in the art. Libraries may contain a diversity of human antibody sequences, such as human Fab, Fv, and scFv fragments, that may be screened against an appropriate target.

[0166] In preferred embodiments, the antibodies used in accordance with the methods of the invention have a high affinity for a hLIGHT polypeptide, or polypeptide fragment or epitope thereof. In one embodiment, the antibodies used in accordance with the methods of the invention have a higher affinity for a hLIGHT antibody than known antibodies (*e.g.*, commercially available monoclonal antibodies discussed elsewhere herein). In a specific embodiment, the antibodies used in accordance with the methods of the invention have a 2- to 10-fold (or more) higher affinity for a hLIGHT antigen than a known anti-hLIGHT antibody as assessed by techniques described herein or known to one of skill in the art (*e.g.*, a BIAcore assay). In accordance with these embodiments, the affinity of the antibodies are, in one embodiment, assessed by a BIAcore assay.

[0167] In a specific embodiment, an antibody that immunospecifically binds a hLIGHT antigen comprises an amino acid sequence of a VH domain and/or an amino acid sequence a VL domain encoded by a nucleotide sequence that hybridizes to (1) the

complement of a nucleotide sequence encoding any one of the VH and/or VL domains depicted in SEQ ID NOS:41, 42, 43, 44 or 45 (VH) and/or SEQ ID NOS:102, 46, 103, 47, 48, 104, 49, 105, 106, or 50 (VL) or (2) the complement of a nucleotide sequence encoding any one of the VH or VL domains of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23) under stringent conditions (*e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C) under highly stringent conditions (*e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3).

[0168] In another embodiment, an antibody that immunospecifically binds a hLIGHT antigen comprises an amino acid sequence of a VH CDR or an amino acid sequence of a VL CDRs encoded by a nucleotide sequence that hybridizes to the complement of a nucleotide sequence encoding any one of the VH CDRs and/or VL CDRs depicted in SEQ ID NOS:11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 (VH CDRs) and/or SEQ ID NOS:84, 26, 85, 86, 27, 87, 88, 28, 89, 2, 30, 31, 32, 33, 34, 93, 35, 94, 95, 96, 36, 97, 98, 99, 37, 100, 101, 38, 39, or 40 (VL CDRs) or (b) the complement of a nucleic acid sequence encoding any one of the VH CDRs and/or VL CDRs of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23) under stringent conditions (*e.g.*, hybridization to filter-bound DNA in 6X SSC at about 45° C followed by one or more washes in 0.2X SSC/0.1% SDS at about 50-65° C), under highly stringent conditions (*e.g.*, hybridization to filter-bound nucleic acid in 6X SSC at about 45° C followed by one or more washes in 0.1X SSC/0.2% SDS at about 68° C), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3)

[0169] The antibodies of the invention include antibodies that are chemically modified, *i.e.*, by the covalent attachment of any type of molecule to the antibody. For

example, but not by way of limitation, the antibody derivatives include antibodies that have been chemically modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, *etc.* Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, *etc.* Additionally, the antibody may contain one or more non-classical amino acids.

[0170] The present invention also provides antibodies that immunospecifically bind to a hLIGHT antigen which comprise a framework region known to those of skill in the art (*e.g.*, a human or non-human fragment). The framework region may, for example, be naturally occurring or consensus framework regions. Most preferably, the framework region of an antibody of the invention is human (see, *e.g.*, Chothia *et al.*, 1998, *J. Mol. Biol.* 278:457-479 for a listing of human framework regions, which is incorporated by reference herein in its entirety). See also Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed.

[0171] In a specific embodiment, the present invention provides for antibodies that immunospecifically bind to a hLIGHT antigen, said antibodies comprising the amino acid sequence of one or more of the CDRs of E1, E13, E63, F19, and/or F23 (*i.e.*, SEQ ID NOS:11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 (VH CDRs) or SEQ ID NOS:84, 26, 85, 86, 27, 87, 88, 28, 89, 2, 30, 31, 32, 33, 34, 93, 35, 94, 95, 96, 36, 97, 98, 99, 37, 100, 101, 38, 39, or 40 (VL CDRs), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728, and human framework regions with one or more amino acid substitutions at one, two, three or more of the following residues: (a) rare framework residues that differ between the murine antibody framework (*i.e.*, donor antibody framework) and the human antibody framework (*i.e.*, acceptor antibody framework); (b) Venier zone residues when differing between donor antibody framework and acceptor antibody framework; (c) interchain packing residues at the VH/VL interface that differ between the donor antibody framework and the acceptor antibody framework; (d) canonical residues which differ between the donor antibody framework and the acceptor antibody framework sequences, particularly the framework regions crucial for the definition of the canonical class of the murine antibody CDR loops; (e) residues that are adjacent to a

CDR; (g) residues capable of interacting with the antigen; (h) residues capable of interacting with the CDR; and (i) contact residues between the VH domain and the VL domain. In certain embodiments, antibodies that immunospecifically bind to a hLIGHT antigen comprising the human framework regions with one or more amino acid substitutions at one, two, three or more of the above-identified residues are antagonistic hLIGHT antibodies.

[0172] The present invention encompasses antibodies that immunospecifically bind to a hLIGHT antigen, said antibodies comprising the amino acid sequence of the VH domain and/or VL domain or an antigen-binding fragment thereof of an antibody produced by the hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728), or of an E1, E13, E63, F19, and/or F23 antibody, having mutations (*e.g.*, one or more amino acid substitutions) in the framework regions. In certain embodiments, antibodies that immunospecifically bind to a hLIGHT antigen comprise the amino acid sequence of the VH domain and/or VL domain or an antigen-binding fragment thereof of E1, E13, E63, F19, and/or F23 with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains.

[0173] The present invention also encompasses antibodies that immunospecifically bind to a hLIGHT antigen, said antibodies comprising the amino acid sequence of the VH domain and/or VL domain of an antibody produced by the hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728, or of an E1, E13, E63, F19, and/or F23 antibody, having mutations (*e.g.*, one or more amino acid residue substitutions) in the hypervariable and framework regions. Preferably, the amino acid substitutions in the hypervariable and framework regions improve binding of the antibody to a hLIGHT antigen.

[0174] In some embodiments, antibodies provided herein decrease or inhibit binding of hLIGHT to HVEM, LTβR and/or DcR3, and/or decrease or inhibit a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in subject (*e.g.*, a human subject). In certain embodiments, antibodies provided herein, such as a human monoclonal anti-hLIGHT antibody, decreases or inhibits binding of a soluble or cell-surface expressed hLIGHT to HVEM or LTβR, and/or decreases or inhibits secretion of CCL20 and/or RANTES after contact with a soluble or cell-surface expressed hLIGHT, in a subject. In some embodiments, the hLIGHT is a SNP variant of hLIGHT, such as 214E-32S, 214K-32S, 214E-32L or 214K-32L. Blocking activity of an antibody provided herein of hLIGHT binding to HVEM, LTβR and/or DCR3 can be detected

using an assay as described in any one of Examples 1-4. Inhibition of biological activity of cells expressing a hLIGHT receptor by a hLIGHT antibody provided herein can be detected using an assay as described in any one of Examples 1-4.

[0175] In other embodiments, antibodies provided herein decrease or inhibit binding of hLIGHT to HVEM, LTβR and/or DcR3 and/or decrease or inhibit a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a cell having a cell surface-expressed hLIGHT receptor (such as, HVEM, LTβR and/or Dc3R). In certain embodiments, antibodies provided herein, such as a human monoclonal anti-hLIGHT antibody, decreases or inhibits binding of a soluble or cell-surface expressed hLIGHT to HVEM or LTβR, and/or decreases or inhibits secretion of CCL20 and/or RANTES, in a cell having a cell surface-expressed hLIGHT receptor after contact with a soluble or cell-surface expressed hLIGHT. In some embodiments, the hLIGHT is a SNP variant of hLIGHT, such as 214E-32S, 214K-32S, 214E-32L or 214K-32L. Blocking activity of an antibody provided herein of hLIGHT binding to HVEM, LTβR and/or DCR3 can be detected using an assay as described in any one of Examples 1-4 Inhibition of biological activity of cells expressing a hLIGHT receptor by a hLIGHT antibody provided herein can be detected using an assay as described in any one of Examples 1-4.

[0176] The present invention also provides for fusion proteins comprising an antibody provided herein that immunospecifically binds to a hLIGHT antigen and a heterologous polypeptide. In some embodiments, the heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed hLIGHT.

[0177] The present invention also provides for panels of antibodies that immunospecifically bind to a hLIGHT antigen. In specific embodiments, the invention provides for panels of antibodies having different association rate constants different dissociation rate constants, different affinities for hLIGHT antigen, and/or different specificities for a hLIGHT antigen. The invention provides panels of about 10, preferably about 25, about 50, about 75, about 100, about 125, about 150, about 175, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, or about 1000 antibodies or more. Panels of antibodies can be used, for example, in 96 well or 384 well plates, such as for assays such as ELISAs.

ANTIBODY CONJUGATES AND FUSION PROTEINS

[0178] In some embodiments, antibodies of the invention are conjugated or recombinantly fused to a diagnostic, detectable or therapeutic agent or any other molecule. The conjugated or recombinantly fused antibodies can be useful, *e.g.*, for monitoring or prognosing the onset, development, progression and/or severity of a hLIGHT-mediated disease as part of a clinical testing procedure, such as determining the efficacy of a particular therapy.

[0179] Such diagnosis and detection can accomplished, for example, by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (^{131}I, ^{125}I, ^{123}I, and ^{121}I,), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}In, ^{113}In, ^{112}In, and ^{111}In,), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Sn; and positron emitting metals using various positron emission tomographies, and non-radioactive paramagnetic metal ions.

[0180] The present invention further encompasses uses of the antibodies of the invention conjugated or recombinantly fused to a therapeutic moiety (or one or more therapeutic moieties). The antibody may be conjugated or recombinantly fused to a therapeutic moiety, such as a cytotoxin, *e.g.*, a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, *e.g.*, alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Therapeutic moieties include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine); alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP), and cisplatin); anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin); antibiotics (*e.g.*, d actinomycin

(formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)); Auristatin molecules (*e.g.*, auristatin PHE, bryostatin 1, and solastatin 10; see Woyke *et al.*, Antimicrob. Agents Chemother. 46:3802-8 (2002), Woyke *et al.*, Antimicrob. Agents Chemother. 45:3580-4 (2001), Mohammad *et al.*, Anticancer Drugs 12:735-40 (2001), Wall *et al.*, Biochem. Biophys. Res. Commun. 266:76-80 (1999), Mohammad *et al.*, Int. J. Oncol. 15:367-72 (1999), all of which are incorporated herein by reference); hormones (*e.g.*, glucocorticoids, progestins, androgens, and estrogens), DNA-repair enzyme inhibitors (*e.g.*, etoposide or topotecan), kinase inhibitors (*e.g.*, compound ST1571, imatinib mesylate (Kantarjian *et al.*, Clin Cancer Res. 8(7):2167-76 (2002)); cytotoxic agents (*e.g.*, paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof and those compounds disclosed in U.S. Patent Nos. 6,245,759, 6,399,633, 6,383,790, 6,335,156, 6,271,242, 6,242,196, 6,218,410, 6,218,372, 6,057,300, 6,034,053, 5,985,877, 5,958,769, 5,925,376, 5,922,844, 5,911,995, 5,872,223, 5,863,904, 5,840,745, 5,728,868, 5,648,239, 5,587,459); farnesyl transferase inhibitors (*e.g.*, R115777, BMS-214662, and those disclosed by, for example, U.S. Patent Nos: 6,458,935, 6,451,812, 6,440,974, 6,436,960, 6,432,959, 6,420,387, 6,414,145, 6,410,541, 6,410,539, 6,403,581, 6,399,615, 6,387,905, 6,372,747, 6,369,034, 6,362,188, 6,342,765, 6,342,487, 6,300,501, 6,268,363, 6,265,422, 6,248,756, 6,239,140, 6,232,338, 6,228,865, 6,228,856, 6,225,322, 6,218,406, 6,211,193, 6,187,786, 6,169,096, 6,159,984, 6,143,766, 6,133,303, 6,127,366, 6,124,465, 6,124,295, 6,103,723, 6,093,737, 6,090,948, 6,080,870, 6,077,853, 6,071,935, 6,066,738, 6,063,930, 6,054,466, 6,051,582, 6,051,574, and 6,040,305); topoisomerase inhibitors (*e.g.*, camptothecin; irinotecan; SN-38; topotecan; 9-aminocamptothecin; GG-211 (GI 147211); DX-8951f; IST-622; rubitecan; pyrazoloacridine; XR-5000; saintopin; UCE6; UCE1022; TAN-1518A; TAN 1518B; KT6006; KT6528; ED-110; NB-506; ED-110; NB-506; and rebeccamycin); bulgarein; DNA minor groove binders such as Hoescht dye 33342 and Hoechst dye 33258; nitidine; fagaronine; epiberberine; coralyne; beta-lapachone; BC-4-1; bisphosphonates (*e.g.*, alendronate, cimadronte, clodronate, tiludronate, etidronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate) HMG-CoA reductase inhibitors, (*e.g.*, lovastatin, simvastatin, atorvastatin,

pravastatin, fluvastatin, statin, cerivastatin, lescol, lupitor, rosuvastatin and atorvastatin); antisense oligonucleotides (*e.g.*, those disclosed in the U.S. Patent Nos. 6,277,832, 5,998,596, 5,885,834, 5,734,033, and 5,618,709); adenosine deaminase inhibitors (*e.g.*, Fludarabine phosphate and 2-Chlorodeoxyadenosine); ibritumomab tiuxetan (Zevalin®); tositumomab (Bexxar®)) and pharmaceutically acceptable salts, solvates, clathrates, and prodrugs thereof.

[0181] Further, an antibody of the invention may be conjugated or recombinantly fused to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, γ-interferon, α-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, *e.g.*, TNF-γ, TNF-γ, AIM I (see, International Publication No. WO 97/33899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, 1994, J. Immunol., 6:1567-1574), and VEGF (see, International Publication No. WO 99/23105), an anti-angiogenic agent, *e.g.*, angiostatin, endostatin or a component of the coagulation pathway (*e.g.*, tissue factor); or, a biological response modifier such as, for example, a lymphokine (*e.g.*, interferon gamma, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-5 ("IL-5"), interleukin-6 ("IL-6"), interleukin-7 ("IL-7"), interleukin 9 ("IL-9"), interleukin-10 ("IL-10"), interleukin-12 ("IL-12"), interleukin-15 ("IL-15"), interleukin-23 ("IL-23"), granulocyte macrophage colony stimulating factor ("GM-CSF"), and granulocyte colony stimulating factor ("G-CSF")), or a growth factor (*e.g.*, growth hormone ("GH")), or a coagulation agent (*e.g.*, calcium, vitamin K, tissue factors, such as but not limited to, Hageman factor (factor XII), high-molecular-weight kininogen (HMWK), prekallikrein (PK), coagulation proteins-factors II (prothrombin), factor V, XIIa, VIII, XIIIa, XI, XIa, IX, IXa, X, phospholipid, and fibrin monomer).

[0182] The present invention encompasses antibodies of the invention recombinantly fused or chemically conjugated (covalent or non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90 or about 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigen-binding fragment of an

antibody of the invention (*e.g.*, a Fab fragment, Fd fragment, Fv fragment, $F(ab)_2$ fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. In one embodiment, the heterologous protein, polypeptide, or peptide that the antibody is fused to is useful for targeting the antibody to a particular cell type, such as a cell that expresses hLIGHT or an hLIGHT receptor. For example, an antibody that immunospecifically binds to a cell surface receptor expressed by a particular cell type (*e.g.*, an immune cell) may be fused or conjugated to a modified antibody of the invention.

[0183] A conjugated or fusion protein of the invention comprises any antibody of the invention described herein and a heterologous polypeptide. In one embodiment, a conjugated or fusion protein of the invention comprises E1, E13, E63, F19, or F23 antibody, or an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide. In another embodiment, a conjugated or fusion protein of the invention comprises an antigen-binding fragment of E1, E13, E63, F19, or F23, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide. In another embodiment, a conjugated or fusion protein of the invention comprises a VH domain having the amino acid sequence of any one of the VH domains depicted in SEQ ID NOS:1, 2, 3, 4 or 5, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and/or a VL domain having the amino acid sequence of any one of the VL domains depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide. In another embodiment, a conjugated or fusion protein of the present invention comprises one or more VH CDRs having the amino acid sequence of any one of the VH CDRs depicted in SEQ ID NOS:11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide. In another embodiment, a conjugated or fusion protein comprises one or more VL CDRs having the amino acid sequence of any one of the VL CDRs depicted in SEQ ID NOS:84, 26, 85, 86, 27, 87, 88, 28, 89, 2, 30, 31, 32, 33, 34, 93, 35, 94, 95, 96, 36, 97, 98, 99, 37, 100, 101, 38, 39,

or 40, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide. In another embodiment, a conjugated or fusion protein of the invention comprises at least one VH domain and at least one VL domain depicted in SEQ ID NOS:1, 2, 3, 4 or 5 and SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide. In yet another embodiment, a conjugated or fusion protein of the invention comprises at least one VH CDR and at least one VL CDR depicted in SEQ ID NOS:11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 and SEQ ID NOS:84, 26, 85, 86, 27, 87, 88, 28, 89, 2, 30, 31, 32, 33, 34, 93, 35, 94, 95, 96, 36, 97, 98, 99, 37, 100, 101, 38, 39, or 40, respectively, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), and a heterologous polypeptide.

[0184] In addition, an antibody of the invention can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alpha-emitters such as ^{213}Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{131}In, ^{131}LU, ^{131}Y, ^{131}Ho, ^{131}Sm, to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo *et al.*, 1998, Clin Cancer Res. 4(10):2483-90; Peterson *et al.*, 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman *et al.*, 1999, Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

[0185] Moreover, antibodies of the invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc.), among others, many of which are commercially available. As described in Gentz *et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, 1984, Cell 37:767), and the "FLAG" tag.

[0186] Methods for fusing or conjugating therapeutic moieties (including polypeptides) to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), Thorpe *et al.*, 1982, Immunol. Rev. 62:119-58; U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, 5,723,125, 5,783,181, 5,908,626, 5,844,095, and 5,112,946; EP 307,434; EP 367,166; EP 394,827; PCT publications WO 91/06570, WO 96/04388, WO 96/22024, WO 97/34631, and WO 99/04813; Ashkenazi *et al.*, Proc. Natl. Acad. Sci. USA, 88: 10535-10539, 1991; Traunecker *et al.*, Nature, 331:84-86, 1988; Zheng *et al.*, J. Immunol., 154:5590-5600, 1995; Vil *et al.*, Proc. Natl. Acad. Sci. USA, 89:11337-11341, 1992, which are incorporated herein by reference in their entireties.

[0187] Fusion proteins may be generated, for example, through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention (*e.g.*, antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten *et al.*, 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson *et al.*, 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308- 313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies, or the encoded antibodies, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, *etc.* of one or more heterologous molecules.

[0188] An antibody of the invention can also be conjugated to a second antibody to form an antibody heteroconjugate as described in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0189] The therapeutic moiety or drug conjugated or recombinantly fused to an antibody of the invention that immunospecifically binds to a hLIGHT antigen should be chosen to achieve the desired prophylactic or therapeutic effect(s). In certain embodiments, the antibody is a modified antibody. A clinician or other medical personnel should consider the following when deciding on which therapeutic moiety or drug to conjugate or recombinantly fuse to an antibody of the invention: the nature of the disease, the severity of the disease, and the condition of the subject.

[0190] Antibodies of the invention may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

PHARMACEUTICAL COMPOSITIONS

[0191] Therapeutic formulations containing one or more antibodies of the invention provided herein can be prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[0192] The antibodies of the invention provided herein can also, for example, be formulated in liposomes. Liposomes containing the molecule of interest are prepared by methods known in the art, such as described in Epstein *et al.* (1985) *Proc. Natl. Acad. Sci. USA* 82:3688; Hwang *et al.* (1980) *Proc. Natl. Acad. Sci. USA* 77:4030; and U.S. Patent Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

[0193] Particularly useful immunoliposomes can be generated by the reverse phase evaporation method with a lipid composition containing phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of an antibody provided herein can be conjugated to the liposomes as described in Martin *et al.* (1982) *J. Biol. Chem.* 257:286-288 via a disulfide interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome; See Gabizon *et al.*, (1989) *J. National Cancer Inst.* 81(19):1484.

[0194] Formulations, such as those described herein, can also contain more than one active compound as necessary for the particular indication being treated. In certain embodiments, formulations comprise an antibody of the invention and one or more active compounds with complementary activities that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended. For example, an antibody of the invention can be combined with one or more other therapeutic agents. Such combined therapy can be administered to the patient serially or simultaneously or in sequence.

[0195] An antibody of the invention can also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA.

[0196] The formulations to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

[0197] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic

polymers containing the antagonist, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 °C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S--S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[0198] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the antibodies of the invention provided herein, and optionally one or more additional prophylactic of therapeutic agents, in a pharmaceutically acceptable carrier. Such pharmaceutical compositions are useful in the prevention, treatment, management or amelioration of a hLIGHT-mediated disease, such as an inflammatory bowl disease, or one or more of the symptoms thereof.

[0199] Pharmaceutical carriers suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[0200] In addition, the antibodies of the invention may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients (such as one or more other prophylactic or therapeutic agents).

[0201] The compositions can contain one or more antibodies of the invention. In one embodiment, the antibodies are formulated into suitable pharmaceutical preparations, such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile

solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. In one embodiment, the antibodies described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, *e.g.*, Ansel (1985) Introduction to Pharmaceutical Dosage Forms, 4th Ed., p. 126).

[0202] In the compositions, effective concentrations of one or more antibodies or derivatives thereof is (are) mixed with a suitable pharmaceutical carrier. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates a hLIGHT-mediated disease or symptom thereof.

[0203] In one embodiment, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected carrier at an effective concentration such that the treated condition is relieved, prevented, or one or more symptoms are ameliorated.

[0204] An antibody of the invention is included in the pharmaceutically acceptable carrier in an effective amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration can be determined empirically by testing the compounds in *in vitro* and *in vivo* systems using routine methods and then extrapolated therefrom for dosages for humans.

[0205] The concentration of antibody in the pharmaceutical composition will depend on, *e.g.*, the physicochemical characteristics of the antibody, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

[0206] In one embodiment, a therapeutically effective dosage produces a serum concentration of antibody of from about 0.1 ng/ml to about 50-100 μg/ml. The pharmaceutical compositions, in another embodiment, provide a dosage of from about 0.001 mg to about 2000 mg of antibody per kilogram of body weight per day. Pharmaceutical dosage unit forms can be prepared to provide from about 0.01 mg, 0.1 mg or 1 mg to about 500 mg, 1000 mg or 2000 mg, and in one embodiment from about 10 mg to about 500 mg of the antibody and/or a combination of other optional essential ingredients per dosage unit form.

[0207] The antibody can be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise

dosage and duration of treatment is a function of the disease being treated and can be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values can also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens can be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[0208] Upon mixing or addition of the antibody, the resulting mixture can be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[0209] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The antibody is, in one embodiment, formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the antibody sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms can be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

[0210] In preferred embodiments, one or more anti-hLIGHT antibodies of the invention are in a liquid pharmaceutical formulation. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or

otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents.

[0211] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA.

[0212] Dosage forms or compositions containing antibody in the range of 0.005% to 100% with the balance made up from non-toxic carrier can be prepared. Methods for preparation of these compositions are known to those skilled in the art.

[0213] Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules can be hard or soft gelatin capsules, while granules and powders can be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

[0214] In certain embodiments, the formulations are solid dosage forms. In certain embodiments, the formulations are capsules or tablets. The tablets, pills, capsules, troches and the like can contain one or more of the following ingredients, or compounds of a similar nature: a binder; a lubricant; a diluent; a glidant; a disintegrating agent; a coloring agent; a sweetening agent; a flavoring agent; a wetting agent; an emetic coating; and a film coating. Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, molasses, polvinylpyrrolidine, povidone, crospovidones, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved

certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0215] The antibodies of the invention can be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition can also be formulated in combination with an antacid or other such ingredient.

[0216] When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0217] The antibody can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is an antibody or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

[0218] In all embodiments, tablets and capsules formulations can be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

[0219] In preferred embodiments, the formulations are liquid dosage forms. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or

suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

[0220] Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

[0221] Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

[0222] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is, in one embodiment, encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, can be diluted with a

sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

[0223] Alternatively, liquid or semi-solid oral formulations can be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. RE28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

[0224] Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

[0225] Parenteral administration, in one embodiment, is characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[0226] Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The antibody diffuses through the outer polymeric membrane in a release rate controlling step. The amount of antibody contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[0227] Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[0228] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0229] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[0230] Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0231] The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

[0232] The unit-dose parenteral preparations can be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration can be sterile, as is known and practiced in the art.

[0233] Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

[0234] Injectables are designed for local and systemic administration. In one embodiment, a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, in certain embodiments more than 1% w/w of the active compound to the treated tissue(s).

[0235] The antibody can be suspended in micronized or other suitable form. The form of the resulting mixture depends upon a number of factors, including the intended

mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

[0236] In other embodiments, the pharmaceutical formulations are lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

[0237] The lyophilized powder is prepared by dissolving a antibody provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

[0238] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

[0239] Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0240] The antibodies of the invention can be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a

microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[0241] The compounds can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[0242] These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

[0243] Other routes of administration, such as transdermal patches, including iontophoretic and electrophoretic devices, and rectal administration, are also contemplated herein.

[0244] Transdermal patches, including iotophoretic and electrophoretic devices, are well known to those of skill in the art. For example, such patches are disclosed in U.S. Patent Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

[0245] For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The weight of a rectal suppository, in one embodiment, is about 2 to 3 gm.

[0246] Tablets and capsules for rectal administration can be manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

[0247] The antibodies and other compositions provided herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, *e.g.*, U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874. In some embodiments, the anti-hLIGHT antibodies of the invention are targeted (or otherwise administered) to the colon, such as in a patient having or at risk of having an IBD.

[0248] In one embodiment, liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art. For example, liposome formulations can be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

METHODS OF ADMINISTRATION AND DOSING

[0249] The present invention further provides for compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease (or symptom thereof).

[0250] In certain embodiments, provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease, such as IBD (*e.g.*, ulcerative colitis or Crohn's disease), or a symptom thereof. IBD symptoms may range from mild to severe and generally depend upon the part of the intestinal tract involved. Exemplary symptoms of IBD include abdominal cramps and pain, bloody diarrhea, severe urgency to have a bowel movement, fever, loss of appetite, weight loss, anemia, fatigue, and/or sores on lower legs, ankles, calves, thighs, and arms. Exemplary intestinal complications of IBD include profuse bleeding from the ulcers, perforation or rupture of the bowel, strictures and obstruction, fistulae (abnormal passage) and perianal disease,

toxic megacolon (*e.g.*, acute nonobstructive dilation of the colon), and/or malignancy (*e.g.*, cancer of the colon or small intestine). Exemplary extraintestinal complications of IBD include arthritis, skin conditions, inflammation of the eye, liver and kidney disorders, and/or bone loss. Any combination of these symptoms may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

[0251] In certain embodiments, provided herein are compositions comprising one or more antibodies of the invention for use in the prevention, management, treatment and/or amelioration of an hLIGHT-mediated disease, such as GVHD, or a symptom thereof. GVHD generally occurs following allogeneic or matched unrelated bone marrow transplants (BMT).

[0252] In some embodiments, the GVHD is acute GVHD. The symptoms of acute GVHD can happen quickly and can be mild or severe. In certain instances, acute GVHD develops within about three months after transplant, such as when blood counts recover after transplant. It certain instances, the acute GVHD affects the skin, gastrointestinal (GI) tract and/or liver. For example, in some patients, acute skin GVHD begins with a rash, for example, on the palms of the patient's hands, soles of the feet, or shoulders. However, the rash can become widespread, and may be itchy and painful and/or might blister and peel. Acute liver GVHD may affect normal functions of the liver, such as liver enzymes, and may in turn, cause jaundice. Acute liver GVHD may also cause the patient's abdomen to become swollen and painful if the liver becomes enlarged. Finally, symptoms of acute gut GVHD (or GVHD of the digestive system) can include diarrhea, mucus or blood in the stool, cramping or abdominal pain, indigestion, nausea and/or loss of appetite. Other general symptoms of acute GVHD can include anemia. low grade fever, and/or being more prone to infections. Any combination of these symptoms of acute GVHD may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

[0253] In other embodiments, the GVHD is chronic GVHD. Chronic GVHD can occur from about three months to about a year or longer after transplant. Chronic GVHD can be mild or severe, and generally includes symptoms similar to those of acute GVHD. Chronic GVHD can affect the skin and digestive system, including the liver but can also involve other organs and the immune system (*e.g.*, making the patient more prone to infections) and/or connective tissues. Symptoms of chronic skin GVHD include a rash, dry skin, tight skin, itchy skin, darkening of the color of the skin,

thickening of the skin, and/or may affect hair (*e.g.*, hair loss, turning gray) or nails (*e.g.*, hard or brittle nails). Chronic gut GVHD can affect the digestive system, mouth, esophagus, lining of the stomach, and/or lining of the bowel, and symptoms can include diarrhea, dry or sore mouth, painful swallowing, low nutrient absorption by the stomach, bloating, stomach cramps,. Chronic liver GVHD can cause damage and scarring of the liver (cirrhosis). Chronic GVHD of the eyes can affect the glands that make tears, causing eyes to become dry, burning and painful or difficult to tolerate bright light. Chronic lung GVHD can cause shortness of breath, wheezing, persistent cough, and/or being more prone to chest infections. Chronic GVHD affects tendons (*e.g.*, inflammation) that connect muscle to bone causing difficulty straightening or bending your arms and legs. Any combination of these symptoms of chronic GVHD may be prevented, managed, treated, and/or ameliorated using the compositions and methods provided herein.

[0254] In a specific embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an E1, E13, E63, F19, and/or F23 antibody. In one embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another specific embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antigen-binding fragment of an E1, E13, E63, F19, and/or F23 antibody. In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antigen-binding fragment of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0255] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains depicted in SEQ ID NOS:1, 2, 3, 4 or 5, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies

comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s depicted in SEQ ID NOS:11, 14, 17, 20, or 23 (*i.e.*, VH CDR1s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s depicted in SEQ ID NOS:12, 15, 18, 21, or 24 (*i.e.*, VH CDR2s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In a preferred embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s depicted in SEQ ID NOS:13, 16, 19, 22, or 25 (*i.e.*, VH CDR3s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0256] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VL domains having an amino acid sequence of any one of the VL domains depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s depicted in SEQ ID NOS:84, 26, 85, 29, 32, 93, 35, 94, 95, or 38 (*i.e.*, VL CDR1s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VL CDR2s having an amino acid sequence of any

one of the VL CDR2s depicted in SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39 (*i.e.*, VL CDR2s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively); or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In a preferred embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s depicted in SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101, or 40 (*i.e.*, VL CDR3s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), ; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0257] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH domains having an amino acid sequence of any one of the VH domains depicted in SEQ ID NOS:1, 2, 3, 4 or 5, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL domains having an amino acid sequence of any one of the VL domains depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0258] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s depicted in SEQ ID NOS:11, 14, 17, 20, or 23 (*i.e.*, VH CDR1s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s depicted in SEQ ID NOS:84, 26, 85, 29, 32, 93, 35, 94, 95, or 38 (*i.e.*, VL CDR1s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another

embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s depicted in SEQ ID NOS:11, 14, 17, 20, or 23 (*i.e.*, VH CDR1s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s depicted in SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39 (*i.e.*, VL CDR2s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR1s having an amino acid sequence of any one of the VH CDR1s depicted in SEQ ID NOS:11, 14, 17, 20, or 23 (*i.e.*, VH CDR1s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s having an amino acid sequence of any one of the VL CDR3s depicted in SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101, or 40 (*i.e.*, VL CDR3s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0259] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s depicted in SEQ ID NOS:12, 15, 18, 21, or 24 (*i.e.*, VH CDR2s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s depicted in SEQ ID NOS:84, 26, 85, 29, 32, 93, 35, 94, 95, or 38 (*i.e.*, VL CDR1s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another

embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s depicted in SEQ ID NOS:12, 15, 18, 21, or 24 (*i.e.*, VH CDR2s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s depicted in SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39 (*i.e.*, VL CDR2s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR2s having an amino acid sequence of any one of the VH CDR2s depicted in SEQ ID NOS:12, 15, 18, 21, or 24 (*i.e.*, VH CDR2s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s having an amino acid sequence of any one of the VL CDR3s depicted in SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101, or 40 (*i.e.*, VL CDR3s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0260] In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s depicted in SEQ ID NOS:13, 16, 19, 22, or 25 (*i.e.*, VH CDR3s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR1s having an amino acid sequence of any one of the VL CDR1s depicted in SEQ ID NOS:84, 26, 85, 29, 32, 93, 35, 94, 95, or 38 (*i.e.*, VL CDR1s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an

antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s depicted in SEQ ID NOS:13, 16, 19, 22, or 25 (*i.e.,* VH CDR3s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR2s having an amino acid sequence of any one of the VL CDR2s depicted in SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39 (*i.e.,* VL CDR2s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises one or more antibodies comprising one or more VH CDR3s having an amino acid sequence of any one of the VH CDR3s depicted in SEQ ID NOS:13, 16, 19, 22, or 25 (*i.e.,* VH CDR3s of the VH depicted in SEQ ID NOS:1, 2, 3, 4 or 5, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23), and one or more VL CDR3s having an amino acid sequence of any one of the VL CDR3s having an amino acid sequence of any one of the VL CDR3s depicted in SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101, or 40 (*i.e.,* VL CDR3s of the VL depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10, respectively), or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23).

[0261] In one embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises a VH domain having the amino acid sequence of the VH domain depicted in any one of SEQ ID NOS:1, 2, 3, 4 or 5 and/or a VL domain having the amino acid sequence of the VL domain depicted in any one of SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, or 10.

[0262] In certain embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody

comprises (a) a VH domain having the amino acid sequence depicted in SEQ ID NO:1 and a VL domain having the amino acid sequence depicted in any one of SEQ ID NOS:82, 6 or 83; (b) a VH domain having the amino acid sequence depicted in SEQ ID NO:2 and a VL domain having the amino acid sequence depicted in SEQ ID NO:7; (c) a VH domain having the amino acid sequence depicted in SEQ ID NO:3 and a VL domain having the amino acid sequence depicted in SEQ ID NO:8; (d) a VH domain having the amino acid sequence depicted in SEQ ID NO:4 and a VL domain having the amino acid sequence depicted in any one of SEQ ID NOS:90, 9, 91 or 92; or (e) a VH domain having the amino acid sequence depicted in SEQ ID NO:5 and a VL domain having the amino acid sequence depicted in SEQ ID NO:10. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0263] In some embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VH domain having the amino acid sequence of the VH domain of an antibody having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively) and/or a VL domain having the amino acid sequence of the VL domain of an antibody having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively).

[0264] In certain embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises (a) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7729 (E1) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7729 (E1); (b) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7842 (E13) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7842 (E13); (c) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7818 (E63) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7818 (E63); (d) a VH domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7819 (F19) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7819 (F19); or (e) a VH domain having the amino

acid sequence of an antibody having ATCC Accession No. PTA-7728 (F23) and a VL domain having the amino acid sequence of an antibody having ATCC Accession No. PTA-7728 (F23). Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0265] In some embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VH CDR1 having the amino acid sequence of the VH CDR1 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VH CDR2 having the amino acid sequence of the VH CDR2 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VH CDR3 having the amino acid sequence of the VH CDR3 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5. In certain embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VH CDR1 and/or a VH CDR2 and/or a VH CDR3 independently selected from a VH CDR1, VH CDR2, VH CDR3 as depicted in any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5.

[0266] The present invention also provides a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises one or more VL CDRs (*i.e.*, VL CDR1, VL CDR2, and/or VL CDR3) having an amino acid sequence of any one of the VL CDRs (*i.e.*, VL CDR1, VL CDR2 and/or VL: CDR3) of E1, E13, E63, F19, and/or F23; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively); or any combination thereof.

[0267] In certain embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody

comprises (1) a VH domain having (a) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:11, 12 and/or 13, respectively, (b) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:14, 15 and/or 16, respectively, (c) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:17, 18, and/or 19, respectively, (d) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:20, 21 and/or 22, respectively, or (e) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:23, 24 and/or 24, respectively, and/or (2) a VL domain having (a) a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:84, 26 or 85; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:86, 27, or 87; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:88, 28, or 89, (b) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:29, 30 and/or 31, respectively, (c) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:32, 33 and/or 34, respectively, (d) a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:93, 35, 94, or 95; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98, or (e) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:38, 39 and/or 40, respectively. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0268] In some embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises (1) a VH domain having (a) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1), (b) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13), (c) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63), (d) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1,

VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19), or (e) a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23), and/or (2) a VL domain having (a) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1), (b) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13), (c) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63), (d) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19), or (e) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23). Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0269] In certain embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises (1) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:11, 12 and/or 13, respectively, and (b) a VL domain having a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:84, 26 or 85; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:86, 27, or 87; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:88, 28, or 89; (2) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:14, 15 and/or 16, respectively, and (b) a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:29, 30 and/or 31, respectively; (3) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:17, 18, and/or 19, respectively, and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:32, 33 and/or 34, respectively; (4) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the

amino acid sequence depicted in SEQ ID NOS:20, 21 and/or 22, respectively, and (b) a VL domain having a VL CDR1 having the amino acid sequence depicted in any one of SEQ ID NOS:93, 35, 94, or 95; a VL CDR2 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98; and/or a VL CDR3 having the amino acid sequence depicted in any one of SEQ ID NOS:96, 36, 97, or 98; or (5) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence depicted in SEQ ID NOS:23, 24 and/or 24, respectively, and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence depicted in SEQ ID NOS:38, 39 and/or 40, respectively. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0270] In some embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises (1) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1), and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7729 (E1); (2) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13) and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7842 (E13); (3) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63) and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7818 (E63); (4) (a) a VH domain having a VH CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19) and a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7819 (F19); or (5) (a) a VH domain having a VH

CDR1, VH CDR2, and/or VH CDR3 having the amino acid sequence of a VH CDR1, VH CDR2, and/or VH CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23) and (b) a VL domain having a VL CDR1, VL CDR2, and/or VL CDR3 having the amino acid sequence of a VL CDR1, VL CDR2, and/or VL CDR3 of an antibody having ATCC Accession No. PTA-7728 (F23). Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0271] In some embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VL CDR1 having the amino acid sequence of the VL CDR1 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VL CDR2 having the amino acid sequence of the VL CDR2 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively). In another embodiment, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VL CDR3 having the amino acid sequence of the VL CDR3 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively). In certain embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VL CDR1 and/or a VL CDR2 and/or a VL CDR3 independently selected from the VL CDR1, VL CDR2, VL CDR3 as depicted in any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma

having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively).

[0272] In some embodiments, a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a (1) VH domain or chain having one or more of (a) a VH CDR1 having the amino acid sequence of a VH CDR1 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), (b) a VH CDR2 having the amino acid sequence of a VH CDR2 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), or (c) a VH CDR3 having the amino acid sequence a VH CDR3 of any one of the VH regions depicted in SEQ ID NOS:1, 2, 3, 4 or 5; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively); and/or (2) a VL domain or chain having one of more of (a) a VL CDR1 having the amino acid sequence of the VL CDR1 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), (b) a VL CDR2 having the amino acid sequence of a VL CDR2 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively), and/or (c) a VL CDR3 having the amino acid sequence of a VL CDR3 of any one of the VL regions depicted in SEQ ID NOS:82, 6, 83, 7, 8, 90, 9, 91, 92, or 10; or of an antibody produced by a hybridoma having ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23, respectively).

[0273] The present invention also provides a composition for use in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises one or more VH CDRs and one or more VL CDRs listed in Table I. In particular, the invention provides for a composition for use in the prevention,

management, treatment and/or amelioration of a hLIGHT-mediated disease comprises an antibody that immunospecifically binds to a hLIGHT epitope, wherein said antibody comprises a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH1 CDR1, a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR3

(SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a

VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38) and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39), and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR1 (SEQ ID NOS:11, 14, 17, 20, or 23), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39), and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); a VH CDR2 (SEQ ID NOS:12, 15, 18, 21 or 24), a VH CDR3 (SEQ ID NOS:13, 16, 19, 22 or 25), a VL CDR1 (SEQ ID NOS:84, 26, 85, 29, 32, 35 or 38), a VL CDR2 (SEQ ID NOS:86, 27, 87, 30, 33, 96, 36, 97, 98, or 39), and a VL CDR3 (SEQ ID NOS:88, 28, 89, 31, 34, 99, 37, 100, 101 or 40); or any combination thereof of the VH CDRs (SEQ ID NOS:11-25) and VL CDRs (SEQ ID NOS:26-40) listed in Table I. The corresponding VH CDRs and VL CDRs of ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19, or F23), may also be used in any of the combinations listed above. Preferably, the antibody is a fully human antibody, such as a fully human monoclonal antibody, and/or a hLIGHT antagonist antibody.

[0274] As discussed in more detail elsewhere herein, a composition of the invention may be used either alone or in combination with other compounds or compositions. Moreover, the antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionucleotides, or toxins. See, *e.g.*, PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[0275] In some embodiments, provided herein are methods for decreasing or inhibiting binding of hLIGHT to HVEM, LTβR and/or DcR3 in a subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT). In one embodiment, the hLIGHT is a SNP variant of hLIGHT, such

as 214E-32S, 214K-32S, 214E-32L or 214K-32L. In some embodiments, a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, is also decreased or inhibited in the subject.

[0276] In certain embodiments, provided herein are methods for decreasing or inhibiting a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a subject (*e.g.*, a human subject), comprising administering to the subject an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed hLIGHT), wherein hLIGHT biological activity is decreased or inhibited by the antibody. In some embodiments, the hLIGHT is a SNP variant of hLIGHT, such as 214E-32S, 214K-32S, 214E-32L or 214K-32L.

[0277] In other embodiments, provided herein are methods for decreasing or inhibiting binding of hLIGHT to HVEM, LTβR and/or DcR3 in a cell having cell surface-expressed hLIGHT, contacting the cell with an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT), such as a hLIGHT polypeptide, a hLIGHT polypeptide fragment, or a hLIGHT epitope. In certain embodiments, the hLIGHT is a SNP variant of hLIGHT, such as 214E-32S, 214K-32S, 214E-32L or 214K-32L. In some embodiments, a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, is also decreased or inhibited in the cell.

[0278] In certain embodiments, provided herein are methods for decreasing or inhibiting a hLIGHT biological activity, such as secretion of CCL20, IL8 and/or RANTES, in a cell having a cell surface-expressed hLIGHT receptor (such as, HVEM, LTβR and/or Dc3R), contacting the cell with an effective amount of an antibody that immunospecifically binds to a hLIGHT polypeptide (*e.g.*, a cell surface-expressed or soluble hLIGHT) wherein hLIGHT biological activity is decreased or inhibited by the antibody. In some embodiments, the hLIGHT is a SNP variant of hLIGHT, such as 214E-32S, 214K-32S, 214E-32L or 214K-32L.

[0279] Antibodies of the present invention may be used, for example, to purify, detect, and target hLIGHT antigens, in both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the modified antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of hLIGHT in biological samples. See, *e.g.*, Harlow *et al.*, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

[0280] The invention also provides methods of preventing, managing, treating and/or ameliorating a hLIGHT-mediated disease by administrating to a subject of an effective amount of an antibody, or pharmaceutical composition comprising an antibody of the invention. In one aspect, an antibody is substantially purified (*i.e.*, substantially free from substances that limit its effect or produce undesired side-effects). In preferred embodiments, the antibody is a fully human monoclonal antibody, such as a fully human monoclonal antagonist antibody. The subject administered a therapy is preferably a mammal such as non-primate (*e.g.*, cows, pigs, horses, cats, dogs, rats *etc.*) or a primate (*e.g.*, a monkey, such as a cynomolgous monkey, or a human). In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a human infant or a human infant born prematurely. In another embodiment, the subject is a human with a hLIGHT-mediated disease.

[0281] Various delivery systems are known and can be used to administer a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), including, but not limited to, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, *etc.* Methods of administering a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), or pharmaceutical composition include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural, and mucosal (*e.g.*, intranasal and oral routes). In a specific embodiment, a prophylactic or therapeutic agent (*e.g.*, an antibody of the present invention), or a pharmaceutical composition is administered intranasally, intramuscularly, intravenously, or subcutaneously. The prophylactic or therapeutic agents, or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, intranasal mucosa, rectal and intestinal mucosa, *etc.*) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Patent Nos. 6,019,968, 5,985,320, 5,985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entirety.

[0282] In a specific embodiment, it may be desirable to administer a prophylactic or therapeutic agent, or a pharmaceutical composition of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion, by topical administration (*e.g.*, by intranasal spray), by injection, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering an antibody of the invention, care must be taken to use materials to which the antibody does not absorb.

[0283] In another embodiment, a prophylactic or therapeutic agent, or a composition of the invention can be delivered in a vesicle, in particular a liposome (see Langer, 1990, Science 249:1527-1533; Treat *et al.*, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

[0284] In another embodiment, a prophylactic or therapeutic agent, or a composition of the invention can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, *supra*; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:20; Buchwald *et al.*, 1980, Surgery 88:507; Saudek *et al.*, 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used to achieve controlled or sustained release of a prophylactic or therapeutic agent (*e.g.*, an antibodies of the invention) or a composition of the invention (see *e.g.*, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, J., Macromol. Sci. Rev. Macromol. Chem. 23:61; see also Levy *et al.*, 1985, Science 228:190; During *et al.*, 1989, Ann. Neurol. 25:351; Howard *et al.*, 1989, J. Neurosurg. 7 1:105); U.S. Patent No. 5,679,377; U.S. Patent No. 5,916,597; U.S. Patent No. 5,912,015; U.S. Patent No. 5,989,463; U.S. Patent No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N-vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a

sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a controlled or sustained release system can be placed in proximity of the therapeutic target, *i.e.*, the nasal passages or lungs, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Controlled release systems are discussed in the review by Langer (1990, Science 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more antibodies of the invention. See, *e.g.*, U.S. Patent No. 4,526,938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.*, 1996, "Intratumoral Radioimmunotherapy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," Radiotherapy & Oncology 39:179- 189, Song *et al.*, 1995, "Antibody Mediated Lung Targeting of Long-Circulating Emulsions," PDA Journal of Pharmaceutical Science & Technology 50:372-397, Cleek *et al.*, 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," Pro. Int'l. Symp. Control. Rel. Bioact. Mater. 24:853-854, and Lam *et al.*, 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," Proc. Int'l. Symp. Control Rel. Bioact. Mater. 24:759-760, each of which is incorporated herein by reference in their entirety.

[0285] In a specific embodiment, where the composition of the invention is a nucleic acid encoding a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), the nucleic acid can be administered *in vivo* to promote expression of its encoded prophylactic or therapeutic agent, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see, *e.g.*, Joliot *et al.*, 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), *etc.* Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

[0286] In a specific embodiment, a composition of the invention comprises one, two or more antibodies of the invention. In another embodiment, a composition of the invention comprises one, two or more antibodies of the invention and a prophylactic or therapeutic agent other than an antibody of the invention. Preferably, the agents are

known to be useful for or have been or are currently used for the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease. In addition to prophylactic or therapeutic agents, the compositions of the invention may also comprise a carrier.

[0287] The compositions of the invention include bulk drug compositions useful in the manufacture of pharmaceutical compositions (*e.g.*, compositions that are suitable for administration to a subject or patient) that can be used in the preparation of unit dosage forms. In a preferred embodiment, a composition of the invention is a pharmaceutical composition. Such compositions comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (*e.g.*, an antibody of the invention or other prophylactic or therapeutic agent), and a pharmaceutically acceptable carrier. Preferably, the pharmaceutical compositions are formulated to be suitable for the route of administration to a subject.

[0288] In a specific embodiment, the term "carrier" refers to a diluent, adjuvant (*e.g.*, Freund's adjuvant (complete and incomplete)), excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc.* Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA. Such compositions will contain a prophylactically or therapeutically effective amount of the antibody, preferably in purified form, together with a suitable amount of carrier so as to provide the form for

proper administration to the patient. The formulation should suit the mode of administration.

[0289] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection. Such compositions, however, may be administered by a route other than intravenous.

[0290] Generally, the ingredients of compositions of the invention are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0291] The invention also provides that an antibody of the invention is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of antibody. In one embodiment, the antibody is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted, *e.g.*, with water or saline to the appropriate concentration for administration to a subject. Preferably, the antibody is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 0.1 mg, at least 0.5 mg, at least 1 mg, at least 2 mg, or at least 3 mg, and more preferably at least 5 mg, at least 10 mg, at least 15 mg, at least 25 mg, at least 30 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 60 mg, at least 75 mg, at least 80 mg, at least 85 mg, at least 90 mg, at least 95 mg, or at least 100 mg. The lyophilized antibody can be stored at between 2 and 8° C in its original container and the antibody can be administered within 12 hours, preferably within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment, an antibody is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the antibody. Preferably, the liquid form of the antibody is supplied in a hermetically sealed container at least 0.1 mg/ml, at least 0.5 mg/ml, or at least 1

mg/ml, and more preferably at least 5 mg/ml, at least 10 mg/ml, at least 15 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 40 mg/ml, at least 50 mg/ml, at least 60 mg/ml, at least 70 mg/ml, at least 80 mg/ml, at least 90 mg/ml, or at least 100 mg/ml.

[0292] The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, *etc.*, and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, *etc.*

[0293] The amount of a prophylactic or therapeutic agent (*e.g.*, an antibody of the invention), or a composition of the invention that will be effective in the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease can be determined by standard clinical techniques.

[0294] Accordingly, a dosage of an antibody or a composition that results in a serum titer of from about 0.1 μg/ml to about 450 μg/ml, and in some embodiments at least 0.1 μg/ml, at least 0.2 μg/ml, at least 0.4 μg/ml, at least 0.5 μg/ml, at least 0.6 μg/ml, at least 0.8 μg/ml, at least 1 μg/ml, at least 1.5 μg/ml, and preferably at least 2 μg/ml, at least 5 μg/ml, at least 10 μg/ml, at least 15 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 30 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 75 μg/ml, at least 100 μg/ml, at least 125 μg/ml, at least 150 μg/ml, at least 200 μg/ml, at least 250 μg/ml, at least 300 μg/ml, at least 350 μg/ml, at least 400 μg/ml, or at least 450 μg/ml can be administered to a human for the prevention, management, treatment and/or amelioration of a hLIGHT-mediated disease. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of a hLIGHT-mediated disease, and should be decided according to the judgment of the practitioner and each patient's circumstances.

[0295] Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0296] For the antibodies of the invention, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. In some embodiments, the dosage administered to the patient is about 1 mg/kg to about 75 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 5 mg/kg

of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of the antibodies of the invention may be reduced by enhancing uptake and tissue penetration of the antibodies by modifications such as, for example, lipidation.

[0297] In one embodiment, approximately 100 mg/kg or less, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less of an antibody the invention is administered 5 times, 4 times, 3 times, 2 times or, preferably, 1 time to manage a hLIGHT-mediated disease. In some embodiments, an antibody of the invention is administered about 1-12 times, wherein the doses may be administered as necessary, *e.g.*, weekly, biweekly, monthly, bimonthly, trimonthly, *etc.*, as determined by a physician. In some embodiments, a lower dose (*e.g.*, 1-15 mg/kg) can be administered more frequently (*e.g.*, 3-6 times). In other embodiments, a higher dose (*e.g.*, 25-100 mg/kg) can be administered less frequently (*e.g.*, 1-3 times). However, as will be apparent to those in the art, other dosing amounts and schedules are easily determinable and within the scope of the invention.

[0298] In a specific embodiment, approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, approximately 0.1 mg/kg or less of an antibody the invention in a sustained release formulation is administered to a subject, preferably a human, to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease. In another specific embodiment, an approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg or less, approximately 0.5 mg/kg or less, or approximately 0.1 mg/kg or less bolus of an antibody the invention not in a sustained release formulation is administered to a subject, preferably a human, to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease, and after a certain period of time, approximately 100 mg/kg, approximately 75 mg/kg or less, approximately 50 mg/kg or less, approximately 25 mg/kg or less, approximately 10 mg/kg or less, approximately 5 mg/kg or less, approximately 1 mg/kg

or less, approximately 0.5 mg/kg or less, or approximately 5 mg/kg or less of an antibody of the invention in a sustained release is administered to said subject (*e.g.*, intranasally or intramuscularly) two, three or four times (preferably one time). In accordance with this embodiment, a certain period of time can be 1 to 5 days, a week, two weeks, or a month.

[0299] In some embodiments, a single dose of an antibody of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease two, three, four, five, six, seven, eight, nine, ten, eleven, twelve times, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, twenty five, or twenty six at bi-weekly (*e.g.*, about 14 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.*, each dose monthly dose may or may not be identical).

[0300] In another embodiment, a single dose of an antibody of the invention is administered to patient to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve times at about monthly (*e.g.*, about 30 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.*, each dose monthly dose may or may not be identical).

[0301] In one embodiment, a single dose of an antibody of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease two, three, four, five, or six times at about bi-monthly (*e.g.*, about 60 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60

mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.*, each bi-monthly dose may or may not be identical).

[0302] In some embodiments, a single dose of an antibody of the invention is administered to a patient to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease two, three, or four times at about tri-monthly (*e.g.*, about 120 day) intervals over the course of a year, wherein the dose is selected from the group consisting of about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, or a combination thereof (*i.e.*, each tri-monthly dose may or may not be identical).

[0303] In certain embodiments, the route of administration for a dose of an antibody of the invention to a patient is intranasal, intramuscular, intravenous, or a combination thereof, but other routes described herein are also acceptable. Each dose may or may not be administered by an identical route of administration. In some embodiments, an antibody of the invention may be administered via multiple routes of administration simultaneously or subsequently to other doses of the same or a different antibody of the invention.

[0304] In certain embodiments, antibodies of the invention are administered prophylactically or therapeutically to a subject. Antibodies of the invention can be prophylactically or therapeutically administered to a subject so as to prevent, lessen or ameliorate a hLIGHT-mediated disease or symptom thereof.

GENE THERAPY

[0305] In a specific embodiment, nucleic acids comprising sequences encoding antibodies of the invention or functional derivatives thereof, are administered to prevent, manage, treat and/or ameliorate a hLIGHT-mediated disease by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In an embodiment of the invention, the nucleic acids produce their encoded antibody, and the antibody mediates a prophylactic or therapeutic effect.

[0306] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0307] For general review of the methods of gene therapy, see Goldspiel *et al.*, 1993, Clinical Pharmacy 12:488-505; Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, 1993, Science 260:926-932 ; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62:191-217; May, 1993, TIBTECH 11(5):155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0308] In a preferred embodiment, a composition of the invention comprises nucleic acids encoding an antibody of the invention, said nucleic acids being part of an expression vector that expresses the antibody or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA 86:8932-8935; Zijlstra *et al.*, 1989, Nature 342:435-438). In some embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[0309] Delivery of the nucleic acids into a subject may be either direct, in which case the subject is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the subject. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0310] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where the sequences are expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, *e.g.*, by constructing them as part of an appropriate nucleic acid expression vector and administering the vector so that the sequences become intracellular, *e.g.*, by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle

bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432) (which can be used to target cell types specifically expressing the receptors), *etc.* In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, *e.g.*, PCT Publications WO 92/06180; WO 92/22635; WO 92/20316; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA 86:8932-8935; and Zijlstra *et al.*, 1989, Nature 342:435-438).

[0311] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller *et al.*, 1993, Meth. Enzymol. 217:581-599). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy can be cloned into one or more vectors, which facilitates delivery of the gene into a subject. More detail about retroviral vectors can be found in Boesen *et al.*, 1994, Biotherapy 6:291-302, which describes the use of a retroviral vector to deliver the mdr 1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes *et al.*, 1994, J. Clin. Invest. 93:644-651; Klein *et al.*, 1994, Blood 83:1467-1473; Salmons and Gunzberg, 1993, Human Gene Therapy 4:129-141; and Grossman and Wilson, 1993, Curr. Opin. in Genetics and Devel. 3:110-114.

[0312] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of

being capable of infecting non-dividing cells. Kozarsky and Wilson, 1993, Current Opinion in Genetics and Development 3:499-503 present a review of adenovirus-based gene therapy. Bout *et al.*, 1994, Human Gene Therapy 5:3-10 demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld *et al.*, 1991, Science 252:431-434; Rosenfeld *et al.*, 1992, Cell 68:143-155; Mastrangeli *et al.*, 1993, J. Clin. Invest. 91:225-234; PCT Publication W094/12649; and Wang *et al.*, 1995, Gene Therapy 2:775-783. In a preferred embodiment, adenovirus vectors are used.

[0313] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh *et al.*, 1993, Proc. Soc. Exp. Biol. Med. 204:289-300; and U.S. Patent No. 5,436,146).

[0314] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a subject.

[0315] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcellmediated gene transfer, spheroplast fusion, *etc.* Numerous techniques are known in the art for the introduction of foreign genes into cells (see, *e.g.*, Loeffler and Behr, 1993, Meth. Enzymol. 217:599-618; Cohen *et al.*, 1993, Meth. Enzymol. 217:618-644; Clin. Pharma. Ther. 29:69-92 (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0316] The resulting recombinant cells can be delivered to a subject by various methods known in the art. Recombinant blood cells (*e.g.*, hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells

envisioned for use depends on the desired effect, patient state, *etc.*, and can be determined by one skilled in the art.

[0317] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, *e.g.*, as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, *etc.*

[0318] In a preferred embodiment, the cell used for gene therapy is autologous to the subject.

[0319] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody of the invention are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see *e.g.*, PCT Publication WO 94/08598; Stemple and Anderson, 1992, Cell 7 1:973-985; Rheinwald, 1980, Meth. Cell Bio. 21A:229; and Pittelkow and Scott, 1986, Mayo Clinic Proc. 61:771).

[0320] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

[0321] DIAGNOSTIC USE OF ANTIBODIES

[0322] Labeled antibodies of the invention and derivatives and analogs thereof, which immunospecifically bind to a hLIGHT antigen can be used for diagnostic purposes to detect, diagnose, or monitor a hLIGHT-mediated disease. The invention provides methods for the detection of a hLIGHT-mediated disease comprising: (a) assaying the expression of a hLIGHT antigen in cells or a tissue sample of a subject using one or more antibodies of the invention that immunospecifically bind to the hLIGHT antigen; and (b) comparing the level of the hLIGHT antigen with a control level, *e.g.*, levels in normal tissue samples (*e.g.*, from a patient not having a hLIGHT-mediated disease, or from the same patient before disease onset), whereby an increase in

the assayed level of hLIGHT antigen compared to the control level of the hLIGHT antigen is indicative of a hLIGHT-mediated disease.

[0323] The invention provides a diagnostic assay for diagnosing a hLIGHT-mediated disease comprising: (a) assaying for the level of a hLIGHT antigen in cells or a tissue sample of an individual using one or more antibodies of the invention that immunospecifically bind to a hLIGHT antigen; and (b) comparing the level of the hLIGHT antigen with a control level, *e.g.*, levels in normal tissue samples, whereby an increase in the assayed hLIGHT antigen level compared to the control level of the hLIGHT antigen is indicative of a hLIGHT-mediated disease. A more definitive diagnosis of a hLIGHT-mediated disease may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the hLIGHT-mediated disease.

[0324] Antibodies of the invention can be used to assay hLIGHT antigen levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (*e.g.*, see Jalkanen *et al.*, 1985, J. Cell. Biol. 101:976-985; and Jalkanen *et al.*, 1987, J. Cell . Biol. 105:3087-3096). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{121}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0325] One aspect of the invention is the detection and diagnosis of a hLIGHT-mediated disease in a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody that immunospecifically binds to a hLIGHT antigen; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject where the hLIGHT antigen is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody above the background level indicates that the subject has a hLIGHT-mediated disease. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0326] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99}Tc. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel *et al.*, "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B.A. Rhodes, eds., Masson Publishing Inc. (1982).

[0327] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled antibody to preferentially concentrate at sites in the subject and for unbound labeled antibody to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0328] In one embodiment, monitoring of a hLIGHT-mediated disease is carried out by repeating the method for diagnosing the a hLIGHT-mediated disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, *etc.*

[0329] Presence of the labeled molecule can be detected in the subject using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0330] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston *et al.*, U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

METHODS OF PRODUCING ANTIBODIES

[0331] Antibodies of the invention that immunospecifically bind to an antigen can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. The practice of the invention employs, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described in the references cited herein and are fully explained in the literature. See, *e.g.*,, Maniatis *et al.* (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook *et al.* (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook *et al.* (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren *et al.* (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[0332] Polyclonal antibodies that immunospecifically bind to an antigen can be produced by various procedures well-known in the art. For example, a human antigen can be administered to various host animals including, but not limited to, rabbits, mice, rats, *etc.* to induce the production of sera containing polyclonal antibodies specific for the human antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0333] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be

produced using hybridoma techniques including those known in the art and taught, for example, in Harlow *et al.*, Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. Other exemplary methods of producing monoclonal antibodies are discussed elsewhere herein, such as *e.g.*, use of the KM mouse™. Additional exemplary methods of producing monoclonal antibodies are provided in the Examples herein.

[0334] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. Briefly, mice can be immunized with a hLIGHT antigen and once an immune response is detected, *e.g.*, antibodies specific for hLIGHT antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution.

[0335] Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilptrack *et al.*, 1997 Hybridoma 16:381-9, incorporated by reference in its entirety). The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0336] Accordingly, the present invention provides methods of generating antibodies by culturing a hybridoma cell secreting a modified antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with a hLIGHT antigen with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind to a hLIGHT antigen.

[0337] Antibody fragments which recognize specific hLIGHT antigens may be generated by any technique known to those of skill in the art. For example, Fab and $F(ab')_2$ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments). $F(ab')_2$ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. Further, the

antibodies of the present invention can also be generated using various phage display methods known in the art.

[0338] For example, antibodies can also be generated using various phage display methods. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (*e.g.*, human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with an scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to a particular antigen can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman *et al.*, 1995, J. Immunol. Methods 182:41-50; Ames *et al.*, 1995, J. Immunol. Methods 184:177-186; Kettleborough *et al.*, 1994, Eur. J. Immunol. 24:952-958; Persic *et al.*, 1997, Gene 187:9-18; Burton *et al.*, 1994, Advances in Immunology 57:191-280; PCT Application No. PCT/GB91/O1 134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0339] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described below. Techniques to recombinantly produce Fab, Fab' and $F(ab')_2$ fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax *et al.*, 1992, BioTechniques 12(6):864-869; Sawai *et al.*, 1995, AJRI 34:26-34; and Better *et al.*,

1988, Science 240:1041-1043 (said references incorporated by reference in their entireties).

[0340] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. The VH and VL domains may also cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[0341] For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human subjects. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also U.S. Patent Nos. 4,444,887 and 4,716,111; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0342] In preferred embodiments, human antibodies are produced. Human antibodies and/or fully human antibodies can be produced using any method known in the art, including the Examples provided herein. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents

endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995, Int. Rev. Immunol. 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, PCT publication Nos. WO 98/24893, WO 96/34096, and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318, and 5,939,598, which are incorporated by reference herein in their entirety. Other methods are detailed in the Examples herein. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0343] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. Methods for producing chimeric antibodies are known in the art. See, *e.g.*, Morrison, 1985, Science 229:1202; Oi *et al.*, 1986, BioTechniques 4:214; Gillies *et al.*, 1989, J. Immunol. Methods 125:191-202; and U.S. Patent Nos. 5,807,715, 4,816,567, 4,816,397, and 6,331,415, which are incorporated herein by reference in their entirety.

[0344] A humanized antibody is an antibody or its variant or fragment thereof which is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and a CDR having substantially the amino acid sequence of a non-human immunoglobulin. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', $F(ab')_2$, Fabc, Fv) in which all or substantially all of the CDR regions correspond to those of a non human immunoglobulin (*i.e.*, donor antibody) and all or substantially all of the framework regions are those of a human

immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Ordinarily, the antibody will contain both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG1, IgG2, IgG3 and IgG4. Usually the constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the class is typically IgG1. Where such cytotoxic activity is not desirable, the constant domain may be of the IgG2 class. Examples of VL and VH constant domains that can be used in certain embodiments of the invention include, but are not limited to, C-kappa and C-gamma-1 (nG1m) described in Johnson *et al.* (1997) *J. Infect. Dis.* 176, 1215-1224 and those described in U.S. Patent No. 5,824,307. The humanized antibody may comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art. The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, *e.g.*, the donor CDR or the consensus framework may be mutagenized by substitution, insertion or deletion of at least one residue so that the CDR or framework residue at that site does not correspond to either the consensus or the import antibody. Such mutations, however, will not be extensive. Usually, at least 75% of the humanized antibody residues will correspond to those of the parental FR and CDR sequences, more often 90%, and most preferably greater than 95%. Humanized antibodies can be produced using variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239,400; International publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka *et al.*, 1994, Protein Engineering 7(6):805-814; and Roguska *et al.*, 1994, PNAS 91:969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.*, U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, WO 9317105, Tan *et al.*, J. Immunol. 169:1119 25 (2002), Caldas *et al.*, Protein Eng. 13(5):353-60 (2000), Morea *et al.*, Methods 20(3):267 79 (2000), Baca *et al.*, J. Biol. Chem. 272(16):10678-84 (1997), Roguska *et al.*, Protein Eng. 9(10):895 904 (1996), Couto *et al.*, Cancer Res. 55 (23 Supp):5973s- 5977s (1995), Couto *et al.*, Cancer Res. 55(8):1717-22 (1995), Sandhu JS, Gene 150(2):409-10 (1994),

and Pedersen *et al.*, J. Mol. Biol. 235(3):959-73 (1994). See also U.S. Patent Pub. No. US 2005/0042664 A1 (Feb. 24, 2005), which is incorporated by reference herein in its entirety. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Patent No. 5,585,089; and Reichmann *et al.*, 1988, Nature 332:323, which are incorporated herein by reference in their entireties.)

[0345] Single domain antibodies, for example, antibodies lacking the light chains, can be produced by methods well-known in the art. See Riechmann *et al.*, 1999, J. Immunol. 231:25-38; Nuttall *et al.*, 2000, Curr. Pharm. Biotechnol. 1(3):253-263; Muylderman, 2001, J. Biotechnol. 74(4):277302; U.S. Patent No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591, and WO 01/44301, each of which is incorporated herein by reference in its entirety.

[0346] Further, the antibodies that immunospecifically bind to a hLIGHT antigen can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" an antigen using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1989, FASEB J. 7(5):437-444; and Nissinoff, 1991, J. Immunol. 147(8):2429-2438).

POLYNUCLEOTIDES ENCODING AN ANTIBODY

[0347] The invention provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention that immunospecifically binds to a hLIGHT epitope. The invention also encompasses polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions, *e.g.*, as defined *supra*, to polynucleotides that encode a modified antibody of the invention.

[0348] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of E1, E13, E63, F19 and F23 are known (see, *e.g.*, SEQ ID NOS:41, 42, 43, 44, 45, 102, 46, 103, 47, 48, 104, 49, 105, 106, and 50; and ATCC Accession Nos. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728, respectively, which are incorporated herein by reference), nucleotide sequences encoding these antibodies and modified versions of these antibodies can be determined using methods well known in the art, *i.e.*, nucleotide codons known to encode particular amino acids are assembled in

such a way to generate a nucleic acid that encodes the antibody. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier *et al.*, 1994, BioTechniques 17:242), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, fragments, or variants thereof, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0349] Alternatively, a polynucleotide encoding an antibody of the invention may be generated from nucleic acid from a suitable source (*e.g.*, a hybridoma having an ATCC Accession No. PTA-7729, PTA-7842, PTA-7818, PTA-7819, or PTA-7728 (E1, E13, E63, F19 or F23). If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0350] In certain embodiments, nucleic acid molecules of the invention comprise or consist of a nucleic acid sequence as depicted in any one of SEQ ID NOS:41, 42, 43, 44, 45 (encoding a VH) and/or SEQ ID NOS:102, 46, 103, 47, 48, 104, 49, 105, 106, or 50 (encoding a VL), or any combination thereof (*e.g.*, as a nucleotide sequence encoding an antibody of the invention, such as a full-length antibody, heavy and/or light chain of an antibody, or a single chain antibody of the invention).

RECOMBINANT EXPRESSION OF AN ANTIBODY

[0351] Recombinant expression of an antibody of the invention (*e.g.*, a full-length antibody, heavy and/or light chain of an antibody, or a single chain antibody of the invention) that immunospecifically binds to a hLIGHT antigen requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule, heavy or light chain of an antibody, or fragment thereof (preferably, but not necessarily, containing the heavy and/or light chain variable domain) of the invention has been obtained, the vector for the production of the

antibody molecule may be produced by recombinant DNA technology using techniques well-known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a fragment thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, *e.g.*, International Publication Nos. WO 86/05807 and WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[0352] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention or fragments thereof, or a heavy or light chain thereof, or fragment thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0353] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention (see, *e.g.*, U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces Pichia*) transformed

with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, NS0, and 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking *et al.*, 1986, Gene 45:101; and Cockett *et al.*, 1990, Bio/Technology 8:2). In preferred embodiments, antibodies of the invention are produced in CHO cells. In a specific embodiment, the expression of nucleotide sequences encoding antibodies of the invention which immunospecifically bind to a hLIGHT antigen is regulated by a constitutive promoter, inducible promoter or tissue specific promoter.

[0354] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such an antibody is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO 12:1791), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. 13:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. 24:5503-5509); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The

pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0355] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0356] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region El or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA 8 1:355-359). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, *etc.* (see, *e.g.*, Bittner *et al.*, 1987, Methods in Enzymol. 153:51-544).

[0357] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2,

BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL7O3O and HsS78Bst cells. In preferred embodiments, fully human, monoclonal anti-hLIGHT antibodies of the invention are produced in mammalian cells, such as CHO cells.

[0358] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, *etc.*), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[0359] A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler *et al.*, 1977, Cell 11:223), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, 1992, Proc. Natl. Acad. Sci. USA 48:202), and adenine phosphoribosyltransferase (Lowy *et al.*, 1980, Cell 22:8-17) genes can be employed in tk-, hgprt- or aprt-cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler *et al.*, 1980, Natl. Acad. Sci. USA 77:357; O'Hare *et al.*, 1981, Proc. Natl. Acad. Sci. USA 78:1527); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neo, which confers resistance to the aminoglycoside G-418 (Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, 1993, Science 260:926-932; and Morgan and Anderson, 1993, Ann. Rev. Biochem. 62:191-217; May, 1993, TIB TECH 11(5):l55-2 15); and *hygro*, which confers resistance to hygromycin (Santerre *et al.*, 1984, Gene 30:147). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in

Ausubel *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli *et al.* (eds.), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin *et al.*, 1981, J. Mol. Biol. 150:1, which are incorporated by reference herein in their entireties.

[0360] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3 (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse *et al.*, 1983, Mol. Cell. Biol. 3:257).

[0361] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, 1986, Nature 322:52; and Kohler, 1980, Proc. Natl. Acad. Sci. USA 77:2197-2199). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0362] Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

KITS

[0363] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

compositions of the invention, such as one or more antibodies provided herein. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[0364] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated hLIGHT antigen as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with the hLIGHT antigen. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of a modified antibody to a hLIGHT antigen (*e.g.*, the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized hLIGHT antigen. The hLIGHT antigen provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above described kit includes a solid support to which hLIGHT antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the hLIGHT antigen can be detected by binding of the said reporter-labeled antibody.

[0365] The following examples are offered by way of illustration, and not by way of limitation.

EXAMPLES

EXAMPLE 1 – GENERATION OF HUMAN ANTI-hLIGHT ANTIBODIES

[0366] In this example, the generation of human anti-hLIGHT monoclonal antibodies using transchromosomal mice (KM mice™) (WO 02/43478, WO 02/092812, Ishida and Lonberg, IBC's 11th Antibody Engineering Meeting. Abstract (2000); and Kataoka, S. IBC's 13th Antibody Engineering Meeting. Abstract (2002)) immunized with soluble recombinant hLIGHT is described. The antibodies described here specifically stained hLIGHT stably transfected cell lines, (EL4-hLIGHT and HEK 293-hLIGHT) and not the parental cell lines. Likewise, they bind to endogenously expressed hLIGHT on the surface of the human T cell hybridoma (II-23.D7) (Ware *et al.* 1986

Lymphokine Res 5 313-24) upon activation. Together, these data indicate that the antibodies immunospecifically bind to hLIGHT. The isolated antibodies recognize one of two epitopes on hLIGHT as determined by cross-blocking experiments, as described below. Moreover, the antibodies were able to block cell surface-expressed hLIGHT binding to soluble receptor-Fc fusion forms of both human HVEM and the LTβR. Soluble hLIGHT induces the secretion of the chemokines CCL20 and RANTES from the human colonic epithelial cell line HT29.14s (ATCC HTB-38) in a dose dependent manor. Incubation of soluble hLIGHT with anti-hLIGHT antibodies blocks hLIGHT-mediated secretion of both CCL20 and RANTES from HT29.14s cells. In addition, pre-incubation of cell surface expressed hLIGHT (EL4-hLIGHT) with these anti-hLIGHT antibodies blocks membrane-bound hLIGHT-induced chemokine secretion from HT29 cells. Together, these results illustrate functional and structural characteristics of the fully human anti-hLIGHT monoclonal antibodies and provide evidence of their usefulness in the treatment of hLIGHT-mediated diseases.

MATERIALS AND METHODS

[0367] Antigen preparation: The antigen used for immunizations in the generation of fully human anti- hLIGHT antibodies was a soluble version of hLIGHT that is truncated to include only the extracellular region, starting from the glycine at amino acid position 66 to Valine 240, and contains a FLAG epitope tag at the amino-terminus of the protein (SEQ ID NO:54). The production of this molecule has been reported previously (Rooney *et al.* 2000 J Biol Chem 275 14307-15).

[0368] Nucleic acid (SEQ ID NO:51) encoding the full-length hLIGHT amino acid sequence (SEQ ID NO:52) has been cloned from activated II23.D7 T cell hybridoma cells by reverse transcriptase-PCR (Mauri *et al.* 1998 Immunity 8 21-30). The II-23 cell line (a D7 subclone) is a human CD4+ T cell hybridoma (Ware *et al.* 1986 Lymphokine Res 5 313-24). The hLIGHT PCR product was subcloned into the mammalian expression vector pcDNA3.1 (+) to create pcDNA3.1-hLIGHT. The extracellular domain (encoding Gly66 to Val240) was amplified from pcDNA3-hLIGHT by PCR using the following primers with incorporated restriction sites:

forward, 5'-GTAGGAGAGATGGTCACCCGCCT-3' (SEQ ID NO:80).

reverse, 5'-GGAACGCGAATTCCCACGTGTCAGACCCATGTCCAAT-3' (SEQ ID NO:81).

[0369] The amplified hLIGHT PCR product was digested with EcoRI and ligated into the SnaB1 and EcoRI sites of pCDNA3.1-VCAM-FLAG, which encodes the VCAM1 leader sequence followed by the FLAG epitope for the production of secreted, N-terminally FLAG-tagged protein (SEQ ID NO:52).

[0370] To produce a stable cell line for the production of soluble hLIGHT, HEK293 cells were transfected using the calcium phosphate method, and stable clones were selected with G418 (Invitrogen, Corp.) and screened for hLIGHT production by ELISA. Soluble hLIGHT was purified from culture supernatants of cells grown in DMEM containing 1.0% defined fetal bovine serum (Hyclone Laboratories, Logan, UT). Soluble hLIGHT was purified by affinity chromatography with anti-FLAG (M2) antibody coupled to agarose beads. Soluble hLIGHT was eluted from the column using 20 mM glycine, 150 mM NaCl, pH 3.0, and pH-neutralized immediately by collection into 50 mM Tris, pH 7.4. Protein concentration was determined by absorbency at 280 nm.

[0371] Nucleotide sequence of a hLIGHT from initiation codon (ATG) to stop (TGA) (SEQ ID NO:51):

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ATGGAGGAGA GTGTCGTACG GCCCTCAGTG TTTGTGGTGG ATGGACAGAC CGACATCCCA   60
TTCACGAGGC TGGGACGAAG CCACCGGAGA CAGTCGTGCA GTGTGGCCCG GGTGGGTCTG  120
GGTCTCTTGC TGTTGCTGAT GGGGGCCGGG CTGGCCGTCC AAGGCTGGTT CCTCCTGCAG  180
CTGCACTGGC GTCTAGGAGA GATGGTCACC CGCCTGCCTG ACGGACCTGC AGGCTCCTGG  240
GAGCAGCTGA TACAAGAGCG AAGGTCTCAC GAGGTCAACC CAGCAGCGCA TCTCACAGGG  300
GCCAACTCCA GCTTGACCGG CAGCGGGGGG CCGCTGTTAT GGGAGACTCA GCTGGGCCTG  360
GCCTTCCTGA GGGGCCTCAG CTACCACGAT GGGGCCCTTG TGGTCACCAA AGCTGGCTAC  420
TACTACATCT ACTCCAAGGT GCAGCTGGGC GGTGTGGGCT GCCCGCTGGG CCTGGCCAGC  480
ACCATCACCC ACGGCCTCTA CAAGCGCACA CCCCGCTACC CCGAGGAGCT GGAGCTGTTG  540
GTCAGCCAGC AGTCACCCTG CGGACGGGCC ACCAGCAGCT CCCGGGTCTG GTGGGACAGC  600
AGCTTCCTGG GTGGTGTGGT ACACCTGGAG GCTGGGGAGG AGGTGGTCGT CCGTGTGCTG  660
GATGAACGCC TGGTTCGACT GCGTGATGGT ACCCGGTCTT ACTTCGGGGC TTTCATGGTG  720
TGA                                                                780
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[0372] Amino acid sequence of a full length hLIGHT 240 aa (SEQ ID NO:52):

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MEESVVRPSV FVVDGQTDIP FTRLGRSHRR QSCSVARVGL GLLLLLMGAG LAVQGWFLLQ   60
LHWRLGEMVT RLPDGPAGSW EQLIQERRSH EVNPAAHLTG ANSSLTGSGG PLLWETQLGL  120
AFLRGLSYHD GALVVTKAGY YYIYSKVQLG GVGCPLGLAS TITHGLYKRT PRYPEELELL  180
VSQQSPCGRA TSSSRVWWDS SFLGGVVHLE AGEEVVVRVL DERLVRLRDG TRSYFGAFMV  240
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[0373] Nucleotide sequence of a soluble FLAG-tagged hLIGHT (VCAM leader sequences shown, followed by FLAG encoding sequence in bold) (SEQ ID NO:53)

ATGCCTGGGA AGATGGTCGT GATCCTTGGA GCCTCAAATA TACTTTGGAT AATGTTTGCA 60
GCTTCTCAAG CTGACTACAA GGACGACGAT GACAAGTACG TAGGAGAGAT GGTCACCCGC 120
CTGCCTGACG GACCTGCAGG CTCCTGGGAG CAGCTGATAC AAGAGCGAAG GTCTCACGAG 180
GTCAACCCAG CAGCGCATCT CACAGGGGCC AACTCCAGCT TGACCGGCAG CGGGGGGCCG 240
CTGTTATGGG AGACTCAGCT GGGCCTGGCC TTCCTGAGGG GCCTCAGCTA CCACGATGGG 300
GCCCTTGTGG TCACCAAAGC TGGCTACTAC TACATCTACT CCAAGGTGCA GCTGGGCGGT 360
GTGGGCTGCC CGCTGGGCCT GGCCAGCACC ATCACCCACG GCCTCTACAA GCGCACACCC 420
CGCTACCCCG AGGAGCTGGA GCTGTTGGTC AGCCAGCAGT CACCCTGCGG ACGGGCCACC 480
AGCAGCTCCC GGGTCTGGTG GGACAGCAGC TTCCTGGGTG GTGTGGTACA CCTGGAGGCT 540
GGGGAGGAGG TGGTCGTCCG TGTGCTGGAT GAACGCCTGG TTCGACTGCG TGATGGTACC 600
CGGTCTTACT TCGGGGCTTT CATGGTGTGA 660

[0374] Amino acid sequence of a soluble FLAG-tagged hLIGHT 183 aa (FLAG in bold) (SEQ ID NO:54):

DYKDDDDKGE MVTRLPDGPA GSWEQLIQER RSHEVNPAAH LTGANSSLTG SGGPLLWETQ 60
LGLAFLRGLS YHDGALVVTK AGYYYIYSKV QLGGVGCPLG LASTITHGLY KRTPRYPEEL 120
ELLVSQQSPC GRATSSSRVW WDSSFLGGVV HLEAGEEVVV RVLDERLVRL RDGTRSYFGA 180
FMV 240

[0375] EL4 (ATCC TIB-39) cells were stably transduced with a retrovirus containing the cDNA encoding full-length hLIGHT for the generation of the EL4-hLIGHT cell line.

[0376] Fc fusion protein preparation: Cloning, expression, and purification of the soluble receptor fusion proteins containing the Fc region of human IgG1 and the ligand-binding domains of human LTβR and human HVEM have been described previously (Rooney *et al.* 2000 Methods Enzymol 322 345-63). Briefly, the extracellular regions of HVEM and the LTβR were isolated by polymerase chain reactions using primers with incorporated restriction endonuclease sites and ligated in-frame into the baculovirus vector pVL1392 (Pharmingen) containing the human Fc IgG1. *Trichoplusia ni* High-Five BTI-TN-5b1-4 (Tn5) insect cells (Invitrogen Corp.) were infected with the LTβR:Fc or HVEM:Fc recombinant baculoviruses for protein production (see antibody and protein purification).

[0377] Mice: Human trans-chromosomic KM mice™ (WO 02/43478, WO 02/092812, Ishida and Lonberg, IBC's 11th Antibody Engineering Meeting. Abstract (2000); and Kataoka, S. IBC's 13th Antibody Engineering Meeting. Abstract (2002)) harboring human chromosome fragments encoding the human immunoglobulin region were obtained from Kirin Brewery Co., Ltd., Japan, and were housed in the animal

facility at Gemini Science (La Jolla, CA). An overview of the technology for producing human antibodies is described in Lonberg and Huszar 1995 Int Rev Immunol 13 65-93. Transgenic animals with one or more human immunoglobulin genes (kappa or lambda) that do not express endogenous immunoglobulins are described, for example in, U.S. Patent No. 5,939,598. Additional methods for producing human antibodies and human monoclonal antibodies are described (see, *e.g.*, WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598). Development of bovine carrying human immunoglobulin genes, TC cows, is described in Ishida and Lonberg (see Ishida 2000 11th Antibody Engineering Meeting, Kuroiwa *et al.* 2004 Nat Genet 36 775-80, Kuroiwa *et al.* 2002 Nat Biotechnol 20 889-94).

[0378] Immunization: FLAG-tagged soluble hLIGHT recombinant protein was mixed with an equal volume of complete Freund's adjuvant (CFA, Sigma) and an emulsion was prepared. Mice were immunized with 10 to 50 μg of protein sub-cutaneously (s.c.) and were boosted s.c. with 10 to 20 μg of protein emulsified in incomplete Freund's adjuvant (IFA, Sigma) at 2-3 week intervals for 2 to 3 boosts. A final intravenous (i.v.) injection of 10 μg of FLAG-tagged soluble hLIGHT without adjuvant was given 3 days prior to fusion.

[0379] Hybridoma production: The mice displaying the highest anti-hLIGHT IgG specific antibody titer in their serum, as determined by the hLIGHT ELISA and FACS using hLIGHT transduced EL4 cells versus EL4 parental cells, were selected for the production of monoclonal antibodies. The spleens were harvested and single cell suspensions were fused to the SP2/O-Ag14 myeloma cell line (ATCC, Manassas, VA) at a ratio of 5:1 with 50% polyethylene glycol (Boehringer Mannheim, Indianapolis, IN). The fusions were plated into 96 well flat bottom plates at an optimal density (here $1x10^6$/ml) in complete DMEM-10 medium (Dulbecco's Modified Engle's Medium with 10% fetal bovine serum (FBS, Invitrogen, Corp.), 1% non-essential amino acids, 2 mM L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin sulfate (all from BioWhittaker, Walkersville, MD), HAT supplement (Sigma), and 10% Hybridoma Cloning Factor (HCF, Biovaris, San Diego, CA)) and cultured at 37°C in a 10% CO_2 incubator. Approximately 2800 wells from 2 fusions were screened by ELISA for human kappa containing hLIGHT specific antibodies. Human anti-hLIGHT IgG antibodies were confirmed by flow cytometric analysis using hLIGHT-EL4 cells versus EL4 parental cells. Positive wells were also tested for receptor blocking activity by pre-

incubation of crude hybridoma extinction culture growth media with EL4-hLIGHT cells and staining with half-saturating HVEM:Fc or LTβR:Fc. Positive wells were expanded and subjected to 3 – 5 rounds of limiting dilution cloning to obtain monoclonal antibodies.

[0380] Antibody and protein purification: For antibody purification, hybridomas were cultured in 2 liter roller bottles at 350 milliliter to 1 liter/bottle or in a 1 liter Integra system (INTEGRA Bioscience, Inc., Ijamsville, MD) with hybridoma-SFM medium (Invitrogen, Corp.) supplemented with ultra low IgG fetal bovine serum (Invitrogen, Corp.).

[0381] The production of human and mouse LTβR:Fc and HVEM:Fc recombinant proteins has been previously reported (Rooney *et al.* 2000 Meth. Enzymol. 322:345-63) and were generated by infecting 1 liter of suspension Tn5 cells for 4 days. Both the human monoclonal antibodies and Fc fusion proteins were purified from culture media using recombinant Protein A-Sepharose Fast Flow gel (Amersham Biosciences). Conditioned medium generated in roller bottles was first concentrated using an Ultrasette tangential flow system (Pall Corp., East Hills, NY). The conditioned medium was filtered with a 0.22 μm vacuum filter unit (Millipore, Bedford, MA) and loaded onto a Protein A-Sepharose Fast Flow column (Amersham Biosciences) of appropriate size for the amount of human antibody in the medium. The column was washed thoroughly with 20 column volumes of PBS and the antibody was eluted with 0.1 M Gly-HCl, pH 3.6, 0.15 M NaCl and neutralized with 1 M Tris-HCl, pH 8.0. The fractions were analyzed by SDS-PAGE and the positive fractions were pooled and concentrated with a centrifugal concentrator (Vivaspin, 50,000 MWCO: Sartorius, Gettingen, Germany).

[0382] Sephadex G-25 desalting columns, (NAP, Amersham Biosciences), were used for buffer exchange to PBS, pH 7.4. Finally, the antibody was filter sterilized using syringe filters with 0.22 μm pore diameters and the antibody concentration was determined by the Lowry method. Pyrogen content was determined using a Limulus Amebocyte Lysate (LAL) assay (Associates of Cape Cod, Falmouth, MA). The limits of detection of this assay are 0.06 EU/mg. If the test was negative, the samples were considered endotoxin free.

[0383] Human IgG quantitation ELISA: To determine the amount of human antibody present in supernatants and purified stocks the following protocol was used.

Goat anti-human Fcγ specific antibody (Jackson Immunoresearch Laboratories, West Grove, PA) was coated to the 96 well plates (Nunc, Denmark) in carbonate buffer at 0.5 μg/well for 1 hour at 37°C. The plates were then blocked with Super block (Pierce, Rockford, IL) for 30 minutes followed by addition of the samples to the plates. Standard curves were generated using total human IgG (Sigma) or purified human IgG1 or IgG4 (Kirin Brewery Co., Ltd). The plates were incubated for 1 hour at 37°C, washed in PBS/1%BSA/0.1%Tween20 (Sigma), and the bound antibody was detected with goat anti-human Fcγ specific antibody conjugated to horseradish peroxidase (HRP, Jackson Immunoresearch Laboratorie, West Grove, PA) for 1 hour at 37°C. The TMB substrate (Sigma) was added for 10 minutes and the reaction was stopped with H_2SO_4 (LabChem, Pittsburgh, PA). The OD was measured at 450 nm on a microplate reader.

[0384] Mammalian cell culture: The human II-23 cell line (D7 subclone), a CD4+ T cell hybridoma line (Ware *et al.* 1986 Lymphokine Res 5 313-24), was maintained in RPMI 1640 containing 10% FBS (HyClone Laboratories, Logan, UT) and 100 U/ml penicillin/100 μg/ml streptomycin (Life Technologies, Grand Island, NY). The human HT29.14s cell line, the EL4-hLIGHT cell line and the 293- hLIGHT cell line were all maintained in DMEM containing 10% FBS (HyClone Laboratories, Logan, UT). All mammalian cells were cultured in a 5% CO_2 humidified incubator at 37°C.

[0385] Anti-hLIGHT antibody detection ELISA: Antibody titers, specificity, and production by hybridomas were determined by ELISA. In brief, 96 well flat bottom plates were coated with 50 μl of FLAG tagged soluble hLIGHT at 5 μg/ml in carbonate buffer (pH 9.4) overnight at 4°C or at 37°C for 1 hour. After washing twice with PBS/0.1% Tween 20, plates were blocked with PBS/1%BSA/0.1%Tween20 at 37°C for 1 hour. The serum, supernatant, or purified antibody was diluted in blocking buffer, added to the wells, and the plates were incubated for 1 hour at 37°C. The plates were washed 4 times with PBS/0.1% Tween 20 and the peroxidase conjugated sheep anti-human kappa detection antibody (The Binding Site, Birmingham, UK) was added at a dilution of 1:2000. Following a 1 hour incubation at 37°C, the plates were washed and the TMB (Sigma) substrate was added and incubated at room temperature for 10 to 30 minutes. The reaction was stopped with H_2SO_4 (LabChem) and a microplate reader measured the optical density at 450 nm.

[0386] Flow cytometry: Antibody titers, specificity, and relative binding affinities were determined by flow cytometric analysis using hLIGHT stable EL4 transduced cell

lines or a 6-15 hr PMA (40 ng/ml) + inonomycin (500 ng/ml) activated II23.D7 T cell line. The cells were washed once in staining buffer: PBS + 2% FBS + 0.01% NaN_3 + 10 mM EDTA, then resuspended in serum, supernatant, or purified antibodies in a volume of 50 µl. The cells were incubated with the antibodies on ice for 20 minutes, washed twice in staining buffer then resuspended in an goat anti-human IgG-APC labeled secondary antibody (Donkey anti-human-APC, Jackson Immunoresearch Laboratories, West Grove, PA). Following a 20 minute incubation on ice, the cells were washed once and fixed 10 minutes with 1% paraformaldehyde or subjected to a final wash, then the cells were resuspended in staining buffer and the samples acquired using FACScan or FACS Calibur flow cytometers (Becton Dickinson Biosciences, Palo Alto, CA). The data were analyzed using CELLQUEST (Becton Dickinson Biosciences) or FLOW JO (TreeStar, Inc., San Carlos, CA) software.

[0387] Anti-hLIGHT antibody cross-blocking assays: An ELISA protocol was used to determine if the antibodies bind the same hLIGHT epitope. NUNC 96 well flat bottom ELISA plates were coated with the human anti-hLIGHT antibodies in carbonate buffer at 2 µg/ml for 1 hour at 37°C. The plates were washed and then blocked with PBS/1%BSA/Tween 20. The human anti-hLIGHT antibodies were then pre-incubated with recombinant human FLAG-tagged soluble hLIGHT for 30 minutes at 4°C. The combinations of antibody-hLIGHT protein were added to the plate and incubated for 1 hour at 4°C. After 3 washes, bound hLIGHT was detected with peroxidase conjugated M2-mouse anti-FLAG epitope tag Ig (Sigma). The percent inhibition was determined using the OD of each sample in the following formula: %inhibition = (max – sample/max)*100.

[0388] Human cytokine analysis. A panel of 8 human cytokines in the growth media of treated HT29.14s cells was measured using multiplex technology and following the manufacturer's instructions (Bio-Rad Laboratories, Hercules, CA). The detection of CCL20 in the culture media of HT29.14s cells was performed by ELISA (R&D systems, Minneapolis, MN) using manufacturers instructions.

[0389] *In vitro* assay for antibody mediated blockade of cell surface expressed LIGHT binding to soluble receptor Fc fusion proteins. 1e5 EL4 hLIGHT cells were incubated with graded concentrations of each antibody for 30 minutes at 4 °C. Sub-saturating amounts of HVEM:Fc-biotin (3 µg/ml) or LTβR:Fc-His (3 µg/ml) (Alexis Biochemicals) were then added to the cells and incubated for 30 minutes at 4 degrees C. The cells were then washed 2x with 200 µl FACS buffer (1 x PBS 2% FBS + 0.02%

azide). HVEM:Fc-biotin or LTβR:Fc-His were detected by a 30 minute incubation with either SA-APC at 2.5 μg/ml or anti-His-HRP respectively. Cells were then analyzed on a FACScaliber (Becton Dickinson) flow cytometers. Dead cells were gated out from the forward scatter vs. side scatter plot and geometric means of each histogram were calculated using FLOWJO (TreeStar, San Carlos, CA, USA).

[0390] Isolation of human anti-hLIGHT antibody genes. Cultured hybridoma cells (124E63, 124F23, 124E1, 124E13 and 124F19), which produce E63 (IgG3), F23 (IgG4), E1 (IgG1), E13 (IgG1) and F19 (IgG1) antibodies, respectively, were collected by centrifugation. Total RNA was purified from these cells using RNEASY kit (QIAGEN Inc., Valencia, CA) following the manufacturer's instructions. The SMART RACE cDNA Amplification Kit (Clontech Co., Ltd., Palo Alto, CA) was used for cloning of cDNA that encodes the variable region of the immunoglobulin genes from total hybridoma cell RNA. Briefly, first strand cDNA was prepared by reverse transcriptase from 2 microgram of RNA. This cDNA was used as a template for polymerase chain reaction (PCR) to amplify the variable region and a part of the constant region of heavy and light chains (VH and VL, respectively). The 3' primers used for amplification of the heavy and light chain genes in the 5' RACE reactions were HH-2 (SEQ ID NO:64) (H chain constant region) and HK-2 (SEQ ID NO:65) (light chain constant region), respectively. The amplified sequences also contained the leader sequences. The reaction was as follows: 2.5 units PFU ULTRA DNA polymerase (Stratagene, La Jolla, CA); 0.2 μM 3' Primer (for Heavy chain: IgG1p, for light chain: hk5, Table 2); 1X Universal Primer Mix A for the 5' end (UMP primer mix A included in the SMART RACE Kit); 200 μM dNTP mix; 1 mM $MgCl_2$; Puff Ultra Buffer (final concentration is 1x); and cDNA template.

[0391] The thermocycling program was 5 cycles of: 94°C x 30 sec, 72°C x 3 min. 5 cycles of : 94°C x 30 sec, 70°C x 30 sec, 72°C x 3 min. 25 cycles of: 94°C x 30 sec, 68°C x 30 sec, 72°C x 3 min followed by an extension at 72°C x 7 min. Amplified DNA fragments were collected by agarose gel electrophoresis, and purified by QIAQUICK Gel Extraction Kit (Qiagen Co., Ltd., Germany). Purified DNA fragments of VH and LV were integrated into PCR 4 Blunt-TOPO vector using the Zero Blunt TOPO PCR Cloning Kit (Invitrogen, Carlsbad, CA), and each construct plasmid was transformed into *E. coli*, and then cloned. Nucleotide sequences of each insert (HV and LV) in the construct plasmids were analyzed using specific universal vector primers M13F (SEQ ID NO:58) and M13R (SEQ ID NO:59). Based on the sequence obtained from VH and

VL, oligonucleotide primers were designed to amplify the respective VH and VL (*see* Table 2).

[0392] cDNAs encoding E63, F23, E1 and F19 VH and VL were PCR subcloned from the PCR4 Blunt-TOPO vectors into the IgG1 expression vector. Because E13 was an IgG1 subtype with a single kappa chain (see below) hybridoma, there was no need to subclone the E13 cDNA into an IgG1 vector for the further analyses.

[0393] First, oligonucleotide primers containing 5'-SalI and 3'-NheI restriction enzyme recognition sites were designed to amplify the variable region of the heavy chain (VH) by PCR. For example, in the case of E63VH, PCR was performed using pTopoE63VH mini-prep DNA as a template, E63HF85 (SEQ ID NO:60) and E63HR38 (SEQ ID NO:61) as primers (*see* Table 2) with PFU ULTRA DNA polymerase. After digestion with NheI and SalI, the PCR product was sub-cloned into the IgG1 expression vector (IDEC Pharmaceuticals, San Diego, CA, N5KG1-Val Lark (a modified vector of N5KG1 (U.S. Patent No. 6,001,358)) that was pre-digested with NheI and SalI (8.9 kilobases DNA fragment). The existence of VH was analyzed by restriction digest.

[0394] Next, oligonucleotide primers containing 5' BglII and 3' BsiWI restriction enzyme recognition sites were designed to amplify the variable region of the light chain (VL) by PCR. For example, following subcloning of the E63VH described above, the E63VL was inserted into the N5KG1-Val Lark-VH vector by digesting the DNA vector with BglII and BsiWI. The 9.1 kb DNA fragment was then isolated. Similar to the VH construct, a primer set for PCR of VL was designed to contain the recognition sites for 5'BglI and 3'BsiWI. These primers, E63LF84 (SEQ ID NO:62) and E63LR43 (SEQ ID NO:63), were used to amplify VL from the pTopoE63VL mini-prep plasmid DNA. The PCR product was digested with BglII and BsiWI and isolated by agarose gel electrophoresis and gel purification. This fragment, containing E63VL, was ligated to the prepared 9.1 kb vector with T4 DNA ligase and used to transform Top10 cells (Invitrogen). Positive *E.coli* transformants were selected. This expression vector, pG1K112E63, was purified, and the presence of both E63VL and E63VH regions were confirmed by restriction analysis.

[0395] Generation of vectors to produce recombinant F23G1, E1G1 and F19G1 antibodies was performed in essentially the same manner as E63G1. PCR amplification of the F23VH was performed using F23HF86 (SEQ ID NO:66) and F23HR55 (SEQ ID NO:67). The F23VL amplification primers were F23LF36 (SEQ ID NO:68) and F23LR43 (SEQ ID NO:69). PCR amplification of the E1VH was performed using

E1HFSal1 (SEQ ID NO:70) and E1HRNheI (SEQ ID NO:71). PCR amplification of E1VL kappa(A), E1VL kappa(B) and E1VL kappa(C) was performed using E1KF2+3BglII (SEQ ID NO:74) paired with either E1KR2BsiWI (SEQ ID NO:75) or E1KR3BsiWI (SEQ ID NO:76). PCR amplification of F19VH was performed using F19HFSalI (SEQ ID NO:72) and F19HRNheI (SEQ ID NO:73). PCR amplification of F19L kappa(A) and F19L kappa(B) was performed using F19KR1+2BsiWI (SEQ ID NO:77) and F19KF1+2+3BglII (SEQ ID NO:79). PCR amplification of F19L kappa(C) was performed using F19KR3BsiWI (SEQ ID NO:78) and F19KF1+2+3BglII (SEQ ID NO:79). The resulting vectors, pKLG1/F23, pKLG1/E1 and pKLG1/F19 are also confirmed by restriction enzyme digest and sequencing. F19L kappa(D) was not PCR amplified due to a reading frameshift, which was detected by sequence analysis, that produced a C-terminal segment of the antibody.

[0396] Nucleotide sequence of cDNA of E63 heavy chain variable region (VH) (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:43):

ATGAAACACC TGTGGTTCTT CCTCCTCCTG GTGGCAGCTC CCAGATGGGT CCTGTCCCAG
60
GTGCAGCTGC AGGAGTCGGG CCCAGGACTG GTGAAGCCTT CGGAGACCCT GTCCCTCACC
120
TGCATTGTCT CTGGTGGCTC CGTCAGCAGT GGTGGTTACT ACTGGAGCTG GATCCGGCAG
180
CCCCCAGGGA AGGGACTGGA GTGGATTGGG TATATCTATT ACAGTGGGAG CACCAACTAC
240
AACCCCTCCC TCAAGAGTCG AGTCACCATA TCAGTAGACA CGTCCAAGAA CCAGTTCTCC
300
CTGAAGCTGA GCTCTGTGAC CGCTGCGGAC ACGGCCGTGT ATTACTGTGC GAGATGGATT
360
ACTATGTTTC GGGGAGTTGG GTTCGACCCC TGGGGCCAGG GAACCCTGGT CACCGTCTCC
420
TCA
480

[0397] Nucleotide sequence of cDNA of E63 kappa light chain variable region (VL) (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:48):

ATGTCGCCAT CACAACTCAT TGGGTTTCTG CTGCTCTGGG TTCCAGCCTC CAGGGGTGAA 60
ATTGTGCTGA CTCAGTCTCC AGACTTTCAG TCTGTGACTC CAAAGGAGAA AGTCACCATC 120
ACCTGCCGGG CCAGTCAGAG CATTGGTAGT AGCTTACACT GGTACCAGCA GAAACCAGAT 180
CAGTCTCCAA AGCTCCTCAT CAAGTATGCT TCCCAGTCCT TCTCAGGGGT CCCCTCGAGG 240

TTCAGTGGCA GTGGATCTGG GACAGATTTC ACCCTCACCA TCAATAGCCT GGAAGCTGAA 300
GATGCTGCAG CATATTACTG TCATCAGAGT AGTAGTTTAC CTCTCACTTT CGGCGGAGGG 360
ACCAAGGTGG AGATCAAA 420

[0398] Nucleotide sequence of cDNA of F23 heavy chain variable region (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:45):

ATGGACCTCC TGCACAAGAA CATGAAACAC CTGTGGTTCT TCCTCCTCCT GGTGGCAGCT 60
CCCAGATGGG TCCTGTCCCA GGTGCAGCTA CAGCAGTGGG GCGCAGGACT GTTGAAGCCT 120
TCGGAGACCC TGTCCCTCAC CTGCGCTGTC TATGGTGGGT CCTTCAGTGG TTACTACTGG 180
AACTGGATCC GCCAGCCCCC AGGGAAGGGG CTGGAGTGGA TTGGGGAAAT CAATCAGTAC 240
AACCCGTCCC TCAAGAGTCG AGTCACCATA TCAGTAGACA CGTCCAAGAA CCAGTTCTCC 300
CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCTGTGT ATTACTGTGC GAGAGAGATA 360
GCAACAGCTG ATAAAGGGTA CTACGGTTTG GACGTCTGGG GCCAAGGGAC CACGGTCACC 420
GTCTCCTCA 480

[0399] Nucleotide sequence of cDNA of F23 kappa light chain variable region (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:50):

ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTTCTGC TGCTCTGGCT CCCAGGTGCC 60
AGATGTGCCA TCCAGTTGAC CCAGTCTCCA TCCTCCCTGT CTGCATCTGT AGGAGACAGA 120
GTCACCATCA CTTGCCGGGC AAGTCAGGGC ATTAGCAGTG CTTTAGCCTG GTATCAGCAG 180
AAACCAGGGA AAGCTCCTAA GCTCCTGATC TATGATGCCT CCAGTTTGGA AAGTGGGGTC 240
CCATCAAGGT TCAGCGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG 300
CAGCCTGAAG ATTTTGCAAC TTATTACTGT CAACAGTTTA ATAGTTACCC GCTCACTTTC 360
GGCGGAGGGA CCAAGGTGGA GATCAAA 420

[0400] Nucleotide sequence of cDNA of E1 heavy chain variable region (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:41):

ATGGAGTTGG GGCTGTGCTG GGTTTTCCTT GTTGCTATTT TAGAAGGTGT CCAGTGTGAG 60
GTGCAGCTGG TGGAGTCTGG GGGAGGCTTG GTACAGCCTG GGGGGTCCCT GAGACTCTCC 120
TGTGCAGCCT CTGGATTCAC CTTCAGTAGA TTTAACATGA ACTGGGTCCG CCAGGCTCCA 180
GGGAAGGGGC TGGAGTGGGT TTCATACATT AGTAGTAGTA GTTATACCAT ATACTACGCA 240
GACTCTGTGA AGGGCCGATT CACCATCTCC AGAGACAATG CCAAGAACTC ACTGGATCTG 300
CAAATGAACA GCCTGAGAGA CGAGGACACG GCTGTGTATT ACTGTGCGAG GAGTATAGCA 360
GCAGCTTTTG ACTACTGGGG CCAGGGAGCC CTGGTCACCG TCTCCTCA 420

[0401] Nucleotide sequence of cDNA of E1 kappa light chain variable region #1 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:102):

ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTTCTGC TGCTCTGGCT CCCAGGTGCC 60
AGATGTGCCA TCCAGTTGAC CCAGTCTCCA TCCTCCCTGT CTGCATCTGT AGGAGACAGA 120
GTCACCATCA CTTGCCGGGC AAGTCAGGGC ATTAGCAGTG CTTTAGCCTG GTATCAGCAG 180
AAACCAGGGA AAGCTCCTAA GCTCCTGATC TATGATGCCT CCAGTTTGGA AAGTGGGGTC 240
CCATCAAGGT TCAGCGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG 300
CAGCCTGAAG ATTTTGCAAC TTATTACTGT CAACAGTTTA ATAGTTACCG TACACTTTTG 360

GCCAGGGGAC CAAGCTGGAG ATCAAA 420

[0402] Nucleotide sequence of cDNA of E1 kappa light chain variable region #2 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:46):

ATGGAAACCC CAGCGCAGCT TCTCTTCCTC CTGCTACTCT GGCTCCCAGA TACCACCGGA 60
GAAATTGTGT TGACGCAGTC TCCAGGCACC CTGTCTTTGT CTCCAGGGGA AAGAGCCACC 120
CTCTCCTGCA GGGCCAGTCA GAGTGTTAGC AGCAGCTACT TAACCTGGTA CCAGCAGAAA 180
CCTGGCCAGG CTCCCAGGCT CCTCATCTAT GGTGCATCCA GCAGGGCCAC TGGCATCCCA 240
GACAGGTTCA GTGGCAGTGG GTCTGGGACA GACTTCACTC TCACCATCAG CAGACTGGAG 300
CCTGAAGATT TTGCAGTGTA TTACTGTCAG CAGTATGGTA GCTCAATGTA CACTTTTGGC 360
CAGGGGACCA AGCTGGAGAT CAAA 420

[0403] Nucleotide sequence of cDNA of E1 kappa light chain variable region #3 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:103):

ATGGAAACCC CAGCGCAGCT TCTCTTCCTC CTGCTACTCT GGCTCCCAGA TACCACCGGA 60
GAAATTGTGT TGACGCAGTC TCCAGGCACC CTGTCTTTGT CTCCAGGGGA AAGAGCCACC 120
CTCTCCTACA GGGCCAGTCA GAGTGTTAGC AGCAGCTACT TAGCCTGGTA CCAGCAGAAA 180
CCTGGCCAGG CTCCCAGGCT CCTCATCTAT GGTGCATCCA ACAGGGCCAC TGGCATCCCA 240
GACAGGTTCA GTGGCAGTGG GTCTGGGACA GACTTCACTC TCACCATCAG CAGACTGGAG 300
CCTGAAGATT TTGCAGTGTA TTACTGTCAG CAGTATGGTA GCTCACCGTG GACGTTCGGC 360
CAAGGGACCA AGGTGGAAAT CAAA 420

[0404] Nucleotide sequence of cDNA of E13 heavy chain variable region (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:42):

ATGGAGTTTG GGCTGAGCTG GATTTTCCTT GCTGCGATTT TAAAAGGTGT CCAGTGTGAG
60
GTGCAGCTGG TGGAGTCTGG GGGAGGCCTG GTAAAGCCTG GGGGGTCCCT TAGACTCTCC
120
TGTGCAGCCT CTGGATTCAC TCTCAGTAAC GCCTGGATGA GCTGGGTCCG CCAGGCTCCA
180
GGGAAGGGGC TGGAGTGGGT TGGCCGTATT AAAAGCAAAA TAGATGGTGG GACAACAGAC
240
TACGCTGCAC CCGTGAAAGG CAGATTCACC ATCTCAAGAG ATGATTCAAA AAACACGCTG
300
TTTCTGCAAA TGAACAGCCT GAAAACCGAG GACACAGCCG TGTATTACTG TACCACAGCA
360
ATGGCTGGTG CGTTTGGCTT TTGGGGCCAG GGAACCCTGG TCACCGTCTC CTCA 420

[0405] Nucleotide sequence of cDNA of E13 kappa light chain variable region (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:47):

```
ATGGAAACCC CAGCGCAGCT TCTCTTCCTC CTGCTACTCT GGCTCCCAGA TACCACCGGA    60
GAAATTGTGT TGACGCAGTC TCCAGGCACC CTGTCTTTGT CTCCAGGGGA AAGAGCCACC   120
CTCTCCTGCA GGGCCAGTCA GAGTGTTAGC AGCAGCTACT TAGCCTGGTA CCAGCAGAAA   180
CCTGGCCAGG CTCCCAGGCT CCTCATCTAT GGTGCATCCA GCAGGGCCAC TGGCATCCCA   240
GACAGGTTCA GTGGCAGTGG GTCTGGGACA GACTTCACTC TCACCATCAG CAGACTGGAG   300
CCTGAAGATT TTGCAGTGTA TTACTGTCAG CAGTATGGTA GCTCACCCAT GTACACTTTT   360
GGCCAGGGGA CCAAGCTGGA GATCAAACGA                                    420
```

[0406] Nucleotide sequence of cDNA of F19 heavy chain variable region (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:44):

```
ATGAAACACC TGTGGTTCTT CCTCCTCCTG GTGGCAGCTC CCAGATGGGT CCTGTCCCAG    60
GTGCAGCTAC AGCAGTGGGG CGCAGGACTG TTGAAGCCTT CGGAGACCCT GTCCCTCACC   120
TGCGCTGTCT ATGGTGGGTC CTTCAGTGGT TACAACTGGC ACTGGATCCG CCAGCCCCCA   180
GGGAAGGGGC TGGAGTGGAT TGGGGAAATC ACTCATAGTG GAAGCACCAA TTACAACCCG   240
TCCCTCAAGA GTCGAGTCAC CATATCAGTA GACACGTCCA AGAACCAGTT CTCCCTGAAG   300
CTGAGCTCTG TGACCGCCGC GGACACGGCT GTGTATTACT GTGTGCGAGA GATTGCAGTG   360
GCTGGTACGG GCTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT CACCGTCTCC   420
TCA                                                                480
```

[0407] Nucleotide sequence of cDNA of F19 kappa light chain variable region #1 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:104):

```
ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTAC TGCTCTGGGT CCCAGGTGCC    60
AGATGTGACA TCCAGTTGAC CCAGTCTCCA TCCTCCCTGT CTGCATCTGT AGGAGACAGA   120
GTCACCATCA CTTGCCGGGT GAGTCAGGGC ATTAGCAGTT ATTTAAATTG GTATCGGCAG   180
AAACCAGGGA AAGTTCCTAA GCTCCTGATC TATAGTGCAT CCAATTTGCA ATCTGGAGTC   240
CCATCTCGGT TCAGTGGCAG TGGATCTGGG ACAGATTTCA CTCTCACTAT CAGCAGCCTG   300
CAGCCTGAAG ATGTTGCAAC TTATTACGGT CAACGGACTT ACAATGCCCC TCCCACTTTC   360
GGCGGAGGGA CCAAGGTGGA GATCAAA                                       420
```

[0408] Nucleotide sequence of cDNA of F19 kappa light chain variable region #2 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:49):

```
ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTTCTGC TGCTCTGGCT CCCAGGTGCC    60
AGATGTGCCA TCCAGTTGAC CCAGTCTCCA TCCTCCCTGT CTGCATCTGT AGGAGACAGA   120
GTCACCATCA CTTGCCGGGC AAGTCAGGGC ATTAACAGTG CTTTTGCCTG GTATCAGCAG   180
AAACCAGGGA AAGCTCCTAA GCTCCTGATC TATGATGCCT CCAGTTTGGA AAGTGGGGTC   240
CCATCAAGGT TCAGCGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG   300
CAGCCTGAAG ATTTTGCAAC TTATTACTGT CAACAGTTTA ATAGTTACCC TCTCACTTTC   360
GGCGGAGGGA CCAAGGTGGA GATCAAA                                       420
```

[0409] Nucleotide sequence of cDNA of F19 kappa chain variable region #3 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:105):

```
ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTCCTGC TGCTCTGGCT CCCAGGTGCC    60
AGATGTGTCA TCTGGATGAC CCAGTCTCCA TCCTTACTCT CTGCATCTAC AGGAGACAGA   120
```

```
GTCACCATCA GTTGTCGGAT GAGTCAGGGC ATTAGCAGTT ATTTAGCCTG GTATCAGCAA   180
AAACCAGGGA AAGCCCCTGA GCTCCTGATC TATGCTGCAT CCACTTTGCA AAGTGGGGTC   240
CCATCAAGGT TCAGTGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCTGCCTG   300
CAGTCTGAAG ATTTTGCAAC TTATTACTGT CAACAGTATT ATAGTTTCCC GTACACTTTT   360
GGCCAGGGGA CCAAGCTGGA GATCAAA                                       420
```

[0410] Nucleotide sequence of cDNA of F19 kappa chain variable region #4 (from initiation codon (ATG) to the end of variable region) (SEQ ID NO:106):

```
ATGGAAGCCC CAGCGCAGCT TCTCTTCCTC CTGCTACTCT GGCTCCCAGA TACCACCGGA    60
GAAATTGTGT TGACACAGTC TCCAGCCACC CTGTCTTTGT CTCCAGGGGA AAGAGCCACC   120
CTCTCCTGCA GGGCCAGTCA GGGTGTTAGC AGCTACTTAG CCTGGTACCA GCAGAAACCT   180
GGCCAGGCTC CCAGGCTCCT CATCTATGAT GCATCCAACA GGGCCACTGG CATCCCAGCC   240
AGGTTCAGTG GCAGTGGGCC TGGGACAGAC TTCACTCTCA CCATCAGCAG CCTAGAGCCT   300
GAAGATTTTG CAGTTTATTA CTGTCAGCAG CGTAGCAACT GGCATCCCGT TCGGCCAAGG   360
GACCAAGGTG GAGATTCAAA                                               420
```

[0411] Amino acid sequence of E63 heavy chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:3):

```
MKHLWFFLLL VAAPRWVLSQ VQLQESGPGL VKPSETLSLT CIVSGGSVSS GGYYWSWIRQ    60
PPGKGLEWIG YIYYSGSTNY NPSLKSRVTI SVDTSKNQFS LKLSSVTAAD TAVYYCARWI   120
TMFRGVGFDP WGQGTLVTVS S                                             180
```

[0412] Amino acid sequence of E63 kappa light chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:8):

```
MSPSQLIGFL LLWVPASRGE IVLTQSPDFQ SVTPKEKVTI TCRASQSIGS SLHWYQQKPD    60
QSPKLLIKYA SQSFSGVPSR FSGSGSGTDF TLTINSLEAE DAAAYYCHQS SSLPLTFGGG   120
TKVEIK                                                              180
```

[0413] Amino acid sequence of F23 heavy chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:5):

```
MDLLHKNMKH LWFFLLLVAA PRWVLSQVQL QQWGAGLLKP SETLSLTCAV YGGSFSGYYW    60
NWIRQPPGKG LEWIGEINQY NPSLKSRVTI SVDTSKNQFS LKLSSVTAAD TAVYYCAREI   120
ATADKGYYGL DVWGQGTTVT VSS                                           180
```

[0414] Amino acid sequence of F23 kappa light chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:10):

```
MDMRVPAQLL GLLLLWLPGA RCAIQLTQSP SSLSASVGDR VTITCRASQG ISSALAWYQQ    60
KPGKAPKLLI YDASSLESGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC QQFNSYPLTF   120
GGGTKVEIK                                                           180
```

[0415] Amino acid sequence of E1 heavy chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:1):

```
MELGLCWVFL VAILEGVQCE VQLVESGGGL VQPGGSLRLS CAASGFTFSR FNMNWVRQAP    60
GKGLEWVSYI SSSSYTIYYA DSVKGRFTIS RDNAKNSLDL QMNSLRDEDT AVYYCARSIA   120
```

AAFDYWGQGA LVTVSS 180

[0416] Amino acid sequence of E1 kappa light chain variable region #1 (E1kappa(A)) (leader sequence (bold) and variable region) (SEQ ID NO:82):

MDMRVPAQLL GLLLLWLPGA RCAIQLTQSP SSLSASVGDR VTITCRASQG ISSALAWYQQ 60
KPGKAPKLLI YDASSLESGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC QQFNSYRTLL 120
ARGPSWRS 180

[0417] Amino acid sequence of cDNA of E1 kappa light chain variable region #2 (E1kappa(B)) (leader sequence (bold) and variable region) (SEQ ID NO:6):

METPAQLLFL LLLWLPDTTG EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLTWYQQK 60
PGQAPRLLIY GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSMYTFG 120
QGTKLEIK 180

[0418] Amino acid sequence of cDNA of E1 kappa light chain variable region #3 (E1kappa(C)) (leader sequence (bold) and variable region) (SEQ ID NO:83):

METPAQLLFL LLLWLPDTTG EIVLTQSPGT LSLSPGERAT LSYRASQSVS SSYLAWYQQK 60
PGQAPRLLIY GASNRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG 120
QGTKVEIK 180

[0419] Amino acid sequence of E13 heavy chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:2):

MEFGLSWIFL AAILKGVQCE VQLVESGGGL VKPGGSLRLS CAASGFTLSN AWMSWVRQAP 60
GKGLEWVGRI KSKIDGGTTD YAAPVKGRFT ISRDDSKNTL FLQMNSLKTE DTAVYYCTTA 120
MAGAFGFWGQ GTLVTVSS 180

[0420] Amino acid sequence of E13 kappa light chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:7):

METPAQLLFL LLLWLPDTTG EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK 60
PGQAPRLLIY GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPMYTF 120
GQGTKLEIKR 180

[0421] Amino acid sequence of F19 heavy chain variable region (leader sequence (bold) and variable region) (SEQ ID NO:4):

MKHLWFFLLL VAAPRWVLSQ VQLQQWGAGL LKPSETLSLT CAVYGGSFSG YNWHWIRQPP 60
GKGLEWIGEI THSGSTNYNP SLKSRVTISV DTSKNQFSLK LSSVTAADTA VYYCVREIAV 120
AGTGYYGMDV WGQGTTVTVS S 180

[0422] Amino acid sequence of cDNA of F19 kappa light chain variable region #1 (F19kappa(A)) (leader sequence (bold) and variable region) (SEQ ID NO:90):

MDMRVPAQLL GLLLLWVPGA RCDIQLTQSP SSLSASVGDR VTITCRVSQG ISSYLNWYRQ 60
KPGKVPKLLI YSASNLQSGV PSRFSGSGSG TDFTLTISSL QPEDVATYYG QRTYNAPPTF 120
GGGTKVEIK 180

[0423] Amino acid sequence of cDNA of F19 kappa light chain variable region #2 (F19kappa(B)) (leader sequence (bold) and variable region) (SEQ ID NO:9):

MDMRVPAQLL GLLLLWLPGA RCAIQLTQSP SSLSASVGDR VTITCRASQG INSAFAWYQQ 60
KPGKAPKLLI YDASSLESGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC QQFNSYPLTF 120
GGGTKVEIK 180

[0424] Amino acid sequence of cDNA of F19 kappa light chain variable region #3 (F19kappa(C)) (leader sequence (bold) and variable region) (SEQ ID NO:91):

MDMRVPAQLL GLLLLWLPGA RCVIWMTQSP SLLSASTGDR VTISCRMSQG ISSYLAWYQQ 60
KPGKAPELLI YAASTLQSGV PSRFSGSGSG TDFTLTISCL QSEDFATYYC QQYYSFPYTF 120
GQGTKLEIK 180

[0425] Amino acid sequence of cDNA of F19 kappa light chain variable region #4 (F19kappa(D)) (leader sequence (bold) and variable region) (SEQ ID NO:92):

MEAPAQLLFL LLLWLPDTTG EIVLTQSPAT LSLSPGERAT LSCRASQGVS SYLAWYQQKP 60
GQAPRLLIYD ASNRATGIPA RFSGSGPGTD FTLTISSLEP EDFAVYYCQQ RSNWHPVRPR 120
DQGGDS 180

Table 2: Synthesized DNA primers

SEQ ID NO:	Name	Sequence 5' to 3'	Length
55	RACEUPS5'	CTAATACGACTCACTATAGGGC	22-mer
56	IgG1p	TCTTGTCCACCTTGGTGTTGCTGGGCTTGTG	31-mer
57	HK5	AGGCACACAACAGAGGCAGTTCCAGATTTC	30-mer
58	M13F	GTAAAACGACGGCCAGTG	18-mer
59	M13R	CAGGAAACAGCTATGAC	17-mer
60	E63HF85	AGAGAGAGAGGTCGACCACCATGAAACACCTGTGGTTCTTC	41-mer
61	E63HR38	GAGAGAGAGAGCTAGCTGAGGAGACGGTGACCAGGGT	37-mer
62	E63LF84	AGAGAGAGAGATCTCTCACCATGTCGCCATCACAACTCATTG	42-mer
63	E63LR43	AGAGAGAGAGCGTACGTTTGATCTCCACCTTGGTCCCTCC	40-mer
64	HH-2	GCTGGAGGGCACGGTCACCACGCTG	25-mer
65	HK-2	GTTGAAGCTCTTTGTGACGGGCGAGC	26-mer
66	F23HF86	AGAGAGAGAGGTCGACCACCATGGACCTCCTGCACAAGAAC	41-mer
67	F23HR55	AGAGAGAGAGGCTAGCTGAGGAGACGGTGACCGT	34-mer
68	F23LF36	AGAGAGAGAGATCTCTCACCATGGACATGAGGGTCCCCGCTC	42-mer
69	F23LR43	AGAGAGAGAGCGTACGTTTGATCTCCACCTTGGTCCCTCC	40-mer
70	E1HFSalI	AGAGAGAGAGGTCGACCACCATGGAGTTGGGGCTGTGCTGG	41-mer

71	E1HRNheI	AGAGAGAGAGGCTAGCTGAGGAGACGGTGACCAGGGC	37-mer
72	F19HFSalI	AGAGAGAGAGGTCGACCACCATGAAACACCTGTGGTTCTTC	41-mer
73	F19HRNheI	AGAGAGAGAGGCTAGCTGAGGAGACGGTGACCGTGGT	37-mer
74	E1KF2+3BglII	AGAGAGAGAGATCTCTCACCATGGAAACCCCAGCGCAGCTTC	42-mer
75	E1KR2BsiWI	AGAGAGAGAGCGTACGTTTGATCTCCAGCTTGGTCCCCTG	40-mer
76	E1KR3BsiWI	AGAGAGAGAGCGTACGTTTGATTTCCACCTTGGTCCCTTG	40-mer
77	F19KR1+2BsiWI	AGAGAGAGAGCGTACGTTTGATCTCCACCTTGGTCCCTCC	40-mer
78	F19KR3BsiWI	AGAGAGAGAGCGTACGTTTGATCTCCAGCTTGGTCCCCTG	40-mer
79	F19KF1+2+3BglII	AGAGAGAGAGATCTCTCACCATGGACATGAGGGTCCCCGCTC	42-mer

[0426] The KM mouse™ is described in, *e.g.*, Fishwild *et al.* 1996, Nat. Biotechnol. 14:845-51; Lonberg *et al.* 2005 Nat. Biotechnol. 9:1117-1125; Tomizuka *et al.* 2000 Proc. Natl. Acad. Sci. USA 97:722-7; Tomizuka 1997 Nat Genet. 16:133-43, each of which is incorporated herein by reference in its entirety. Due to the nature of the KM mouse™ (*e.g.*, more than one kappa chain gene was integrated into the murine genome upon generation of the kappa transgenic strain) it is possible to have more than one kappa light chain cDNA expressed from a clonal hybridoma. To determine if this is the case, a minimum of ten cDNA clones are sequenced. In cases where more than one kappa light chain antibody cDNA is isolated (*e.g.*, E1 and F19), several constructs are generated containing the various pairs of heavy chain cDNA combined with each kappa cDNA. These expression constructs are transfected into 293F cells using 293FECTIN (Invitrogen, San Diego, CA). Seventy-two hour culture supernatants are then tested for antibody activity to identify the correct heavy and light chain pair(s) that immunospecifically binds to hLIGHT (*e.g.*, by Western blot, ELISA or other similar method). Please refer to Example 3 below for an exemplary method of characterizing antibodies (*e.g.*, E1 and F19) having with multiple kappa chains.

[0427] Production of recombinant human anti-hLIGHT antibody from 293F cells: Suspension cultures of 293F cells were maintained in Freestyle 293 expression medium while shaking at ~120 rpm/min in an 8% CO_2 humidified incubator at 37 °C. For transient expression of recombinant antibodies, 3 x10^7 293F cells were transfected with 30 μg of each plasmid encoding the recombinant IgG1 versions of either the E63 or F23 anti-hLIGHT antibodies using 293-fectin (Invitrogen, Carlsbad, CA) following manufacturer's instructions. Transfectants were allowed to grow in suspension in 30 mls of FREESTYLE 293 expression medium for 5 days under normal growth

conditions. Growth medium was harvested and cells removed by centrifugation at a speed of 300 g followed by filtration through a 0.22 μm filter. The antibody concentration present in this unpurified material is determined by hIgG ELISA and used for *in vitro* assays to assess the functional properties of the subclass switched antibodies.

RESULTS

[0428] KM mice™ were immunized with soluble recombinant FLAG-tagged hLIGHT in CFA/IFA. Several of the mice raised anti-hLIGHT specific antibodies, with a range in human IgG hLIGHT specific titers measured by ELISA and FACS analysis staining of hLIGHT-EL4 cells. Splenocytes from the highest responders were fused with myeloma cells to generate human anti-hLIGHT producing hybridomas. The production of anti-hLIGHT antibodies by the individual hybridomas was determined in the primary screen by anti-hLIGHT ELISA. In this screen the anti-FLAG antibody was coated on the plate to capture FLAG-tagged recombinant hLIGHT in a successful effort to mask the FLAG epitope and prevent isolation of anti-FLAG antibody producing hybridomas. Media from ELISA positive clones was used in a secondary screen by flow cytometry staining the hLIGHT-EL4 cell line to confirm the identification of antibodies that immunospecifically bind to the native form of hLIGHT.

[0429] The positive hybridomas were tested for antagonistic activity by ranking the capacity of the antibodies produced by the hybridoma to block HVEM:Fc and LTβR:Fc binding to hLIGHT-EL4 cells. This blocking activity was normalized to antibody concentration determined by human IgG ELISA. The top 15 candidates were cloned by limiting dilution to yield monoclonal hybridomas, while the rest were frozen. Small scale purifications were produced from extinction cultures (<1 mg) for these 15 antibodies for further characterization and ranking based on the following criteria: relative binding affinity for hLIGHT, the ability to block human HVEM:Fc and LTβR:Fc binding to hLIGHT-EL4 cells, cross-blocking each other, and the ability to block soluble and cell surface-expressed hLIGHT-mediated chemokine secretion from the colonic epithelial cell line HT29.14s. Based on these studies, properties of the top 5 selected candidates (E1, E13, E63, F23 and F19) are presented in FIG. 3.

[0430] E1, E13, E63, F23 and F19 anti-hLIGHT monoclonal antibodies each bound specifically to the activated human T cell line (II23.D7) and the stable hLIGHT expressing cell line hLIGHT-EL4, but not to parental EL4 or resting II23.D7 cells (FIG. 1A). The binding of these human anti-hLIGHT antibodies reached saturation (FIG. 1B).

The functional steady-state binding affinity of each antibody was determined by titrating the amount of antibody needed to label hLIGHT-EL4 cells (FIGS. 2A and 2B). Non-linear regression analysis was performed to determine the functional binding affinity measurement or EC50 for each candidate (FIG. 3). A range of functional affinities was observed. A low EC50 as well as a high level of staining (mean fluorescence intensity (MFI)) at saturation were both considered ideal during the ranking and selection process.

[0431] The antibodies were tested by ELISA to determine if they compete with one another for binding to soluble hLIGHT (FIG. 4). Two hLIGHT epitope groups were identified in this analysis. The "E antibodies" (E1, E13, and E63) crossblock each another, and the "F antibodies" (F19 and F23) cross-block each other. However, the "E antibodies" were not able to cross-block the "F antibodies" and *vice versa*. As expected, all antibodies blocked themselves in this assay.

[0432] The ability of E1, E13, E63, F23 and F19 to block the human HVEM:Fc and LTβR:Fc fusion proteins to cell surface expressed hLIGHT using a flow cytometric based assays is shown in FIGS. 5A and 5B, and FIGS. 6A and 6B respectively. In these experiments, graded amounts of each antibody were added to the EL4-hLIGHT cell line followed by the addition of a sub-saturating amount of the receptor fusion protein. The receptor fusion proteins were detected by either anti-His antibodies for His-tagged LTβR:Fc or streptavidin-PE for biotinylated HVEM:Fc. As shown, each of the antibodies blocked either receptor fusion protein from binding hLIGHT, in contrast to the fully human anti-influenza M2 antibody control which had no effect on either Fc-receptor binding. In each experiment, all antibodies blocked receptor binding in a dose dependent manner enabling analysis by non-linear regression to determine the IC_{50} dose (FIG. 3). These values were taken into consideration when ranking the potential candidates.

[0433] To directly prove the antagonistic antibodies of the invention block hLIGHT-mediated signaling, an assay to measure hLIGHT-mediated signaling *in vitro* was established. For this purpose, the colonic epithelial cell line HT29.14s, which expresses both LTβR and HVEM, was treated with graded amounts of soluble hLIGHT and growth media was analyzed for the presence of secreted cytokines over a several day time-course. Using standard ELISAs and suspension array multiplex analysis, it was determined that hLIGHT induces CCL20, IL-8 and RANTES in a dose dependent manner (FIG. 7 and FIGS. 8A and 8B). FIG. 7 represents a dose titration of soluble

hLIGHT harvested at day 3. Recombinant TNF was used as a positive control for chemokine induction through the TNF receptors, while lymphotoxin ($LT\alpha_1\beta_2$) was used as a positive control for signaling through the LTβR. FLAG tagged bacterial alkaline phosphatase (FLAG-BAP) was used as a tagged irrelevant protein negative control. As expected, levels of chemokines produced by contacting the cells with hLIGHT were equivalent to those induced by LTαβ , whereas TNF was more effective at inducing CCL20 and IL-8, but induced similar levels of RANTES. This cellular response assay is used to measure hLIGHT signaling and assess the capacity of antibodies of the invention to block hLIGHT-mediated signaling events *in vitro*.

[0434] In the hLIGHT-mediated HT29.14s CCL20 induction assay, graded amounts of the anti-hLIGHT antibodies were pre-incubated with a constant amount of recombinant soluble hLIGHT, then added to HT29.14s cells (FIG. 9). Chemokine levels were assayed on day 3 or 4 post treatment and compared to levels induced by soluble hLIGHT alone or soluble hLIGHT pre-incubated with an irrelevant fully human anti-influenza M2 protein as an isotype control. In these assays, the antibodies of the invention tested herein blocked soluble hLIGHT-mediated CCL20 induction in a dose dependent manner. In some cases, non-linear regression analysis was able to produce IC50 values.

[0435] Without wishing to be bound by any particular mechanism or theory, it is believed that signaling initiated by cell surface hLIGHT binding to its cognate receptors on other cells may be critical for exerting observed T cell co-stimulatory activity through HVEM interactions or increased chemokine production through LTβR expressed on cells of stromal or epithelial origin in the gut, spleen or lymph nodes. Induction of CCL20 in the gut seems to be regulated more by the expression of LTβR ligands on cells that come in contact with epithelial cells than by soluble factors (Rumbo *et al.* 2004 Gastroenterology 127 213-23). Therefore, a cell surface hLIGHT signaling assay was developed to assess our antibodies ability to block cell surface hLIGHT. In this assay formalin fixed hLIGHT-EL4 cells were used to induce chemokines by incubating them with HT29.14s cells in a similar fashion to the soluble hLIGHT assay. These cells induced CCL20 and RANTES to equivalent levels as soluble hLIGHT. When graded amounts of anti-hLIGHT antibodies were pre-incubated with fixed hLIGHT-EL4 cells, the induction of RANTES was blocked to levels observed when no hLIGHT expressing cells were added (FIG. 10). In identical experiments CCL20 was likewise inhibited.

Taken together, these data indicate that the antibodies of the invention can block both soluble and membrane bound hLIGHT signaling *in vitro*.

EXAMPLE 2– CHARACTERIZATION OF COMMERCIALLY AVAILABLE MOUSE ANTI-HUMAN MONOCLONAL ANTIBODIES

[0436] Antibody cross-blocking. Cross-blocking experiments were conducted as described in Example 1 using mouse anti-hLIGHT monoclonal antibodies available from R&D Systems ("R&D mouse mAb") and Abnova ("Abnova mouse mAb"), as well as the human anti-hLIGHT monoclonal antibodies identified in Example 1, to assess which hLIGHT epitope that the antibodies bind. Results are presented in FIG. 11.

[0437] The results show that the R&D mouse mAb binds to the same epitope as the human E1, E13, and E63 monoclonal antibodies ("human E antibodies"), as well as the same epitope as the human F19 and F23 monoclonal antibodies ("human F antibodies"). Thus, in contrast to the human anti-hLIGHT E & F monoclonal antibodies identified in Example 1, which were found to immunospecifically bind to only one of two distinct epitopes, the R&D mouse mAb binds to both hLIGHT epitope groups. That is, the human E antibodies and the human F antibodies identified in Example 1 did not cross-block each other. Human E antibodies cross-blocked other human E antibodies, and human F antibodies cross-blocked other human F antibodies; whereas the human E antibodies and human F antibodies all were able to cross-block the R&D mouse mAb. Similarly, the R&D mouse mAb cross-blocked the human E antibodies as well as the human F antibodies.

[0438] The results also show that the Abnova mouse mAb does not bind either epitope that is bound by the human E antibodies and the human F antibodies. That is, the Abnova mouse mAb was not cross-blocked by any of human E1, E13, E63, F19 or F23 antibodies, nor was the Abnova mouse mAb able to cross-block any of the human E1, E13, E63, F19 or F23 antibodies.

[0439] Blocking activity of antibodies for HVEM:Fc binding to 293 hLIGHT cells. E1, E13 and F19 human anti-hLIGHT monoclonal antibodies, the R&D mouse mAb, commercially available goat anti-hLIGHT polyclonal antibodies (R&D Systems), and rabbit anti-hLIGHT polyclonal antibodies (eBioscience) were tested for their ability to block binding of HVEM:Fc to 293 cells expressing hLIGHT as described in Example 1. The results are shown in FIG. 12 and FIG. 14B. All four monoclonal antibodies were able to inhibit binding in a dose-dependent manner, as determined by FACS analysis.

The R&D goat polyclonal antibodies were also able to inhibit binding of the HVEM:Fc, whereas the eBioscience rabbit polyclonal antibody was not.

[0440] Blocking activity of antibodies for LTβR:Fc binding to 293 hLIGHT cells. E1 and E13 human anti-hLIGHT monoclonal antibodies, the R&D mouse mAb, commercially available goat anti-hLIGHT polyclonal antibodies (R&D Systems), and rabbit anti-hLIGHT polyclonal antibodies (eBioscience) were tested for their ability to block binding of LTβR:Fc to 293 cells expressing hLIGHT as described in Example 1. The results are shown in FIG. 13 and FIG. 14B. All four monoclonal antibodies were able to inhibit binding in a dose dependent manner, as determined by FACS analysis. The R&D goat polyclonal antibodies were also able to inhibit binding of the LTβR:Fc, whereas the rabbit eBioscience polyclonal antibody was not.

[0441] Binding to native and denatured hLIGHT. Five micrograms of soluble human LIGHT was either boiled in 2 x SDS sample buffer (denatured) or untreated (native), and then both were serially diluted in 6x increments. 5 µl of each hLIGHT dilution was spotted simultaneously onto hydrated 0.2 µm PVDF membranes (Invitrogen, Carlsbad, CA) using an 8 multi-channel pipette. The blots were allowed to air dry then re-hydrated, blocked (1 x TBST (Tris-buffered saline Tween-20) +2.5% skim milk + 0.02% sodium azide). Each blot was probed with 5 µg/ml of each primary antibody (see below). The blots were washed 3x in 1x TBST followed by biotinylated secondary Abs (Biotin-Goat αHuman (Vector Labs, Burlingame, CA), Biotin-Goat α mouse (Jackson labs, Bar Harbor, ME), Biotin-Mouse α goat (Sigma-Aldrich corp., St. Louis, MO)) at 5 µg/ml. The blots were washed 3x in 1x TBST followed by super SA-HRP (Amersham Biosciences, Piscataway, NJ). Chemiluminescence was used for detection using the ECL detection kit (Amersham Biosciences, Piscataway, NJ) and signal was visualized by exposure to X-OMAT AR imaging film (Kodak, Rochester, New York)

[0442] The primary antibodies tested were the E1, E13, E63, F19, F23 human anti-hLIGHT mAb (see Example 1), murine anti-hLIGHT monoclonal antibodies commercially available from R&D Systems ("R&D mouse mAb") and Abnova ("Abnova mouse mAb"), a goat anti-hLIGHT polyclonal antibody preparation (R&D Systems "R&D goat pAb") and two rabbit anti-hLIGHT polyclonal antibody preparations (eBioscience ("eBioscience rabbit pAb") and Peprotech ("Peprotech rabbit pAb")).

[0443] The results are shown in FIG. 15 and FIG. 16. The human anti-hLIGHT monoclonal "E antibodies" of the invention (E1, E13 and E63) tested in this assay immunospecifically bind to both native and denatured forms of soluble hLIGHT (FIG. 15A and FIG. 16). Antibody E63 immunospecifically binds to lower concentrations of native hLIGHT (lowest limit of detection is 3.9 ng native hLIGHT) than denatured hLIGHT (lowest limit of detection is 139 ng denatured hLIGHT). Antibody E1 also immunospecifically binds to lower concentrations of native hLIGHT (lowest limit of detection is 23 ng native hLIGHT) as compared to denatured hLIGHT (lowest limit of detection is 139 ng denatured hLIGHT). Antibody E13 immunospecifically binds to both native and denatured forms of hLIGHT with the lowest limit of detection of 0.64 ng for both forms of hLIGHT.

[0444] In contrast to the human anti-hLIGHT monoclonal"E antibodies," the human anti-hLIGHT monoclonal "F antibodies" of the invention (F19 and F23) tested in this assay immunospecifically bind to the native form of soluble hLIGHT (lowest limit of detection is 23 ng native hLIGHT), but not the denatured form, even at highest (>5000 ng) concentrations of denatured hLIGHT (FIG. 15A and FIG. 16).

[0445] Each of the commercially available mouse anti-hLIGHT monoclonal antibodies (R&D mouse mAb and Abnova mouse mAb) tested in this assay immunospecifically bind to both the native and denatured forms of soluble hLIGHT. The R&D mouse mAb immunospecifically binds to lower concentrations of native hLIGHT (lowest limit of detection is 23 ng native hLIGHT) as compared to denatured hLIGHT (lowest limit of detection is 139 ng denatured hLIGHT). The Abnova mouse mAb immunospecifically binds to about equal concentrations of both the native and denatured forms of soluble hLIGHT (lowest limit of detection is 0.64 ng native or denatured hLIGHT, respectively).

[0446] The three commercially available anti-hLIGHT polyclonal antibody preparations (R&D goat pAb, eBioscience rabbit pAb, and Peprotech rabbit pAb) each bound to both native and denatured forms of soluble hLIGHT. The R&D goat pAb immunospecifically binds to slightly lower concentrations of native hLIGHT (lowest limit of detection is 0.04 ng native hLIGHT) as compared to denatured hLIGHT (lowest limit of detection is 0.13 ng denatured hLIGHT). The eBioscience rabbit pAb also immunospecifically binds to slightly lower concentrations of native hLIGHT (lowest limit of detection is 0.4 ng native hLIGHT) as compared to denatured hLIGHT (lowest limit of detection is 1.2 ng denatured hLIGHT). Similarly, the Peprotech rabbit pAb

also immunospecifically binds to slightly lower concentrations of native hLIGHT (lowest limit of detection is 0.04 ng native hLIGHT) as compared to denatured hLIGHT (lowest limit of detection is 0.13 ng denatured hLIGHT).

[0447] Inhibition of biological activity of cells expressing a hLIGHT receptor. Experiments were also undertaken as described in Example 1 to determine whether the commercially available mouse anti-hLIGHT monoclonal antibodies were able to competitively block soluble hLIGHT from binding to cell surface-expressed LTßR and HVEM on HT29.14s cells. The results are presented in FIG. 17 (CCL20) and FIG. 18 (RANTES), and show that neither the R&D mouse mAb nor the Abnova mouse mAb was able to inhibit LIGHT-mediated CCL20 or RANTES chemokine production by these cells, whereas human E13 and human F23 mAbs were able to reduce chemokine secretion to background levels.

EXAMPLE 3 – CHARACTERIZATION OF KAPPA CHAINS OF F19 AND E1 HUMAN ANTI-hLIGHT ANTIBODIES

[0448] The procedures discussed in Example 1 were used to find a preferred kappa chain—heavy chain pair of the antibodies produced by the E1 and F19 hybridomas. Based on the results of these experiments, it was shown that E1kappa(B) (SEQ NO:6) is the preferred kappa light chain of the hLIGHT antibodies produced by the E1 hybridoma, and F19kappa(B) (SEQ ID NO: 9) is the preferred kappa light chain of the hLIGHT antibodies produced by the F19 hybridoma.

[0449] Recombinant single kappa chain antibodies were generated by transient transfection of mammalian expression vectors containing the heavy chain genes paired with each of the individual kappa chain genes that existed in the parental hybridoma cells. This material was then tested in parallel with the purified antibodies generated from the respective parental hybridomas.

[0450] Antibody binding assays were performed as described in Example 1. The kappa chain—heavy chain pair comprising the E1kappa(B) or F19kappa(B) specifically stained hLIGHT stably transfected cell lines, (HEK 293-hLIGHT) to an equivalent degree compared to the respective parental hybridoma produced antibodies (FIG. 19).

[0100] Cross-blocking ELISA experiments were performed as indicated in Example 1, and the results indicated that these recombinant antibodies recognize the same epitopes on hLIGHT as their parental hybridoma Abs (Figure 20).

[0452] The single kappa chain recombinant antibodies were further tested as described in Example 1 for their ability to block cell surface-expressed hLIGHT binding to soluble receptor-Fc fusion forms of both human HVEM and the LTβR (FIG. 21), Levels of blockade were not identical to the parental Abs.

[0453] Finally, the recombinant single kappa antibodies were tested for their ability to inhibit LIGHT-mediated CCL20 secretion from HT29 colonic epithelial cells as described in Examples 1 and 2 (FIG. 22 and FIG. 23). In these experiments, incubation of soluble hLIGHT with anti-hLIGHT antibodies blocks hLIGHT-mediated secretion of CCL20 from HT29.14s cells similar to the parental hybridomas.

[0454] In addition, the single kappa chain recombinants also maintain the specificity of the parental hybridoma produced antibodies in the dot blot assessment of native vs. denatured LIGHT (data not shown).

[0455] Together, these results indicate that the E1kappa(B) (SEQ ID NO:6) is the preferred kappa light chain for use in combination with the E1 heavy chain (SEQ ID NO:1), and the F19kappa(B) (SEQ ID NO:9) is the preferred kappa light chain for use in combination with the F19 heavy chain (SEQ ID NO:4).

EXAMPLE 4 – ANTIBODY BINDING AND ANTIBODY MEDIATED BLOCKADE OF HVEM:FC AND LTβR:FC BINDING TO SINGLE NUCLEOTIDE POLYMORPHISM (SNP) VARIANTS OF LIGHT

[0456] At least two non-synonymous single nucleotide polymorphism (SNP) variants exist for human LIGHT (FIG. 24). One SNP variant encodes either a glutamic acid (E) or an lysine (K) at amino acid position 214, and the other SNP variant encodes either a serine (S) or a leucine (L) at amino acid position 32. As shown in FIGS. 24A-24B, the allelic frequency of each SNP variant across a variety of ethnic populations varies. Thus, hLIGHT antibodies that bind a given SNP variant may be more efficacious in the treatment or prevention of an hLIGHT-mediated disease, or symptom, thereof in those ethnic populations having a higher incidence of the given SNP variant.

[0457] In this example, hLIGHT antibodies provided herein were shown to bind non-synonymous hLIGHT SNP variants that are present in hLIGHT extracellular and cytoplasmic domains. The binding of these antibodies to SNP variants also correlated with the ability of the antibody to effectively block HVEM:Fc and LTβR:Fc to the

hLIGHT SNP variant, and also effectively block biological activity of cells expressing a hLIGHT receptor.

[0458] Antibody binding. Dose titrations of F23 and E1kappa(B) antibodies were performed as in Example 1 to determine if these antibodies bind cell surface-expressed hLIGHT SNP variants. An EL4 cell line was used in these experiments, which was prepared essentially as described in Example 1, and stably surface-expressed the respective hLIGHT SNP variant. As shown in FIGS 25A and 25C, respectively, each of the F23 and E1kappa(B) antibodies bound both of the 214E-32S and 214E-32L SNP variants. However, as shown in FIG. 25B, only the F23, and not E1kappa(B) antibody, recognized the 214K-32S SNP variant.

[0459] The F23 (an IgG1), F19, E63 and E1kappa(B) antibodies were also tested to determine if there was a difference between the ability of the "F antibodies" and the "E antibodies" to recognize either form of SNP variant. As shown in FIG. 26A and 26B, the F23 and F19 antibodies bind both 214E and 214K SNP forms of hLIGHT. However, the E63 and E1kappa(B) antibodies bind only the predominant form of LIGHT 214E, and not 214K (FIGS. 26A and 26B).

[0460] Blocking activity of antibodies for HVEM:Fc and LTβR:Fc binding to LIGHT SNP variant 214K-32S. Since the F23 antibody bound both the predominant form (214E) and less predominant form (214K) of LIGHT variants, it was next determined whether the F23 antibody could block binding of HVEM:Fc or LTβR:Fc. Antibody-mediated blockade of the receptor fusion proteins was performed as in Example 1. In brief, the cell line EL4-214K-32S was incubated with increasing amounts of anti-LIGHT antibodies followed by the addition of either HVEM:Fc or LTβR:Fc. The effects of this preincubation on receptor binding was assessed by detection of either HVEM:Fc or LTβR:Fc as in Example 1. As shown in FIG. 25D, the F23 antibody effectively blocked both HVEM:Fc and LTβR:Fc binding to the LIGHT 214K-32S variant.

[0461] Inhibition of cell surface LIGHT SNP variant-mediated biological activity of cells expressing a LIGHT receptor. This study was undertaken to determine if human anti-hLIGHT monoclonal antibodies previously shown to bind to both 214K and 214E hLIGHT SNP variants were also able to effecitvely block RANTES secretion in human colonic epithelial cells, HT29.14s, which express both LTβR and HVEM, by either cell-surface expressed hLIGHT 214E or 214K SNP variant, or soluble hLIGHT SNP variants

thereof. In the cell surface expressed LIGHT-mediated HT29.14s RANTES induction assay, graded amounts of anti-hLIGHT antibodies were pre-incubated with a constant number of cells that express SNP variants of hLIGHT (214K or 214E). Chemokine levels were assayed on day 3 post-treatment and compared to levels induced by soluble hLIGHT alone, cells expressing hLIGHT alone or cells pre-incubated with an irrelevant human IgG as an isotype control protein.

[0462] In these assays, the antibodies provided herein (F19 and F23) blocked soluble hLIGHT and both cell surface expressed hLIGHT SNP variant (214E or 214K)-mediated RANTES induction in a dose dependent manner. The commercially available mouse anti-hLIGHT monoclonal antibody available from R&D systems (the R&D mouse mAb, as in Example 1) was not able to block either soluble or cell surface expressed hLIGHT-mediated chemokine secretion, regardless of SNP variant. Both the cell surface-expressed hLIGHT variants and soluble recombinant hLIGHT positive controls induced equivalent levels of RANTES, and pre-incubation of the negative control isotype hIgG with either the cell surface-expressed hLIGHT variants or soluble recombinant hLIGHT did not reduce the RANTES levels significantly.

[0463] Discussion. Of the thirty plus single nucleotide polymorphisms (SNPs) in the hLIGHT genomic locus, at least two non-synonymous hLIGHT exist with frequency data associated with them (FIG. 24). One encodes a glutamic acid (~0.9) or a lysine (0.1) at amino acid position 214 of hLIGHT and resides in the extracellular region of hLIGHT. The other encodes either a serine (0.99) or a leucine (0.011) at amino acid residue 32 and resides in the cytoplasmic region of hLIGHT. The hLIGHT genomic locus resides in a chromosomal region, ch19p13.3, that has contains a susceptibility locus for inflammatory bowel disease (Rioux *et al.* (2000) Am J Hum Genet. 66:1863-70), and thus suggests that a SNP may be a correlate of IBD disease frequency. Therefore, it was of interest to determine if the antagonistic anti-hLIGHT antibodies provided herein were able to recognize non-synonymous SNP variants of hLIGHT.

[0464] In this example, we tested the ability of the anti-hLIGHT antibodies to bind hLIGHT SNP variants stably expressed on the surface of EL4 cell lines. As shown in FIGS 25A and 25B, F23 binds both SNP variants 214E and 214K, while E1kappa(B) binds only the predominant form 214E. F23 likewise blocks either HVEM:Fc or LTBR:Fc binding to these cells (FIG. 25D). As expected, the cytoplasmic SNP does not appear to affect binding of either antibody (FIG. 25C). When "E antibodies" and "F antibodies" were tested, only the F antibodies were able to bind to both 214K and 214E

SNP variants (FIGS. 26A and 26B). The commercial R&D mouse mAb antibody was also able to bind both SNP variants (data not shown).

[0465] In addition to the anti-hLIGHT antibody blockade of soluble versions of the receptors to LIGHT SNP variants *in vitro*, cell surface hLIGHT SNP-mediated chemokine induction was also inhibited by anti-hLIGHT antibodies of this invention. In this assay, EL4 cell lines expressing either 214E or 214K hLIGHT SNP variants were fixed with formalin and used to treat the HT29 colonic epithelial cell line. As shown in FIG. 27, these cell lines alone induced similar levels of RANTES compared to 1 μg soluble LIGHT. Anti-hLIGHT "F antibodies" were tested by pre-incubating the hLIGHT-expressing cell lines with graded amounts of antibody and compared to isotype controls or the commercially available R&D mouse mAb. Both F23 and F19kappa(B) inhibited RANTES secretion mediated by either SNP variant expressing cell line. However, the R&D mouse mAb and the human isotype negative control did not inhibit RANTES secretion by either LIGHT SNP variant. This was despite the fact that the R&D mouse mAb was able to bind both SNP variants. These results not only demonstrate that the F23 and F19kappa(B) antibodies of this invention block either signaling by LIGHT SNP variant, but also display superiority to the commercial R&D mouse mAb.

EXAMPLE 5 – IN VIVO EFFICACY STUDY OF 124F23 IN ACUTE XENOGENEIC GRAFT VERSUS HOST DISEASE MODEL

[0466] In this example, the *in vivo* efficacy of an anti-hLIGHT antibody provided herein was evaluated in a murine acute xenogeneic graft-versus-host disease model (GVHD). The F23 antibody was shown in this model to decrease overall gross pathology (diarrhea, peritoneal inflammation and ascites, and intestinal inflammation) and histopathology (inflammation severity, inflammation extent, villus damage/atrophy, and percent involvement), as well as a decrease in the number of T cells in the spleen.

[0467] Purification of human PBMC from whole blood: Whole blood was collected from healthy donors between the ages of 18 and 50 by the normal blood donor program at Scripps Green Hospital (La Jolla, CA), and heparin was added to prevent clotting. No race, ethnicity, or gender was specified. The blood was diluted in PBS and then underlayed with FICOLL-PLAQUE Plus (Amersham Biosciences). The mononuclear cells were separated from the serum and platelets by centrifugation at 1800 RPM without the brake. The interface containing the PBMC was then collected and washed two times with PBS.

[0468] Acute Graft Versus Host Disease *In Vivo* Model: An acute xenogeneic graft versus host disease model was used to test the therapeutic potential of the F23 (124F23G1) human anti-human LIGHT antibody *in vivo* (Watanabe *et al.* 2006 1006. Clin Immunol. 120 247-59), essentially as outlined in FIG. 28. Briefly, severe combined immunodeficient (SCID) male mice aged 5-10 weeks were injected on day -2 with 20 μg rat anti-mouse IL2 receptor-beta (IL2Rβ) chain antibody (TMβ1, Tanaka *et al.* 1993 J Exp Med. 178 1103) to deplete endogenous murine natural killer cells. The following day (day -1), the mice received 2.5 Gy of sub-lethal irradiation using a cesium source to allow migration of the human cells to the intestinal tract. The next day (day 0) the mice received 10 million total human peripheral blood mononuclear cells in PBS by intraperitoneal injection followed immediately by intravenous injection of human anti-human LIGHT (124F23G1) or negative control hIgG1 (anti-dinitrophenol (anti-DNP), Kirin Brewery Co. Ltd.) antibodies at a dose of 100 μg in 100 μl PBS. The human T cells expand and induce a graft versus host like disease and symptoms thereof, resulting in, for example, weight loss, hematuria, hydroperitoneum, inflammatory cell infiltrates in the liver and intestinal tract, and eventually death. The disease is primarily mediated by human T cells as transfer of T cells alone induces similar symptoms. Body weight was determined every 3–4 days and mice received the anti-IL2Rβ antibody weekly. At day 12 the mice were sacrificed and analyzed for gross pathology and symptoms of disease, the spleens were collected for flow cytometric analysis and cecums for histology, and serum was collected for human cytokine and antibody analysis (Watanabe *et al.* 1006. Clin Immunol. 120 247-59).

[0469] *In vivo* functional analysis of human anti-human LIGHT monoclonal antibodies. The gross pathology observed at day 12 was scored as follows: diarrhea (0 or 1), hemorrhaging in the intestine and peritoneal cavity, and peritonitis (each ranked 0, 1, 2 or 3 as none, mild, moderate, or severe, respectively). The sum of all disease symptoms was used to determine the total gross pathology score. As shown in FIG. 29, mice that received the control antibody or PBMCs alone (no antibody injection) all displayed symptoms of GVHD, with higher pathology scores than mice that received 124F23G1 anti-LIGHT antibody.

[0470] Histopathological analysis was performed on H&E sections of the cecum and scored as follows: inflammation severity, inflammation extent, villus damage/atrophy and percent involvement (each ranked 0, 1, 2 or 3 as none, mild, moderate, or severe, respectively). The final score was a sum of each category, with a maximum score of 12

for each mouse. As shown in FIG. 30, mice that received either the control antibody or PBMCs alone (no antibody injection) had similar histopathology, whereas the mice injected with 124F23G1 had no histological signs of disease. An example of the histology of the cecum observed in the anti-LIGHT treated animals is illustrated in FIG. 31A, which shows a uniform villus structure, sub-mucosa and muscle layer, as well as a lack of ascites or blood. In contrast, histology the cecum from a control antibody treated animal has prominent hallmarks of disease, including sub-mucosa filled with ascites, signs of intestinal bleeding indicated by clusters of erythrocytes and prominent lymphocyte infiltrates (FIG. 31B).

[0471] Analyses of the spleens were in agreement with the gross pathology and histopathology. Human T cells were present in the spleens of mice treated with the control antibodies, but the number of human T cells in 124F23G1 treated animals were significantly lower than the number of T cells in the control animals (FIG. 32).

[0472] In follow-up studies, both T cell depleting (IgG1) and/or non-depleting (IgG4PE) versions of the anti-hLIGHT antibodies can be used to assess the mechanism of disease amelioration, such as whether T cells are being blocked by the antibody or instead undergo apoptosis.

[0473] Discussion: Acute Graft-versus-host disease (GVHD) is a major complication associated with allogeneic hematopoietic stem cell transplantation. GVHD is generally defined as the broad attack against host tissues by donor T cells. Following transplantation, systemic immunosuppression is the current method for preventing GVHD, however this can lead to opportunistic pathogen infections and relapse of leukemia. Therefore, blockade of T cell co-stimulatory signals is one of the more promising alternatives to immunosuppressants. Recent reports indicate that LIGHT-HVEM costimulation of T cells plays a critical pathogenic role in GVHD (Xu *et al.* (2007) 109:4097-4104). Thus, antagonistic anti-LIGHT antibodies may have therapeutic efficacy for GVHD. The *in vivo* efficacy demonstrated in the acute xenogeneic GVHD model demonstrates this potential.

[0474] An acute xenogeneic model of GVHD where human PBMCs are injected into sub-lethally irradiated SCID mice depleted of NK cells (FIG. 28). In this model, irradiation initiates intestinal damage and T cells mediate to the intestinal inflammation of the disease. Animals show severe signs of disease within approximately 12 days post PBMC injection. Disease hallmarks include intestinal inflammation manifested in hemorrhaging, ascites and villus atrophy. In an initial study, treatment of mice with 100

micrograms of anti-LIGHT antibody (124F23G1) reduced the observed gross pathology in the intestine (FIG. 29). Likewise this reduction was corroborated by a more refined analysis by histopathology of the cecum, where anti-LIGHT antibody treatment lead to no detectable disease (FIG. 30). FIG. 31A shows representative H&E stained section of the cecum from an anti-LIGHT treated animal. In contrast, the cecum of a control antibody treated animal displays hallmarks of severe inflammation in the intestine, including red patches of cells indicative of hemorrhaging, the grossly involuted fluid filled sub-mucosa, and lymphocyte infiltrate (FIG, 31B). In this model, the transferred human T cells are primarily responsible for disease induction and splenic T cell numbers tend to correlate with disease severity. Anti-LIGHT antibody treatment significantly reduced total human T cell numbers in the spleen (FIG. 32). Thus, taken together, these data indicate that anti-LIGHT antibodies showed *in vivo* efficacy in this model, significantly reducing signs of disease relative to the negative control.

EXAMPLE 6 – X-RAY CRYSTALLOGRAPHIC ANALYSIS OF A HUMAN LIGHT / ANTI-HUMAN LIGHT ANTIBODY (F23) INTERACTION

[0475] The F23G1 antibody (or Fab fragment thereof) is used to assess the nature of preferential recognition of native trimeric hLIGHT. Structural analysis enables the identification of specific contact amino acid residues between the anti-hLIGHT antibody and the hLIGHT molecule to further define the conformational epitope recognized by the antibody. Crystallization of LIGHT-anti-LIGHT Fab complexes is performed by standard methods of sitting drop vapor diffusion (see, *e.g.*, McRee 1993 *In:* Practical Protein Crystallography (Academic Press, San Diego, CA) at pp. 1-23; Rhodes 1993 *In:* Crystallography Made Crystal Clear (Academic Press, San Diego, CA) at pp. 8-10, 29-38. The crystals are analyzed using a SYNCHROTRON, and the data analyzed using the CCP4 software suite (Science & Technology Facilities Council, Computational Science and Engineering Department), which is a collection of disparate programs covering most of the computations required for macromolecular crystallography. As those skilled in the art will appreciate, other hLIGHT antibodies provided herein can be similarly used to determine hLIGHT epitope binding and amino acid contact residues.

EXAMPLE 7 – IN VIVO EFFICACY STUDY OF 124F23 IN COLITIS DISEASE MODEL

[0476] Human T cell transfer model of colitis. Analogous to the CD4+/CD45Rbhi transfer model of mouse colitis described in Morrissey *et al.* (1993) J Exp Med. 178 237, RAG-/- mice are injected with human naïve T cells (CD45RA+CD45RO-). In this

model, an HLA transgenic strain (C57BL/6NTac-[KO]*Abb*-[Tg]DR-4) matched to the HLA type of a human donor is backcrossed onto a RAG-/- (B6.129S6-Rag2^{tm1Fwa}N12) background to enable antigen presentation between mouse recipient APCs and the human donor T cells. This interaction is necessary for T cell recognition of gut microflora, which is thought to be responsible for activation and homing of T cells to the gut. Animals experience weight loss and wasting disease, along with intestinal inflammation not seen in the RAG-/- mice.

[0477] In certain groups, a human-anti-hLIGHT antibody (*e.g.*, F23) is administered at a dose of 100 μg (or, *e.g.*, ranging from 2 μg - 500 μg) per animal by intravenous injection simultaneously with human donor T cell administration. In certain groups, the anti-hLIGHT antibody is administered at various time intervals before and/or after human donor T cell administration. Because the anti-LIGHT antibodies bind LIGHT expressed on the surface of activated T cells, symptoms of disease are prevented and/or treated. In follow-up studies, both T cell depleting (IgG1) and/or non-depleting (IgG4PE) versions of the anti-hLIGHT antibodies can be used to assess the mechanism of disease amelioration. For example, IgG4 anti-LIGHT antibodies are able to block T cell co-stimulation and survival.

EXAMPLE 8 - IBD MODEL OF HUMAN DISEASE IN HUMAN LIGHT KNOCK-IN MICE

[0478] As discussed elsewhere herein, LIGHT has previously been implicated in IBD disease pathology (see, *e.g.*, Wang *et al.* 2005 J. Immunol. 174:8173-82; Wang *et al.* 2004 J. Clin. Invest. 113:826-35; Cohavy *et al.* 2005 J. Immunol. 174:646-53). In this example, a hLIGHT knock-in mouse model of IBD is created, and human anti-hLIGHT monoclonal antibodies of the invention are administered to the animal to assess the *in vivo* efficacy of these antibodies in the treatment of IBD. Because these antibodies have previously been shown to block hLIGHT receptor binding, blocking hLIGHT biological activity (see, *e.g.*, Examples 1-4), and treating GVHD (Example 5), it is expected that hLIGHT antibodies of the invention are also effective in treating IBD.

[0479] LIGHT knock-in generation. Mice disrupted for the mouse LIGHT gene that also have a targeted insertion of the human LIGHT gene are generated using standard methods of gene targeting by homologous recombination. In brief, gene-targeted mouse ES cells are produced by electroporation of a gene-targeting construct into wild-type ES cells. Homologous recombination between the genome of the ES cell and two regions of

homology in the targeting vector that flank the human LIGHT gene result in the replacement of the mouse LIGHT gene with the human LIGHT gene. A blastocyst is then implanted into pseudo-pregnant females leading to chimeric mouse generation. Breeding produces the homologous LIGHT knock-in animals.

[0480] IBD models of human disease. The hLIGHT knock-in animals are used in established models of IBD. One established model of IBD includes the administration of dextran sodium sulfate (DSS) in drinking water (see, *e.g.*, Mähler *et al.* 1998 Am J Physiol. 274G544-51). Briefly, experimental colitis is induced by giving 3.5% (w/v) DDS (mol. wt. 36,100-45,000; TbD Consultancy, Uppsala, Sweden) in acidified drinking water ad libitum for 5 days. DDS administration is then stopped, and mice receive acidified drinking water alone for 16 days until necropsy on day 21. This dose induces moderate to sever colitis while minimizing the mortality, though other doses may be used. The large intestine is then collected, and the cecum is separated from the colon. Standard tissue fixation and H&E staining is then performed to determine severity of inflammation and lesions. The mice are assessed for pathology, histopathology, wasting syndrome and/or death.

[0481] A second established model of IBD includes rectal administration of trinitrobenzene sulfonic acid (TNBS) (see, *e.g.*, Neurath, *et al.* 1995 J Exp Med. 182 1281-90). Briefly, to induce colitis, mice are briefly anesthetized with metofane, and a 3.5F catheter is then carefully inserted into the solon, such that the time is about 4 cm. proximal to the anus. To induce colitis, 0.5 mg of hapten reagent TNBS (Sigma, St. Louis, MO) in 50% ethanol (to break the instestinal barrier) is inserted into the lumen of the colon via the catheter fitted onto a 1 ml syringe. In control experiments, mice receive 50% ethanol alone. The total injection volume is 100 µl in both groups allowing TNBS or ethanol to reach the entire colon, including the cecum and appendix. Animals are then kept in a vertical position for 30 seconds and returned to their cages. , or the CD4+/CD45Rbhi transfer model of mouse colitis (see, *e.g.*, Morrissey, *et al.* 1993 J Exp Med. 178 237-44). Anti-LIGHT antibodies can then be used for treatment and prevention of established disease, such as in doses of 2-500 µg per animal, essentially as described above. The large instestine is then collected, and the cecum is separated from the colon. At various time points thereafter, the intestine is removed, and standard tissue fixation and H&E staining is then performed to determine severity of inflammation and lesions. The mice are assessed for pathology, histopathology, wasting syndrome and/or death.

[0482] A third established model of IBD is the CD4+/CD45RBhi transfer model of mouse colitis (see, *e.g.*, Morrissey, *et al.* 1993 J Exp Med. 178 237-44). Briefly, purified CD4+ lymph node T cells are sorted according to their expression of CD45RB and injected into the hLIGHT knock-in mice. Standard tissue fixation and H&E staining is then performed to determine severity of inflammation and lesions. The mice are assessed for pathology, histopathology, wasting syndrome and/or death.

[0483] Anti-LIGHT antibodies (*e.g.*, doses of 2-500 μg per animal) can be used with any IBD model, such as those described above, to assess the efficacy in the treatment and prevention of IBD, essentially as described above. Because these antibodies have previously been shown to block hLIGHT receptor binding, blocking hLIGHT biological activity (see, *e.g.*, Examples 1-4), and treating GVHD (Example 5), it is expected that hLIGHT antibodies of the invention are also effective in treating IBD.

[0484] The embodiments of the present invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present invention and are covered by the following claims. Furthermore, as used in this specification and claims, the singular forms "a," "an" and "the" include plural forms unless the content clearly dictates otherwise. Thus, for example, reference to "an antibody" includes a mixture of two or more such antibodies, and the like. Additionally, ordinarily skilled artisans will recognize that operational sequences must be set forth in some specific order for the purpose of explanation and claiming, but the present invention contemplates various changes beyond such specific order.

[0485] The contents of all references described herein are hereby incorporated by reference.

[0486] Other embodiments are within the following claims.

WHAT IS CLAIMED IS:

1. An isolated antibody that
is fully human and specifically binds to a hLIGHT epitope,wherein the antibody comprises:

(a) a VH CDR1, VH CDR2 and VH CDR3 of an antibody produced by a hybridoma having ATCC Accession NO. PTA-7819 and
(b) a VL CDR1, VL CDR2 and VL CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819.

2. An isolated antibody that is fully human and specifically binds to a hLIGHT epitope, wherein the antibody comprises:

(a) a heavy chain variable region comprising
a VH CDR1 of SEQ ID NO:20,
a VH CDR2 of SEQ ID NO:21, and
a VH CDR3 of SEQ ID NO:22

and

(b) a light chain variable region comprising:
(1) a VL CDR1 of SEQ ID NO: 93, a VL CDR2 of SEQ ID NO: 96 and a VL CDR3 of SEQ ID NO: 99,
(2) a VL CDR1 of SEQ ID NO: 35, a VL CDR2 of SEQ ID NO: 36 and a VL CDR3 of SEQ ID NO: 37,
(3) a VL CDR1 of SEQ ID NO: 94, a VL CDR2 of SEQ ID NO: 97 and a VL CDR3 of SEQ ID NO: 100, or
(4) a VL CDR1 of SEQ ID NO: 95, a VL CDR2 of SEQ ID NO: 98 and a VL CDR3 of SEQ ID NO: 101.

3. The antibody of claim 1 or 2, wherein the antibody is an antagonist antibody.

4. The antibody of claim 3,

wherein the antibody competes with HVEM, LTβR, or a fusion protein thereof, for binding to cell surface-expressed hLIGHT or soluble hLIGHT, or

wherein the antibody partially or completely inhibits binding of HVEM, LTBR, DcR3, or any combination thereof, to cell surface-expressed hLIGHT or soluble hLIGHT, or

wherein the antibody partially or completely inhibits hLIGHT-mediated secretion of CCL20, IL-8, RANTES, or any combination thereof, from a cell having a cell surface-expressed hLIGHT receptor.

5. The antibody of claim 1 or 2, wherein the antibody comprises (a) a VH of an antibody produced by a hybridoma having ATCC Accession NO. PTA-7819; and/or (b) a VL of an antibody produced by the hybridoma having ATCC Accession No. PTA-7819.

6. The antibody of claim 1 or 2, wherein the isolated antibody is an antibody produced by the hybridoma of ATCC Accession No. PTA-7819.

7. The antibody of claim 1 or 2, wherein the antibody comprises:

(a) a heavy chain variable region (VH) having the 20 -141 residues of amino acid sequence depicted in SEQ ID NOs:4; and/or

(b) a light chain variable region (VL) having the 23 -129 residues of the amino acid sequence depicted in SEQ ID NO: 9, the 23 -129 residues of the amino acid sequence depicted in SEQ NO: 90, the 23 - 129 residues of the amino acid sequence depicted in SEQ ID NO: 91 or the 21-126 residues of the amino acid sequence depicted in SEQ ID NO: 92.

8. The antibody of claim 1 or 2, wherein the antibody comprises

(a) a VH encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in SEQ ID NO: 44, and/or

(b) a VL encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in any one of SEQ ID NOS: 49, 104, 105 or 106.

9. The antibody of claim 1 or 2, wherein the antibody comprises

(a) a VH CDR1 encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NOS:20, and/or

(b) a VH CDR2 encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NOS:21, and/or

(c) a VH CDR3 encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NOS:22, and/or

(d) a VL CDR1 encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence encoding the amino acid sequence as depicted in any one of SEQ ID NOS: 35 93, 94 and 95, and/or

(e) a VL CDR2 encoded by a nucleotide sequence that hybridize under stringent conditions to the complement of a nucleotide sequence encoding the amino acid sequence as depicted in any one of SEQ ID NOS: 36, 96, 97 and 98, and/or

(f) a VL CDR3 encoded by a nucleotide sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence encoding the amino acid sequence as depicted in any one of SEQ ID NOS:37,99, 100 and 101.

10. The antibody of claim 1 or 2, wherein the antibody comprises an IgG constant domain, optionally an IgG1 or IgG4 domain.

11. The antibody of claim 1 or 2,

wherein the antibody is a fully human antibody, or

wherein the antibody is a chimeric or humanized antibody, or

wherein the antibody is an antigen binding fragment, or

wherein the antibody is a Fab fragment, F(ab')2 fragment, single chain Fv (sFv), diabody,

triabody, or minibody.

12. The antibody of claim 1 or 2, wherein the antibody is a monoclonal antibody or a recombinant antibody.

13. A composition comprising the antibody of any one of claims 1 to 12.

14. An isolated nucleic acid molecule

(i) comprising or consisting of a nucleic acid sequence that encodes (a) a VH amino acid sequence of an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819; and/or (b) a VL amino acid sequence of an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819, or

(ii) comprising a nucleic acid sequence that encodes (a) a VH CDR1, VH CDR2 and/or VH CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819, and/or (b) a VL CDR1, VL CDR2 and/or VL CDR3 of an antibody produced by a hybridoma having ATCC Accession No. PTA-7819, or a combination thereof, or

(iii) comprising or consisting of a nucleic acid sequence that encodes an antibody produced by a hybridoma deposited as ATCC Accession No. PTA-7819,

(iv) comprising (a) a sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in SEQ ID NO: 44; and/or (b) a sequence that hybridizes under stringent conditions to the complement of a nucleotide sequence as depicted in any one of the SEQ ID NOS:49, 104, 105 or 106.

15. A vector comprising the nuclei acid molecule of claim 14.

16. A host cell comprising the vector of claim 15.

17. A method of producing the antibody of claim 1 or 2, the method comprising culturing the host cell of claim 16 under conditions that promote production of the antibody.

18. A hybridoma that produces an antibody as claimed in claim 1 or 2, the hybridoma optionally having ATCC Accession No. PTA-7819.

19. The composition of claim 13

(i) for use in a method for alleviating one or more symptoms of inflammatory bowel disease (IBD) in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(ii) for use in a method for alleviating one or more symptoms of graft-versus-host disease (GVHD) in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(iii) for use in a method for decreasing or inhibiting binding of hLIGHT to HVEMLTβR, DcR3, or any combination thereof, in a human in need thereof, the method comprising administering to the human an effective amount of the composition, or

(iv) for use in a method for decreasing or inhibiting the secretion of CCL20, IL-8, RANTES, or any combination thereof, in a human in need thereof, the method comprising administering to the human an effective amount of the composition.

20. A kit comprising the antibody of claim 1 or 2, or the composition of claim 13.

ANTAGONISTIC HUMAN LIGHT-SPECIFIC HUMAN MONOCLONAL ANTIBODIES

ABSTRACT

Provided herein are antibodies, such as fully human antibodies, that immunospecifically bind to an hLIGHT polypeptide. Also provided are isolated nucleic acids encoding antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide. Further provided are vectors and host cells comprising nucleic acids encoding antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide. Also provided are methods of making antibodies, such as fully human antibodies, that immunospecifically bind to a hLIGHT polypeptide. Also provided herein is a method of treating a hLIGHT- mediated disease in a subject comprising administering to the subject an antibody, such as a fully human antibody, that immunospecifically binds to a hLIGHT polypeptide. In preferred embodiments, that anti-hLIGHT antibodies provided herein will ameliorate, neutralize or otherwise inhibit hLIGHT biological activity *in vivo* (*e.g.*, the hLIGHT- mediated production or secretion of CCL20, IL-8 or RANTES from a cell expressing a hLIGHT receptor). Also provided herein is a method for the detection of hLIGHT in a sample as well as a method for ameliorating, neutralizing or otherwise inhibiting hLIGHT activity, e.g., in a human subject suffering from a disorder in which hLIGHT activity is detrimental.

FIGURE 1