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(54) Title: ANTIBODY BINDS TO TRBV5-1 SEGMENT OF HUMAN TCR DOMAIN

(57) Abstract: 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain. 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 treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, uses of the antibodies or pharmaceutical compositions thereof for treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, and uses of the antibodies according to the invention and other therapeutically active compounds for treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

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ANTIBODY BINDS TO TRBV5-1 SEGMENT OF HUMAN TCR DOMAIN

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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain. 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 treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, uses of the antibodies or pharmaceutical compositions thereof for treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, and uses of the antibodies according to the invention and other therapeutically active compounds for treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

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 a number of disorders and diseases.

Autoimmune diseases in part are caused by autoreactive T-lymphocytes (Haroon N et al., Arthritis Rheum. 2013 Oct; 65(10):2645-54., Duarte J. et al., PloS One 2010 May 10; 5(5):e10558; Konig M. et al., Front Immunol 2016 Jan 25; 7:11). The major role in the appearance of autoreactive T-lymphocyte clones is played by the interaction of the antigen-recognizing T cell receptor (TCR) with proteins of the major histocompatibility complex (MHC, HLA), which present on their surface the processed peptides of intracellular proteins or those of proteins of pathogenic organisms.

The prior art provides that a T cell receptor sequence is a marker allowing to identify a T-lymphocyte clone involved in the pathogenesis of an autoimmune disease. T cell receptor subunits belong structurally to the immunoglobulin superfamily and are formed from several gene segments. The variable regions of TCR form the antigen-binding center of TCR. This means that they are clone-specific, that is, they are different in those T-lymphocytes that react to different antigens.

T lymphocytes (T cells) are stimulated when antigens bind to T cell receptors thereof. The TCR, a defining structure of T cells, is a transmembrane heterodimer consisting of either an alpha and beta chain or delta and gamma chain linked by a disulphide bond. Within these chains there are complementary determining regions (CDRs) which determine the antigen to which the TCR will bind. TCR development occurs through a lymphocyte specific process of gene recombination, which assembles a final sequence from a large number of potential segments. This genetic recombination of TCR gene segments in somatic T cells occurs during the early stages of development in the thymus. The TCRα gene locus contains variable (V) and joining (J) gene segments (Vα and Jα), whereas the TCRβ locus contains a D gene segment in addition to Vβ and Jβ segments. Accordingly, the α chain is generated from VJ recombination and the β chain is involved in VDJ recombination.

The TCR α chain gene locus consists of 46 variable segments (TRAV), 8 joining segments (TRAJ) and the constant region. The TCR β chain gene locus consists of 48 variable segments (TRBV) followed by two diversity segments (TRBD), 12 joining segments (TRBJ) and two constant regions. (Bio-Rad. Mini-review | An overview of T cell receptors [Electronic resource] // Bio-Rad. URL: https://www.bio-rad-antibodies.com/t-cell-receptor-minireview.html).

The T cell receptor interacts with an antigen non-covalently bound to the MHC molecule by six complementary determining regions (CDRs): three alpha chain regions and three beta chain regions. These CDRs represent variable regions, variable domain loops of the T cell receptor – Valpha (TRAV) and Vbeta (TRBV).

Relationship between TCR CD4+ T cells and development of type 1 diabetes mellitus is known from the prior art (Mai T. Tran ET ALL., T cell receptor recognition of hybrid insulin peptides bound to HLA-DQ8, NATURE COMMUNICATIONS, 2021, 12:5110, https://doi.org/10.1038/s41467-021-25404-x, Maki Nakayama ET ALL., Using the T Cell Receptor as a Biomarker in Type 1 Diabetes, Front. Immunol., 17 November 2021, Sec. Immunological Tolerance and Regulation, https://doi.org/10.3389/fimmu.2021.777788).

Patent document WO2020010250 provides an antibody that specifically binds to the T cell receptor beta-chain variable region (TCRßV).

Patent documents WO2019132738 and WO2020139171 provide an antibody that specifically binds to the beta-chain variable domain region of the human T cell receptor belonging to the TRBV9 family.

Therefore, there is an actual need to create antibodies that specifically bind to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

Disclosure of the invention (detailed description of the invention)

The authors of the present group of inventions have developed antibodies that specifically bind to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain and have high binding affinity parameters for the TRBV5-1 segment of the human T cell receptor beta-chain variable domain. Furthermore, the antibodies according to the invention are humanized, stable in human serum and thermostable, and also have antibody-dependent cell-mediated cytotoxicity (ADCC).

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 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 affinity 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 generally bind an antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally 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 off rate constant koff can be measured using bio-layer interferometry, for example, using Octet™ system.

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

The term "R^2" 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 "ED_{50}" (EC_{50}) (50% effective dose/concentration, half maximal effective concentration) refers to concentrations of a formulation producing 50% biological effect (which may include cytotoxicity).

The human "T cell receptor" is a heterodimeric protein complex located on the surface of a T cell. The receptor is only present on T cells. The main function of the T cell receptor is to specifically recognize processed antigens associated with molecules of the main histocompatibility complex (MHC).

The terms "anti-TRBV5-1 antibody", "antibody to TRBV5-1", "antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain", "antibody that specifically binds to the TRBV5-1 segment" are interchangeable in the context of the present application and refer to an antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

ADCC — antibody-dependent cell-mediated cytotoxicity.

ADCP — antibody-dependent cellular phagocytosis.

NFAT — nuclear factor of activated T cells.

Luc — luciferase.

FBS — fetal bovine serum.

CD3 — cluster of differentiation 3.

CD16 — cluster of differentiation 16.

CD20 — cluster of differentiation 20.

CD64 — cluster of differentiation 64.

PBMCs — peripheral blood mononuclear cells.

PE — phycoerythrin.

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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, 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 or SEQ ID NO: 3;

(ii) CDR2 with the amino acid sequence EIX_1KLX_2S, where

X_1=T or S

X_2=A, F or M; and

(iii) CDR3 with the amino acid sequence $QQWNYPX_3LX_4$, where

X_3=L, R or Y;

X_4=S or T;

and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 12;

(ii) CDR2 with the amino acid sequence $YINPX_5X_6GRTGYNQKX_7QX_8$, where

X_5= Y or W;

X_6= Q or N;

X_7= F or L;

X_8= A or G;

and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 18.

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.

In one embodiment of the invention, the antibody according to the invention is a humanized antibody.

A humanized antibody is intended to mean an antibody whose amino acid sequence is at least 95% homologous to reference sequences of human immunoglobulins (according to the IMGT database). Use of humanized antibodies reduces the risk of an immune response from the human body when they are used.

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 can be further subdivided into hyper-variability regions called complementarity determining regions (CDRs), interspersed between regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of heavy and light chains contain 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, and slightly cross-reacts with other proteins.

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 Kd 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 lower.

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 CDR2 with an amino acid

sequence that is selected from the group: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.

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: 8, SEQ ID NO: 9, SEQ ID NO: 10 or SEQ ID NO: 11.

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 or SEQ ID NO: 3;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7;

and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10 or SEQ ID NO: 11.

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: 4 and

CDR3 with the amino acid sequence of SEQ ID NO: 8; 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: 5 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; or

(iii) 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: 5 and

CDR3 with the amino acid sequence of SEQ ID NO: 8; or

(iv) 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: 4 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; or

(v) 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: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 8; or

(vi) 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: 9; or

(vii) 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: 7 and

CDR3 with the amino acid sequence of SEQ ID NO: 10; or

(viii) 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: 6 and

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

(ix) 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: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 10; or

(x) 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: 9.

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: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17.

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 the amino acid sequence of SEQ ID NO: 12;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 18.

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: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(ii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 14 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(iii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 15 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(iv) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(v) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 17 and

CDR3 with the amino acid sequence of SEQ ID NO: 18.

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 or SEQ ID NO: 3;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7;

and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10 or SEQ ID NO: 11.; and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 12;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 18.

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: 4 and

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

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(ii) (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: 5 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; 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: 5 and

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

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 14 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(iv) (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: 4 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 14 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(v) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 14 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(vi) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 13 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; 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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(viii) (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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; 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: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(x) (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: 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: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xi) (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: 5 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xii) (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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xiii) (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: 7 and
CDR3 with the amino acid sequence of SEQ ID NO: 10; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 17 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xiv) (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: 5 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xv) (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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xvi) (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: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xvii) (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: 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: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xviii) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(ixx) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 10; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 17 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xx) (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: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 17 and
CDR3 with the amino acid sequence of SEQ ID NO: 18.

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: 19, 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 or SEQ ID NO: 28.

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: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34.

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: 19, 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 or SEQ ID NO: 28; and

(b) a heavy chain variable domain that comprises an amino acid sequence that is selected from the group: SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34.

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

(i) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 29; or

(ii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 20 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 29; or

(iii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 21 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 30; or

(iv) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 22 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 30; or

(v) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 23 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 30; or

(vi) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 23 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 31; or

(vii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32; or

(viii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 22 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32; or

(ix) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 24 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32; or

(x) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 26 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32; or

(xi) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 21 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(xii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(xiii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 25 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 34; or

(xiv) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 20 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(xv) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 22 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(xvi) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 24 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(xvii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 26 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(xviii) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 23 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33; or

(ixx) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 27 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 34; or

(xx) (a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 28 and

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 34.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is a full-length IgG antibody.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is a full-length IgG antibody which is of human IgG1, IgG2, IgG3 or IgG4 isotype.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is a full-length IgG antibody which is of human IgG1 isotype.

In some embodiments of the invention, the monoclonal antibody comprises, in the Fc fragment, mutations S239D and I332E, 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 G236A, S239D and I332E mutations, 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: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44.

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: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51 or SEQ ID NO: 52.

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: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44, and

(b) a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51 or SEQ ID NO: 52.

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

(i) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 35, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 45; or

(ii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 36, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 46; or

(iii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 37, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 47; or

(iv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 38, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 47; or

(v) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 39, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 48; or

(vi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 39, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 49; or

(vii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 35, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or

(viii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 38, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or
(ix) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 40, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or
(x) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 42, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or
(xi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 37, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(xii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 35, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(xiii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 41, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52; or
(xiv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 36, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(xv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 38, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(xvi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 40, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(xvii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 42, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(xviii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 39, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or
(ixx) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 43, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52; or
(xx) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 44, and
(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is an antibody that is selected from the group: 04-002, 04-004, 04-009, 04-013, 04-016, 04-024, 04-042, 04-045, 04-046, 04-047, 03-008, 03-010, 03-015, 03-023, 03-024, 03-026, 03-027, 03-028, 03-036 or 03-038.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-002.

Antibody 04-002 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 35; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 45.

Antibody 04-002 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 29.

Antibody 04-002 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: 4,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 13,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-004.

Antibody 04-004 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 36; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 46.

Antibody 04-004 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 20;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 29.

Antibody 04-004 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: 5,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 13,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-009.

Antibody 04-009 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 37; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 47.

Antibody 04-009 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 21;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 30.

Antibody 04-009 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: 5,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 14,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-013.

Antibody 04-013 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 38; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 47.

Antibody 04-013 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 22;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 30.

Antibody 04-013 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: 4,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 14,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-016.

Antibody 04-016 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 39; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 48.

Antibody 04-016 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 23;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 30.

Antibody 04-016 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: 6,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 14,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-024.

Antibody 04-024 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 39; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 49.

Antibody 04-024 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 23;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 31.

Antibody 04-024 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: 6,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 13,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-042.

Antibody 04-042 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 35; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50.

Antibody 04-042 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32.

Antibody 04-042 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: 4,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 15,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-045.

Antibody 04-045 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 38; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50.

Antibody 04-045 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 22;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32.

Antibody 04-045 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: 4,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 15,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-046.

Antibody 04-046 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 40; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50.

Antibody 04-046 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 24;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32.

Antibody 04-046 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: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 15,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 04-047.

Antibody 04-047 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 42; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50.

Antibody 04-047 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 26;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 32.

Antibody 04-047 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: 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: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 15,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-008.

Antibody 03-008 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 37; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-008 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 21;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-008 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: 5,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-010.

Antibody 03-010 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 35; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-010 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 19;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-010 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: 4,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-015.

Antibody 03-015 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 41; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

Antibody 03-015 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 25;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 34.

Antibody 03-015 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: 7,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 10, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 17,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-023.

Antibody 03-023 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 36; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-023 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 20;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-023 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: 5,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-024.

Antibody 03-024 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 38; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-024 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 22;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-024 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: 4,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-026.

Antibody 03-026 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 40; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-026 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 24;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-026 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: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-027.

Antibody 03-027 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 42; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-027 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 26;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-027 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: 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: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-028.

Antibody 03-028 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 39; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51.

Antibody 03-028 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 23;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 33.

Antibody 03-028 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: 6,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 8, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 16,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-036.

Antibody 03-036 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 43; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

Antibody 03-036 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 27;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 34.

Antibody 03-036 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: 6,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 10, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 17,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

In some embodiments of the invention, the monoclonal antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is antibody 03-038.

Antibody 03-038 includes:

(a) a light chain comprising the amino acid sequence of SEQ ID NO: 44; and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

Antibody 03-038 includes:

(a) a light chain variable domain that comprises the amino acid sequence of SEQ ID NO: 28;

(b) a heavy chain variable domain that comprises the amino acid sequence of SEQ ID NO: 34.

Antibody 03-038 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: 9, and

(b) a heavy chain variable domain comprising:

(i) CDR1 (Kabat) with the amino acid sequence of SEQ ID NO: 12,

(ii) CDR2 (Kabat) with the amino acid sequence of SEQ ID NO: 17,

(iii) CDR3 (Kabat) with the amino acid sequence of SEQ ID NO: 18.

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 that specifically bind to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain according to the invention have high binding affinity parameters for the TRBV5-1 segment of the human T cell receptor beta-chain variable domain. Furthermore, the antibodies according to the invention are humanized, stable in human serum and thermostable, and also have antibody-dependent cell-mediated cytotoxicity (ADCC).

Nucleic acid molecule

In one aspect, the present invention relates to a nucleic acid that encodes any above antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

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 unnatural nucleotides or not, and being either a double-strand DNA or RNA, a single-strand DNA or RNA, or transcription products of said DNAs.

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 that encodes an amino acid sequence selected from SEQ ID NO: 53-86. 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 invention may be isolated from any source that produces the monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain. 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 04-002, 04-042, 03-010, and includes a nucleotide sequence with SEQ ID NO: 53.

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 04-004, 03-023, and includes a nucleotide sequence with SEQ ID NO: 54.

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 04-009, 03-008, and includes a nucleotide sequence with SEQ ID NO: 55.

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 04-013, 04-045, 03-024, and includes a nucleotide sequence with SEQ ID NO: 56.

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 04-016, 04-024, 03-028, and includes a nucleotide sequence with SEQ ID NO: 57.

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 04-046, 03-026, and includes a nucleotide sequence with SEQ ID NO: 58.

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 03-015, and includes a nucleotide sequence with SEQ ID NO: 59.

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 03-027, 04-047, and includes a nucleotide sequence with SEQ ID NO: 60.

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 03-036, and includes a nucleotide sequence with SEQ ID NO: 61.

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 03-038, and includes a nucleotide sequence with SEQ ID NO: 62.

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 antibodies 04-002, 04-004, and includes a nucleotide sequence with SEQ ID NO: 63.

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 antibodies 04-009, 04-013, 04-016, and includes a nucleotide sequence with SEQ ID NO: 64.

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 04-024, and includes a nucleotide sequence with SEQ ID NO: 65.

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 antibodies 04-042, 04-045, 04-046, 04-047, and includes a nucleotide sequence with SEQ ID NO: 66.

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 antibodies 03-008, 03-010, 03-023, 03-024, 03-026, 03-027, 03-028, and includes a nucleotide sequence with SEQ ID NO: 67.

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 antibodies 03-015, 03-036, 03-038, and includes a nucleotide sequence with SEQ ID NO: 68.

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 04-002, 04-042, 03-010, and includes a nucleotide sequence with SEQ ID NO: 69.

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 04-004, 03-023, and includes a nucleotide sequence with SEQ ID NO: 70.

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 04-009, 03-008, and includes a nucleotide sequence with SEQ ID NO: 71.

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 04-013, 04-045, 03-024, and includes a nucleotide sequence with SEQ ID NO: 72.

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 04-016, 04-024, 03-028, and includes a nucleotide sequence with SEQ ID NO: 73.

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 04-046, 03-026, and includes a nucleotide sequence with SEQ ID NO: 74.

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 03-015, 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 of antibodies 03-027, 04-047, 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 of antibody 03-036, 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 of antibody 03-038, 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 heavy chain 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 of antibody 04-004, 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 of antibodies 04-009, 04-013, 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 of antibody 04-016, 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 of antibody 04-024, 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 of antibodies 04-042, 04-045, 04-046, 04-047, 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 of antibodies 03-008, 03-010, 03-023, 03-024, 03-026, 03-027, 03-028, 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 of antibodies 03-015, 03-036, 03-038, and includes a nucleotide sequence with SEQ ID NO: 86.

The nucleic acid molecules may be used to express the recombinant monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, 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 driven by its promoter.

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 gene may be cloned into a vector such that the signal peptide is linked in-frame to the amino 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, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, and includes transformation of the cell with the above vector.

In one aspect, the present invention relates to a host cell to produce any above antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain 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 available. 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain may be isolated from a culture medium using standard protein purification techniques. Plant host cells include e.g. Nicotiana, Arabidopsis, duckweed, corn, wheat, potato, etc. Bacterial host cells include Escherichia and Streptomyces species. Yeast host cells include Schizosaccharomyces pombe, Saccharomyces cerevisiae and Pichia pastoris.

Furthermore, the level of production of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain from various cell lines will have a different glycosylation profile as compared to each other. However, the monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, encoded by the nucleic acid molecules described herein or comprising the 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

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 for treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which 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 for treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which comprises any above-mentioned 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 for improvement, prophylaxis, or treatment of diseases or disorders that may be mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

The term "disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain" refers to all diseases or disorders that are either directly, or indirectly associated with the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, including etiology, development, progression, persistence or pathology 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. Further, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

"Prophylaxis" according to the present invention is a set of measures aimed at preventing diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

The term "disorder" means any condition that would benefit from treatment or prophylaxis according to the present invention. The definition of the term includes chronic and acute disorders or diseases including those pathological conditions that predispose a mammal to the disorder in question.

"Therapeutically effective amount" refers to that amount of the therapeutic agent being administered during treatment or prophylaxis which will relieve to some extent one or more of the symptoms of the disease for which treatment or prophylaxis is provided. The therapeutically effective amount may vary according to factors such as the particular condition for which treatment or prophylaxis is provided, the age, sex and weight of the patient, and whether the monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is being administered as a stand-alone treatment or prophylaxis and/or in combination with one or more additional drugs, methods of treatment or prophylaxis.

In one aspect, the subject of treatment or prophylaxis, 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 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, and at least one other therapeutically active compound.

In one aspect, the present invention relates to a pharmaceutical composition for treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which comprises 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 treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which comprises 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 treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which comprises any above antibody or antigen-binding fragment thereof and at least one other therapeutically active compound that is an antibody, insulin preparations, 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: insulin preparations, glucocorticoids, β2 adrenergic receptor agonists, M-type cholinergic receptor antagonists, budesonide, azathioprine, methotrexate, dapsone or any combination thereof.

In some embodiments of the pharmaceutical composition, the disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is selected from the group: type I diabetes mellitus, delayed progression of stage 2 to stage 3 type I diabetes mellitus, high blood glucose, impaired glucose tolerance, prediabetes, rejection of nickel implants or prostheses, sarcoidosis, berylliosis, celiac disease or dermatitis herpetiformis.

Therapeutic use of monoclonal antibody or antigen-binding fragment thereof that specifically binds to TRBV5-1 segment of human T cell receptor beta-chain variable domain

In one aspect, the antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is used in the treatment or prophylaxis of diseases or disorders mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

In one aspect, the subject of treatment or prophylaxis, 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 of treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which comprises administering to a subject in need of such treatment or prophylaxis any above antibody or antigen-binding fragment thereof or above pharmaceutical composition, in a therapeutically effective amount.

In one aspect, the present invention relates to a method of treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, which comprises administering to a subject in need of such treatment or prophylaxis 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 or prophylaxis, the disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is selected from the group: type I diabetes mellitus, delayed progression of stage 2 to stage 3 type I diabetes mellitus, high blood glucose, impaired glucose tolerance, prediabetes, rejection of nickel implants or prostheses, sarcoidosis, berylliosis, celiac disease or dermatitis herpetiformis.

In some embodiments of the method of treatment or prophylaxis, the other therapeutically active compound is an antibody, insulin preparations, small molecule, hormone therapy agent, or 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 treatment or prophylaxis, in a subject in need of such treatment or prophylaxis, of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

In one aspect, the present invention relates to the use of the above antibody or antigen-binding fragment thereof or the above pharmaceutical composition and at least one other therapeutically active compound for treatment or prophylaxis, in a subject in need of such treatment or prophylaxis, of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

In some embodiments of the use, the disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is selected from the group: type I diabetes mellitus, delayed progression of stage 2 to stage 3 type I diabetes mellitus, high blood glucose, impaired glucose tolerance, prediabetes, rejection of nickel implants or prostheses, sarcoidosis, berylliosis, celiac disease or dermatitis herpetiformis.

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

The uses or methods used herein relating to the antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain and therapeutic agent to a patient in need of treatment or prophylaxis, 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain and therapeutic agent to a patient in need of treatment or prophylaxis, 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain and therapeutic agent to a patient in need of treatment or prophylaxis, 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain and therapeutic agent to a patient in need of treatment or prophylaxis, 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 the TRBV5-1 segment of the human T cell receptor beta-chain variable domain may be administered without further therapeutic treatment or prophylaxis, i.e. as an independent therapy.

In some embodiments of the method of treatment or prophylaxis or the use, the antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain may be administered in combination with other therapeutically active compound selected from the group: insulin preparations, glucocorticoids, β2 adrenergic receptor agonists, M-type cholinergic receptor antagonists, budesonide, azathioprine, methotrexate, dapsone or any combination thereof.

In some embodiments, the method of treatment or prophylaxis or the use will require pretreatment that is selected from the group: histamine receptor blockers, glucocorticoids, antiemetics, paracetamol or any combination thereof.

The antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment 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, infusion or implantation. 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 prophylaxis or the use, the antibody or antigen-binding fragment that specifically binds to the TRBV5-1 segment 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 prophylaxis or the use, the antibody or antigen-binding fragment that specifically binds to the TRBV5-1 segment 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 of treatment or prophylaxis or the use, a suitable dose of the monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment according to the present invention will be in the range of 0.1–200 mg/kg.

Brief description of drawings

Figure 1 is a map of the vector bearing the genetic sequence of anti-TRBV5-1 antibody light chain.

Figure 2 is a map of the vector bearing the genetic sequence of anti-TRBV5-1 antibody heavy chain.

For Figures 1–2

Name	**Definition**
EBV ori	Origin site of Epstein-Barr virus replication
AmpR	Beta-lactamase gene that confers resistance to ampicillin. It enables selection of E.coli cell culture
hCMV-promotor	Eukaryotic promoter of human cytomegalovirus
Cmv enhancer	Enhancer sequence of human cytomegalovirus
Intron A	Acceptor site
Kozak	Kozak consensus sequence for translation initiation
START	Start codon
Leader IgK	Murine IgK signal leader peptide
aTRBV51-VH	Sequence of heavy chain variable domain of anti-TRBV5-1 antibody
HC	Sequence of HC heavy chain constant domain of IgG1 antibody.
aTRBV51-VL	Sequence of light chain variable domain of anti-TRBV5-1 antibody

CK	Sequence of k light chain constant domain of IgG1 antibody
STOP	Stop codon
SV40 PA term	Transcription terminator, polyadenylation signal of SV40 virus

Figure 3 is an electrophoregram of antibodies that do not comprise (reducing conditions) additional disulfide bonds between heavy and light chains in 4-15% PAAG.

1) molecular protein markers; molecular weights (kDa) corresponding to lanes; 2) 04-002; 3) 04-004; 4) 04-009; 5) 04-013; 6) 04-016; 7) 04-024; 8) 04-042; 9) 04-045; 10) 04-046; 11) 04-047.

Figure 4 is an electrophoregram of antibodies that comprise (non-reducing conditions) additional disulfide bonds between heavy and light chains in 4-15% PAAG.

1) molecular protein markers; molecular weights (kDa) corresponding to lanes; 2) 04-002; 3) 04-004; 4) 04-009; 5) 04-013; 6) 04-016; 7) 04-024; 8) 04-042; 9) 04-045; 10) 04-046; 11) 04-047.

Figure 5 is a graph showing no ability in antibodies 04-002 and 03-010 to induce antibody-dependent cellular phagocytosis (ADCP) in a reporter cell assay.

Figure 6 is a graph showing no non-specific activation of the NFAT signaling cascade by antibodies 04-002, 04-016 and 04-024 in a reporter cell assay.

Figure 7 is a graph showing no non-specific activation of the NFAT signaling cascade by antibodies 03-010 and 03-015 in a reporter cell assay.

Figure 8 is a graph showing the ability of antibodies 04-002, 04-016, 04-024 and 03-010 to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in a suspension of peripheral blood mononuclear cells (PBMCs).

Figure 9 is a histogram showing a change in the level of relative expression of the TRBV5-1 gene in human peripheral mononuclear blood cells (PBMCs) in the presence of anti-TRBV5-1 antibody.

Figure 10 is a graph showing no complement-dependent cytotoxicity (CDC) of antibodies 04-002 and 03-010.

Figure 11 is a graph showing no ability of antibody 04-002 to deplete NK cell populations in human PBMCs.

Figure 12 is a graph showing no ability of antibody 04-002 to deplete B cell populations in human PBMCs.

Figure 13 is a graph showing no ability of antibody 04-002 to deplete bulk T cell populations in human PBMCs.

Figure 14 is a graph showing no ability of antibody 04-002 to deplete monocyte populations in human PBMCs.

Figure 15 is a graph showing the percentage of TRBV5-1-positive cells in the presence of anti-TRBV5-1 antibody in murine blood samples among human CD45- and CD3-positive cell population on day 18.

** - p-value $\leq$ 0.01

The statistical analysis was performed using the Kraskel-Wallis test and the Dunn test for multiple comparisons.

Figure 16 is a graph showing the percentage of TRBV5-1-positive cells in murine spleen samples among human CD45- and CD3-positive cell population on day 18.

*** - p-value $\leq$ 0.001

The statistical analysis was performed using the Kraskel-Wallis test and the Dunn test for multiple comparisons.

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, which were 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 subcloned 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

For the expression of the antibodies described in the application materials, variants of expression plasmids intended for expression of antibodies in prokaryotic cells *(E.coli)*, transient expression in eukaryotic cells (e.g., in CHO cells) were applied. Beside the antibody expression cassette the vectors contained: an origin of replication which allows replication of said plasmid in *E. coli*, genes which confer resistance in *E. coli* to various antibiotics (e.g. to ampicillin, kanamycin).

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 subcloned nucleic acid sequences were verified by DNA sequencing. For transient transfections, larger quantities of the plasmids were prepared by plasmid preparation from transformed *E. coli* cultures.

Example 1. Selection of anti-TRBV5-1 antibody sequences.

Anti-TRBV5-1 antibody molecules were created using structural data obtained *in silico*. *In silico* scaffolding was performed using the internal algorithm of JSC "Biocad". The PrepWizard instrument from Schrodinger Suite 2021–3 was employed to prepare the structures. Thereafter, folding was carried out using the Prime tool from Schrodinger 2021-3.

The approach of sequential modification of the amino acid composition of variable domains was applied.

The amino acid sequences of antibodies were optimized *in silico*, to thus produce the antibodies shown in Table 1.

Table 1. Anti-TRBV5-1 antibodies.

Name of antibody
04-002
04-004
04-009
04-013
04-016

04-024
04-042
04-045
04-046
04-047
03-008
03-010
03-015
03-023
03-024
03-026
03-027
03-028
03-036
03-038

Example 2. Analysis of humanization of heavy and light chain variable fragments of anti-TRBV5-1 antibodies.

Table 2 shows the result of the analysis of the humanization of heavy and light chain variable fragments of anti-TRBV5-1 antibodies as compared to control product 01-010 whose sequences are known from the international application WO2020142672.

Table 2. Degree of humanization of variable fragments of antibody.

Name of antibody	VH humanization, %	VL humanization, %
04-002	85.7	85.7
04-004	85.7	86.8
04-009	85.7	86.8
04-013	85.7	85.7
04-016	85.7	86.8
04-024	85.7	86.8
04-042	85.7	85.7
04-045	85.7	85.7
04-046	85.7	86.8
04-047	85.7	86.8
03-008	85.7	86.8
03-010	85.7	85.7

03-015	86.7	85.7
03-023	85.7	86.8
03-024	85.7	85.7
03-026	85.7	86.8
03-027	85.7	86.8
03-028	85.7	86.8
03-036	86.7	85.7
03-038	86.7	85.7
01-010	82.7	84.6

Thus, the heavy and light chain variable fragments of the developed anti-TRBV5-1 antibodies according to the invention have a humanization degree of more than 85%.

Example 3. Obtaining of sequences of anti-TRBV5-1 antibodies.

The genes of the heavy and light chain variable domains of the anti-TRBV5-1 antibodies according to the invention selected from the group in Table 1 were assembled by *de novo* synthesis from oligonucleotides. Based on amino acid sequences, nucleotide sequences were selected; the codon composition was optimized for CHO expressor cells. Partially complementary primers with 20 bp overlap were selected for each variable fragment sequence, PCR was performed. The resulting fragments were combined by PCR with the CK constant domain sequence for the light chain variable domain and with the CH1-CH2-CH3 heavy chain constant domain sequences for the heavy chain variable domain, and cloned as part of the pintA expression vector (Figures 1-2). Plasmids were assembled by restriction-ligation or ligase-free cloning methods. Nucleotide sequences of the gene were confirmed by DNA sequencing according to the Sanger method. Plasmid DNA preparation was produced by way of purification from E.Coli cell culture using a Qiagen's *commercial kit.* The resulting DNA was used to transiently produce proteins in the CHO cell line.

Example 4. Modification of Fc heavy chain constant domain of anti-TRBV5-1 antibodies 04-002, 04-016, 04-024.

To produce antibodies with improved properties, the heavy chain constant domain was modified by way of deletion of the C-terminal amino acids glycine and lysine (delGK). This modification allows for increased homogeneity of the protein preparation.

The genetic constructs were assembled by way of cloning sequences of heavy chain variable fragments of antibodies 04-002, 04-016, 04-024 as part of the pintA vector, combining them with sequences of CH1-CH2-CH3 heavy chain constant domains with delGK modification. Cloning was performed by restriction-ligase method, the resulting sequences were confirmed by Sanger sequencing.

Plasmid DNA preparation was produced by way of purification from E.Coli cell culture using a Qiagen's commercial kit. The resulting DNA was used to transiently produce proteins in the CHO cell line.

Example 5. Production of antibody preparations and determination of functional activity of antibodies.

To produce antibodies, we transfected CHO cells cultured for 24 hours with a fucose analog to a density of 1.8-2.2 million/ml, with plasmid DNA complexed with polyethylene amine. A day after transfection, the cells were cultured with cell growth supplements at lower temperatures. Antibody titer was measured using OctetRed96 (Pall) according to the manufacturer's standard guidelines on proA biosensors 4-7 days after cell transfection; the culture liquid comprising subject antibodies was then diluted to 3-10 μg/ml and incubated with J.RT3-T3.5-TRBV5-1 cells. Following incubation with secondary fluorescently labeled a-hFc-PE antibodies (Jackson ImmunoResearch), cell fluorescence was measured on a flow cytometer to confirm binding of anti-TRBV5-1 antibodies to TRBV5-1 antigen, indicating functional activity of antibodies. J.RT3-T3.5-TRBV5-1 cells stained only with secondary antibodies were used as a negative binding control; J.RT3-T3.5-TRBV5-1 cells stained with a commercial anti-TRBV5-1 antibody (Beckman Coulter IM2285) were used as positive control.

Table 3 shows that 20 produced anti-TRBV5-1 antibodies bind to the TRBV5-1 antigen expressed at cell surface as part of a multiprotein TRC-CD3 complex.

Table 3. Concentration and functional activity of anti-TRBV5-1 antibodies produced in the transient expression system based on Chinese hamster CHO cells.

Antibody	Antibody concentration, mg/l	Binding to J.RT3-T3.5-TRBV5-1 cell line, mean fluorescence intensity
04-002	98.6	540
04-004	46.7	490
04-009	48.3	521
04-013	63.9	418
04-016	141.6	447
04-024	116	547
04-042	53.2	473
04-045	66	400
04-046	65.7	361
04-047	65.9	397

03-008	80.1	775
03-010	110.7	810
03-015	121.3	663
03-023	87.2	730
03-024	56	1124
03-026	69.1	585
03-027	66	1064
03-028	121.7	796
03-036	127.4	658
03-038	108.1	633
Negative control	-	81
Positive control	-	441

Example 6. Purification of antibodies from suspension culture of mammalian cells.

Antibodies were purified from CHO cell growth medium. The cell culture fluid was clarified after 7 days of producing by centrifugation at 8000g followed by filtration through a 0.22 μm filter. Proteins were isolated using 5 ml gravity chromatography columns from Thermo Scientific filled with 0.5-1 ml of Protein A sorbent. Clarified culture liquid was passed through a column, the sorbent was then washed with a phosphate-buffer saline (PBS) pH 7.4, and antibodies were eluted with 0.1M glycine buffer pH 3.0. Solutions of eluted antibodies were adjusted to neutral using 1 M TrisHCl buffer (pH 8.0). Next, antibodies were transferred to PBS (pH 7.4) by dialysis, concentrated when necessary and purified using gel filtration on a Superdex 200 Increase 10/300 GL column equilibrated with PBS. Target peaks were collected, filtered through a 0.22 μm filter and stored at -80 °C. Purity of the resulting protein solution was evaluated using SDS gel electrophoresis (Figures 3-4) and analytical HPLC.

Example 7. Measurement of affinity constants for interaction between anti-TRBV5-1 antibodies and target antigen (TRBV5-1 segment).

Experiments to study antibody affinity for the human TRAV1-2/TRBV5-1 antigen were carried out on a ForteBio Octet RED 384 instrument using Protein A sensors (ForteBio). The analysis was carried out at 30 °C using a kinetic buffer solution (4.3 mM Na2HPO4; 136.9 mM NaCl, 1.5 mM KH2PO4; 2.7 mM KCl; the volume fraction of added Tween 20 was 0.1%; the mass fraction of added BSA was 0.1%; pH 7.4). Before the measurements, sensors were regenerated using a 10 mM glycine solution supplemented with HCl (pH 2.0). The regeneration process consisted of three repetitions of the following steps: 5 seconds in a regenerating solution and 5 seconds of neutralization in a kinetic buffer solution. Antibodies were immobilized on the

sensor surface in a kinetic buffer solution for 300 s. Concentration of antibodies to be immobilized was 10 μg/ml. After immobilization, the baseline in kinetic buffer solution (120 s) was recorded. At the association stage (duration – 60 s), sensors with loaded antibodies were immersed in wells with a solution of analyte (TRAV1-2/TRBV5-1 antigen) prepared in a kinetic buffer solution. Sensograms with analyte concentrations of 10 μg/ml (217.4 nM) and 2.5 μg/ml (54.4 nM) were recorded for each test antibody. A kinetic buffer solution devoid of the antigen was used as a reference signal (reference sensogram). After the association stage, dissociation of the antibody-antigen complex was recorded for 300 seconds. At the dissociation stage, the sensors were immersed in wells with kinetic buffer solution to record the baseline. To verify nonspecific interaction between the analyte and the sensors (negative control), we used sensors not loaded with antibodies. At the loading step, the negative control sensors were immersed into antibody-free sodium acetate buffer, and all other steps were similar to those used for the sensors loaded with antibodies).

Binding curves after subtracting a reference signal were analyzed using the Octet Data Analysis software. Approximation was carried out with 2 sensograms using a 1:1 interaction model. Affinity of the subject antibodies is within the range of 8.4 to 69.4 nM.

Table 4. Measurement of kinetic constant for interaction between antibodies and TRAV1-2/TRBV5-1 antigen.

Antibody	c***, nM	Response*, nm	KD, M	Kon, $M^{-1}s^{-1}$	Kdis, s^{-1}	R^2
03-008	217.4	0.835	8.44E-09	1.31E+05	1.11E-03	0.9991
	54.4	0.3006				
03-010	217.4	0.8362	1.38E-08	1.26E+05	1.75E-03	0.9982
	54.4	0.3295				
03-015	217.4	0.5342	3.58E-08	8.76E+04	3.13E-03	0.9982
	54.4	0.1918				
03-023	217.4	0.8078	1.91E-08	1.16E+05	2.22E-03	0.9992
	54.4	0.2983				
03-024	217.4	0.7988	2.78E-08	1.16E+05	3.23E-03	0.9981
	54.4	0.2867				
03-026	217.4	0.748	3.91E-08	9.94E+04	3.89E-03	0.9981
	54.4	0.2526				
03-027	217.4	0.8223	2.18E-08	1.52E+05	3.32E-03	0.9951
	54.4	0.3201				

Antibody	c***, nM	Response*, nm	KD, M	Kon, $M^{-1}s^{-1}$	Kdis, s^{-1}	R^2
03-028	217.4	0.7749	2.03E-08	1.16E+05	2.35E-03	0.999
	54.4	0.2952				
03-036	217.4	0.3893	4.26E-08	1.37E+05	5.84E-03	0.9952
	54.4	0.1469				
03-038	217.4	0.7606	3.03E-08	1.11E+05	3.35E-03	0.9976
	54.4	0.2816				
04-002	217.4	0.8309	2.81E-08	8.74E+04	2.46E-03	0.9986
	54.4	0.2866				
04-004	217.4	0.859	2.20E-08	1.38E+05	3.03E-03	0.9957
	54.4	0.3522				
04-009	217.4	0.8347	1.30E-08	1.17E+05	1.51E-03	0.9991
	54.4	0.3278				
04-013	217.4	0.8322	3.26E-08	1.34E+05	4.35E-03	0.9967
	54.4	0.313				
04-016	217.4	0.8699	2.31E-08	1.31E+05	3.03E-03	0.9979
	54.4	0.3303				
04-024	217.4	0.8888	1.97E-08	1.31E+05	2.57E-03	0.9985
	54.4	0.344				
04-042	217.4	0.7618	1.46E-08	1.13E+05	1.66E-03	0.9986
	54.4	0.2805				
04-045	217.4	0.7081	2.72E-08	1.09E+05	2,95E-03	0.9981
	54.4	0.2577				
04-046	217.4	0.7196	2.90E-08	1.26E+05	3.65E-03	0,9978
	54.4	0.2572				
04-047	217.4	0,7226	2,00E-08	1,36E+05	2,73E-03	0,9964
	54.4	0,2673				
01-010	217.4	0,6916	6,94E-08	1,45E+05	1,00E-02	0,9893
	54.4	0,2157				
Negative control**	217.4	-0,0072	n/a	n/a	n/a	n/a
	54.4	-0,0121				
Response* – a signal level achieved at the end of association step;						

Antibody	c***, nM	Response*, nm	KD, M	Kon, $M^{-1}s^{-1}$	Kdis, s^{-1}	R^2
negative control** – test of nonspecific interaction between analyte (TRAV1-2/TRBV5-1 antigen) and sensors not loaded with antibodies; c*** – concentration of analyte (TRAV1-2/TRBV5-1 antigen)						

Conclusion: anti-TRBV5-1 antibodies according to the invention specifically bind to the human TRBV5-1 antigen. Affinity of resulting antibodies exceeds that of antibody 01-010.

Example 8. Analysis of affinity constants for interaction of anti-TRBV5-1 antibodies with Fcgamma and FcRn receptors.

Measurements were carried out according to the procedure of the streptavidin sensor (SA Biosensors) manufacturer and OctetRed96 (Pall) user manual. Sensors were prepared in the same manner as in the analysis of affinity constant for the target antigen.

Next, the sensors were bound to the corresponding biotinylated receptor in a 1-fold kinetic buffer, then transferred to solutions of anti-TRBV5-1 antibodies in a kinetic buffer at different concentrations, and lastly, the sensors were immersed in wells with a kinetic buffer.

The resulting data was eventually processed in the Octet Data Analysis 8.2 software using the 1:1 or 2:1 model. The resulting affinity constants are shown in Table 5.

Table 5. Affinity constant for interaction of anti-TRBV5-1 antibody 04-002 with Fcgamma and FcRn receptors, data was obtained using the Octet Red96 instrument, constants were calculated in the Octet Data Analysis 8.2 software.

Receptor name	Antibody 04-002
FcγRIa , KD, M-1	1,4E-09
FcγRIIa-131R, KD, M-1	2E-07
FcγRIIa-131H, KD, M-1	2E-07
FcγRIIb, KD, M-1	2E-07
FcγRIIIa-158V, KD, M-1	2E-08
FcγRIIIa-158F, KD, M-1	3E-08
FcRn, KD, M-1	1.7E-08

Conclusion: antibody 04-002 shows high affinity for FcyR IIIa158V and IIIa158F receptors, which potentially improves the effector properties of the subject antibody.

Example 9. Stability of anti-TRBV5-1 antibodies under storage in human serum.

In this study, stability was understood as the preservation of full-length antibody molecules in human serum at +37 °C *in vitro*. To determine stability, samples of test antibodies were diluted in human serum to a concentration of 25 μg/ml and stored at +37 °C in a thermostat for 14 days in

a volume of 150 µl in micro-samples supplemented with sodium merthyolate up to 0.1%. Samples of unsupplemented human serum used for subsequent determination of the background concentration values of the samples in question were stored under similar conditions. Following storage, the concentration of antibodies in samples was determined by enzyme-linked immunosorbent assay (ELISA) with antibody calibrating titration from 250 ng/ml to 3.9 ng/ml. Calibration samples and samples for reference were diluted to desired concentration immediately before the experiment.

For ELISA, an antigen comprising the target human TRBV5-1 segment was adsorbed on a plate at a concentration of 2.5 µg/ml in 0.1M carbonate buffer pH 9.5. The plate was washed, the wells were then blocked with 0.5% milk powder solution in washing buffer for 1 hour. 0.1% Tween-20 solution in PBS was used as washing buffer. Following blocking, solutions of test antibodies and calibrating solutions were added to the plate; all samples were diluted in a blocking solution and incubated at 37 °C for 1 hour on a plate shaker. The plate was washed and to the wells a solution of horseradish peroxidase-conjugated goat antibodies to human Ig Fc portion (a-hFc-HRP) was added and incubated at 37 °C for 1 hour on a plate shaker. Thereafter, the wells were washed, thereto was added a TMB solution and, following staining, the reaction was stopped by a 10% sulfuric acid solution. Staining in wells was recorded at 450 nm absorption using a Tecan plate fluorescence reader.

Before ELISA, samples taken out from storage and reference samples were diluted 500 times with a buffer to target concentration of 50 ng/ml, and concentration of test antibodies was determined based on ELISA results. Stability of antibodies was expressed as the ratio of concentration of samples removed from storage to concentration of original samples multiplied by 100%. Reduction of concentration to no more than 60% in incubated samples was considered sufficient for further study (Table 6).

Table 6. Relative stability of antibodies stored in human serum for 14 days at +37 ° C.

Name of antibody	Antibody concentration in a freshly prepared human serum sample (µg/ml)	Antibody concentration following 14 days of storage in human serum at 37 °C (µg/ml)	Proportion of full-length antibody molecules remaining in sample following storage in serum (%)
04-002	18.8	17	90
04-016	19.2	19.9	100
04-024	25.3	20.9	82

The table shows the percentage of remaining full-length antibody molecules in serum following incubation as compared to antibody content in samples before incubation, and also shows antibody concentrations. It was shown that anti-TRBV5-1 antibodies according to the invention are stable when stored in human serum.

Example 10. Testing stability of antibodies.

HPLC was employed to determine the difference between samples of test antibodies before and after heating at 50 degrees for 48 hours. Peak areas and their ratios for each product were evaluated in pairwise manner. Comparison criteria were changes in peak areas and ratio of peak areas between a product stored at 4 degrees and the same product incubated at 50 degrees for 48 hours.

Table 7 shows changes in peak areas for target molecules.

Table 7. Changes in proportion of monomer in antibody products subjected to thermal stress.

Name of antibody	% ratio of peaks			
		Σaggregates, %	monomer, %	Σfragments, %
01-010	before heating	3.4	96.4	0.2
	following heating	1.1	92	6.9
04-002	before heating	1.2	98	0.8
	following heating	1	95.4	3.6

Thus, antibody 04-002 has a higher thermal stability compared to antibody 01-010.

Example 11. Ability of antibodies to induce ADCC in reporter cell assay.

The assay used Jurkat-NFAT-Luc-CD16 cell line stably expressing surface CD16 and comprising the firefly luciferase gene expressed under the control of NFAT promoter; as target cells was employed the J.RT3-T3.5-TRBV5-1 line stably expressing a T cell receptor beta-chain variable domain that includes the TRBV5-1 segment.

The assay was performed in a white 96-well culture plate designed for luminescence assays. Each well with suspension contained 25,000 Jurkat-NFAT-Luc-CD16 effector cells, 8,000 J.RT3-T3.5-TRBV5-1 target cells, as well as test antibodies at a concentration as indicated in the graph. The final volume of cell suspension and antibodies in a well was 100 µl; all suspension components were prepared in RPMI-1640 medium comprising 5% FBS and 2 mM glutamine. After all components were added, the plates were incubated for 5 hours at 37°C, 5% CO_2. Then, the luminescence intensity in wells was measured using the One-Glo luciferase assessment kit (Promega). Measurements were carried out on a plate reader.

It was shown that antibodies 04-002, 04-004, 04-009, 04-013, 04-016, 04-024, 04-042, 04-045, 04-046, 04-047, 03-028, 03-015, 03-036, 03-038, 03-026, 03-008, 03-010, 03-023, 03-024, 03-027 induce antibody-dependent cell-mediated cytotoxicity in a reporter assay, half-maximal effective antibody concentration (EC50) is shown in Table 8.

Table 8. Antibody-dependent cell-mediated cytotoxicity of antibodies according to the invention in reporter assay.

Antibody	half-maximal effective antibody concentration (EC50), ng/ml
04-002	55.2
04-004	77.5
04-009	38.5
04-013	96.7
04-016	41.1
04-024	45,3
04-042	44,9
04-045	64,2
04-046	71
04-047	73,1
03-008	62,8
03-010	45,3
03-015	44,2
03-023	27,7
03-024	19
03-026	30,8
03-027	36,3
03-028	52,1
03-036	77,3
03-038	62,1
01-010	170,6

Example 12. Ability of antibodies to induce ADCP in reporter cell assay.

The reporter cell assay for testing the ability of antibodies to induce ADCP used Jurkat-NFAT-Luc-CD64 cell line stably expressing surface CD64 and comprising the firefly luciferase gene expressed under the control of NFAT promoter; as target cells was employed J.RT3-T3.5-

TRBV5-1 stably expressing a T cell receptor beta-chain variable domain that includes the TRBV5-1 segment.

The assay was performed in a white 96-well culture plate designed for luminescence assays. Each well with suspension contained 30,000 Jurkat-NFAT-Luc-CD64 effector cells, 30,000 J.RT3-T3.5-TRBV5-1 target cells, as well as test antibodies. The anti-CD20 antibody Rituximab having ADCP activity was used as positive control. The final volume of the cell suspension and antibodies in a well was 100 µl, all components of the suspension were prepared in RPMI-1640 medium comprising 5% FBS. After adding all the components, the plates were incubated for 16 hours at +37°C, 5%CO2, and then, using a One-Glo luciferase assay kit (Promega), we measured the luminescence intensity in the wells. Luminescence was measured using a plate reader.

It was shown that antibodies 04-002 and 03-010 do not induce ADCP in a reporter cell assay. Shown are mean values with standard deviations for two replicates (Figure 5).

Example 13. Analysis of nonspecific activation of NFAT signaling cascade by antibodies 03-010, 03-015, 04-002, 04-016 and 04-024.

Reporter cell assay to test activating properties of antibodies used the J.RT3-T3.5-TRBV5-1-NFAT-Luc cell line which stably surface-expresses the T cell receptor β-chain variable domain comprising the TRBV5-1 segment, and which comprises a firefly luciferase gene expressed under the control of NFAT promoter. The assay was performed in a white 96-well culture plate designed for luminescence assays. Each well with suspension contained 50,000 J.RT3-T3.5-TRBV5-1-NFAT-Luc cells, as well as test antibodies. as a control was used anti-CD3 antibody OKT3 which was pre-incubated with cross-linking antibodies against the antibody Fc portion. The final volume of cell suspension and antibodies in a well was 100 µl; all suspension components were prepared in RPMI-1640 medium comprising 5% FBS and 2 mM glutamine. After adding all the components, the plates were incubated for 16 hours at +37°C, 5%CO_2, and then, using a One-Glo luciferase assay kit (Promega), we measured the luminescence intensity in the wells. Luminescence was measured using a plate reader.

It was shown that antibodies 03-010, 03-015, 04-002, 04-016 and 04-024 did not induce significant activation of the J.RT3-T3.5-TRBV5-1-NFAT-Luc reporter cell line. Provided are mean values with standard deviations (Figures 6 and 7).

Example 14. Analysis of ADCC activity of antibodies 04-002, 04-016, 04-024 and 03-010 in suspension of peripheral blood mononuclear cells.

PBMC-based cellular assay was performed to evaluate the ability of antibodies to induce ADCC under realistic conditions. The assay was performed in a 96-well culture plate for suspension cultures. Suspension in each well contained 500,000 freshly isolated PBMCs from a

healthy donor and the biotinylated antibody indicated in the graph at the specified concentration. The final volume of cell suspension was 200 µl per well. All suspension components were prepared in RPMI-1640 medium comprising 5% FBS and 2 mM glutamine. After mixing PBMCs and antibodies, the plate was incubated for 24 h at 37°C, 5% CO_2. Next, the proportion of TRBV5-1-positive T cells in suspensions was determined. To this end, cellular precipitates from each plate well were stained with corresponding anti-TRBV5-1 biotinylated antibody at a concentration of 1 µg/ml, followed by staining with PE-fluorescently labeled streptavidin. The proportion of T cells in suspensions was determined by direct staining with a fluorescently labeled antibody against CD3. The analysis was performed on a flow cytofluorimeter.

It was shown that antibodies 04-002, 04-016, 04-024 and 03-010 induce antibody-dependent cell-mediated cytotoxicity in human PBMCs, the half-maximal effective antibody concentration (EC50) is shown in Figure 8.

Example 15. Analysis of depletion of native TRBV5-1 T cells in human PBMCs by real-time PCR.

In order to analyze depletion of T cells expressing the T cell receptor β-chain variable domain comprising the TRBV5-1 segment by real-time PCR (qPCR), one million cells were taken from each of samples that were incubated in the presence of candidate 04-002, as well as from each of intact samples whose preparation is described in Example 14. Cellular precipitates were placed in an RLT buffer (Qiagen) and RNA was isolated therefrom using Qiagen RNeasy mini kit reagents according to the manufacturer's protocol. Spectrophotometric determination of isolated RNA amounts was performed on the NanoDrop 8000 instrument (Thermo Scientific). Resulting RNA was qualitatively analysed using denaturing RNA gel electrophoresis. Genomic DNA residues were removed using DNase (New England Biolabs). cDNA synthesis using RNA matrix was performed using SuperScript IV First-Strand Synthesis System (Invitrogen) according to the manufacturer's protocol. 1 µg of RNA was used for each reverse transcription reaction. For quantitative PCR, SYBR Green I Quantitative RT-PCR Kit (Syntol) was used. PCR was performed in three technical replicates for each sample. Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) gene was used as a reference to normalize the resulting quantitative assessment values. Real-time PCR was performed in the StepOne™ Real-Time PCR System amplifier (Applied Bioscience). Level of TRBV5-1 expression was determined by Pfaffl with correction for amplification efficiency.

Thus, it is shown (Figure 9) that antibody 04-002 induces antibody-dependent cell-mediated cytotoxicity eliminating a population of T cells bearing on its surface the T cell receptor β-chain variable domain comprising the TRBV5-1 segment.

Example 16. Ability of antibodies to induce CDC in reporter cell assay.

CDC assay used the J.RT3-T3.5-TRBV5-1 cell line. The assay was conducted in a 96-well culture plate. Suspension in each well contained 50,000 J.RT3-T3.5-TRBV5-1 cells, as well as test antibodies at the specified concentration and a human serum complement diluted 1:4. The final volume of the cell suspension in a well was 150 µl, all components of the suspension were prepared in RPMI-1640 medium comprising 0.1% BSA. The plate was then incubated for 4 h at 37 °C with 5% CO_2. 15 µl of AlamarBlue reagent was added to each well and the plate was incubated for 16 hours at +37 °C, 5% CO2.

Fluorescence was measured at an excitation wavelength of 544 nm and emission wavelength of 590 nm using a plate reader.

It was shown that antibodies 04-002 and 03-010 do not induce complement-dependent cytotoxicity in the assay (Figure 10). The graph shows mean values with standard deviations.

Example 17. Analysis of autocytotoxic activity mediated by anti-TRBV5-1 antibodies.

Autocytotoxicity assay was performed in a 96-well culture plate for suspension cultures. The suspension contained per well 300,000 freshly isolated PBMCs from healthy donors and an antibody as shown in the graph at the specified concentration, the final volume of the cell suspension in a well was 150 µl. All suspension components were prepared in RPMI-1640 medium comprising 5% FBS and 2 mM glutamine. After mixing PBMCs and antibodies, the plate was incubated for 16 h at 37°C, 5% CO_2. Then, the proportion of CD56+, CD19+, CD3+ and CD14+ subpopulations of PBMCs in suspensions was measured by direct staining of the suspensions with fluorescent-labeled antibodies against the corresponding CDs and subsequent cell analysis using a flow cytofluorometer. As positive control was used anti-CD20 antibody (GA101) which induces depletion of B cells, in the concentration range from 1 to 100 µg/ml.

The graphs show mean values and standard deviations for two replications (Figures 11-14).

Conclusion: antibody 04-002 does not exhibit the ability to deplete populations of NK cells, B cells, and it also does not affect the total population of T cells, except for those that carry TRBV5-1, as follows from the results (Figure 13) according to which the level of T cells drops by about 5% at a concentration of antibody 04-002 ranging from 1 to 100 µg/ml.

Example 18. Analysis of antibody effector properties in *in vivo* NSIG mouse model in blood and spleen samples.

Two groups of NSIG mice were administered with human peripheral blood mononuclear cells from a healthy donor (administration into the retro-orbital sinus, 10^7 cells per mouse; administration volume: 200 µl). On the next day, on day 7 and on day 16, one group of mice was administered with anti-TRBV5-1 antibody 04-002 (n=9) (intraperitoneal administration, dosage: 10 µg/kg; administration volume: 200 µl). The control group of animals (n=8) was not

administered with the antibody. On day 18 after cell administration, percentage of TRBV5-1-positive cells in animal blood and spleen samples was assessed by flow cytometry. TRBV5-1-positive cells were detected among a population of human CD45- and CD3-positive cells. Figures 15 (blood samples) and 16 (spleen samples) show the percentage of TRBV5-1-positive cells for each animal, median ± interquartile range. It was shown that the blood and spleen samples of NSIG mice with circulating human peripheral mononuclear cells, following administration of monoclonal antibody 04-002, exhibited a significant depletion in the population of CD3-positive cells expressing the T cell receptor β-chain variable domain comprising the TRBV5-1 segment.

Claims

1. A monoclonal antibody or antigen-binding fragment thereof that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, 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 or SEQ ID NO: 3;

(ii) CDR2 with the amino acid sequence EIX_1KLX_2S, where

X_1=T or S

X_2=A, F or M; and

(iii) CDR3 with the amino acid sequence $QQWNYPX_3LX_4$, where

X_3=L, R or Y;

X_4=S or T;

and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 12;

(ii) CDR2 with the amino acid sequence $YINPX_5X_6GRTGYNQKX_7QX_8$, where

X_5= Y or W;

X_6= Q or N;

X_7= F or L;

X_8= A or G;

and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 18.

2. 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: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.

3. 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: 8, SEQ ID NO: 9, SEQ ID NO: 10 or SEQ ID NO: 11.

4. 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 or SEQ ID NO: 3;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7;

and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10 or SEQ ID NO: 11.

5. The monoclonal antibody or antigen-binding fragment thereof according to any one of claims 1-4, 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: 4 and

CDR3 with the amino acid sequence of SEQ ID NO: 8; 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: 5 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; or

(iii) 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: 5 and

CDR3 with the amino acid sequence of SEQ ID NO: 8; or

(iv) 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: 4 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; or

(v) 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: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 8; or

(vi) 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: 9; or

(vii) 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: 7 and

CDR3 with the amino acid sequence of SEQ ID NO: 10; or

(viii) 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: 6 and

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

(ix) 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: 6 and

CDR3 with the amino acid sequence of SEQ ID NO: 10; or

(x) 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: 9.

6. 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: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17.

7. The monoclonal antibody or antigen-binding fragment thereof according to any one of claims 1 or 6, wherein the heavy chain variable domain comprises:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 12;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 18.

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

(i) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(ii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 14 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(iii) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 15 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(iv) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(v) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 17 and

CDR3 with the amino acid sequence of SEQ ID NO: 18.

9. The monoclonal antibody or antigen-binding fragment thereof according to any one of claims 1-8, 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 or SEQ ID NO: 3;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7;

and

(iii) CDR3 with an amino acid sequence that is selected from the group: SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10 or SEQ ID NO: 11.; and

(b) a heavy chain variable domain comprising:

(i) CDR1 with the amino acid sequence of SEQ ID NO: 12;

(ii) CDR2 with an amino acid sequence that is selected from the group: SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16 or SEQ ID NO: 17;

and

(iii) CDR3 with the amino acid sequence of SEQ ID NO: 18.

10. The monoclonal antibody or antigen-binding fragment thereof according to claim 9, 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: 4 and

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

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(ii) (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: 5 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 13 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; 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: 5 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 14 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(iv) (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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 14 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(v) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 14 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(vi) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and

(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 13 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; 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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(viii) (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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; 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: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(x) (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: 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: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 15 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(xi) (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: 5 and

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

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(xii) (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: 4 and

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

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(xiii) (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: 7 and

CDR3 with the amino acid sequence of SEQ ID NO: 10; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 17 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(xiv) (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: 5 and

CDR3 with the amino acid sequence of SEQ ID NO: 9; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

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

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(xv) (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: 4 and
CDR3 with the amino acid sequence of SEQ ID NO: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xvi) (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: 9; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xvii) (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: 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: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(xviii) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 8; and
(b) a heavy chain variable domain comprising:
CDR1 with the amino acid sequence of SEQ ID NO: 12,
CDR2 with the amino acid sequence of SEQ ID NO: 16 and
CDR3 with the amino acid sequence of SEQ ID NO: 18; or
(ixx) (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: 6 and
CDR3 with the amino acid sequence of SEQ ID NO: 10; and
(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 17 and

CDR3 with the amino acid sequence of SEQ ID NO: 18; or

(xx) (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: 9; and

(b) a heavy chain variable domain comprising:

CDR1 with the amino acid sequence of SEQ ID NO: 12,

CDR2 with the amino acid sequence of SEQ ID NO: 17 and

CDR3 with the amino acid sequence of SEQ ID NO: 18.

11. 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: 19, 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 or SEQ ID NO: 28.

12. 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: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34.

13. The monoclonal antibody or antigen-binding fragment thereof according to any one of claims 1 or 11-12, wherein:

(a) the light chain variable domain comprises an amino acid sequence that is selected from the group: SEQ ID NO: 19, 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 or SEQ ID NO: 28; and

(b) the heavy chain variable domain comprises an amino acid sequence that is selected from the group: SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 or SEQ ID NO: 34.

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

(i) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 29; or

(ii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 20 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 29; or

(iii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 21 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 30; or

(iv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 22 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 30; or

(v) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 23 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 30; or

(vi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 23 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 31; or

(vii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 32; or

(viii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 22 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 32; or

(ix) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 24 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 32; or

(x) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 26 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 32; or

(xi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 21 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(xii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 19 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(xiii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 25 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 34; or

(xiv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 20 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(xv) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 22 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(xvi) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 24 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(xvii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 26 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(xviii) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 23 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 33; or

(ixx) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 27 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 34; or

(xx) (a) the light chain variable domain comprises the amino acid sequence of SEQ ID NO: 28 and

(b) the heavy chain variable domain comprises the amino acid sequence of SEQ ID NO: 34.

15. The monoclonal antibody according to any one of claims 1–14, wherein the antibody that specifically binds to the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is a full-length IgG antibody.

16. The monoclonal antibody according to claim 15, wherein the full-length IgG antibody is of human IgG1, IgG2, IgG3 or IgG4 isotype.

17. The monoclonal antibody according to claim 16, wherein the full-length IgG antibody is of human IgG1 isotype.

18. The monoclonal antibody according to claim 17, wherein the antibody comprises 446G and 447K deletion according to the EU numbering scheme for amino acids of antibodies in the CH3 region.

19. The monoclonal antibody according to claim 17, wherein the antibody comprises S239D and I332E mutations according to the EU numbering scheme for amino acids of antibodies.

20. The monoclonal antibody according to claim 17, wherein the antibody comprises G236A, S239D and I332E mutations according to the EU numbering scheme for amino acids of antibodies.

21. 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: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44.

22. 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: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51 or SEQ ID NO: 52.

23. The monoclonal antibody according to any one of claims 1 or 21–22, comprising:

(i) (a) a light chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43 or SEQ ID NO: 44, and

(b) a heavy chain comprising an amino acid sequence that is selected from the group: SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51 or SEQ ID NO: 52.

24. The monoclonal antibody according to claim 23, comprising:

(i) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 35, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 45; or

(ii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 36, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 46; or

(iii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 37, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 47; or

(iv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 38, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 47; or

(v) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 39, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 48; or

(vi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 39, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 49; or

(vii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 35, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or

(viii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 38, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or

(ix) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 40, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or

(x) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 42, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 50; or

(xi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 37, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(xii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 35, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(xiii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 41, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52; or

(xiv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 36, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(xv) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 38, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(xvi) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 40, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(xvii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 42, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(xviii) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 39, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 51; or

(ixx) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 43, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52; or

(xx) (a) a light chain comprising the amino acid sequence of SEQ ID NO: 44, and

(b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 52.

25. The nucleic acid that encodes the antibody or antigen-binding fragment thereof according to any one of claims 1–24.

26. The nucleic acid according to claim 25, wherein the nucleic acid is DNA.

27. An expression vector comprising the nucleic acid according to any one of claims 25–26.

28. A method for producing a host cell to produce the antibody or antigen-binding fragment thereof according to any one of claims 1–24, including cell transformation by the vector according to claim 27.

29. A host cell for producing the antibody or antigen-binding fragment thereof according to any one of claims 1–24, comprising the nucleic acid according to any one of claims 25 to 26.

30. A method for producing the antibody or antigen-binding fragment thereof according to any one of claims 1–24, comprising culturing the host cell according to claim 29 in a growth medium under conditions sufficient to produce said antibody, followed by isolation and purification of the resulting antibody.

31. A pharmaceutical composition, comprising the antibody or antigen-binding fragment thereof according to any one of claims 1–24 in a therapeutically effective amount in combination with one or more pharmaceutically acceptable excipients.

32. The pharmaceutical composition, comprising the antibody or antigen-binding fragment thereof according to any one of claims 1–24 and at least one other therapeutically active compound.

33. The pharmaceutical composition according to claim 32, wherein the other therapeutically active compound is an antibody, insulin preparations, a small molecule, a hormone therapy agent or any combination thereof.

34. The pharmaceutical composition according to any one of claims 31 or 32, intended for treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

35. The pharmaceutical composition according to claim 34, wherein the disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is selected from the group: type I diabetes mellitus, delayed progression of stage 2 to stage 3 type I diabetes mellitus, high blood glucose, impaired glucose tolerance, prediabetes, rejection of nickel implants or prostheses, sarcoidosis, berylliosis, celiac disease or dermatitis herpetiformis.

36. A method for treatment or prophylaxis of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain, comprising administering to a subject in need of such treatment or prophylaxis the antibody or antigen-binding fragment thereof according to any one of claims 1–24 or the pharmaceutical composition according to any one of claims 31 or 32 in a therapeutically effective amount.

37. The method for treatment or prophylaxis of a disease or disorder according to claim 36, wherein the disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is selected from the group: type I diabetes mellitus, delayed progression of stage 2 to stage 3 type I diabetes mellitus, high blood glucose, impaired glucose tolerance, prediabetes, rejection of nickel implants or prostheses, sarcoidosis, berylliosis, celiac disease or dermatitis herpetiformis.

38. Use of the antibody or antigen-binding fragment thereof according to any one of claims 1–24 or the pharmaceutical composition according to any one of claims 31–32 for treatment or prophylaxis, in a subject in need of such treatment or prophylaxis, of a disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain.

39. The use according to claim 38, wherein the disease or disorder mediated by the TRBV5-1 segment of the human T cell receptor beta-chain variable domain is selected from the group: type I diabetes mellitus, delayed progression of stage 2 to stage 3 type I diabetes mellitus, high blood glucose, impaired glucose tolerance, prediabetes, rejection of nickel implants or prostheses, sarcoidosis, berylliosis, celiac disease or dermatitis herpetiformis.

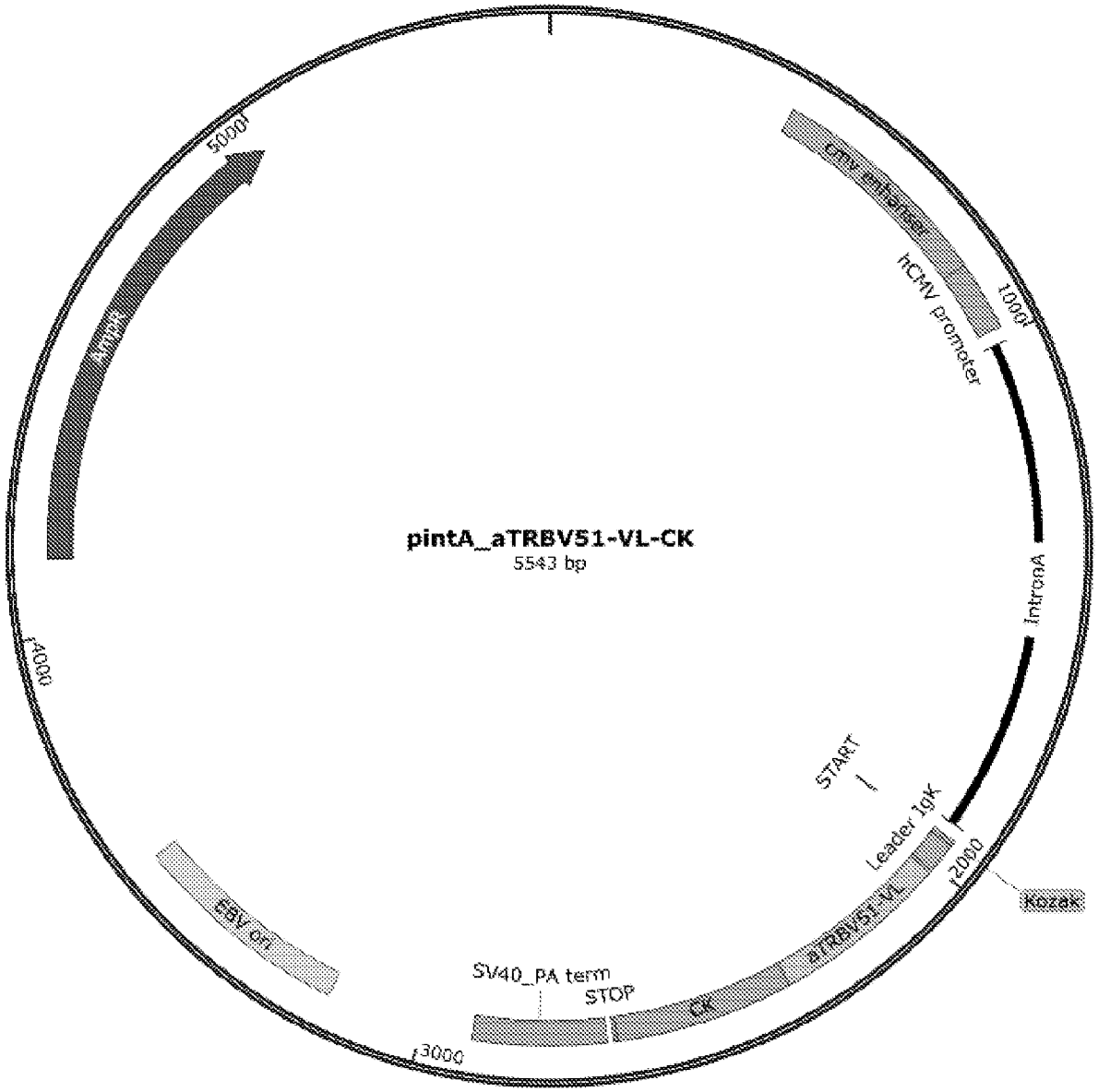

pintA_aTRBV51-VL-CK
5543 bp
5000
Amp R
Cmv enhancer
hCMV promoter
1000
IntronA
2000
START
Leader IgK
2050
Kozak
aTRBV51-VL
CK
STOP
SV40_PA term
3000
EBV ori
4000

Figure 1


pIntA aTRBV5-1-VH-Hc
6248 bp
6000
1000
5000
2000
4000
3000
cmv enhancer
hCMV promoter
KanR
IntronA
START
Leader IgK
Kozak
aTRBV5-1 VH
Hc
STOP
SV40_PA term
EBV ori

Figure 2

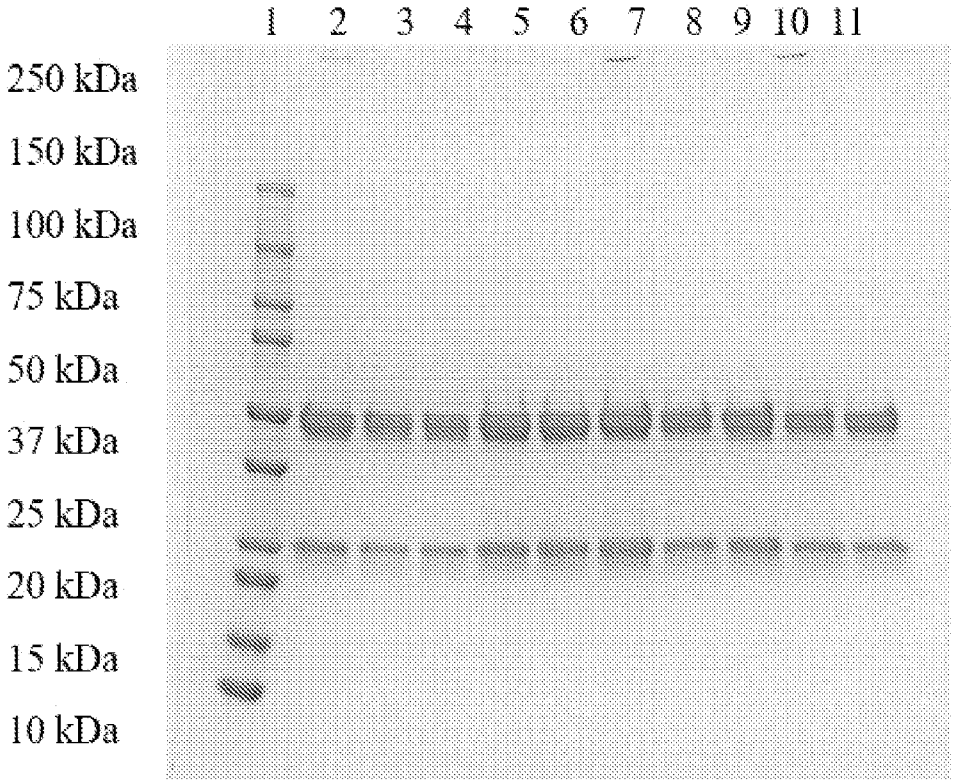

1 2 3 4 5 6 7 8 9 10 11
250 kDa
150 kDa
100 kDa
75 kDa
50 kDa
37 kDa
25 kDa
20 kDa
15 kDa
10 kDa

Figure 3

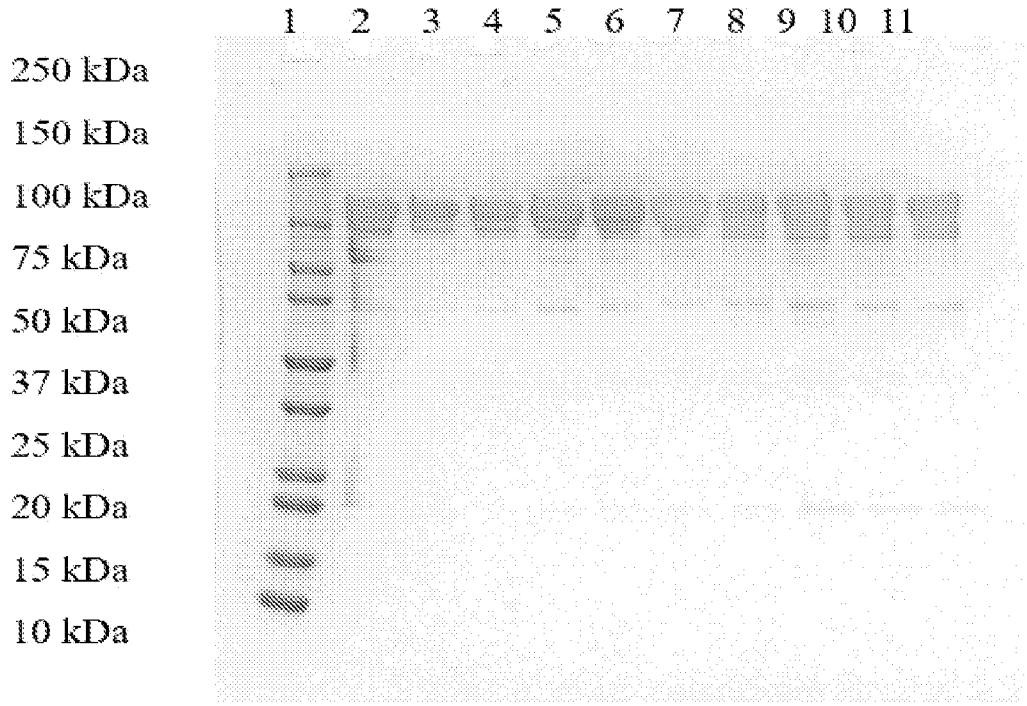


Figure 4

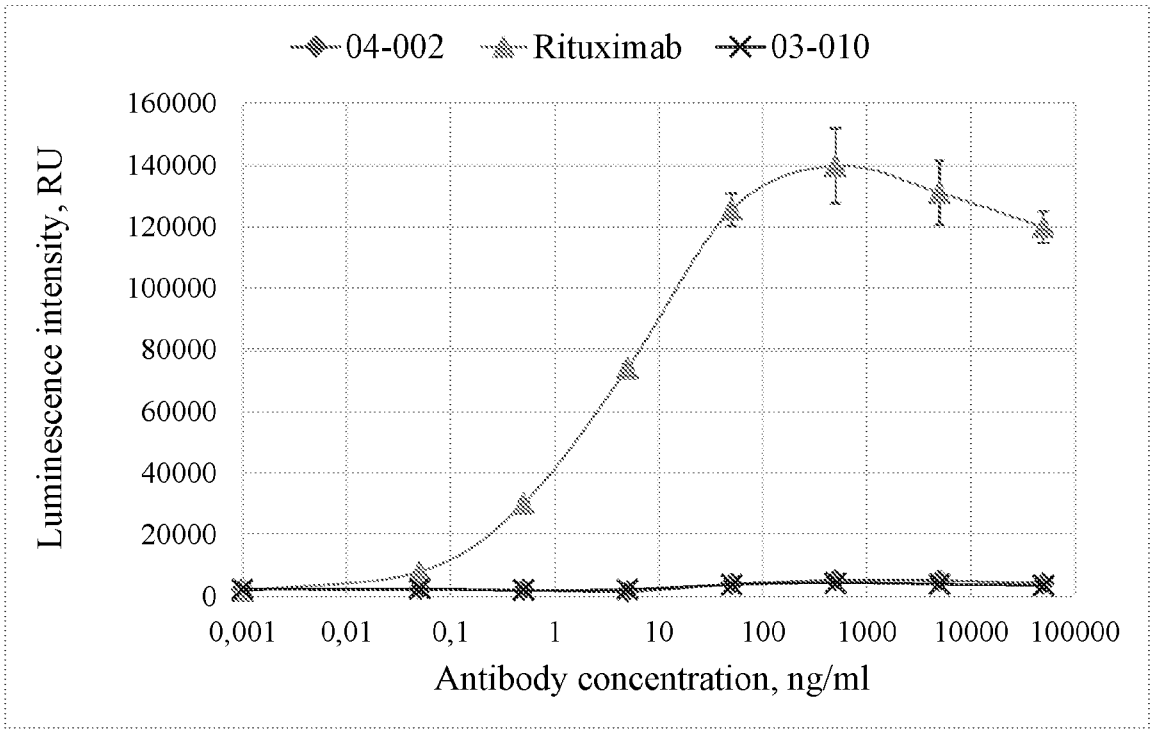


Figure 5

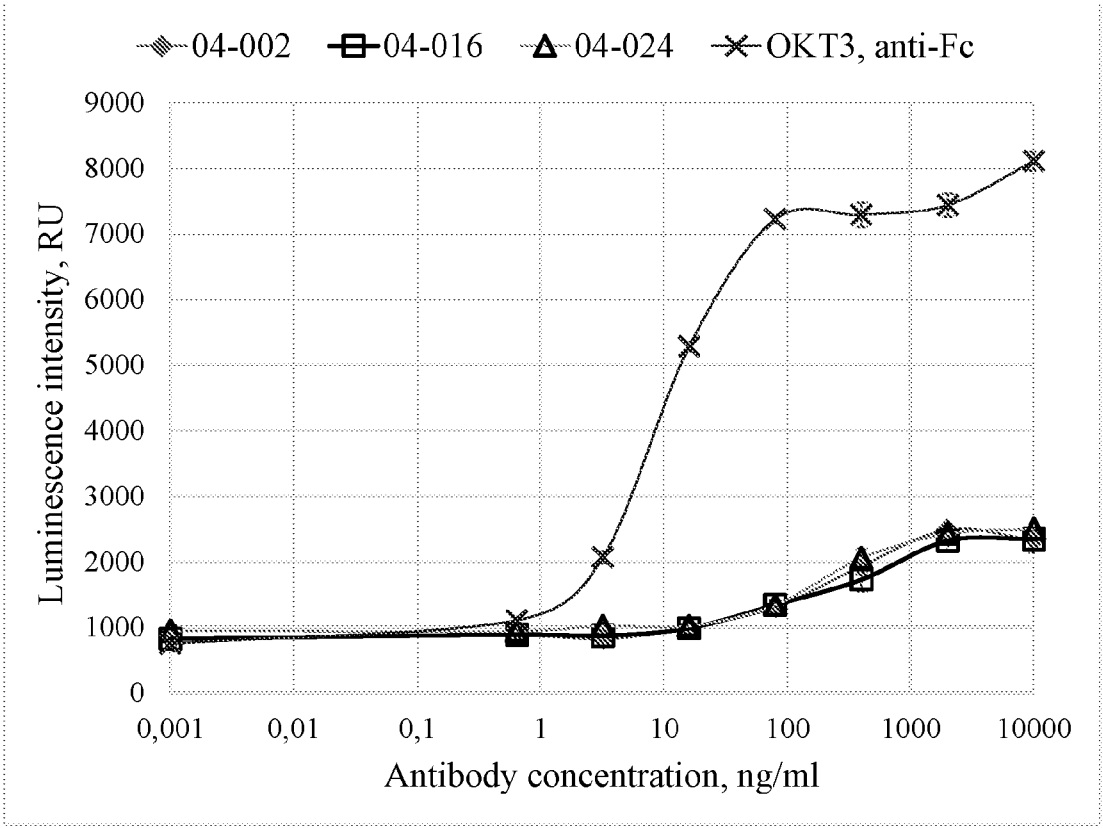

04-002
04-016
04-024
OKT3, anti-Fc
Luminescence intensity, RU
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0,001
0,01
0,1
1
10
100
1000
10000
Antibody concentration, ng/ml

Figure 6

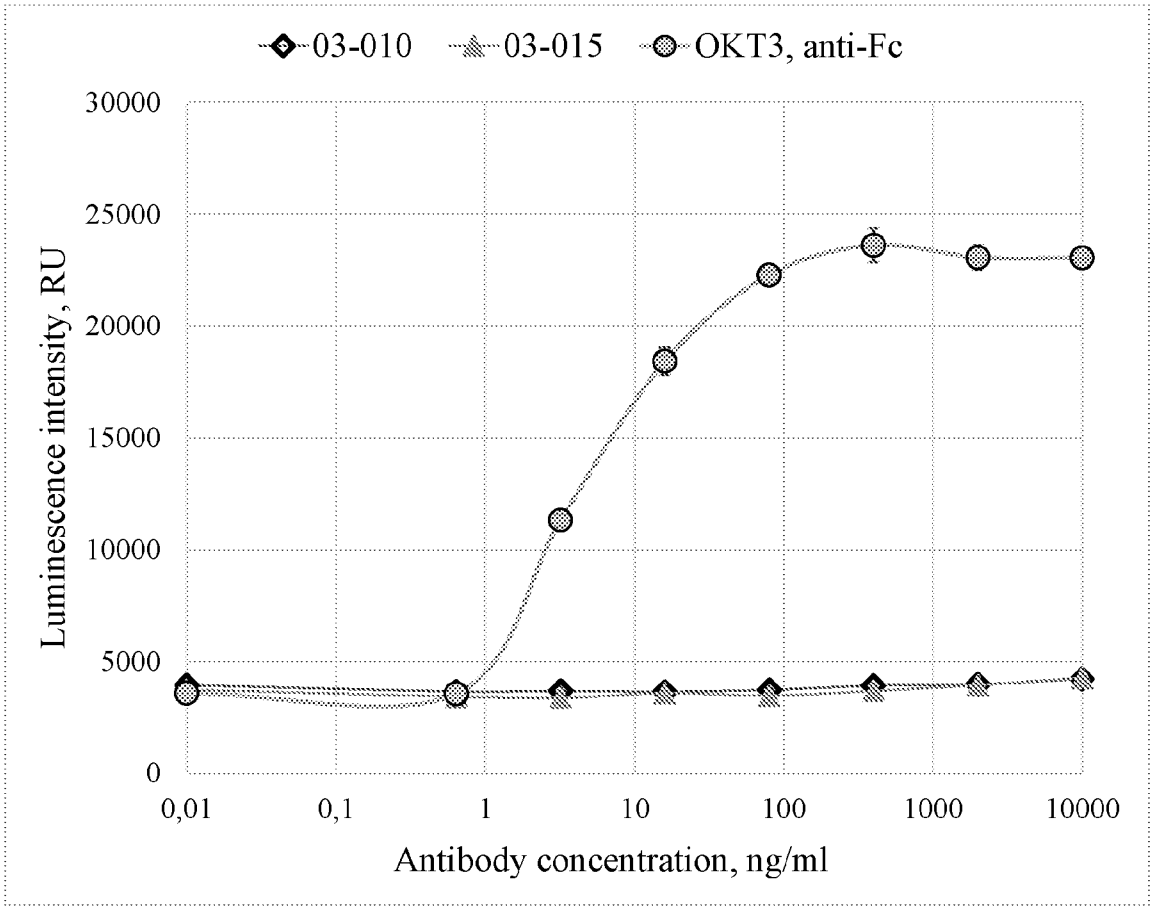

03-010
03-015
OKT3, anti-Fc
30000
25000
20000
15000
10000
5000
0
Luminescence intensity, RU
0,01
0,1
1
10
100
1000
10000
Antibody concentration, ng/ml

Figure 7

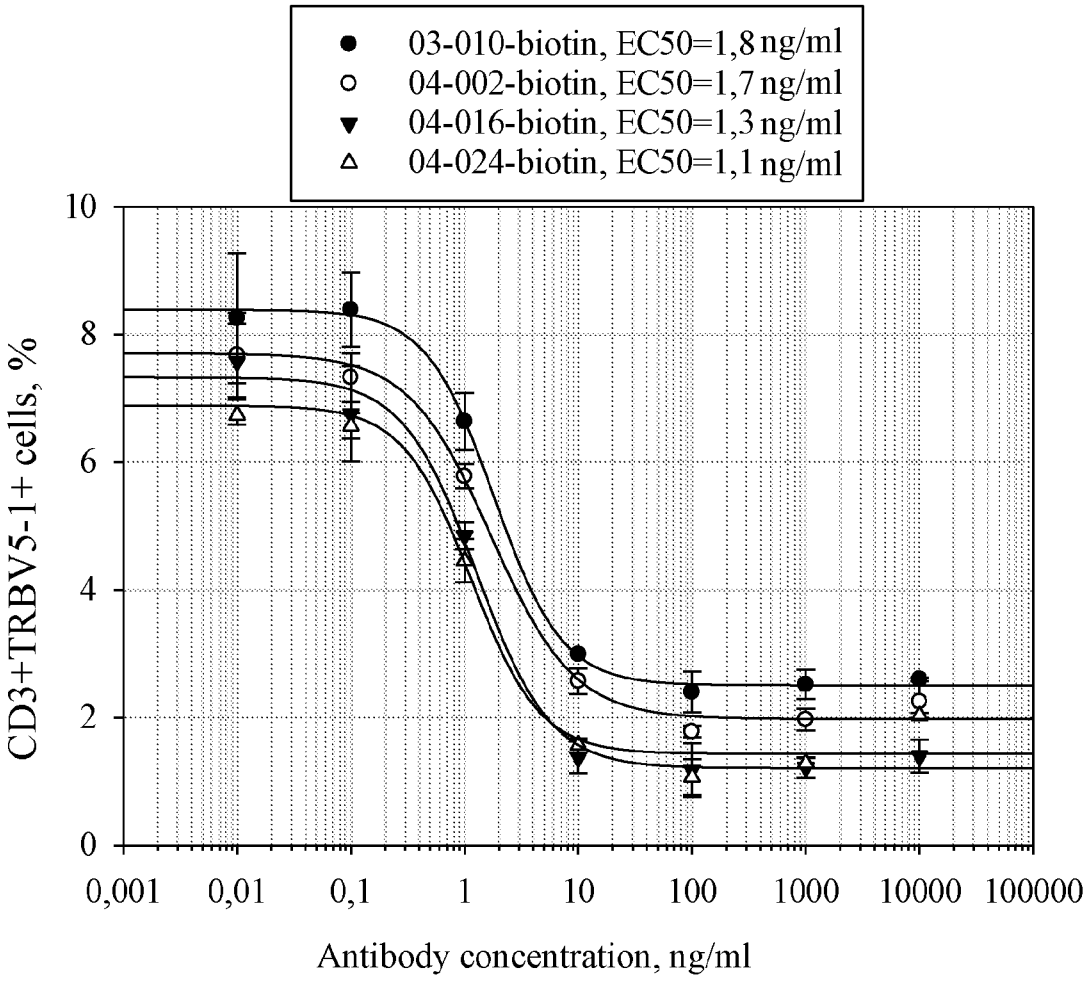


Figure 8

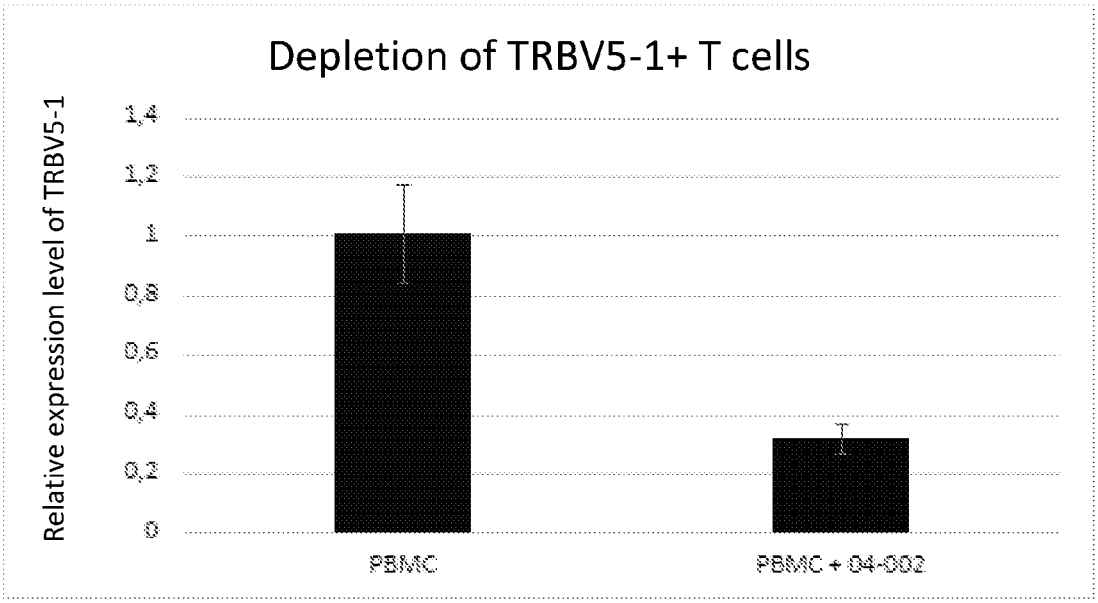


Figure 9

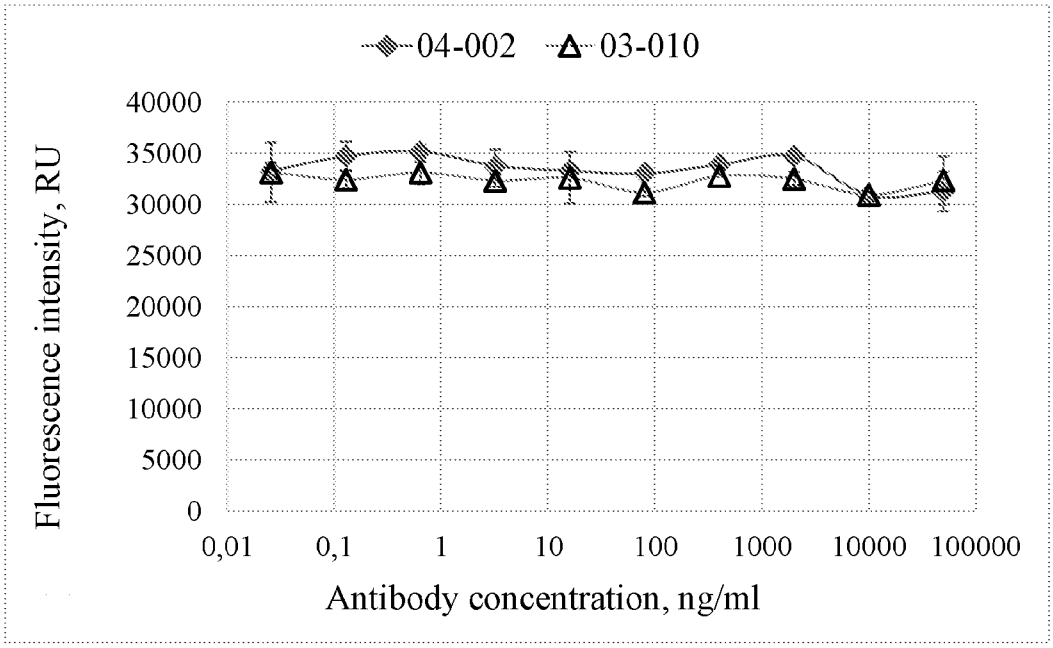


Figure 10

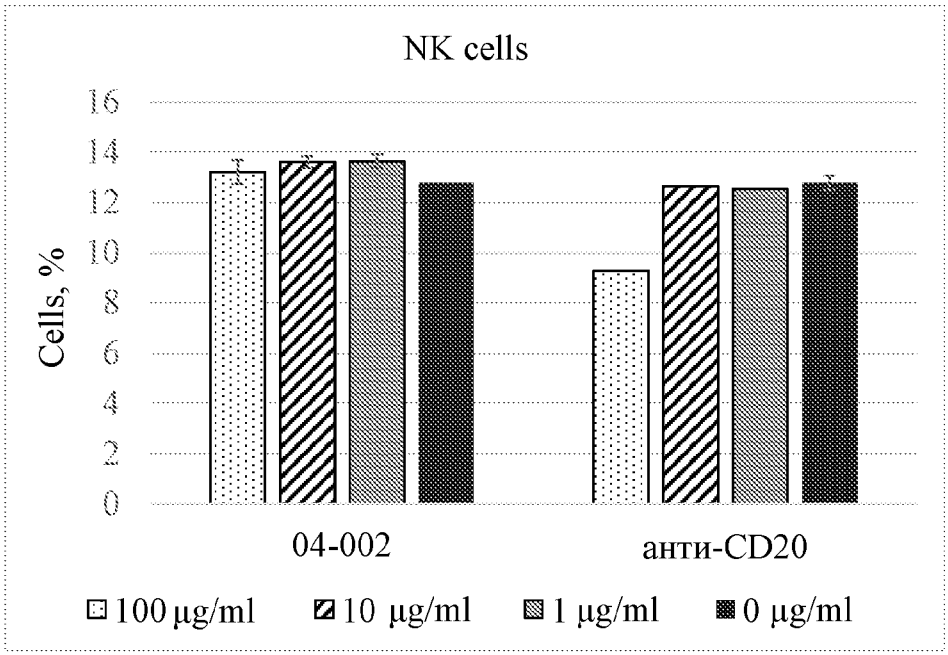


Figure 11

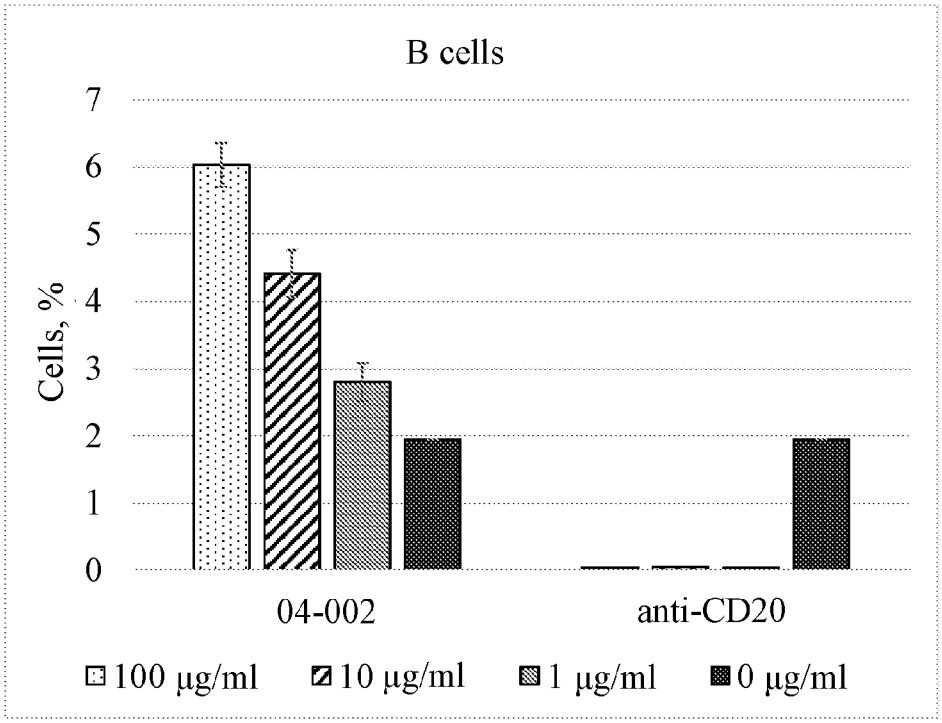


Figure 12

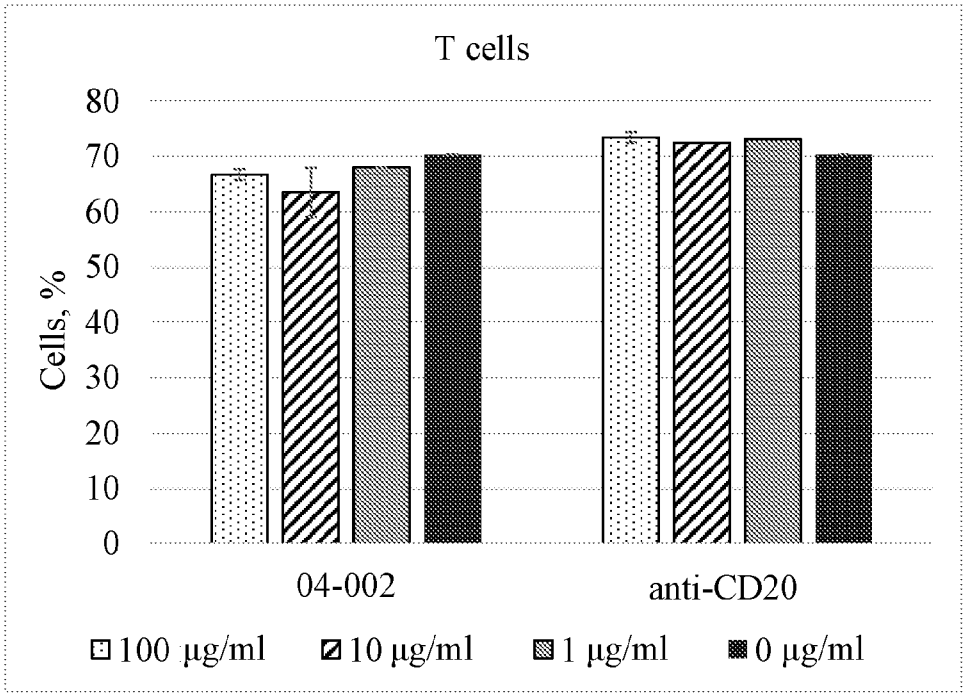


Figure 13

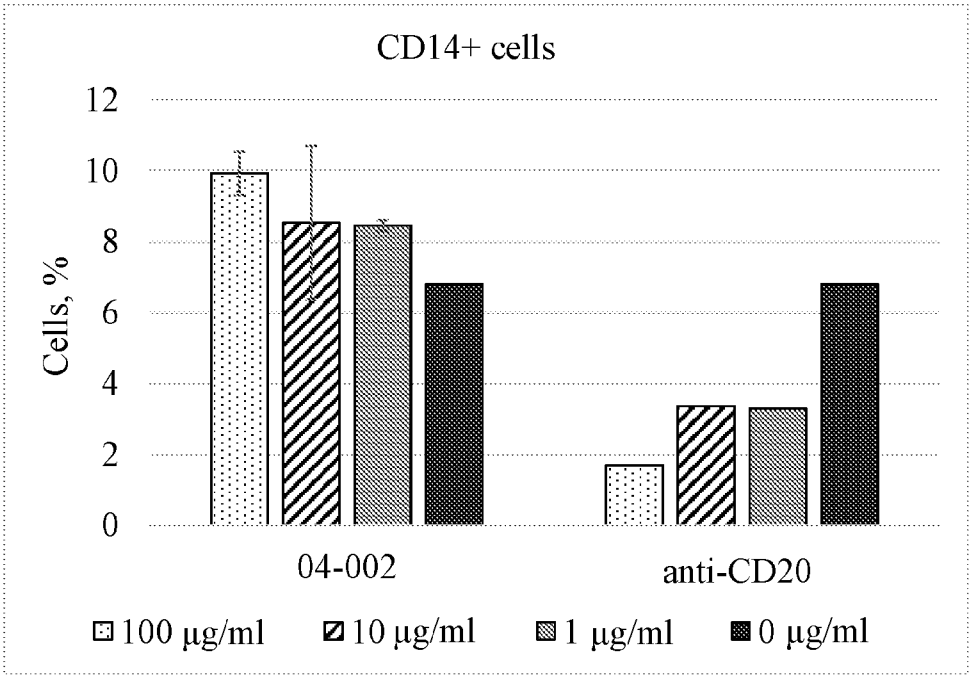


Figure 14

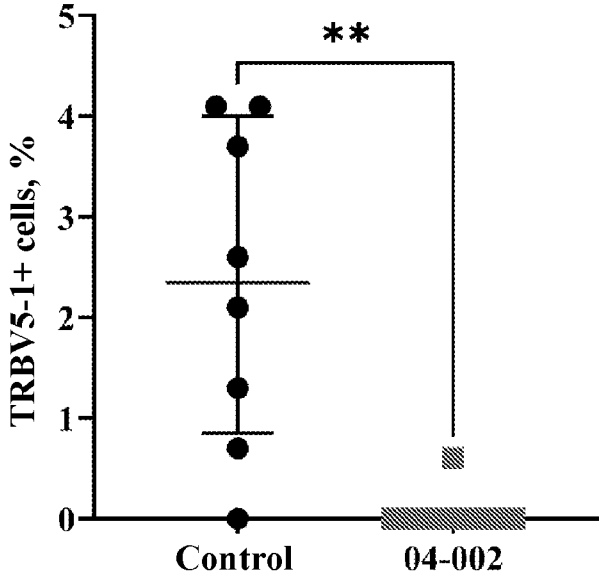


Figure 15

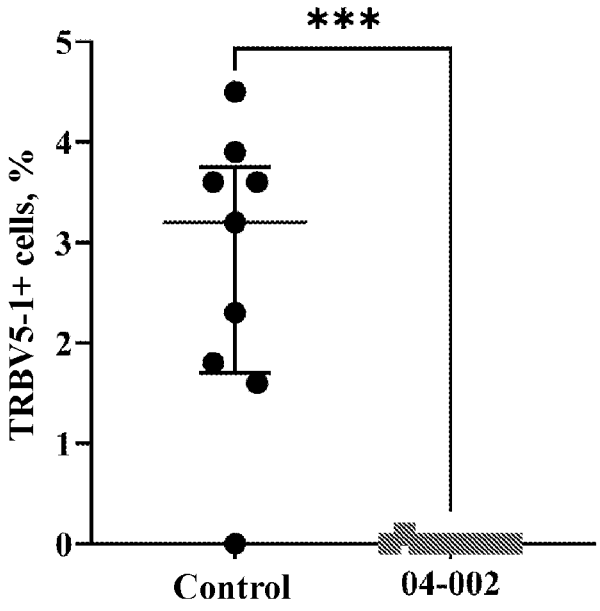


Figure 16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/RU 2024/050243

A. CLASSIFICATION OF SUBJECT MATTER

(see extra sheet)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K; C12P; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

E-Library, EAPATIS, EMBL-EBI, Espacenet, Google Patents, Google Scholar, NCBI, PATENTSCOPE, PatSearch, PubMed, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 3904387 A1 (JOINT STOCK COMPANY "BIOCAD"), 03.11.2021, claims	1-39
A	WO 2021/155112 A1 (UNIV PENNSYLVANIA), 05.08.2021, claims, SEQ ID NO:98, 100, 102, 103	1-39
A	WO 2022/046920 A2 (MARENGO THERAPEUTICS INC), 03.03.2022, abstract, claims, SEQ ID NO:1163, 1165, 1166, 1168, 1169, 1170	1-39

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 2025 (27.01.2025)	05 March 2025 (05.03.2025)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/RU 2024/050243

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. [X] forming part of the international application as filed:

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

C07K 16/28 (2006.01)
C12P 21/08 (2006.01)
A61K 39/395 (2006.01)
A61P 3/10 (2006.01)
A61P 37/02 (2006.01)
A61P 43/00 (2006.01)