

BTLA ANTIBODIES

CROSS-REFERENCE

This application claims the benefit of United Kingdom Application No. 1820554.2, filed 17 December 2018, which application is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

This invention relates generally to antibodies or antigen binding fragments that bind to human B and T lymphocyte attenuator (BTLA) and uses thereof. More specifically, the invention relates to agonistic antibodies that bind human BTLA and modulate its activity, and their use in treating inflammatory, autoimmune and proliferative diseases and disorders.

BACKGROUND

The immune system must achieve a balance between the destruction of pathogens or dangerously mutated cells and tolerance of healthy self-tissue and innocuous commensals. To facilitate this balance the activity of immune cells is influenced by the integration of signals from multiple stimulatory and inhibitory receptors that attune cells to their environment. These surface-expressed receptors present attractive targets for the therapeutic modulation of immune responses. Many human diseases result from aberrant or unwanted activation of the immune system including autoimmune diseases, transplant rejection and graft-versus-host disease. Agonist agents capable of inducing signaling through inhibitory receptors could dampen these unwanted immune responses.

B and T lymphocyte attenuator (BTLA; also designated CD272) is an inhibitory member of the CD28 family of receptors that also includes CD28, CTLA-4, ICOS, and PD-1 (Watanabe et al., Nat Immunol. 4:670-679, 2003) It is widely expressed throughout the immune system on both myeloid and lymphoid cells (Han et al., J Immunol. 172:5931-9, 2004). Following engagement by its ligand herpesvirus entry mediator (HVEM), BTLA recruits the phosphatases SHP-1 and SHP-2 to its cytoplasmic domain (Sedy et al., Nat Immunol. 6:90-8, 2005), which in turn inhibit the signaling cascades of activating receptors. Mice lacking an intact BTLA gene show hyperproliferative B and T cell responses *in vitro*, higher titers to DNP-KLH post-immunization

and an increased sensitivity to EAE (Watanabe et al, Nat. Immunol, 4:670-679, 2003). If observed until old age BTLA knock-out mice spontaneously develop autoantibodies, an autoimmune hepatitis like disease and inflammatory cell infiltrates in multiple organs (Oya et al., Arthritis Rheum 58: 2498-2510, 2008). This evidence indicates that the BTLA inhibitory receptor plays a crucial role in maintaining immune homeostasis and inhibiting autoimmunity. Furthermore, HVEM-BTLA signaling is involved in the regulation of mucosal inflammation and infection immunity (Shui et al., J Leukoc Biol. 89:517-523, 2011).

Therapeutic agents that are capable of modulating BTLA function to inhibit autoreactive lymphocytes in the context of autoimmune disorders would be highly desirable.

It has previously been shown that monoclonal antibodies binding to mouse BTLA can act as agonists, inducing signaling through the receptor to inhibit immune cell responses. In the presence of agonist anti-BTLA antibody (mAb), anti-CD3 and anti-CD28 activated T-cells show reduced IL-2 production and proliferation (Kreig et al., J. Immunol., 175, 6420-6472, 2005).

Furthermore, anti-mouse-BTLA agonist antibodies have been shown to ameliorate disease in murine models of graft-versus-host disease (Sakoda et al., Blood. 117:2506-2514; Albring et al., J Exp Med. 207:2551-9, 2010). Agonist antibodies targeting the human BTLA receptor have been shown to inhibit T cell responses *ex-vivo* (see Otsuki et al., Biochem Biophys Res Commun 344:1121-7, 2006; and WO2011/014438), but have not yet been translated to the clinic.

There is a need in the art to discover new and useful agents, such as antibodies or antigen-binding antibody fragments, capable of modulating BTLA.

BRIEF SUMMARY OF THE DISCLOSURE

The present invention relates to anti-human BTLA agonist antibodies or antibody fragments thereof having one or more desirable properties, including high binding affinities, high agonist potency, high agonist efficacy, good pharmacokinetics and low antigenicity in human subjects. The invention also relates to use of the antibodies or antibody fragments of the invention in the treatment of disease.

According to a first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds BTLA, wherein the antibody has a heavy chain and/or light chain with at least one complementarity-determining region (CDR) as present in an antibody selected from the group consisting of 11.5.1, 2.8.6, 12F11, 14D4, 15B6, 15C6, 16E1, 16F10, 16H2, 1H6, 21C7, 24H7, 26B1, 26F3, 27G9, 3A9, 3E8, 4B1, 4D3, 4D5, 4E8, 4H4, 6G8, 7A1, 8B4, 8C4, 6.2 and 831, as identified in Table 1 and described herein.

According to a second aspect of the invention there is provided an isolated nucleic acid comprising a nucleotide sequence that encodes a heavy chain polypeptide or a light chain polypeptide of the isolated antibody or an antigen-binding fragment thereof of the first aspect of the invention.

According to a third aspect of the invention there is provided a vector comprising the nucleic acid of the second aspect of the invention.

According to a fourth aspect of the invention there is provided a host cell comprising the nucleic acid sequence according to the second aspect of the invention or the vector according to the third aspect of the invention.

According to a fifth aspect of the invention there is provided a method of producing an antibody or an antigen-binding fragment thereof according to the first aspect of the invention, comprising the step of culturing the host cell of the fourth aspect of the invention under conditions for production of said antibody or an antigen-binding fragment thereof, and optionally isolating and/or purifying said antibody or an antigen-binding fragment thereof.

According to a sixth aspect of the invention there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment thereof of the first aspect of the invention, or that produced by the fifth aspect of the invention.

According to a seventh aspect of the invention there is provided a method of preparing a pharmaceutical composition, the method comprising formulating antibody or an antigen-binding fragment thereof in accordance with the first aspect of the invention, or one produced in accordance with the fifth aspect of the invention into a composition including at least one

additional component. In a particular embodiment, the at least one additional component is a pharmaceutically acceptable excipient.

According to an eighth aspect of the invention there is provided a method of treating a BTLA-related disease in a patient, comprising administering to the patient a therapeutically effective amount of the antibody or antigen-binding fragment thereof of the first aspect of the invention or the pharmaceutical composition of the sixth aspect of the invention.

DETAILED DESCRIPTION

The inventors have identified particularly strong agonist antibodies to BTLA which are predicted to be more efficacious than current antibodies at suppressing T cell responses and thus be particularly useful in the treatment of immune mediated disorders.

As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a molecule" optionally includes a combination of two or more such molecules, and the like.

It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

It is to be understood that one, some, or all of the properties of the various embodiments described herein may be applied to any aspect unless the content clearly dictates otherwise. Furthermore, that the various embodiments may be combined to form other embodiments of the present invention. These and other aspects of the invention will become apparent to one of skill in the art. These and other embodiments of the invention are further described by the detailed description that follows.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press;

and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of ordinary skill with a general dictionary of many of the terms used in this disclosure.

The term "about" as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se.

Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

The numbering of amino acids in the variable domain, CDRs and framework regions (FRs), of an antibody follow, unless otherwise indicated, the Kabat definition as set forth in Kabat et al. Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991).

The terms "B and T lymphocyte attenuator" and "BTLA" are used interchangeably and, unless the context dictates otherwise, with reference to either the protein or gene (or other nucleic acid encoding all or part of BTLA). The human BTLA sequences encompass all human isotype and variant forms. A representative example of full length human BTLA is disclosed in Genbank under accession number: AJ717664.1. Another representative polypeptide sequence of human BTLA is disclosed in SEQ ID NO: 23, which only differs from that in AJ717664.1 by two natural variant single nucleotide polymorphisms. Despite allelic variations, a human BTLA polypeptide sequence will typically have at least 90% sequence identity (such as at least 95%, 96%, 97%, 98%, 99% or 100%) to human BTLA in SEQ ID NO: 23.

A representative example of full length cynomolgus (cyno) BTLA is disclosed in Genbank under accession number: XP_005548224. A reference polypeptide sequence of cyno BTLA is disclosed in SEQ ID NO: 24. A cyno BTLA polypeptide sequence will typically have at least 90% sequence identity (such as at least 95%, 96%, 97%, 98%, 99% or 100%) to cyno BTLA as disclosed in SEQ ID NO: 24.

The term sequence identity is well known in the art. For the purposes of this invention, when determining whether a target sequence meets a defined limit (e.g. 90% identity), it is considered to meet the defined limit if it is identified as such using the BLAST (Basic local alignment search tool) algorithm (see Altschul et al. J Mol Biol 215:403-410, 1990) or Smith-Waterman algorithm (see Smith and Waterman. J Mol. Biol. 147:195-197, 1981).

Antibodies and antigen-binding fragments of antibodies

An antibody is an immunoglobulin molecule capable of specific binding to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, or combinations of the foregoing through at least one antigen recognition site, located in the variable domain of the immunoglobulin molecule. In particular, as used herein, the term "antibody" encompasses intact polyclonal antibodies, intact monoclonal antibodies, multispecific antibodies such as bispecific antibodies generated from at least two intact antibodies, chimeric antibodies, humanised antibodies, human antibodies, and any other modified immunoglobulin molecule comprising an antigen recognition site so long as the antibodies exhibit the desired biological activity.

The term "antibody" as used herein, refers to an immunoglobulin molecule which specifically binds to an antigen and comprises an FcR binding site which may or may not be functional.

As used herein, a BTLA agonist antibody (or antibody fragment) refers to an antibody (or antibody fragment) that binds to BTLA and enhances its coinhibitory signal to T and/or B cells.

The antigen-binding site refers to the part of a molecule that binds to all or part of the target antigen. In an antibody molecule it may be referred to as the antibody antigen-binding site and comprises the part of the antibody that specifically binds to all or part of the target antigen.

Where an antigen is large, an antibody may only bind to a particular part of the antigen, which part is termed an epitope. An antibody antigen-binding site may be provided by one or more antibody variable domains. Preferably, an antibody antigen-binding site comprises an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH).

The invention also encompassed antibody-fragments that comprise an antigen-binding site. Thus, the term "antigen-binding fragment thereof", when referring to an antibody refers to antibody fragments, such as Fab, Fab', F(ab')₂, diabodies, Fv fragments and single chain Fv (scFv) mutants that possess an antigen recognition site, and thus, the ability to bind to an antigen.

Antigen-binding immunoglobulin (antibody) fragments are well known in the art. Such fragment need not have a functional Fc receptor binding site.

As used herein the terms “antibody fragment molecules of the invention”, “antibody fragment” and “antigen-binding fragment thereof”, are used interchangeably herein.

The term “BTLA-binding molecule” as used herein, refers to both antibodies and binding fragments thereof capable of binding to BTLA.

There are five major classes (i.e., isotypes) of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (subtypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Unless dictated otherwise by contextual constraints the antibodies of the invention can be from one of these classes or subclasses of antibodies. Heavy-chain constant domains that correspond to the different classes of antibodies are typically denoted by the corresponding lower-case Greek letter α , δ , ϵ , γ , and μ , respectively. Light chains of the antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

"Native antibodies" are usually heterotetrameric Y-shaped glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. Each heavy chain comprises one variable domain (VH) and a constant region, which in the case of IgG, IgA, and IgD antibodies, comprises three domains termed C_{H1} , C_{H2} , and C_{H3} (IgM and IgE have a fourth domain, C_{H4}). In IgG, IgA, and IgD classes the C_{H1} and

C_H2 domains are separated by a flexible hinge region, which is a proline and cysteine rich segment of variable length (from about 10 to about 60 amino acids in various IgG subclasses). The variable domains in both the light and heavy chains are joined to the constant domains by a "J" region of about 12 or more amino acids and the heavy chain also has a "D" region of about 10 additional amino acids. Each class of antibody further comprises inter-chain and intra-chain disulfide bonds formed by paired cysteine residues. The heavy chain variable region (VH) and light chain variable region (VL) can each be further subdivided into regions of hypervariability, termed CDRs, interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL, comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g. effector cells) and the first component (C1q) of the classical complement system.

The antibody or antigen-binding fragment thereof of the invention may be from any animal species including murine, rat, human, or any other origin (including chimeric or humanised antibodies). In some embodiments, the antibody or antigen-binding antibody fragment is monoclonal, e.g. a monoclonal antibody. In some embodiments, the antibody or antigen-binding fragment thereof is a human or humanised antibody or antigen-binding fragment thereof. A non-human antibody or antigen-binding fragment thereof may be humanised by recombinant methods to reduce its immunogenicity in man.

An antibody or antigen-binding fragment thereof of the invention may be identified using well-known methods. For example, the antigen-binding moiety may have been selected using phage display or other antigen-binding selection or panning approach. Such antigen-binding moiety could then be incorporated into an antibody framework (e.g. fused to the constant and hinge regions of, for example an IgG1 or IgG4 molecule).

The term "monoclonal antibody" ("mAb") as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, e.g., the individual antibodies comprising the population are identical except for possible mutations, e.g., naturally occurring mutations, that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character

of the antibody or fragment thereof, as not being a mixture of discrete antibodies or antigen-binding fragments. A mAb is highly specific, being directed against a single antigenic site/epitope.

A mAb may be produced by hybridoma, recombinant, transgenic or other techniques known to those skilled in the art. For example, a monoclonal antibody or antigen-binding fragment thereof in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein (*Nature* 256:495, 1975) or may be made by recombinant DNA methods such as described in U.S. Pat. No. 4,816,567 and 6,331,415. The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., *Nature* 1991; 352:624-628 and Marks et al., *J. Mol. Biol.* 1991; 222:581- 597, for example.

The term monoclonal may also be ascribed to an antigen-binding fragment of an antibody of the invention. It merely means that the molecule is produced or present in a single clonal form.

A "human" antibody (HumAb) refers to an antibody having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region is also derived from human germline immunoglobulin sequences. The human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

Human antibodies can be prepared by administering an immunogen/antigen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge, but whose endogenous loci have been disabled, e.g., immunized xenomice (see, e.g., U.S. Patent Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE (trade mark) technology). See also, for example, Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present

extra chromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, *Nat. Biotech.* 23:1117-1125 (2005). See also, e.g., U.S. Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Patent No. 5,770,429 describing HUMAB™ technology; U.S. Patent No. 7,041,870 describing K-M MOUSE™ technology, and U.S. Patent Application Publication No. US2007/0061900, describing VELOCIMOUSE™ technology. Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor *J. Immunol.* 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., *J. Immunol.* 147:86 (1991)) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Patent No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyixue*, 26:265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology*, 20:927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clinical Pharmacology*, 27:185-91 (2005).

The terms "human" antibodies and "fully human" antibodies are used synonymously. This definition of a human antibody specifically excludes a humanised antibody comprising non-human antigen-binding residues.

As used herein, a "humanised antibody" refers to an antibody in which some, most or all of the amino acids outside the CDRs of a non-human antibody are replaced with corresponding amino acids derived from human immunoglobulins. In some embodiments, humanised antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. The humanised antibody may

comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences but are included to further refine and optimize antibody performance. In one embodiment of a humanised form of an Ab, some, most or all the amino acids outside the CDRs have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible provided they do not abrogate the ability of the antibody to bind to a particular antigen. A "humanised" antibody retains an antigenic specificity similar to that of the original antibody. In general, a humanised antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin, and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanised antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see, e.g., Jones et al, *Nature* 321:522-525 (1986); Riechmann et al, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). See also, e.g., Vaswani and Hamilton, *Ann. Allergy, Asthma & Immunol.* 1:105-115 (1998); Harris, *Biochem. Soc. Transactions* 23:1035-1038 (1995); Hurle and Gross, *Curr. Op. Biotech.* 5:428-433 (1994); and U.S. Patent Nos. 6,982,321 and 7,087,409.

As used herein, an "engineered antibody" refers to an antibody, which may be a humanized antibody, wherein particular residues have been substituted for others so as to diminish an adverse effect or property. Such substitution could be within a CD domain. For example, as described herein (see Example 21), the CDRH2 of the humanised antibody 3E8 was modified with an N57Q substitution to remove deamidation potential, and a K63S substitution to reduce predicted immunogenicity.

A "chimeric antibody" refers to an antibody in which the variable regions are derived from one species and the constant regions are derived from another species, such as an antibody in which the variable regions are derived from a mouse antibody and the constant regions are derived from a human antibody or vice versa. The term also encompasses an antibody comprising a V region from one individual from one species (e.g., a first mouse) and a constant region from another individual from the same species (e.g., a second mouse). The term "antigen (Ag)" refers to the

molecular entity used for immunization of an immunocompetent vertebrate to produce the antibody (Ab) that recognizes the Ag or to screen an expression library (e.g., phage, yeast or ribosome display library, among others). Herein, Ag is termed more broadly and is generally intended to include target molecules that are specifically recognized by the Ab, thus including portions or mimics of the molecule used in an immunization process for raising the Ab or in library screening for selecting the Ab.

A "bispecific" or "bifunctional" antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature*, 305:537-539 (1983)). Methods for making bispecific antibodies are within the purview of those skilled in the art. For example, bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai, et al, (1990) *Clin. Exp. Immunol.* 79: 315-321, Kostelny, et al, (1992) *J Immunol.* 148:1547- 1553. In addition, bispecific antibodies may be formed as "diabodies" (Holliger, et al, (1993) *PNAS USA* 90:6444-6448) or as "Janusins" (Traunecker, et al, (1991) *EMBO J.* 10:3655-3659 and Traunecker, et al, (1992) *Int. J. Cancer Suppl.* 7:51-52).

Generally, the term "epitope" refers to the area or region of an antigen to which an antibody specifically binds, i.e., an area or region in physical contact with the antibody. Thus, the term "epitope" refers to that portion of a molecule capable of being recognized by and bound by an antibody at one or more of the antibody's antigen-binding regions. Typically, an epitope is defined in the context of a molecular interaction between an "antibody, or antigen-binding portion thereof (Ab), and its corresponding antigen. Epitopes often consist of a surface grouping of molecules such as amino acids or sugar side chains and have specific three- dimensional structural characteristics as well as specific charge characteristics. In some embodiments, the epitope can be a protein epitope. Protein epitopes can be linear or conformational. In a linear epitope, all of the points of interaction between the protein and the interacting molecule (such as an antibody) occur linearly along the primary amino acid sequence of the protein. A "nonlinear epitope" or "conformational epitope" comprises non- contiguous polypeptides (or amino acids) within the antigenic protein to which an antibody specific to the epitope binds. The term

"antigenic epitope" as used herein, is defined as a portion of an antigen to which an antibody can specifically bind as determined by any method well known in the art, for example, by conventional immunoassays.

An antibody that "specifically binds" to an epitope is a term well understood in the art, and methods to determine such specific binding are also well known in the art. A molecule is said to exhibit "specific binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell, protein or substance than it does with alternative cells, proteins or substances.

A variety of assay formats may be used to select an antibody or peptide that specifically binds a molecule of interest. For example, solid-phase ELISA immunoassay, immunoprecipitation, Biacore™ (GE Healthcare, Piscataway, NJ), KinExA, fluorescence-activated cell sorting (FACS), Octet™ (ForteBio, Inc., Menlo Park, CA) and Western blot analysis are among many assays that may be used to identify an antibody that specifically reacts with an antigen or a receptor, or ligand binding portion thereof, that specifically binds with a cognate ligand or binding partner. Typically, a specific or selective reaction will be at least twice the background signal or noise, more typically more than 10 times background, even more typically, more than 50 times background, more typically, more than 100 times background, yet more typically, more than 500 times background, even more typically, more than 1000 times background, and even more typically, more than 10,000 times background. Also, an antibody is said to "specifically bind" an antigen when the equilibrium dissociation constant (K_D or K_D , as used interchangeably herein) is < 7 nM.

According to the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds BTLA, wherein the antibody has a heavy chain and/or light chain with at least one CDR an antibody selected from the group consisting of 11.5.1, 2.8.6, 12F11, 14D4, 15B6, 15C6, 16E1, 16F10, 16H2, 1H6, 21C7, 24H7, 26B1, 26F3, 27G9, 3A9, 3E8, 4B1, 4D3, 4D5, 4E8, 4H4, 6G8, 7A1, 8B4, 8C4, 6.2 and 831, as disclosed in Table 1 and described herein. In one embodiment, the antibody or antigen-binding fragment thereof competes for binding to BTLA with its natural ligand HVEM. In another embodiment, the antibody or antigen-binding fragment thereof does not interfere with binding of HVEM.

In additional embodiments, the isolated antibody which binds human BTLA is selected from the group consisting of 11.5.1 and 2.8.6, wherein the antibody specifically binds BTLA and induces signaling through the receptor.

By an antibody selected from the group consisting of 11.5.1, 2.8.6, 12F11, 14D4, 15B6, 15C6, 16E1, 16F10, 16H2, 1H6, 21C7, 24H7, 26B1, 26F3, 27G9, 3A9, 3E8, 4B1, 4D3, 4D5, 4E8, 4H4, 6G8, 7A1, 8B4, 8C4, 6.2 and 831, as disclosed in Table 1 and described herein, means any antibody or antigen-binding fragment thereof which comprises one or more, such as VH CDR 1, 2 and 3, or VL CDR 1, 2 and 3, or VH CDR 1, 2 and 3 and VL CDR 1, 2 and 3, from any of the antibodies disclosed in Table 1 (whether murine, humanized or humanised/engineered).

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VH CDR that has an amino acid sequence as set forth in any of SEQ ID NO: 7, SEQ ID NO: 8 or SEQ ID NO: 9, with from 0 to 3 amino acid modifications, such as 0, 1, 2, or 3 amino acid modifications. In certain embodiments, the amino acid modifications include, but not limited to, amino acid substitution, addition, deletion, or chemical modification, without eliminating the antibody binding affinity or T-cell inhibitory effect of the modified amino acid sequence, as compared to the unmodified amino acid sequence.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VH CDR with an amino acid sequence as set forth in any of SEQ ID NO: 193, SEQ ID NO: 194, or SEQ ID NO: 195, with from 0 to 3 amino acid modifications.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 7, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 8, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 9.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA,

comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 193, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 194, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 195.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 12, with from 0 to 3 amino acid modifications.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 196, SEQ ID NO: 197, or SEQ ID NO: 12, with from 0 to 3 amino acid modifications.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 10, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 11, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 12.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 196, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 197, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 12.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain

variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 7, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 8, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 9, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 10, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 11, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 12.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 193, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 194, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 195, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 196, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 197, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 12.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, with from 0 to 3 amino acid modifications.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 199, SEQ ID NO: 200, or SEQ ID NO: 201, with from 0 to 3 amino acid modifications.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid

sequence as set forth in SEQ ID NO: 1, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 2, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 3.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 199, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 200, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 201.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 4, SEQ ID NO: 5 or SEQ ID NO: 6.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 202, SEQ ID NO: 203, or SEQ ID NO: 6.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 4, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 5, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 6.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 202, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 203, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 6.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 1, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 2, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 3, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 4, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 5, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 6.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 199, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 200, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 201, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 202, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 203, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 6.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VH CDR with an amino acid sequence as set forth in (1) SEQ ID NO: 31, 32, or 33, with from 0 to 3 amino acid modifications; (2) SEQ ID NO: 37, 38, or 39, with from 0 to 3 amino acid modifications; (3) SEQ ID NO: 43, 44, or 45, with from 0 to 3 amino acid modifications; (4) SEQ ID NO: 43, 56, or 57, with from 0 to 3 amino acid modifications; (5) SEQ ID NO: 61, 62, or 63, with from 0 to 3 amino acid modifications; (6) SEQ ID NO: 31, 32, or 69, with from 0 to 3 amino acid modifications; (7) SEQ ID NO: 73, 74, or 75, with from 0 to 3 amino acid modifications; (8) SEQ ID NO: 79, 80, or 81, with from 0 to 3 amino acid modifications; (9) SEQ ID NO: 85, 86, or 87, with from 0 to 3 amino acid modifications; (10) SEQ ID NO: 61, 92,

or 93, with from 0 to 3 amino acid modifications; (11) SEQ ID NO: 97, 98, or 99, with from 0 to 3 amino acid modifications; (12) SEQ ID NO: 103, 104, or 105, with from 0 to 3 amino acid modifications; (13) SEQ ID NO: 109, 110, or 111, with from 0 to 3 amino acid modifications; (14) SEQ ID NO: 85, 110, or 117, with from 0 to 3 amino acid modifications; (15) SEQ ID NO: 121, 122, or 123, with from 0 to 3 amino acid modifications; (16) SEQ ID NO: 127, 128, or 129, with from 0 to 3 amino acid modifications; (17) SEQ ID NO: 133, 134, or 135, with from 0 to 3 amino acid modifications; (18) SEQ ID NO: 139, 140, or 141, with from 0 to 3 amino acid modifications; (19) SEQ ID NO: 145, 146, or 147, with from 0 to 3 amino acid modifications; (20) SEQ ID NO: 31, 32, or 33, with from 0 to 3 amino acid modifications; (21) SEQ ID NO: 31, 32, or 159, with from 0 to 3 amino acid modifications; (22) SEQ ID NO: 169, 170, or 171, with from 0 to 3 amino acid modifications; (23) SEQ ID NO: 61, 62, or 63, with from 0 to 3 amino acid modifications; (24) SEQ ID NO: 31, 182, or 183, with from 0 to 3 amino acid modifications; (25) SEQ ID NO: 187, 188, or 189, with from 0 to 3 amino acid modifications; (26) SEQ ID NO: 193, 194, or 195, with from 0 to 3 amino acid modifications; (27) SEQ ID NO: 199, 200, or 201, with from 0 to 3 amino acid modifications; (28) SEQ ID NO: 205, 206, or 207, with from 0 to 3 amino acid modifications; (29) SEQ ID NO: 211, 212, or 213, with from 0 to 3 amino acid modifications; (30) SEQ ID NO: 127, 386, or 129, with from 0 to 3 amino acid modifications; (33) SEQ ID NO: 205, 206, or 207, with from 0 to 3 amino acid modifications; (34) SEQ ID NO: 127, 388, or 129, with from 0 to 3 amino acid modifications; or (35) SEQ ID NO: 205, 387, or 207, with from 0 to 3 amino acid modifications.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in (1) SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively; (2) SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39, respectively; (3) SEQ ID NO: 43, SEQ ID NO: 44, and SEQ ID NO: 45, respectively; (4) SEQ ID NO: 43, SEQ ID NO: 56, and SEQ ID NO: 57, respectively; (5) SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively; (6) SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 69, respectively; (7) SEQ ID NO: 73, SEQ ID NO: 74, and SEQ ID NO: 75, respectively; (8) SEQ ID NO: 79, SEQ ID NO: 80, and SEQ ID NO: 81, respectively; (9) SEQ ID NO: 85, SEQ ID

NO: 86, and SEQ ID NO: 87, respectively; (10) SEQ ID NO: 61, SEQ ID NO: 92, and SEQ ID NO: 93, respectively; (11) SEQ ID NO: 97, SEQ ID NO: 98, and SEQ ID NO: 99, respectively; (12) SEQ ID NO: 103, SEQ ID NO: 104, and SEQ ID NO: 105, respectively; (13) SEQ ID NO: 109, SEQ ID NO: 110, and SEQ ID NO: 111, respectively; (14) SEQ ID NO: 85, SEQ ID NO: 110, and SEQ ID NO: 117, respectively; (15) SEQ ID NO: 121, SEQ ID NO: 122, and SEQ ID NO: 123, respectively; (16) SEQ ID NO: 127, SEQ ID NO: 128, and SEQ ID NO: 129, respectively; (17) SEQ ID NO: 133, SEQ ID NO: 134, and SEQ ID NO: 135, respectively; (18) SEQ ID NO: 139, SEQ ID NO: 140, and SEQ ID NO: 141, respectively; (19) SEQ ID NO: 145, SEQ ID NO: 146, and SEQ ID NO: 147, respectively; (20) SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively; (21) SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 159, respectively; (22) SEQ ID NO: 169, SEQ ID NO: 170, and SEQ ID NO: 171, respectively; (23) SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively; (24) SEQ ID NO: 31, SEQ ID NO: 182, and SEQ ID NO: 183, respectively; (25) SEQ ID NO: 187, SEQ ID NO: 188, and SEQ ID NO: 189, respectively; (26) SEQ ID NO: 193, SEQ ID NO: 194, and SEQ ID NO: 195, respectively; (27) SEQ ID NO: 199, SEQ ID NO: 200, and SEQ ID NO: 201, respectively; (28) SEQ ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively; (29) SEQ ID NO: 211, 212, and 213, respectively; (30) SEQ ID NO: 127, 386, and 129, respectively; (31) SEQ ID NO: 205, 206, and 207, respectively; (32) SEQ ID NO: 127, 388, and 129, respectively; or (33) SEQ ID NO: 205, 387, and 207, respectively, wherein from 0 to 3 amino acid modifications can be present in any CDR/SEQ ID NO:.

According to a variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR with an amino acid sequence as set forth in (1) SEQ ID NO: 34, 35, or 36; (2) SEQ ID NO: 40, 41, or 42; (3) SEQ ID NO: 46, 47, or 48; (4) SEQ ID NO: 58, 59, or 60; (5) SEQ ID NO: 64, 65, or 66; (6) SEQ ID NO: 34, 35, or 72; (7) SEQ ID NO: 76, 47, or 78; (8) SEQ ID NO: 82, 83, or 84; (9) SEQ ID NO: 88, 89, or 90; (10) SEQ ID NO: 94, 95, or 96; (11) SEQ ID NO: 100, 101, or 102; (12) SEQ ID NO: 64, 107, or 108; (13) SEQ ID NO: 88, 89, or 114; (14) SEQ ID NO: 124, 125, or 126; (15) SEQ ID NO: 34, 35, or 36; (16) SEQ ID NO: 136, 137, or 138; (17) SEQ ID NO: 142, 143, or 144; (18) SEQ ID NO: 148, 149, or 150;; (19) SEQ ID NO: 136, 137, or 162; (20) SEQ ID NO: 34, 35, or 36; (21) SEQ ID NO: 172, 173, or 174; (22) SEQ ID NO: 64, 65, or 180; (23) SEQ ID NO: 136, 137, or 186; (24) SEQ ID NO: 190, 191, or 192; (25)

SEQ ID NO: 196, 197, or 12; (26) SEQ ID NO: 202, 203, or 6; (27) SEQ ID NO: 142, 209, or 210; or (28) SEQ ID NO: 214, 35, or 216; (29) SEQ ID NO: 10, 11, or 12; (30) SEQ ID NO: 4, 5, or 6; or (31) SEQ ID NO: 142, 143, or 210, wherein from 0 to 3 amino acid modifications can be present in any CDR/SEQ ID NO:.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in (1) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (2) SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively; (3) SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, respectively; (4) SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, respectively; (5) SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively; (6) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 72, respectively; (7) SEQ ID NO: 76, SEQ ID NO: 47, and SEQ ID NO: 78, respectively; (8) SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, respectively; (9) SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, respectively; (10) SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, respectively; (11) SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, respectively; (12) SEQ ID NO: 64, SEQ ID NO: 107, and SEQ ID NO: 108, respectively; (13) SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively; (14) SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, respectively; (15) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (16) SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, respectively; (17) SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, respectively; (18) SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively; (19) SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 162, respectively; (20) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (21) SEQ ID NO: 172, SEQ ID NO: 173, and SEQ ID NO: 174, respectively; (22) SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 180, respectively; (23) SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 186, respectively; (24) SEQ ID NO: 190, SEQ ID NO: 191, and SEQ ID NO: 192, respectively; (25) SEQ ID NO: 196, SEQ ID NO: 197, and SEQ ID NO: 12, respectively; (26) SEQ ID NO: 202, SEQ ID NO: 203, and SEQ ID NO: 6, respectively; (27) SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively; (28) SEQ ID NO: 214, SEQ ID NO: 35, and SEQ ID NO: 216, respectively; (29)

SEQ ID NO: 10, 11, or 12, respectively; (30) SEQ ID NO: 4, 5, or 6, respectively; or (31) SEQ ID NO: 142, 143, or 210, respectively, wherein from 0 to 3 amino acid modifications can be present in any CDR/SEQ ID NO:.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein (1) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (2) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively; (3) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 43, SEQ ID NO: 44, and SEQ ID NO: 45, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, respectively; (4) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 43, SEQ ID NO: 56, and SEQ ID NO: 57, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, respectively; (5) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively; (6) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 69, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 72, respectively; (7) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 73, SEQ ID NO: 74, and SEQ ID NO: 75, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 47, and SEQ ID NO: 78, respectively; (8) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 79, SEQ ID NO: 80, and SEQ ID NO: 81, respectively, and

CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, respectively; (9) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 86, and SEQ ID NO: 87, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, respectively; (10) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 92, and SEQ ID NO: 93, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, respectively; (11) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 97, SEQ ID NO: 98, and SEQ ID NO: 99, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, respectively; (12) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 103, SEQ ID NO: 104, and SEQ ID NO: 105, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 107, and SEQ ID NO: 108, respectively; (13) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 109, SEQ ID NO: 110, and SEQ ID NO: 111, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively; (14) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 110, and SEQ ID NO: 117, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively; (15) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 121, SEQ ID NO: 122, and SEQ ID NO: 123, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, respectively; (16) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 128, and SEQ ID NO: 129, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (17) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 133, SEQ ID NO: 134, and SEQ ID NO: 135, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, respectively; (18) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 139, SEQ ID NO: 140, and SEQ ID NO: 141, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence

as set forth in SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, respectively; (19) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 145, SEQ ID NO: 146, and SEQ ID NO: 147, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively; (20) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively; (21) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 159, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 162, respectively; (22) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 169, SEQ ID NO: 170, and SEQ ID NO: 171, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 172, SEQ ID NO: 173, and SEQ ID NO: 174, respectively; (23) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 180, respectively; (24) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 182, and SEQ ID NO: 183, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 186, respectively; (25) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 187, SEQ ID NO: 188, and SEQ ID NO: 189, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 190, SEQ ID NO: 191, and SEQ ID NO: 192, respectively; (26) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 193, SEQ ID NO: 194, and SEQ ID NO: 195, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 196, SEQ ID NO: 197, and SEQ ID NO: 12, respectively; (27) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 199, SEQ ID NO: 200, and SEQ ID NO: 201, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 202, SEQ ID NO: 203, and SEQ ID NO: 6, respectively; (28) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO:

209, and SEQ ID NO: 210, respectively; (29) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 214, SEQ ID NO: 35, and SEQ ID NO: 216, respectively; (30) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 386, and SEQ ID NO: 129, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (31) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively; (32) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 388, and SEQ ID NO: 129, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (33) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively; or (34) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 210, respectively; wherein from 0 to 3 amino acid modifications can be present in any CDR/SEQ ID NO:.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising: (1) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, or SEQ ID NO: 33, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, or SEQ ID NO: 36; (2) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 37, SEQ ID NO: 38, or SEQ ID NO: 39, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 40, SEQ ID NO: 41, or SEQ ID NO: 42; (3) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 43, SEQ ID NO: 44, or SEQ ID NO: 45, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 46, SEQ ID NO: 47, or SEQ ID NO: 48; (4) at least

one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 43, SEQ ID NO: 56, or SEQ ID NO: 57, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 58, SEQ ID NO: 59, or SEQ ID NO: 60; (5) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, or SEQ ID NO: 63, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, or SEQ ID NO: 66; (6) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, or SEQ ID NO: 69, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, or SEQ ID NO: 72; (7) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 73, SEQ ID NO: 74, or SEQ ID NO: 75, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 47, or SEQ ID NO: 78; (8) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 79, SEQ ID NO: 80, or SEQ ID NO: 81, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 82, SEQ ID NO: 83, or SEQ ID NO: 84; (9) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 86, or SEQ ID NO: 87, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, or SEQ ID NO: 90; (10) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 92, or SEQ ID NO: 93, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 94, SEQ ID NO: 95, or SEQ ID NO: 96; (11) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 97, SEQ ID NO: 98, or SEQ ID NO: 99, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 100, SEQ ID NO: 101, or SEQ ID NO: 102; (12) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 103, SEQ ID NO: 104, or SEQ ID NO: 105, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 107, or SEQ ID NO: 108; (13) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 109, SEQ ID NO: 110, or SEQ ID NO: 111, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, or SEQ ID NO: 114; (14) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 110, or SEQ ID NO: 117, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, or SEQ ID NO: 114; (15) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 121, SEQ ID NO: 122, or SEQ ID NO: 123, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 124, SEQ ID NO: 125, or SEQ ID NO: 126; (16) at least one VH CDR with an amino acid sequence as set forth in

SEQ ID NO: 127, SEQ ID NO: 128, or SEQ ID NO: 129, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, or SEQ ID NO: 36; (17) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 133, SEQ ID NO: 134, or SEQ ID NO: 135, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, or SEQ ID NO: 138; (18) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 139, SEQ ID NO: 140, or SEQ ID NO: 141, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, or SEQ ID NO: 144; (19) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 145, SEQ ID NO: 146, or SEQ ID NO: 147, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, or SEQ ID NO: 150; (20) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, or SEQ ID NO: 33, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, or SEQ ID NO: 150; (21) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, or SEQ ID NO: 159, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, or SEQ ID NO: 162; (22) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 169, SEQ ID NO: 170, or SEQ ID NO: 171, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 172, SEQ ID NO: 173, or SEQ ID NO: 174; (23) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, or SEQ ID NO: 63, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, or SEQ ID NO: 180; (24) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 182, or SEQ ID NO: 183, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, or SEQ ID NO: 186; (25) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 187, SEQ ID NO: 188, or SEQ ID NO: 189, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 190, SEQ ID NO: 191, or SEQ ID NO: 192; (26) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 193, SEQ ID NO: 194, or SEQ ID NO: 195, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 196, SEQ ID NO: 197, or SEQ ID NO: 12; (27) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 199, SEQ ID NO: 200, or SEQ ID NO: 201, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 202, SEQ ID NO: 203, or SEQ ID NO: 6; (28) at least one VH CDR with an amino acid sequence as set forth in SEQ ID

NO: 205, SEQ ID NO: 206, or SEQ ID NO: 207, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, or SEQ ID NO: 210; (29) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 211, SEQ ID NO: 212, or SEQ ID NO: 213, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 214, SEQ ID NO: 35, or SEQ ID NO: 216; (30) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 386, or SEQ ID NO: 129, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, or SEQ ID NO: 36; (31) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 206, or SEQ ID NO: 207, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, or SEQ ID NO: 210; (32) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 388, or SEQ ID NO: 129, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, or SEQ ID NO: 36; (33) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, or SEQ ID NO: 207, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, or SEQ ID NO: 210; or (34) at least one VH CDR with an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, or SEQ ID NO: 207, and at least one VL CDR with an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, or SEQ ID NO: 210; wherein from 0 to 3 amino acid modifications can be present in any CDR/SEQ ID NO:.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 13, or a sequence with at least 90% sequence identity thereto. In other embodiments, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17 or 21.

For any embodiment disclosed herein that refers to at least 90% sequence identity it is understood that this includes any sequence identity from 90% to 100%, i.e. at least 90% at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% and 100%.

In other embodiments, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 301, 302, 303, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 324, 306, 326, 327, 330, 331, 13, 17, 21, 382, 384, 389, 390 and 378.

In other embodiments, the heavy chain variable region comprises an amino acid sequence as set forth in SEQ ID NO: 301, 302, 303, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 324, 306, 326, 327, 330, 331, 13, 17, 21, 382, 384, 389, 390 and 378, with up to 10 modifications, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid modifications therein.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 14, or a sequence with at least 90% sequence identity thereto. In other embodiments, the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15 or 19.

In other embodiments, the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 351, 352, 353, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 366, 367, 368, 369, 370, 372, 351, 374, 375, 376, 377, 380, 381, 14, 15, 19, 383, 385 or 378.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 13, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 14.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain

variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 14.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein: (1) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15; or (2) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 21, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA, comprising a heavy chain and a light chain, wherein: (1) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 301, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 351; (2) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 302, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 352; (3) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 303, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 353; (4) the heavy chain comprises a heavy chain variable region comprising an amino

[illegible]

[illegible]

has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 370; (20) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 321, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 370; (21) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 322, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 372; (22) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 324, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 374; (23) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 306, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 375; (24) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 326, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 376; (25) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 327, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 377; (26) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15; (27) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 21, and the

light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19; (28) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 330, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 380; (29) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 331, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 381; (30) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 382, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 383; (31) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 384, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 385; (32) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 389, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 383; (33) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 390, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 385; or (34) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 390, and the light chain comprises a light chain variable region comprising an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 378.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 14.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 21 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 301 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 351.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 302 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 352.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 303 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 353.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 305 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 355.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 306 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 356.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 307 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 357.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 308 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 358.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 309 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 359.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 310 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 360.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 311 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 361.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 312 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 362.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 313 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 363.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 314 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 364.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 315 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 364.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 316 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 366.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 317 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 367.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 318 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 368.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 319 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 369.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 320 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 370.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 321 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 370.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 322 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 372.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 324 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 374.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 306 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 375.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 326 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 376.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 327 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 377.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 17 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 15.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 21 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 330 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 380.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 331 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 381.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 382 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 383.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 384 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 385.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 389 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 383.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 390 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 385.

In one embodiment, the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 390 and the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 378.

In other embodiments, the heavy chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 13.

In other embodiments, the heavy chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 17.

In other embodiments, the heavy chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 21.

In other embodiments, the heavy chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 301, 302, 303, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 324, 306, 326, 327, 330, 331, 382, 384, 389, or 390.

In other embodiments, the light chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 14.

In other embodiments, the light chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 15.

In other embodiments, the light chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 19.

In other embodiments, the light chain variable region polypeptide has at least 92%, at least 95%, at least 97%, at least 98% or at least 99% identity with the sequence disclosed in SEQ ID NO: 351, 352, 353, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 364, 366, 367, 368, 369, 370, 372, 374, 375, 376, 377, 380, 381, 383, 385, or 378.

According to another variation of the first aspect of the invention there is provided an isolated antibody or an antigen-binding fragment thereof having primary VH domain, primary VL domain, CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of any antibody clone as set forth in **Table 1**. In certain embodiments, provided herein is an isolated antibody selected from the antibody clones as set forth in **Table 1**.

Table 1. Exemplary BTLA Agonistic Antibodies

Clone	Scheme	SEQ ID NOs							
		CDR H1	CDR H2	CDR H3	CDR L1	CDR L2	CDR L3	VH	VL
10B1	Kabat	31	32	33	34	35	36	301	351
12F11	Kabat	37	38	39	40	41	42	302	352
14D4	Kabat	43	44	45	46	47	48	303	353
15B6	Kabat	43	56	57	58	59	60	305	355
15C6	Kabat	61	62	63	64	65	66	306	356
16E1	Kabat	31	32	69	34	35	72	307	357
16F10	Kabat	73	74	75	76	47	78	308	358
16H2	Kabat	79	80	81	82	83	84	309	359
1H6	Kabat	85	86	87	88	89	90	310	360
21C7	Kabat	61	92	93	94	95	96	311	361
24H7	Kabat	97	98	99	100	101	102	312	362
26B1	Kabat	103	104	105	64	107	108	313	363
26F3	Kabat	109	110	111	88	89	114	314	364
27G9	Kabat	85	110	117	88	89	114	315	364
3A9	Kabat	121	122	123	124	125	126	316	366
3E8	Kabat	127	128	129	34	35	36	317	367
4B1	Kabat	133	134	135	136	137	138	318	368
4D3	Kabat	139	140	141	142	143	144	319	369
4D5	Kabat	145	146	147	148	149	150	320	370
4E8	Kabat	31	32	33	148	149	150	321	370

Clone	Scheme	SEQ ID NOs							
		CDR H1	CDR H2	CDR H3	CDR L1	CDR L2	CDR L3	VH	VL
4H4	Kabat	31	32	159	136	137	162	322	372
6G8	Kabat	169	170	171	172	173	174	324	374
7A1	Kabat	61	62	63	64	65	180	306	375
8B4	Kabat	31	182	183	136	137	186	326	376
8C4	Kabat	187	188	189	190	191	192	327	377
2.8.6	Kabat	193	194	195	196	197	12	17	15
11.5.1	Kabat	199	200	201	202	203	6	21	19
6.2	Kabat	205	206	207	142	209	210	330	380
831	Kabat	211	212	213	214	35	216	331	381
humanised 2.8.6	IMGT	7	8	9	10	11	12	13	14
2.8.6	IMGT	7	8	9	10	11	12	17	15
11.5.1	IMGT	1	2	3	4	5	6	21	19
Humanised 3E8	Kabat	127	386	129	34	35	36	382	383
Humanised 6.2	Kabat	205	206	207	142	209	210	384	385
Engineered humanised 3E8	Kabat	127	388	129	34	35	36	389	383
Engineered humanised 6.2 (2 nd)	Kabat	205	387	207	142	209	210	390	385
Engineered humanised 6.2	Kabat	205	387	207	142	143	210	390	378

In particular embodiments, the heavy chain or light chain also comprise a constant region. If the molecule is a full-length IgG-type antibody molecule, the heavy chain may comprise three constant domains.

In certain embodiments the isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA exhibits a K_D for binding to human BTLA of at most about $10 \times 10^{-9}M$. In certain embodiments the isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA exhibits a K_D for binding to human BTLA of at most about $4 \times 10^{-9}M$. In certain embodiments the isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA exhibits a K_D for binding to human BTLA of at most about $1 \times 10^{-9}M$.

In certain embodiments, an isolated antibody (e.g., humanised) of the invention binds human BTLA at 37°C with a K_D of no more than about 10 nM ($1 \times 10^{-8}M$); suitably no more than about 1 nM; more suitably are embodiments in which the antibodies have K_D values at 37°C of no

more than about 500 pM (5×10^{-10} M), 200pM, 100 pM, 50 pM, 20 pM, 10 pM, 5pM or even 2 pM. The term “about”, as used in this context means $\pm 10\%$.

In certain embodiments, an isolated antibody (e.g., humanised) of the invention binds human BTLA at 37°C with an on rate of at least 1.0×10^5 (1/Ms). In certain embodiments, an isolated antibody (e.g., humanised) of the invention binds human BTLA at 37°C with an on rate of at least 2.0×10^5 (1/Ms), 3.0×10^5 (1/Ms), 4.0×10^5 (1/Ms), 5.0×10^5 (1/Ms), 6.0×10^5 (1/Ms), or 7.0×10^5 (1/Ms).

In certain embodiments, an isolated antibody (e.g., humanised) of the invention binds human BTLA at 37°C with an off rate of no more than or less than 1.0×10^{-3} (1/s). In certain embodiments, an isolated antibody (e.g., humanised) of the invention binds human BTLA at 37°C with an off rate of no more than or less than 3.0×10^{-4} (1/s). In certain embodiments, an isolated antibody (e.g., humanised) of the invention binds human BTLA at 37°C with an off rate of no more than or less than 2.0×10^{-4} (1/s), or 1.0×10^{-4} (1/s).

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2, and wherein said antibody binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2; does not inhibit binding of BTLA to herpes virus entry mediator (HVEM), as determined for example by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 3.0×10^{-4} (1/s) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator

(BTLA) with an off rate from 3.0×10^{-4} (1/s) to 1.0×10^{-3} (1/s) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

Methods for characterizing the properties of an antibody or antigen-binding fragment thereof of the invention are well known in the art. A suitable method for determining binding specificity using surface plasmon resonance (SPR) at 37°C is described in Example 2. A suitable method for determining whether the tested antibody/fragment thereof inhibits binding of BTLA to herpes virus entry mediator (HVEM) is described in Example 4; this also employs surface plasmon resonance (SPR). A suitable method for determining whether the tested antibody/fragment thereof inhibits proliferation of T cells in vitro, is a mixed lymphocyte reaction assay such as that described in Example 9. Suitable methods for determining the site of binding of an antibody/fragment thereof to BTLA can utilise x-ray crystallography or flow cytometry of mutated receptors, such as by the method described in Example 5

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM) as determined for example by surface plasmon resonance (SPR) using a method such as that described in Example 4; and wherein said antibody inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that

described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 3.0×10^{-4} (1/s) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibody or antigen binding fragment thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with an off rate from 3.0×10^{-4} (1/s) to 1.0×10^{-3} (1/s) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM) as determined for example by surface plasmon resonance (SPR) using a method such as that described in Example 4; and wherein said antibody inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface

plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 1.0×10^{-3} (1/s) and an on rate of at least 5.0×10^5 (1/Ms), each as measured by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM) as determined for example by surface plasmon resonance (SPR) using a method such as that described in Example 4; and wherein said antibody inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method

such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 2 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2, wherein said antibody inhibits binding of BTLA to herpes virus entry mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of less than 1.0×10^6 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 1.0×10^{-3} (1/s), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds cynomolgus B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-

binding fragment thereof binds residue H68 of BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on off rate of less than 1×10^{-3} (1/s) as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2, wherein said antibody inhibits binding of BTLA to herpes virus entry mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds cynomolgus B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 2 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA), wherein said antibody binds cynomolgus BTLA with a KD of at least 5 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as

that described in Example 2; and wherein said antibody inhibits binding of BTLA to herpes virus entry mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA), wherein said antibody binds cynomolgus BTLA with a KD of at least than 50 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some

embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD from 1400 nM to 3500 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an on rate of at least 2.0×10^5 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an off rate of less than 10.0×10^{-1} (1/s), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on rate from 1.7×10^5 (1/Ms) to 2.5×10^5 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry

mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in Example 4; and inhibits proliferation of T cells in in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an off rate of less than 3.0×10^{-1} (1/s), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an off rate from 3.0×10^{-1} (1/s) to 5.0×10^{-1} (1/s), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with a K_D of at least 150 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with a K_D from 150 nM to 1500 nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds to an epitope that blocks binding of 286 antibody. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments of the first aspect of the invention, provided herein are isolated agonistic antibodies or antigen binding fragments thereof that specifically binds human B and T Lymphocyte Attenuator (BTLA) with a K_D from 40nM to 1200nM, as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM) as determined by surface plasmon resonance (SPR) using a method such as that described in

Example 4; and inhibits proliferation of T cells in in vitro, as determined for example by a mixed lymphocyte reaction assay using a method such as that described in Example 9. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an on rate of at least 1.0×10^5 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an on rate from 1.0×10^5 (1/Ms) to 10×10^5 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an off rate of less than 6.0×10^{-1} (1/s), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, said antibody or antigen binding fragment thereof binds human BTLA with an off rate from 6.0×10^{-1} (1/s) to 10.0×10^{-2} (1/s), as determined by surface plasmon resonance (SPR) at 37°C using a method such as that described in Example 2. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92 as determined by x-ray crystallography or by flow cytometry of mutated receptors using a method such as that described in Example 5. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123. In some embodiments, the antibody or antigen-binding fragment thereof binds residue H68 of human BTLA. In some embodiments, the antibody or antigen-binding fragment thereof binds a residue of human BTLA selected from: N65 and A64.

In certain embodiments the isolated antibody or an antigen-binding fragment thereof of the invention that specifically binds human BTLA increases BTLA activity and/or signaling through the receptor.

In particular embodiments, the antibody of the invention is selected from the group consisting of: a human antibody, a humanised antibody, a chimeric antibody, a multispecific antibody (such as a bispecific antibody).

In particular embodiments, the antigen-binding fragment of the invention is selected from the group consisting of: scFv, sc(Fv)², dsFv, Fab, Fab', (Fab')₂ and diabody.

In particular embodiments, the heavy chain and light chain molecules that form the antigen-binding fragment are connected by a flexible linker. There are many commonly used flexible linkers and the choice of linker can be made by a person of skill in the art.

The peptide linker connecting scFv VH and VL domains joins the carboxyl terminus of one variable region domain to the amino terminus of another variable domain without significantly compromising the fidelity of the VH-VL pairing and antigen-binding sites. Peptide linkers can vary from 10 to 25 amino acids in length and are typically, but not always, composed of hydrophilic amino acids such as glycine (G) and serine (S). The linker can be one that is found in natural multi-domain proteins (e.g. see Argos P. *J Mol Biol.* 211:943-958, 1990; and. Heringa G. *Protein Eng.* 15:871-879, 2002), or adapted therefrom.

Commonly used flexible linkers have sequences consisting primarily of stretches of Gly and Ser residues ("GS" linker). An example of the most widely used flexible linker has the sequence of (Gly-Gly-Gly-Gly-Ser)_n. By adjusting the copy number "n", the length of this GS linker can be altered to achieve appropriate separation of the functional domains, or to maintain necessary inter-domain interactions. Generally, the (GGGGS)₃ peptide is used as an scFv peptide linker (Leith et al., *Int. J. Oncol.* 24:765-771, 2004; Holiger et al. *Proc. Natl. Acad. Sci. U.S.A.* 90:6444-6448, 1993). This 15-amino acid linker sequence [designated as the (GGGGS)₃ linker] is used in the Recombinant Phage Antibody System (RPAS kit) commercially available from Amersham. Several other linkers have also been used to create scFV molecules (e.g. KESGSVSSEQLAQFRSLD and EGKSSSGSGSESKST; Bird et al., *Science* 242:432-426, 1988).

The inventors have mapped the epitopes on BTLA where the potent 2.8.6 and 11.5.1 agonist and the other antibodies disclosed herein bind.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106, E92, Y39, K41, R42, Q43, E45, S47, D35, T78, K81, S121, L123, H68, N65, A64.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds a residue of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106, E92.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds at least two residues of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106, E92.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds at least three residues of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds at least five residues of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds all of the residues of human BTLA selected from: D52, P53, E55, E57, E83, Q86, E103, L106 and E92.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds a residue of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47.

In a particular embodiment, the antibody or antigen-binding fragment thereof of the invention binds at least two residues of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds all of the residues of human BTLA selected from: Y39, K41, R42, Q43, E45 and S47.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds a residue of human BTLA selected from: D35, T78, K81, S121 and L123.

In a particular embodiment, the antibody or antigen-binding fragment thereof of the invention binds at least two residues of human BTLA selected from: D35, T78, K81, S121 and L123.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds residue H68 of human BTLA

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds a residue of human BTLA selected from: N65 and A64.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention binds both the N65 and A64 residues of human BTLA.

The numbering of the residues, such as K41 refers to the amino acid (K; lysine) at position 41; wherein the numbering refers to the position in human BTLA polypeptide as disclosed in SEQ ID NO: 23.

In particular embodiments, the antibody of the invention is an IgG1, IgG2 or IgG4 antibody. In particular embodiments the antibody is a murine or human antibody.

In a particular embodiment, the antibody or antigen-binding fragment thereof of the invention is a humanised antibody.

In a particular embodiment, the antibody or antigen-binding fragment thereof of the invention is a fully human antibody.

In a particular embodiment, the antibody or antigen-binding fragment thereof of the invention acts as an agonist inducing signaling through the BTLA receptor.

The antibodies (or antigen-binding fragments thereof) of the invention are particularly potent agonists.

In a particular embodiment, the antibody or antigen-binding fragment thereof of the invention have EC50s of not more than 1nM.

The agonist antibodies (or antigen-binding fragments thereof) of the invention have particularly high efficacy.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention inhibits T cell proliferation by at least 20%, suitably by at least 30%, more suitably by at least 40%.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention inhibits T cell IFN-gamma production by at least 50%, suitably by at least 75%, more suitably by at least 95%, as measured for example by ELISA of supernatants in an *in vitro* mixed lymphocyte reaction.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention inhibits T cell IL-2 production by at least 50%, suitably by at least 75%, more suitably by at least 95%, as measured for example by ELISA of supernatants in an *in vitro* mixed lymphocyte reaction.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention inhibits T cell IL-17 production by at least 50%, suitably by at least 75%, more suitably by at least 95%, as measured for example by ELISA of supernatants in an *in vitro* mixed lymphocyte reaction.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention reduces mortality in a murine GVHD model by at least 50%, suitably by at least 75%, more suitably by at least 95%, using a method such as that described in Example 12.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention reduces weight loss in a murine T-cell colitis model by at least 50%, suitably by at least 75%, more suitably by at least 95%, using a method such as that described in Example 11.

In a particular embodiment the antibody or antigen-binding fragment thereof of the invention reduces colon inflammation in a murine T-cell colitis model by at least 50%, suitably by at least 75%, more suitably by at least 95%, using a method such as that described in Example 11.

In certain aspects, the invention also relates to an isolated polypeptide comprising the VL domains or the VH domains of any of the antibodies or antigen-binding fragments thereof described herein.

In a particular embodiment, the isolated polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 13 or 14, or a sequence with at least 90% identity thereto.

Nucleic acid molecules

The antibody or antigen-binding fragment thereof of the invention will be encoded by nucleic acid. The antibody or antigen-binding fragment thereof may be encoded by a single nucleic acid molecule or it may be encoded by two or more nucleic acid molecules. For example, as the antigen binding site is typically formed by the coming together of a heavy chain variable

polypeptide region and a light chain variable polypeptide region, the two variable (heavy and light) polypeptide regions may be encoded by separate nucleic acid molecules. Alternatively, for example in the case of an ScFv, they may be encoded by the same nucleic acid molecule.

According to a second aspect of the invention there is provided one or more nucleic acid molecules that encode an antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention.

From the primary amino acid sequence of the polypeptide(s) encoding an antibody or antigen-binding fragment thereof of the invention the person of skill in the art is able to determine suitable nucleotide sequence(s) that encodes the polypeptide(s) and, if desired, one that is codon-optimised (e.g. see Mauro and Chappell. Trends Mol Med. 20(11):604-613, 2014).

As used herein, when there is reference to a previous aspect of the invention, e.g. “in accordance with the first (or second etc.) aspect of the invention”, it is understood to also cover any recited variation of said aspect (e.g. variation of the first (or second etc.) aspect).

According to a variation of the second aspect of the invention there is provided an isolated nucleic acid comprising a nucleotide sequence that encodes a heavy chain variable region polypeptide or a light chain variable region polypeptide of the invention. A heavy chain variable polypeptide or a light chain variable polypeptide of the invention refers to the individual polypeptide chains that include amino acids that make up part of the antigen-binding site. Of course, the said polypeptides may also comprise other domains such as constant domains, hinge regions, and an Fc region, such as one comprising one or more Fc receptor binding sites.

According to another variation of the second aspect of the invention there is provided an isolated nucleic acid which comprises one or more nucleotide sequence encoding polypeptides capable of forming an antibody or antigen-binding fragment of the invention. In particular embodiments, the said polypeptides may also comprise other domains such as constant domains, hinge regions, and an Fc region, such as one comprising one or more Fc receptor binding sites.

One of the nucleic acid molecules may encode just the polypeptide sequence that comprises the VL domain of the antibody or fragment thereof. One of the nucleic acid molecules may encode just the polypeptide sequence that comprises the VH domain of the antibody or fragment thereof.

However, the nucleic acid molecule may also encode both VH and VL domain containing polypeptide sequences capable of forming the antibody or antibody fragment thereof of the invention.

The nucleic acid molecule(s) that encode the antibody or antigen-binding fragment thereof of the invention, such as according to the first aspect of the invention, may be, or may be part of, a vector (such as a plasmid vector, cosmid vector or viral vector, or an artificial chromosome) that may comprise other functional regions (elements) such as one or more promoters, one or more origins or replication, one or more selectable marker(s), and one or more other elements typically found in expression vectors. The cloning and expression of nucleic acids that encode proteins, including antibodies, is well established and well within the skill of the person in the art.

According to a third aspect of the invention there is provided a vector comprising the nucleic acid of the second aspect of the invention. In particular embodiments, the vector is a plasmid vector, cosmid vector, viral vector, or an artificial chromosome.

The nucleic acids of the invention, including vector nucleic acids that comprise nucleotide sequences that encode the polypeptides capable of forming an antibody of the invention or an antigen-binding fragments thereof, may be in purified/isolated form.

Isolated/purified nucleic acids that encode an antibody or antigen-binding fragment thereof of the invention will be free or substantially free of material with which they are naturally associated, such as other proteins or nucleic acids with which they are found in their natural environment, or the environment in which they are prepared (e.g. cell culture) when such preparation is by recombinant DNA technology practised *in vitro* or *in vivo*.

In particular embodiments, the nucleic acids of the invention are greater than 80%, such as greater than 90%, greater than 95%, greater than 97% and greater than 99% pure.

Thus, according to another variation of the third aspect of the invention there is provided a vector comprising a nucleic acid or nucleotide sequence that encodes a heavy chain variable polypeptide or a light chain variable polypeptide of the invention. In a particular embodiment, the vector comprises nucleic acid that encodes both the heavy and light chain variable regions. In particular

embodiments, the said polypeptides may also comprise other domains such as constant domains, hinge regions, and an Fc region, such as one comprising one or more Fc receptor binding sites.

The nucleic acid and/or vector of the invention may be introduced into a host cell. The introduction may employ any available technique. For eukaryotic cells, suitable techniques may include calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, e.g. vaccinia or, for insect cells, baculovirus. Introducing nucleic acid in the host cell, in particular a eukaryotic cell may use a viral or a plasmid-based system. The plasmid system may be maintained episomally or may be incorporated into the host cell or into an artificial chromosome. Incorporation may be either by random or targeted integration of one or more copies at single or multiple loci. For bacterial cells, suitable techniques may include calcium chloride transformation, electroporation and transfection using bacteriophage.

In one embodiment, the nucleic acid of the invention is integrated into the genome (e.g. chromosome) of the host cell. Integration may be promoted by inclusion of sequences that promote recombination with the genome, in accordance with standard techniques.

Host cells

A further aspect of the present invention provides a host cell containing nucleic acid as disclosed herein. Such a host cell may be *in vitro* and may be in culture.

The host cell can be from any species, such as a bacterium or yeast but suitably the host cell is an mammalian cell such as a human cell or rodent cell, for example a HEK293T cell or CHO-K1 cell.

Thus, according to a fourth aspect of the invention there is provided a host cell comprising the nucleic acid sequence according to the second aspect of the invention or the vector according to third aspect of the invention.

The host cell can be treated so as to cause or allow expression of the protein of the invention from the nucleic acid, e.g. by culturing host cells under conditions for expression of the encoding nucleic acid. The purification of the expressed product may be achieved by methods known to one of skill in the art.

Thus, the nucleic acids of the invention, including vector nucleic acids that comprise nucleotide sequences that encode the polypeptides capable of forming the antibodies of the invention or antigen-binding fragments thereof, may be present in an isolated host cell. The host cell is typically part of a clonal population of host cells. As used herein, reference to a host cell also encompasses a clonal population of said cell. A clonal population is one that has been grown from a single parent host cell. The host cell can be from any suitable organism. Suitable host cells include bacterial, fungal or mammalian cells.

The host cell may serve to assist in amplifying the vector nucleic acid (such as with a plasmid) or it may serve as the biological factory to express the polypeptide(s) of the invention that form the BTLA antibody or antigen-binding fragment thereof of the invention. A suitable host for amplifying the vector nucleic acid could be a bacterial or fungal cell, such as an *Escherichia coli* cell or *Saccharomyces cerevisiae* cell. A suitable host for expressing the proteins of the invention (i.e. the polypeptides making up the human BTLA-binding antibody or antigen-binding fragment thereof of the invention) would be a mammalian cell such as a HEK293T or CHO-K1 cell. In a particular embodiment, the host cell is a mammalian cell, such as a HEK293T or CHO-K1 cell.

A variety of host-expression vector systems may be utilized to express a BTLA-binding molecule as described herein (see e.g. U.S. Pat. No. 5,807,715). 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 CEA proteins (Foecking et al., *Gene*, 45:101 (1986); and Cockett et al., *Bio/Technology*, 8:2 (1990)). 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 protein of the disclosure. 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, HEK, VERY, BHK, HeLa, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0, CRL703O and HsS78Bst cells.

Antibody production

According to a fifth aspect of the invention there is provided a method of producing an antibody or an antigen-binding fragment thereof according to the first aspect of the invention, comprising the step of culturing the host cell of the fourth aspect of the invention under conditions for production of said an antibody or antigen-binding fragment thereof, and optionally isolating and/or purifying said antibody or antigen-binding fragment thereof.

According to a variation of the fifth aspect of the invention there is provided a method of producing an antibody or an antigen-binding fragment thereof that binds to human BTLA, comprising the step of culturing the host cell that comprises nucleic acid encoding the polypeptide(s) that form the antibody or the antigen-binding fragment thereof that binds to human BTLA under conditions for production of said antibody or antigen-binding fragment thereof, optionally further comprising isolating/purifying said antibody or antigen-binding fragment thereof.

By isolated/purified we mean that the antibody or antigen-binding fragment thereof of the invention, or polypeptides that make up these molecules, will be free or substantially free of material with which they are naturally associated, such as other proteins or nucleic acids with which they are found in their natural environment, or the environment in which they are prepared (e.g. cell culture) when such preparation is by recombinant DNA technology practised *in vitro* or *in vivo*.

According to a variation of the fifth of the invention there is provided a method for preparing an antibody or antigen-binding fragment thereof that specifically binds human BTLA, the method comprising the steps of:

- a) providing a host cell comprising one or more nucleic acid molecules encoding the amino acid sequence of a heavy chain variable domain and a light chain variable domain which when expressed are capable of combining to create a human BTLA-binding molecule;
- b) culturing the host cell expressing the encoded amino acid sequence; and c) isolating the antibody or antigen-binding fragment molecule.

The one or more nucleic acid molecules are those describe above that encode for polypeptides capable of forming an antibody or antigen-binding fragment thereof of the invention that specifically binds human BTLA.

In a particular embodiment, the antibody or antigen-binding fragment thereof comprises: i) a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 1, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 2, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 3; and

ii) a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 4, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 5, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 6.

In a particular embodiment, the antibody or antigen-binding fragment thereof comprises: i) a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 7, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 8, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 9; and

ii) a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 10, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 11, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 12.

In a particular embodiment, the antibody or antigen-binding fragment thereof comprises:

- i) a heavy chain variable region comprising an amino acid sequence disclosed in SEQ ID NO: 13, or a sequence with at least 90% sequence identity thereto; and
- ii) a light chain variable region comprising an amino acid sequence disclosed in SEQ ID NO: 14, or a sequence with at least 90% sequence identity thereto.

In various embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region

comprising three CDRs: CDRH1, CDRH2 and CDRH3, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein (1) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (2) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively; (3) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 43, SEQ ID NO: 44, and SEQ ID NO: 45, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, respectively; (4) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 43, SEQ ID NO: 56, and SEQ ID NO: 57, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, respectively; (5) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively; (6) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 69, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 72, respectively; (7) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 73, SEQ ID NO: 74, and SEQ ID NO: 75, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 47, and SEQ ID NO: 78, respectively; (8) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 79, SEQ ID NO: 80, and SEQ ID NO: 81, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, respectively; (9) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 86, and SEQ ID NO: 87, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, respectively; (10) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 92, and SEQ ID NO: 93, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96,

respectively; (11) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 97, SEQ ID NO: 98, and SEQ ID NO: 99, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, respectively; (12) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 103, SEQ ID NO: 104, and SEQ ID NO: 105, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 107, and SEQ ID NO: 108, respectively; (13) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 109, SEQ ID NO: 110, and SEQ ID NO: 111, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively; (14) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 110, and SEQ ID NO: 117, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively; (15) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 121, SEQ ID NO: 122, and SEQ ID NO: 123, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, respectively; (16) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 128, and SEQ ID NO: 129, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (17) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 133, SEQ ID NO: 134, and SEQ ID NO: 135, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, respectively; (18) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 139, SEQ ID NO: 140, and SEQ ID NO: 141, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, respectively; (19) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 145, SEQ ID NO: 146, and SEQ ID NO: 147, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively; (20) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively; (21) CDRH1, CDRH2, CDRH3 have an

amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 159, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 162, respectively; (22) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 169, SEQ ID NO: 170, and SEQ ID NO: 171, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 172, SEQ ID NO: 173, and SEQ ID NO: 174, respectively; (23) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 180, respectively; (24) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 182, and SEQ ID NO: 183, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 186, respectively; (25) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 187, SEQ ID NO: 188, and SEQ ID NO: 189, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 190, SEQ ID NO: 191, and SEQ ID NO: 192, respectively; (26) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 193, SEQ ID NO: 194, and SEQ ID NO: 195, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 196, SEQ ID NO: 197, and SEQ ID NO: 12, respectively; (27) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 199, SEQ ID NO: 200, and SEQ ID NO: 201, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 202, SEQ ID NO: 203, and SEQ ID NO: 6, respectively; (28) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively; (29) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 214, SEQ ID NO: 35, and SEQ ID NO: 216, respectively; (30) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 386, and SEQ ID NO: 129, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (31) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ

ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively; (32) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 388, and SEQ ID NO: 129, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively; (33) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively; or (34) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, and SEQ ID NO: 207, respectively, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 210, respectively; wherein from 0 to 3 amino acid modifications can be present in any CDR/SEQ ID NO:

Conditions for the production of the antibody or an antigen-binding fragment thereof of the invention and purification of said molecules are well-known in the art.

One way of attending to this is to prepare a clonal population of cells capable of expressing the antibody or fragment thereof of the invention and culturing these in a suitable growth medium for a period of time and at a temperature conducive to allow for expansion/growth of the cell population and expression of the protein(s) of interest. If the protein(s) of interest (e.g. antibody of invention) is expressed within the host cells then the cells may be lysed (e.g. using a mild detergent or sonication) to release the contents of the cell (and thus the protein of interest) into the surrounding medium (which could be the culture medium or another medium that the cells have been reconstituted in) and this medium is then subjected to purification processes. If the protein(s) of interest (e.g. antibody of invention) is secreted into the growth medium, then the medium is subjected to purification processes. Antibody purification typically involves isolation of antibody from, for example the medium or from the culture supernatant of a hybridoma cell line using well-established methods typically involving chromatography (e.g., using affinity chromatography, anionic and/or cationic exchange chromatography, size-exclusion chromatography or other separation techniques) to separate the protein of interest from unwanted host-derived proteins and other cellular contaminants (e.g. nucleic acids, carbohydrates etc.).

The purified proteins may also be subjected to a virus inactivation step. Finally, the purified protein of interest may, for example, be lyophilised or formulated ready for storage, shipment and subsequent use. Preferably the protein of interest (e.g. antibody or antigen-binding fragment thereof of the invention) will be substantially free from contaminating proteins which were originally present in the culture medium following expression or cell-lysis.

In certain embodiments, the antibody or antigen-binding fragment thereof of the invention will be at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% pure.

The proteins of the invention (antibody or antigen-binding fragment thereof of the invention) can be formulated into a suitable composition.

Compositions

While the BTLA-binding molecule may be administered alone, in certain embodiments administration is of a pharmaceutical composition wherein the BTLA-binding molecule is formulated with at least one pharmaceutically-acceptable excipient. The excipient may be a suitable pharmaceutical carrier solute. Such carriers are well known in the art and include phosphate buffered saline solutions, water, liposomes, various types of wetting agents, sterile solutions, etc. Compositions comprising such carriers can be formulated by well-known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. The dosage regimen will be determined by the attending physician and clinical factors.

According to a sixth aspect of the invention there is provided a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of the antibody or antigen-binding fragment thereof of the first aspect of the invention, or that produced by the fifth aspect of the invention. In a particular embodiment, the composition comprises phosphate buffered saline.

A "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of the active ingredient to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered. The pharmaceutical composition will include one or more pharmaceutically

acceptable excipients. The term excipient in this context refers to any additive, such as fillers, solubilisers, carriers, vehicles, additives and the like.

The pharmaceutical compositions can comprise one or more pharmaceutically acceptable excipients, including, e.g., water, ion exchangers, proteins, buffer substances, and salts. Preservatives and other additives can also be present. The excipient can be a solvent or dispersion medium. Suitable formulations for use in therapeutic methods disclosed herein are described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

"Pharmaceutically acceptable" excipients are those which can reasonably be administered to a subject mammal to provide an effective dose of the active ingredient employed. Pharmaceutical compositions of the invention are prepared for storage by mixing the composition with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable excipients 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 dextrans; 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(TM), PLURONICS(TM) or polyethylene glycol (PEG). Lyophilized HER2 antibody formulations are described in WO 97/04801.

The pharmaceutical compositions to be used for *in vivo* administration must be sterile. This can be readily accomplished by filtration through sterile filtration membranes.

The route of administration of the BTLA binding moiety molecule, e.g., an antibody, or antigen-binding fragment thereof can be, for example, oral, parenteral, by inhalation or topical. The term parenteral as used herein includes, e.g., intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, rectal, or vaginal administration.

Pharmaceutical compositions for parenteral administration include sterile aqueous or non-aqueous solutions, and suspensions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, aqueous solutions, or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishes, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. In addition, the composition might comprise proteinaceous carriers, like, e.g., serum albumin or immunoglobulin, in certain embodiments of human origin. For intravenous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required. As noted above, these are all referred to herein as excipients.

Compositions for injection can be administered with medical devices known in the art. For example, with a hypodermic needle. Needleless injection devices, such as those disclosed in US Patent Nos: 6620135 and 5312335 could also be utilised.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder, liquid or semi-solid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included as required.

An antibody or antigen-binding fragment thereof of the present invention may be formulated in liquid, semi-solid or solid forms depending on the physicochemical properties of the molecule and the route of delivery. Formulations may include excipients, or combinations of excipients, for example: sugars, amino acids and surfactants. Liquid formulations may include a wide range of antibody concentrations and pH. Solid formulations may be produced by lyophilisation, spray drying, or drying by supercritical fluid technology, for example.

The pharmaceutical composition can be administered as a single dose, multiple doses or over an established period of time in an infusion. Dosage regimens also can be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). In particular, parenteral formulations can be a single bolus dose, an infusion or a loading bolus dose followed with one or more maintenance doses. These compositions can be administered at specific fixed or variable intervals, e.g., once a day, or on an "as needed" basis.

Dosages

The amount of the BTLA-binding molecule, or the pharmaceutical formulation containing such molecule, which will be therapeutically effective can be determined by standard clinical techniques, such as through dose ranging clinical trials. 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 the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula:

Dose(ml.) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

Therapeutically effective doses of the pharmaceutical compositions for the treatment of BTLA-related diseases or disorders, as discussed herein, will vary depending upon many different factors, including means of administration, target site, physiological state of the patient, weight or patient, sex of patient, age of patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. The therapeutically effective dose is likely to have been determined from clinical trials and is something that the attending physician can determine using treatment guidelines. Usually, the patient is a human, but non-human mammals can also be treated. Treatment dosages can be titrated using routine methods known to those of skill in the art to optimize safety and efficacy.

In various embodiments, the BTLA-binding molecule is administered at a concentration of about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, or about 20 mg/kg.

A pharmaceutical composition of the invention may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. Such combination would likely be with other immunosuppressives such as one selected from: corticosteroids, cyclosporine, azathioprine, sulfasalazine, methotrexate, mycophenolate, tacrolimus and fingolimod, or other biologics such as infliximab, adalimumab, ustekinumab, tocilizumab and rituximab.

According to a seventh aspect of the invention there is provided a method of preparing a pharmaceutical composition, the method comprising formulating an antibody or an antigen-binding fragment thereof in accordance with the first aspect of the invention, or one produced in accordance with the fifth aspect of the invention into a composition including at least one additional component. In a particular embodiment, the at least one additional component is a pharmaceutically acceptable excipient.

Kits

Further, the product (e.g. BTLA binding molecule or a pharmaceutical composition thereof) can be packaged and sold in the form of a kit. Such articles of manufacture can have labels or

package inserts indicating instructions about the product and the appropriate use of the product for the treatment of a subject suffering from or predisposed to a disease or disorder.

Thus, according to one aspect of the invention there is provided a kit comprising an antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention or the pharmaceutical composition in accordance with the sixth aspect of the invention. Suitably, such a kit includes a package insert comprising instructions for use.

Therapy/Medical uses

An antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof may be used in therapy, typically as a medicament.

In certain embodiments, an antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof may be used for treating or preventing any disease or condition in a subject in need thereof.

BTLA is involved in down-regulating immune responses and there are many diseases or conditions that could be treated by suppressing host T-cells and/or B-cells (e.g. see Crawford & Wherry. Editorial: Therapeutic potential of targeting BTLA. *J Leukocyte Biol.* 86:5-8, 2009). Diseases or conditions that could benefit from treatment with an anti-BTLA agonist are referred to herein as “BTLA-related diseases”. BTLA-related diseases include inflammatory or autoimmune diseases, and disorders of excessive immune cell proliferation.

Specific BTLA-related diseases that can be treated with the BTLA-binding molecules of the invention include: Addison's disease, allergy, alopecia areata, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-phospholipid syndrome, asthma (including allergic asthma), autoimmune haemolytic anaemia, autoimmune hepatitis, autoimmune pancreatitis, autoimmune polyendocrine syndrome, Behcet's disease, bullous pemphigoid, cerebral malaria, chronic inflammatory demyelinating polyneuropathy, coeliac disease, Crohn's disease, Cushing's Syndrome, dermatomyositis, diabetes mellitus type 1, eosinophilic granulomatosis with polyangiitis, graft versus host disease, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hidradenitis Suppurativa, inflammatory fibrosis (e.g., scleroderma, lung fibrosis, and cirrhosis), juvenile arthritis, Kawasaki disease, leukemia, lymphoma, lymphoproliferative

disorders, multiple sclerosis, myasthenia gravis, myeloma, neuromyelitis optica, pemphigus, polymyositis, primary biliary cholangitis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, transplant rejection, transverse myelitis, ulcerative colitis, uveitis, vasculitis, vitiligo and Vogt-Koyanagi-Harada Disease.

According to an eighth aspect of the invention there is provided an antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention or the pharmaceutical composition in accordance with the sixth aspect of the invention for use in therapy.

In a particular embodiment, the therapy is treatment or prevention of a BTLA-related disease.

In a particular embodiment, the BTLA-related disease is one caused by decreased expression and/or activity of BTLA in a subject. In particular, any disease or disorder characterised by the presence or activity of T or B cells can be treated with a BTLA agonist antibody or antigen-binding fragment of the invention.

In one embodiment, the BTLA-related disease is an inflammatory disease (such as rheumatoid arthritis), an autoimmune disease or disorder (such as graft versus host) or a proliferative disease or disorder (such as cancer).

In a particular embodiment, the therapy is treatment or prevention of inflammatory or autoimmune diseases, and disorders of excessive immune cell proliferation.

According to a variation of the eighth aspect of the invention there is provided a method of treating a patient in need thereof, comprising administering to the patient an antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention or the pharmaceutical composition in accordance with the sixth aspect of the invention. In a particular embodiment the patient in need of treatment, or to be treated, has (or is suffering from) a BTLA-related disease. In a particular embodiment, the patient in need of treatment, or to be treated, has (or is suffering from) an inflammatory disease, an autoimmune disease, or a disorder of excessive immune cell proliferation.

In a particular embodiment, the antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention or the pharmaceutical composition in accordance with the sixth aspect of the invention is administered to a patient in need thereof in a pharmaceutically acceptable amount.

In a variation of this aspect there is provided an antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention or the pharmaceutical composition in accordance with the sixth aspect of the invention for use in a method of treating a patient in need thereof. In a particular embodiment, the method is for treating or preventing a BTLA- related disease. In particular embodiments, the method is for treating or preventing inflammatory or autoimmune diseases, and disorders of excessive immune cell proliferation.

In a further variation of this aspect there is provided use of an antibody or antigen-binding fragment thereof in accordance with the first aspect of the invention or the pharmaceutical composition in accordance with the sixth aspect of the invention in the manufacture of a medicament for the treatment of a patient in need thereof.

In one embodiment, the therapy is for treating a BTLA-related disease. Suitably, the BTLA-related disease is an inflammatory disease (such as asthma), an autoimmune disease or disorder (such as rheumatoid arthritis) or an immunoproliferative disease or disorder (such as lymphoma).

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is used to suppress T-cells and/or B-cells.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is used for treating or preventing a disease or condition in a subject in need thereof selected from the group consisting of: Addison's disease, allergy, alopecia areata, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-phospholipid syndrome, asthma (including allergic asthma), autoimmune haemolytic anaemia, autoimmune hepatitis, autoimmune pancreatitis, autoimmune polyendocrine syndrome, Behcet's disease, bullous pemphigoid, cerebral malaria, chronic inflammatory demyelinating polyneuropathy, coeliac disease, Crohn's disease, Cushing's Syndrome, dermatomyositis, diabetes mellitus type 1, eosinophilic granulomatosis with

polyangiitis, graft versus host disease (GVHD), Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hidradenitis Suppurativa, inflammatory fibrosis (e.g., scleroderma, lung fibrosis, and cirrhosis), juvenile arthritis, Kawasaki disease, leukemia, lymphoma, lymphoproliferative disorders, multiple sclerosis (MS), myasthenia gravis, myeloma, neuromyelitis optica, pemphigus, polymyositis, primary biliary cholangitis, primary sclerosing cholangitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, transplant rejection, transverse myelitis, ulcerative colitis, uveitis, vasculitis, vitiligo and Vogt-Koyanagi-Harada Disease.

In particular embodiments, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is used for treating or preventing a disease or condition in a subject in need thereof selected from the group consisting of: GVHD, colitis, rheumatoid arthritis, psoriasis and MS. In one embodiment, the immunoproliferative disease is cancer. Suitably the cancer is a leukemia or a lymphoma.

In another embodiment, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is for use in the prevention or treatment of transplant rejection.

In another embodiment, the invention relates to the prevention or treatment of graft versus host disease.

In another embodiment, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is for use in the treatment of rheumatoid arthritis.

In other embodiments, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is for use in the treatment of diabetes, such as type 1 diabetes.

In another embodiment, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is for use in the treatment of psoriasis.

In another embodiment, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is for use in the treatment of multiple sclerosis.

In another embodiment, the antibody or antigen-binding fragment thereof of the invention or a pharmaceutical composition comprising said antibody or antigen-binding fragment thereof is for use in the treatment of colitis.

The term "effective amount" or "therapeutically effective amount" refers to a dosage or an amount of a drug that is sufficient to ameliorate the symptoms in a patient or to achieve a desired biological outcome, *e.g.*, with cancer, an increased death of tumour cells, reduced tumour size, increased progression free survival or overall survival etc. As disclosed elsewhere herein, the effective amount will typically be assessed through extensive human clinical studies.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of them mean "including but not limited to", and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and

drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

The invention will now be further described with reference to the following non-limiting Examples and accompanying Figures.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1

Binding of antibodies to human and cynomolgus BTLA in soluble and cell expressed forms. (a) Surface plasmon resonance (SPR) binding curves for soluble monomeric human BTLA extracellular domain injected at increasing concentrations over immobilized anti-BTLA antibody; graphs show SPR signal after reference and blank subtraction. (b) Association and dissociation rates for binding to human or cynomolgus BTLA as calculated by curve fitting using BiaEvaluation software. (c) Binding of antibody 2.8.6, compared to isotype control antibody, to a human BTLA or cynomolgus BTLA expressing Jurkat cell line. (d) EC50s for antibody binding to transfected cell lines, as calculated by non-linear curve fitting using GraphPad Prism software

Figure 2

(a) Blockade of ligand binding by anti-BTLA antibodies was assessed by SPR. Human BTLA extracellular domain was immobilized on the sensor chip. Human HVEM was injected to confirm binding, then allowed to fully dissociate. A saturating concentration of anti-BTLA antibody was then injected, followed immediately by a second injection of HVEM. (b) Equilibrium binding of HVEM after injection of antibody was expressed as a percent of HVEM binding prior to antibody injection. Saturation of BTLA with clone 11.5.1, but not with clone 2.8.6, blocked subsequent binding of ligand.

Figure 3

Epitope mapping of anti-BTLA antibodies. (a) HEK293T cells transfected with BTLA constructs in a bicistronic vector also expressing GFP were stained with Pacific Blue conjugated anti-BTLA antibody. Clone 11.5.1 binds to cells transfected with wild-type receptor (left) but not to cells transfected with BTLA having a Y39R mutation (right). (b) Binding to each BTLA mutant construct was expressed as a percentage of binding to wild-type BTLA for clones 2.8.6 and 11.5.1. (c) Mutations Y39R and K41E which selectively eliminate binding of clone 11.5.1 were mapped onto the crystal structure of human BTLA (black residues). Residues critical for binding of the ligand HVEM are highlighted in grey.

Figure 4

(a) The crystal structure of human BTLA extracellular domain in complex with the Fab' fragment of clone 2.8.6. Residues on BTLA which are buried at the interface are highlighted in black. (b) The epitope of antibody 2.8.6 is shown (black residues) in relation to the HVEM binding site (grey residues).

Figure 5

(a) Strategy for creation of a chimeric BTLA gene in humanised-BTLA mice. A section of human genomic DNA from the beginning of exon 2 to the end of exon 3 was inserted into the mouse locus replacing the mouse sequence from the beginning of exon 2 to the end of exon 4. The sequences at the exon-intron junction at the beginning of mouse exon 2 and end of mouse exon 4 were left intact to ensure proper splicing.

Figure 6

(a) Protocol for T cell transfer assay to assess anti-BTLA antibodies *in vivo*. A mixture of humanised and wild-type OVA specific CD4 T cells was injected into recipient mice. The next day mice were immunised with ovalbumin in Alum to activate the transferred cells and 24 hours later were dosed with anti-human-BTLA antibody or isotype control. Eight days after initial cell transfer the ratio of humanised to wild-type cells in the transferred population in the spleen was assessed by flow cytometry. (b) Clone 11.5.1 and to a lesser extent 2.8.6 both reduced expansion of the humanised cells relative to the wild-type. Graph shows pooled data from two (for 11.5.1) or three (for 2.8.6) repeat experiments.

Figure 7

Effect of anti-BTLA clone 2.8.6 on CD4 T-cell proliferation in a mixed lymphocyte reaction *in vitro*. T cells from humanised C57BL/6 mice were stained with CellTraceViolet and added to Mitomycin C treated Balb/c stimulator cells in the presence of anti-BTLA antibody or isotype control. After 96 hours, proliferation of humanised CD4 cells was assessed and normalised to proliferation in the absence of antibody. Clone 2.8.6 inhibited proliferation of humanised cells with an IC₅₀ of 0.029 nM and had a maximal effect of 42% inhibition of proliferation.

Figure 8

(a) Effect of clone 2.8.6 in a T cell colitis model. RAG knockout recipient mice were injected with CD45RBhiCD25-CD4⁺ T cells from humanised BTLA mice and treated with 200µg 2.8.6 or isotype control antibody on days 7, 21 and 35. Isotype control treated mice progressively lost weight from 3 weeks onwards, whilst 2.8.6 treated mice were spared. (b) 8 weeks after cell transfer colons were processed to extract lamina propria lymphocytes and the total number of inflammatory cells extracted per colon was calculated. Isotype control treated mice had significantly more infiltrating immune cells than 2.8.6 treated mice. (c) Colon weight to length ratios were calculated as a marker of inflammation and thickening. 2.8.6 treatment prevented the increase in weight to length ratio seen in isotype control treated mice.

Figure 9

(a) Effect of BTLA antibodies in a parent-to-F1 model of GVHD. C57BL/6 splenocytes and bone marrow cells from humanised-BTLA mice were injected into CB6F1 recipient mice, which were then treated with anti-BTLA antibody or isotype control. Untreated mice developed clinical GVHD with progressive weight loss, dermatitis and diarrhea and were culled when they reached pre-specified humane endpoints. 2.8.6 and 11.5.1 antibody treated mice were relatively spared, with survival comparable to control mice reconstituted with syngeneic cells. (b) 5 weeks after cell transfer mice were culled and colon weight to length ratio was calculated as a marker of gut inflammation. 2.8.6 and 11.5.1 treatment prevented the colon thickening seen in untreated mice.

Figure 10

(a) Effect of D265A mutated clone 11.5.1 in a T cell transfer assay *in vivo*. This mutated antibody, which does not bind Fc receptors, no longer inhibited proliferation of humanised

BTLA cells, instead lead to enhanced proliferation due to receptor blockade. (b) The D265A mutated 11.5.1 antibody no longer inhibited T cell proliferation in a mixed lymphocyte reaction.

Figure 11

Anti-BTLA antibodies do not fix complement. Splenocytes from humanised BTLA mice were incubated with 10% rabbit complement for 1 hour at 37°C in the presence of 20µg/ml BTLA antibody, isotype control or positive control (a depleting CD20 antibody). Anti-CD20 antibody depleted the majority of B cells confirming the activity of the rabbit complement, but BTLA antibodies did not deplete either B or T cells, even though both these populations stain positive for BTLA.

Figure 12

Anti-BTLA antibodies do not cause antibody-dependent-cell-mediated cytotoxicity. Splenocytes from humanised BTLA mice were incubated for 24 hours at 37°C in the presence of 20µg/ml BTLA antibody, isotype control or positive control (a depleting CD20 antibody). Anti-CD20 antibody depleted the majority of B cells by inducing ADCC by effector cells in the mixture, but BTLA antibodies did not deplete either B or T cells, even though both these populations stain positive for BTLA.

Figure 13

Anti-BTLA antibodies do not deplete B or T cells *in vivo*. Humanised BTLA mice were injected with 200µg of 2.8.6 antibody. At 24 hours spleens and bone marrow were collected and cell populations assessed by flow cytometry. 2.8.6 did not deplete B or T cells in the spleen or affect the frequency of different B cell precursor populations in the bone marrow.

Figure 14

BTLA expression levels on B cells or CD4⁺ T cells from humanised mice following 6 days of *in vivo* incubation with antibodies 2.8.6 or 11.5.1, compared to BTLA expression on cells from mice injected with isotype control antibody.

EXAMPLES

In the examples that follow it is shown that antibodies 11.5.1 and 2.8.6 bind to human BTLA with high affinity. Using transgenic mice expressing the human receptor it is shown that,

following binding to BTLA, these antibodies inhibit T cell responses *in vitro* and *in vivo* and are able to ameliorate disease in murine models of inflammatory bowel disease and graft- versus-host disease. Whilst these agonist effects are dependent on Fc-receptor binding, the antibodies do not cause depletion of BTLA expressing cells via cytotoxicity and do not induce receptor down-modulation.

Example 1. Generation and sequencing of anti-BTLA antibodies

Antibodies recognizing the human immune cell receptor BTLA were generated by BioGenes GmbH via immunizing mice with the extracellular region of human BTLA (BTLA^{K31-R151}). Splenocytes from immunized mice were fused with Sp2/0-Ag14 myeloma cells and resulting hybridomas selected for reactivity with human BTLA by ELISA of supernatants, in conjunction with dilution cloning. Antibodies were isotyped from hybridoma supernatant using a Rapid Mouse Isotyping Kit (RayBiotech). The antibodies produced by clones 2.8.6 and 11.5.1 were both found to be IgG1k.

To sequence the immunoglobulin variable domains, RNA was extracted from hybridomas using TRIzol Reagent (ThermoFisher) as per the manufacturer's instructions. RNA was reverse transcribed to produce cDNA using primers specific for the first constant domain of the heavy chain or for the constant domain of the light chain, and Super Script II Reverse Transcriptase (Invitrogen) as per manufacturer's instructions.

PCR was then performed using primers targeting conserved regions of the immunoglobulin locus as previously described (Tiller et al., J Immunol Methods. 350:183-193, 2009) and PCR products were sequenced. In some cases identification of functional light chain was complicated by abundant non-functional kappa light chain cDNA from the fusion myeloma cell line, and to resolve this a previously described technique was employed, adding excess primer specific for the non-functional chain CDR3 to force truncation of the aberrant chain product (Yuan et al. J Immunol Methods. 294:39553-61, 2005).

Variable domain sequences were assessed using the NCBI IgBlast tool to determine the location of the CDRs.

Example 2. Binding to soluble human and cynomolgus BTLA

The binding affinity and kinetics of the BTLA agonist antibodies of the present invention (2.8.6 and 11.5.1) to human or cynomolgus BTLA were determined by surface plasmon resonance using the Biacore T200 (GE Healthcare). Mouse antibody capture kit (GE Healthcare) was used to coat a Series S CM5 Sensor Chip (GE Healthcare) with polyclonal anti-mouse IgG. Anti-BTLA antibody was then captured onto the biosensor surface and a negative control antibody (clone Mopc21; Biolegend) captured in the reference channel. Various concentrations of monomeric soluble human BTLA extracellular domain (BTLA^{K31-R151}) (from SEQ ID NO: 23) or soluble cynomolgus macaque BTLA extracellular domain (BTLA^{K31-R151}) (from SEQ ID NO: 24) were then injected over the immobilized antibodies in the buffer 10 mM Hepes, 150 mM NaCl, 0.005% v/v Surfactant P20, pH 7.4 (HBS-P) at 37°C, in a single cycle kinetics analysis (**Fig. 1a**). Association and dissociation rates were fitted using BiaEvaluation Software (GE Healthcare) after reference and blank subtractions, and dissociation constants were calculated (**Fig. 1b**). Clone 2.8.6 binds human BTLA with a KD of 0.65 nM and cynomolgus BTLA with a KD of 7.89 nM. Clone 11.5.1 binds human BTLA with a KD of 0.75 nM and cynomolgus BTLA with a KD of 0.99 nM. In a separate experiment against human BTLA only, Clone 2.8.6 bound human BTLA with a KD of 0.37 nM and Clone 11.5.1 bound human BTLA with a KD of 0.53 nM.

Example 3. Binding to BTLA on cells

The ability of the BTLA agonist antibodies of the present invention (2.8.6 and 11.5.1) to bind to human or cynomolgus BTLA expressed on the cell surface was assessed by flow cytometry. A lentiviral transfection system was used to express full length human or cynomolgus BTLA in a Jurkat T cell line. 1×10^5 cells per well were plated in 96 well U-bottom plates. BTLA antibody binding versus mIgG1 isotype control (clone MOPC-21, Biolegend #400165) was assessed at twelve concentrations by 1 in 3 serial dilution in FACS buffer (PBS, 2% FCS, 0.05% sodium azide), starting at a concentration of 90 µg/ml. Non-specific antibody binding was prevented by addition of Fc block (Biolegend #101319). Antibodies were incubated with cells for 30 minutes on ice, then cells were washed twice with FACS buffer prior to staining with an AF647 conjugated anti-mIgG1 secondary antibody (Biolegend #406618). Secondary antibody was incubated for 30 minutes on ice, then cells were washed and resuspended in FACS buffer for analysis on a flow cytometer. The geometric mean fluorescent intensity of secondary antibody

was plotted for each concentration and the EC₅₀ for receptor binding calculated by non-linear curve fitting using GraphPad Prism software. Clone 11.5.1 binds to human BTLA expressing cells with an EC₅₀ of 0.016 nM and cynomolgus BTLA expressing cells with an EC₅₀ of 0.0057 nM. Clone 2.8.6 binds to human BTLA expressing cells with an EC₅₀ of 0.085 nM and cynomolgus BTLA expressing cells with an EC₅₀ of 0.16 nM (**Fig. 1c-d**).

Example 4. Competition with the natural ligand HVEM for binding to BTLA

The ability of the BTLA agonist antibodies of the present invention (2.8.6 and 11.5.1) to block natural ligand binding to BTLA was assessed by surface plasmon resonance using the Biacore T200 (GE Healthcare). Human BTLA extracellular domain (BTLA^{31K-151R}) was covalently coupled to a CM5 Sensor chip using amine coupling. Human HVEM extracellular domain, fused to mouse IgG1 Fc, was then injected over the immobilized hBTLA in HBS-P buffer at 37°C, and allowed to fully dissociate. A saturating amount of anti-BTLA antibody (2.8.6 or 11.5.1) was then injected, followed immediately by a second injection of human HVEM-mFc at the same concentration as the initial injection (**Fig. 2a**). Equilibrium HVEM binding (in Resonance Units) after saturation of BTLA with antibody was expressed as a percentage of binding prior to antibody injection (**Fig. 2b**). If HVEM binding following saturation with antibody was >90% of the binding prior to antibody injection then the antibody was considered non-blocking.

Example 5. Binding epitope of antibody 11.5.1 on human BTLA

The functional epitope of the antibody 11.5.1 on human BTLA was determined by flow cytometry assessment of binding to a panel of single residue mutants of the receptor expressed on the cell surface. Constructs encoding the human extracellular region of BTLA with the transmembrane and intracellular regions of murine CD28 were cloned into the bi-cistronic mammalian expression vector pGFP2-n2 (BioSignal Packard Ltd), which also encodes GFP. Mutant constructs varying by one amino acid were prepared using the "drastic" mutagenesis approach (Davis et al. Proc Natl Acad Sci USA. 95, 5490-4 (1998)). Plasmids (2 µg/well) were transfected into HEK- 293T cells in 6 well plates using Genejuice transfection reagent (Novagen; 6 µl/well). Mock and no-transfection controls were included with each experiment. Cells were harvested at 48 hours and stained with fluorochrome-conjugated anti-BTLA antibody at 10 µg/ml, alongside a Live/Dead marker, in PBS, 0.05% azide, 2% FCS (FACS buffer) for 1 h at 4°C. Cells were washed, pelleted and resuspended in 200 µl FACS buffer before being analysed

on a BD FACSCanto flow cytometer. GFP-positive (transfected) viable cells were gated and analysed for binding of anti-BTLA antibodies (an example of the binding analysis for clone 11.5.1 is shown in **Fig. 3a**). For each mutant the Geo-mean of anti-BTLA antibody binding to transfected cells was expressed as a percentage of binding to the wild-type receptor (**Fig. 3b**). A panel of anti-BTLA antibodies was assessed and any mutation that eliminated binding of all antibodies was excluded from the analysis, on the assumption that such mutations lead to drastic changes in protein folding or expression rather than indicating an antibody epitope. The mutations Y39R and K41E completely abolish binding of antibody 11.5.1 whilst leaving binding of 2.8.6 unaffected. These mutations are mapped onto the human BTLA crystal structure (Compaan et al., J Biol Chem. 280:39553-61, 2005) in **Fig. 3c** (black residues), indicating the binding epitope of 11.5.1. Residues required for HVEM binding (Gln37, Arg42, Pro59, His127; from patent publication number WO2017004213) are also mapped onto the structure in grey demonstrating that 11.5.1 binds to an epitope very close to the HVEM binding site.

Example 6. Crystal structure of the Fab' fragment of 2.8.6 in complex with human BTLA

The structural epitope of antibody 2.8.6 on human BTLA was determined by solving the crystal structure of antibody Fab in complex with human BTLA extracellular domain. The heavy and light variable domains of antibody 2.8.6 were cloned into the pOPIN VH and pOPIN VL expression vectors (Addgene), which encode the first constant domain of the mouse IgG1 heavy chain (with a 6xHistidine tag) and the constant domain of the mouse Ig kappa chain, respectively. These vectors were transiently co-transfected into HEK293T cells to produce the Fab' fragment of anti-BTLA 2.8.6, which was purified by Ni-NTA purification. Human BTLA Ig-V set domain (BTLA^{S33-D135}) was cloned into the pGMT7 vector and expressed in BL21(DE3)pLysS *E. coli* cells (Novagen) to produce inclusion bodies. The inclusion bodies were isolated from the cell pellet by sonication and washed repeatedly with a wash solution containing 0.5% Triton X-100. The purified BTLA inclusion bodies were solubilized in a denaturant solution containing 6 M guanidine hydrochloride. The solubilized protein solution was diluted slowly in refolding buffer [0.1 M Tris-HCl (pH 8.0), 0.6 M L-arginine, 2 mM ethylenediaminetetraacetic acid, 3.73 mM cystamine, and 6.73 mM cysteamine] to a final protein concentration of 1–2 μ M and then stirred for 48 h at 4°C. The refolded mixture of BTLA was then concentrated with a VIVA FLOW50 system (Sartorius). BTLA was purified by gel filtration on a Superdex 75 column (GE Healthcare).

The purified BTLA and Fab' were mixed and purified as a complex by size exclusion chromatography. The crystal suitable for data collection was obtained in 0.2 M calcium acetate, 0.1 M imidazole pH 8.0, 10%(w/v) PEG 8000 at 293°K by the hanging drop vapor- diffusion method. The final dataset was collected at the Photon Factory, and the structure was determined by molecular replacement using the structure of BTLA (PDB ID: 2AW2 chain A) and anti-PD1- Fab (PDB ID: 5GGS chain C, D) as search probes.

The residues on BTLA at the interface with antibody 2.8.6 are A50, G51, D52, P53, E83, D84, R85, Q86, E103, P104, V105, L106, P107, N108, D135.

Example 7. Development of humanised BTLA mice

To provide a platform to assess anti human-BTLA antibodies in mouse models, a knock-in strain of C57Bl/6 mice was developed expressing a chimeric form of BTLA with the human extracellular region and the murine transmembrane and signaling regions. A section of human genomic DNA from the beginning of exon 2 to the end of exon 3 was inserted into the mouse locus replacing the mouse sequence from the beginning of exon 2 to the end of exon 4. The sequences at the exon-intron junction at the beginning of mouse exon 2 and end of mouse exon 4 were left intact to ensure proper splicing (**Fig. 5**).

Example 8. Inhibition of antigen-specific T cell proliferation *in vivo*

The ability of the BTLA agonist antibodies of the present invention (2.8.6 and 11.5.1) to inhibit antigen specific T cell proliferation *in vivo* was assessed using a sensitive T-cell transfer assay (**Fig. 6a**). In this assay, 5×10^5 T-cells, comprising a mixture of purified OTII (TCR transgenic) CD4⁺ T cells specific for ovalbumin (OVA) from mice expressing homozygous human BTLA (hBTLA), and from OT-II mice expressing the wild-type murine BTLA receptor (The Jackson Laboratory), were transferred into non- transgenic C57BL/6 recipients. The transferred cells were distinguished from host cells using the CD45.2 (versus CD45.1) allotypic marker. The wild-type donor cells also expressed green fluorescent protein under the control of the human ubiquitin C promoter to allow them to be distinguished from the humanised donor cells by flow cytometry. The day after T cell transfer, the recipient mice were immunised with 100 µg ovalbumin (Sigma-Aldrich) in 100 µl PBS mixed with 100 µl Imject Alum (ThermoFisher), to induce expansion of the T cells. On the second day, the mice were dosed with 200 µg of antibody, intraperitoneally. Eight days following the initial transfer of the T cells, the ratio of the

humanised BTLA-expressing and wild-type OVA-specific T-cells in the spleen was determined by flow cytometry. In this way, it was possible to track the expansion or contraction of the humanised cells, which bind the anti-human BTLA antibodies, relative to the wild-type controls, which do not. Both antibodies 2.8.6 and 11.5.1 led to reduced expansion of the humanised BTLA cells relative to the wild-type controls indicating that they are inducing signaling through the inhibitory BTLA receptor, which leads to reduced T cell proliferation (**Fig. 6b**).

Example 9. Inhibition of T cell proliferation in a mixed lymphocyte reaction

The ability of the BTLA agonist antibodies of the present invention (2.8.6 and 11.5.1) to inhibit proliferation of primary T cells from the humanised mice *in vitro* was assessed using a mixed lymphocyte reaction (MLR). Splenocytes from Balb/c mice were treated with Mitomycin C for 30 mins at 37°C then washed and used as stimulator cells. T cells were purified from the spleens of humanised BTLA mice, by negative selection using magnetic-activated cell sorting (Mojosort Mouse CD3 T cell isolation kit, Biolegend #480023), and stained with CellTrace Violet Cell Proliferation Kit (ThermoFisher) to use as responder cells. 4×10^5 stimulator cells and 2×10^5 responder cells per well were mixed in 96-well U- bottom plates with various concentrations of anti-BTLA or isotype control antibody (clone MOPC-21, Biolegend #400165). Serial 1 in 3 dilutions of antibody were assessed starting at a concentration of 1 µg/ml for a total of 10 concentrations. Polyclonal anti-mHVEM antibody (R&D systems #AF2516) was also added to all wells at 401 µg/ml to block any baseline signaling through the BTLA pathway and accentuate the effects of agonist antibodies. After 96 hours, dilution of CellTrace Violet in responder cells was assessed by flow cytometry as a marker of proliferation. Proliferation in the presence of anti-BTLA antibody or isotype control was compared to proliferation in the absence of antibody. CD4⁺ and CD8⁺ populations were gated out and analysed separately. Both antibodies 2.8.6 and 11.5.1 reduced proliferation of human-BTLA expressing T cells, indicating that they induce inhibitory signaling through the human BTLA receptor. Clone 2.8.6 inhibited CD4 T cells with an IC₅₀ of 0.029 nM and had a maximal effect of 42% inhibition of proliferation (**Fig. 7**). Clone 11.5.1 inhibited CD4 T cells with an IC₅₀ of 0.016 nM and had a maximal effect of 33% inhibition of proliferation.

Example 10. Inhibition of NFkB signalling in human BTLA or cynomolgus BTLA transfected Jurkat T cell lines

The ability of the BTLA agonist antibodies of the present invention (2.8.6 and 11.5.1) to inhibit NFkB signalling was assessed using a BTLA transfected reporter T cell line. A Jurkat T cell line stably transfected with an expression cassette that includes NF-κB-responsive transcriptional elements upstream of a minimal CMV promoter (mCMV)-GFP cassette (Source BioSciences #TR850A-1) was used as a reporter cell line for NFkB signalling. A lentiviral transfection system was used to express full length human or cynomolgus BTLA in this reporter cell line. These cells were mixed with a stimulator cell line comprised of bw5147 cells expressing an anti-CD3 ScFv construct on their surface as described by Leitner et al. J Immunol Methods. 2010 Oct 31;362(1-2):131-41. The stimulator cell line was also transfected with murine FcγRIIB to provide Fc receptors for presentation of the agonist BTLA antibodies. 5×10^4 reporter cells per well were mixed in 96 well U-bottom plates with 5×10^4 stimulator cells in the presence of various concentrations of BTLA antibody or isotype control (clone MOPC-21, Biolegend #400165). After 24 hours incubation at 37°C, cells were pelleted and stained for flow cytometry with a viability dye (Zombie Aqua, Biolegend #423101) and a mouse CD45 antibody (Pe-Cy7 conjugated clone 104, Biolegend #109830) to separate stimulator (murine) from responder (human) cells. Geometric mean of GFP expression was assessed for each antibody concentration and normalized to GFP expression in the absence of antibody. Clone 2.8.6 inhibited human BTLA transfected cells with an IC₅₀ of 0.06 nM and cynomolgus BTLA transfected cells with an IC₅₀ of 0.22 nM. Clone 11.5.1 inhibited human BTLA transfected cells with an IC₅₀ of 0.033 nM and cynomolgus BTLA transfected cells with an IC₅₀ of 0.14 nM.

Example 11. Treatment of a T cell driven mouse model of colitis by antibody 2.8.6

The ability of the BTLA agonist antibody 2.8.6 to ameliorate a T cell driven model of colitis was assessed using the humanised mice. This T cell transfer model has previously been described as a murine model of inflammatory bowel disease (Ostanin et al., Am J Physiol Gastrointest Liver Physiol. 296:G135-46, 2009). CD45RB^{hi}CD25-CD4⁺ T cells sorted from spleens and lymph nodes of humanised BTLA mice were injected intraperitoneally into Rag1 KO recipients, (Rag1^{tm1Mom}, The Jackson Laboratory), at a dose of 5×10^5 cells per mouse. The transferred T cells cause an inflammatory colitis that develops after approximately 3 weeks and leads to diarrhea and weight loss. Rag1 KO cagemates that did not receive transferred T cells serve as

non- diseased controls. On days 7, 21 and 35 after T cell transfer the recipient mice were injected intraperitoneally with 200 µg of 2.8.6 or isotype control antibody. All mice were weighed regularly, and at 8 weeks colons were weighed and measured and inflammatory infiltration assessed by histology, as well as by cell counting and flow cytometry of extracted lamina propria leucocytes. Antibody 2.8.6 prevented weight loss (**Fig. 8a**) and significantly reduced inflammatory infiltration of colons (**Fig. 8b**). Colon inflammation in diseased mice led to an increased colon weight:length ratio that was not seen in 2.8.6 treated mice (**Fig. 8c**).

Example 12. Treatment of a mouse model of graft-versus-host disease (GVHD)

The effects of the anti-BTLA agonist antibodies were assessed in a non-lethal parent-into-F1 model of GVHD. Bone marrow cells (BMCs) and splenocytes were harvested from humanised BTLA donor mice (C57BL/6 background; H2^b). 2x10⁷ BMCs and 10⁷ splenocytes were injected intravenously into CB6F1 (H2^{b/d}) recipients that had been lethally irradiated with 9 Gy total body irradiation. Irradiated CB6F1 mice reconstituted with syngeneic BMCs and splenocytes served as non-diseased controls. On the day of immune cell transfer mice were injected intraperitoneally with 200 µg anti-BTLA antibody or isotype control. Mice were weighed regularly and GVHD was monitored by calculating relative loss of body weight and by clinical observation. Mice were culled 5 weeks after immune cell transfer or when they reached a humane endpoint (which included >20% weight loss relative to starting weight in the first 14 days, or >15% weight loss at any other time). At the time of death colons were weighed and measured and a colon weight:length ratio calculated as a marker of colon inflammation, which is a prominent clinical feature of GVHD. Both antibodies 2.8.6 and 11.5.1 significantly reduced weight loss, leading to increased survival (**Fig. 9a**) and prevented colon inflammation (**Fig. 9b**).

Example 13. Agonist activity of antibody 11.5.1 is dependent on Fc receptor binding

Antibody 11.5.1 was recombinantly expressed as a mIgG1k containing a D265A mutation which has previously been described as significantly reducing Fc receptor binding (Clynes et al., Nat Med. 6:443-446, 2000). This mutated antibody was assessed in the T cell transfer assay described in Example 8. The parental 11.5.1 antibody inhibited proliferation of humanised T cells as its net effect is agonism of the BTLA receptor. The FcR-null D265A mutation, however, led to enhanced proliferation of humanised T cells suggesting that the FcR-null mutation removes the antibody's agonistic effect, leaving only the effect of receptor blockade (**Fig. 10a**).

The D265A mutated 11.5.1 antibody was also assessed in the *in vitro* MLR assay described in Example 9. Again, the parental 11.5.1 antibody inhibited proliferation of humanised T cells as its net effect is agonism of the BTLA receptor. The FcR-null D265A mutation removes the antibody's agonistic effect, so this antibody showed no effect in this assay (**Fig. 10b**). The FcR null 11.5.1 antibody did not enhance proliferation of humanised cells in this assay as HVEM was blocked (by the addition of polyclonal anti-HVEM antibody) so there was no baseline signaling through the pathway to be blocked by the BTLA blocking antibody.

Example 14. Antibodies 2.8.6 and 11.5.1 do not fix complement *in vitro*

Splenocytes from humanised mice were incubated with 10% baby rabbit complement (BioRad) and anti-BTLA antibodies (or an isotype control or a positive control depleting anti-CD20 antibody; clone SA271G2 from Biolegend) at 20 µg/ml for 15 min at 37°C. Whilst anti-CD20 antibody depleted the majority of B220⁺ B cells, anti-BTLA antibodies did not deplete either B220⁺ or CD4⁺ cells (**Fig. 11**), even though both these populations stain positively for BTLA.

Example 15. Antibodies 2.8.6 and 11.5.1 do not induce ADCC *in vitro*

Whole splenocytes (including myeloid effector cells) from humanised mice were incubated with anti-BTLA antibodies (or isotype control or depleting anti-CD20 antibody SA271G2) at 20 µg/ml for 24 hours at 37°C. Whilst anti-CD20 antibody depleted the majority of B220⁺ cells, anti-BTLA antibodies did not deplete either B220⁺ or CD4⁺ cells (**Fig. 12**), even though both these populations stain positively for BTLA.

Example 16. Antibodies 2.8.6 and 11.5.1 do not deplete BTLA expressing cells *in vivo*

Humanised BTLA mice were injected intraperitoneally with 200 µg anti-BTLA antibody or isotype control. At 24 hours spleens were harvested and the frequency of different cell populations identified by flow cytometry. Anti-BTLA antibody had no effect on the frequency or absolute number of B or T cells in the spleen or on the number of B cell precursors in the bone marrow (**Fig. 13**).

Example 17. Antibodies 2.8.6 and 11.5.1 stabilize expression of BTLA on immune cells *in vivo*

Humanised mice were injected intraperitoneally with 10 mg/kg of antibody 2.8.6 or 11.5.1. Six days after injection mice were humanely sacrificed and spleens harvested and processed to single

cell suspension for assessment by flow cytometry. Cells were stained with a cocktail of antibodies to identify immune cell subsets and with fluorescently conjugated anti-BTLA antibody that had a non-competing epitope with the antibody that had been injected. The geometric mean of BTLA staining following *in vivo* incubation with anti-BTLA antibody was normalized to the geometric mean of BTLA staining (using the same staining antibody) following incubation with isotype control. BTLA expression was significantly higher on B cells and CD4 T cells from mice that had been injected with either clone 2.8.6 or 11.5.1, compared to mice that had been injected with isotype control (**Fig. 14**). This suggests that clones 2.8.6 and 11.5.1 stabilise expression of BTLA on the cell surface *in vivo*, rather than inducing receptor down-modulation, as has been observed with other BTLA antibodies in the prior art (M.-L. del Rio et al. / Immunobiology 215 (2010) 570–578). For the purposes of immunosuppression an agonist antibody that stabilizes expression of the receptor presents the benefit of enabling prolonged high levels of inhibitory signaling through the pathway compared to a downmodulating antibody.

Example 18. Tolerability and side effects in animal models

There were no tolerability issues or side effects noted in any animal studies with antibodies 2.8.6 or 11.5.1.

Example 19. Humanisation of antibody 2.8.6

Antibody 2.8.6 was humanised by CDR grafting on to homologous human germline framework regions (See SEQ ID NO: 13 -14). IGHV2-5*08 was used for the heavy chain and IGKV3-11*01 for the light chain. After humanisation, binding to BTLA was assessed by SPR. Humanised 2.8.6 bound to monomeric BTLA with a K_D of 0.73 nM.

Example 20. Characterisation of exemplary BTLA antibodies

Described in this example is characterisation of exemplary mIgG1 BTLA antibodies provided herein in addition to 2.8.6 and 11.5.1. Various clones listed in **Table 1** were evaluated for their binding affinity to BTLA and inhibition efficiency of lymphocytes (**Table 2**). For each antibody, the association rate (“on rate”) and dissociation rate (“off rate”) for binding human BTLA, and K_D for binding human or cynomolgus BTLA were measured according to the method described in Example 2, fitting curves for injection of BTLA extracellular domain at a single concentration.

Inhibition efficiency of individual antibodies on T cells was also evaluated at a single concentration of 10 µg/ml. MLR assay was performed for each individual antibody according to the method as described in Example 9 (two biological repeats as shown in **Table 3**); anti-CD3 assay was performed according to the method described below (two biological repeats, **Table 3**); and inhibition of NFκB signalling in human BTLA transfected Jurkat T cell line by each antibody was determined according to the method as described in Example 10 (**Table 3**). The average inhibition of T cells relative to isotype control in various *in vitro* stimulation assays for each exemplary antibody was calculated as a mean of the percentage inhibition of all assay results (**Table 2** and **Table 3**).

The ability of the BTLA agonist antibodies to inhibit anti-CD3 and anti-CD28 induced T cell activation was assessed as follows. Splenocytes from humanised BTLA mice were processed to single cell suspension and treated with ACK buffer to lyse red blood cells. Cells were stained with CFSE (Biolegend Cat #423801) to enable tracking of cell proliferation. 2×10^5 cells per well were plated in 96 well U-bottom plates with soluble anti-CD3 antibody (clone 145.2C11; Biolegend #100339) and anti-CD28 (clone 37.51; Biolegend #102115) each at a concentration of 50 ng/ml, and soluble anti-BTLA antibody or isotype control at a concentration of 10 µg/ml. After 72 hours cells were analysed by flow cytometry to assess proliferation (“antiCD3/CD28 (CD4 T cell proliferation)”) and T cell activation by staining of surface expressed activation markers (“antiCD3/CD28 (CD69+ CD4 T cells)”). For each BTLA antibody the percentage inhibition compared to isotype control antibody was calculated.

Further, for each BTLA antibody, their ligand blocking capability, *e.g.*, competition with HVEM for binding to BTLA, was assessed according to the method as described in Example 4, and the results are presented as “Yes” for more than 90% inhibition of HVEM-BTLA binding, and “No” for less than 10% inhibition of HVEM-BTLA binding. Functional epitope of each BTLA antibody was also determined according to the method as described in Example 5. The “epitope” column in **Table 2** summarizes the epitope group that each individual BTLA antibody binds to. Antibodies 2.8.6, 6.2, 831, 16H2, 7A1, 16F10, 6G8, 3E8, 4E8, 15C6, 12F11, 10B1, 15B6, 4D3, 16E1, 4D5 and 3A9 all bind to a first epitope (named “epitope 1” in the table) comprising at least one critical residue selected from the list: D52, P53, E55, E57, E83, Q86, E103, L106 and E92. Antibodies binding to epitope 1 do not compete with the ligand HVEM for binding to BTLA.

Antibodies 11.5.1, 14D4, 1H6, 8C4, 27G9, 26F3 all bind to a different second epitope (“epitope 2”) comprising at least one critical residue selected from the list: Y39, K41, R42, Q43, E45 and S47. Antibodies binding to epitope 2 do compete with the ligand HVEM for binding to BTLA. Antibody 26B1 binds to a third epitope (“epitope 3”) comprising at least one critical residue selected from the list: D35, T78, K81, S121 and L123. Antibodies binding to epitope 3 do compete with the ligand HVEM for binding to BTLA. Antibodies 24H7, 4B1, 8B4, 4H4 all bind to a different fourth epitope (“epitope 4”) comprising the critical residue H68. Antibodies binding to epitope 4 do not compete with the ligand HVEM for binding to BTLA. Antibody 21C7 binds to a different fifth epitope (“epitope 5”) comprising at least one critical residue selected from the list: N65 and A64. Antibodies binding to epitope 5 do not compete with the ligand HVEM for binding to BTLA.

Example 21. Humanisation and CDR engineering of BTLA antibodies 3E8 and 6.2

The variable domains of 3E8 and 6.2 were humanised by germlining to homologous human germline framework regions (Seq ID No. 382 – 385). For 3E8 the acceptor frameworks selected were VH1-1-08 and JH6 for the heavy chain and VK3-L6 and JK2 for the light chain. For 6.2 the acceptor frameworks selected were VH3-3-21 and JH6 for the heavy chain and VK2-A19 and JK4 for the light chain.

It is sometimes possible to substitute certain residues in the CDRs of an antibody to remove undesirable characteristics without significantly impacting target binding. The CDRH2 of the humanised antibody 6.2 was modified with D54E and N56Q substitutions (Seq ID No. 387) to remove deamidation potential (the engineered humanised VH sequence of 6.2 is given in Seq ID No. 390). Similarly, the CDRH2 of the humanised antibody 3E8 was modified with an N57Q substitution (Seq ID No. 388) to remove deamidation potential, and a K63S substitution to reduce predicted immunogenicity, as determined by Lonza’s Epibase analysis (the engineered humanised VH sequence of 3E8 is given in Seq ID No. 389).

Table 2. Characterisation of binding affinity and inhibitory effect of exemplary antibodies

Clone	Ligand Blocking	Human BTLA On rate (1/Ms)	Human BTLA Off rate (1/s)	Human BTLA KD (nM)	Cyno BTLA KD (nM)	Average inhibitory effect <i>in vitro</i>	Epitope
2.8.6	No	6.46E+05	4.23E-04	0.65	7.89	39%	1
24H7	No	2.43E+05	1.60E-04	0.66	-	30%	4
11.5.1	Yes	6.03E+05	4.49E-04	0.75	0.99	30%	2
14D4	Yes	2.54E+05	3.77E-04	1.49	1.83	33%	2
6.2	No	6.30E+05	1.07E-03	1.70	9.71	35%	1
4B1	No	5.77E+05	1.85E-03	3.21	-	29%	4
8B4	No	5.38E+05	4.40E-03	8.17	-	29%	4
16H2	No	3.97E+05	3.27E-03	8.25	160.1	34%	1
1H6	Yes	7.72E+05	6.90E-03	8.94	6.08	31%	2
8C4	Yes	3.63E+05	5.76E-03	15.89	161.48	19%	2
26B1	Yes	3.23E+05	9.70E-03	30.03	167.66	21%	3
7A1	No	4.13E+05	1.66E-02	40.17	-	24%	1
21C7	No	9.30E+05	4.06E-02	43.65	-	18%	5
16F10	No	5.81E+05	2.83E-02	48.78	-	-	1
6G8	No	3.18E+05	1.67E-02	52.42	-	-	1
3E8	No	5.43E+05	6.08E-02	111.98	607.46	41%	1
4E8	No	1.75E+05	3.14E-02	180.00	-	-	1
27G9	Yes	1.92E+05	8.38E-02	436.86	653.63	16%	2
15C6	No	1.93E+05	1.38E-01	718.44	-	-	1
12F11	No	2.15E+05	1.55E-01	722.33	-	24%	1
10B1	No	4.22E+05	5.21E-01	1233.36	-	21%	1
15B6	No	4.47E+05	5.76E-01	1287.18	-	14%	1
4D3	No	1.52E+05	2.51E-01	1651.32	-	-	1
4H4	No	2.03E+05	3.47E-01	1708.23	-	26%	4
26F3	Yes	9.21E+05	2.02E+00	2195.81	809.75	9%	2
16E1	No	7.30E+05	2.13E+00	2923.69	-	15%	1
4D5	No	2.70E+05	7.90E-01	2929.18	-	-	1
3A9	No	4.06E+05	1.63E+00	4006.90	-	19%	1

Table 3. Inhibitory effect assay results of exemplary antibodies

Clone	MLR (CD4 T cell proliferation)		AntiCD3/CD28 (CD4 T cell proliferation)		AntiCD3/CD28 (CD69+ CD4 T cells)		T cell reporter (NFκB signaling)	Average
	repeat 1	repeat 2	repeat 1	repeat 2	repeat 1	repeat 2		
2.8.6	30%	36%	23%	35%	58%	67%	22%	39%
24H7	23%	31%	13%	23%	52%	44%	22%	30%
6.2	31%	35%	19%	21%	53%	61%	26%	35%
11.5.1	23%	18%	21%	28%	50%	47%	19%	30%
11.5.1 D265A	-3%	1%	-3%	-9%	-47%	-26%	-13%	-14%
4B1	33%	30%	14%	18%	47%	41%	23%	29%
14D4	39%	26%	24%	29%	43%	52%	16%	33%
831	25%	34%	10%	8%	50%	53%	24%	29%
16H2	40%	26%	11%	23%	51%	60%	29%	34%
1H6	31%	16%	26%	19%	47%	53%	26%	31%
8B4	33%	23%	20%	4%	51%	47%	24%	29%
21C7	8%	17%	10%	-4%	39%	35%	23%	18%
3E8	43%	35%	27%	35%	52%	64%	30%	41%
7A1	23%	29%	14%	17%	28%	38%	20%	24%
26B1	12%	10%	11%	19%	35%	30%	29%	21%
8C4	42%	-2%	12%	4%	29%	29%	21%	19%
27G9	9%	8%	10%	13%	24%	22%	24%	16%
12F11	28%	23%	5%	9%	30%	40%	30%	24%
15C6	19%	8%	2%	-2%	12%	19%	9%	10%
26F3	9%	-5%	4%	0%	19%	17%	20%	9%
4D3	12%	9%	-4%	-2%	6%	2%	26%	7%
10B1	16%	25%	8%	14%	24%	36%	27%	21%
16E1	33%	8%	4%	8%	9%	23%	22%	15%
15B6	7%	13%	9%	16%	13%	20%	21%	14%
3A9	7%	24%	9%	9%	22%	34%	27%	19%
4H4	10%	17%	14%	22%	43%	52%	25%	26%
No antibody	3%	-3%	1%	-6%	2%	-9%	2%	-1%

SEQUENCE LISTING:

SEQ ID NO: 1

GDSITSAY

SEQ ID NO: 2

ISYSGST

SEQ ID NO: 3

ARSHYYGYFDY

SEQ ID NO: 4

ETIDSYGDSL

SEQ ID NO: 5

RAS

SEQ ID NO: 6

QQTDEDPYT

SEQ ID NO: 7

GFSLT TYG

SEQ ID NO: 8

MWPGGRT

SEQ ID NO: 9

VRGDYDYDYAMDY

SEQ ID NO: 10

SSVSY

SEQ ID NO: 11

ATS

SEQ ID NO: 12

HQWSSNPYT

SEQ ID NO: 13 - Humanised antibody 2.8.6 VH region

QVTLKESGPALVKPTQTLTLCTVSGFSLTTYGVHWIRQPPGKALEWLGVMPGGR
TSYNPSLKSRLTITKDNSKSQVVLMTNMDPVDATYYCVRGDYDYDYAMDYWG
QGTLVTVSS

SEQ ID NO: 14 - Humanised antibody 2.8.6 VL region

EIVLTQSPATLSLSPGERATLSCRASSSVSYMHWYQQKPGQAPRPLIYATSNRATGIP
ARFSGSGSGTDYTLTISSLEPEDFAVYYCHQWSSNPYTFGGGTKLEIK

SEQ ID NO:15 - Mouse Ab 2.8.6 VL region

QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPKPWIYATSNLASGV
PARFSGSGSGTSYSLTISRMEAEDAATYYCHQWSSNPYTFGGGTKLEIK

SEQ ID NO:16

caaattgtctctcccagtcctcagcaatcctgtctgcctcctcaggggagaaggtcacaatgactgcagggccagttcaagttaagt
acatgcactggtaccagcagaagccaggatcctcccccaccctggatttatgccacatccaacctggcttctggagtcctcgtcgc
ttcagtggcagtggtctgggaccttactctctcacaatcagcagaatggaggtgaagatgctgccacttattactgccaccagtg
agtagtaaccgtacacgttcggaggggggaccaagctggaataaaac

SEQ ID NO:17 = Mouse Ab 2.8.6 VH region

QVQLKESGPGLVAPSQLSITCTVSGFSLTTYGVHWVRQSPGKGLEWLGVMPGGR
TSYNPAPMSRLSISKDNSKSQVFLKMNSLQTDDTAMYYCVRGDYDYDYAMDYW
QGQTSVTVSS

SEQ ID NO:18

caggtgcagctgaaggagtctggacctggcctggcgcctcacagagcctgtccatcactgcactgtctctgggttttcattaacc
acctatggtgtacactgggttcgccagtctccaggaaagggtctggagtggctgggagtaatgtggcctggtggaagaacaagtata
atccggctccatgtccagactgagcatcagcaaagacaactccaagagccaagtttcttaaaatgaacagtctgcaaactgatgac

acggccatgtactactgtgtcagaggggactatgaatacgattactatgctatggactactgggtcaaggaaacctcagtcaccgtctcctca
g

SEQ ID NO:19 - Mouse Ab 11.5.1 VL region

DIVLTQSPASLAVSLGQRATISCRASETIDSYGDSLMHWYQQKAGQPPKLLIYRASNL
ESGIPARFSGSGSRTDFTLTINPVEADDVATYYCQQTDEDPTYTFGGGTKLEIK

SEQ ID NO:20

gacattgtgtgacccaatctccagcttcttggctgtgtctctagggcagagggccaccatcctgcagagccagtgaactattgat
agttatggcgatagttaatgcactgggtaccagcagaaagcaggacagccacccaaactcctcatctatcgtgcatccaacctagaatct
gggatccctgccaggttcagtggtcgtgggtctcggacagacttcacccaccattaatcctgtggaggctgatgatgttgcaacctat
tactgtcagcaaaactgatgaggatccgtacacgttcggaggggggaccaagctggaataaaa

SEQ ID NO:21 - Mouse Ab 11.5.1 VH region

EVQLQESGPSLVKPSQTLSTCSVTGDSITSAYWNWIRKFPGNKLEYMGYISYSGSTY
FNPSLKSRISITRNTSKNQYYLQLNSVTTEDTATYYCARSHYYGYFFDYWGHGTTLTVS
S

SEQ ID NO:22

gaggtgcagcttcaggagtcaggacctagcctcgtgaaacctctcagactctgtccctcacctgttctgtcactggcgactccatcacc
agtgttactggaactggatccggaattccaggggaataaacttgagtacatgggtacataagctacagtggtagcacttacttcaat
ccatctctcaaaagtcgaatctccatcactcgaaacacatccaagaaccagtactacctgcagttgaattctgtgactactgaggacaca
gccacatattactgtgcaagatctcattactacggctactacttggactactggggccatggcaccactctcacagtctctca

SEQ ID NO:23 - Human (Homo sapiens) BTLA polypeptide. Positions 1-30 is signal sequence,
31-151 is extracellular region, 152-178 is transmembrane region and 179 to end is intracellular
region

MKTLPAMLGTGKLFVFFLIPYLDIWNHKGESCDVQLYIKRQSEHSILAGDPFELEC
PVKYCANRPHVTWCKLNGTTCVKLEDRQTSWKEEKNISFFILHFEPVLPNDNGSYRC
SANFQSNLIESHSTTL YVTDVKSASERPSKDEMASRPWLLYRLPLGGLPLLITTCFCL

FCCLRRHQGKQNELSDTAGREINLVDAHLKSEQTEASTRQNSQVLLSETGIYDNDPD
LCFRMQEGS EVYSNPCLEENKPGIVYASLNHSHVIGPNSRLARNVKEAPTEYASICVRS

SEQ ID NO:24 – cynomolgus monkey (*Macaca fascicularis*) BTLA polypeptide.

MKTLPAMLGSGRLFWVFLIPYLDIWNHKGESCDVQLYIKRQSYHSIFAGDPFKLECPV
KYCAHRPQVTWCKLNGTTCVKLEGRHTSWKQEKNSFFILHFEPVLPDNGSYRCSANF
LSAIIESHSTTLYVTDVKSASERPSKDEMASRPWLLYSLLPLGGLPLLITTCFCLFCFLRR
HQGKQNELSDTTGREITLVDVPFKSEQTEASTRQNSQVLLSETGIYDNEPDCFRCMQEGS
EVYSNPCLEENKPGIYASLNHSIIGLNSRQARNVKEAPTEYASICVRS

Table 4. Exemplary CDR Sequences

SEQ ID NOs	Amino Acid Sequences	SEQ ID NOs	Amino Acid Sequences
31	SYGIS	114	WQGTTFPQT
32	EIYPRSGNTYYNEKFKG	117	TYYGSSQYYFDY
33	NYGSSYPFAY	121	DYYIN
34	SASSSVSSSYLH	122	RIYPGSGNTYYNEKFKG
35	RTSNLAS	123	GYGNSDY
36	QQWSGYPFT	124	RASQSIGTRIH
37	DYYMN	125	YASESIS
38	DINPNNGGTSYNQKFKG	126	QQSNSWPYT
39	WRQLRSDY	127	SYAIR
40	LASQTIGTWLA	128	EIYPRSGNTYYNENFKG
41	AATSLAD	129	SGGASYTMDY
42	QQLYSTPLT	133	SYGLI
43	SYWMH	134	EIYPRSGSTYYNEWFKG
44	MIHPNNGIPNYNEKFKS	135	RRGTGDGFDY
45	EGYYGSEGYFDV	136	SASQGISNYLN
46	SASSSISYIH	137	YTSSLHS
47	DTSKLAS	138	QQYIELPFT
48	HQRSTYPYT	139	DYYMH
56	MIHPNSGSTNYNEKFKS	140	YIYPNNGGNGYNQKFKG

SEQ ID NOs	Amino Acid Sequences	SEQ ID NOs	Amino Acid Sequences
57	KRGGLGDY	141	GDYYGSLRLTFAY
58	RASKSVSTSGYSYMH	142	KSSQSLLYSSNQKNYLA
59	LASNLES	143	WASTRES
60	QHSRELPYT	144	QQYYSYPLT
61	SSWMN	145	TYGVS
62	RIYPGDGDTNYNGKFKG	146	WINTYSGVPTYADDFKG
63	RGYGYLAY	147	VTILHWYFDV
64	KASQDVSTAVA	148	RASQEISGYLS
65	SASYRYT	149	AASTLDS
66	QQHYSTPYT	150	LQYASYPFT
69	GYGSSYGfAY	159	RRGAGDGFYD
72	QQWSGYPWT	162	QQYSKLPT
73	SGYYWN	169	DHTIH
74	YISYDGSNNYNPSLKN	170	YIYPRDGSTKYNEKFKG
75	IYGNYYAMDY	171	SNWNFDY
76	SASSSVSYMH	172	KASQDVGTA
78	QQWSSNPPT	173	WASTRRT
79	DYYMI	174	QQYSSYPLT
80	NINPNNGGTTYNQKFKG	180	QQHYSTPWT
81	GGLRPLYFDY	182	EIYPRSGTTYNEKFKG
82	KASENVDYVS	183	RISSGSGVDY
83	GASNRYT	186	QQYSELPWT
84	GQSYSYPLT	187	SGYDWH
85	NTYMH	188	YISYSGSTNYNPSLKS
86	RIDPANGNTKYDPKFQG	189	GTPVVAEDYFDY
87	TYYGSSQHYFDY	190	RSSTGAVTTSNYAN
88	KSSQSLLDSDGKTYLN	191	ATNNRAP
89	LVSKLDS	192	ALWYSNHLV
90	WQDTHFPQT	193	TYGVH
92	RIYPGDGDANYNGKFKG	194	VMWPGGRTSYNPAPMS
93	EGHYYGSGYRWYLDV	195	GDYEYDYYAMDY
94	RASENIYSNLA	196	RASSSVSYMH
95	AATNLAD	197	ATSNLAS
96	QHFRGAPFT	199	SAYWN
97	DYEIH	200	YISYSGSTYFNPSLKS
98	PIDPDTGNTAYNQNLKG	201	SHYYGYFFDY
99	GGYDSDWGFAY	202	RASETIDSYGDSLMMH
100	RSSKSLLHSNGNTFLF	203	RASNLES

SEQ ID NOs	Amino Acid Sequences	SEQ ID NOs	Amino Acid Sequences
101	RMSDLAS	205	SYGMS
102	MQHLEYPFT	206	SIRSDGNTYYPDSVKG
103	DYYLN	207	GGYYGSSPYY
104	LIDPYNGGSSCNQKFKG	209	WASTRDS
105	GNAMDY	210	QQYYNYLT
107	WASTRHT	211	SGYSWH
108	QQHYIIPYM	212	YIHYSGSTNYNPSLKS
109	NTYMY	213	GPHRYDGVWFAY
110	RIDPANGNTKYAPKFQG	214	SASSSISSNYLH
111	LYYGSSYDYFDY	216	QQGTNIPLT
386	EIYPRSGNTYYAQKFQG	388	EIYPRSGQTYAQSFG
387	SIRSEGQTYYPDSVKG		

Table 5. Exemplary Primary VH and VL Sequences

SEQ ID NOs	Amino Acid Sequences
301	QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWIGEI YPRSGNTYYNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARNYG SSYPFAYWGQGTLLTVSA
302	EVQLQQSGPELVKPGASVKISCKASGYTFTDYYMNWVKQSHGKSLEWIGD INPNNGGTSYNQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCARWR QLRSDYWGQGTTTLTVSS
303	QVQLQQPGAELVKPRASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIG MIHPNNGIPNYNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYHCAREG YYGSEGYFDVWGTGTTTVTVSS
305	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIG MIHPNSGSTNYNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARKR GGLGDYWGQGTSVTVSS
306	QVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPGKGLEWIG RIYPGDGDTNYNGKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFCARR GYGYLAYWGQGTLLTVSA
307	QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWIGEI YPRSGNTYYNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARGYG SSYGFAYWGQGTLLTVSA
308	DVQLQESGPELVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMG YISYDGSNNYNPSLKNRISITRDTSKNQFFLKLNSVTTEDTATYYCASIYGN YYAMDYWGQGTSVTVSS

SEQ ID NOs	Amino Acid Sequences
309	EVQLQQSGPELVQPGASVKISCKASGYTFTDYMIWVKQSHGKSLEWIGNI NPNNGGTTYNQKFKGKATLTVDKSSSTAYMGLPSLTSEDSAVYYCARGGL RPLYFDYWGQGTTTLTVSS
310	EVQLQQSVAELVRPGASVKLSCTASGFNIKNTYMHWVKQRPEQGLEWIGR IDPANGNTKYDPKFQGKATITADTSSNTAYVQLSSLTSEDTAIYYCALTYY GSSQHYFDYWGQGTTTLTVSS
311	QIQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKKRPKGKLEWIGRI YPGDGDANYNGKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYFCAGEGH YYGSGYRWYLDVWGTGTTVTVSS
312	QVQLQQSGAELVRPGASVTLSCASGYTFTDYEIHVKQTLVHGLEWIGPI DPDTGNTAYNQNLKGKAILTADKSSSTAYMELRSLTSEDSAVYYCTRGGY DSDWGFAYWGQGTTLTVSA
313	EVQLQQSGPVLVKPGASVKMSCKASGYTFTDYLNWVKQSHGKSLEWIG LIDPYNGGSSCNQKFKGKATLTVDKSSSTAYMDLNSLTSEDSAVYYCARG NAMDYWGQGTSTVTVSS
314	EVQLQQSVAELVRPGASVKLSCTASGFNIKNTYMYWVKQRPEQGLEWIGR IDPANGNTKYAPKFQGKATITADTSSNTAYLQLSSLTSEDTAIYYCALLYYG SSYDYFDYWGQGTTTLTVSS
315	EVQLQQSVAELVRPGASVKLSCTASGFNIKNTYMHWVKQRPEQGLEWIGR IDPANGNTKYAPKFQGKATITADTSSNTAYLQLSSLTSEDTAIYYCALTYYG SSQYYFDYWGQGTTTLTVSS
316	QVQLKQSGAELVRPGASVKLSCKASGYTFTDYINWVKQRPQGQLEWIAR IYPGSGNTYYNEKFKGKATLTAEKSSSTAYMQLSSLTSEDSAVYFCARGYG NSDYWGQGTTLTVSS
317	QVQLQQSGAELARPGASVRLSCKASGYTFTSYAIRWVKQRTGQGLEWIGEI YPRSGNTYYNENFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARSGG ASYTMDYWGQGTSTVTVSS
318	QVQLQQSGAELARPGASVRLSCKASGYTFTSYGLIWLKQRTGQGLEWIGEI YPRSGSTYYNEWFKGKATLTADKSSNTAFMELRSLTSEDSAVYFCARRRG TGDGFDYWGQGTILTVSS
319	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYMHWVKQSHGKSLEWIG YIYPNNGGNGYNQKFKGKATLTVDKSSSTAYMELRSLTSEDSAVYYCAIG DYYGSLRLTFAYWGQGTTLTVSA
320	QIQLVQSGPELKKPGETVKISCKASGYTFTTYGVSWVKQAPGKVLKWMG WINTYSGVPTYADDFKGRFAFSLETSASTAYLQISNLKNEDTATYFCAPVT TILHWYFDVWGTGTTVTVSS
321	QVQLQQSGAELARPGASVRLSCKASGYTFTSYGISWVKQRTGQGLEWIGEI YPRSGNTYYNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARNYG SSYPFAYWGQGTTLTVSA

SEQ ID NOs	Amino Acid Sequences
322	QVQLQQSGAELARPGASVKLSCKASGYTFTSYGISWVKQRTGQGLEWIGEI YPRSGNTYYNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARRRG AGDGFYWGQGTTTLTVSS
324	QDQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWKQRPEQGLEWIGY IYPRDGSTKYNEKFKGKATLTADKSSSTAYMQLNSLTSEDSAVYFCASSN WNFDYWGQGTTTLTVSS
326	QVQLQQSGAELARPGASVKLPCKASGYTFTSYGISWVKQRTGQGLEWIGEI YPRSGTYYNEKFKGKATLTADKSSSTAYMELRSLTSEDSAVYFCARRIS GSGVDYWGQGTTTLTVSS
327	DVQLQESGPGMVKPSQSLSTCTVTGYSITSGYDWHWIRHFPGNKLEWMG YISYSGSTNYPNPSLKSRISITHDTSKNHFFLKLNSVTTEDTATYYCARGTPV VAEDYFDYWGQGTTTLTVSS
330	EVKLVESGGGLVKPGGSLKLSCAASGFTLSSYGMSWVRQIPEKRLEWVASI RSDGNTYYPDSVKGRFIISRDNARNILYLMSSLRSEDAMYYCTRGGYYG SSPYWYGQGTTTLTVSS
331	DVQLQESGPDLVKPSQSLSVTCTVTGYSITSGYSWHWIRQFPGNKLEWMG YIHYSGSTNYPNPSLKSRISITRDTSKNQFFLQLSSVTTEDTATYYCASGPHRY DGVWFAYWGQGLTVTVSS
351	ENVLTQSPAIMAASLGQKVTMTCSASSSVSSSYLHWYQQKSGASPKPLIHR TSNLASGVPARFSGSGSGTSYSLTISSVEAEDDATYYCQQWSGYPTFGGG TKLEIK
352	DIQMTQSPASQSASLGESVTITCLASQTIGTWLAWYQQKPGKSPQLLIYAAT SLADGVPSRFSGSGSGTKFSFKISLQAEDFVSYYCQQLYSTPLTFGAGTKL ELK
353	QIVLTQSPAIMSASPGEKVTMTCSASSSISYIHWYQQKPGTSPKRWIYDTSK LASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQRSTYPYTFGGGTKL EIK
355	DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHYQQKPGQPPKLLI YLASNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPYTFGG GTKLEIK
356	DIVMTQSHKFMSTSVGDRV SITCKASQDVSTAVAWYQQKPGQSPKLLIYS ASYRYTGVPDRFTGSGSGTDFTFISSVQAEDLAVYYCQQHSTPYTFGGG TKLEIK
357	ENVLTQSPAIMAASLGQKVTMTCSASSSVSSSYLHWYQQKSGASPKPLIHR TSNLASGVPARFSGSGSGTSYSLTISSVEAEDDATYYCQQWSGYPTFGGG TKLEIK
358	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMHYQQKSGTSPKRWIYDTS KLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPPTFGSGTK LEIK

SEQ ID NOs	Amino Acid Sequences
359	NIVMTQSPKSMMSVGERVTLSCKASENVDTYVSWYQQKPEQSPKLLIYG ASNRYTGVPDRFTGSGSATDFTLTISVQAEDLADYHCGQSYSYPLTFGAG TKLELI
360	DVVMQTQPLTSLVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRPQGSPKRL IYLVSKLDSGVPDRFTGSGSGTDFTLKISRVEAEDLGVYYCWQDTHFPQTF GGGTKLEIK
361	DIQMTQSPASLSVSVGETVTITCRASENIYSNLAWYQQKQKSPQLLVYAA TNLADGVPSRFSGSGSGTQYSLKINSLQSEDFGSYYCQHFRGAPFTFGSGTK LEIK
362	DIVMTQATPSVPVTPGESVSISCRSSKSLHNSNGNTFLFWFLQRPQGSPQLLI YRMSDLASGVPDRFSGSGSGTAFTLRISRVEAEDVGIYYCMQHLEYPFTFG SGTKLEIK
363	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQEKPGQSPKLLIYW ASTRHTGVPDRFTGSGSGTDYILNISSVQAEDLALYYCQQHYIIPYMFGGGT KLEIK
364	DVVMQTQPLTSLVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRPQGSPKRL IYLVSKLDSGVPDRFTGSGSGTDFTLKISRVEAEDLGVYYCWQDTHFPQTF GGGTKLEIK
366	DILLTQSPAILSVSPGERVSFSCRASQSIGTRIHWWYQQRNGSPRLLIKYASES ISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQSNSWPYTFGGGTKLEIK
367	ENVLTQSPAIMAASLGQKVTMTCSASSSVSSSYLHWYQQKSGASPKPLIHR TSNLASGVPARFSGSGSGTSYSLTISVVEAEDDATYYCQQWSGYPTFTFGSGT KLEIK
368	DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTVKLLIYYTS SLHSGVPSRFSGSGSGTDYSLTISNLEPEDIATYYCQQYIELPFTFGSGTKLEI K
369	DIVMSQSPSSLAVSVGEKVTMSCKSSQSLLYSSNQKNYLAWYQQKPGQSP KLLIYWASTRESGVPDRFTGSGSGTDFTLTISVKAEDLAVYYCQQYYSSYP LTFGAGTKLELK
370	DIQMTQSPSSLASLGERVSLTCRASQEISGYLSWLQQKPDGTIKRLIYAAS LDGVPKRFGRSGSDYSLTISLESEDFADYYCLQYASYPFTFGSGTKLEI K
372	DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTVKLLIYYTS SLHSGVPSRFSGSGSGTDYSLTISNLEPEDIATYYCQQYSKLPFTFGSGTKLE IK
374	DIVMTQSHKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYW ASTRRTGVPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPLTFGAGT KLELK
375	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYS ASYRYTGVPDRFTGSGSGTDFTTISVQAEDLAVYYCQQHYSTPWTFGGG TKLEIK

SEQ ID NOs	Amino Acid Sequences
376	DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTVKLLIYYTS SLHSGVPSRFSGSGSGTDYSLTISNLEPEDIATYYCQQYSELPWTFGGGTKL EIK
377	QAVVTQESALSTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDHLFTGLIG ATNNRAPGVPARFSGSLIGDKAALTITGAQTEDEAIYFCALWYSNHLVFGG GTKLTVLG
378	DIVMTQSPLSLPVTGPGEPAISCKSSQSLLYSSNQKNYLAWYQQKPGQSPKL LIYWASTRESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQYYNYLTF GGGTKVEIK
380	DIVMSQSPSSLPVSVGEKISMTCKSSQSLLYSSNQKNYLAWYQQKPGQSPK LLIYWASTRDSGVPDRFIGSGSGTDFTLTINSVKAEDLAVYYCQQYYNYLT FGAGTKLELK
381	EIVLTQSPPTMAASPGEKITITCSASSISSNYLHWYQQKPGFSPKLLIYRTSN LASGVPARFSGSGSGTSYSLTIGTMEAEDVATYYCQQGTNIPLTFGAGTKL EIK
382	QVQLVQSGAELKKPGASVKVSCASGYTFTSYAIRWVRQATGQGLEWMG EIYPRSGNTYYAQKFQGRATLTADKSISTAYMELSSLRSEDVAVYFCARSG GASYTMDYWGQGTTVTVSS
383	ENVLTQSPATLSLSPGERATLSCSASSSVSSSYLHWYQQKPGQSPRPLIHRTS NLASGIPARFSGSGSGTDYTLTISSLEPEDFAVYYCQQWSGYPTFGSGTKL EIK
384	EVQLVESGGGLVKPGGSLRLSCAASGFTLSSYGMSWVRQAPGKGLEWVA SIRSDGNTYYPD SVKGRFTISRDN AKNSLYLQMSSLRAEDTAVYYCTRGGY YGSSPYYWGQGTTVTVSS
385	DIVMTQSPLSLPVTGPGEPAISCKSSQSLLYSSNQKNYLAWYQQKPGQSPQL LIYWASTRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQYYNYLTF GGGTKVEIK
389	QVQLVQSGAELKKPGASVKVSCASGYTFTSYAIRWVRQATGQGLEWMG EIYPRSGQTYAQSFQGRATLTADKSTSTAYMELSSLRSEDVAVYFCARSG GASYTMDYWGQGTTVTVSS
390	EVQLVESGGGLVKPGGSLRLSCAASGFTLSSYGMSWVRQAPGKGLEWVA SIRSEGQTYYPDSVKGRFTISRDN AKNTLYLQMSSLRAEDTAVYYCTRGGY YGSSPYYWGQGTTVTVSS

CLAIMS:

What is claimed is:

1. An isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VH CDR that has an amino acid sequence as set forth in any of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID NO: 9 with from 0 to 3 amino acid modifications.
2. An isolated antibody or an antigen-binding fragment thereof that binds human BTLA comprising at least one VH CDR that has an amino acid sequence as set forth in any of SEQ ID NO: 31, 32, 33, 37, 38, 39, 43, 44, 45, 56, 57, 61, 62, 63, 69, 73, 74, 75, 79, 80, 81, 85, 86, 87, 92, 93, 97, 98, 99, 103, 104, 105, 109, 110, 111, 117, 121, 122, 123, 127, 128, 129, 133, 134, 135, 139, 140, 141, 145, 146, 147, 159, 169, 170, 171, 182, 183, 187, 188, 189, 193, 194, 195, 199, 200, 201, 205, 206, 207, 211, 212, 213, 386, 387 and 388 with from 0 to 3 amino acid modifications.
3. An isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR that has an amino acid sequence as set forth in SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 12.
4. An isolated antibody or an antigen-binding fragment thereof that specifically binds human BTLA comprising at least one VL CDR that has an amino acid sequence as set forth in SEQ ID NO: 34, 35, 36, 40, 41, 42, 46, 47, 48, 58, 59, 60, 64, 65, 66, 72, 76, 78, 82, 83, 84, 88, 89, 90, 94, 95, 96, 100, 101, 102, 107, 108, 114, 124, 125, 126, 136, 137, 138, 142, 143, 144, 148, 149, 150, 162, 172, 173, 174, 180, 186, 190, 191, 192, 196, 197, 202, 203, 209, 210, 214 or 216, with from 0 to 3 amino acid modifications.
5. An isolated human antibody or an antigen-binding fragment thereof that specifically binds B and T lymphocyte attenuator (BTLA), comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein (i) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3,

respectively, with from 0 to 3 amino acid modifications; or (ii) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9, respectively, with from 0 to 3 amino acid modifications.

6. An isolated human antibody or an antigen-binding fragment thereof that specifically binds B and T lymphocyte attenuator (BTLA), comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in (1) SEQ ID NO: 31, 32, or 33, with from 0 to 3 amino acid modifications; (2) SEQ ID NO: 37, 38, or 39, with from 0 to 3 amino acid modifications; (3) SEQ ID NO: 43, 44, or 45, with from 0 to 3 amino acid modifications; (4) SEQ ID NO: 43, 56, or 57, with from 0 to 3 amino acid modifications; (5) SEQ ID NO: 61, 62, or 63, with from 0 to 3 amino acid modifications; (6) SEQ ID NO: 31, 32, or 69, with from 0 to 3 amino acid modifications; (7) SEQ ID NO: 73, 74, or 75, with from 0 to 3 amino acid modifications; (8) SEQ ID NO: 79, 80, or 81, with from 0 to 3 amino acid modifications; (9) SEQ ID NO: 85, 86, or 87, with from 0 to 3 amino acid modifications; (10) SEQ ID NO: 61, 92, or 93, with from 0 to 3 amino acid modifications; (11) SEQ ID NO: 97, 98, or 99, with from 0 to 3 amino acid modifications; (12) SEQ ID NO: 103, 104, or 105, with from 0 to 3 amino acid modifications; (13) SEQ ID NO: 109, 110, or 111, with from 0 to 3 amino acid modifications; (14) SEQ ID NO: 85, 110, or 117, with from 0 to 3 amino acid modifications; (15) SEQ ID NO: 121, 122, or 123, with from 0 to 3 amino acid modifications; (16) SEQ ID NO: 127, 128, or 129, with from 0 to 3 amino acid modifications; (17) SEQ ID NO: 133, 134, or 135, with from 0 to 3 amino acid modifications; (18) SEQ ID NO: 139, 140, or 141, with from 0 to 3 amino acid modifications; (19) SEQ ID NO: 145, 146, or 147, with from 0 to 3 amino acid modifications; (20) SEQ ID NO: 31, 32, or 33, with from 0 to 3 amino acid modifications; (21) SEQ ID NO: 31, 32, or 159, with from 0 to 3 amino acid modifications; (22) SEQ ID NO: 169, 170, or 171, with from 0 to 3 amino acid modifications; (23) SEQ ID NO: 61, 62, or 63, with from 0 to 3 amino acid modifications; (24) SEQ ID NO: 31, 182, or 183, with from 0 to 3 amino acid

- modifications; (25) SEQ ID NO: 187, 188, or 189, with from 0 to 3 amino acid modifications; (26) SEQ ID NO: 193, 194, or 195, with from 0 to 3 amino acid modifications; (27) SEQ ID NO: 199, 200, or 201, with from 0 to 3 amino acid modifications; (28) SEQ ID NO: 205, 206, or 207, with from 0 to 3 amino acid modifications; (29) SEQ ID NO: 211, 212, or 213, with from 0 to 3 amino acid modifications; (30) SEQ ID NO: 127, 386, or 129, with from 0 to 3 amino acid modifications; (33) SEQ ID NO: 205, 206, or 207, with from 0 to 3 amino acid modifications; (34) SEQ ID NO: 127, 388, or 129, with from 0 to 3 amino acid modifications; or (35) SEQ ID NO: 205, 387, or 207, with from 0 to 3 amino acid modifications.
7. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein (i) CDRL1, CDRL2, CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, respectively, with from 0 to 3 amino acid modifications; or (ii) CDRL1, CDRL2, CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 10, 11, 12, respectively, with from 0 to 3 amino acid modifications.
8. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in (1) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, with from 0 to 3 amino acid modifications; (2) SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, with from 0 to 3 amino acid modifications; (3) SEQ ID NO: 46, SEQ ID NO: 47, and SEQ ID NO: 48, respectively, with from 0 to 3 amino acid modifications; (4) SEQ ID NO: 58, SEQ ID NO: 59, and SEQ ID NO: 60, respectively, with from 0 to 3 amino acid modifications; (5) SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively, with from 0 to 3 amino acid modifications; (6) SEQ ID NO: 34, SEQ ID

NO: 35, and SEQ ID NO: 72, respectively, with from 0 to 3 amino acid modifications; (7) SEQ ID NO: 76, SEQ ID NO: 47, and SEQ ID NO: 78, respectively, with from 0 to 3 amino acid modifications; (8) SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, respectively, with from 0 to 3 amino acid modifications; (9) SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, respectively, with from 0 to 3 amino acid modifications; (10) SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, respectively, with from 0 to 3 amino acid modifications; (11) SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, respectively, with from 0 to 3 amino acid modifications; (12) SEQ ID NO: 64, SEQ ID NO: 107, and SEQ ID NO: 108, respectively, with from 0 to 3 amino acid modifications; (13) SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively, with from 0 to 3 amino acid modifications; (14) SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, respectively, with from 0 to 3 amino acid modifications; (15) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, with from 0 to 3 amino acid modifications; (16) SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, respectively, with from 0 to 3 amino acid modifications; (17) SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, respectively, with from 0 to 3 amino acid modifications; (18) SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively, with from 0 to 3 amino acid modifications; (19) SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 162, respectively, with from 0 to 3 amino acid modifications; (20) SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, with from 0 to 3 amino acid modifications; (21) SEQ ID NO: 172, SEQ ID NO: 173, and SEQ ID NO: 174, respectively, with from 0 to 3 amino acid modifications; (22) SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 180, respectively, with from 0 to 3 amino acid modifications; (23) SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 186, respectively, with from 0 to 3 amino acid modifications; (24) SEQ ID NO: 190, SEQ ID NO: 191, and SEQ ID NO: 192, respectively, with from 0 to 3 amino acid modifications; (25) SEQ ID NO: 196, SEQ ID NO: 197, and SEQ ID NO: 12, respectively, with from 0 to 3 amino acid modifications; (26) SEQ ID NO: 202, SEQ ID NO: 203, and SEQ ID NO: 6, respectively, with from 0 to 3 amino acid modifications; (27) SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO:

- 210, respectively, with from 0 to 3 amino acid modifications; (28) SEQ ID NO: 214, SEQ ID NO: 35, and SEQ ID NO: 216, respectively, with from 0 to 3 amino acid modifications; (29) SEQ ID NO: 10, 11, or 12, respectively, with from 0 to 3 amino acid modifications; (30) SEQ ID NO: 4, 5, or 6, respectively, with from 0 to 3 amino acid modifications; or (31) SEQ ID NO: 142, 143, or 210, respectively, with from 0 to 3 amino acid modifications.
9. An isolated human antibody or an antigen-binding fragment thereof that specifically binds-BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 1, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 2, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 3, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 4, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 5, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 6.
 10. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and CDRH3, wherein CDRH1 has an amino acid sequence as set forth in SEQ ID NO: 7, CDRH2 has an amino acid sequence as set forth in SEQ ID NO: 8, and CDRH3 has an amino acid sequence as set forth in SEQ ID NO: 9, and the light chain comprises a light chain variable region comprising three CDRs: CDRL1, CDRL2 and CDRL3, wherein CDRL1 has an amino acid sequence as set forth in SEQ ID NO: 10, CDRL2 has an amino acid sequence as set forth in SEQ ID NO: 11, and CDRL3 has an amino acid sequence as set forth in SEQ ID NO: 12.
 11. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising three CDRs: CDRH1, CDRH2 and

acid sequence as set forth in SEQ ID NO: 76, SEQ ID NO: 47, and SEQ ID NO: 78, respectively, with from 0 to 3 amino acid modifications; (8) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 79, SEQ ID NO: 80, and SEQ ID NO: 81, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 82, SEQ ID NO: 83, and SEQ ID NO: 84, respectively, with from 0 to 3 amino acid modifications; (9) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 86, and SEQ ID NO: 87, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 90, respectively, with from 0 to 3 amino acid modifications; (10) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 92, and SEQ ID NO: 93, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96, respectively, with from 0 to 3 amino acid modifications; (11) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 97, SEQ ID NO: 98, and SEQ ID NO: 99, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 100, SEQ ID NO: 101, and SEQ ID NO: 102, respectively, with from 0 to 3 amino acid modifications; (12) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 103, SEQ ID NO: 104, and SEQ ID NO: 105, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 107, and SEQ ID NO: 108, respectively, with from 0 to 3 amino acid modifications; (13) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 109, SEQ ID NO: 110, and SEQ ID NO: 111, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively, with from 0 to 3 amino acid modifications; (14) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 85, SEQ ID NO: 110,

and SEQ ID NO: 117, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 88, SEQ ID NO: 89, and SEQ ID NO: 114, respectively, with from 0 to 3 amino acid modifications; (15) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 121, SEQ ID NO: 122, and SEQ ID NO: 123, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 124, SEQ ID NO: 125, and SEQ ID NO: 126, respectively, with from 0 to 3 amino acid modifications; (16) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 128, and SEQ ID NO: 129, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, with from 0 to 3 amino acid modifications; (17) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 133, SEQ ID NO: 134, and SEQ ID NO: 135, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 138, respectively, with from 0 to 3 amino acid modifications; (18) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 139, SEQ ID NO: 140, and SEQ ID NO: 141, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 144, respectively, with from 0 to 3 amino acid modifications; (19) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 145, SEQ ID NO: 146, and SEQ ID NO: 147, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively, with from 0 to 3 amino acid modifications; (20) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 148, SEQ ID NO: 149, and SEQ ID NO: 150, respectively,

with from 0 to 3 amino acid modifications; (21) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 159, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 162, respectively, with from 0 to 3 amino acid modifications; (22) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 169, SEQ ID NO: 170, and SEQ ID NO: 171, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 172, SEQ ID NO: 173, and SEQ ID NO: 174, respectively, with from 0 to 3 amino acid modifications; (23) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 61, SEQ ID NO: 62, and SEQ ID NO: 63, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 180, respectively, with from 0 to 3 amino acid modifications; (24) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 31, SEQ ID NO: 182, and SEQ ID NO: 183, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 136, SEQ ID NO: 137, and SEQ ID NO: 186, respectively, with from 0 to 3 amino acid modifications; (25) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 187, SEQ ID NO: 188, and SEQ ID NO: 189, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 190, SEQ ID NO: 191, and SEQ ID NO: 192, respectively, with from 0 to 3 amino acid modifications; (26) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 193, SEQ ID NO: 194, and SEQ ID NO: 195, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 196, SEQ ID NO: 197, and SEQ ID NO: 12, respectively, with from 0 to 3 amino acid modifications; (27) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 199, SEQ ID NO: 200, and SEQ ID NO: 201, respectively, with from 0 to

3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 202, SEQ ID NO: 203, and SEQ ID NO: 6, respectively, with from 0 to 3 amino acid modifications; (28) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively, with from 0 to 3 amino acid modifications; (29) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 211, SEQ ID NO: 212, and SEQ ID NO: 213, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 214, SEQ ID NO: 35, and SEQ ID NO: 216, respectively, with from 0 to 3 amino acid modification; (30) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 386, and SEQ ID NO: 129, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, with from 0 to 3 amino acid modification; (31) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 206, and SEQ ID NO: 207, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively, with from 0 to 3 amino acid modification; (32) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 127, SEQ ID NO: 388, and SEQ ID NO: 129, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 34, SEQ ID NO: 35, and SEQ ID NO: 36, respectively, with from 0 to 3 amino acid modification,; (33) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, and SEQ ID NO: 207, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 209, and SEQ ID NO: 210, respectively, with from 0 to

- 3 amino acid modification; or (34) CDRH1, CDRH2, CDRH3 have an amino acid sequence as set forth in SEQ ID NO: 205, SEQ ID NO: 387, and SEQ ID NO: 207, respectively, with from 0 to 3 amino acid modification, and CDRL1, CDRL2, and CDRL3 have an amino acid sequence as set forth in SEQ ID NO: 142, SEQ ID NO: 143, and SEQ ID NO: 210, respectively, with from 0 to 3 amino acid modification.
12. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 13, or a sequence with at least 90% identity thereto.
 13. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 14, or a sequence with at least 90% identity thereto.
 14. The antibody antigen-binding fragment thereof of any of the preceding claims, wherein the heavy chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13, and wherein the light chain variable region comprises an amino acid sequence that has at least 90% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 14, and wherein the antibody specifically binds to BTLA.
 15. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 17, or 21, or a sequence with at least 90% identity thereto.
 16. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 15, 19, or a sequence with at least 90% identity thereto.
 17. The antibody antigen-binding fragment thereof of any of the preceding claims, wherein:
(1) the heavy chain comprises a heavy chain variable region comprising an amino acid

- sequence as set forth in SEQ ID NO: 17, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 15; or (2) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 21, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 19, and wherein the antibody specifically binds to BTLA.
18. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 301, 302, 303, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 324, 326, 327, 330, 331, 382, 384, 389, or 390 or a sequence with at least 90% identity thereto.
19. An isolated human antibody or an antigen-binding fragment thereof that specifically binds BTLA, comprising a heavy chain and a light chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 351, 352, 353, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 366, 367, 368, 369, 370, 372, 374, 375, 376, 377, 378, 380, 381, 383 or 385 or a sequence with at least 90% identity thereto.
20. The antibody antigen-binding fragment thereof of any of the preceding claims, wherein: (1) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 301, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 351; (2) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 302, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 352; (3) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 303, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 353; (4) the heavy chain comprises a heavy chain variable region comprising an amino acid

sequence as set forth in SEQ ID NO: 305, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 355; (5) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 306, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 356; (6) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 307, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 357; (7) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 308, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 358; (8) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 309, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 359; (9) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 310, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 360; (10) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 311, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 361; (11) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 312, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 362; (12) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 313, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 363; (13) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 314, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 364; (14)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 315, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 364; (15)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 316, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 366; (16)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 317, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 367; (17)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 318, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 368; (18)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 319, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 369; (19)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 320, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 370; (20)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 321, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 370; (21)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 322, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 372; (22)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 324, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 374; (23)

the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 306, and the light chain comprises a light chain

variable region comprising an amino acid sequence as set forth in SEQ ID NO: 375; (24) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 326, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 376; (25) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 327, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 377; (26) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 17, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 15; (27) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 21, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 19; (29) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 330, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 380; (30) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 331, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 381; and wherein the antibody specifically binds to BTLA; (31) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 382, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 383; (32) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 384, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 385; (33) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 389, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 383; (34) the heavy chain comprises a heavy chain variable region

comprising an amino acid sequence as set forth in SEQ ID NO: 390, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 385; or (35) the heavy chain comprises a heavy chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 390, and the light chain comprises a light chain variable region comprising an amino acid sequence as set forth in SEQ ID NO: 378, and wherein the antibody binds to BTLA.

21. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein the heavy chain or light chain also comprise a constant region.
22. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein the heavy chain and light chain are connected by a flexible linker to form a single-chain antibody.
23. The antibody or antigen-binding fragment thereof of any of the preceding claims, which binds a residue of BTLA selected from: A50, G51, D52, P53, E83, D84, R85, Q86, E103, P104, V105, L106, P107, N108, D135.
24. The antibody or antigen-binding fragment thereof of claim 23, which binds a residue of BTLA selected from: Y39 and/or K41.
25. The antibody or antigen-binding fragment thereof of claim 23 or 24, which binds a residue of BTLA selected from: Y39 and K41.
26. The antibody or antigen-binding fragment thereof of any of the preceding claims, which is an IgG1, IgG2 or IgG4 antibody.
27. The antibody of any of the preceding claims, which is selected from the group consisting of: a human antibody, a humanised antibody, a chimeric antibody and a multispecific antibody (such as a bispecific antibody).
28. The antigen-binding fragment according to any of claims 1 to 26, which is selected from the group consisting of: scFv, sc(Fv)₂, dsFv, Fab, Fab', (Fab')₂ and a diabody.
29. The antibody or antigen-binding fragment thereof of any of the preceding claims, which is monoclonal.

30. The antibody or antigen-binding fragment thereof of any preceding claim, wherein said antibody or antigen-binding fragment thereof agonizes human BTLA expressed on the surface of an immune cell, wherein said immune cell is optionally a T cell.
31. The antibody or antigen-binding fragment thereof of any preceding claim, wherein binding of said antibody or antigen-binding fragment thereof to human BTLA expressed on the surface of an immune cell decreases proliferation of said cell relative to a comparable immune cell not bound by said antibody or antigen-binding fragment thereof, and wherein said cell is optionally a T cell.
32. The antibody or antigen-binding fragment thereof of claim 31, wherein said decrease in cell proliferation is measured by an assay described in Example 8 or Example 9.
33. The antibody or antigen-binding fragment thereof of claim 31 or 32, wherein said decrease in cell proliferation is measured in vitro or in vivo.
34. The antibody or antigen-binding fragment thereof of any one of claims 31-33, wherein said decrease in cell proliferation is at least about 10%, 15%, 20%, 25%, 30%, 40%, or 50%.
35. The antibody or antigen-binding fragment thereof of any one of claims 31-33, wherein said decrease in cell proliferation is from about 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 10% to 15%, 20% to 50%, 20% to 40%, or 20% to 30%.
36. The antibody or antigen-binding fragment thereof of any preceding claim, wherein said antibody or antigen-binding fragment thereof comprises a domain that binds to an Fc receptor.
37. The antibody or antigen-binding fragment thereof of claim 36, wherein said Fc receptor is expressed on the surface of an immune cell.
38. The antibody or antigen-binding fragment thereof of claim 37, wherein said immune cell is an antigen presenting cell.
39. The antibody or antigen-binding fragment thereof of claim 38, wherein said antigen presenting cell is a dendritic cell, macrophage, monocyte, or neutrophil.

40. The antibody or antigen-binding fragment thereof of any one of claims 36-39, wherein said antibody or antigen-binding fragment thereof binds to human BTLA expressed on the surface of a T cell.
41. The antibody or antigen-binding fragment thereof of claim 40, wherein said binding to said Fc receptor expressed on the surface of said immune cell and said binding of said antibody or antigen-binding fragment thereof to human BTLA on the surface of said T cell results in the cell surface of said immune cell and the cell surface of said T cell to be within 250Å, 200Å, 150Å, or 100Å.
42. The antibody or antigen-binding fragment thereof of claim 40, wherein said binding to said Fc receptor expressed on the surface of said immune cell and said binding of said antibody or antigen-binding fragment thereof to human BTLA on the surface of said T cell results in the cell surface of said immune cell and the cell surface of said T cell to be within 250Å to 100Å, 200Å to 100Å, 150Å to 100Å, 200Å to 150Å, or 250Å to 150Å.
43. The antibody or antigen-binding fragment thereof of any one of claims 36-42, wherein said Fc receptor is FcγRIIB.
44. The antibody or antigen-binding fragment thereof of any preceding claim, wherein binding of said antibody or antigen-binding fragment thereof to human BTLA expressed on the surface of an immune cell decreases NFκB signaling of said immune cell relative to a comparable immune cell not bound by said antibody or antigen-binding fragment thereof, and wherein said immune cell is optionally a T cell.
45. The antibody or antigen-binding fragment thereof of claim 44, wherein said decrease in NFκB signaling of said immune cell is measured by an assay described in Example 10.
46. The antibody or antigen-binding fragment thereof of claim 44 or 45, wherein said decrease in NFκB signaling of said immune cell is at least about 10%, 15%, 20%, 25%, 30%, or 40%.
47. The antibody or antigen-binding fragment thereof of claim 44 or 45, wherein said decrease in NFκB signaling of said immune cell is from about 10% to 40%, 10% to 30%, 10% to 20%, 20% to 40%, or 20% to 30%.

48. The antibody or antigen-binding fragment thereof of any preceding claim, wherein binding of said antibody or antigen-binding fragment thereof to human BTLA expressed on the surface of an immune cell decreases dephosphorylation of a cytoplasmic domain of said human BTLA.
49. The antibody or antigen-binding fragment thereof of claim 48, wherein said dephosphorylation is mediated by CD45 expressed on the surface of said immune cell.
50. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with a K_D of less than 10 nM, each as determined by surface plasmon resonance (SPR) at 37°C, and wherein said antibody binds cynomolgus BTLA with a K_D of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C; does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
51. The antibody or antigen-binding fragment thereof of claim 50, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms) at 37°C.
52. The antibody or antigen-binding fragment thereof of claim 50 or 51, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 3.0×10^{-4} (1/s) at 37°C.
53. The antibody or antigen-binding fragment thereof of any one of claims 50 to 52, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an off rate from 3.0×10^{-4} (1/s) to 1.0×10^{-3} (1/s).
54. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and wherein said

- antibody inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
55. The antibody or antigen-binding fragment thereof of claim 54, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 3.0×10^{-4} (1/s).
56. The antibody or antigen-binding fragment thereof of claim 54 or 55, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C.
57. The antibody or antigen-binding fragment thereof of any one of claims 54 to 56, wherein said antibody or antigen-binding fragment thereof wherein said antibody binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C.
58. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with an off rate from 3.0×10^{-4} (1/Ms) to 1.0×10^{-3} (1/Ms) as measured by surface plasmon resonance (SPR) at 37°C, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and wherein said antibody inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
59. The antibody or antigen-binding fragment thereof of claim 58, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C.
60. The antibody or antigen-binding fragment thereof of claim 58 or 59, wherein said antibody or antigen-binding fragment thereof binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C.

61. The antibody or antigen-binding fragment thereof of any one of claims 58 to 60, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of at least 5.0×10^5 (1/Ms).
62. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with an off rate of less than 1.0×10^{-3} (1/Ms) and an on rate of at least 5.0×10^5 (1/Ms), each as measured by surface plasmon resonance (SPR) at 37°C, wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and wherein said antibody inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
63. The antibody or antigen-binding fragment thereof of claim 62, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C.
64. The antibody or antigen-binding fragment thereof of claim 62 or 63, wherein said antibody or antigen-binding fragment thereof binds cynomolgus BTLA with a KD of less than 20 nM, as determined by surface plasmon resonance (SPR) at 37°C.
65. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 2 nM, as determined by surface plasmon resonance (SPR) at 37°C, wherein said antibody inhibits binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
66. The antibody or antigen-binding fragment thereof of claim 65, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with an on rate of less than 1.0×10^6 (1/Ms), as determined by surface plasmon resonance (SPR) at 37°C.
67. The antibody or antigen-binding fragment thereof of claim 65 or 66, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte

- Attenuator (BTLA) with an off rate of less than 1.0×10^{-3} (1/s), as determined by surface plasmon resonance (SPR) at 37°C.
68. The antibody or antigen-binding fragment thereof of any one of claims 65 to 67, wherein said antibody or antigen-binding fragment thereof binds cynomolgus B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C.
69. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on off rate of less than 1×10^{-3} (1/s), wherein said antibody inhibits binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
70. The antibody or antigen-binding fragment thereof of claim 69, wherein said antibody or antigen-binding fragment thereof binds cynomolgus B and T Lymphocyte Attenuator (BTLA) with a KD of less than 10 nM, as determined by surface plasmon resonance (SPR) at 37°C.
71. The antibody or antigen-binding fragment thereof of claim 69 or 70, wherein said antibody or antigen-binding fragment thereof binds human B and T Lymphocyte Attenuator (BTLA) with a KD of less than 2 nM, as determined by surface plasmon resonance (SPR) at 37°C.
72. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA), wherein said antibody binds cynomolgus BTLA with a KD of at least 5 nM, as determined by surface plasmon resonance (SPR) at 37°C; and wherein said antibody inhibits binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.
73. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T

Lymphocyte Attenuator (BTLA), wherein said antibody binds cynomolgus BTLA with a KD of at least than 50 nM, as determined by surface plasmon resonance (SPR) at 37°C; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in vitro, as determined by a mixed lymphocyte reaction assay.

74. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD from 1400 nM to 3500 nM, as measured by surface plasmon resonance (SPR) at 37°C; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in in vitro, as determined by a mixed lymphocyte reaction assay.
75. The antibody or antigen-binding fragment thereof of claim 74, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an on rate of at least 2.0×10^5 (1/Ms), as measured by surface plasmon resonance (SPR) at 37°C.
76. The antibody or antigen-binding fragment thereof of claim 74 or 75, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an off rate of less than 10.0×10^{-1} (1/s), as measured by surface plasmon resonance (SPR) at 37°C.
77. The antibody or antigen-binding fragment thereof of any one of claims 74 to 76, wherein said antibody or antigen-binding fragment thereof binds to an epitope that blocks binding of antibody 4H4.
78. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with an on rate from 1.7×10^5 (1/Ms) to 2.5×10^5 (1/Ms), as measured by surface plasmon resonance (SPR) at 37°C; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in in vitro, as determined by a mixed lymphocyte reaction assay.

79. The antibody or antigen-binding fragment thereof of claim 78, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an off rate of less than 3.0×10^{-1} (1/s), as measured by surface plasmon resonance (SPR) at 37°C.
80. The antibody or antigen-binding fragment thereof of claim 78 or 79, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an off rate from 3.0×10^{-1} (1/s) to 5.0×10^{-1} (1/s), as measured by surface plasmon resonance (SPR) at 37°C.
81. The antibody or antigen-binding fragment thereof of any one of claims 78 to 80, wherein said antibody or antigen-binding fragment thereof binds human BTLA with a KD of at least 150 nM, as measured by surface plasmon resonance (SPR) at 37°C.
82. The antibody or antigen-binding fragment thereof of any one of claims 78 to 81, wherein said antibody or antigen-binding fragment thereof binds human BTLA with a KD from 150 nM to 1500 nM, as measured by surface plasmon resonance (SPR) at 37°C.
83. The antibody or antigen-binding fragment thereof of any one of claims 78 to 82, wherein said antibody or antigen-binding fragment thereof binds to an epitope that blocks binding of 286 antibody.
84. The antibody or antigen-binding fragment thereof of any of the preceding claims, wherein said antibody or antigen-binding fragment thereof specifically binds human B and T Lymphocyte Attenuator (BTLA) with a KD from 40nM to 1200nM, as measured by surface plasmon resonance (SPR) at 37°C; and wherein said antibody does not inhibit binding of BTLA to herpes virus entry mediator (HVEM); and inhibits proliferation of T cells in in vitro, as determined by a mixed lymphocyte reaction assay.
85. The antibody or antigen-binding fragment thereof of claim 84, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an on rate of at least 1.0×10^5 (1/Ms), as measured by surface plasmon resonance (SPR) at 37°C.
86. The antibody or antigen-binding fragment thereof of claim 84 or 85, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an on rate from 1.0×10^5 (1/Ms) to 10×10^5 (1/Ms), as measured by surface plasmon resonance (SPR) at 37°C.

87. The antibody or antigen-binding fragment thereof of any one of claims 84 to 86, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an off rate of less than 6.0×10^{-1} (1/s), as measured by surface plasmon resonance (SPR) at 37°C.
88. The antibody or antigen-binding fragment thereof of any one of claims 84 to 87, wherein said antibody or antigen-binding fragment thereof binds human BTLA with an off rate from 6.0×10^{-1} (1/s) to 10.0×10^{-2} (1/s), as measured by surface plasmon resonance (SPR) at 37°C.
89. An isolated nucleic acid which comprises one or more nucleotide sequences encoding polypeptides capable of forming an antibody or antigen-binding fragment as claimed in any of claims 1 to 88.
90. A host cell comprising the nucleic acid sequence according to claim 89.
91. A method of producing an antibody or an antigen-binding fragment thereof that binds to BTLA, comprising the step of culturing the host cell of claim 90, under conditions for production of said antibody or an antigen-binding fragment thereof, optionally further comprising isolating and/or purifying said antibody or an antigen-binding fragment thereof.
92. A method for preparing a human antibody or antigen-binding fragment thereof that specifically binds BTLA, the method comprising the steps of:
- 1) providing a host cell comprising one or more nucleic acid molecules encoding the amino acid sequence of a heavy chain and a light chain which when expressed are capable of combining to create an antibody or antigen-binding molecule;
 - 2) culturing the host cell expressing the encoded amino acid sequence; and
 - 3) isolating the antibody or antigen-binding molecule of any of claims 1 to 88.
93. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any of claims 1 to 88 and at least one pharmaceutically acceptable excipient.
94. An antibody or antigen-binding fragment thereof in accordance with any of claims 1 to 88, or the pharmaceutical composition in accordance with claim 93, for use in therapy.

95. An antibody or antigen-binding fragment thereof in accordance with any of claims 1 to 88, or the pharmaceutical composition in accordance with claim 93, for use in the treatment or prevention of inflammatory or autoimmune diseases, and disorders of excessive immune cell proliferation.