

Monoclonal antibody or antigen-binding fragment thereof that specifically binds to TNF-like ligand 1A (TL1A), and use thereof

Field of the invention

The present invention relates to the field of biotechnology and medicine, in particular to a monoclonal antibody or antigen-binding fragment thereof that specifically binds to TNF-like ligand 1A (TL1A). The invention further relates to nucleic acids encoding said antibody, expression vectors, host cells and methods for producing same, methods for producing the antibodies according to the invention, pharmaceutical compositions comprising the antibody according to the invention, pharmaceutical compositions comprising the antibody according to the invention and other therapeutically active compounds, methods for treating TNF-like ligand 1A (TL1A)-mediated diseases or disorders, uses of the antibodies or pharmaceutical compositions thereof for treating TL1A-mediated diseases or disorders, and uses of the antibodies and other therapeutically active compounds for treating TL1A-mediated diseases or disorders.

Background of the invention

Monoclonal antibodies in the form of chimeric, humanized or fully human molecules have proven to be useful as effective medicine for treating multiple disorders and diseases.

TL1A (TNF-like ligand 1A) protein, also known as TNFSF15 (TNF superfamily member 15) and VEGI (vascular endothelial growth inhibitor) is a pro-inflammatory cytokine, a member of the tumor necrosis factor family, with a molecular weight of about 61.5 kDa in the form of a biologically active soluble trimer.

TL1A is initially expressed as a transmembrane protein consisting of 251 amino acid residues with a molecular weight of about 28.1 kDa (<https://www.uniprot.org/uniprotkb/O95150/entry>). In the general structure of the TL1A monomer there are three topological domains: an unstructured cytoplasmic domain (35 AARs), a helical transmembrane region (21 AARs) and an extracellular C-terminal region (195 AARs). Under the

influence of various factors, TL1A can be cleaved from the membrane by the ADAM17 protease (also known as TACE (TNF α -converting enzyme)); further, the polypeptide chain is cleaved between alanine residue 71 and leucine residue 72 to form a monomer of 180 amino acid residues (Zhai, Y., Ni, J., Jiang, G.-W., Lu, J., Xing, L., Lincoln, C., Carter, K. C., Janat, F., Kozak, D., Xu, S., Rojas, L., Aggarwal, B. B., Ruben, S., Li, L.-Y., Gentz, R., Yu, G.-L. *VEGI, a novel cytokine of the tumor necrosis factor family, is an angiogenesis inhibitor that suppresses the growth of colon carcinomas in vivo.* (1999) *FASEB J.* 13, 181–189, doi: 10.1096/fasebj.13.1.181).

On the surface of the native TL1A monomer there is a pronounced hydrophobic site leading to the formation of a biologically active trimer (Zhan C., Yan Q., Patskovsky Yu., Li Z., Toro R., Meyer A., Cheng H., Brenowitz M., Nathenson S.G., Almo S.C., *Biochemical and Structural Characterization of the Human TL1A Ectodomain.* (2009) *Biochemistry*: 48(32): 7636–7645, doi: 10.1021/bi900031w).

TL1A is expressed by monocytes, macrophages, dendritic cells, synovial fibroblasts and endothelial cells in response to being stimulated by microbial antigens, immune complexes and other factors (Hsu, H., Viney, J. *The tale of TL1A in inflammation.* *Mucosal Immunol* 4, 368–370 (2011). doi.org/10.1038/mi.2011.20).

The main receptor for TL1A is DR3 (death receptor 3), also known as TNFRSF25 (TNF receptor superfamily member 25).

The DR3 receptor is primarily expressed on activated lymphocytes such as NK cells and T cells (Aiba Y, Nakamura M. *The role of TL1A and DR3 in autoimmune and inflammatory diseases.* *Mediators Inflamm.* 2013;2013:258164. doi: 10.1155/2013/258164. Epub 2013 Dec 21. PMID: 24453414; PMCID: PMC3880748).

TL1A-DR3 interaction can induce both the development of an inflammatory response and apoptosis, the processes that are involved in the regulation of innate and acquired immunity. The DR3 receptor contains the so-called "death domain" (DD) in the cytoplasmic domain thereof. After binding to TL1A, the activated DR3 at the first stage interacts with the adapter protein TRADD in cellular cytoplasm by means of DD; thereafter the formation of a complex with other proteins such as TRAF2 and RIP1 takes place. This receptor-associated signaling complex, also called complex I, can activate MAPKs signaling pathways such as ERK, JNK, and p38, and also the NF κ B and PI3K pathways. Activation of these signaling pathways promotes proliferation and increase in the inflammatory response via increased expression of antiapoptotic proteins, cytokines and chemokines. Activation of NF κ B leads to induction of cellular inhibitors of apoptosis proteins 1/2 (cIAP1/2). Blocking of the complex I-mediated activation of antiapoptotic genes or improper formation and/or functioning of the complex causes DR3-mediated cytotoxicity. Blocking of intracellular protein synthesis by antibiotic cycloheximide does not lead to NF κ B activation,

resulting, in turn, in the shutdown of apoptosis inhibitor proteins, dissociation of RIPK1 from complex I and interaction of RIPK1 with the FADD adaptor protein and caspase 8. Next, initiator caspase 8 activates a cascade of effector caspases 3 and 7, leading to cell apoptosis. Another variant of the development of cell death involves proteins FADD, RIP3, RIP1 and effector protein MLKL to form an intracellular complex called a necrosome; the activity of caspase 8 is blocked in this case. It eventually triggers necroptosis, a form of programmed cell death accompanied by a strong immune response. It has been shown that TL1A-DR3 interaction in lymphocytes primarily activates proinflammatory pathways, rather than apoptosis (Bittner S, Ehrenschwender M. *Multifaceted death receptor 3 signaling-promoting survival and triggering death. FEBS Lett.* 2017 Sep;591(17):2543-2555. doi: 10.1002/1873-3468.12747. Epub 2017 Jul 20. PMID: 28686297; L. Wen, L. Zhuang, X. Luo, and P. Wei, "TL1A-induced NF- κ B activation and c-IAP2 production prevent DR3-mediated apoptosis in TF-1 cells," *The Journal of Biological Chemistry*, vol. 278, no. 40, pp. 39251–39258, 2003; Bamias G, Jia LG, Cominelli F. *The tumor necrosis factor-like cytokine 1A/death receptor 3 cytokine system in intestinal inflammation. Curr Opin Gastroenterol.* 2013 Nov;29(6):597-602. doi: 10.1097/MOG.0b013e328365d3a2. PMID: 24100723).

TL1A is the only known ligand for DR3, but also binds to the soluble decoy receptor DcR3, also known as TNFRSF6B (TNF receptor superfamily member 6B). This interaction does not lead to further biological effects, but is a way to maintain the concentration of TL1A in the blood at the required level. In turn, DcR3 is a secreted receptor capable of binding and neutralizing three TNF family ligands: FasL, LIGHT, TL1A. Studies comparing lymphocytes of the lamina propria in patients with chronic intestinal inflammation to those of healthy volunteers from a control group have shown that DcR3 was elevated at sites of active intestinal inflammation, as well as in the blood of patients; this is likely a secondary compensatory mechanism in response to increased expression of proinflammatory TL1A (Xu WD, Li R, Huang AF. *Role of TL1A in Inflammatory Autoimmune Diseases: A Comprehensive Review. Front Immunol.* 2022 Jul 14;13:891328. doi: 10.3389/fimmu.2022.891328; Bamias G, Jia LG, Cominelli F. *The tumor necrosis factor-like cytokine 1A/death receptor 3 cytokine system in intestinal inflammation. Curr Opin Gastroenterol.* 2013 Nov;29(6):597-602. doi: 10.1097/MOG.0b013e328365d3a2. PMID: 24100723; Zhan C, Patskovsky Y, Yan Q, Li Z, Ramagopal U, Cheng H, Brenowitz M, Hui X, Nathenson SG, Almo SC. *Decoy strategies: the structure of TL1A:DcR3 complex. Structure.* 2011 Feb 9;19(2):162-71. doi: 10.1016/j.str.2010.12.004. PMID: 21300286; Spyros I. Siakavellas, Giorgos Bamias, *Tumor Necrosis Factor-like Cytokine TL1A and Its Receptors DR3 and DcR3: Important New Factors in Mucosal Homeostasis and Inflammation, Inflammatory Bowel Diseases, Volume 21, Issue 10, 1 October 2015, Pages 2441–2452, <https://doi.org/10.1097/MIB.0000000000000492>*).

In intestinal homeostasis, the TL1A-DR3 signaling pathway performs a protective

function, being part of both innate and acquired immunity. Disruption of the barrier function of the intestinal epithelial mucosa leads to contamination of adjacent tissues with microorganisms whose structural components lead to stimulation of antigen-presenting cells (APCs) via Toll-like receptors or Fc γ receptors, thereby increasing the expression of TL1A, leading to the expansion and differentiation of CD4⁺ and CD8⁺ T cells, and to TCR-MHCII-independent production of inflammatory cytokines such as IFN γ , IL-6, TNF α , GM-CSF, IL-5, IL-13, and IL-22. TL1A also costimulates NK cells and innate lymphoid cells (ILCs). The interaction between TL1A and Tregs constitutively expressing DR3 results in proliferation thereof, but at the same time inhibits the suppressor function thereof (Valatas V, Kolios G, Bamias G. *TL1A (TNFSF15) and DR3 (TNFRSF25): A Co-stimulatory System of Cytokines With Diverse Functions in Gut Mucosal Immunity*. *Front Immunol*. 2019 Mar 27;10:583. doi: 10.3389/fimmu.2019.00583. PMID: 30972074; Spyros I. Siakavellas, Giorgos Bamias, *Tumor Necrosis Factor-like Cytokine TL1A and Its Receptors DR3 and DcR3: Important New Factors in Mucosal Homeostasis and Inflammation, Inflammatory Bowel Diseases, Volume 21, Issue 10, 1 October 2015, Pages 2441–2452*, <https://doi.org/10.1097/MIB.0000000000000492>; Wallace KL, Zheng LB, Kanazawa Y, Shih DQ. *Immunopathology of inflammatory bowel disease*. *World J Gastroenterol*. 2014 Jan 7;20(1):6-21. doi: 10.3748/wjg.v20.i1.6; Holmkvist P, Roepstorff K, Uronen-Hansson H, Sandén C, Gudjonsson S, Patschan O, Grip O, Marsal J, Schmidtchen A, Hornum L, Erjefält JS, Håkansson K, Agace WW. *A major population of mucosal memory CD4⁺ T cells, coexpressing IL-18R α and DR3, display innate lymphocyte functionality*. *Mucosal Immunol*. 2015 May;8(3):545-58. doi: 10.1038/mi.2014.87. Epub 2014 Oct 1. PMID: 25269704; PMCID: PMC4424383).

The TL1A-DR3 signaling pathway is a mediator of several autoimmune diseases, including chronic inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC). IBD is thought to result from a combination of genetic and environmental factors leading to an excessive inappropriate immune response against the commensal microflora in genetically susceptible people. The pathogenesis of chronic intestinal inflammation takes place, inter alia, due to overexpression of TL1A in the APCs in the lamina propria region in response to stimulation by intestinal microflora in patients with Crohn's disease and ulcerative colitis, but not in the intestinal tissues of healthy donors. TL1A expression level in patients with Crohn's disease correlated with severity of inflammation, especially at sites with significant inflammation (Giorgos Bamias, Charles Martin III, Marco Marini. *Expression, Localization, and Functional Activity of TL1A, a Novel Th1-Polarizing Cytokine in Inflammatory Bowel Disease*. *J Immunol* November 1, 2003, 171 (9) 4868-4874; doi.org/10.4049/jimmunol.171.9.4868).

TL1A, via interaction with DR3, activates effector T cells, mainly Th1, Th2, Th9, Th17,

as well as all ILC groups. As a result, immune cells produce cytokines and chemokines promoting the migration of circulating leukocytes, monocytes from the systemic bloodstream, development and maintenance of chronic inflammation in the intestine. TL1A, as a costimulator of IL-12 and IL-18, induces Th1 to produce IFN γ and TNF α ; the both lead to IFN α -mediated activation of tissue macrophages and to additional TNF α expression by the latter. These cytokines trigger apoptosis in intestinal epithelial cells and differentiation of stem cells into myofibroblasts. Activated myofibroblasts are the source of matrix metalloproteinases, enzymes capable of degrading extracellular matrix proteins, causing tissue degradation. Th2 cells produce IL-13 that activates NK cells, increases intestinal permeability and induces apoptosis in intestinal epithelial cells. Th17 cells secrete IL-17A, IL-17F responsible for the migration of neutrophils to sites of inflammation and promoting the proliferation of myofibroblasts and collagen deposition, resulting in fibrosis (Valatas V, Kolios G, Bamias G. *TL1A (TNFSF15) and DR3 (TNFRSF25): A Co-stimulatory System of Cytokines With Diverse Functions in Gut Mucosal Immunity. Front Immunol. 2019 Mar 27;10:583. doi: 10.3389/fimmu.2019.00583. PMID: 30972074; Spyros I. Siakavellas, Giorgos Bamias, Tumor Necrosis Factor-like Cytokine TL1A and Its Receptors DR3 and DcR3: Important New Factors in Mucosal Homeostasis and Inflammation, Inflammatory Bowel Diseases, Volume 21, Issue 10, 1 October 2015, Pages 2441–2452, https://doi.org/10.1097/MIB.0000000000000492; Wallace KL, Zheng LB, Kanazawa Y, Shih DQ. Immunopathology of inflammatory bowel disease. World J Gastroenterol. 2014 Jan 7;20(1):6-21. doi: 10.3748/wjg.v20.i1.6; Kokkotis G, Bamias G. TL1A as a therapeutic target in inflammatory bowel disease. Expert Rev Clin Immunol. 2022 Jun;18(6):551-555. doi: 10.1080/1744666X.2022.2074401. Epub 2022 May 12. PMID: 35507314; Baumgart DC, Sandborn WJ. Crohn's disease. Lancet. 2012 Nov 3;380(9853):1590-605. doi: 10.1016/S0140-6736(12)60026-9. Epub 2012 Aug 20. Erratum in: Lancet. 2013 Jan 19;381(9862):204. PMID: 22914295; Chen L, Ruan G, Cheng Y, Yi A, Chen D, Wei Y. The role of Th17 cells in inflammatory bowel disease and the research progress. Front Immunol. 2023 Jan 9;13:1055914. doi: 10.3389/fimmu.2022.1055914. PMID: 36700221; PMCID: PMC9870314; Yamada A, Arakaki R, Saito M, Tsunematsu T, Kudo Y, Ishimaru N. Role of regulatory T cell in the pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2016 Feb 21;22(7):2195-205. doi: 10.3748/wjg.v22.i7.2195. PMID: 26900284; PMCID: PMC4734996).*

Accordingly, it is TL1A, not TNF α or any other proinflammatory cytokine, that is the initial upper-level cytokine in the pathogenesis of IBD. TL1A costimulates T cells and induces the secretion of a wide range of proinflammatory cytokines, including TNF α , but not vice versa, which fact may be the reason for the relatively low efficacy of anti-TNF α drugs in IBD therapy (Holmkvist P, Roepstorff K, Uronen-Hansson H, et al. *A major population of mucosal memory*

CD4+ T cells, coexpressing IL-18Ra and DR3, display innate lymphocyte functionality. Mucosal Immunol. 2015;8(3):545-558. doi:10.1038/mi.2014.87; Jin S, Chin J, Seeber S, et al. TL1A/TNFSF15 directly induces proinflammatory cytokines, including TNF α , from CD3+CD161+ T cells to exacerbate gut inflammation. Mucosal Immunol. 2013;6(5):886-899. doi:10.1038/mi.2012.124).

Blocking of the TL1A-DR3 inflammatory signaling pathway can be useful for the treatment of a wide range of inflammatory and/or autoimmune diseases, not limited to Crohn's disease and ulcerative colitis. Accordingly, such an approach can be useful in the treatment of bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, intestinal fibrosis, liver fibrosis, fibrotic pulmonary diseases, including systemic sclerosis-associated interstitial lung disease (Adam W. Clarke, Lynn Poulton, Doris Shim, David Mabon, Danyal Butt, Matthew Pollard, Vanya Pande, Jean Husten, Jacquelyn Lyons, Chen Tian & Anthony G. Doyle (2018) *An anti-TL1A antibody for the treatment of asthma and inflammatory bowel disease*, *mAbs*, 10:4, 664-677, DOI: 10.1080/19420862.2018.1440164; Rana Herro, Haruka Miki, Gurupreet S. Sethi, David Mills, Amit Kumar Mehta, Xinh-Xinh Nguyen, Carol Feghali-Bostwick, Marina Miller, David H. Broide, Rachel Soloff, Michael Croft; *TL1A Promotes Lung Tissue Fibrosis and Airway Remodeling. J Immunol* 1 November 2020; 205 (9): 2414–2422. <https://doi.org/10.4049/jimmunol.2000665>; Jacob, N., Kumagai, K., Abraham, J.P. et al. *Direct signaling of TL1A-DR3 on fibroblasts induces intestinal fibrosis in vivo. Sci Rep* 10, 18189 (2020). <https://doi.org/10.1038/s41598-020-75168-5>; Hachulla, E., Agard, C., Allanore, Y. et al. *French recommendations for the management of systemic sclerosis. Orphanet J Rare Dis* 16 (Suppl 2), 322 (2021). <https://doi.org/10.1186/s13023-021-01844-y>; Song, YJ., Choi, I.A., Meylan, F. et al. *Circulating TNF-like protein 1A (TL1A) is elevated early in rheumatoid arthritis and depends on TNF. Arthritis Res Ther* 22, 106 (2020). <https://doi.org/10.1186/s13075-020-02198-9>; Li L, Fu L, Zhou P, Lu Y, Zhang L, Wang W, Nie J, Zhang D, Liu Y, Wu B, Chen T. *Effects of tumor necrosis factor-like ligand 1A (TL1A) on imiquimod-induced psoriasiform skin inflammation in mice. Arch Dermatol Res.* 2020 Sep;312(7):481-490. doi: 10.1007/s00403-019-02030-8. Epub 2020 Jan 18. PMID: 31953572).

Patent documents WO2015073580, WO2017196663 disclose antibodies to TL1A.

In connection with the above, there is a need to create antibodies that specifically bind to TL1A.

Disclosure of the invention (detailed description of the invention)

The authors of the present group of inventions have developed antibodies that specifically bind to TL1A and have high affinity parameters for binding to TL1A. The antibodies according to the invention are efficient inhibitors of DR3 (TNFRSF25) receptor-mediated activity. The

antibodies according to the invention have a high affinity for the FcRn receptor to increase the product circulation time in the blood of patients. Furthermore, the antibodies according to the invention are stable in human serum and resistant to high temperatures. The antibodies according to the invention inhibit the release of interferon gamma in the presence of IL-12 and IL-18, as well as various proinflammatory cytokines in the presence of IL-12, IL-18 and IL-15. The antibodies according to the invention do not induce direct and cross-linked apoptosis of CHO-tmTL1A cells expressing the membrane-bound form of TL1A, and do not lead to the development of cytokine release syndrome.

Definitions and general methods

Unless defined otherwise herein, all technical and scientific terms used in connection with the present invention will have the same meaning as is commonly understood by those skilled in the art.

Furthermore, unless otherwise required by context, singular terms shall include plural terms, and the plural terms shall include the singular terms. Typically, the present classification and methods of cell culture, molecular biology, immunology, microbiology, genetics, analytical chemistry, organic synthesis chemistry, medical and pharmaceutical chemistry, as well as hybridization and chemistry of protein and nucleic acids described herein are well known by those skilled and widely used in the art. Enzyme reactions and purification methods are performed according to the manufacturer's guidelines, as is common in the art, or as described herein.

The term "KD" in this description refers to the affinity constant (or equilibrium dissociation constant), which is calculated from the ratio of Kd to Ka (i.e. Kd/Ka), and it is expressed as a molar concentration (M).

"Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g. an antibody) and its binding partner (e.g. an antigen). Unless indicated otherwise, "binding affinity" refers to intrinsic (characteristic, true) binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g. antibody and antigen). The affinity of a molecule X for its binding partner Y can generally be represented by the equilibrium dissociation constant (KD). The preferred Kd value is about 200 nM, 150 nM, 100 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 8 nM, 6 nM, 4 nM, 2 nM, 1 nM, or less. Affinity can be measured by common methods known in the art, including those described in the present description. Low-affinity antibodies typically bind an antigen slowly and tend to dissociate readily, whereas high-affinity antibodies typically bind an antigen faster and tend to remain bound longer. A variety of methods for measuring binding affinity are known in the art, any one of these methods may be used for the purposes of the present invention.

The term "Kd", "koff" or "kdis" refers to the off rate constant of a particular interaction between a binding molecule and antigen. The koff dissociation rate constant can be measured using bio-layer interferometry: for example, using the Octet™ system; as well as by surface plasmon resonance: for example, using the Biacore™ system.

The term "Ka", "kon" or "on-rate" refers to the association rate constant.

The term "R²" refers to the coefficient of determination.

The term "Response" refers to an antibody-antigen binding signal.

The term "in vitro" refers to a biological entity, a biological process, or a biological reaction outside the body under artificial conditions. For example, a cell grown in vitro is to be understood as a cell grown in an environment outside the body, e.g. in a test tube, a culture vial, or a microtiter plate.

The term "ED₅₀" (EC₅₀) (50% effective dose/concentration, half maximal effective concentration) refers to concentrations of a formulation producing 50% biological effect (which may include cytotoxicity).

The terms "anti-TL1A antibody", "antibody to TL1A", "antibody that specifically binds to TL1A" are interchangeable in the context of the present application and refer to an antibody that specifically binds to TL1A.

Antigen — a protein which the antibody (antibodies) in question specifically binds to.

Genetic construct (plasmid) — an artificially created circular DNA molecule comprising various elements necessary for the expression of target genes and replication within organisms.

Proliferation — division of cells.

Reporter cell line — a cell line carrying a reporter gene for evaluation of intracellular signaling.

Transient production — the production of protein from a temporary producer.

Transfection — a method for DNA delivery where foreign DNA molecules are delivered to a cell using chemical or physical methods: as part of liposomal complexes, as a result of electroporation, and the like.

Chromatography — a method of separation and analysis of mixtures of substances, as well as a study of physico-chemical properties of substances. It is based on distribution of substances between two phases – the stationary phase (solid phase or liquid coated on an inert carrier) and the mobile phase (gas or liquid phase, eluent).

Cytokines — small proteins that regulate the immune response.

ADCC — antibody-dependent cellular cytotoxicity.

ADCP — antibody-dependent cellular phagocytosis.

C1q — protein complex of the C1q complement system (complement component 1q).

CD16 — cluster of differentiation 16, also FcγRIIIa, has 2 isoforms: V158 (or V176) — high affinity receptor, F158 (or F176) — low affinity receptor.

CD32 — cluster of differentiation 32, also FcγRIIA, has 2 isoforms: H131 — high affinity receptor, R131 — low affinity receptor

CD4 — cluster of differentiation 4.

CHO — Chinese hamster ovary cell line.

DcR3 — decoy receptor 3, DR3, as well as tumor necrosis factor receptor superfamily member 6B, TNFRSF6B).

DR3 — death receptor 3, DR3, as well as tumor necrosis factor receptor superfamily member 25, TNFRSF25.

Fc (fragment crystallizable) — constant fragment region of an antibody.

FcRn — a neonatal receptor for the human IgG Fc region that protects antibodies from degradation in lysosomes/endosomes of cells after uptake.

FcγRs — receptors for the immunoglobulin G Fc fragment (receptors for the IgG Fc fragment).

HRP — horseradish peroxidase.

LIGHT — a protein, member 14 of the tumor necrosis factor- α superfamily, TNFSF14.

Luc — luciferase.

NFAT — the nuclear factor of activated T-cells.

PBMC — peripheral blood mononuclear cells.

TL1A — TNF-like ligand 1A, also a tumor necrosis factor α superfamily member 15 (TNF superfamily member 15, TNFSF15), a vascular endothelial growth inhibitor, VEGI-251. The term TL1A refers to any naturally occurring form of TL1A, whether monomeric or multimeric, including dimers, trimers, and the like, which can originate from any suitable organism. The term TL1A as used herein refers to TL1A (TNFSF15) of any mammal such as a human, rat, mouse, ferret, pig, rabbit, as well as a non-human primate.

tmTL1A — membrane-bound or transmembrane form of TL1A.

TNBS — 2,4,6-trinitrobenzenesulfonic acid.

Tris-HCl is a buffer solution comprising tris(hydroxymethyl)aminomethane and hydrochloric acid (HCl).

HPLC — high-performance liquid chromatography.

VE — vertical electrophoresis.

IL-12 — interleukin-12.

IL-13 — interleukin-13.

IL-15 — interleukin-15.

IL-18 — interleukin-18.

IL-5 — interleukin-5.

IL-6 — interleukin-6.

ELISA — enzyme-linked immunosorbent assay.

TNF α — tumor necrosis factor alpha.

As used in the present description and claims that follow, unless otherwise dictated by the context, the words "include" and "comprise", or variations thereof such as "includes", "including", "comprises", or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Antibody

The present invention relates to a monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A.

The term "monoclonal antibody" or "mAb" refers to an antibody that is synthesized and isolated as an individual clonal population of cells.

The antibody of the invention is a recombinant antibody.

The term "recombinant antibody" refers to an antibody that is expressed in a cell or cell line comprising nucleotide sequence(s) encoding an antibody, wherein said nucleotide sequence(s) is (are) not associated with the cell in nature.

In one aspect, the present invention relates to a monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A comprising:

(a) a light chain variable domain comprising:

(i) CDR1 with the amino acid sequence RASQX₁X₂SX₃X₄X₅LX₆, where

X₁=S or G;

X₂=I or V;

X₃=S or G;

X₄= T, S or 0;

X₅= Y or W;

X₆=N or A;

(ii) CDR2 with the amino acid sequence X₇ASX₈X₉X₁₀X₁₁, where

X₇=G, A or K;

X₈=S, T or R;

X₉=L or R;

X₁₀=Q or A;

X₁₁=S, T or A; and

(iii) CDR3 with the amino acid sequence QQX₁₂X₁₃SX₁₄X₁₅X₁₆X₁₇X₁₈X₁₉, where

X_{12} = A, Y or 0;

X_{13} = N, G or 0;

X_{14} =Y, F or S;

X_{15} =R, S, P or G;

X_{16} =T, I, L or P;

X_{17} =L, P, T or S;

X_{18} =T, P, I or 0;

X_{19} =D, T or 0;

and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence $X_{20}YX_{21}X_{22}S$, where

X_{20} =D, S or G;

X_{21} =Y, A or D;

X_{22} =W or M;

(ii) CDR2 with the amino acid sequence $X_{23}IX_{24}X_{25}X_{26}GX_{27}X_{28}TX_{29}YX_{30}X_{31}SX_{32}KX_{33}$,

where

X_{23} =E, T or A;

X_{24} =N, Q, A, G, I, L, M, S, T, V or R;

X_{25} =H, T or S;

X_{26} =S or G;

X_{27} =N, R or G;

X_{28} =0 or S;

X_{29} =D, T, Y or S;

X_{30} =N or A;

X_{31} =P or D;

X_{32} =L, V or M;

X_{33} =S or G; and

(iii) CDR3 with the amino acid sequence

$X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}YX_{44}X_{45}X_{46}X_{47}X_{48}$, where

X_{34} = G, S or 0;

X_{35} =G, R or 0;

X_{36} =F, G or 0;

X_{37} =S, T, R or 0;

X_{38} =G, S or L;

X_{39} =S or W;

X₄₀=P, V, W or T;

X₄₁=N, P, G or D;

X₄₂=Y, E, S or F;

X₄₃=Y, I or D;

X₄₄=A, E, R or O;

X₄₅=M, Y, D or O;

X₄₆= D or O;

X₄₇=V, Y, E or O;

X₄₈= Y or O.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

- (a) a light heavy chain variable domain comprising:
 - (i) CDR1 with the amino acid sequence of SEQ ID NO: 1;
 - (ii) CDR2 with the amino acid sequence of SEQ ID NO: 6; and
 - (iii) CDR3 with the amino acid sequence of SEQ ID NO: 11; and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 with the amino acid sequence of SEQ ID NO: 16;
 - (ii) CDR2 with the amino acid sequence EIX₁HSGNTDYNPSLKS, where X₁=N, Q, A, G, I, L, M, S, T or V; and
 - (iii) CDR3 with the amino acid sequence of SEQ ID NO: 33.

In one embodiment of the invention, the antibody according to the invention is an isolated antibody.

The term "isolated" used to describe various antibodies according to the present description refers to an antibody which has been identified and isolated and/or regenerated from a cell or cell culture, in which the antibody is expressed. Impurities (contaminant components) from natural environment are materials which typically interfere with diagnostic or therapeutic uses of the polypeptide, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. The isolated polypeptide is typically prepared by at least one purification step.

The term "antibody" or "immunoglobulin" (Ig) as used in the present description includes whole antibodies. The term "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds. Each heavy chain comprises a heavy chain variable region (abbreviated referred to in the present description as VH) and a heavy chain constant region. Each light chain consists of a light chain variable region (abbreviated referred to in the present description as VL) and light chain constant region. The light chain constant domain can be CK (kappa light chain constant domain) or CL (lambda light chain constant

domain). Preferably the light chain is a kappa (κ) light chain, and the light chain constant domain is preferably CK.

Antibodies according to the invention can be of any class (e.g., IgA, IgD, IgE, IgG, and IgM, preferably IgG), or subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2, preferably IgG1).

VL and VH regions may be further subdivided into hyper-variability regions called complementarity determining regions (CDRs), located between regions that are more conserved, termed framework regions (FRs). Each VH and VL is composed of three CDRs and four FRs, arranged from N-terminus to C-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of heavy and light chains form a binding domain that interacts with an antigen.

The constant regions of antibodies may mediate the binding of 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 term "antigen-binding portion" of antibody or "antigen-binding fragment", as used in the present description, refers to one or more antibody fragments that retain the ability to specifically bind to an antigen. It was shown that the antigen-binding function of antibody can be performed by fragments of a full-length antibody. Examples of binding fragments which are included within the term "antigen-binding portion" of an antibody include (i) Fab-fragment, monovalent fragment, consisting of VL, VH, CL and CH1 domains; (ii) F(ab')₂ fragment, a bivalent fragment comprising two Fab-fragments linked by a disulfide bridge at the hinge region; (iii) Fd-fragment consisting of VH and CH1 domains; (iv) Fv-fragment consisting of VL and VH domains of a single arm of an antibody; (v) dAb-fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH/VHH domain. In addition, two regions of the Fv-fragment, VL and VH, are encoded by different genes, they can be joined using recombinant methods using a synthetic linker that enables to receive them as a single protein chain in which the VL and VH regions are paired to form monovalent molecules (known as a single-chain Fv (scFv); see e.g. Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). It is assumed that such single-stranded molecules are also included within the term "antigen-binding portion" of antibody. Such antibody fragments are produced using conventional techniques known to those skilled in the art, and these fragments are screened in the same manner as intact antibodies are.

"Kabat numbering scheme" or "numbering according to Kabat" as used in the present application refers to the system for numbering of amino acid residues that are more variable (i.e. hypervariable) than other amino acid residues in variable regions of heavy and light chains of antibody (Kabat et al. Ann. N.Y. Acad. Sci., 190:382-93 (1971); Kabat et al. Sequences of Proteins

of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 (1991)).

The antibody of the present invention "which specifically binds" to a target antigen refers to an antibody that binds an antigen with sufficient affinity such that the antibody can be used as a diagnostic and/or therapeutic agent targeting a protein or cell or tissue expressing the antigen.

The term "specifically binds to" a particular polypeptide or an epitope on a particular target polypeptide may be described by example of a molecule having a K_d for the target of at least about 200 nM, or at least about 150 nM, or at least about 100 nM, or at least about 60 nM, or at least about 50 nM, or at least about 40 nM, or at least about 30 nM, or at least about 20 nM, or at least about 10 nM, or at least about 8 nM, or at least about 6 nM, or at least about 4 nM, or at least about 2 nM, or at least about 1 nM, or at least about 100 pM or less.

In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or epitope on a polypeptide.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 10.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 10; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

(i) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,

CDR2 with the amino acid sequence of SEQ ID NO: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 11; or

(ii) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 2,

CDR2 with the amino acid sequence of SEQ ID NO: 7 and

CDR3 with the amino acid sequence of SEQ ID NO: 12; or

(iii) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 3,

CDR2 with the amino acid sequence of SEQ ID NO: 8 and

CDR3 with the amino acid sequence of SEQ ID NO: 13; or

(iv) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 4,

CDR2 with the amino acid sequence of SEQ ID NO: 9 and

CDR3 with the amino acid sequence of SEQ ID NO: 14 or

(v) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 5,

CDR2 with the amino acid sequence of SEQ ID NO: 10 and

CDR3 with the amino acid sequence of SEQ ID NO: 15.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, or SEQ ID NO: 32.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, or SEQ ID NO: 32; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

(i) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 20 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(ii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 21 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(iii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 22 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(iv) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 23 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(v) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 24 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vi) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 25 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(vii) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 26 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(viii) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 27 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(ix) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 28 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(x) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 29 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(xi) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 17,
CDR2 with the amino acid sequence of SEQ ID NO: 30 and
CDR3 with the amino acid sequence of SEQ ID NO: 34; or
(xii) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 18,
CDR2 with the amino acid sequence of SEQ ID NO: 31 and
CDR3 with the amino acid sequence of SEQ ID NO: 35; or
(xiii) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 19,
CDR2 with the amino acid sequence of SEQ ID NO: 32 and
CDR3 with the amino acid sequence of SEQ ID NO: 36.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 10; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15; and

(b) a heavy chain variable domain comprising:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, or SEQ ID NO: 32; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

(i) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,

CDR2 with the amino acid sequence of SEQ ID NO: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 20 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(ii) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,

CDR2 with the amino acid sequence of SEQ ID NO: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 21 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(iii) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,

CDR2 with the amino acid sequence of SEQ ID NO: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 22 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(iv) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 23 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(v) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 24 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vi) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 25 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vii) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 26 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(viii) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 27 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(ix) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 28 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(x) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 29 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(xi) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 2,
CDR2 with the amino acid sequence of SEQ ID NO: 7 and
CDR3 with the amino acid sequence of SEQ ID NO: 12; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 17,
CDR2 with the amino acid sequence of SEQ ID NO: 30 and
CDR3 with the amino acid sequence of SEQ ID NO: 34; or
(xii) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 3,

CDR2 with the amino acid sequence of SEQ ID NO: 8 and
CDR3 with the amino acid sequence of SEQ ID NO: 13; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 17,
CDR2 with the amino acid sequence of SEQ ID NO: 30 and
CDR3 with the amino acid sequence of SEQ ID NO: 34; or

(xiii) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 4,
CDR2 with the amino acid sequence of SEQ ID NO: 9 and
CDR3 with the amino acid sequence of SEQ ID NO: 14; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 18,
CDR2 with the amino acid sequence of SEQ ID NO: 31 and
CDR3 with the amino acid sequence of SEQ ID NO: 35; or

(xiv) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 5,
CDR2 with the amino acid sequence of SEQ ID NO: 10 and
CDR3 with the amino acid sequence of SEQ ID NO: 15; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 19,
CDR2 with the amino acid sequence of SEQ ID NO: 32 and
CDR3 with the amino acid sequence of SEQ ID NO: 36.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a light chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes a heavy chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54 or SEQ ID NO: 55.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

(a) a light chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41; and

(b) a heavy chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54 or SEQ ID NO: 55.

In some embodiments of the invention, the monoclonal antibody or antigen-binding fragment thereof includes:

(i) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 42; or

(ii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 43; or

(iii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 44; or

(iv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 45; or

(v) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 46; or

(vi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 47; or

(vii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 48; or

(viii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 49; or

(ix) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 50; or

(x) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 51; or

(xi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 38 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 52; or

(xii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 39 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 53; or

(xiii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 40 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 54; or

(xiv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 41 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 55.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is a full-length IgG antibody.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is a full-length IgG antibody that is of human IgG1, IgG2, IgG3 or IgG4 isotype.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is a full-length IgG antibody that is of human IgG1 isotype.

In some embodiments of the invention, the monoclonal antibody comprises, in the Fc fragment, mutations M252Y, S254T, T256E, according to the EU numbering scheme of amino acids of antibodies, in the CH2 region (Edelman G.M. et al., Proc. Natl. Acad. Sci. USA 63 (1969) pp. 78-85; Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD, (1991).

In some embodiments of the invention, the monoclonal antibody comprises mutations L234A and L235A, according to the EU numbering scheme of amino acids of antibodies, in the CH2 region.

In some embodiments of the invention, the monoclonal antibody comprises deletions 446G and 447K, according to the EU numbering scheme of amino acids of antibodies, in the CH3 region.

In some embodiments of the invention, the monoclonal antibody includes a light chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 or SEQ ID NO: 60.

In some embodiments of the invention, the monoclonal antibody includes a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73 or SEQ ID NO: 74.

In some embodiments of the invention, the monoclonal antibody includes:

(i) (a) a light chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 or SEQ ID NO: 60, and

(b) a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73 or SEQ ID NO: 74.

In some embodiments of the invention, the monoclonal antibody includes:

(i) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 61; or

(ii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 62; or

(iii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 63; or

(iv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 64; or
- (v) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 65; or
- (vi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 66; or
- (vii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 67; or
- (viii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 68; or
- (ix) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 69; or
- (x) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 70; or
- (xi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 57, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 71; or
- (xii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 58, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 72; or
- (xiii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 59, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 73; or
- (xiv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 60, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 74.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is an antibody that is selected from the group: 01-001, 05-001, 05-002, 05-006, 05-008, 05-010, 05-011, 05-013, 05-014, 05-015, 03-001, 03-002, 04-001 or 04-002.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 01-001.

Antibody 01-001 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 61.

Antibody 01-001 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 42.

Antibody 01-001 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 20,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-001.

Antibody 05-001 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 62.

Antibody 05-001 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 43.

Antibody 05-001 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 21,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-002.

Antibody 05-002 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 63.

Antibody 05-002 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 44.

Antibody 05-002 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 22,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-006.

Antibody 05-006 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 64.

Antibody 05-006 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 45.

Antibody 05-006 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 23,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-008.

Antibody 05-008 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 65.

Antibody 05-008 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 46.

Antibody 05-008 includes:

(a) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and

(b) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 24,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-010.

Antibody 05-010 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 66.

Antibody 05-010 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 47.

Antibody 05-010 includes:

(a) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and

(b) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 25,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-011.

Antibody 05-011 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 67.

Antibody 05-011 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 48.

Antibody 05-011 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 26,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-013.

Antibody 05-013 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 68.

Antibody 05-013 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 49.

Antibody 05-013 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 27,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-014.

Antibody 05-014 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 69.

Antibody 05-014 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 50.

Antibody 05-014 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 28,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 05-015.

Antibody 05-015 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 70.

Antibody 05-015 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 37;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 51.

Antibody 05-015 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 1,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 6,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 11, and

(b) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 16,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 29,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 33.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 03-001.

Antibody 03-001 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 57; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 71.

Antibody 03-001 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 38;

- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 52.

Antibody 03-001 includes:

(a) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 2,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 7,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 12, and

(b) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 17,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 30,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 34.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 03-002.

Antibody 03-002 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 58; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 72.

Antibody 03-002 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 39;

- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 53.

Antibody 03-002 includes:

- (a) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 3,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 8,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 13, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 17,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 30,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 34.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 04-001.

Antibody 04-001 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 59; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 73.

Antibody 04-001 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 40;
- (b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 54.

Antibody 04-001 includes:

- (a) a light chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 4,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 9,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 14, and
- (b) a heavy chain variable domain comprising:
 - (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 18,
 - (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 31,
 - (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 35.

In some embodiments of the invention, the monoclonal antibody that specifically binds to TL1A is antibody 04-002.

Antibody 04-002 includes:

- (a) a light chain comprising the amino acid sequence of SEQ ID NO: 60; and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 74.

Antibody 04-002 includes:

- (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 41;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 55.

Antibody 04-002 includes:

(a) a light chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 5,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 10,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 15, and

(b) a heavy chain variable domain comprising:

- (i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 19,
- (ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 32,
- (iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 36.

The hypervariable regions of variable domains of light and heavy chains (LCDR1, 2, 3 and HCDR1, 2, 3) of all the above antibodies are provided in accordance with the Kabat nomenclature. Those skilled will appreciate that the hypervariable regions of variable domains of light and heavy chains (LCDR1, 2, 3 and HCDR1, 2, 3) may also be represented in accordance with other commonly known numbering scheme, for example, IMGT, Chothia or AbM. Thus, all of the above antibodies which are characterized by means of hypervariable regions of variable domains of light and heavy chains (LCDR1, 2, 3 and HCDR1, 2, 3) using the IMGT, Chothia or AbM numbering scheme are also encompassed by the present invention.

The antibodies according to the invention that specifically bind to TL1A have high binding affinity parameters for TL1A. The antibodies according to the invention are efficient inhibitors of DR3 (TNFRSF25) receptor-mediated activity. The antibodies according to the invention have a high affinity for the FcRn receptor to increase the product circulation time in the blood of patients. Furthermore, the antibodies according to the invention are stable in human serum and resistant to high temperatures. The antibodies according to the invention inhibit the release of interferon gamma in the presence of IL-12 and IL-18, as well as various proinflammatory cytokines in the presence of IL-12, IL-18 and IL-15. The antibodies according to the invention do not induce direct and cross-linked apoptosis of CHO-tmTL1A cells expressing the membrane-bound form of TL1A, and do not lead to the development of cytokine release syndrome.

Nucleic acid molecule

In one aspect, the present invention relates to a nucleic acid that encodes any one of the above antibody or antigen-binding fragment thereof that specifically binds to TL1A.

In any one of said embodiments, the nucleic acid molecules may be isolated.

The terms "nucleic acid", "nucleic sequence", "nucleic acid sequence", "polynucleotide", "oligonucleotide", "polynucleotide sequence" and "nucleotide sequence", used interchangeably in

the present description, mean a precise sequence of nucleotides, modified or not, determining a fragment or a region of a nucleic acid, containing or not containing unnatural nucleotides, and being either a double-strand DNA or RNA, a single-strand DNA or RNA, or transcription products of said DNAs, or reverse transcription products of said RNAs.

Unless otherwise indicated, the term nucleotide sequence encompasses its complement. Thus, a nucleic acid having a particular sequence should be understood as one which encompasses the complementary strand thereof with the complementary sequence thereof.

An "isolated" nucleic acid molecule is one which is identified and separated from at least one nucleic acid molecule-impurity. An isolated nucleic acid molecule is different from the form or set in which it is found under natural conditions. Thus, an isolated nucleic acid molecule is different from a nucleic acid molecule that exists in cells under natural conditions.

In one aspect, the present invention relates to a nucleic acid molecule comprising a nucleotide sequence encoding an amino acid sequence selected from SEQ ID NO: 75–112. A nucleic acid molecule may also comprise any combination of said nucleotide sequences.

As would be appreciated by those skilled in the art, because of the redundancy of the genetic code, a variety of different DNA sequences can encode the amino acid sequence of the light chain or heavy chain of the antibody according to the invention or fragments thereof (VH, VL, CDR, etc.). It is well within the skill of those trained in the art to create these alternative DNA sequences encoding one and the same amino acid sequences. Such variant DNA sequences are within the scope of the present invention.

In some embodiments of the invention, the nucleic acid is DNA.

The nucleic acid molecule of the present invention may be isolated from any source that produces the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A. In certain embodiments of the invention, the nucleic acid molecule of the invention may be synthesized by way of chemical synthesis, rather than isolated.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of antibodies 01–001, 05–001, 05–002, 05–006, 05–008, 05–010, 05–011, 05–013, 05–014, 05–015, and includes a nucleotide sequence with SEQ ID NO: 75.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of antibody 03–001, and includes a nucleotide sequence with SEQ ID NO: 76.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of antibody 03–002, and includes a nucleotide sequence with SEQ ID NO: 77.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of antibody 04-001, and includes a nucleotide sequence with SEQ ID NO: 78.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain variable domain of antibody 04-002, and includes a nucleotide sequence with SEQ ID NO: 79.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 01-001, and includes a nucleotide sequence with SEQ ID NO: 80.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-001, and includes a nucleotide sequence with SEQ ID NO: 81.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-002, and includes a nucleotide sequence with SEQ ID NO: 82.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-006, and includes a nucleotide sequence with SEQ ID NO: 83.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-008, and includes a nucleotide sequence with SEQ ID NO: 84.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-010, and includes a nucleotide sequence with SEQ ID NO: 85.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-011, and includes a nucleotide sequence with SEQ ID NO: 86.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-013, and includes a nucleotide sequence with SEQ ID NO: 87.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-014, and includes a nucleotide sequence with SEQ ID NO: 88.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 05-015, and includes a nucleotide sequence with SEQ ID NO: 89.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 03-001, and includes a nucleotide sequence with SEQ ID NO: 90.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 03-002, and includes a nucleotide sequence with SEQ ID NO: 91.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 04-001, and includes a nucleotide sequence with SEQ ID NO: 92.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain variable domain of antibody 04-002, and includes a nucleotide sequence with SEQ ID NO: 93.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of antibodies 01-001, 05-001, 05-002, 05-006, 05-008, 05-010, 05-011, 05-013, 05-014, 05-015, and includes a nucleotide sequence with SEQ ID NO: 94.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of antibody 03-001, and includes a nucleotide sequence with SEQ ID NO: 95.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of antibody 03-002, and includes a nucleotide sequence with SEQ ID NO: 96.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of antibody 04-001, and includes a nucleotide sequence with SEQ ID NO: 97.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the light chain of antibody 04-002, and includes a nucleotide sequence with SEQ ID NO: 98.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 01-001, and includes a nucleotide sequence with SEQ ID NO: 99.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–001, and includes a nucleotide sequence with SEQ ID NO: 100.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–002, and includes a nucleotide sequence with SEQ ID NO: 101.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–006, and includes a nucleotide sequence with SEQ ID NO: 102.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–008, and includes a nucleotide sequence with SEQ ID NO: 103.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–010, and includes a nucleotide sequence with SEQ ID NO: 104.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–011, and includes a nucleotide sequence with SEQ ID NO: 105.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–013, and includes a nucleotide sequence with SEQ ID NO: 106.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–014, and includes a nucleotide sequence with SEQ ID NO: 107.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 05–015, and includes a nucleotide sequence with SEQ ID NO: 108.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 03–001, and includes a nucleotide sequence with SEQ ID NO: 109.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 03–002, and includes a nucleotide sequence with SEQ ID NO: 110.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 04-001, and includes a nucleotide sequence with SEQ ID NO: 111.

In some embodiments of the invention, the nucleic acid is a nucleic acid that encodes the amino acid sequence of the heavy chain of antibody 04-002, and includes a nucleotide sequence with SEQ ID NO: 112.

The nucleic acid molecules may be used to express the recombinant monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A.

Vector

In one aspect, the present invention relates to an expression vector comprising any one of the above nucleic acid molecules that encode the corresponding amino acid sequences of the antibody that specifically binds to TL1A, or portions thereof (for example, heavy chain and/or light chain binding domain sequences). The present invention relates to a vector suitable for the expression of any one of nucleotide sequences described herein.

The term "vector" as used herein means a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked.

As used in the present description, the term "expression" is defined as the transcription and/or translation of a particular nucleotide sequence.

In some embodiments of the invention, the vector is a plasmid, i.e. a circular double stranded piece of DNA into which additional DNA segments may be inserted.

In some embodiments of the invention, the vector is a viral (expression) vector, wherein additional DNA segments may be inserted into the viral genome.

In some embodiments of the invention, the vectors are capable of autonomous replication in a host cell into which they are introduced (e.g. bacterial vectors having a bacterial site of replication origin and episomal vectors). In further embodiments of the invention, the vectors (e.g. non-episomal vectors) may be integrated into the genome of a host cell upon introduction into a host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operably linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors").

In some embodiments of the invention, expression vectors include plasmids, retroviruses, adenoviruses, adeno-associated viruses (AAVs), plant viruses, such as cauliflower mosaic virus, tobacco mosaic virus, cosmids, YACs, and the like. DNA molecules may be inserted into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of DNA. An expression vector and expression control sequences may be chosen to be compatible with the expression host cell used.

In one embodiment of the invention, DNA molecules encoding partially or fully heavy and light chain sequences can be inserted into distinct vectors.

In one embodiment, any combination of the above DNA molecules is introduced into the same expression vector.

In one embodiment of the invention, DNA molecules may be introduced into an expression vector by standard methods (e.g. ligation of complementary restriction sites on a gene fragment of antibody and vector, or blunt end ligation if no restriction sites are present).

In some embodiments of the invention, a suitable vector is one that includes restriction sites such that any VH or VL sequence can easily be inserted and expressed, as described above. A recombinant expression vector can also encode a signal peptide that facilitates secretion of an antibody chain from a host cell. An antibody chain sequence may be cloned into a vector such that the signal peptide is linked in-frame to the N-terminus of an immunoglobulin chain. A signal peptide may be an immunoglobulin signal peptide or a heterologous signal peptide (i.e. a signal peptide from a non-immunoglobulin protein).

In some embodiments of the invention, the vector may include an expression control sequence. The term "expression control sequence" as used in the present description refers to polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are inserted. It will be understood by those skilled in the art that the design of an expression vector, including the selection of expression control sequences, may depend on such factors as the choice of the type of a host cell to be transformed, the required level of expression of antibody, and so forth. Expression control sequences include appropriate transcription initiation and termination sequences, promoter sequences, enhancer sequences and/or insulator sequences; efficient RNA processing signals such as splicing sites and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (e.g., Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such expression control sequences differs depending upon the host organism; in prokaryotes, such expression control sequences typically include a promoter, a ribosome binding site, as well as transcription termination sequences; in eukaryotes, such expression control sequences typically include promoters and transcription termination sequences. Preferred expression control sequences for an expression host cell in a mammal include viral elements that ensure high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from a retroviral LTR (long terminal repeat), cytomegalovirus (CMV) (such as a CMV enhancer/promoter), simian virus 40 (SV40) (such as a SV40 promoter/enhancer), adenovirus, (e.g. the major late promoter adenovirus (AdMLP)), polyomavirus and strong mammalian promoters such as TTR promoter, native immunoglobulin

promoter or actin promoter. Expression control sequences encompass at least all components whose presence is important for expression and processing.

In some embodiments of the invention, in addition to antibody chain genes and expression control sequences, the recombinant expression vectors of the invention may carry additional sequences, such as sequences that regulate replication of a vector in host cells (e.g. origins of replication) and selectable marker genes. The selectable marker gene facilitates the selection of host cells into which a vector has been introduced.

Host cell

In one aspect, the present invention relates to a method for producing a host cell to produce any above antibody or antigen-binding fragment thereof that specifically binds to TL1A, and includes transformation of the cell with the above vector.

In one aspect, the present invention relates to a host cell for producing any above antibody or antigen-binding fragment thereof that specifically binds to TL1A, comprising any one of the above nucleic acids.

The term "host cell" as used herein refers to a cell into which a recombinant expression vector has been introduced. The present invention relates to host cells, which may include, for example, the above-described vector according to the invention. The present invention further relates to host cells that comprise, for example, a nucleotide sequence encoding a heavy chain or antigen-binding portions thereof, a nucleotide sequence encoding a light chain or antigen-binding portions thereof, or both. It should be understood that "host cell" refers not only to a particular subject cell but to the progeny of such cell as well. Since modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to a parental cell; however, such cells are still included within the scope of the term "host cell" as used herein.

Nucleic acid molecules encoding the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A according to the invention and vectors comprising these nucleic acid molecules may be used for transfection of a mammalian cell, plant cell, bacterial cell, or yeast cell. Transfection may be carried out by any known method for introducing polynucleotides into a host cell. Methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, cationic polymer-nucleic acid complex transfection, transfection by electroporation, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, encapsulation of the polynucleotides in liposomes, and direct microinjection of DNA into nuclei. In addition, the nucleic acid molecules may be introduced into mammalian cells by viral (expression) vectors.

Mammalian cell lines used as hosts for transformation are well known in the art and include a plurality of immortalized cell lines. These include, e.g., Chinese hamster ovary (CHO) cells, NS0 cells, SP2 cells, HEK-293T cells, FreeStyle 293 cells (Invitrogen), NIH-3T3 cells, HeLa cells, baby hamster kidney (BHK) cells, African green monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), A549, SK-HEP1, HUH7, Hep-RG cells and a number of other cell lines. Cell lines are selected by way of determining which cell lines have high expression levels and provide for necessary characteristics of the protein being produced. Other cell lines that may be used are insect cell lines, such as Sf9 or Sf21 cells. When recombinant expression vectors encoding the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A are introduced into mammalian host cells, the antibodies or fragments thereof are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibodies or fragments thereof in host cells or, more preferably, secretion of the antibodies or fragments thereof into the culture medium in which the host cells are grown. The monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A may be isolated from culture medium using standard protein purification techniques. Plant host cells include e.g. Nicotiana, Arabidopsis, duckweed, corn, wheat, potato, etc. Bacterial host cells include, for example, genera such as Escherichia and Streptomyces. Yeast host cells include Schizosaccharomyces pombe, Saccharomyces cerevisiae and Pichia pastoris.

Furthermore, level of production of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A from a production cell line may be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under certain conditions.

It is likely that the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A from various cell lines will have a different glycosylation profile as compared to one another. However, the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A encoded by nucleic acid molecules described herein, or comprising amino acid sequences provided herein are part of the present invention, regardless of the glycosylation of the binding molecules, and, in general, regardless of the presence or absence of post-translational modifications.

The above host cell does not relate to a host cell produced using human embryos.

The above host cell does not relate to a host cell produced by modifying the genetic integrity of human germline cells.

Method for producing antibody

In one aspect, the present invention relates to a method for producing the antibody or antigen-binding fragment thereof that specifically binds to TL1A, comprising culturing the above

host cell in a growth medium under conditions sufficient to produce said antibody or fragment thereof, followed by isolation and purification of the resulting antibody or fragment thereof.

Pharmaceutical compositions

Another aspect of the invention is a pharmaceutical composition comprising, as an active ingredient (or as the only active ingredient), the monoclonal antibody according to the present invention or antigen-binding fragment thereof that specifically binds to TL1A.

In one aspect, the present invention relates to a pharmaceutical composition that comprises any above-mentioned antibody or antigen-binding fragment thereof in combination with one or more pharmaceutically acceptable excipients.

In one aspect, the present invention relates to a pharmaceutical composition used for treating a TL1A-mediated disease or disorder, which comprises any above antibody or antigen-binding fragment thereof in combination with one or more pharmaceutically acceptable excipients.

In one aspect, the present invention relates to a pharmaceutical composition used for treating a TL1A-mediated disease or disorder, which comprises any above antibody or antigen-binding fragment thereof in a therapeutically effective amount in combination with one or more pharmaceutically acceptable excipients.

"Pharmaceutical composition" means a composition comprising an antibody according to the invention and at least one of components selected from the group consisting of pharmaceutically acceptable and pharmacologically compatible fillers, solvents, diluents, carriers, auxiliary, distributing and sensing agents, delivery agents.

The term "pharmaceutically acceptable" refers to one or more compatible liquid or solid components that are suitable for administration in a mammal, preferably in a human.

The term "excipient" is used herein to describe any ingredient other than the antibody according to the present invention. These are substances of inorganic or organic nature which are used in the pharmaceutical production/manufacturing in order to give drug products the necessary physicochemical properties.

In some embodiments, the compositions are intended to improve the condition or treat diseases or disorders that may be mediated by TL1A.

The term "disease or disorder mediated by TL1A" refers to any disease or disorder that is either directly, or indirectly associated with TL1A, including pathogenesis, progression, recurrence or chronification of a disease or disorder.

"Treat", "treatment" and "therapy" refer to a method of alleviating or abrogating a biological disorder and/or at least one of attendant symptoms thereof.

The term "disorder" means any condition that would benefit from treatment according to the present invention. The definition of the term includes chronic and acute disorders or

diseases including those pathological conditions that predispose the mammal to the disorder in question.

"Therapeutically effective amount" refers to that amount of the therapeutic agent being administered during treatment which will relieve to some extent one or more of the symptoms of the disease being treated. A therapeutically effective amount may vary according to factors such as the particular condition being treated, the age, sex and weight of the patient, and whether the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A is being administered as a stand-alone treatment and/or in combination with one or more additional drugs, treatments.

In one aspect, the subject of treatment, or patient, is a human subject. Said subject may be either male or female, of any age.

The pharmaceutical compositions of the present invention and methods of preparation thereof will be undoubtedly apparent to those skilled in the art. The pharmaceutical compositions should preferably be manufactured in compliance with the GMP (Good Manufacturing Practice) requirements.

In some embodiments of the pharmaceutical composition, it may include a buffer composition, tonicity agents (osmolyte or osmotic agent), stabilizers and/or solubilizers.

The pharmaceutical composition according to the invention is a stable composition.

A pharmaceutical composition is "stable" if the active agent retains physical stability and/or chemical stability and/or biological activity thereof during the specified shelf life at a storage temperature, for example, of 2–8 °C. Preferably, the active agent retains both physical and chemical stability, as well as biological activity. Storage period is adjusted based on the results of stability test in accelerated or natural aging conditions.

In some embodiments, the pharmaceutical composition is an injectable dosage form.

In some embodiments, the injectable dosage form is an infusion solution.

In some embodiments, the injectable dosage form is a solution for subcutaneous administration.

Injectable formulations may be manufactured without limitation, in unit dosage form, such as in ampoules, vials, plastic containers, pre-filled syringes, autoinjection devices.

In some embodiments, the pharmaceutical composition is a pharmaceutical composition provided in dry, i.e. powder or granular, form for reconstitution with a suitable solvent (e.g., sterile pyrogen-free water) prior to administration. Such medicinal formulation may be prepared by, for example, lyophilization, i.e. a process, which is known in the art as freeze drying, and which involves freezing a product followed by removal of solvent from frozen material.

In some embodiments, the pharmaceutical composition is a lyophilizate for preparing a solution for infusion.

In some embodiments, the pharmaceutical composition is a lyophilizate for preparing a solution for subcutaneous administration.

In some embodiments, the pharmaceutical composition is a concentrate for preparing a solution for infusion.

In some embodiments, the pharmaceutical composition is a concentrate for preparing a solution for subcutaneous administration.

In one aspect, the present invention relates to a pharmaceutical composition that comprises a monoclonal antibody according to the present invention or antigen-binding fragment thereof that specifically binds to TL1A, and at least one other therapeutically active compound.

In one aspect, the present invention relates to a pharmaceutical composition for treating a TL1A-mediated disease or disorder, comprising any above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound.

In one aspect, the present invention relates to a pharmaceutical composition comprising any above antibody or antigen-binding fragment thereof and further at least one other therapeutically active compound.

In one aspect, the present invention relates to a pharmaceutical composition for treating a TL1A-mediated disease or disorder, comprising any above antibody or antigen-binding fragment thereof and further at least one other therapeutically active compound.

In one aspect, the present invention relates to a pharmaceutical composition for treating a TL1A-mediated disease or disorder, comprising any above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound, which is an antibody, a small molecule, a hormone therapy agent or any combination thereof.

In some embodiments of the pharmaceutical composition, the other therapeutically active compound is selected from the group that includes: azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, glucocorticosteroids (GCs), long-acting β 2-agonists (LABAs), long-acting anticholinergics (LAACs), hydroxychloroquine, prednisolone, methylprednisolone, belimumab, anifrolumab, acitretin, apremilast, tacrolimus, mycophenolate mofetil or any combination thereof.

In some embodiments of the pharmaceutical composition, the TL1A-mediated disease or disorder is selected from the group: Crohn's disease, ulcerative colitis, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic sclerosis-associated interstitial lung disease (SSc-ILD), intestinal fibrosis, liver fibrosis or fibrotic pulmonary diseases.

Therapeutic use of monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A

In one aspect, the antibody or antigen-binding fragment thereof that specifically binds to TL1A is used in the treatment of diseases or disorders mediated by TL1A.

In one aspect, the subject of treatment, or patient, is a human subject. Said subject may be either male or female, of any age.

In one aspect, the present invention relates to a method for treating a TL1A-mediated disease or disorder, comprising administering in a subject in need of such treatment any above antibody or antigen-binding fragment thereof or said pharmaceutical composition, in a therapeutically effective amount.

In one aspect, the present invention relates to a method for treating a TL1A-mediated disease or disorder, comprising administering in a subject in need of such treatment any above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound in a therapeutically effective amount.

In some embodiments of the method of treatment, the TL1A-mediated disease or disorder is selected from the group: Crohn's disease, ulcerative colitis, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic sclerosis-associated interstitial lung disease (SSc-ILD), intestinal fibrosis, liver fibrosis or fibrotic pulmonary diseases.

In some embodiments of the method of treatment, the other therapeutically active compound is an antibody, small molecule, hormone therapy agent, or any combination thereof.

In one aspect, the present invention relates to the use of the above antibody or antigen-binding fragment thereof or the above pharmaceutical composition for treating in a subject in need of such treatment a TL1A-mediated disease or disorder.

In one aspect, the present invention relates to the use of the above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound for treating in a subject in need of such treatment a TL1A-mediated disease or disorder.

In some embodiments of the use, the TL1A-mediated disease or disorder is selected from the group: Crohn's disease, ulcerative colitis, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic sclerosis-associated interstitial lung disease (SSc-ILD), intestinal fibrosis, liver fibrosis or fibrotic pulmonary diseases.

In some embodiments of the use, the other therapeutically active compound is an antibody, small molecule, hormone therapy agent, or any combination thereof.

The uses or methods used herein relating to the antibody or antigen-binding fragment thereof that specifically binds to TL1A with one or more other therapeutic agents are contemplated to mean, refer to and include the following:

1) simultaneous administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to TL1A and therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,

2) simultaneous administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to TL1A and therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,

3) sequential administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to TL1A and therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and

4) sequential administration of such combination of the antibody or antigen-binding fragment thereof that specifically binds to TL1A and therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner, whereupon they are concurrently, consecutively, or jointly released at the same and/or different times to said patient, where each portion may be administered by either the same or different routes.

The antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered without further therapeutic treatment, i.e. as an independent therapy.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with other therapeutically active compound selected from the group: azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, glucocorticosteroids (GCs), long-acting β 2-agonists (LABAs), long-acting anticholinergics (LAACs), hydroxychloroquine, prednisolone, methylprednisolone, belimumab, anifrolumab, acitretin, apremilast, tacrolimus, mycophenolate mofetil or any combination thereof.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with

other therapeutically active compound that is selected from the group: azathioprine, 6-mercaptopurine, methotrexate or any combination thereof.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with other therapeutically active compound that is selected from the group: glucocorticosteroids, long-acting β 2 agonists, long-acting anticholinergics or any combination thereof.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with methotrexate.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with other therapeutically active compound that is selected from the group: hydroxychloroquine, prednisolone, methylprednisolone, azathioprine, belimumab, anifrolumab or any combination thereof.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with other therapeutically active compound that is selected from the group: acitretin, apremilast, methotrexate or any combination thereof. Furthermore, the subject may concomitantly receive topical therapy.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment thereof that specifically binds to TL1A may be administered in combination with other therapeutically active compound that is selected from the group: methotrexate, tacrolimus, mycophenolate mofetil, azathioprine or any combination thereof.

The antibody or antigen-binding fragment thereof that specifically binds to TL1A and the pharmaceutical composition according to the present invention are suitable for parenteral administration in the form of sterile medicinal products intended for administration into the body of a subject by breaching the integrity of the skin or mucous membranes, bypassing the gastrointestinal tract by means of injection or infusion. In particular, it is contemplated that parenteral administration includes, inter alia, subcutaneous, intraperitoneal, intramuscular, intravenous, intraarterial, intrathecal, intraventricular, intraurethral, intracranial, intrasynovial, transdermal injection or infusion; and kidney dialytic infusion techniques.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment that specifically binds to TL1A or the pharmaceutical composition is administered intravenously.

In some embodiments, intravenous administration is carried out by using infusion, prolonged infusion, or long-lasting continuous infusion.

In some embodiments of the method of treatment or the use, the antibody or antigen-binding fragment that specifically binds to TL1A or the pharmaceutical composition is administered subcutaneously.

In some embodiments, subcutaneous administration is carried out by using subcutaneous injection.

In some embodiments of the method for treating or the use, a suitable dose of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to TL1A according to the present invention will be in the range of 0.1–200 mg/kg.

Brief description of the drawings

Figure 1 is the map of an expression vector for transient production of protein, carrying the genetic sequence of the human TL1A (TNFSF15) antigen, in eukaryotic cells.

Figure 2 is the map of an expression vector for transient production of protein in eukaryotic cells, carrying the gene sequence of the heavy chain of the antibody to TL1A according to the invention.

Figure 3 is the map of a vector for transient production of protein in eukaryotic cells, carrying the gene sequence of the light chain of the antibody to TL1A according to the invention.

Comments for Figures 1–3.

Name	Definition
eCMV pCMV	A regulatory element consisting of an enhancer (eCMV) and a promoter (pCMV) in cytomegalovirus (CMV), which element is necessary to initiate transcription of mRNA of the target transgene (TL1A antigen or antibodies according to the invention).
AV MLP	Adenovirus major late promoter necessary to enhance the transcription of mRNA of the target transgene (TL1A antigen or antibodies according to the invention) by means of a cap-independent mechanism, without involving eIF-4F (eukaryotic initiation factor). The chimeric intron stabilizes the target mRNA and increases the probability of nuclear transport thereof.
Kozak	The Kozak consensus sequence surrounding the initiation codon and necessary to enhance the initiation of translation of the target transgene (TL1A antigen or antibodies according to the invention).

SP	Signal peptide — an N-terminal amino acid sequence that provides co- or post-translational translocation of the target transgene (TL1A antigen or antibodies according to the invention) to the secretory pathway from the cell into culture fluid.
PT	Peptide tag to simplify the purification of the TL1A antigen.
Linker	Flexible glycine-serine linker that separates the target TL1A antigen from the peptide tag.
TL1A (TNFSF15)	Sequence of TL1A (TNFSF15) antigen.
VH	Heavy chain variable domain of the antibodies according to the invention.
HC IgG1	Sequence of heavy chain constant domains (CH1, CH2 and CH3) of human immunoglobulin IgG1, as well as of the hinge region thereof. This sequence can be a wild-type sequence or include the following amino acid substitutions selected from the group: 1) 446G and 447K deletion or 2) L234A and L235A mutations or 3) M252Y, S254T, T256E mutations or any combination thereof. According to EU numbering scheme of amino acids of antibodies.
VL	Light chain variable domain of the antibodies according to the invention
CK	Sequence of the light chain constant domain of the human immunoglobulin IgG1 of the kappa family.
Stop	Stop codon(s) to terminate the translation of the target transgene (antibodies according to the invention).
poly(A)	Polyadenylation signal to terminate the transcription and polyadenylation of mRNA.
EBNA1 site	Regulatory element of the Epstein-Barr virus, which is a 20-fold repeat of EBNA1 protein binding site, directing the plasmid to the transcriptionally active regions of the cell nucleus. Functions as the "eukaryotic replication origin".
pAmpR	Weak constitutive promoter of the beta-lactamase gene. Induces the expression of the beta-lactamase gene in response to changed levels of peptidoglycan (PG) metabolites taking place when being exposed to β -lactams (antibiotics).

AmpR	Sequence encoding beta-lactamase hydrolyzing the beta-lactam ring of appropriate antibiotics. Provides prokaryotic cells (e.g. <i>E. coli</i>) with ampicillin resistance.
ori	High-copy replication origin that functions in prokaryotic cells (for example, <i>E. coli</i>).

Figure 4 is the map of a vector for stable production of protein in eukaryotic cells, carrying the gene sequence of the heavy chain of the antibody to TL1A according to the invention.

Figure 5 is the map of a vector for stable production of protein in eukaryotic cells, carrying the gene sequence of the light chain of the antibody to TL1A according to the invention.

Comments for Figures 4–5.

Name	Definition
HS4	Hypersensitive site of open chromatin 4; an insulator used to enhance the efficiency of transcription of the transgene by unwinding nearby chromatin.
eCMV pEF-1 α	Hybrid regulatory element consisting of a cytomegalovirus (CMV) enhancer and an eukaryotic translation elongation factor (EF-1 α) promoter, which are necessary for the initiation of transcription of mRNA of the target transgene (encoding the antibodies according to the invention); as well as consisting of an EF-1 α intron, which promotes the stability of the given mRNA.
Kozak	The Kozak consensus sequence surrounding the initiation codon and necessary to enhance the initiation of translation of the target transgene (TL1A antigen or antibodies according to the invention).
SP	Signal peptide — an N-terminal amino acid sequence that provides co- or post-translational translocation of the antibodies according to the invention to the secretory pathway from the cell into culture fluid.
VH	Heavy chain variable domain of the antibodies according to the invention.
HC IgG1	Sequence of heavy chain constant domains (CH1, CH2 and CH3) of human immunoglobulin IgG1, as well as of the hinge region thereof. This sequence can be a wild-type sequence or include the following amino acid substitutions selected from the group: 1) 446G and 447K deletion or 2) L234A and L235A mutations or 3) M252Y, S254T, T256E mutations or any combination thereof. According to EU numbering scheme of amino acids of antibodies.
VL	Light chain variable domain of the antibodies according to the invention.

CK	Sequence of the light chain constant domain of the human immunoglobulin IgG1 of the kappa family.
Stop	Stop codon to terminate the translation of the target transgene (antibodies according to the invention).
poly(A)	Polyadenylation signal to terminate the transcription and polyadenylation of mRNA.
MAR	MAR (matrix attachment region) of the human β -globin gene, which region is used to maintain the episome copy number in eukaryotic cells by way of binding to the nuclear matrix in interphase, as well as to enhance the efficiency of expression of the target transgene (antibodies according to the invention) due to partial insulator properties for unwinding nearby chromatin.
ori	High-copy replication origin that functions in prokaryotic cells (for example, <i>E. coli</i>).
AmpR	Sequence encoding beta-lactamase that provides prokaryotic cells (e.g. <i>E. coli</i>) with resistance to ampicillin.
pAmpR	Constitutive promoter of the beta-lactamase gene.
pSV40	Eukaryotic promoter of the simian virus SV-40, which promoter is necessary for the constitutive expression of the selectable marker gene in mammalian cells.
PurR	Puromycin resistance gene. Allows selection of transfected mammalian cell culture.
BsR	Blasticidin resistance gene. Allows selection of transfected mammalian cell culture.

Figure 6 is a graph showing evaluation of the interaction between antibody 01-001 and CHO-tmTL1A cells expressing the membrane-bound form of human TL1A.

Figure 7 is a graph showing evaluation of the inhibition of release of interferon gamma (IFN γ) by antibody 01-001 in response to TL1A on primary cells activated by IL-12 and IL-18.

Figure 8 is a graph showing evaluation of the inhibition of release of tumor necrosis factor alpha (TNF α) by antibody 01-001 in response to TL1A on primary cells activated by IL-12, IL-18 and IL-15.

Figure 9 is a graph showing evaluation of the inhibition of IL-13 release by antibody 01-001 in response to TL1A on primary cells activated by IL-12, IL-18 and IL-15.

Figure 10 is a graph showing evaluation of the inhibition of IL-6 release by antibody 01-001 in response to TL1A on primary cells activated by IL-12, IL-18 and IL-15.

Figure 11 is a graph showing evaluation of the inhibition of IL-17 release by antibody 01-001 in response to TL1A on primary cells activated by IL-12, IL-18 and IL-15.

Figure 12 is a graph showing evaluation of the inhibition of IL-5 release by antibody 01-001 in response to TL1A on primary cells activated by IL-12, IL-18 and IL-15.

Figure 13 is a graph showing evaluation of the inhibition of GM-CSF release by antibody 01-001 in response to TL1A on primary cells activated by IL-12, IL-18 and IL-15.

Figure 14 is a graph showing the results of comparing the efficacy of antibody 01-001 to placebo control in a TNBS-induced rat model of ulcerative colitis.

Examples

The following examples are provided for better understanding of the invention. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

Materials and general methods

General information regarding the nucleotide sequences of human immunoglobulin light and heavy chains is given in: Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991). Amino acids of antibody chains are numbered according to EU numbering (Edelman, G.M., et al., Proc. Natl. Acad. Sci. USA 63 (1969) 78-85; Kabat, E.A., et al., Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, National Institutes of Health, Bethesda, MD, (1991).

Recombinant DNA techniques

Standard methods were used to manipulate DNA as described in Sambrook, J. et al, Molecular cloning: A laboratory manual; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989. The molecular biological reagents were used according to the manufacturer protocols.

Gene synthesis

Desired gene segments were prepared from oligonucleotides made by chemical synthesis. The gene segments of 300-1400 bp long, flanked by singular restriction sites, were assembled by annealing and ligation of oligonucleotides including PCR amplification and subsequently cloned via the restriction sites. The DNA sequences of the cloned gene fragments were confirmed by DNA sequencing.

DNA sequence determination

DNA sequences were determined by Sanger sequencing.

DNA and protein sequence analysis and sequence data management

The Unipro's UGENE suite version 1.29 and SnapGene version 6.1 were used for sequence creation, mapping, analysis, annotation and illustration.

Expression vectors

To produce the antibodies described herein, we used variants of genetic constructs intended for the expression of a transgene in eukaryotic cells (for example, in Chinese hamster ovary (CHO) cells), as well as for maintaining plasmid copy number in prokaryotic cells (for example, *E. coli*). In addition to the transgene encoding the sequence of a given antibody, the vectors contained all the elements necessary for the expression of protein in eukaryotic cells, as well as all the elements necessary for maintaining plasmid copy number in prokaryotic cells.

The fusion genes comprising the subject antibody chains as described below were generated by PCR and/or gene synthesis and assembled using known recombinant methods and techniques by connection of the according nucleic acid segments, e.g. using unique restriction sites in the corresponding vectors. The resulting nucleic acid sequences were verified by DNA sequencing. For eukaryotic cell transfections, larger quantities of the plasmids were prepared by preparation thereof from transformed *E. coli* cultures.

Example 1. Preparation of recombinant TL1A antigens.

Soluble recombinant human (*Homo sapiens*), rhesus macaque (*Macaca mulatta*), Javanese macaque (*Macaca fascicularis*), rat (*Rattus norvegicus*) and mouse (*Mus musculus*) TL1A (TNFSF15) protein was obtained by producing same in CHO-K1 suspension cell line by transient transfection. Antigens for immunization, selection, kinetic and cellular tests included the secreted form of the human TL1A (TNFSF15) antigen (<https://www.uniprot.org/uniprotkb/O95150>) fused with various peptide tags. By way of analogy, we also used the secreted form of Rhesus macaque (<https://www.uniprot.org/uniprotkb/F6S8F9>), Javanese macaque (<https://www.uniprot.org/uniprotkb/G7PRK8>), rat (<https://www.uniprot.org/uniprotkb/Q8K3Y7>) and mouse (<https://www.uniprot.org/uniprotkb/Q5UBV8>) TNFSF15.

To generate the above antigens, we used plasmid variants designed both for transient expression of the transgene in eukaryotic cells (for example, Chinese hamster ovary (CHO) cells) and for maintaining copy number in prokaryotic cells (for example, *E. coli*). The nucleotide sequences of the genes encoding the above antigens were prepared by *de novo* synthesis. The sequences were codon-optimized for expression in CHO cells. Next, the resulting sequences were cloned into a plasmid vector either using SalI/NotI restriction sites or using ligase-free molecular cloning techniques. The assembly quality was verified by Sanger sequencing. The resulting genetic constructs comprised all the necessary elements for protein expression in eukaryotic cells, and also all the necessary elements to maintain plasmid copy number in prokaryotic cells. Figure 1 shows an exemplary map of the vector encoding human TL1A as a transgene.

Antigens were generated in established cell line obtained from Chinese hamster ovary cells (CHO-K1) according to published protocols [Biotechnol Bioeng. 2005 Sep 20; 91(6):670-677, Liao Metal., 2004; Biotechnol Lett. 2006 Jun;28(11):843-848; Biotechnol Bioeng. 2003 Nov 5;84(3):332-342]. 1 day before the transient transfection, the cell culture was reseeded in an individual flask. After achieving an optimal concentration, the cell culture was reseeded into bioreactors for further manipulations. Suspension culture was conducted in flasks on orbital shaker using serum-free media. For transient expression, cells were transfected using linear polyethylenimine (PEI) mixed with plasmid DNA in growth medium B (RPMI) in individual test tubes. Next, we evaluated transfection efficiency using a flow cytometer and a technique known in the art. 48 hours after the transient transfection, cell culture supplements were added to the cells, and the cells were left to culture for 5–6 days. After the culturing time, the culture liquid was clarified using a filtration system.

The resulting antigens were purified in two steps. The first step included the use of metal-chelate affinity chromatography. The second step included size-exclusion chromatography.

Example 2. Obtaining of sequences of variable domains of antibodies against TL1A using human antibody selection in a naive Fab library.

The human TL1A (TNFSF15) antigen was immobilized on the surface of specifically treated test tubes during 3 rounds of selection by phage display. For the third round of selection, the rat TNFSF15 antigen was immobilized in the same manner. The human TL1A (TNFSF15) antigen was used for the fourth round of selection. The fifth and sixth rounds of selection (if necessary) were performed with both human TL1A antigen and rat/mouse TNFSF15 (for distinct libraries).

All of the above antigens were immobilized on the surface of specifically treated test tubes. The plastic was then washed with a phosphate-buffer saline supplemented with 0.1% Tween 20 and blocked with a solution of non-fat milk or bovine serum albumin in the same phosphate-buffer saline. A naive library of human antibodies was used as a library for selection. To this end, it was diluted in a phosphate-buffer saline supplemented with skimmed milk and an additional neutral protein with peptide tags used in the above TL1A antigens (for screening out non-specifically binding phage particles). Immunoassay test tubes with the immobilized antigen were then incubated with libraries.

Unbound phage particles were removed by multiple washings with a solution of a phosphate-buffer saline comprising 0.1% Tween 20. Phage particles bound to the antigen were eluted with a glycine-HCl buffer (pH 2.2), thereafter the solution was neutralized with a 1M solution of Tris-HCl (pH 7.6). *E. coli* cells were infected with phages, grown in culture medium and used in the next selection round. Polyclonal phage enzyme-linked immunosorbent assay

(ELISA) was used for enrichment of libraries against target antigens and assessment of presence of non-specifically binding phage particles.

To perform ELISA, high-adsorption plates were immobilized with the target human, rhesus macaque, Javanese macaque, mouse and rat TL1A (TNFSF15) antigens, as well as with non-target neutral proteins with peptide tags used in the target TL1A antigens. The analysis was performed according to the standard ELISA protocol.

After the fifth and sixth rounds of selection on the target TL1A (TNFSF15) antigens, the polyclonal phage ELISA showed sufficient enrichment of libraries. For sequencing of monoclones, those libraries were selected which showed exceeded signal to the target TL1A (TNFSF15) antigens by more than 5 fold, as compared to non-homologous control proteins. Based on the results of polyclonal phage ELISA, we selected 9 libraries for which phagemid DNA was isolated from *E. coli* culture according to the standard manufacturer's (Qiagen) protocol. It was then used to transform electrocompetent *E. coli* cells, followed by cell sorting to monoclones and determination of an unambiguous sequence of genetic constructs by Sanger sequencing (according to the standard protocol). As a result of sequencing, 115 clones were analyzed, which contained 21 unique combinations of Fab fragments of heavy and light chains of antibodies. Of these, one sequence was selected for further study based on its non-obvious structural features, degree of identity to the human sequence and other criteria.

Sequences of variable domains of antibody 01-001 that specifically binds to TL1A (TNFSF15) were thus produced.

Example 3. Obtaining of sequences of variable domains of antibodies against TL1A using selection in immune libraries.

Recombinant soluble human TL1A antigens with various peptide tags were used to immunize several guanacos (*Lama guanicoe*). All animals received alternating antigens with distinct peptide tags to minimize a non-target immune response to them.

In some cases, guanacos were weekly administered with human TL1A antigen in Freund's adjuvant over the period of 6 weeks. Before each new administration of the antigen, 25 ml of blood was collection to further isolate a peripheral blood mononuclear cell (PBMC) fraction.

In some cases, guanacos were administered with human TL1A antigen in Freund's adjuvant over the period of 16 weeks. Before each new administration of the antigen, 25 ml of blood was collection to further isolate a PBMC fraction.

The obtained blood sera were analyzed using ELISA according to the standard protocol for determining the titers of antibodies to the human TL1A antigens used. Blood samples with antibody titer corresponding to accepted internal criteria were used as starting material for PBMC isolation.

PBMC fraction was isolated from the blood of immunized animals. Next, total RNA was isolated. The isolated RNA served as a matrix for cDNA synthesis using reverse transcriptase and random hexameric and oligo(dT) oligonucleotides as a primer.

The isolated cDNA was used as a basis for constructing two Fab-phage libraries comprising combinations of sequences of variable domains of heavy chain of the immunized guanacos and human light chains (both kappa and lambda).

The human TL1A antigen was immobilized on the surface of specifically treated test tubes for 4 rounds of selection by phage display. The fifth round was performed for the mouse TNFSF15 antigen. The selection was performed by the phage display method described above.

Sequencing revealed four unique sequences of Fab fragments of heavy and light chains of the antibodies. All of them were transferred to Koff screening.

Thus, we obtained the sequences of variable domains of the following antibodies of the invention: 03-001, 03-002, 04-001, 04-002.

Example 4. Obtaining of sequences of variable domains of antibodies against TL1A that do not comprise glycosylation sites in CDR regions.

In order to eliminate the potential glycosylation site in CDR2 of the heavy chain variable domain of antibody 01-001, we synthesized genetic constructs encoding the heavy chain variable domain of 01-001 with substitutions in CDR2 (sequences are shown in Table 1). We thus produced sequences of variable domains of the following antibodies of the invention: 05-001, 05-002, 05-006, 05-008, 05-010, 05-011, 05-013, 05-014, 05-015. A sequence of the light chain variable domain of antibody 01-001 was used as the light chain variable domain of all the above-mentioned antibodies of the invention.

Table 1. Sequences of CDR2 of the heavy chain variable domains of said antibodies according to the invention (numbering according to Kabat E.A. et al., 1991).

Antibody	Heavy chain CDR2 sequence	Substitution with respect to 01-001
01-001	EINHS ¹ GNTDYNPSLKS	-
05-001	EIQHS ¹ GNTDYNPSLKS	N52Q
05-002	EIAHS ¹ GNTDYNPSLKS	N52A
05-006	EIGH ¹ SGNTDYNPSLKS	N52G
05-008	EIIHS ¹ GNTDYNPSLKS	N52I
05-010	EILHS ¹ GNTDYNPSLKS	N52L
05-011	EIMHS ¹ GNTDYNPSLKS	N52M
05-013	EISH ¹ SGNTDYNPSLKS	N52S
05-014	EITH ¹ SGNTDYNPSLKS	N52T

05-015	EIVHSGNTDYNPSLKS	N52V
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Example 5. Construction of genetic constructs encoding sequences of full-length antibodies against TL1A for producing same in eukaryotic cells.

The nucleotide sequences of variable domains of antibodies were synthesized *de novo*. The sequences were codon-optimized for expression in CHO cells. Selected sequences of variable domains of antibodies were cloned into expression vectors comprising sequences of constant domains of human immunoglobulin IgG1 according to the standard procedure. To this end, we generated PCR products containing the genes of the heavy and light chain variable domains of the antibodies. In the course of PCR, the desired overlaps (sequence regions identical for insertion and vector) of 20-30 nucleotide long were added to the 5' and 3' ends of the molecule for further molecular cloning by ligase-free methods.

The heavy chain variable domain was cloned into a vector comprising a sequence encoding the heavy chain constant domains of human immunoglobulin IgG1.

In some cases, the resulting vector comprised all the elements necessary for the transient generation of protein in eukaryotic cells (for example, in Chinese hamster ovary (CHO) cells). Figure 2 is a schematic map of such vector.

In some cases, the resulting vector comprised all the elements necessary for constant generation of protein in eukaryotic cells (for example, in Chinese hamster ovary (CHO) cells). Figure 4 is a schematic map of such vector.

The light chain variable domain was cloned into a vector comprising a sequence of light chain constant domain of IgG1 kappa immunoglobulin.

In some cases, the resulting vector comprised all the elements necessary for the transient generation of protein in eukaryotic cells (for example, in Chinese hamster ovary (CHO) cells). Figure 3 is a schematic map of such vector.

In some cases, the resulting vector comprised all the elements necessary for constant generation of protein in eukaryotic cells (for example, in Chinese hamster ovary (CHO) cells). Figure 5 is a schematic map of such vector.

The assembly quality was verified by Sanger sequencing. The resulting genetic constructs comprised all the elements necessary for protein expression in eukaryotic cells.

Example 6. Generation and purification of antibodies against TL1A.

In some instances, the full-length antibodies were generated in Chinese hamster ovary cell culture (the CHO-K1 cell line) using the above genetic constructs for transient generation of protein in eukaryotic cells. Example 1 describes preparation of and culturing of the cell culture.

In some instances, the full-length antibodies were generated in Chinese hamster ovary cell culture (the CHO-S cell line) using the above genetic constructs for constant generation of protein in eukaryotic cells.

The full-length antibodies were purified in two steps. Affinity chromatography using a chromatographic sorbent with protein A ligand was used at the first stage. Next, we performed viral inactivation and filtered the solution using a 0.22 μm filter. The second step of chromatographic purification was carried out using a multimodal anion exchange sorbent.

Purity of the resulting molecules was evaluated using polyacrylamide gel electrophoresis (vertical gel electrophoresis, VEP) using a technique known in the art (Table).

Purity of the resulting molecules was further evaluated by high-performance liquid chromatography (HPLC) which is known in the art (Table).

Table 2. Monomer content by VEP and HPLC, %

Antibody	Monomer content (VEP), %	Monomer content (HPLC), %
01-001	95.8	87.1
03-001	84.0	98.7
03-002	82.3	99.4
04-001	86.5	97.6
04-002	91.2	96.9
05-001	88.2	83.1
05-002	87.0	87.1
05-006	88.0	83.3
05-008	85.9	80.5
05-010	88.1	76.4
05-011	84.4	76.7
05-013	88.4	83.4
05-014	86.5	80.1
05-015	85.6	79.0

Example 7. Determination of dissociation constant for antibodies according to the invention with respect to human and animal TL1A (TNFSF15) by biolayer interferometry.

The degree of interaction between the resulting antibodies and TL1A antigens was evaluated by bio-layer interferometry on ForteBio Octet RED 384 using dedicated AR2G sensors (ForteBio). Protein was immobilized on the surface of activated sensors followed by quenching of unreacted groups, recording of baseline, recording of analyte association, recording of analyte dissociation. Baseline, as well as all other analysis steps, were recorded in a kinetic buffer (based

on Na_2HPO_4 and KH_2PO_4 , supplemented with NaCl, KCl, 0.1% Tween 20, 0.1% bovine serum albumin). The resulting data was processed using the Octet Data Analysis (Version 9.0) software and using the 1:1 interaction model. The processing results are shown in Table .

Table 3. Equilibrium dissociation constants (KD) for antibodies and human TL1A according to kinetic tests using ForteBio

Antibody	KD, mol/l	kon, 1/(Ms)	kdis, 1/s
01-001	Exceeded instrument detection limit ($<1*10^{-12}$)	$3.83*10^5$	Exceeded instrument detection limit($<1*10^{-7}$)
03-001	$4.84*10^{-10}$	$5.80*10^5$	$2.81*10^{-4}$
03-002	$2.73*10^{-10}$	$6.15*10^5$	$1.68*10^{-4}$
04-001	$9.29*10^{-12}$	$2.93*10^5$	$2.72*10^{-6}$
04-002	Exceeded instrument detection limit ($<1*10^{-12}$)	$2.81*10^5$	Exceeded instrument detection limit($<1*10^{-7}$)
05-001	$4.43*10^{-8}$	$2.92*10^5$	$1.29*10^{-4}$
05-002	$1.98*10^{-10}$	$4.29*10^5$	$2.35*10^{-4}$
05-006	$5.87*10^{-10}$	$3.88*10^5$	$2.28*10^{-4}$
05-008	$1,81*10^{-10}$	$3.82*10^5$	$2.34*10^{-4}$
05-010	$1,81*10^{-10}$	$4.24*10^5$	$2.07*10^{-4}$
05-011	$6.40*10^{-10}$	$3.69*10^5$	$2.36*10^{-4}$
05-013	$6.39*10^{-10}$	$3.02*10^5$	$1,93*10^{-4}$
05-014	$7.11*10^{-10}$	$3.38*10^5$	$2.40*10^{-4}$
05-015	$2.58*10^{-10}$	$4.71*10^5$	$2.88*10^{-4}$

Accordingly, all test antibodies according to the invention show a high degree of interaction with human TL1A.

Table 4. Equilibrium dissociation constants (KD) for antibodies and rhesus macaque and Javanese macaque TL1A (TNFSF15) (with identical sequence) according to kinetic tests using ForteBio.

Antibody	KD, mol/l	kon, 1/(Ms)	kdis, 1/s
01-001	$4.93*10^{-12}$	$2.16*10^5$	$1.06*10^{-6}$
03-001	$1.64*10^{-9}$	$2.46*10^5$	$4.03*10^{-4}$
03-002	$8.63*10^{-10}$	$2.23*10^5$	$1,93*10^{-4}$

Thus, all of the above antibodies according to the invention show a high degree of interaction with rhesus macaque and Javanese macaque TL1A (TNFSF15) (sequences are identical).

Table 5. Equilibrium dissociation constants (KD) for antibodies and rat TL1A (TNFSF15) according to kinetic tests using ForteBio

Antibody	KD, mol/l	kon, 1/(Ms)	kdis, 1/s
01-001	$1.44 \cdot 10^{-11}$	$2.34 \cdot 10^5$	$3.38 \cdot 10^{-6}$
03-002	$4.08 \cdot 10^{-9}$	$4.63 \cdot 10^6$	$1.89 \cdot 10^{-2}$

Accordingly, all of the above antibodies according to the invention show a high degree of interaction with rat TL1A (TNFSF15).

Example 8. Evaluation of affinity of antibodies according to the invention for human and animal TL1A (TNFSF15) by surface plasmon resonance (SPR).

The interaction between 01-001 and humans and animal TL1A (TNFSF15) antigens was evaluated by surface plasmon resonance (SPR) on a Biacore 8K instrument. The antigens were immobilized through amine binding on the surface of a carboxymethyl dextran-coated sensor chip (CM5). Human, rhesus macaque, Javanese macaque, green monkey, ferret, pig, rabbit and rat TL1A (TNFSF15) antigens were diluted in a kinetic phosphate buffer solution (PBS) supplemented with KCl, NaCl, Tween 20, and passed over the surface of the chip using an immobilization buffer based on $\text{C}_2\text{H}_3\text{NaO}_2$ (pH 4.0 ± 0.1). Next, the surface of the chip was activated by introducing a mixture of activators, thereafter an antibody solution was introduced. The immobilization level was determined by changes in surface plasmon resonance. To correct possible signal distortion, one of the detection channels was used as a reference one, i.e. the antibody solution was not introduced through the channel at the appropriate stage. Active carboxyl groups were deactivated using a kinetic solution.

The calculated values of the equilibrium dissociation constants (KD) are shown in Table 6.

Table 6. Equilibrium dissociation constants (KD) for 01-001 and human and animal TL1A (TNFSF15) (including assessment of amino acid sequence identity between the secreted portion of animal TNFSF15 and human TNFSF15).

Species	Identity between TL1A and Homo sapiens, %	TL1A code in UniProt database	KD with TL1A antigen, mol/l
Human	100	O95150	$7.96 \cdot 10^{-11}$
Green monkey	99	A0A0D9RKK8	$6.84 \cdot 10^{-9}$

Species	Identity between TL1A and Homo sapiens, %	TL1A code in UniProt database	KD with TL1A antigen, mol/l
Javanese macaque	98	G7PRK8	7.60×10^{-10}
Rhesus macaque	98	F6S8F9	7.60×10^{-10}
Ferret	88	M3XRG1	5.88×10^{-10}
Pig	87	I3LL00	7.54×10^{-10}
Rabbit	83	G1T1T1	9.19×10^{-9}
Rat	76	Q8K3Y7	6.74×10^{-11}

Accordingly, antibody 01-001 interacts with the human TL1A antigen with a high degree of affinity, the resulting KD value was 7.96×10^{-11} M. Furthermore, 01-001 shows a high affinity for the rhesus macaque, Javanese macaque, green monkey, ferret, pig, rabbit and rat TL1A (TNFSF15). Based on these data, rat, Javanese macaque, rhesus macaque, minipig, ferret, green monkey and rabbit are relevant species for preclinical studies.

Example 9. Specificity of binding of antibodies according to the invention to human TL1A (TNFSF15) homologues.

To assess the non-targeted binding of antibody 01-001 to closest human TL1A homologues, we evaluated affinity of 01-001 for TRAIL (TNFSF10), FASL (TNFSF6), LIGHT (TNFSF14), EDA-A1 and EDA-A2 proteins, whose extracellular portions are identical to those of human TL1A by 39%, 35%, 34%, 36%, 36%, respectively. Binding affinity was assessed by bio-layer interferometry on a ForteBio Octet RED 384 instrument using dedicated AR2G sensors (ForteBio) according to the above procedure. The study included analysis of antigens with various peptide tags. Human TL1A, produced as described above, was used as a positive control.

Calculated values of equilibrium dissociation constants (KD) are shown in Table 7.

Table 7. Equilibrium dissociation constants (KD) for 01-001 and human TL1A (TNFSF15) homologues according to kinetic tests using ForteBio

Human antigen	KD, mol/l	kon, 1/(Ms)	kdis, 1/s
TL1A (TNFSF15)	Exceeded instrument detection limit ($<1 \times 10^{-12}$)	3.83×10^5	Exceeded instrument detection limit ($<1 \times 10^{-7}$)
TRAIL (TNFSF10)	--	No binding detected	--
FASL (TNFSF6)	--	No binding detected	--
LIGHT (TNFSF14)	--	No binding detected	--
EDA-A1	--	No binding detected	--

EDA-A2	--	No binding detected	--
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Thus, the method showed no interaction between antibody 01-001 and any of test proteins of the tumor necrosis factor (TNF) family, but showed binding to human TL1A on the same plate which was used to test the homologous proteins. Accordingly, antibody 01-001 is highly selective with respect to binding to human TL1A, but not to its closest homologous proteins of the TNF family.

Example 10. Determination of thermal stability of antibodies according to the invention.

Thermal stability of antibody was evaluated by thermal stress at 50 °C for 48 hours in three buffer solutions having distinct compositions: buffer solution 1 with pH 5.0; buffer solution 2 with pH 6.0, and buffer solution 3 with pH 7.0. Homogeneity was controlled by SEC HPLC, which is known in the art. The study results are shown in Tables 7–9.

Table 7. Study of intact and thermostatic samples of antibody 01-001 in buffer solution 1 with pH 5.0 by HPLC.

Thermostation time, h	Proportion of monomer, %	High molecular weight impurities, %	Low molecular weight impurities, %
0	87.0	12.7	0.3
24	86.8	11.0	2.2
36	85.1	12.3	2.6
48	85.0	12.1	2.9

Table 8. Study of intact and thermostatic samples of antibody 01-001 in 20 mM buffer solution 2 with pH 6.0 by HPLC.

Thermostation time, h	Proportion of monomer, %	High molecular weight impurities, %	Low molecular weight impurities, %
0	87.2	12.4	0.4
24	86.0	12.0	2.0
36	85.8	12.1	2.1
48	85.5	12.0	2.5

Table 9. Study of intact and thermostatic samples of antibody 01-001 in buffer solution 3 with pH 7.0 by HPLC.

Thermostation time, h	Proportion of monomer, %	High molecular weight impurities, %	Low molecular weight impurities, %
0	86.3	13.3	0.4
24	84.5	13.6	1.9

36	83.7	14.0	2.3
48	82.0	15.4	2.6

Thus, changes in main peak area (of monomer 01-001) in the three test buffer solutions under heating for 48 hours were 2.0–4.3%, showing high thermal stability of antibody 01-001.

Example 11. Determination of aggregation temperature of antibodies according to the invention.

Next, the aggregation temperature of antibody 01-001 was determined by dynamic light scattering (DLS), which is known in the art.

Aggregation temperature was determined in the following steps: determination of aggregation temperature of antibody by DLS, thermostating of antibody at 50 °C for 48 hours, analysis of samples following thermostating by HPLC, analysis of particle size of samples by DLS. Intact samples – test antibody in the above buffer solutions, which antibody was not subjected to thermostating at 50 °C for 48 hours, but was incubated at 2–8 °C – were used as a control. The study results are shown in Table 10.

Table 10. Study of intact and thermostated samples of antibody 01-001 by DLS using HPLC.

Buffer solution	Before thermal stress				After thermal stress			
	Radius of eluted fraction, Rh, nm	PD of eluted fraction, %	Intensity of eluted fraction	Mean radius of particles, Rh, nm	Radius of eluted fraction, Rh, nm	PD of eluted fraction, %	Intensity of eluted fraction	Mean radius of particles, Rh, nm
No. 1 (pH 5.0)	5.7	11.5	94.8	6.0	6.0	18.7	94.1	6.0
No. 2 (pH 6.0)	6.3	29.2	100	5.6	n/d	n/d	n/d	n/d
No. 3 (pH 7.0)	6.1	9.9	100	5.8	7.0	23.4	98.9	6.2

Note: PD — polydispersity; n/d — not determined.

Aggregation temperatures of antibody 01-001 determined in the analysis were: 65.92 °C for buffer solution 1 (pH 5.0); 66.03 °C for buffer solution 2 (pH 6.0), and 63.99° C for buffer solution 3 (pH 7.0).

Example 12. Determination of melting temperatures of antibodies according to the invention.

Melting temperature of antibody 01-001 was determined by differential scanning fluorimetry (DSF). According to the method, stability of a sample is directly proportional to difference between temperature of the blank solution (the solution in which the antibody is present) and that of the sample. The results of the study are shown in Table 11.

Table 1. Melting temperatures of samples 01-001

Sample	Group of peaks on melt curve, °C							
	Bin A	Bin B	Bin C	Bin D	Bin E	Bin F	Bin G	Bin H
Buffer solution 1 (pH 5.0)	n/d	n/d	55.0	n/d	n/d	n/d	n/d	n/d
Antibody 01-001 in buffer solution 1 (pH 5.0)	47.4	51.2	54.8	60.9	65.2	71.5	75.4	n/d
Buffer solution 2 (pH 6.0)	55.2	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Antibody 01-001 in buffer solution 2 (pH 6.0)	55.3	63.0	70.3	73.4	75.7	n/d	n/d	n/d
Buffer solution 3 (pH 7.0)	55.2	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Antibody 01-001 in buffer solution 3 (pH 7.0)	55.0	64.8	67.3	70.3	77.5	n/d	n/d	n/d

Note: n/d – not detected.

Melting temperatures of antibody 01-001 determined in the analysis were: 47.4–60.9 °C for buffer solution 1 (pH 5.0); 64.8 °C for buffer solution 2 (pH 6.0) and 63.0 °C for buffer solution 3 (pH 7.0).

Example 13. Determination of changes in kinetic properties of antibodies according to the invention under long-term heating.

To further evaluate the stability of antibody 01-001, we determined changes in kinetic properties thereof following the above-described incubation at 50 °C for 48 hours in three distinct buffer solutions. Affinity of samples 01-001 to human TL1A was determined using biolayer interferometry on the ForteBio Octet RED 384 instrument and dedicated AR2G sensors (ForteBio) as described above. The results of the study are shown in Table 12.

Table 2. Equilibrium dissociation constants (KD) for intact and thermostated samples of antibody 01-001 and human TL1A in distinct buffer solutions

Buffer solution	Time of exposure to 50°C, h	KD, mol/l	kon, 1/(Ms)	kdis, 1/s
Buffer solution 1 (pH 5.0)	0	$3.85 \cdot 10^{-11}$	$4.53 \cdot 10^5$	$1.74 \cdot 10^{-5}$
	24	$1.36 \cdot 10^{-11}$	$3.95 \cdot 10^5$	$5.38 \cdot 10^{-6}$
	36	$1.04 \cdot 10^{-11}$	$3.98 \cdot 10^5$	$4.12 \cdot 10^{-6}$
	48	$1.87 \cdot 10^{-11}$	$3.89 \cdot 10^5$	$7.27 \cdot 10^{-6}$
Buffer solution 2 (pH 6.0)	0	$<1 \cdot 10^{-12}$	$4.55 \cdot 10^5$	$3.77 \cdot 10^{-7}$
	24	$3.35 \cdot 10^{-11}$	$5.01 \cdot 10^5$	$1.68 \cdot 10^{-5}$
	36	$4.11 \cdot 10^{-11}$	$4.57 \cdot 10^5$	$1.88 \cdot 10^{-5}$
	48	$5.12 \cdot 10^{-11}$	$4.36 \cdot 10^5$	$2.23 \cdot 10^{-5}$
Buffer solution 3 (pH 7.0)	0	$1.25 \cdot 10^{-11}$	$3.65 \cdot 10^5$	$4.55 \cdot 10^{-6}$
	24	$2.88 \cdot 10^{-11}$	$3.70 \cdot 10^5$	$1.06 \cdot 10^{-5}$
	36	$2.54 \cdot 10^{-11}$	$3.68 \cdot 10^5$	$9.32 \cdot 10^{-6}$
	48	$3.29 \cdot 10^{-11}$	$3.58 \cdot 10^5$	$1.18 \cdot 10^{-5}$

Based on the results of the experiment, antibody 01-001 is highly resistant to long-term heating, while maintaining high affinity for human TL1A.

Example 14. Determination of posttranslational modifications of antibodies according to the invention.

To determine the posttranslational modifications of antibody 01-001, we checked for the presence and profile of glycosylation of the molecule, presence of predicted disulfide bonds, content and location of trisulfides, thioesters and free cysteines; as well as their changes following the above-described incubation of 01-001 in three buffer solutions at 50 °C for 48 hours.

The analytical experiment determined posttranslational modifications of samples 01-001 by ultra-high performance liquid chromatography with mass spectrometric detection. Posttranslational modification library which was used to analyze and process all provided samples was constructed using standard samples (N-terminal form of glutamic acid, succinimide form of asparagin/glutamine, etc.) and antibody 01-001 in three buffer solutions described above. The data resulted from the analytical experiment was processed using the Protein Metrics software.

The study confirmed the native molecular weight of antibody 01-001. It was shown that in the 01-001 antibody, two standard N-glycosylation sites of IgG1 immunoglobulins (at the Asn297 residue in the CH2 heavy chain constant domain) are occupied. No glycosylation of Fab domain

was detected. The results indicate non-occupation of the theoretical site of N-glycosylation in CDR2 of heavy chain variable domain of antibody 01-001.

Samples 01-001 did not exhibit any oxidized forms of methionine and tryptophan, and no N-terminal pyriform of glutamic acid was detected. The analytical experiment confirmed the location of disulfide bonds in 01-001. No improperly crosslinked disulfide bonds, trisulfides, and thioesters were found.

No significant changes in posttranslational modifications were detected following incubation of 01-001 at 50 °C for 48 hours.

Example 15. Determination of stability of antibodies according to the invention in human blood serum.

Stability of 01-001 in normal human blood serum was determined for 14 and 28 days at 37 °C. To this end, we evaluated the ability of antibody 01-001 to bind human TL1A following incubation under said conditions using ELISA according to a standard procedure. Briefly, recombinant TL1A was introduced into pretreated wells of a high-absorption plate, thereafter human blood serum samples comprising a known amount of antibody 01-001 were added (before incubation at 37 °C). After a series of washings, the reaction was developed using a conjugate of polyclonal antibodies to human IgG Fc fragment with horseradish peroxidase, and the solution optical density was determined using a spectrophotometer at a wavelength of 450 nm. Next, we determined the content of 01-001 in the blood serum sample by comparing the data to the calibration curve reflecting solution optical density-antibody concentration dependence.

The study showed that human serum preserves 70% of initially introduced molecules of 01-001 following 14 days of incubation at 37 °C, and 63% following 28 days. Mean stability of IgG1 monoclonal antibodies in human serum is conventionally considered to be 60% of functional molecules preserved over a period of a month (28 days) at +37 °C. Thus, antibody 01-001 stability is above the mean value.

Example 16. Interaction between antibodies according to the invention and membrane-bound form of human TL1A on cell surface.

01-001-human TL1A interaction on the surface of eukaryotic cells was evaluated using CHO-tmTL1A cells stably expressing the membrane-bound form of human TL1A by flow cytometry using commercial phycoerythrin (PE)-labeled antibodies specific for the human IgG Fc fragment. The CHO-K1-S cell line not expressing the membrane-bound form of human TL1A was used as a negative control.

Cell suspensions were incubated with serial dilutions 01-001 on ice in the dark, then washed from unbound 01-001, thereafter the precipitated cells were incubated with secondary staining antibodies to the human IgG Fc fragment on ice in the dark. Next, the cells were washed

from unbound secondary antibodies, resuspended in a staining buffer, and the fluorescence intensity was measured on a flow cytometer. The dependence of median fluorescence intensity on product concentration was evaluated. The results of the study are shown in Figure 6.

Thus, 01-001 interacts with the membrane-bound form of human TL1A on the surface of eukaryotic cells. Intensity of the effect is directly dependent on the concentration of 01-001, EC_{50} values are in the nanogram range (163.8 ng/ml).

Based on the results, CHO-tmTL1A cells stably expressing the membrane-bound form of human TL1A were selected for further *in vitro* tests to investigate the potential mechanism of action of 01-001 and to evaluate Fc-mediated antibody functions.

Example 17. Inhibition of interaction between soluble human TL1A and human DR3 receptor by antibodies according to the invention on cell line surface.

The effect of antibody 01-001 on interaction between soluble TL1A and DR3 on TF-1 NF- κ B Luc cl.4 cell line surface was determined by flow cytometry using commercial human biotin-labeled TL1A. To this end, cell suspension was incubated with serial dilutions of 01-001 and a solution of biotinylated TL1A, washed from unbound 01-001 and TL1A, thereafter cell precipitates were incubated with a solution of phycoerythrin-streptavidin conjugate on ice in the dark. The cells were washed from unbound conjugate, resuspended in a staining buffer, and the fluorescence intensity was measured on a flow cytometer. The dependence of median fluorescence intensity on product concentration was evaluated. EC_{50} was 1113 ng/ml.

Accordingly, 01-001 inhibits the interaction between soluble human TL1A (TNFSF15) and the human DR3 receptor (TNFRSF25) on TF-1 NF- κ B Luc cl.4 cell line surface. Intensity of the effect is directly dependent on the concentration of 01-001, EC_{50} values are in the microgram range (1113 ng/ml). This property of 01-001 proves it to be effective in preventing the activation of proinflammatory signaling cascade mediated by TL1A-DR3 interaction.

Example 18. Comparison of inhibition of interaction of soluble human TL1A with DR3 receptor and DcR3 decoy receptor by antibodies according to the invention.

The ability of 01-001 to inhibit the interaction of TL1A with the DcR3 and DR3 receptors was evaluated using ELISA according to the standard procedure. Briefly, human DR3 (TNFRSF25) and human DcR3 (TNFRSF6B) soluble proteins were immobilized on the surface of plate wells, thereafter serial dilutions of 01-001 product were incubated with biotinylated human TL1A. Next, solutions of 01-001 with biotinylated TL1A were added to the immobilized receptors. We performed detection using streptavidin-HRP conjugate and measured the optical density (OD) signal on a microplate reader. Percentage of inhibition of TL1A-DR3 and TL1A-DcR3 interactions by 01-001 was determined. EC_{50} values were 1.5 ng/ml for TL1A-cellular DR3 receptor interaction and 67.7 ng/ml for TL1A-soluble DcR3 decoy receptor interaction.

The results of the experiment show that antibody 01-001 selectively inhibits the interaction between human TL1A and the target cellular DR3 receptor; whereas its inhibition of interaction between TL1A and the DcR3 decoy receptor, a natural antagonist of TL1A, is significantly less (by 45 times).

Example 19. Inhibition of caspase-dependent apoptosis mediated by TL1A-DR3 interaction by antibodies according to the invention.

TL1A binding to the naturally-occurring DR3 receptor under cycloheximide-affected synthesis of inhibitor of apoptosis protein cIAP2 included in the NFkB signaling pathway results in activation of caspases and induction of apoptosis. The ability of the antibodies according to the invention to inhibit TL1A-mediated apoptosis in the presence of cycloheximide was evaluated in a cell assay using the TF-1 cell line expressing the DR3 receptor. To this end, the cell suspension was incubated with serial dilutions of the antibodies according to the invention and a solution of human TL1A in the presence of cycloheximide; a solution of the reagent for detection of caspase-3/7 by luminescence intensity was then introduced, and, following further incubation, the luminescence signal was measured on a plate reader. The results of the study are shown in Table 13.

Table 3. EC₅₀ values for inhibition of caspase signaling of the TF-1 cell line by antibodies according to the invention.

Antibody	EC ₅₀ , ng/ml	Antibody	EC ₅₀ , ng/ml
01-001	218	05-006	566
03-001	9585	05-008	450
03-002	1914	05-010	334
04-001	943	05-011	508
04-002	421	05-013	>15000
05-001	508	05-014	>15000
05-002	377	05-015	>15000

Thus, the above antibodies according to the invention inhibit the initiation of apoptosis mediated by TL1A-DR3 interaction in the presence of cycloheximide. Intensity of the effect is directly dependent on the concentration of 01-001, EC₅₀ values are in the nanogram range (218–287 ng/ml).

Example 20. Determination of changes in inhibiting properties of antibodies according to the invention under long-term heating.

To further evaluate the stability of antibody 01-001, we determined changes in functional properties thereof for inhibition of TL1A-mediated apoptosis following the above-described

incubation at 50 °C for 48 hours in three distinct buffer solutions. The inhibitory activity was determined using the caspase-3/7 luminescence assay described above. The results of the study are shown in Table 14.

Table 4. EC₅₀ and EC₉₀ values for inhibition of caspase signaling of the TF-1 cell line by intact and thermostated samples of antibody 01-001 in distinct buffer solutions

Buffer solution	Time of exposure to 50°C, h	EC ₅₀ , ng/ml	EC ₉₀ , ng/ml
Buffer solution 3 (pH 7.0)	0	208.96	716
	24	282.27	1234
	36	308.19	1052
	48	417.34	1350
Buffer solution 2 (pH 6.0)	0	316.82	993
	24	540.21	1182
	36	418.44	894
	48	536.11	1300
Buffer solution 1 (pH 5.0)	0	517.71	1016
	24	474.94	1217
	36	339.41	985
	48	433.32	1148

Based on the results of the experiment, antibody 01-001 has significant resistance to long-term heating, while maintaining biological properties thereof relating to inhibition of caspase signaling mediated by TL1A-DR3 interaction.

Example 21. Inhibition of TL1A-DR3 interaction-mediated activation of NFκB signaling pathway by antibodies according to the invention.

To further confirm the effect of the antibodies according to the invention on TL1A-mediated activation of DR3, the efficiency of inhibition and NFκB signaling pathway was evaluated. To this end, the cell suspension of the TF-1 NF-κB Luc cl.4 reporter line expressing the DR3 receptor and carrying the luciferase gene under the control of an NFκB-responsive element was incubated with serial dilutions of the antibodies according to the invention and a solution of human TL1A with the same concentration. The luciferase enzyme was detected by measuring a luminescence signal on a microplate reader. The results of the study are shown in Table 15.

Table 5. EC₅₀ values for inhibition of NFκB signaling pathway of TF-1 NF-κB Luc cl.4 cell line by antibodies according to the invention.

Antibody	EC ₅₀ , μg/ml
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01-001	0.72
03-001	9.67
03-002	6.36

Thus, the antibodies of the invention efficiently inhibit the TL1A-DR3 interaction-mediated activation of NF κ B signaling pathway. The effect is directly dependent on the concentration of the products; EC₅₀ values are in the nanogram and microgram concentration ranges.

Example 22. Inhibition of release of interferon gamma in response to TL1A in the presence of IL-12 and IL-18 by antibodies according to the invention.

IL-12 and IL-18 have been shown to induce TCR (T cell receptor)-independent production of interferon gamma (IFN γ) in CD4⁺ T lymphocytes, and increased concentration of soluble TL1A or IL-15 (for example, in the case of inflammatory bowel diseases) may enhance this effect.

The ability of 01-001 to inhibit the release of IFN γ in response to TL1A was evaluated on IL-12/IL-18-activated PBMCs isolated from the whole blood of a healthy volunteer using enzyme-linked immunosorbent assay (ELISA). Briefly, PBMCs were incubated with solutions of human cytokines TL1A, IL-12, IL-18 and with serial dilutions of 01-001 for 20–24 hours. PBMCs activated by IL-12 and IL-18 (without TL1A) were used as a control of TL1A-independent release of IFN γ ; inactive PBMCs (cell control) were used as a negative control of IFN γ release. After the incubation time, the amount of IFN γ in supernatants was determined using ELISA, and the optical density signal was measured on a microplate reader. The results are shown in Figure 7.

Thus, 01-001 inhibits the release of IFN γ in response to TL1A on primary blood cells activated by IL-12 and IL-18. The effect is directly dependent on the concentration of product 01-001; EC₅₀ values are in the nanogram concentration range (496.5 ng/ml).

Example 23. Inhibition of cytokine release in response to TL1A in the presence of IL-12, IL-18 and IL-15 by antibodies according to the invention.

It has been shown that the presence of soluble TL1A together with IL-12, IL-18 and IL-15 leads to significantly increased production of a number of proinflammatory cytokines such as IFN γ , IL-6, GM-CSF, IL-5, IL-13, TNF- α and IL-22 in CD45RO⁺CD4⁺T- lymphocytes.

The ability of 01-001 to inhibit the release of cytokines TNF- α , IL-13, IL-6, IL-17, IL-5, GM-CSF in response to TL1A was evaluated on T-lymphocytes isolated from IL-12/IL-18/IL-15-activated PBMCs of a healthy volunteer using multiplex analysis. T-lymphocytes activated by IL-12, IL-18 and IL-15 without TL1A were used as a control of TL1A-independent cytokine release, whereas inactive T-lymphocytes were used as a negative control of cytokine release.

T-lymphocytes were incubated with solutions of human cytokines TL1A, IL-12, IL-18, IL-15 and with serial dilutions of 01-001 for 96 hours. After the incubation time, the amount of

cytokines TNF- α , IL-13, IL-6, IL-17, IL-5, and GM-CSF in supernatants was determined using multiplex analysis, and the fluorescence signal was measured. The results are shown in Figures 8–13.

Thus, antibody 01-001 inhibits the release, from blood cells, of proinflammatory cytokines TNF- α , IL-13, IL-6, IL-17, IL-5, GM-CSF in response to TL1A combined with IL-12, IL-18 and IL-15. The effect is directly dependent on the concentration of product 01-001; EC₅₀ values are in the nanogram concentration range (12.07–126.6 ng/ml). According to the results, the use of 01-001 will result in decreased severity of symptoms of TL1A-mediated diseases or disorders.

Example 24. Affinity of antibodies according to the invention to Fc γ receptors

The affinity of 01-001 for Fc γ receptors (Fc γ RIIa-131H, Fc γ RIIa-131R, Fc γ RIIIa-158V, Fc γ RIIIa-158F, Fc γ RIIb, Fc γ RIIIb) was determined by analyzing changes in surface plasmon resonance (SPR). The affinity of 01-001 for Fc γ RIa was determined by bio-layer interferometry (BLI). Calculated values of equilibrium dissociation constants (KD) are shown in Table 16.

Table 16. Equilibrium dissociation constants (KD) for 01-001 to Fc γ receptors

Sample	Affinity for receptor						
	Fc γ RIIa-131H, KD (M)	Fc γ RIIa-131R, KD (M)	Fc γ RIIIa-158V, KD (M)	Fc γ RIIIa-158F, KD (M)	Fc γ RIIb, KD (M)	Fc γ RIa, KD (M)	Fc γ RIIIb, KD (M)
01-001	5.41x10 ⁻⁴	3.30x10 ⁻⁴	5.50x10 ⁻⁵	4.19x10 ⁻⁴	3.60x10 ⁻⁴	3.00x10 ⁻⁶	—*

* KD values were not determined due to low-affinity binding

Thus, 01-001 has a low affinity for all Fc γ receptors.

Example 25. Affinity of antibodies according to the invention to FcRn.

Evaluation of product affinity for FcRn receptor is important, since the time of product circulation in bloodstream and product half-life in the body are affected by the degree of binding to the receptor.

Comparative analysis of affinity of 01-001 for FcRn receptor was performed on the ForteBio Octet RED 384 instrument according to the above-described procedure, using dedicated streptavidin SA biosensors (ForteBio). To control the analysis, we used a reproduced antibody to TL1A PF-06480605 according to patent WO2021260577 (Pfizer Inc.) and a reproduced antibody to TNF-alpha (tumor necrosis factor alpha) adalimumab. Calculated values of equilibrium dissociation constants (KD) are shown in Table 17.

Table 17. Antibody affinity for FcRn receptor according to the results of kinetic assays using ForteBio.

Antibody	KD, mol/l	kon, 1/(Ms)	kdis, 1/s
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01-001	$1.20 \cdot 10^{-9}$	$1.27 \cdot 10^6$	$1.53 \cdot 10^{-3}$
PF-06480605	$1.04 \cdot 10^{-8}$	$2.14 \cdot 10^6$	$2.23 \cdot 10^{-2}$
Adalimumab	$1.17 \cdot 10^{-8}$	$1.78 \cdot 10^6$	$2.09 \cdot 10^{-2}$

Conclusion: the test antibody according to the invention shows high affinity for FcRn, exceeding that of control antibodies.

Example 26. Affinity of antibodies according to the invention for C1q.

The affinity of 01-001 for C1q was determined by analyzing changes in surface plasmon resonance (SPR). KD values were not determined due to low-affinity binding of 01-001 to C1q.

Example 27. Evaluation of induction of antibody-dependent cellular cytotoxicity (ADCC) by antibodies according to the invention.

The ability of 01-001 to induce antibody-dependent cellular cytotoxicity against cells expressing the membrane-bound form of TL1A was evaluated in a reporter cellular assay. CHO-tmTL1A cells were used as target cells, and Jurkat-based reporter cell lines carrying a luciferase-encoding gene under the control of NFAT-responsive elements and expressing a high-affinity or low-affinity CD16 receptor were used as effector cells. Suspensions of target and effector cell lines were incubated with serial dilutions of 01-001 product, and the luminescence signal was measured on a microplate reader.

The results of the experiment showed that 01-001 does not induce antibody-dependent cellular cytotoxicity mediated by high-affinity and low-affinity CD16 receptor against CHO-tmTL1A cells expressing the membrane-bound form of TL1A.

Example 28. Evaluation of induction of antibody-dependent cellular phagocytosis (ADCP) by antibodies according to the invention.

The ability of 01-001 to induce antibody-dependent cellular phagocytosis against cells expressing the membrane-bound form of TL1A was evaluated in a reporter cellular assay. CHO-tmTL1A cells were used as target cells, and Jurkat-based reporter cell lines carrying a luciferase-encoding gene under the control of NFAT-responsive elements and expressing a high-affinity receptor CD32 or low-affinity receptor CD32 were used as effector cells. Suspensions of target and effector cell lines were incubated with serial dilutions of 01-001, and the luminescence signal was measured on a microplate reader.

The results of the experiment showed that 01-001 does not induce antibody-dependent cellular phagocytosis against CHO-tmTL1A cells expressing the membrane-bound form of TL1A.

Example 29. Evaluation of induction of complement-dependent cytotoxicity (CDC) by antibodies according to the invention.

The ability of 01-001 to induce complement-dependent cytotoxicity was evaluated using a cellular assay which determines CDC based on decreased cell viability and ability to metabolize the Resazurin vital dye, which in turn results in a decreased fluorescence signal.

CHO-tmTL1A expressing the membrane-bound form of TL1A were used as target cells.

The results of the experiment showed that 01-001 does not induce complement-dependent cytotoxicity against CHO-tmTL1A cells expressing the membrane-bound form of TL1A.

Example 30. Evaluation of induction of direct and cross-linked apoptosis by antibodies according to the invention.

The ability of 01-001 to induce direct and cross-linked apoptosis against CHO-tmTL1A cells expressing the membrane-bound form of TL1A was determined by flow cytometry using annexin V to detect apoptotic cells.

To assess direct apoptosis, solutions of serial dilutions of 01-001 were added to CHO-tmTL1A cell suspension and then incubated for 24 hours. To assess cross-link apoptosis, Fc-specific cross-link antibodies were added to the system followed by incubation with a mixture of PE (phycoerythrin)-labeled annexin V and 7-aminoactinomycin D in the dark at room temperature. 1% solution of hydrogen peroxide was used as a positive control. Percentage of annexin V positive population was determined on a flow cytometer.

According to the results, 01-001 does not induce direct and cross-linked apoptosis of CHO-tmTL1A cells expressing the membrane-bound form of TL1A.

Example 31. Evaluation of change in level of PBMC release of cytokine in response to exposure to antibodies according to the invention.

Evaluation of cytokine release in response to exposure to 01-001 leads to a conclusion on potential risk of developing cytokine release syndrome, thus it has a prognostic value for confirming the safety of the invention.

The ability of 01-001 to induce the release of 23 cytokines: eotaxin, GM-CSF, IFN α 2, IFN γ , IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17A, IL1RA, IL-1 α , IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-7, MIP-1 α , MIP-1 β , TNF α , TNF β , VEGF was determined using PBMCs from 10 healthy volunteers. HUVEC monolayer was incubated with PBMCs and 01-001 for 24 hours; after the incubation time, the amount of cytokines in supernatants was determined using multiplex analysis.

According to the results, use of 01-001 does not lead to the development of cytokine release syndrome.

Example 32. Efficacy of antibodies according to the invention in treatment of inflammatory diseases of mammalian intestine.

Efficacy of antibody 01-001 in vivo was determined on a TNBS-induced model of ulcerative colitis. Rats received a four-fold dose of trinitrobenzenesulfonic acid (TNBS) in 40%

ethanol by intrarectal administration on postnatal days 23, 35, 48 and 59. The control animals received an equivalent volume of ethanol free of TNBS. All animals developed focal colitis characterized by ulceration of the colon with inflammatory infiltrate and varying degrees of fibrosis. Antibody treatment was initiated a few days after the onset of colitis stimulation (on postnatal days 26–57).

Treatment response was determined by changes in body weight of animals, stool consistency and bleeding, and also we performed histology of sections of the large intestine to determine the degree of inflammation thereof. A semi-quantitative score scale of general intestinal inflammation was used to evaluate the efficacy of antibody 01-001:

- 1) Severity of inflammation: absent = 0, mild = 1, moderate = 2, severe = 3.
- 2) Depth of inflammation: absent = 0, only mucous membrane = 1, mucous and submucosal membranes = 2, transmural = 3.
- 3) Crypt damage: one third damaged = 1, two thirds damaged = 2, no crypts, but surface epithelium is present = 3, no crypts and surface epithelium = 4.
- 4) Proportion of field of view affected by inflammation: none = 0, 1–25% = 1, 26–50% = 2, 51–75% = 3, 76–100% = 4.

We evaluated six independent fields of view, summed up their scores, and assigned the total to an individual animal. The evaluation results are shown in Table 18.

Table 18. Cumulative score for intestinal inflammation of individual animal.

Product	Animal number	Total score
01-001	1	7
	2	3
	3	3
	4	10
	5	4
	6	7
	7	3
	8	0
	9	3
	10	0
No product (control group)	11	13
	12	23
	13	7
	14	4

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	15	15
	16	25
	17	9
	18	21
	19	7
	20	15

Thus, administration of antibody 01-001 significantly reduced multiple symptoms of the disease ($p < 0.002$ according to the Mann-Whitney U test, Figure 14).

Claims

1. A monoclonal antibody or antigen-binding fragment thereof that specifically binds to TNF-like ligand 1A (TL1A), comprising:

(a) a light chain variable domain comprising:

(i) CDR1 with the amino acid sequence RASQX₁X₂SX₃X₄X₅LX₆, where

X₁=S or G;

X₂=I or V;

X₃=S or G;

X₄= T, S or O;

X₅= Y or W;

X₆=N or A;

(ii) CDR2 with the amino acid sequence X₇ASX₈X₉X₁₀X₁₁, where

X₇=G, A or K;

X₈=S, T or R;

X₉=L or R;

X₁₀=Q or A;

X₁₁=S, T or A; and

(iii) CDR3 with the amino acid sequence QQX₁₂X₁₃SX₁₄X₁₅X₁₆X₁₇X₁₈X₁₉, where

X₁₂= A, Y or O;

X₁₃= N, G or O;

X₁₄=Y, F or S;

X₁₅=R, S, P or G;

X₁₆=T, I, L or P;

X₁₇=L, P, T or S;

X₁₈=T, P, I or O;

X₁₉=D, T or O; and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence X₂₀YX₂₁X₂₂S, where

X₂₀=D, S or G;

X₂₁=Y, A or D;

X₂₂=W or M;

(ii) CDR2 with the amino acid sequence X₂₃IX₂₄X₂₅X₂₆GX₂₇X₂₈TX₂₉YX₃₀X₃₁SX₃₂KX₃₃,

where

X₂₃=E, T or A;

X₂₄=N, Q, A, G, I, L, M, S, T, V or R;

X₂₅=H, T or S;

X₂₆=S or G;

X₂₇=N, R or G;

X₂₈=0 or S;

X₂₉=D, T, Y or S;

X₃₀=N or A;

X₃₁=P or D;

X₃₂=L, V or M;

X₃₃=S or G; and

(iii) CDR3 with the amino acid sequence

X₃₄X₃₅X₃₆X₃₇X₃₈X₃₉X₄₀X₄₁X₄₂X₄₃YX₄₄X₄₅X₄₆X₄₇X₄₈, where

X₃₄= G, S or 0;

X₃₅=G, R or 0;

X₃₆=F, G or 0;

X₃₇=S, T, R or 0;

X₃₈=G, S or L;

X₃₉=S or W;

X₄₀=P, V, W or T;

X₄₁=N, P, G or D;

X₄₂=Y, E, S or F;

X₄₃=Y, I or D;

X₄₄=A, E, R or 0;

X₄₅=M, Y, D or 0;

X₄₆= D or 0;

X₄₇=V, Y, E or 0;

X₄₈= Y or 0.

2. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, comprising:

(a) a light heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 1;

(ii) CDR2 with the amino acid sequence of SEQ ID NO: 6; and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 16;

(ii) CDR2 with the amino acid sequence EIX₁HSGNTDYNPSLKS, where

X₁=N, Q, A, G, I, L, M, S, T or V; and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 33.

3. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5.

4. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 10.

5. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15.

6. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 10; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15.

7. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, comprising:

(i) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,

CDR2 with the amino acid sequence of SEQ ID NO: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 11; or

(ii) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 2,

CDR2 with the amino acid sequence of SEQ ID NO: 7 and

CDR3 with the amino acid sequence of SEQ ID NO: 12; or

(iii) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 3,

CDR2 with the amino acid sequence of SEQ ID NO: 8 and

CDR3 with the amino acid sequence of SEQ ID NO: 13; or

(iv) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 4,

CDR2 with the amino acid sequence of SEQ ID NO: 9 and

CDR3 with the amino acid sequence of SEQ ID NO: 14 or

(v) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 5,

CDR2 with the amino acid sequence of SEQ ID NO: 10 and

CDR3 with the amino acid sequence of SEQ ID NO: 15.

8. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19.

9. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, or SEQ ID NO: 32.

10. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36.

11. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, or SEQ ID NO: 32; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36.

12. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, comprising:

(i) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 20 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(ii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 21 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(iii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 22 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(iv) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 23 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(v) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 24 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vi) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 25 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 26 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(viii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 27 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(ix) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 28 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(x) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,

CDR2 with the amino acid sequence of SEQ ID NO: 29 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(xi) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 17,

CDR2 with the amino acid sequence of SEQ ID NO: 30 and

CDR3 with the amino acid sequence of SEQ ID NO: 34; or

(xii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 18,

CDR2 with the amino acid sequence of SEQ ID NO: 31 and

CDR3 with the amino acid sequence of SEQ ID NO: 35; or

(xiii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 19,

CDR2 with the amino acid sequence of SEQ ID NO: 32 and

CDR3 with the amino acid sequence of SEQ ID NO: 36.

13. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, comprising:

(a) a light chain variable domain comprising:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9 or SEQ ID NO: 10; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 or SEQ ID NO: 15; and

(b) a heavy chain variable domain comprising:

(i) CDR1 with an amino acid sequence that is selected from the group: SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18 or SEQ ID NO: 19;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, or SEQ ID NO: 32; and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36.

14. The monoclonal antibody or antigen-binding fragment thereof according to claim 13, comprising:

(i) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 20 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(ii) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 21 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(iii) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 22 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(iv) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 23 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(v) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 24 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vi) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 25 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(vii) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 26 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(viii) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 27 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or

(ix) (a) a light chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 28 and

CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(x) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 1,
CDR2 with the amino acid sequence of SEQ ID NO: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 11; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 16,
CDR2 with the amino acid sequence of SEQ ID NO: 29 and
CDR3 with the amino acid sequence of SEQ ID NO: 33; or
(xi) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 2,
CDR2 with the amino acid sequence of SEQ ID NO: 7 and
CDR3 with the amino acid sequence of SEQ ID NO: 12; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 17,
CDR2 with the amino acid sequence of SEQ ID NO: 30 and
CDR3 with the amino acid sequence of SEQ ID NO: 34; or
(xii) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 3,
CDR2 with the amino acid sequence of SEQ ID NO: 8 and
CDR3 with the amino acid sequence of SEQ ID NO: 13; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 17,
CDR2 with the amino acid sequence of SEQ ID NO: 30 and
CDR3 with the amino acid sequence of SEQ ID NO: 34; or
(xiii) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 4,
CDR2 with the amino acid sequence of SEQ ID NO: 9 and
CDR3 with the amino acid sequence of SEQ ID NO: 14; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 18,
CDR2 with the amino acid sequence of SEQ ID NO: 31 and
CDR3 with the amino acid sequence of SEQ ID NO: 35; or
(xiv) (a) a light chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 5,

CDR2 with the amino acid sequence of SEQ ID NO: 10 and
CDR3 with the amino acid sequence of SEQ ID NO: 15; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 19,
CDR2 with the amino acid sequence of SEQ ID NO: 32 and
CDR3 with the amino acid sequence of SEQ ID NO: 36.

15. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the light chain variable domain comprises an amino acid sequence that is selected from the group: SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41.

16. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein the heavy chain variable domain comprises an amino acid sequence that is selected from the group: SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54 or SEQ ID NO: 55.

17. The monoclonal antibody or antigen-binding fragment thereof according to claim 1, wherein:

(a) the light chain variable domain comprises an amino acid sequence that is selected from the group: SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40 or SEQ ID NO: 41; and

(b) the heavy chain variable domain comprises an amino acid sequence that is selected from the group: SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54 or SEQ ID NO: 55.

18. The monoclonal antibody or antigen-binding fragment thereof according to claim 17, wherein:

(i) (a) a light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 42; or

(ii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 43; or

(iii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 44; or

- (iv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 45; or
(v) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 46; or
(vi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 47; or
(vii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 48; or
(viii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 49; or
(ix) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 50; or
(x) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 37
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 51; or
(xi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 38
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 52; or
(xii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 39
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 53; or
(xiii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 40
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 54; or
(xiv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 41
and
(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 55.

19. The monoclonal antibody according to any one of claims 1–18, wherein the antibody that specifically binds to TL1A is a full-length IgG antibody.

20. The monoclonal antibody according to claim 19, wherein the full-length IgG antibody is of human IgG1, IgG2, IgG3 or IgG4 isotype.

21. The monoclonal antibody according to claim 20, wherein the antibody comprises 446G and 447K deletion according to the EU numbering scheme for amino acids of antibodies in the CH3 region.

22. The monoclonal antibody according to claim 20, wherein the antibody comprises L234A and L235A mutations according to the EU numbering scheme for amino acids of antibodies.

23. The monoclonal antibody according to claim 20, wherein the antibody comprises M252Y, S254T, T256E mutations according to the EU numbering scheme for amino acids of antibodies.

24. The monoclonal antibody according to claim 1, comprising a light chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 or SEQ ID NO: 60.

25. The monoclonal antibody according to claim 1, comprising a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73 or SEQ ID NO: 74.

26. The monoclonal antibody according to claim 1, comprising:

(i) (a) a light chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59 or SEQ ID NO: 60, and

(b) a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73 or SEQ ID NO: 74.

27. The monoclonal antibody according to claim 26, comprising:

(i) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 61; or

(ii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 62; or

(iii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 63; or

(iv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 64; or

- (v) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 65; or
- (vi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 66; or
- (vii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 67; or
- (viii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 68; or
- (ix) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 69; or
- (x) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 56, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 70; or
- (xi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 57, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 71; or
- (xii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 58, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 72; or
- (xiii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 59, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 73; or
- (xiv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 60, and
- (b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 74.

28. A nucleic acid that encodes the antibody or antigen-binding fragment thereof according to any one of claims 1–27.

29. The nucleic acid according to claim 28, wherein the nucleic acid is DNA.

30. An expression vector comprising the nucleic acid according to any one of claims 28–29.

31. A method for producing a host cell to produce the antibody or antigen-binding fragment thereof according to any one of claims 1–27, including cell transformation by the vector according to claim 31.

32. A host cell for producing the antibody or antigen-binding fragment thereof according to any one of claims 1–27, comprising the nucleic acid according to any one of claims 28–29.

33. A method for producing the antibody or antigen-binding fragment thereof according to any one of claims 1–27, comprising culturing the host cell according to claim 32 in a growth medium under conditions sufficient to produce said antibody, followed by isolation and purification of the resulting antibody.

34. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof according to any one of claims 1–27 in combination with one or more pharmaceutically acceptable excipients.

35. The pharmaceutical composition according to claim 34, comprising the antibody or antigen-binding fragment thereof according to any one of claims 1–27 and at least one other therapeutically active compound.

36. The pharmaceutical composition according to claim 35, wherein the other therapeutically active compound is an antibody, a small molecule, a hormone therapy agent or any combination thereof.

37. The pharmaceutical composition according to any of claims 34 or 35 for treating of a TL1A-mediated disease or disorder.

38. The pharmaceutical composition according to claim 37, wherein the TL1A-mediated disease or disorder is selected from the group: Crohn's disease, ulcerative colitis, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic sclerosis-associated interstitial lung disease (SSc-ILD), intestinal fibrosis, liver fibrosis or fibrotic pulmonary diseases.

39. A method for treating a TL1A-mediated disease or disorder, comprising administering to a subject in need of such treatment the antibody or antigen-binding fragment thereof according to any one of claims 1–27 or the pharmaceutical composition according to any one of claims 34–36.

40. The method according to claim 39 of the antibody or antigen-binding fragment thereof according to any one of claims 1–27 or the pharmaceutical composition according to any one of claims 34–35 and at least one other therapeutically active compound.

41. The method for treating a disease or disorder according to claim 40, wherein the other therapeutically active compound is an antibody, a small molecule, a hormone therapy agent or any combination thereof.

42. The method for treating a disease or disorder according to any one of claims 39–41, wherein the TL1A-mediated disease or disorder is selected from the group: Crohn's disease, ulcerative colitis, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic sclerosis-associated interstitial lung disease (SSc-ILD), intestinal fibrosis, liver fibrosis or fibrotic pulmonary diseases.

43. Use of the antibody or antigen-binding fragment thereof according to any one of claims 1–27 or the pharmaceutical composition according to any one of claims 34–35 for treating a TL1A-mediated disease or disorder.

44. The use according to claim 43 of the antibody or antigen-binding fragment thereof according to any one of claims 1–27 or the pharmaceutical composition according to any one of claims 34–35 and at least one other therapeutically active compound for treating a TL1A-mediated disease or disorder.

45. The use according to claim 44, wherein the other therapeutically active compound is an antibody, a small molecule, a hormone therapy agent or any combination thereof.

46. The use according to any one of claims 43–45, wherein the TL1A-mediated disease or disorder is selected from the group: Crohn's disease, ulcerative colitis, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, systemic sclerosis-associated interstitial lung disease (SSc-ILD), intestinal fibrosis, liver fibrosis or fibrotic pulmonary diseases.