(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
25 February 2021 (25.02.2021)

(10) **International Publication Number**
WO 2021/032961 A1

(51) **International Patent Classification:**
C07K 16/28 (2006.01) *C12N 5/0783* (2010.01)
A61K 35/17 (2015.01)

(21) **International Application Number:**
PCT/GB2020/051956

(22) **International Filing Date:**
14 August 2020 (14.08.2020)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
1911799.3 16 August 2019 (16.08.2019) GB
2010760.3 13 July 2020 (13.07.2020) GB
2012172.9 05 August 2020 (05.08.2020) GB

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2021/032961 A1

(54) **Title:** EX VIVO GAMMA DELTA T CELL POPULATIONS

(57) **Abstract:** The invention relates to *ex vivo* methods of modulating Vδ1 T cells using anti-Vδ1 antibodies or fragments thereof.

EX VIVO GAMMA DELTA T CELL POPULATIONS

FIELD OF THE INVENTION

The invention relates to populations of gamma delta T cells contacted with anti-TCR delta variable 1 (anti-Vδ1) antibodies.

BACKGROUND OF THE INVENTION

The growing interest in T cell immunotherapy for cancer has focused on the evident capacity of subsets of CD8+ and CD4+ alpha beta (αβ) T cells to recognize cancer cells and to mediate host-protective functional potentials, particularly when de-repressed by clinically mediated antagonism of inhibitory pathways exerted by PD-1, CTLA-4, and other receptors. However, αβ T cells are MHC-restricted which can lead to graft versus host disease.

Gamma delta T cells (γδ T cells) represent a subset of T cells that express on their surface a distinct, defining γδ T-cell receptor (TCR). This TCR is made up of one gamma (γ) and one delta (δ) chain, each of which undergoes chain rearrangement but have a limited number of V genes as compared to αβ T cells. The main TGRV gene segments encoding Vγ are TRGV2, TRGV3, TRGV4, TRGV5, TRGV8, TRGV9 and TRGV11 and non-functional genes TRGV10, TRGV11, TRGVA and TRGVB. The most frequent TRDV gene segments encode Vδ1, Vδ2, and Vδ3, plus several V segments that have both Vδ and Vα designation (Adams *et al.*, 296:30-40 (2015) *Cell Immunol.*). Human γδ T cells can be broadly classified based on their TCR chains, as certain γ and δ types are found on cells more prevalently, though not exclusively, in one or more tissue types. For example, most blood-resident γδ T cells express a Vδ2 TCR, commonly Vγ9Vδ2, whereas this is less common among tissue-resident γδ T cells such as those in the skin, which more frequently use the Vδ1 TCR paired with gamma chains, for example often paired with Vγ4 in the gut.

To exploit γδ T cells for immunotherapy requires either a means to expand the cells *in situ* or to harvest them and expand them *ex vivo* prior to re-infusion. The latter approach has previously been described using the addition of exogenous cytokines, for example see WO2017/072367 and WO2018/212808. Methods for expanding a patients' own γδ T cells has been described using pharmacologically modified forms of hydroxy-methyl but-2-enyl pyrophosphate (HMBPP) or clinically-approved aminobisphosphonates. By these approaches, over 250 cancer patients have been treated, seemingly safely, but with only rare incidences of complete remission. However, there is still a need for activating agents that have the proven capacity to expand large numbers of γδ T cells.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided an *ex vivo* method of modulating Vδ1 T cells comprising administering a human, anti-TCR delta variable 1 (anti-Vδ1) antibody or fragment thereof, which binds to an epitope of a variable delta 1 (Vδ1) chain of a γδ T cell receptor (TCR) comprising one or more amino acid residues within amino acid regions:

(i) 3-20 of SEQ ID NO: 1; and/or

(ii) 37-77 of SEQ ID NO: 1

to a cell population comprising Vδ1 T cells.

According to a further aspect of the invention, there is provided an *ex vivo* method of modulating Vδ1 T cells comprising administering an anti-Vδ1 antibody or fragment thereof which comprises one or more of:

a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-25;

a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 26-37 and SEQUENCES: A1-A12 (of Table 2); and/or

a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 38-61,

to a cell population comprising Vδ1 T cells.

According to a further aspect of the invention, there is provided a Vδ1 T cell population obtained by the *ex vivo* method as defined herein.

According to a further aspect of the invention, there is provided a composition comprising the Vδ1 T cell population as defined herein.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising the Vδ1 T cell population as defined herein.

According to a further aspect of the invention, there is provided a method of treating a cancer, an infectious disease or an inflammatory disease in a subject in need thereof, comprising administering a therapeutically effective amount of the Vδ1 T cell population or the pharmaceutical composition as defined herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: ELISA Detection of Directly Coated Antigen with Anti-Vδ1Ab (REA173, Miltenyi Biotec). Detection was seen only with those antigens which contain the Vδ1 domain. Leucine zipper (LZ) format seems more potent than Fc format which is consistent with cell-based flow competition assay (data not shown).

Figure 2: Polyclonal phage DELFIA data for DV1 selections. A) Heterodimer selections: heterodimeric LZ TCR format in round 1 and 2, with deselections on heterodimeric LZ TCR in both rounds. B) Homodimer selections: round 1 performed using homodimeric Fc fusion TCR with deselection on human IgG1 Fc followed by round 2 on heterodimeric LZ TCR with deselection on heterodimeric LZ TCR. Each graph contains two bars for each target to represent selections from different libraries.

Figure 3: IgG capture: left) Sensorgrams of interaction of anti-L1 IgG with L1, right) steady state fits, if available. All experiments were performed at room temperature on MASS-2 instrument. Steady state fitting according to Langmuir 1:1 binding.

Figure 4: Results of TCR Downregulation Assay for clones 1245_P01_E07, 1252_P01_C08, 1245_P02_G04, 1245_P01_B07 and 1251_P02_C05 (**A**) or clones 1139_P01_E04, 1245_P02_F07, 1245_P01_G06, 1245_P01_G09, 1138_P01_B09, 1251_P02_G10 and 1252_P01_C08 (**B**).

Figure 5: Results of T cell degranulation Assay for clones 1245_P01_E07, 1252_P01_C08, 1245_P02_G04, 1245_P01_B07 and 1251_P02_C05 (**A**) or clones 1139_P01_E04, 1245_P02_F07, 1245_P01_G06, 1245_P01_G09, 1138_P01_B09 and 1251_P02_G10 (**B**).

Figure 6: Results of Killing Assay (THP-1 flow-based assay) for clones 1245_P01_E07, 1252_P01_C08, 1245_P02_G04, 1245_P01_B07 and 1251_P02_C05 (**A**) or clones 1139_P01_E04, 1245_P02_F07, 1245_P01_G06, 1245_P01_G09, 1138_P01_B09 and 1251_P02_G10 (**B**).

Figure 7: Epitope mapping data for 1245_P01_E07. Graphical representation of epitope binding site of 1245_P01_E07 on SEQ ID NO: 1.

Figure 8: Epitope mapping data for 1252_P01_C08. Graphical representation of epitope binding site of 1252_P01_C08 on SEQ ID NO: 1.

Figure 9: Epitope mapping data for 1245_P02_G04. Graphical representation of epitope binding site of 1245_P02_G04 on SEQ ID NO: 1.

Figure 10: Epitope mapping data for 1251_P02_C05. Graphical representation of epitope binding site of 1251_P02_C05 on SEQ ID NO: 1.

Figure 11: Epitope mapping data for 1141_P01_E01. Graphical representation of epitope binding site of 1141_P01_E01 on SEQ ID NO: 1.

Figure 12: Total cell counts during Experiment 1 of Example 10. Samples were cultured with varying concentration of anti-Vδ1 antibodies described herein and compared to samples cultured with comparator antibodies or controls. Graphs show total cell counts at (A) day 7, (B) day 14 and (C) day 18.

Figure 13: Analysis of Vδ1 T cells during Experiment 1 of Example 10. Graphs show (A) percentage of Vδ1 T cells, (B) Vδ1 T cell count and (C) Vδ1 fold change in the samples at day 18.

Figure 14: Total cell counts during Experiment 2 of Example 10. Samples were cultured with varying concentration of anti-Vδ1 antibodies described herein and compared to samples cultured with comparator antibodies or controls. Graphs show total cell counts at (A) day 7, (B) day 11, (C) day 14 and (D) day 17.

Figure 15: Analysis of Vδ1 T cells during Experiment 2 of Example 10. Graphs show (A) percentage of Vδ1 T cells, (B) Vδ1 T cell count and (C) Vδ1 fold change in the samples at day 17.

Figure 16: Cell composition analysis. The cell types present in the samples (including non-Vδ1 cells) were measured on day 17 of Experiment 2. Cells were harvested and analysed by flow cytometry for surface expression of Vδ1, Vδ2 and αβTCR. The percentage values are also provided in **Table 6**.

Figure 17: SYTOX-flow killing assay results. Cell functionality was tested using the SYTOX-flow killing assay and results are presented for (A) Experiment 1 at day 14 using cells in a 10:1 Effector-to-Target (E:T) ratio, and (B) Experiment 2 at day 17 (post freeze-thaw) using cells at a 1:1 and 10:1 E:T ratio.

Figure 18: **Total cell count post freeze-thaw.** Graph shows the total cell counts after 7 days of culturing cells post freeze-thaw for cultures contacted with B07, C08, E07, G04 or OKT-3 antibodies prior to freezing.

5 **Figure 19:** **Monitoring cell expansion.** Total cell counts were monitored until day 42 for cells cultured post freeze-thaw.

Figure 20: **Anti-Vδ1 antibody conferred modulation and proliferation of tumour-infiltrating-lymphocyte (TILs) in human tumours.** Studies on renal cell carcinoma (RCC)
10 +/- antibodies **A)** Fold-increase in TIL Vδ1+ cells. **B)** Total numbers of TIL Vδ1+ cells. **C)** Example gating strategy **D)** Comparative cell-surface phenotypic profile of TIL Vδ1+ cells. **E)** Analysis of the TIL Vδ1-negative gated fraction.

DETAILED DESCRIPTION OF THE INVENTION

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Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. As used herein, the following terms have the meanings ascribed to them below.

20

Gamma delta (γδ) T cells represent a small subset of T cells that express on their surface a distinct, defining T Cell Receptor (TCR). This TCR is made up of one gamma (γ) and one delta (δ) chain. Each chain contains a variable (V) region, a constant (C) region, a transmembrane region and a cytoplasmic tail. The V region contains an antigen binding site. There are two
25 major sub-types of human γδ T cells: one that is dominant in the peripheral blood and one that is dominant in non-haematopoietic tissues. The two sub-types may be defined by the type of δ and/or γ present on the cells. For example, γδ T cells that are dominant in peripheral blood primarily express the delta variable 2 chain (Vδ2). γδ T cells that are dominant in non-haematopoietic tissues (*i.e.* are tissue-resident) primarily express the delta variable 1 (Vδ1)
30 chain. References to "Vδ1 T cells" refer to γδ T cells with a Vδ1 chain, *i.e.* $V\delta1^{+}$ T cells.

References to "delta variable 1" may also referred to as Vδ1 or Vd1, while a nucleotide encoding a TCR chain containing this region may be referred to as "TRDV1". Antibodies or fragments thereof which interact with the Vδ1 chain of a γδ TCR, are all effectively antibodies
35 or fragments thereof which bind to Vδ1 and may referred to as "anti-TCR delta variable 1 antibodies or fragments thereof" or "anti-Vδ1 antibodies or fragments thereof".

Additional references are made herein to other delta chains such as the “delta variable 2” chain. These can be referred to in a similar manner. For example, delta variable 2 chains can be referred to as Vδ2, while a nucleotide encoding a TCR chain containing this region may be referred to as “TRDV2”. In preferred embodiments antibodies or fragments thereof which interact with the Vδ1 chain of a γδ TCR, do not interact with other delta chains such as Vδ2

References to ‘gamma variable chains’ are also made herein. These may be referred to as γ-chains or Vγ, while a nucleotide encoding a TCR chain containing this region may be referred to as TRGV. For example, TRGV4 refers to Vγ4 chain. In a preferred embodiments, antibodies or fragments thereof which interact with the Vδ1 chain of a γδ TCR, do not interact with gamma chains such as Vγ4.

The term “antibody” includes any antibody protein construct comprising at least one antibody variable domain comprising at least one antigen binding site (ABS). Antibodies include, but are not limited to, immunoglobulins of types IgA, IgG, IgE, IgD, IgM (as well as subtypes thereof). The overall structure of Immunoglobulin G (IgG) antibodies assembled from two identical heavy (H)-chain and two identical light (L)-chain polypeptides is well established and highly conserved in mammals (Padlan (1994) *Mol. Immunol.* 31:169-217).

A conventional antibody or immunoglobulin (Ig) is a protein comprising four polypeptide chains: two heavy (H) chains and two light (L) chains. Each chain is divided into a constant region and a variable domain. The heavy (H) chain variable domains are abbreviated herein as VH, and the light (L) chain variable domains are abbreviated herein as VL. These domains, domains related thereto and domains derived therefrom, may be referred to herein as immunoglobulin chain variable domains. The VH and VL domains (also referred to as VH and VL regions) can be further subdivided into regions, termed “complementarity determining regions” (“CDRs”), interspersed with regions that are more conserved, termed “framework regions” (“FRs”). The framework and complementarity determining regions have been precisely defined (Kabat *et al.* Sequences of Proteins of Immunological Interest, *Fifth Edition U.S. Department of Health and Human Services*, (1991) NIH Publication Number 91-3242). There are also alternative numbering conventions for CDR sequences, for example those set out in Chothia et al. (1989) Nature 342: 877-883. In a conventional antibody, 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 conventional antibody tetramer of two heavy immunoglobulin chains and two light immunoglobulin chains is formed with the heavy and the light immunoglobulin chains inter-connected by *e.g.* disulphide bonds, and the heavy chains similarly connected. The heavy chain constant region includes three

domains, CH1, CH2 and CH3. The light chain constant region is comprised of one domain, CL. The variable domain of the heavy chains and the variable domain of the light chains are binding domains that interact with an antigen. The constant regions of the antibodies typically mediate the binding of the antibody to host tissues or factors, including various cells of the
5 immune system (*e.g.* effector cells) and the first component (C1q) of the classical complement system.

A fragment of the antibody (which may also referred to as “antibody fragment”, “immunoglobulin fragment”, “antigen-binding fragment” or “antigen-binding polypeptide”) as
10 used herein refers to a portion of an antibody (or constructs that contain said portion) that specifically binds to the target, the delta variable 1 (Vδ1) chain of a γδ T cell receptor (*e.g.* a molecule in which one or more immunoglobulin chains is not full length, but which specifically binds to the target). Examples of binding fragments encompassed within the term antibody fragment include:
15 (i) a Fab fragment (a monovalent fragment consisting of the VL, VH, CL and CH1 domains);
(ii) a F(ab')2 fragment (a bivalent fragment consisting of two Fab fragments linked by a disulphide bridge at the hinge region);
(iii) a Fd fragment (consisting of the VH and CH1 domains);
20 (iv) a Fv fragment (consisting of the VL and VH domains of a single arm of an antibody);
(v) a single chain variable fragment, scFv (consisting of VL and VH domains joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules);
25 (vi) a VH (an immunoglobulin chain variable domain consisting of a VH domain);
(vii) a VL (an immunoglobulin chain variable domain consisting of a VL domain);
(viii) a domain antibody (dAb, consisting of either the VH or VL domain);
(ix) a minibody (consisting of a pair of scFv fragments which are linked via CH3 domains); and
30 (x) a diabody (consisting of a noncovalent dimer of scFv fragments that consist of a VH domain from one antibody connected by a small peptide linker a VL domain from another antibody).

“Human antibody" refers to antibodies having variable and constant regions derived from
35 human germline immunoglobulin sequences. Human subjects administered with said human antibodies do not generate cross-species antibody responses (for example termed HAMA responses - human-anti-mouse antibody) to the primary amino acids contained within said

antibodies. Said human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g*. mutations introduced by random or site-specific mutagenesis or by somatic mutation), for example in the CDRs and in particular CDR3. However, the term is not intended to include antibodies in which CDR sequences derived from 5 the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (*e.g*. a mouse) that is transgenic for human 10 immunoglobulin genes or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences, may also be referred to as "recombinant human antibodies".

Substituting at least one amino acid residue in the framework region of a non-human 15 immunoglobulin variable domain with the corresponding residue from a human variable domain is referred to as "humanisation". Humanisation of a variable domain may reduce immunogenicity in humans.

"Specificity" refers to the number of different types of antigens or antigenic determinants to 20 which a particular antibody or fragment thereof can bind. The specificity of an antibody is the ability of the antibody to recognise a particular antigen as a unique molecular entity and distinguish it from another. An antibody that "specifically binds" to an antigen or an epitope is a term well understood in the art. A molecule is said to exhibit "specific binding" if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular 25 target antigen or epitope, than it does with alternative targets. An antibody "specifically binds" to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances.

"Affinity", represented by the equilibrium constant for the dissociation of an antigen with an 30 antigen-binding polypeptide (KD), is a measure of the binding strength between an antigenic determinant and an antigen-binding site on the antibody (or fragment thereof): the lesser the value of the KD, the stronger the binding strength between an antigenic determinant and the antigen-binding polypeptide. Alternatively, the affinity can also be expressed as the affinity constant (KA), which is 1/KD. Affinity can be determined by known methods, depending on 35 the specific antigen of interest.

Any KD value less than 10^{-6} is considered to indicate binding. Specific binding of an antibody, or fragment thereof, to an antigen or antigenic determinant can be determined in any suitable known manner, including, for example, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA) and sandwich competition
5 assays, equilibrium dialysis, equilibrium binding, gel filtration, ELISA, surface plasmon resonance, or spectroscopy (*e.g.* using a fluorescence assay) and the different variants thereof known in the art.

"Avidity" is the measure of the strength of binding between an antibody, or fragment thereof,
10 and the pertinent antigen. Avidity is related to both the affinity between an antigenic determinant and its antigen binding site on the antibody and the number of pertinent binding sites present on the antibody.

"Human tissue Vδ1+ cells," and "haemopoietic and blood Vδ1+ cells" and "tumour infiltrating
15 lymphocyte (TIL) Vδ1+ cells," are defined as Vδ1+ cells contained in or derived from either human tissue or the haemopoietic blood system or human tumours respectively. All said cell types can be identified by their (i) location or from where they are derived and (ii) their expression of the Vδ1+ TCR.

20 "Modulating antibodies" are antibodies that confer a measurable change including, but not limited to, a measurable change in cell cycle, and/or in cell number, and/or cell viability, and/or in one or more cell surface markers, and/or in the secretion of one or more secretory molecules (e.g., cytokines, chemokines, leukotrienes, etc.), and/or a function (such as cytotoxicity towards a target cell or diseased cell), upon contacting or binding to a cell expressing the
25 target to which the antibody binds.

A method of "modulating" a cell, or population thereof, refers to a method wherein in at least one measurable change in said cell or cells, or secretion therefrom, is triggered to generate one or more "modulated cells".

30

An "immune response" is a measurable change in at least one cell, or one cell-type, or one endocrine pathway, or one exocrine pathway, of the immune system (including but not limited to a cell-mediated response, a humoral response, a cytokine response, a chemokine response) upon addition of a modulating antibody.

35

An "immune cell" is defined as a cell of the immune system including, but not limited to, CD34+ cells, B-Cells, CD45+ (lymphocyte common antigen) cells, Alpha-Beta T-cells, Cytotoxic T-

cells, Helper T-cells, Plasma Cells, Neutrophils, Monocytes, Macrophages, Red Blood Cells, Platelets, Dendritic Cells, Phagocytes, Granulocytes, Innate lymphoid cells, Natural Killer (NK) cells and Gamma Delta T-cells. Typically, immune cells are classified with the aid of combinatorial cell surface molecule analysis (e.g., via flow cytometry) to identify or group or cluster to differentiate immune cells into sub-populations. These can be then still further sub-divided with additional analysis. For example, CD45+ lymphocytes can further sub-divided into vδ positive populations and vδ negative populations.

“Model systems” are biological models or biological representations designed to aid in the understanding of how a medicine such as an antibody or fragment thereof may function as a medicament in the amelioration of a sign or symptom of disease. Such models typically include the use of in vitro, ex vivo, and in vivo diseased cells, non-diseased cells, healthy cells, effector cells, and tissues etc., and in which the performance of said medicaments are studied and compared.

“Diseased cells” exhibit a phenotype associated with the progression of a disease such as a cancer, an infection such as a viral infection, or an inflammatory condition or inflammatory disease. For example, a diseased cell may be a tumour cell, an autoimmune tissue cell or a virally infected cell. Accordingly said diseased cells may be defined as tumorous, or virally infected, or inflammatory.

“Healthy cells” refers to normal cells that are not diseased. They may also be referred to as “normal” or “non-diseased” cells. Non-diseased cells include non-cancerous, or non-infected, or non-inflammatory cells. Said cells are often employed alongside relevant diseased cells to determine the diseased cell specificity conferred by a medicament and/or better understand the therapeutic index of a medicament.

“Diseased-cell-specificity” is a measure of how effective an effector cell or population thereof, (such as, for example, a population of Vδ1+ cells) is at distinguishing and killing diseased cells, such as cancer cells, whilst sparing non-diseased or healthy cells. This potential can be measured in model systems and may involve comparing the propensity of an effector cell, or a population of effector cells, to selectively kill or lyse diseased cells versus the potential of said effector cell/s to kill or lyse non-diseased or healthy cells. Said diseased-cell-specificity can inform the potential therapeutic index of a medicament.

“Enhanced diseased-cell specificity” describes a phenotype of an effector cell such as, for example, a Vδ1+ cell, or population thereof, which has been modulated to further increase its

capacity to specifically kill diseased cells. This enhancement can be measured in a variety of ways inclusive of fold-change, or percentage increase, in diseased-cell killing specificity or selectivity.

5 Suitably, the antibody or fragment thereof (*i.e.* polypeptide) of the invention is isolated. An "isolated" polypeptide is one that is removed from its original environment. The term "isolated" may be used to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.* an isolated antibody that specifically binds Vδ1, or a fragment thereof, is substantially free of antibodies that specifically bind antigens other than Vδ1). The 10 term "isolated" may also be used to refer to preparations where the isolated antibody is sufficiently pure to be administered therapeutically when formulated as an active ingredient of a pharmaceutical composition, or at least 70-80% (w/w) pure, more preferably, at least 80-90% (w/w) pure, even more preferably, 90-95% pure; and, most preferably, at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

15

Suitably, the polynucleotides used in the present invention are isolated. An "isolated" polynucleotide is one that is removed from its original environment. For example, a naturally-occurring polynucleotide is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, 20 it is cloned into a vector that is not a part of its natural environment or if it is comprised within cDNA.

The antibody or fragment thereof may be a "functionally active variant" which also includes naturally occurring allelic variants, as well as mutants or any other non-naturally occurring 25 variants. As is known in the art, an allelic variant is an alternate form of a (poly)peptide that is characterized as having a substitution, deletion, or addition of one or more amino acids that does essentially not alter the biological function of the polypeptide. By way of non-limiting example, said functionally active variants may still function when the frameworks containing the CDRs are modified, when the CDRs themselves are modified, when said CDRs are grafted 30 to alternate frameworks, or when N- or C-terminal extensions are incorporated. Further, CDR containing binding domains may be paired with differing partner chains such as those shared with another antibody. Upon sharing with so called 'common' light or 'common' heavy chains, said binding domains may still function. Further, said binding domains may function when multimerized. Further, 'antibodies or fragments thereof' may also comprise functional variants 35 wherein the VH or VL or constant domains have been modified away or towards a different canonical sequence (for example as listed at IMGT.org) and which still function.

For the purposes of comparing two closely-related polypeptide sequences, the "% sequence identity" between a first polypeptide sequence and a second polypeptide sequence may be calculated using NCBI BLAST v2.0, using standard settings for polypeptide sequences (BLASTP). For the purposes of comparing two closely-related polynucleotide sequences, the "% sequence identity" between a first nucleotide sequence and a second nucleotide sequence may be calculated using NCBI BLAST v2.0, using standard settings for nucleotide sequences (BLASTN).

Polypeptide or polynucleotide sequences are said to be the same as or "identical" to other polypeptide or polynucleotide sequences, if they share 100% sequence identity over their entire length. Residues in sequences are numbered from left to right, *i.e.* from N- to C-terminus for polypeptides; from 5' to 3' terminus for polynucleotides.

A "difference" between sequences refers to an insertion, deletion or substitution of a single amino acid residue in a position of the second sequence, compared to the first sequence. Two polypeptide sequences can contain one, two or more such amino acid differences. Insertions, deletions or substitutions in a second sequence which is otherwise identical (100% sequence identity) to a first sequence result in reduced % sequence identity. For example, if the identical sequences are 9 amino acid residues long, one substitution in the second sequence results in a sequence identity of 88.9%. If first and second polypeptide sequences are 9 amino acid residues long and share 6 identical residues, the first and second polypeptide sequences share greater than 66% identity (the first and second polypeptide sequences share 66.7% identity).

Alternatively, for the purposes of comparing a first, reference polypeptide sequence to a second, comparison polypeptide sequence, the number of additions, substitutions and/or deletions made to the first sequence to produce the second sequence may be ascertained. An "addition" is the addition of one amino acid residue into the sequence of the first polypeptide (including addition at either terminus of the first polypeptide). A "substitution" is the substitution of one amino acid residue in the sequence of the first polypeptide with one different amino acid residue. Said substitution may be conservative or non-conservative. A "deletion" is the deletion of one amino acid residue from the sequence of the first polypeptide (including deletion at either terminus of the first polypeptide).

A "conservative" amino acid substitution is an amino acid substitution in which an amino acid residue is replaced with another amino acid residue of similar chemical structure and which is expected to have little influence on the function, activity or other biological properties of the

polypeptide. Such conservative substitutions suitably are substitutions in which one amino acid within the following groups is substituted by another amino acid residue from within the same group:

Group	**Amino acid residue**
Non-polar aliphatic	Glycine
	Alanine
	Valine
	Methionine
	Leucine
	Isoleucine
Aromatic	Phenylalanine
	Tyrosine
	Tryptophan
Polar uncharged	Serine
	Threonine
	Cysteine
	Proline
	Asparagine
	Glutamine
Negatively charged	Aspartate
	Glutamate
Positively charged	Lysine
	Arginine
	Histidine

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Suitably, a hydrophobic amino acid residue is a non-polar amino acid. More suitably, a hydrophobic amino acid residue is selected from V, I, L, M, F, W or C.

As used herein, numbering of polypeptide sequences and definitions of CDRs and FRs are as
10 defined according to the Kabat system (Kabat *et al*., 1991, herein incorporated by reference in its entirety). A “corresponding” amino acid residue between a first and second polypeptide sequence is an amino acid residue in a first sequence which shares the same position according to the Kabat system with an amino acid residue in a second sequence, whilst the amino acid residue in the second sequence may differ in identity from the first. Suitably
15 corresponding residues will share the same number (and letter) if the framework and CDRs are the same length according to Kabat definition. Alignment can be achieved manually or by using, for example, a known computer algorithm for sequence alignment such as NCBI BLAST v2.0 (BLASTP or BLASTN) using standard settings.

References herein to an "epitope" refer to the portion of the target which is specifically bound by the antibody or fragment thereof. Epitopes may also be referred to as "antigenic determinants". An antibody binds "essentially the same epitope" as another antibody when they both recognize identical or sterically overlapping epitopes. Commonly used methods to determine whether two antibodies bind to identical or overlapping epitopes are competition assays, which can be configured in a number of different formats (*e.g.* well plates using radioactive or enzyme labels, or flow cytometry on antigen-expressing cells) using either labelled antigen or labelled antibody.

Epitopes found on protein targets may be defined as "linear epitopes" or "conformational epitopes". Linear epitopes are formed by a continuous sequence of amino acids in a protein antigen. Conformational epitopes are formed of amino acids that are discontinuous in the protein sequence, but which are brought together upon folding of the protein into its three-dimensional structure.

The term "vector", as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian and yeast vectors). Other vectors (*e.g.* non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the 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 operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.* replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions, and also bacteriophage and phagemid systems. The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. Such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell, for example, when said progeny are employed to make a cell line or cell bank which is then optionally stored, provided, sold, transferred, or employed to manufacture an antibody or fragment thereof as described herein.

References to “subject”, “patient” or “individual” refer to a subject, in particular a mammalian subject, to be treated. Mammalian subjects include humans, non-human primates, farm animals (such as cows), sports animals, or pet animals, such as dogs, cats, guinea pigs, rabbits, rats or mice. In some embodiment, the subject is a human. In alternative embodiments, the subject is a non-human mammal, such as a mouse.

The term "sufficient amount" means an amount sufficient to produce a desired effect. The term "therapeutically effective amount" is an amount that is effective to ameliorate a symptom of a disease or disorder. A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy.

As used herein, the term “about” when used herein includes up to and including 10% greater and up to and including 10% lower than the value specified, suitably up to and including 5% greater and up to and including 5% lower than the value specified, especially the value specified. The term “between”, includes the values of the specified boundaries.

A disease or disorder is “ameliorated” if the severity of a sign or symptom of the disease or disorder, the frequency with which such a sign or symptom is experienced by a subject, or both, is reduced.

As used herein, “treating a disease or disorder” means reducing the frequency and/or severity of at least one sign or symptom of the disease or disorder experienced by a subject.

“Cancer,” as used herein, refers to the abnormal growth or division of cells. Generally, the growth and/or life span of a cancer cell exceeds, and is not coordinated with, that of the normal cells and tissues around it. Cancers may be benign, pre-malignant or malignant. Cancer occurs in a variety of cells and tissues, including the oral cavity (e.g., mouth, tongue, pharynx, etc.), digestive system (e.g., esophagus, stomach, small intestine, colon, rectum, liver, bile duct, gall bladder, pancreas, etc.), respiratory system (e.g., larynx, lung, bronchus, etc.), bones, joints, skin (e.g., basal cell, squamous cell, meningioma, etc.), breast, genital system, (e.g., uterus, ovary, prostate, testis, etc.), urinary system (e.g., bladder, kidney, ureter, etc.), eye, nervous system (e.g., brain, etc.), endocrine system (e.g., thyroid, etc.), and hematopoietic system (e.g., lymphoma, myeloma, leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, etc.).

Methods of modulating γδ T cells

According to a first aspect of the invention, there is provided an *ex vivo* method of modulating delta variable 1 chain (Vδ1) T cells comprising administering an anti-Vδ1 antibody or fragment thereof as defined herein to a cell population comprising Vδ1 T cells. It will be understood that 5 "administering" the antibody or fragment thereof includes "contacting" the Vδ1 T cells.

Modulation of Vδ1 T cells may include:

- expansion of the Vδ1 T cells, *e.g.* by selectively increasing the number of Vδ1 T cells or promotion of survival of Vδ1 T cells;
10 - stimulation of the Vδ1 T cells, *e.g.* by increasing Vδ1 T cell potency, *i.e.* increasing target cell killing;
- prevention of Vδ1 T cell exhaustion, *e.g.* by increasing persistence of the Vδ1 T cells;
- degranulation of Vδ1 T cells;
- immunosuppression of the Vδ1 T cells, *e.g.* by downregulation of Vδ1 TCR cell surface 15 expression, *i.e.* by causing Vδ1 TCR internalisation or reduced expression of Vδ1 TCR protein, or blocking the Vδ1 TCR from binding;
- reducing Vδ1 T cell number, *e.g.* by inhibition of Vδ1 T cell proliferation or by inducing Vδ1 T cell death (*i.e.* killing Vδ1 T cells).

20 Such modulation of Vδ1 T cells may include, for example, Vδ1 T cell activation or Vδ1 T cell inhibition. In one embodiment, the Vδ1 T cells are activated by administering an anti-Vδ1 antibody or fragment thereof as defined herein. In an alternative embodiment, the Vδ1 T cells are inhibited by administering an anti-Vδ1 antibody or fragment thereof as defined herein. In an alternative embodiment, the Vδ1 T cells are not inhibited upon administration of an anti-25 Vδ1 antibody or fragment thereof as defined herein to a patient.

In one embodiment, the modulation of Vδ1 T cells comprises administering an anti-TCR delta 1 variable antibody or fragment thereof to Vδ1 T cells in a culture (*i.e. in vitro* or *ex vivo*). The Vδ1 T cells may be present in a mixed cell population, *e.g.* in a cell population comprising 30 other lymphocyte cell types (*e.g.* αβ T cells or NK cells).

In one embodiment, the cell population comprising Vδ1 T cells is isolated (*i.e.* from a sample as described herein) prior to administration of the anti-Vδ1 antibody or fragment thereof. In a further embodiment, the cell population is enriched for T cells prior to administration of the 35 anti-Vδ1 antibody or fragment thereof. In a yet further embodiment, the cell population is enriched for γδ T cells prior to administration of the anti-Vδ1 antibody or fragment thereof.

The method may also be performed on a cell population comprising a purified fraction of γδ T cells. In such embodiments, the cell population is depleted of cells types other than γδ T cells present in the sample, such as αβ T cells and/or NK cells, prior to administration of the anti-Vδ1 antibody or fragment thereof. The cell population may additionally, or alternatively, be enriched of cells types which may contain Vδ1, such as T cells and/or γδ cells, prior to administration of the anti-Vδ1 antibody or fragment thereof. For example, prior to culturing the sample, the sample may be enriched for T cells, or enriched for γδ T cells, or depleted of αβ T cells or depleted of non-γδ T cells. In one embodiment, the sample is first depleted of αβ T cells and then enriched for CD3+ cells. Enrichment or depletion may be achieved using techniques known in the art, such as using magnetic beads coated with antibodies that bind to molecules on the cell surface relevant to the phenotype to be enriched/depleted.

The presence of cell types other than lymphocytes in cell culture, may inhibit Vδ1 cell expansion. Such cells, *e.g.* stromal, epithelial, tumour and/or feeder cells, may be removed prior to culture. Thus, in one embodiment, the cell population is not in direct contact with stromal cells during culture. Examples of stromal cells include fibroblasts, pericytes, mesenchymal cells, keratinocytes, endothelial cells and non-haematological tumour cells. Preferably, the lymphocytes are not in direct contact with fibroblasts during culture. In one embodiment, the cell population is not in direct contact with epithelial cells during culture. In one embodiment, the cell population is not in direct contact with tumour cells and/or feeder cells during culture.

In one embodiment, the method comprises culturing the Vδ1 T cells in the absence of substantial stromal cell contact. In a further embodiment, the method comprises culturing the Vδ1 T cells in the absence of substantial fibroblast cell contact.

In one embodiment, the method comprises culturing the Vδ1 T cells in media which is substantially free of serum (*e.g.* serum-free media or media containing a serum-replacement (SR)). Thus, in one embodiment, the method comprises culturing in serum-free media. Such serum free medium may also include serum replacement medium, where the serum replacement is based on chemically defined components to avoid the use of human or animal derived serum. In an alternative embodiment, the method comprises culturing in media which contains serum (*e.g.* human AB serum or fetal bovine serum (FBS)). In one embodiment, the media contains serum-replacement. In one embodiment, the media contains no animal-derived products.

It will be appreciated that a sample cultured in serum-free media has the advantage of avoiding issues with filtration, precipitation, contamination and supply of serum. Furthermore, animal derived products are not favoured for use in clinical grade manufacturing of human therapeutics. Use of serum-free media for the cells, particularly Vδ1 T cells, substantially increases the number of cells obtained from the sample compared to the use of media containing AB serum.

In one embodiment, the anti-Vδ1 antibody or fragment thereof is in a soluble or immobilized form. For example, the antibody or fragment thereof may be administered to the Vδ1 T cells in a soluble form. Alternatively, the antibody or fragment thereof may be administered to the Vδ1 T cells when the antibody or fragment thereof is bound or covalently linked to a surface, such as a bead or plate (*i.e.* in an immobilized form). In one embodiment, the antibody is immobilized on a surface, such as Fc-coated wells. Alternatively, the antibody or fragment thereof is bound to the surface of a cell (*e.g.* immobilized on the surface of an antigen presenting cell (APC)). In another embodiment, the antibody is not immobilized on a surface when the cell population is contacted with the antibody.

The cell population contacted by the anti-Vδ1 antibody or fragment thereof may be obtained from a variety of sample types (methods of isolation are further described below). In one embodiment, the sample is a non-haematopoietic tissue sample. References herein to "non-haematopoietic tissues" or "non-haematopoietic tissue sample" include skin (*e.g.* human skin) and gut (*e.g.* human gut). Non-haematopoietic tissue is a tissue other than blood, bone marrow, lymphoid tissue, lymph node tissue, or thymus tissue. In one embodiment, the non-haematopoietic tissue sample is skin (*e.g.* human skin). In some embodiments, the cell population (*e.g.* γδ T cells) is not obtained from particular types of samples of biological fluids, such as blood or synovial fluid. In some embodiments, the cell population (*e.g.* γδ T cells) is obtained from skin (*e.g.* human skin), which can be obtained by methods known in the art. For example, the cell population may be obtained from the non-haematopoietic tissue sample by culturing the non-haematopoietic tissue sample on a synthetic scaffold configured to facilitate cell egress from the non-haematopoietic tissue sample. Alternatively, the methods can be applied to a cell population (*e.g.* γδ T cells) obtained from the gastrointestinal tract (*e.g.* colon or gut), mammary gland, lung, prostate, liver, spleen, pancreas, uterus, vagina and other cutaneous, mucosal or serous membranes.

In an alternative embodiment, the sample is a haematopoietic sample or fraction thereof (*i.e.* the cell population is obtained from a haematopoietic sample or a fraction thereof). References herein to "haematopoietic sample" or "haematopoietic tissue sample" include blood (such as

peripheral blood or umbilical cord blood), bone marrow, lymphoid tissue, lymph node tissue, thymus tissue, and fractions or enriched portions thereof. The sample is preferably blood including peripheral blood or umbilical cord blood or fractions thereof, including buffy coat cells, leukapheresis products, peripheral blood mononuclear cells (PBMCs) and low density mononuclear cells (LDMCs). In some embodiments the sample is human blood or a fraction thereof. The cells may be obtained from a sample of blood using techniques known in the art such as density gradient centrifugation. For example, whole blood may be layered onto an equal volume of FICOLL-HYPAQUE followed by centrifugation at 400xg for 15-30 minutes at room temperature. The interface material will contain low density mononuclear cells which can be collected and washed in culture medium and centrifuged at 200xg for 10 minutes at room temperature.

The cell population may be obtained from a cancer tissue sample (*i.e.* the γδ T cells may also be resident in cancer tissue samples), *e.g.* tumours of the breast or prostate. In some embodiments, the cell population may be from human cancer tissue samples (*e.g.* solid tumour tissues). In other embodiments, the cell population may be from a sample other than human cancer tissue (*e.g.* a tissue without a substantial number of tumour cells). For example, the cell population may be from a region of skin (*e.g.* healthy skin) separate from a nearby or adjacent cancer tissue. Thus, in some embodiments, the cell population is not obtained from cancer tissue (*e.g.* human cancer tissue).

The cell population may be obtained from human or non-human animal tissue. Therefore, the method may additionally comprise a step of obtaining a cell population from human or non-human animal tissue. In one embodiment the sample has been obtained from a human. In an alternative embodiment, the sample has been obtained from a non-human animal subject.

Expansion of γδ T cells

In one embodiment, the modulation comprises activation of the Vδ1 T cells, in particular expansion of the Vδ1 T cells. Therefore, according to an aspect of the invention, there is provided an *ex vivo* method of expanding Vδ1 T cells comprising administering an anti-Vδ1 antibody or fragment thereof as defined herein to a cell population comprising Vδ1 T cells. Such expansion of Vδ1 T cells may be achieved through the selective increase in number of Vδ1 T cells and/or through the promotion of survival of Vδ1 T cells. In one embodiment, the expansion of Vδ1 T cells comprises administering an anti-TCR delta 1 variable antibody or fragment thereof to Vδ1 T cells in a culture (*i.e. in vitro* or *ex vivo*). The Vδ1 T cells may be

present in a mixed cell population, *e.g.* in a cell population comprising other lymphocyte cell types (*e.g.* αβ T cells or NK cells).

The invention therefore provides *ex vivo* methods for producing an enriched γδ T cell (*e.g.* Vδ1 T cell) population. The enriched population can be produced from an isolated mixed cell populations (*e.g.* obtained from samples taken from patients/donors) by a method comprising contacting the mixed cell population, or a purified fraction thereof, with the antibody or fragment thereof. Said antibody (or fragment thereof) selectively expands Vδ1 T cells by binding to an epitope specific to a Vδ1 chain of a γδ TCR.

Also provided is an expanded Vδ1 T cell population obtained according to the method as defined herein. According to this aspect of the invention, it will be appreciated that such an expanded population of Vδ1 T cells may be obtained and/or expanded *in vitro* or *ex vivo*. In one aspect, there is provided an expanded Vδ1 population obtained according to the method as defined herein, wherein the Vδ1 population is isolated and expanded *in vitro* or *ex vivo*.

Antibodies or fragments thereof as described herein may be used in methods of expanding γδ T cells (*e.g.* Vδ1 T cells). These methods may be carried out *in vitro.* If the expansion methods are carried out *in vitro*, the antibodies (or fragments thereof) may be applied to isolated γδ T cells (*e.g.* Vδ1 T cells) obtained as described above. In some embodiments, the γδ T cells are expanded from a cell population that has been isolated from a non-haematopoietic tissue sample. In an alternative embodiment, the γδ T cells are expanded from a cell population that has been isolated from a haematopoietic tissue sample, such as a blood sample.

Expansion of γδ T cells (*e.g.* Vδ1 T cells) may comprise culturing the sample in the presence of the antibody or fragment thereof as described herein, and a cytokine. Cytokines may include interleukins, lymphokines, interferons, colony stimulating factors and chemokines. In one embodiment, the cytokine is selected from the group consisting of interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-12 (IL-12), interleukin-18 (IL-18), interleukin-21 (IL-21), interleukin-33 (IL-33), insulin-like growth factor 1 (IGF-1), interleukin-1β (IL-1β), interferon-γ (IFN-γ) and stromal cell-derived factor-1 (SDF-1). It will be understood that references to the cytokines as described herein, may include any compound that has the same activity as said cytokine with respect to its ability to promote similar physiological effects on Vδ1 T cells in culture and includes, but is not limited to, mimetics, or any functional equivalent thereof.

In one embodiment, said cytokine is a common cytokine receptor gamma-chain (γ_c) family of cytokines. In a further embodiment, the γ_c-cytokine is selected from: IL-2, IL 4, IL-7, IL-9, IL-12, IL-15, IL-21 or mixtures thereof.

5 The cytokine (*e.g.* an interleukin) used may be of human or animal origin, preferably of human origin. It may be a wild-type protein or any biologically active fragment or variant, that is, to say, capable of binding its receptor. Such binding may induce activation of γδ T cells in the conditions of a method according to the invention. More preferably, the cytokines may be in soluble form, fused or complexed with another molecule, such as for example a peptide,
10 polypeptide or biologically active protein. Preferably, a human recombinant cytokine is used. More preferably, the range of interleukin concentration could vary between 1-10000 U/ml, even more preferably between 100-1000 U/ml.

In a further embodiment, the cytokine is a chemokine. It will be further appreciated that the
15 chemokine will vary and be selected depending on the sample used to obtain the γδ T cells.

In one embodiment, the method comprises culturing the cell population in the presence of IL-2, IL-9 and/or IL-15. In a further embodiment, the method comprises culturing the cell population in the presence of IL-2 and/or IL-15 (*i.e.* IL-2, IL-15 or a combination thereof). In an
20 alternative embodiment, the method comprises culturing the cell population in the presence of IL-9 and/or IL-15 (*i.e.* IL-9, IL-15 or a combination thereof). In one embodiment, the method comprises the cell population in the presence of IL-2, IL-9 and/or IL-15, and an additional growth factor (for example, IL-21). In other embodiments, the method comprises culturing a cell population in a medium devoid of growth factors other than IL-2 and/or IL-15. In alternative
25 embodiments, the method comprises culturing a cell population in a medium devoid of growth factors other than IL-9 and/or IL-15. In a further embodiment, the method comprises culturing a cell population in a medium which consists of a basal medium supplemented with IL-2, IL-9 and/or IL-15. In a further embodiment, the method comprises culturing a cell population in a medium which consists of a basal medium supplemented with IL-2 and/or IL-15.

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In one embodiment, the method comprises culturing the cell population in the presence of IL-21.

In one embodiment, the method comprises culturing the cell population in the presence of
35 IL-4. The physiological effects promoted by IL-4 on Vδ1 T cells (as described in WO2016/198480), include the decrease of NKG2D and NCR expression levels, the inhibition of cytotoxic function and improved selective survival. Furthermore, it has previously been

shown that the absence of IL-4 during the later days of culture can change the physiological properties of the cells towards a more appropriate phenotype for use as an anti-tumour or anti-viral treatment. Therefore, in one embodiment, the method of expansion comprises further culturing the sample in the absence of growth factors having IL-4-like activity, such as IL-4. In 5 one embodiment, the method of expansion comprises culturing the sample in the absence of IL-4.

In one embodiment, the cytokine is a growth factor having interleukin-15-like activity, *i.e.* any compound that has the same activity as IL-15 with respect to its ability to promote similar 10 physiological effects on Vδ1 T cells in culture and includes, but is not limited to, IL-15 and IL-15 mimetics, or any functional equivalent of IL-15, including IL-2 and IL-7. The physiological effects promoted by IL-15, IL-2 and IL-7 on cultured Vδ1 T cells (as described in WO2016/198480) were essentially equivalent, namely, the induction of cell differentiation towards a more cytotoxic phenotype. Furthermore, it has previously been shown that the 15 absence of IL-2, IL-7 and IL-15 during the initial days of culture contributed to the starvation and apoptosis of contaminant cells (including TCRαβ+ T and Vδ2+ T cells), which critically depend on these cytokines for survival. Therefore, in one embodiment, the method of expansion comprises first culturing the sample in the absence of growth factors having IL-15-like activity.

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Thus, in one embodiment, the method comprises culturing the cell population in a first culture medium comprising IL-4 and then culturing the cell population in a second culture medium comprising IL-15.

25 In one embodiment, the first culture medium is in the absence of IL-15, IL-2 and/or IL-7. In one embodiment, the second culture medium is in the absence of IL-4.

Thus, in one embodiment, the method of expansion comprises:

(1) culturing cells in the sample in a first culture medium comprising an antibody or 30 fragment thereof as described herein and IL-4; in the absence of IL-15, IL-2 and IL-7; and

(2) culturing the cells obtained in step (1) in a second culture medium comprising an antibody or fragment thereof as described herein and IL-15, in the absence of IL-4.

As described herein, the culture media, may also contain other growth factors, including 35 cytokines that can further enhance the expansion of Vδ1 T cells. Examples of such cytokines include, but are not limited to: (i) IFN-γ and any growth factor having IFN-γ-like activity, (ii) IL-21 and any growth factor having IL-21-like activity and (iii) IL-1β and any growth factor

having IL-1β-like activity. Examples of other growth factors that can be added include co-stimulatory molecules such as a human anti-SLAM antibody, any soluble ligand of CD27, or any soluble ligand of CD7. Any combination of these growth factors can be included in the media.

In one embodiment, the first or second culture medium, or both culture media, comprises one or more additional cytokines. The first and/or second culture medium may comprise a second, a third and/or a fourth cytokine. In a further embodiment, the additional cytokines are selected from IL-21, IFN-γ and IL-1β.

In one embodiment, the method comprises culturing the cell population in the presence of IL-15 and a factor selected from the group consisting of IL-2, IL-4, IL-21, IL-6, IL-7, IL-8, IL-9, IL-12, IL-18, IL-33, IGF-1, IL-1β, IFN-γ, human platelet lysate (HPL), and stromal cell-derived factor-1 (SDF-1).

Expansion of γδ T cells may comprise culturing the sample in the presence of at least one further T cell mitogen. The term “a T cell mitogen” (which may also be referred to as “a γδ TCR agonist”) means any agent that can stimulate T cells through TCR signalling including, but not limited to, plant lectins such as phytohemagglutinin (PHA) and concanavalin A (ConA) and lectins of non-plant origin. In one embodiment, the T cell mitogen is an anti-CD3 monoclonal antibody (mAb). Other mitogens include phorbol 12-myristate-13-acetate (TPA) and its related compounds, such as mezerein, or bacterial compounds (*e.g.* Staphylococcal enterotoxin A (SEA) and Streptococcal protein A). The T cell mitogen may be soluble or immobilized and more than one T cell mitogen may be used in the method of expansion.

As used herein, references to “expanded” or “expanded population of γδ T cells” includes populations of cells which are larger or contain a larger number of cells than a non-expanded population. Such populations may be large in number, small in number or a mixed population with the expansion of a proportion or particular cell type within the population. It will be appreciated that the term “expansion method” refers to processes which result in expansion or an expanded population. Thus, expansion or an expanded population may be larger in number or contain a larger number of cells compared to a population which has not had an expansion step performed or prior to any expansion step. It will be further appreciated that any numbers indicated herein to indicate expansion (*e.g.* fold-increase or fold-expansion) are illustrative of an increase in the number or size of a population of cells or the number of cells and are indicative of the amount of expansion.

In one embodiment, the method comprises culturing the cell population for at least 5 days (*e.g.* at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, at least 18 days, at least 21 days, at least 28 days, or longer, *e.g.* from 5 days to 40 days, from 7 days to 35 days, from 14 days to 28 days, or about 21 days). In a further embodiment, the method comprises culturing the cell population for at least 7 days, such as at least 11 days or at least 14 days.

In further embodiments, method comprises culturing the cell population for a duration (*e.g.* at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, at least 18 days, at least 21 days, at least 28 days, or longer, *e.g.* from 5 days to 40 days, from 7 days to 35 days, from 14 days to 28 days, or about 21 days) in an amount effective to produce an expanded population of γδ T cells.

In one embodiment, the cell population is cultured for a period of 5 to 60 days, such as at least 7 to 45 days, 7 to 21 days, or 7 to 18 days. If the method includes an isolation culture period (*e.g.* of 1 to 40 days, such as 14 to 21 days), the isolation and expansion steps, in some embodiments, can last between 21 and 39 days.

The method may comprise regular addition of the anti-Vδ1 antibody or fragment thereof and/or growth factor during culturing. For example, the anti-Vδ1 antibody or fragment thereof and/or growth factor could be added every 2 to 5 days, more preferably every 3 to 4 days. In one embodiment, the anti-Vδ1 antibody or fragment thereof and/or growth factor is added after 7 days of culture and every 3 to 4 days thereafter.

Methods of expansion provide an expanded population of γδ T cells that is greater in number than a reference population. In some embodiments, the expanded population of γδ T cells (*e.g.* Vδ1 T cells) is greater in number than the isolated population of γδ T cells prior to the expansion step (*e.g.* at least 2-fold in number, at least 5-fold in number, at least 10-fold in number, at least 25-fold in number, at least 50-fold in number, at least 60-fold in number, at least 70-fold in number, at least 80-fold in number, at least 90-fold in number, at least 100-fold in number, at least 200-fold in number, at least 300-fold in number, at least 400-fold in number, at least 500-fold in number, at 600-fold in number, at least 1,000-fold in number, or more relative to the isolated population of γδ T cells prior to the expansion step). In one embodiment, the expanded population of γδ T cells (*e.g.* Vδ1 T cells) is greater in number than a population cultured for the same length of time without the presence of the antibody or fragment thereof. In one embodiment, the expanded population of γδ T cells (*e.g.* Vδ1 T cells) is greater in

number than a population cultured for the same length of time in the presence of TS8.2 or TS-1.

Methods of expansion provide an expanded population of Vδ1 T cells that has a higher percentage of Vδ1 T cells than a reference population. In some embodiments, the expanded population of Vδ1 T cells contains greater than about 50% Vδ1 T cells, such as greater than about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 87%, 90%, 91%, 92%, 93%, 94% or 95% vδ1 T cells. In a further embodiment, the expanded population of Vδ1 T cells contains greater than about 85% Vδ1 T cells, such as greater than about 90% Vδ1 T cells.

In some embodiments, the expanded population of γδ T cells (*e.g.* Vδ1 T cells) contains less than about 10% αβ T cells, such as less than about 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, 0.2%, 0.1% or 0.05% αβ T cells. In a further embodiment, the expanded population of Vδ1 T cells contains less than about 1% αβ T cells. T cells with αβ receptors are highly reactive, therefore suitable cell populations for administration to patients in the context of the present invention can only contain low levels of αβ T cells. The antibodies described herein may be used to selectively expand the Vδ1 T cell population which reduces the need for extensive purification methods after expansion in order to remove αβ T cells.

In some embodiments, the expanded population of γδ T cells (*e.g.* Vδ1 T cells) contains less than about 10% Vδ2 T cells, such as less than about 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, 0.2%, 0.1% or 0.05% Vδ2 T cells. In a further embodiment, the expanded population of Vδ1 T cells contains less than about 0.5% Vδ2 T cells.

In some embodiments, the expanded population of γδ T cells (*e.g.* Vδ1 T cells) contains less than about 10% Natural Killer (NK) cells (also referred to as CD56+CD3- cells), such as less than about 5%, 4%, 3%, 2.5%, 2%, 1.5% or 1% NK cells. In a further embodiment, the expanded population of Vδ1 T cells contains less than about 2% NK cells.

An increase or decrease in expression of cell surface markers can be additionally or alternatively used to characterize one or more expanded populations of Vδ1 T cells, including CD27, CD69, TIGIT, PD-1 and TIM-3. In some embodiments, the expanded population of Vδ1 T cells expresses a high level of CD27 ($CD27^{high}$). For example, more than about 70%, such as more than about 80%, 85%, 90% of the expanded population of Vδ1 T cells expresses CD27 (*i.e.* CD27+). In some embodiments, the expanded population of Vδ1 T cells has a greater mean expression of CD27, relative to the isolated population of Vδ1 T cells, *e.g.* prior to expansion. In some embodiments, the expanded population of Vδ1 T cells expresses a low

level of CD69, TIGIT, PD-1 and/or TIM-3. For example, less than about 40%, such as less than about 30% of the expanded population of Vδ1 T cells expresses CD69, TIGIT, PD-1 and/or TIM-3. In some embodiments, the expanded population of Vδ1 T cells has a lower mean expression of one or more of the markers selected from the group consisting of CD69, TIGIT, PD-1 and TIM-3, relative to the isolated population of Vδ1 T cells.

Numerous basal culture media suitable for use in the proliferation of γδ T cells are available, in particular medium, such as AIM-V, Iscoves medium and RPMI-1640 (Life Technologies), EXVIVO-10, EXVIVO-15 or EXVIVO-20 (Lonza), in the presence of serum or plasma. The medium may be supplemented with other media factors as defined herein, such as serum, serum proteins and selective agents, such as antibiotics. For example, in some embodiments, RPMI-1640 medium containing 2 mM glutamine, 10% FBS, 10 mM HEPES, pH 7.2, 1% penicillin-streptomycin, sodium pyruvate (1 mM; Life Technologies), non-essential amino acids (*e.g.* 100 µM Gly, Ala, Asn, Asp, Glu, Pro and Ser; 1X MEM non-essential amino acids (Life Technologies)), and 10 µl/L β-mercaptoethanol. In an alternative embodiment, AIM-V medium may be supplemented with CTS Immune serum replacement and amphotericin B. In certain embodiments, the media may be further supplemented with IL-2, IL-4, IL-9 and/or IL-15 as described herein. Conveniently, cells are cultured at 37°C in a humidified atmosphere containing 5% CO_2 in a suitable culture medium during isolation and/or expansion.

Addition of other factors in the expansion culture of γδ T cells may also be used. In one embodiment, such factors are used in the expansion which selectively promote the expansion of γδ T cells. For example, expansion may additionally comprise addition of exogenous cytokines to the expansion culture, such as interleukins. Such expansion may comprise culturing the γδ T cells in the presence of IL-2 and IL-15. Alternatively, expansion may comprise culturing the γδ T cells in the presence of IL-9 and IL-15. It will be appreciated that any expansion step is performed for a duration of time effective to produce an expanded population of γδ T cells.

Methods of expanding γδ T cells may comprise a population doubling time of less than 5 days (*e.g.* less than 4.5 days, less than 4.0 days, less than 3.9 days, less than 3.8 days, less than 3.7 days, less than 3.6 days, less than 3.5 days, less than 3.4 days, less than 3.3 days, less than 3.2 days, less than 3.1 days, less than 3.0 days, less than 2.9 days, less than 2.8 days, less than 2.7 days, less than 2.6 days, less than 2.5 days, less than 2.4 days, less than 2.3 days, less than 2.2 days, less than 2.1 days, less than 2.0 days, less than 46 hours, less than 42 hours, less than 38 hours, less than 35 hours, less than 32 hours).

Methods of isolating γδ T cells

As described herein, antibodies (or fragments thereof) may be applied to γδ T cells in culture, *i.e.* γδ T cells, which have been obtained from a sample. In one embodiment, the cell population is isolated from a sample prior to administering the anti-Vδ1 antibody or fragment thereof. Therefore, there is provided a method of modulating (in particular, expanding) Vδ1 T cells comprising administering an anti-Vδ1 antibody or fragment thereof as defined herein to a population of γδ T cells (*e.g.* a cell population comprising Vδ1 T cells) isolated from a sample.

γδ T cells that are dominant in non-haematopoietic tissues (*i.e.* are tissue-resident) primarily contain the delta variable 1 chain, therefore anti-Vδ1 antibodies described herein find particular use in γδ T cells isolated from non-haematopoietic tissues. Thus, in one embodiment, the sample is a non-haematopoietic tissue sample, such as skin. Alternatively, methods of the invention may be used to expand the population of Vδ1 T cells in a sample which does not primarily contain the Vδ1 chain, *e.g.* a blood sample. Therefore, the method may be used to increase the number of Vδ1 T cells in a sample.

References herein to “isolation” or “isolating” of cells, in particular of γδ T cells, refer to methods or processes wherein cells are removed, separated, purified, enriched or otherwise taken out from a tissue or a pool of cells. It will be appreciated that such references include the terms “separated”, “removed”, “purified”, “enriched” and the like. Isolation of γδ T cells includes the isolation or separation of cells from an intact non-haematopoietic tissue sample or from the stromal cells of the non-haematopoietic tissue (*e.g.* fibroblasts or epithelial cells). Such isolation may alternatively or additionally comprise the isolation or separation of γδ T cells from other haematopoietic cells (*e.g.* αβ T cells or other lymphocytes). Isolation may be for a defined period of time, for example starting from the time the tissue explant or biopsy is placed in the isolation culture and ending when the cells are collected from culture, such as by centrifugation or other means for transferring the isolated cell population to expansion culture or used for other purposes, or the original tissue explant or biopsy is removed from the culture. The isolation step may be for at least about 3 days to about 45 days. In one embodiment, the isolation step is for at least about 10 days to at least 28 days. In a further embodiment, the isolation step is for at least 14 days to at least 21 days. The isolation step may therefore be for at least 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days, 31 days, 32 days, about 35 days, about 40 days, or about 45 days. It can be appreciated that although cell proliferation may not be substantial during this isolation step, it is not necessarily

absent. Indeed for someone skilled in the art it is recognized that isolated cells may also start to divide to generate a plurality of such cells within the isolation vessel containing the sample.

Thus, references herein to “isolated γδ T cells”, “isolated γδ T cell population” or “isolated population of γδ T cells” will be appreciated to refer to γδ cells that have been isolated, separated, removed, purified or enriched from the sample, such as a non-haematopoietic tissue sample of origin, such that the cells are out of substantial contact with cells contained within the intact (non-haematopoietic tissue) sample. References herein to “isolated Vδ1 T cells”, “isolated Vδ1 T cell population”, “isolated population of Vδ1 T cells”, “separated Vδ1 T cells”, “separated Vδ1 T cell population” or “separated population of Vδ1 T cells” will be appreciated to refer to Vδ1 T cells that have been isolated, separated, removed, purified or enriched from the sample, such as a non-haematopoietic tissue sample of origin, such that the cells are out of substantial contact with cells contained within the intact (non-haematopoietic tissue) sample.

The cell population may be obtained by any suitable method that allows isolation of lymphocytes, in particular Vδ1 T cells, from human or non-human animal samples, such as a non-haematopoietic tissue sample. One such method is set out in Clark *et al.* (2006) *J. Invest. Dermatol.* 126(5): 1059-70, which describes a three-dimensional skin explant protocol for isolating lymphocytes from human skin. An explant may be adhered to a synthetic scaffold to facilitate lymphocyte egress from the explant onto the scaffold. A synthetic scaffold refers to a non-native three-dimensional structure suitable to support cell growth. Synthetic scaffolds may be constructed from materials such as polymers (*e.g.* natural or synthetic polymers, e.g. poly vinyl pyrolidones, polymethylmethacrylate, methyl cellulose, polystyrene, polypropylene, polyurethane), ceramics (*e.g.* tricalcium phosphate, calcium aluminate, calcium hydroxyapatite), or metals (tantalum, titanium, platinum and metals in the same element group as platinum, niobium, hafnium, tungsten, and combinations of alloys thereof). Biological factors (*e.g.* collagens (*e.g.* collagen I or collagen II), fibronectins, laminins, integrins, angiogenic factors, anti-inflammatory factors, glycosaminoglycans, vitrogens, antibodies and fragments thereof, cytokines (*e.g.* IL-2 or IL-15, and combinations thereof) may be coated onto the scaffold surface or encapsulated within the scaffold material to enhance cell adhesion, migration, survival, or proliferation, according to methods known in the art. This and other methods can be used to isolate a cell population from a number of other non-haematopoietic tissue types, *e.g.* gut, prostate and breast. Other examples of suitable methods of isolation utilise “crawl-out” methods which may include the culturing of the cell population and/or sample in the presence of cytokines and/or chemokines sufficient to induce the isolation or separation of γδ T cells, in particular Vδ1 T cells. Isolation of γδ T cells from the sample (*e.g.* non-

haematopoietic tissue sample) may comprise culturing the sample in the presence of IL-2 and IL-15.

5 Non-haematopoietic tissue resident lymphocytes can be harvested and separated from stromal cells, such as dermal fibroblasts, *e.g.* by firm pipetting. The lymphocyte harvest may further be washed through a 40μm nylon mesh in order to retain fibroblast aggregates that may have become loose during the process. Lymphocytes may also be isolated using fluorescent or magnetic associated cell sorting using, for example, CD45 antibodies.

10 Alternatively, isolation of γδ T cells from the sample (*e.g.* a haematopoietic tissue sample) may comprise culturing the sample in the presence of a T cell mitogen (*e.g.* a γδ TCR agonist) and a cytokine (in particular a common cytokine receptor gamma-chain (γ_c) family of cytokines), as described in WO2012/156958. As another alternative, isolation of γδ T cells from the sample (*e.g.* a haematopoietic tissue sample) may comprise culturing the sample in
15 the presence of a T cell mitogen and a cytokine as described in WO2016/198480.

Isolation of γδ T cells may comprise culturing the sample in the presence of at least one cytokine. For example, the method may comprise culturing the sample in the presence of at least agent, such as a chemokine. It will be further appreciated that chemokines will be
20 selected depending on the γδ T cells being isolated. Furthermore, the chemokines will vary and be selected depending on the sample used for isolation of the γδ T cells.

Isolation of γδ T cells may comprise further culturing the sample in the presence of at least one cytokine. Said cytokine may be different to the cytokine used in the initial culture.

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Isolation methods may comprise culturing the sample. References herein to “culturing” include the addition of the sample, including isolated, separated, removed, purified or enriched cells from the sample, to media comprising growth factors and/or essential nutrients required and/or preferred by the cells and/or sample. It will be appreciated that such culture conditions may
30 be adapted according to the cells or cell population to be isolated from the sample or may be adapted according to the cells or cell population to be isolated and expanded from the sample.

In certain embodiments, culturing of the sample is for a duration of time sufficient for the isolation of γδ T cells from the sample. In certain embodiments, the duration of culture is at
35 least 14 days. In certain embodiments, the duration of culture is less than 45 days, such as less than 30 days, such as less than 25 days. In a further embodiment, the duration of culture

is between 14 days and 35 days, such as between 14 days and 21 days. In a yet further embodiment, the duration of culture is about 21 days.

In particular embodiments, the γδ T are collected from the culture after culturing of the sample. Collection of the γδ T cells may include the physical collection of γδ T cells from the culture, isolation of the γδ T cells from other lymphocytes (*e.g.* αβ T cells and/or NK cells) or isolation and/or separation of the γδ T cells from other cells present in the sample, *e.g.* stromal cells such as fibroblasts. In one embodiment, γδ T cells are collected by mechanical means (*e.g.* pipetting). In a further embodiment, γδ T cells are collected by means of magnetic separation and/or labelling. In a yet further embodiment, the γδ T cells are collected by flow cytometric techniques such as FACS. Thus, in certain embodiments, the γδ T cells are collected by means of specific labelling the γδ T cells. It will be appreciated that such collection of γδ T cells may include the physical removal from the culture of the sample, transfer to a separate culture vessel or to separate or different culture conditions.

It will be appreciated that such collecting of γδ T cells is performed after a duration of time sufficient to achieve an isolated population of γδ T cells from the sample. In certain embodiments, the γδ T cells are collected after at least one week, at least 10 days, at least 11 days, at least 12 days, at least 13 days or at least 14 days of culturing of the sample. Suitably, the γδ T cells are collected after 40 days or less, such as 38 days or less, 36 days or less, 34 days or less, 32 days or less, 30 days or less, 28 days or less, 26 days or less or 24 days or less. In one embodiment, the γδ T cells are collected after at least 14 days of culturing of the sample. In a further embodiment, the γδ T cells are collected after 14 to 21 days of culturing of the sample.

In one embodiment, the sample is cultured in media which is substantially free of serum (*e.g.* serum-free media or media containing a serum-replacement (SR)). Thus, in one embodiment, the sample is cultured in serum-free media. Such serum free medium may also include serum replacement medium, where the serum replacement is based on chemically defined components to avoid the use of human or animal derived serum. In one embodiment, the media contains no animal-derived products. In an alternative embodiment, the sample is cultured in media which contains serum (*e.g.* human AB serum or fetal bovine serum (FBS)).

Culture media may additionally include other ingredients that can assist in the growth and expansion of the γδ T cells. Examples of other ingredients that may be added, include, but are not limited to, plasma or serum, purified proteins such as albumin, a lipid source such as low

density lipoprotein (LDL), vitamins, amino acids, steroids and any other supplements supporting or promoting cell growth and/or survival.

γδ T cells that are dominant in the blood are primarily Vδ2 T cells, while the γδ T cells that are dominant in the non-haematopoietic tissues are primarily Vδ1 T cells, such that Vδ1 T cells comprise about 70-80% of the non-haematopoietic tissue-resident γδ T cell population. In one preferred embodiment, the isolated γδ T cells comprise a population of Vδ1 T cells.

Antibodies or fragments thereof

Provided herein are antibodies or fragments thereof capable of specifically binding to the delta variable 1 chain (Vδ1) of a γδ T Cell Receptor (TCR).

In one embodiment, the antibody or fragment thereof is an scFv, Fab, Fab', F(ab')2, Fv, variable domain (*e.g.* VH or VL), diabody, minibody or monoclonal antibody. In a further embodiment, the antibody or fragment thereof is an scFv.

Antibodies described herein can be of any class, *e.g.* IgG, IgA, IgM, IgE, IgD, or isotypes thereof, and can comprise a kappa or lambda light chain. In one embodiment, the antibody is an IgG antibody, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. In a further embodiment, the antibody may be in a format, such as an IgG format, that has been modified to confer desired properties, such as having the Fc mutated to reduce effector function, extend half life, alter ADCC, or improve hinge stability. Such modifications are well known in the art.

In one embodiment, the antibody or fragment thereof is human. Thus, the antibody or fragment thereof may be derived from a human immunoglobulin (Ig) sequence. The CDR, framework and/or constant region of the antibody (or fragment thereof) may be derived from a human Ig sequence, in particular a human IgG sequence. The CDR, framework and/or constant region may be substantially identical for a human Ig sequence, in particular a human IgG sequence. An advantage of using human antibodies is that they are low or non-immunogenic in humans.

An antibody or fragment thereof can also be chimeric, for example a mouse-human antibody chimera.

Alternatively, the antibody or fragment thereof is derived from a non-human species, such as a mouse. Such non-human antibodies can be modified to increase their similarity to antibody variants produced naturally in humans, thus the antibody or fragment thereof can be partially

or fully humanised. Therefore, in one embodiment, the antibody or fragment thereof is humanised.

Antibodies targeted to epitopes

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Provided herein are antibodies (or fragments thereof) which bind to an epitope of the Vδ1 chain of a γδ TCR. Such binding may optionally have an effect on γδ TCR activity, such as activation or inhibition.

10 In one embodiment, the epitope may be an activating epitope of a γδ T cell. An "activating" epitope can include, for example, stimulating a TCR function, such as degranulation, TCR downregulation, cytotoxicity, proliferation, mobilisation, increased survival or resistance to exhaustion, intracellular signaling, cytokine or growth factor secretion, phenotypic change, or a change in gene expression. For example, the binding of the activating epitope may stimulate 15 expansion (*i.e.* proliferation) of the γδ T cell population, preferably the Vδ1+ T cell population. Accordingly, these antibodies can be used to modulate γδ T cell activation, and, thereby, to modulate the immune response. Therefore, in one embodiment, binding of the activating epitope downregulates the γδ TCR. In an additional or alternative embodiment, binding of the activating epitope activates degranulation of the γδ T cell. In a further additional or alternative 20 embodiment, binding of the activating epitope activates γδ T cell killing.

Alternatively, the antibodies (or fragments thereof) may have a blocking effect by prevention of the binding or interaction of another antibody or molecule. In one embodiment, the present invention provides isolated antibodies or fragments thereof that block Vδ1 and prevent TCR 25 binding (*e.g.* through steric hinderance). By blocking Vδ1, the antibody may prevent TCR activation and/or signalling. The epitope may be an inhibitory epitope of a γδ T cell. An "inhibitory" epitope can include, for example, blocking TCR function, thereby inhibiting TCR activation.

30 The epitope is preferably comprised of at least one extracellular, soluble, hydrophillic, external or cytoplasmic portion of the Vδ1 chain of a γδ TCR.

In particular, the epitope does not comprise an epitope found in a hypervariable region of the Vδ1 chain of the γδ TCR, in particular CDR3 of the Vδ1 chain. In a preferred embodiment, the 35 epitope is within the non-variable region of the Vδ1 chain of the γδ TCR. It will be appreciated that such binding allows for the unique recognition of the Vδ1 chain without the restriction to the sequences of the TCR which are highly variable (in particular CDR3). Various γδ TCR

complexes which recognise MHC-like peptides or antigen may be recognised in this way, solely by presence of the Vδ1 chain. As such, it will be appreciated that any Vδ1 chain-comprising γδ TCR may be recognised using the antibodies or fragments thereof as defined herein, irrespective of the specificity of the γδ TCR. In one embodiment, the epitope comprises one or more amino acid residues within amino acid regions 1-24 and/or 35-90 of SEQ ID NO: 1, *e.g.* the portions of the Vδ1 chain which are not part of the CDR1 and/or CDR3 sequences. In one embodiment, the epitope does not comprise amino acid residues within amino acid region 91-105 (CDR3) of SEQ ID NO: 1.

In a similar manner to the well characterised αβ T cells, γδ T cells utilize a distinct set of somatically rearranged variable (V), diversity (D), joining (J), and constant (C) genes, although γδ T cells contain fewer V, D, and J segments than αβ T cells. In one embodiment, the epitope bound by the antibodies (or fragments thereof) does not comprise an epitope found in the J region of the Vδ1 chain (e.g. one of the four J regions encoded in the human delta one chain germline: SEQ ID NO: 131 (J1*0) or 132 (J2*0) or 133 (J3*0) or 134 (J4*0)). In one embodiment, the epitope bound by the antibodies (or fragments thereof) does not comprise an epitope found in the C-region of the Vδ1 chain (e.g. SEQ ID NO: 135 (C1*0) which contains the C-terminal juxtamembrane/transmembrane regions). In one embodiment, the epitope bound by the antibodies (or fragments thereof) does not comprise an epitope found in the N-terminal leader sequence of the Vδ1 chain (e.g. SEQ ID NO:129). The antibody or fragment may therefore only bind in the V region of the Vδ1 chain (e.g. SEQ ID NO: 130). Thus, in one embodiment, the epitope consists of an epitope in the V region of the γδ TCR (*e.g.* amino acid residues 1-90 of SEQ ID NO: 1).

Reference to the epitope are made in relation to the Vδ1 sequence derived from the sequence described in Luoma *et al.* (2013) *Immunity* 39: 1032-1042, and RCSB Protein Data Bank entries: 4MNH and 3OMZ, shown as SEQ ID NO: 1:

AQKVTQAQSSVSMPVRKAVTLNCLYETSWWSYYIFWYKQLPSKEMIFLIRQGSDEQNAKS
GRYSVNFKKAAKSVALTISALQLEDSAKYFCALGESLTRADKLIFGKGTRVTVEPNIQNPDPA
VYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNK
SDFACANAFNNSIIPEDTFFPSPESS (SEQ ID NO: 1)

SEQ ID NO: 1 represents a soluble TCR comprising a V region (also referred to as the variable domain), a D region, a J region and a TCR constant region. The V region comprises amino acid residues 1-90, the D region comprises amino acid residues 91-104, the J region comprises amino acid residues 105-115 and the constant region comprises amino acid

residues 116-209. Within the V region, CDR1 is defined as amino acid residues 25-34 of SEQ ID NO: 1, CDR2 is defined as amino acid residues 50-54 of SEQ ID NO: 1, and CDR3 is defined as amino acid residues 93-104 of SEQ ID NO: 1 (Xu et al., PNAS USA 108(6):2414-2419 (2011)).

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Therefore, in one embodiment, the isolated antibody or fragment thereof binds to an epitope of a variable delta 1 (Vδ1) chain of a γδ T cell receptor (TCR) comprising one or more amino acid residues within amino acid regions:

(i) 3-20 of SEQ ID NO: 1; and/or

10 (ii) 37-77 of SEQ ID NO: 1.

In a further embodiment, antibodies or fragments thereof additionally recognize the polymorphic V region comprising amino acid residues 1-90 epitope of SEQ ID NO:128. Hence, amino acids 1-90 of SEQ ID NO:1 and the polymorphic germline variant sequence (amino

15 acids 1-90 SEQ ID NO:128) may be considered interchangeable when defining epitopes described herein. Antibodies of the invention can recognize both variants of this germline sequence. By way of example, where it is stated that antibodies or fragments thereof as defined herein recognize epitopes comprising one or more amino acid residues within amino acid regions 1-24 and/or 35-90 of SEQ ID NO:1 this also refers to the same regions of SEQ

20 ID NO:128; specifically amino acid regions 1-24 and/or 35-90 of SEQ ID NO:128.

In one embodiment, antibodies or fragments thereof recognize one or more amino acid residues within amino acid regions 1-90 of SEQ ID NO:1 and the equivalently located amino acids of regions 1-90 in SEQ ID NO:128. More specifically, in one embodiment antibodies or

25 fragments thereof as defined herein recognize a human germline epitope wherein said germline encodes either an alanine (A) or valine (V) at position 71 of SEQ ID NO:1.

In one embodiment, the epitope comprises one or more, such as two, three, four, five, six, seven, eight, nine, ten or more amino acid residues within the described regions.

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In a further embodiment, the epitope comprises one or more (such as 5 or more, such as 10 or more) amino acid residues within amino acid region 3-20 of SEQ ID NO: 1. In an alternative embodiment, the epitope comprises one or more (such as 5 or more, such as 10 or more) amino acid residues within amino acid region 37-77 of SEQ ID NO: 1 (such as amino acid

35 region 50-54). In a yet further embodiment, the epitope comprises one or more (such as 5 or more, such as 10 or more) amino acid residues within amino acid region 3-20 (such as 5-20

or 3-17) and one or more (such as 5 or more, such as 10 or more) amino acid residues within amino acid region 37-77 (such as 62-77 or 62-69) of SEQ ID NO: 1.

It will be further understood that said antibody (or fragment thereof) does not need to bind to all amino acids within the defined range. Such epitopes may be referred to as linear epitopes. For example, an antibody which binds to an epitope comprising amino acid residues within amino acid region 5-20 of SEQ ID NO: 1, may only bind with one or more of the amino acid residues in said range, *e.g.* the amino acid residues at each end of the range (*i.e.* amino acids 5 and 20), optionally including amino acids within the range (*i.e.* amino acids 5, 9, 16 and 20).

In one embodiment, the epitope comprises at least one of amino acid residues 3, 5, 9, 10, 12, 16, 17, 20, 37, 42, 50, 53, 59, 62, 64, 68, 69, 72 or 77 of SEQ ID NO: 1. In further embodiments, the epitope comprises one, two, three, four, five, six, seven, eight, nine, ten, eleven or twelve amino acids selected from amino acid residues 3, 5, 9, 10, 12, 16, 17, 20, 37, 42, 50, 53, 59, 62, 64, 68, 69, 72 or 77 of SEQ ID NO: 1.

In one embodiment, the epitope comprises one or more amino acid residues within the following amino acid regions of SEQ ID NO: 1 (or SEQ ID NO:128, as described above):

(i) 3-17;
(ii) 5-20;
(iii) 37-53;
(iv) 50-64;
(v) 59-72;
(vi) 59-77;
(vii) 62-69; and/or
(viii) 62-77.

In a further embodiment, the epitope comprises one or more amino acid residues within amino acid regions: 5-20 and 62-77; 50-64; 37-53 and 59-72; 59-77; or 3-17 and 62-69, of SEQ ID NO: 1. In a further embodiment, the epitope consists of one or more amino acid residues within amino acid regions: 5-20 and 62-77; 50-64; 37-53 and 59-72; 59-77; or 3-17 and 62-69, of SEQ ID NO: 1.

In a further embodiment, the epitope comprises amino acid residues: 3, 5, 9, 10, 12, 16, 17, 62, 64, 68 and 69 of SEQ ID NO: 1, or suitably consists of amino acid residues: 3, 5, 9, 10, 12, 16, 17, 62, 64, 68 and 69 of SEQ ID NO: 1. In a further embodiment, the epitope comprises amino acid residues: 5, 9, 16, 20, 62, 64, 72 and 77 of SEQ ID NO: 1, or suitably consists of

amino acid residues: 5, 9, 16, 20, 62, 64, 72 and 77 of SEQ ID NO: 1. In yet further embodiment, the epitope comprises the amino acid residues: 37, 42, 50, 53, 59, 64, 68, 69, 72, 73 and 77 of SEQ ID NO: 1, or suitably consists of amino acid residues: 37, 42, 50, 53, 59, 64, 68, 69, 72, 73 and 77 of SEQ ID NO: 1. In a further embodiment, the epitope comprises the amino acid residues: 50, 53, 59, 62 and 64 of SEQ ID NO: 1, or suitably consists of amino acid residues: 50, 53, 59, 62 and 64 of SEQ ID NO: 1. In a further embodiment, the epitope comprises amino acid residues: 59, 60, 68 and 72 of SEQ ID NO: 1, or suitably consists of amino acid residues: 59, 60, 68 and 72 of SEQ ID NO: 1.

In one embodiment, the epitope comprises one or more amino acid residues within amino acid regions 5-20 and/or 62-77 of SEQ ID NO: 1. In a further embodiment, the epitope consists of one or more amino acid residues within amino acid regions 5-20 and 62-77 of SEQ ID NO: 1. In an alternative further embodiment, the epitope comprises one or more amino acid residues within amino acid regions 5-20 or 62-77 of SEQ ID NO: 1. Antibodies or fragments thereof having such epitopes may have some or all of the sequences of 1245_P01_E07, or such antibodies or fragments thereof may be derived from 1245_P01_E07. For example, antibodies or fragments thereof having one or more CDR sequences of 1245_P01_E07 or one or both of the VH and VL sequences of 1245_P01_E07 may bind such epitopes.

In one embodiment, the epitope comprises one or more amino acid residues within amino acid region 50-64 of SEQ ID NO: 1. In a further embodiment, the epitope consists of one or more amino acid residues within amino acid region 50-64 of SEQ ID NO: 1. Antibodies or fragments thereof having such epitopes may have some or all of the sequences of 1252_P01_C08, or such antibodies or fragments thereof may be derived from 1252_P01_C08. For example, antibodies or fragments thereof having one or more CDR sequences of 1252_P01_C08 or one or both of the VH and VL sequences of 1252_P01_C08 may bind such epitopes.

In one embodiment, the epitope comprises one or more amino acid residues within amino acid regions 37-53 and/or 59-77 of SEQ ID NO: 1. In a further embodiment, the epitope consists of one or more amino acid residues within amino acid regions 37-53 and 59-77 of SEQ ID NO: 1. In an alternative further embodiment, the epitope comprises one or more amino acid residues within amino acid regions 37-53 or 59-77 of SEQ ID NO: 1. Antibodies or fragments thereof having such epitopes may have some or all of the sequences of 1245_P02_G04, or such antibodies or fragments thereof may be derived from 1245_P02_G04. For example, antibodies or fragments thereof having one or more CDR sequences of 1245_P02_G04 or one or both of the VH and VL sequences of 1245_P02_G04 may bind such epitopes.

In one embodiment, the epitope comprises one or more amino acid residues within amino acid region 59-72 of SEQ ID NO: 1. In a further embodiment, the epitope consists of one or more amino acid residues within amino acid region 59-72 of SEQ ID NO: 1. Antibodies or fragments thereof having such epitopes may have some or all of the sequences of 1251_P02_C05, or
5 such antibodies or fragments thereof may be derived from 1251_P02_C05. For example, antibodies or fragments thereof having one or more CDR sequences of 1251_P02_C05 or one or both of the VH and VL sequences of 1251_P02_C05 may bind such epitopes.

In one embodiment, the epitope does not comprise amino acid residues within amino acid
10 region 11-21 of SEQ ID NO: 1. In one embodiment, the epitope does not comprise amino acid residues within amino acid region 21-28 of SEQ ID NO: 1. In one embodiment, the epitope does not comprise amino acid residues within the amino acid region 59 and 60 of SEQ ID NO: 1. In one embodiment, the epitope does not comprise amino acid residues within the amino acid region 67-82 of SEQ ID NO: 1.
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In one embodiment, the epitope is not the same epitope bound by a commercially available anti-Vδ1 antibody, such as TS-1 or TS8.2. As described in WO2017197347, binding of TS-1 and TS8.2 to soluble TCRs was detected when the δ1 chain included Vδ1 J1 and Vδ1 J2 sequences but not to the Vδ1 J3 chain, indicating that the binding of TS-1 and TS8.2 involved
20 critical residues in the delta J1 and delta J2 region.

References to “within” herein include the extremities of the define range. For example, “within amino acid regions 5-20” refers to all of amino acid resides from and including residue 5 up to and including residue 20.
25

Various techniques are known in the art to establish which epitope is bound by an antibody. Exemplary techniques include, for example, routine cross-blocking assays, alanine scanning mutational analysis, peptide blot analysis, peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and
30 chemical modification of antigens can be employed. Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry (as described in Example 9). In general terms, the hydrogen/deuterium exchange method involves deuterium-labelling the protein of interest, followed by binding the antibody to the deuterium-labelled protein. Next,
35 the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of

the interface. As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labelled residues which correspond to the specific amino acids with which the antibody interacts.

Antibody sequences

The isolated anti-Vδ1 antibodies, or fragments thereof, may be described with reference to their CDR sequences.

In one embodiment, the anti-Vδ1 antibody or fragment thereof comprises one or more of:

a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-25;

a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 26-37 and SEQUENCES: A1-A12; and/or

a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 38-61.

In one embodiment, the isolated anti-Vδ1 antibody or fragment thereof comprises a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-25. In one embodiment, the antibody or fragment thereof comprises a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 26-37 and SEQUENCES: A1-A12 (of Table 2). In one embodiment, the antibody or fragment thereof comprises a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 38-61.

In one embodiment, the antibody or fragment thereof comprises a CDR3 comprising a sequence having at least 85%, 90%, 95%, 97%, 98% or 99% sequence identity with any one of SEQ ID NOs: 2-25. In one embodiment, the antibody or fragment thereof comprises a CDR2 comprising a sequence having at least 85%, 90%, 95%, 97%, 98% or 99% sequence identity with any one of SEQ ID NOs: 26-37 and SEQUENCES: A1-A12 (of Table 2). In one embodiment, the antibody or fragment thereof comprises a CDR1 comprising a sequence having at least 85%, 90%, 95%, 97%, 98% or 99% sequence identity with any one of SEQ ID NOs: 38-61.

In one embodiment, the antibody or fragment thereof comprises a CDR3 consisting of a sequence having at least 85%, 90%, 95%, 97%, 98% or 99% sequence identity with any one of SEQ ID NOs: 2-25. In one embodiment, the antibody or fragment thereof comprises a CDR2 consisting of a sequence having at least 85%, 90%, 95%, 97%, 98% or 99% sequence identity
5 with any one of SEQ ID NOs: 26-37 and SEQUENCES: A1-A12 (of Table 2). In one embodiment, the antibody or fragment thereof comprises a CDR1 consisting of a sequence having at least 85%, 90%, 95%, 97%, 98% or 99% sequence identity with any one of SEQ ID NOs: 38-61.

10 In one embodiment the antibody or fragment thereof comprises a VH region comprising a CDR3 sequence sharing at least 80% sequence identity with any one of SEQ ID NOs: 2-13 and/or a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25. In one embodiment, the antibody or fragment thereof comprises a VH region comprising a CDR3 consisting of a sequence having at least
15 80% sequence identity with any one of SEQ ID NOs: 2-13 and/or a VL region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25.

In one embodiment, the antibody or fragment thereof comprises a VH region comprising a
20 CDR3 comprising a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 2-13 and/or a VL region comprising a CDR3 comprising a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 14-25. In one embodiment, the antibody or fragment thereof comprises a VH region comprising a CDR3 consisting of a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 2-13 and/or a VL region
25 comprising a CDR3 consisting of a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 14-25.

In one embodiment, the antibody or fragment thereof comprises a VH region comprising a CDR3 comprising a sequence having at least 95% sequence identity with any one of SEQ ID
30 NOs: 2-13 and/or a VL region comprising a CDR3 comprising a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 14-25. In one embodiment, the antibody or fragment thereof comprises a VH region comprising a CDR3 consisting of a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 2-13 and/or a VL region comprising a CDR3 consisting of a sequence having at least 95% sequence identity with any
35 one of SEQ ID NOs: 14-25.

In one embodiment, the antibody or fragment thereof comprises a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-13 and a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25. In one embodiment, the antibody or fragment thereof comprises a VH region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-13 and a VL region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25.

In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-7, in particular 2-6, such as 2, 3 or 4 and a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-19, in particular 14-18, such as 14, 15 or 16. In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-7, in particular 2-6, such as 2, 3 or 4 and a VL region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-19, in particular 14-18, such as 14, 15 or 16.

In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 comprising a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 2-7, in particular 2-6, such as 2, 3 or 4 and/or a VL region comprising a CDR3 comprising a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 14-19, in particular 14-18, such as 14, 15 or 16. In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 consisting of a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 2-7, in particular 2-6, such as 2, 3 or 4 and/or a VL region comprising a CDR3 consisting of a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 14-19, in particular 14-18, such as 14, 15 or 16.

In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 comprising a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 2-7, in particular 2-6, such as 2, 3 or 4 and/or a VL region comprising a CDR3 comprising a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 14-19, in particular 14-18, such as 14, 15 or 16. In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 consisting of a sequence

having at least 95% sequence identity with any one of SEQ ID NOs: 2-7, in particular 2-6, such as 2, 3 or 4 and/or a VL region comprising a CDR3 consisting of a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 14-19, in particular 14-18, such as 14, 15 or 16.

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In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 8-13, in particular 8, 9, 10 or 11 and/or a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs:
10 20-25, in particular 20, 21, 22 or 23. In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 8-13, in particular 8, 9, 10 or 11 and/or a VL region comprising a CDR3 consisting of a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 20-25, in particular 20, 21, 22 or 23.

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In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 comprising a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 8-13, in particular 8, 9, 10 or 11 and/or a VL region comprising a CDR3 comprising a sequence having at least 90% sequence identity with any one of SEQ ID NOs:
20 20-25, in particular 20, 21, 22 or 23. In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 consisting of a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 8-13, in particular 8, 9, 10 or 11 and/or a VL region comprising a CDR3 consisting of a sequence having at least 90% sequence identity with any one of SEQ ID NOs: 20-25, in particular 20, 21, 22 or 23.

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In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 comprising a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 8-13, in particular 8, 9, 10 or 11 and/or a VL region comprising a CDR3 comprising a sequence having at least 95% sequence identity with any one of SEQ ID NOs:
30 20-25, in particular 20, 21, 22 or 23. In one embodiment, the antibody or fragment thereof, which comprises a VH region comprising a CDR3 consisting of a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 8-13, in particular 8, 9, 10 or 11 and/or a VL region comprising a CDR3 consisting of a sequence having at least 95% sequence identity with any one of SEQ ID NOs: 20-25, in particular 20, 21, 22 or 23.

35

Embodiments which refer herein to “at least 80%” or “80% or greater”, will be understood to include all values equal to or greater than 80%, such as 85%, 90%, 95%, 97%, 98%, 99% or

100% sequence identity. In one embodiment, the antibody or fragment thereof comprises at least 85%, such as at least 90%, at least 95%, at least 97%, at least 98% or at least 99% sequence identity to the specified sequence.

5 Instead of percentage sequence identity, the embodiments may also be defined with one or more amino acid changes, for examples one or more additions, substitutions and/or deletions. In one embodiment, the sequence may comprise up to five amino acid changes, such as up to three amino acid changes, in particular up to two amino acid changes. In a further embodiment, the sequence may comprise up to five amino acid substitutions, such as up to
10 three amino acid substitutions, in particular up to one or two amino acid substitutions. For example, CDR3 of the antibody or fragment thereof comprises or more suitably consists of a sequence having no more than 2, more suitably no more than 1 substitution(s) compared to any one of SEQ ID NOs: 2-25.

15 Suitably any residues of CDR1, CDR2 or CDR3 differing from their corresponding residues in SEQ ID NO: 2-61 and SEQUENCES: A1-A12 are conservative substitutions with respect to their corresponding residues. For example, any residues of CDR3 differing from their corresponding residues in SEQ ID NOs: 2-25 are conservative substitutions with respect to their corresponding residues.

20

In one embodiment, the antibody or fragment thereof comprises:

(i) a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-13;

(ii) a VH region comprising a CDR2 comprising a sequence having at least 80% sequence
25 identity with any one of SEQ ID NOs: 26-37;

(iii) a VH region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 38-49;

(iv) a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25;

30 (v) a VL region comprising a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQUENCES: A1-A12; and/or

(vi) a VL region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 50-61.

35 In one embodiment, the antibody or fragment thereof comprises a heavy chain with:

(i) a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-13;

(ii) a VH region comprising a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 26-37; and
(iii) a VH region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 38-49.

In one embodiment, the antibody or fragment thereof comprises a light chain with:
(i) a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25;
(ii) a VL region comprising a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQUENCES: A1-A12; and
(iii) a VL region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 50-61.

In one embodiment, the antibody or fragment thereof comprises (or consists of) a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2, 3, 4, 5 or 6, such as 2, 3, 4 or 5, in particular 2, 3 or 4. In one embodiment, the antibody or fragment thereof comprises (or consists of) a VH region comprising a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 26, 27, 28, 29 or 30, such as 26, 27, 28 or 29, in particular 26, 27 or 28. In one embodiment, the antibody or fragment thereof comprises (or consists of) a VH region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs:38, 39, 40, 41 or 42, such as 38, 39, 40 or 41, in particular 38, 39 or 40.

In one embodiment, the antibody or fragment thereof comprises (or consists of) a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 8, 9, 10 or 11. In one embodiment, the antibody or fragment thereof comprises (or consists of) a VH region comprising a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 32, 33, 34 or 35. In one embodiment, the antibody or fragment thereof comprises (or consists of) a VH region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 44, 45, 46 or 47.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 2, a CDR2 comprising a sequence of SEQ ID NO: 26, and a CDR1 comprising a sequence of SEQ ID NO: 38. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 2, the CDR2 consists of a sequence of SEQ ID NO: 26, and the CDR1 consists of a sequence of SEQ ID NO: 38.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 3, a CDR2 comprising a sequence of SEQ ID NO: 27, and a CDR1 comprising a sequence of SEQ ID NO: 39. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 3, the CDR2 consists of a sequence of SEQ ID NO: 27, and the CDR1 consists of a sequence of SEQ ID NO: 39.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 4, a CDR2 comprising a sequence of SEQ ID NO: 28, and a CDR1 comprising a sequence of SEQ ID NO: 40. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 4, the CDR2 consists of a sequence of SEQ ID NO: 28, and the CDR1 consists of a sequence of SEQ ID NO: 40.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 5, a CDR2 comprising a sequence of SEQ ID NO: 29, and a CDR1 comprising a sequence of SEQ ID NO: 41. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 5, the CDR2 consists of a sequence of SEQ ID NO: 29, and the CDR1 consists of a sequence of SEQ ID NO: 41.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 6, a CDR2 comprising a sequence of SEQ ID NO: 30, and a CDR1 comprising a sequence of SEQ ID NO: 42. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 6, the CDR2 consists of a sequence of SEQ ID NO: 30, and the CDR1 consists of a sequence of SEQ ID NO: 42.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 8, a CDR2 comprising a sequence of SEQ ID NO: 32, and a CDR1 comprising a sequence of SEQ ID NO: 44. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 8, the CDR2 consists of a sequence of SEQ ID NO: 32, and the CDR1 consists of a sequence of SEQ ID NO: 44.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 9, a CDR2 comprising a sequence of SEQ ID NO: 33, and a CDR1 comprising a sequence of SEQ ID NO: 45. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 9, the CDR2 consists of a sequence of SEQ ID NO: 33, and the CDR1 consists of a sequence of SEQ ID NO: 45.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 10, a CDR2 sequence of SEQ ID NO: 34, and a CDR1 sequence of SEQ ID NO: 46. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 10, the CDR2 consists of a sequence of SEQ ID NO: 34, and the CDR1 consists of a sequence of SEQ ID NO: 46.

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In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 11, a CDR2 sequence of SEQ ID NO: 35, and a CDR1 sequence of SEQ ID NO: 47. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 11, the CDR2 consists of a sequence of SEQ ID NO: 35, and the CDR1 consists of a sequence of SEQ ID NO: 47.

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In one embodiment, the antibody or fragment thereof comprises (or consists of) a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 14-25, such as SEQ ID NOs: 14, 15, 16, 17 or 18 such as 14, 15, 16 or 17, in particular 14, 15 or 16. In one embodiment, the antibody or fragment thereof comprises
15 (or consists of) a VL region comprising a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQUENCES: A1-A12 (of Table 2), such as SEQUENCES: A1, A2, A3, A4 or A5, such as A1, A2, A3 or A4, in particular A1, A2 or A3. In one embodiment, the antibody or fragment thereof comprises (or consists of) a VL region comprising a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs:
20 50-61, such as SEQ ID NOs: 50, 51, 52, 53 or 54, such as 50, 51, 52 or 53, in particular 50, 51 or 52.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 14, a CDR2 comprising a sequence of SEQUENCE: A1, and a CDR1 comprising a sequence
25 of SEQ ID NO: 50. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 14, the CDR2 consists of a sequence of SEQUENCE: A1, and the CDR1 consists of a sequence of SEQ ID NO: 50.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO:
30 15, a CDR2 comprising a sequence of SEQUENCE: A2, and a CDR1 comprising a sequence of SEQ ID NO: 51. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 15, the CDR2 consists of a sequence of SEQUENCE: A2, and the CDR1 consists of a sequence of SEQ ID NO: 51.

35 In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 16, a CDR2 comprising a sequence of SEQUENCE: A3, and a CDR1 comprising a sequence of SEQ ID NO: 52. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 16,

the CDR2 consists of a sequence of SEQUENCE: A3, and the CDR1 consists of a sequence of SEQ ID NO: 52.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 17, a CDR2 comprising a sequence of SEQUENCE: A4, and a CDR1 comprising a sequence of SEQ ID NO: 53. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 17, the CDR2 consists of a sequence of SEQUENCE: A4, and the CDR1 consists of a sequence of SEQ ID NO: 53.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 18, a CDR2 comprising a sequence of SEQUENCE: A5, and a CDR1 comprising a sequence of SEQ ID NO: 54. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 18, the CDR2 consists of a sequence of SEQUENCE: A5, and the CDR1 consists of a sequence of SEQ ID NO: 54.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 20, a CDR2 comprising a sequence of SEQUENCE: A7, and a CDR1 comprising a sequence of SEQ ID NO: 56. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 20, the CDR2 consists of a sequence of SEQUENCE: A7, and the CDR1 consists of a sequence of SEQ ID NO: 56.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 21, a CDR2 comprising a sequence of SEQUENCE: A8, and a CDR1 comprising a sequence of SEQ ID NO: 57. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 21, the CDR2 consists of a sequence of SEQUENCE: A8, and the CDR1 consists of a sequence of SEQ ID NO: 57.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 22, a CDR2 comprising a sequence of SEQUENCE: A9, and a CDR1 comprising a sequence of SEQ ID NO: 58. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 22, the CDR2 consists of a sequence of SEQUENCE: A9, and the CDR1 consists of a sequence of SEQ ID NO: 58.

In one embodiment, the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 23, a CDR2 comprising a sequence of SEQUENCE: A10, and a CDR1 comprising a sequence of SEQ ID NO: 59. In one embodiment, the CDR3 consists of a sequence of SEQ ID NO: 23,

the CDR2 consists of a sequence of SEQUENCE: A10, and the CDR1 consists of a sequence of SEQ ID NO: 59.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 2, a CDR2 comprising a sequence of SEQ ID NO: 26, a CDR1 comprising a sequence of SEQ ID NO: 38, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 14, a CDR2 comprising a sequence of SEQUENCE: A1, and a CDR1 comprising a sequence of SEQ ID NO: 50. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 2, the HCDR2 consists of a sequence of SEQ ID NO: 26, the HCDR1 consists of a sequence of SEQ ID NO: 38, the LCDR3 consists of a sequence of SEQ ID NO: 14, the LCDR2 consists of a sequence of SEQUENCE: A1, and the LCDR1 consists of a sequence of SEQ ID NO: 50.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 3, a CDR2 comprising a sequence of SEQ ID NO: 27, a CDR1 comprising a sequence of SEQ ID NO: 39, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 15, a CDR2 comprising a sequence of SEQUENCE: A2, and a CDR1 comprising a sequence of SEQ ID NO: 51. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 3, the HCDR2 consists of a sequence of SEQ ID NO: 27, the HCDR1 consists of a sequence of SEQ ID NO: 39, the LCDR3 consists of a sequence of SEQ ID NO: 15, the LCDR2 consists of a sequence of SEQUENCE: A2, and the LCDR1 consists of a sequence of SEQ ID NO: 51.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 4, a CDR2 comprising a sequence of SEQ ID NO: 28, a CDR1 comprising a sequence of SEQ ID NO: 40, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 16, a CDR2 comprising a sequence of SEQUENCE: A3, and a CDR1 comprising a sequence of SEQ ID NO: 52. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 4, the HCDR2 consists of a sequence of SEQ ID NO: 28, the HCDR1 consists of a sequence of SEQ ID NO: 40, the LCDR3 consists of a sequence of SEQ ID NO: 16, the LCDR2 consists of a sequence of SEQUENCE: A3, and the LCDR1 consists of a sequence of SEQ ID NO: 52.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 5, a CDR2 comprising a sequence of SEQ ID NO: 29, a CDR1 comprising a sequence of SEQ ID NO: 41, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 17, a CDR2 comprising a sequence of SEQUENCE: A4, and a CDR1 comprising a sequence of SEQ ID NO: 53. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 5, the HCDR2 consists of a sequence of SEQ ID NO: 29, the HCDR1 consists of a sequence of

SEQ ID NO: 41, the LCDR3 consists of a sequence of SEQ ID NO: 17, the LCDR2 consists of a sequence of SEQUENCE: A4, and the LCDR1 consists of a sequence of SEQ ID NO: 53.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 6, a CDR2 comprising a sequence of SEQ ID NO: 30, a CDR1 comprising a sequence of SEQ ID NO: 42, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 18, a CDR2 comprising a sequence of SEQUENCE: A5, and a CDR1 comprising a sequence of SEQ ID NO: 54. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 6, the HCDR2 consists of a sequence of SEQ ID NO: 30, the HCDR1 consists of a sequence of SEQ ID NO: 42, the LCDR3 consists of a sequence of SEQ ID NO: 18, the LCDR2 consists of a sequence of SEQUENCE: A5, and the LCDR1 consists of a sequence of SEQ ID NO: 54.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 7, a CDR2 comprising a sequence of SEQ ID NO: 31, a CDR1 comprising a sequence of SEQ ID NO: 43, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 19, a CDR2 comprising a sequence of SEQUENCE: A6, and a CDR1 comprising a sequence of SEQ ID NO: 55. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 7, the HCDR2 consists of a sequence of SEQ ID NO: 31, the HCDR1 consists of a sequence of SEQ ID NO: 43, the LCDR3 consists of a sequence of SEQ ID NO: 19, the LCDR2 consists of a sequence of SEQUENCE: A6, and the LCDR1 consists of a sequence of SEQ ID NO: 55.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 8, a CDR2 comprising a sequence of SEQ ID NO: 32, a CDR1 comprising a sequence of SEQ ID NO: 44, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 20, a CDR2 comprising a sequence of SEQUENCE: A7, and a CDR1 comprising a sequence of SEQ ID NO: 56. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 8, the HCDR2 consists of a sequence of SEQ ID NO: 32, the HCDR1 consists of a sequence of SEQ ID NO: 44, the LCDR3 consists of a sequence of SEQ ID NO: 20, the LCDR2 consists of a sequence of SEQUENCE: A7, and the LCDR1 consists of a sequence of SEQ ID NO: 56.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 9, a CDR2 comprising a sequence of SEQ ID NO: 33, a CDR1 comprising a sequence of SEQ ID NO: 45, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 21, a CDR2 comprising a sequence of SEQUENCE: A8, and a CDR1 comprising a sequence of SEQ ID NO: 57. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 9, the HCDR2 consists of a sequence of SEQ ID NO: 33, the HCDR1 consists of a sequence of

SEQ ID NO: 45, the LCDR3 consists of a sequence of SEQ ID NO: 21, the LCDR2 consists of a sequence of SEQUENCE: A8, and the LCDR1 consists of a sequence of SEQ ID NO: 57.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 10, a CDR2 comprising a sequence of SEQ ID NO: 34, a CDR1 comprising a sequence of SEQ ID NO: 46, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 22, a CDR2 comprising a sequence of SEQUENCE: A9, and a CDR1 comprising a sequence of SEQ ID NO: 58. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 10, the HCDR2 consists of a sequence of SEQ ID NO: 34, the HCDR1 consists of a sequence of SEQ ID NO: 46, the LCDR3 consists of a sequence of SEQ ID NO: 22, the LCDR2 consists of a sequence of SEQUENCE: A9, and the LCDR1 consists of a sequence of SEQ ID NO: 58.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 11, a CDR2 comprising a sequence of SEQ ID NO: 35, a CDR1 comprising a sequence of SEQ ID NO: 47, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 23, a CDR2 comprising a sequence of SEQUENCE: A10, and a CDR1 comprising a sequence of SEQ ID NO: 59. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 11, the HCDR2 consists of a sequence of SEQ ID NO: 35, the HCDR1 consists of a sequence of SEQ ID NO: 47, the LCDR3 consists of a sequence of SEQ ID NO: 23, the LCDR2 consists of a sequence of SEQUENCE: A10, and the LCDR1 consists of a sequence of SEQ ID NO: 59.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 12, a CDR2 comprising a sequence of SEQ ID NO: 36, a CDR1 comprising a sequence of SEQ ID NO: 48, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 24, a CDR2 comprising a sequence of SEQUENCE: A11, and a CDR1 comprising a sequence of SEQ ID NO: 60. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO: 12, the HCDR2 consists of a sequence of SEQ ID NO: 36, the HCDR1 consists of a sequence of SEQ ID NO: 48, the LCDR3 consists of a sequence of SEQ ID NO: 24, the LCDR2 consists of a sequence of SEQUENCE: A11, and the LCDR1 consists of a sequence of SEQ ID NO: 60.

In one embodiment, the VH region comprises a CDR3 comprising a sequence of SEQ ID NO: 13, a CDR2 comprising a sequence of SEQ ID NO: 37, a CDR1 comprising a sequence of SEQ ID NO: 49, and the VL region comprises a CDR3 comprising a sequence of SEQ ID NO: 25, a CDR2 comprising a sequence of SEQUENCE: A12, and a CDR1 comprising a sequence of SEQ ID NO: 61. In one embodiment, the HCDR3 consists of a sequence of SEQ ID NO:

13, the HCDR2 consists of a sequence of SEQ ID NO: 37, the HCDR1 consists of a sequence of SEQ ID NO: 49, the LCDR3 consists of a sequence of SEQ ID NO: 25, the LCDR2 consists of a sequence of SEQUENCE: A12, and the LCDR1 consists of a sequence of SEQ ID NO: 61.

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In one embodiment, the antibody or fragment thereof comprises one or more CDR sequences as described in **Table 2**. In a further embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1252_P01_C08 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such

10 as all) CDR sequences of clone 1245_P01_E07 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1245_P02_G04 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1245_P02_B07 as described in **Table 2**. In an alternative embodiment, the antibody or

15 fragment thereof comprises one or more (such as all) CDR sequences of clone 1251_P02_C05 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1139_P01_E04 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone

20 1245_P02_F07 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1245_P01_G06 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1245_P01_G09 as described in **Table 2**. In an alternative embodiment, the antibody or

25 fragment thereof comprises one or more (such as all) CDR sequences of clone 1138_P01_B09 as described in **Table 2**. In an alternative embodiment, the antibody or fragment thereof comprises one or more (such as all) CDR sequences of clone 1251_P02_G10 as described in **Table 2**.

30 Suitably the VH and VL regions recited above each comprise four framework regions (FR1-FR4). In one embodiment, the antibody or fragment thereof comprises a framework region (*e.g.* FR1, FR2, FR3 and/or FR4) comprising a sequence having at least 80% sequence identity with the framework region in any one of SEQ ID NOs: 62-85. In one embodiment, the antibody or fragment thereof comprises a framework region (*e.g.* FR1, FR2, FR3 and/or FR4)

35 comprising a sequence having at least 90%, such as at least 95%, 97% or 99% sequence identity with the framework region in any one of SEQ ID NOs: 62-85. In one embodiment, the antibody or fragment thereof comprises a framework region (*e.g.* FR1, FR2, FR3 and/or FR4)

comprising a sequence in any one of SEQ ID NOs: 62-85. In one embodiment, the antibody or fragment thereof comprises a framework region (*e.g.* FR1, FR2, FR3 and/or FR4) consisting of a sequence in any one of SEQ ID NOs: 62-85.

5 The antibodies described herein may be defined by their full light chain and/or heavy chain variable sequences. In one embodiment the antibody or fragment thereof comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62-85. In one embodiment the antibody or fragment thereof consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62-85.

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In one embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62-73. In one embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs:
15 62-73. In a further embodiment, the VH region comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62, 63, 64, 65 or 66, such as 62, 63, 64 or 65, in particular 62, 63 or 64. In a further embodiment, the VH region consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62, 63, 64, 65 or 66, such as 62, 63, 64 or 65, in particular 62, 63 or 64. In a further embodiment,
20 the VH region comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 68, 69, 70, 71, 72 or 73, such as 68, 69, 70 or 71. In a further embodiment, the VH region consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 68, 69, 70, 71, 72 or 73, such as 68, 69, 70 or 71.

25 In one embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 74-85. In one embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 74-85. In a further embodiment, the VL region comprises an amino acid sequence having at
30 least 80% sequence identity with any one of SEQ ID NOs: 74, 75, 76, 77 or 78, such as 74, 75, 76 or 77, in particular 74, 75, or 76. In a further embodiment, the VL region consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 74, 75, 76, 77 or 78, such as 74, 75, 76 or 77, in particular 74, 75, or 76. In a further embodiment, the VL region comprises an amino acid sequence having at least 80% sequence identity with
35 any one of SEQ ID NOs: 80, 81, 82, 83, 84 or 85, such as 80, 81, 82 or 83. In a further embodiment, the VL region consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 80, 81, 82, 83, 84 or 85, such as 80, 81, 82 or 83.

In a further embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62-73 and a VL region comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 74-85. In a further embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62-73 and a VL region consisting of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 74-85.

In one embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 63 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 62 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 64 (1245_P02_G04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 68 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 69 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 70 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 71 (1245_P01_G09).

In one embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 63 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 62 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 64 (1245_P02_G04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 68 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 69 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 70 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 71 (1245_P01_G09).

In one embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 75 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 74 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 76 (1245_P02_G04). In an alternative embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 80 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 81 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 82 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof comprises a VL region comprising an amino acid sequence of SEQ ID NO: 83 (1245_P01_G09).

In one embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 75 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 74 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 76 (1245_P02_G04). In an alternative embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 80 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 81 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 82 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof comprises a VL region consisting of an amino acid sequence of SEQ ID NO: 83 (1245_P01_G09).

In one embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 63 (1252_P01_C08) and a VL region comprising an amino acid sequence of SEQ ID NO: 75 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 62 (1245_P01_E07) and a VL region comprising an amino acid sequence of SEQ ID NO: 74 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 64 (1245_P02_G04) and a VL region comprising an amino acid sequence of SEQ ID NO: 76 (1245_P02_G04). In an alternative embodiment, the antibody or fragment thereof comprises

a VH region comprising an amino acid sequence of SEQ ID NO: 68 (1139_P01_E04) and a VL region comprising an amino acid sequence of SEQ ID NO: 80 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 69 (1245_P02_F07) and a VL region comprising an amino acid sequence of SEQ ID NO: 81 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 70 (1245_P01_G06) and a VL region comprising an amino acid sequence of SEQ ID NO: 82 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof comprises a VH region comprising an amino acid sequence of SEQ ID NO: 71 (1245_P01_G06) and a VL region comprising an amino acid sequence of SEQ ID NO: 83 (1245_P01_G09).

In one embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 63 (1252_P01_C08) and a VL region consisting of an amino acid sequence of SEQ ID NO: 75 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 62 (1245_P01_E07) and a VL region consisting of an amino acid sequence of SEQ ID NO: 74 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 64 (1245_P02_G04) and a VL region consisting of an amino acid sequence of SEQ ID NO: 76 (1245_P02_G04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 68 (1139_P01_E04) and a VL region consisting of an amino acid sequence of SEQ ID NO: 80 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 69 (1245_P02_F07) and a VL region consisting of an amino acid sequence of SEQ ID NO: 81 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 70 (1245_P01_G06) and a VL region consisting of an amino acid sequence of SEQ ID NO: 82 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof comprises a VH region consisting of an amino acid sequence of SEQ ID NO: 71 (1245_P01_G09) and a VL region consisting of an amino acid sequence of SEQ ID NO: 83 (1245_P01_G09).

For fragments comprising both the VH and VL regions, these may be associated either covalently (*e.g.* via disulphide bonds or a linker) or non-covalently. The antibody fragment described herein may comprise an scFv, *i.e.* a fragment comprising a VH region and a VL region joined by a linker. In one embodiment, the VH and VL region are joined by a (*e.g.*

synthetic) polypeptide linker. The polypeptide linker may comprise a $(Gly_4Ser)_n$ linker, where n = from 1 to 8, *e.g.* 2, 3, 4, 5 or 7. The polypeptide linker may comprise a $[(Gly_4Ser)_n(Gly_3AlaSer)_m]_p$ linker, where n = from 1 to 8, *e.g.* 2, 3, 4, 5 or 7, m = from 1 to 8, *e.g.* 0, 1, 2 or 3, and p = from 1 to 8, *e.g.* 1, 2 or 3. In a further embodiment, the linker comprises
5 SEQ ID NO: 98. In a further embodiment, the linker consists of SEQ ID NO: 98.

In one embodiment, the antibody or fragment thereof comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs:86-97. In a further embodiment, the antibody or fragment thereof comprises an amino acid sequence of any one
10 of SEQ ID NOs: 86-97. In a yet further embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NO: 87 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NO: 86 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NO: 88 (1245_P02_G04). In an alternative
15 embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NO: 92 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NO: 93 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NO: 94 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof
20 comprises an amino acid sequence of SEQ ID NO: 95 (1245_P01_G09).

In one embodiment, the antibody or fragment thereof consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 86-97. In a further embodiment, the antibody or fragment thereof consists of an amino acid sequence of any one
25 of SEQ ID NOs: 86-97. In a yet further embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NO: 87 (1252_P01_C08). In an alternative embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NO: 86 (1245_P01_E07). In an alternative embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NO: 88 (1245_P02_G04). In an alternative embodiment,
30 the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NO: 92 (1139_P01_E04). In an alternative embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NO: 93 (1245_P02_F07). In an alternative embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NO: 94 (1245_P01_G06). In an alternative embodiment, the antibody or fragment thereof consists of
35 an amino acid sequence of SEQ ID NO: 95 (1245_P01_G09).

It will be understood by a person skilled in the art that scFv constructs may be designed and made inclusive of N-terminal and C-terminal modifications to aid with translation, purification and detection. For example, at the N-terminus of an scFv sequence, an additional methionine and/or alanine amino acid residue may be included ahead of the canonical VH sequences (e.g. starting QVQ or EVQ). At the C-terminus (i.e. C-terminal to the canonical VL domain sequence ending as per the IMGT definition), additional sequences may be included such as (i) a partial sequence of the constant domain and/or (ii) additional synthetic sequences inclusive of tags, such as His-tags and Flag-tags, to aid with purification and detection. In one embodiment, SEQ ID NO: 124 is added to the C-terminus of any one of SEQ ID NOs: 86, 88-90, 92-97. In one embodiment, SEQ ID NO: 125 is added to the C-terminus of any one of SEQ ID NOs: 86, 88-90, 92-97. In one embodiment, SEQ ID NO: 126 is added to the C-terminus of any one of SEQ ID NOs: 87 or 91. In one embodiment, SEQ ID NO: 127 is added to the C-terminus of any one of SEQ ID NOs: 87 or 91. It is well understood that said scFv N- or C-terminal sequences are optional and can be removed, modified or substituted if alternate scFv design, translation, purification or detection strategies are adopted.

As described herein, the antibodies may be in any format. In a preferred embodiment, the antibody is in an IgG1 format. Therefore, in one embodiment, the antibody or fragment thereof comprises an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 111-122. In a further embodiment, the antibody or fragment thereof comprises an amino acid sequence of any one of SEQ ID NOs: 111-122. In a yet further embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NOs: 111-116, such as SEQ ID NOs: 111-113 and 116. In a yet further embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NOs: 117-122, such as SEQ ID NOs: 117-120. In a yet further embodiment, the antibody or fragment thereof comprises an amino acid sequence of SEQ ID NOs: 111, 112, 116-120, such as SEQ ID NOs: 111, 112 or 116, or SEQ ID NOs: 117-120.

In one embodiment, the antibody or fragment thereof consists of an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 111-122. In a further embodiment, the antibody or fragment thereof consists of an amino acid sequence of any one of SEQ ID NOs: 111-122. In a yet further embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NOs: 111-116, such as SEQ ID NOs: 111-113 and 116. In a yet further embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NOs: 117-122, such as SEQ ID NOs: 117-120. In a yet further embodiment, the antibody or fragment thereof consists of an amino acid sequence of SEQ ID NOs: 111, 112, 116-120, such as SEQ ID NOs: 111, 112 or 116, or SEQ ID NOs: 117-120.

In one embodiment, the antibody binds to the same, or essentially the same, epitope as, or competes with, an antibody or fragment thereof as defined herein. One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-Vδ1 antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-Vδ1 antibody, the reference antibody is allowed to bind to a Vδ1 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the Vδ1 chain is assessed. If the test antibody is able to bind to Vδ1 following saturation binding with the reference anti-Vδ1 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-Vδ1 antibody. On the other hand, if the test antibody is not able to bind to the Vδ1 chain following saturation binding with the reference anti-Vδ1 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-Vδ1 antibody.

The present invention also includes anti-Vδ1 antibodies that compete for binding to Vδ1 with an antibody or fragment thereof as defined herein, or an antibody having the CDR sequences of any of the exemplary antibodies described herein. For example, competitive assays can be performed with the antibody in order to determine what proteins, antibodies, and other antagonists compete for binding to the Vδ1 chain with the antibody and/or share the epitope. These assays are readily known to those of skill in the art; they evaluate competition between antagonists or ligands for a limited number of binding sites on a protein, *e.g.*, Vδ1. The antibody (or fragment thereof) is immobilized or insolubilized before or after the competition and the sample bound to the Vδ1 chain is separated from the unbound sample, for example, by decanting (where the antibody was pre-insolubilized) or by centrifuging (where the antibody was precipitated after the competitive reaction). Also, the competitive binding may be determined by whether the function is altered by the binding or lack of binding of the antibody to the protein, *e.g.* whether the antibody molecule inhibits or potentiates the enzymatic activity of, for example, a label. ELISA and other functional assays may be used, as known in the art and described herein.

Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the target antigen. That is, a 1 -, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay. Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the target antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

Additional routine experimentation (*e.g.* peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

In some embodiments, the antibody or fragment thereof contains a modified effector function through alteration to the sugars linked to Asn 297 (EU numbering scheme). In a further said modification, Asn 297 is not fucosylated or exhibits reduced fucosylation (i.e., a defucosylated antibody or a non-fucosylated antibody). Fucosylation includes the addition of the sugar fucose to a molecule, for example, the attachment of fucose to N-glycans, O-glycans and glycolipids. Accordingly, in a defucosylated antibody, fucose is not attached to the carbohydrate chains of the constant region. The antibody may be modified to prevent or inhibit fucosylation of the antibody. Typically, glycosylation modifications involve expressing said antibody or fragment thereof in a host cell containing alternate glycosylation processing capabilities either through targeted engineering or through targeted or serendipitous host or clone selection (e.g. see Example 13). These and other effector modifications are discussed further in recent reviews such as by Xinhua Wang et al. (2018) Protein & Cell 9: 63-73 and by Pereira et al. (2018) mAbs 10(5): 693-711 and which are hereby incorporated.

Antibody sequence modifications

The antibodies and fragments thereof may be modified using known methods. Sequence modifications to antibody molecules described herein can be readily incorporate by those skilled in the art. The following examples are non-limiting.

During antibody discovery and sequence recovery from phage libraries, desired antibody variable domains may be re-formatted into full length IgG by sub-cloning. To accelerate the process, variable domains are often transferred using restriction enzymes. These unique restriction sites may introduce additional/alternate amino acids and away from the canonical sequence (such canonical sequences may be found, for example, in the international ImMunoGeneTics [IMGT] information system, see http://www.imgt.org). These may be introduced as kappa or lambda light chain sequence modifications.

Kappa light chain modifications

The variable kappa light chain variable sequences may be cloned using restriction sites (*e.g.* Nhe1-Not1) during re-formatting into full length IgG. More specifically, at the kappa light chain

N-terminus, an additional Ala-Ser sequence was introduced to support cloning. Preferably, this additional AS sequence is then removed during further development such to generate the canonical N-terminal sequence. Hence, in one embodiment, kappa light chain containing antibodies described herein do not contain an AS sequence at their N-termini, *i.e.* SEQ ID NOs: 74, 76-78 and 80-85 do not comprise the initial AS sequence. In a further embodiment, SEQ ID NOs: 74 and 76-78 do not comprise the initial AS sequence. It will be understood that this embodiment also applies to other sequences included herein which contain this sequence (*e.g.* SEQ ID NOs: 86, 88-90 and 92-97).

Additional amino acid changes may be made to support cloning. For example, for the antibodies described herein, at the kappa light-chain variable-domain/constant domain border a valine-to-alanine change was introduced to support cloning. This resulted in a kappa constant domain modification. Specifically, this results in the constant domain beginning RTAAAPS (from a NotI restriction site). Preferably, this sequence can be modified during further development to generate the canonical kappa light-chain constant regions which start with RTVAAPS. Hence, in one embodiment kappa light chain containing antibodies described herein contain a constant domain stating with the sequence RTV. Therefore, in one embodiment, sequence RTAAAPS of SEQ ID NOs: 111-114 and 117-122 is replaced with sequence RTVAAPS.

Lambda light chain modifications

Similar to the kappa example above, the lambda light chain variable domains may also be cloned by introducing restriction sites (*e.g.* Nhe1-Not1) during re-formatting into full length IgG. More specifically, at the lambda light chain N-terminus, an additional Ala-Ser sequence may be introduced to support cloning. Preferably, this additional AS sequence is then removed during further development such to generate the canonical N-terminal sequence. Hence, in one embodiment, lambda light chain containing antibodies described herein do not contain an AS sequence at their N-termini *i.e.* SEQ ID NOs: 75 and 79 do not comprise the initial AS sequence. It will be understood that this embodiment also applies to other sequences included herein which contain this sequence (*e.g.* SEQ ID NOs: 87, 91, 115 and 116). In one embodiment, SEQ ID NO: 75 does not contain the initial six residues, *i.e.* the ASSYEL sequence is removed.

As another example, for the antibodies described herein at the lambda light-chain variable-domain/constant domain border a lysine-to-alanine sequence change was introduced to support cloning. This resulted in a lambda constant domain modification. Specifically, this results in the constant domain beginning with GQPAAAPS (from a NotI restriction site).

Preferably, this sequence can be modified during further development such to generate the canonical lambda light constant region which starts GQPKAAPS. Hence, in one embodiment, lambda light chain containing antibodies described herein contain a constant domain starting with the sequence GQPK. Therefore, in one embodiment, sequence GQPAAAPS of SEQ ID NO: 115 or 116 is replaced with sequence GQPKAAPS.

Heavy chain modifications

Typically, human variable heavy chain sequences start with either the basic glutamine (Q) or acidic glutamate (E). However, both such sequences are then known to convert to the acidic amino acid residue, pyro-glutamate (pE). The Q to pE conversion results in a charge change to the antibody, whilst an E to pE conversion does not change the charge of the antibody. Hence to avoid a variable charge-change over time one option is to modify a starting heavy chain sequence from Q to E in the first instance. Hence, in one embodiment, the heavy chain of antibody described herein contains a Q to E modification at the N-terminus. In particular, the initial residue of SEQ ID NOs: 62, 64 and/or 67-71 may be modified from Q to E. It will be understood that this embodiment also applies to other sequences included herein which contain this sequence (*e.g.* SEQ ID NOs: 86, 88, 91-97 and 111, 112, 115, 117-120).

Furthermore, the C-terminus of the IgG1 constant domain ends with PGK. However, the terminal basic lysine (K) is then often cleaved during expression (*e.g.* in CHO cells). This in turn results in charge change to the antibody through varied loss of the C-terminal lysine residue. Therefore, one option is to remove the lysine in the first instance resulting in a uniform and consistent heavy chain C-terminus sequence ending in PG. Hence, in one embodiment, the heavy chain of an antibody described herein has the terminal K removed from its C-terminus. In particular, the antibody of the invention may comprise any one of SEQ ID NOs: 111-122 where the terminal lysine residue has been removed.

Optional allotype modifications

During antibody discovery, specific human allotypes may be employed. Optionally, the antibodies can be switched to differing human allotypes during development. By way of non-limiting example, for the kappa chain there are three human allotypes designated Km1, Km1,2 and Km3 which define three Km alleles (using allotype numbering): Km1 correlates with valine 153 (IMGT V45.1) and leucine 191 (IMGT L101); Km1,2 correlates with alanine 153 (IMGT A45.1) and leucine 191 (IMGT L101); and Km3 correlates with alanine 153 (IMGT A45.1) and valine 191 (IMGT V101). Optionally, one can therefore modify a sequence from one allotype to another by standard cloning approaches. For example, a L191V (IMGT L101V) change will

convert a Km1,2 allotype to a Km3 allotype. For further reference on such allotypes see Jefferis and Lefranc (2009) *MAbs* 1(4):332-8, which is herein incorporated by reference.

Hence in one embodiment an antibody described herein contains amino acid substitutions derived from another human allotype of the same gene. In a further embodiment, the antibody contains a L191V (IMGT L101V) substitution to the kappa chain to convert the c-domain from a km1,2 to a km3 allotype.

Antibody binding

The antibody or fragment thereof may bind to the Vδ1 chain of a γδ TCR with a binding affinity (KD) as measured by surface plasmon resonance of less than 1.5×10^{-7} M (*i.e.* 150 nM). In a preferred embodiment, the KD is less than 1.5×10^{-7} M (i.e. 150 nM). In a further embodiment, the KD is 1.3×10^{-7} M (*i.e.* 130 nM) or less, such as 1.0×10^{-7} M (*i.e.* 100 nM) or less. In a yet further embodiment, the KD is less than 5.0×10^{-8} M (*i.e.* 50 nM), such as less than 4.0×10^{-8} M (*i.e.* 40 nM), less than 3.0×10^{-8} M (*i.e.* 30 nM) or less than 2.0×10^{-8} M (*i.e.* 20 nM). For example, according to one aspect, there is provided a human anti-Vδ1 antibody which binds to the Vδ1 chain of a γδ TCR with a binding affinity (KD) as measured by surface plasmon resonance of less than 1.5×10^{-7} M (*i.e.* 150 nM).

In one embodiment, the antibody or fragment thereof binds to the Vδ1 chain of a γδ TCR with a binding affinity (KD) as measured by surface plasmon resonance of less than 4.0×10^{-8} M (*i.e.* 40 nM), less than 3.0×10^{-8} M (*i.e.* 30 nM) or less than 2.0×10^{-8} M (*i.e.* 20 nM).

In one embodiment, the binding affinity of the antibody or fragment thereof is established by coating the antibody or fragment thereof directly or indirectly (*e.g.* by capture with an anti-human IgG Fc) onto the surface of a sensor (*e.g.* an amine high capacity chip or equivalent), wherein the target bound by the antibody or fragment thereof (*i.e.* the Vδ1 chain of a γδ TCR) is flowed over the chip to detect binding. Suitably, a MASS-2 instrument (which may also be referred to as Sierra SPR-32) is used at 25 °C in PBS + 0.02 % Tween 20 running buffer at 30 µl/min.

Described herein are other assays which may be used to define antibody function. For example, the antibody or fragment thereof described herein may be assessed by γδ TCR engagement, *e.g.* measuring downregulation of the γδ TCR upon antibody binding. Surface expression of the γδ TCR following application of the antibody or fragment thereof (optionally presented on the surface of a cell) can be measured, *e.g.* by flow cytometry. The antibody or

fragment thereof described herein may also be assessed by measuring γδ T cell degranulation. For example, expression of CD107a, a marker for cell degranulation, can be measured following application of the antibody or fragment thereof (optionally presented on the surface of a cell) to γδ T cells, *e.g.* by flow cytometry. The antibody or fragment thereof described herein may also be assessed by measuring γδ T cell killing activity (to test if the antibody has an effect on the killing activity of the γδ T cell). For example, target cells may be incubated with γδ T cells in the presence of the antibody or fragment thereof (optionally presented on the surface of a cell). Following incubation, the culture may be stained with a cell viability dye to distinguish between live and dead target cells. The proportion of dead cells can then be measured, *e.g.* by flow cytometry.

As described herein, the antibodies or fragments thereof used in the assays may be presented on a surface, for example the surface of a cell, such as a cell comprising an Fc receptor. For example, the antibodies or fragments thereof may be presented on the surface of THP-1 cells, such as TIB-202™ cells (available from American Type Culture Collection (ATCC)). Alternatively, the antibodies or fragments thereof may be used directly in the assays.

In such functional assays, output may be measured by calculating the half maximal concentration, also referred to as “EC50” or “effective concentration at 50 percent”. The term "IC50" refers to the inhibitory concentration. Both EC50 and IC50 may be measured using methods known in the art, such as flow cytometry methods. For the avoidance of doubt, the values of EC50 in the present application are provided using IgG1 formatted antibody. Such values can be easily converted based on the molecular weight of the antibody format for equivalent values as follows:

$$(\mu g/ml) / (MW \text{ in kDa}) = \mu M$$

The EC50 for downregulation of the γδ TCR upon antibody (or fragment) binding may be less than 0.50 µg/ml, such as less than 0.40 µg/ml, 0.30 µg/ml, 0.20 µg/ml, 0.15 µg/ml, 0.10 µg/ml or 0.05 µg/ml. In a preferred embodiment, the EC50 for downregulation of the γδ TCR upon antibody (or fragment) binding is less than 0.10 µg/ml. In particular, the EC50 for downregulation of the γδ TCR upon antibody (or fragment) binding may be less than 0.06 µg/ml, such as less than 0.05 µg/ml, 0.04 µg/ml or 0.03 µg/ml. In particular, said EC50 values are when the antibody is measured in an IgG1 format. For example, the EC50 γδ TCR downregulation value can be measured using flow cytometry (*e.g.* as described in the assay of Example 6).

The EC50 for γδ T cell degranulation upon antibody (or fragment) binding may be less than 0.050 μg/ml, such as less than 0.040 μg/ml, 0.030 μg/ml, 0.020 μg/ml, 0.015 μg/ml, 0.010 μg/ml or 0.008 μg/ml. In particular, the EC50 for γδ T cell degranulation upon antibody (or fragment) binding may be less than 0.005 μg/ml, such as less than 0.002 μg/ml. In a preferred 5 embodiment, the EC50 for γδ T cell degranulation upon antibody (or fragment) binding is less than 0.007 μg/ml. In particular, said EC50 values are when the antibody is measured in an IgG1 format. For example, the γδ T cell degranulation EC50 value can be measured by detecting CD107a expression (*i.e.* a marker of cell degranulation) using flow cytometry (*e.g.* as described in the assay of Example 7). In one embodiment, CD107a expression is measured 10 using an anti-CD107a antibody, such as anti-human CD107a BV421 (clone H4A3) (BD Biosciences).

The EC50 for γδ T cell killing upon the antibody (or fragment) binding may be less than 0.50 μg/ml, such as less than 0.40 μg/ml, 0.30 μg/ml, 0.20 μg/ml, 0.15 μg/ml, 0.10 μg/ml or 0.07 15 μg/ml. In a preferred embodiment, the EC50 for γδ T cell killing upon the antibody (or fragment) binding is less than 0.10 μg/ml. In particular, the EC50 for γδ T cell killing upon the antibody (or fragment) binding may be less than 0.060 μg/ml, such as less than 0.055 μg/ml, in particular less than 0.020 μg/ml or 0.010 μg/ml. In particular, said EC50 values are when the antibody is measured in an IgG1 format. For example, the EC50 γδ T cell killing value can be 20 measured by detecting proportion of dead cells (*i.e.* using a cell viability dye) using flow cytometry following incubation of the antibody, γδ T cell and target cells (*e.g.* as described in the assay of Example 8). In one embodiment, death of the target cell is measured using a cell viability dye is Viability Dye eFluor™ 520 (ThermoFisher).

25 In the assays described in these aspects, the antibody or fragment thereof may be presented on the surface of a cell, such as a THP-1 cell, for example TIB-202™ (ATCC). The THP-1 cells are optionally labelled with a dye, such as CellTracker™ Orange CMTMR (ThermoFisher).

30 Antibodies (or fragments) can be obtained and manipulated using the techniques disclosed for example in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (2012) 4th Edition Cold Spring Harbour Laboratory Press.

Monoclonal antibodies can be produced using hybridoma technology, by fusing a specific 35 antibody-producing B cell with a myeloma (B cell cancer) cell that is selected for its ability to grow in tissue culture and for an absence of antibody chain synthesis.

A monoclonal antibody directed against a determined antigen can, for example, be obtained by:

a) immortalizing lymphocytes obtained from the peripheral blood of an animal previously immunized with a determined antigen, with an immortal cell and preferably with myeloma cells, in order to form a hybridoma,

b) culturing the immortalized cells (hybridoma) formed and recovering the cells producing the antibodies having the desired specificity.

Alternatively, the use of a hybridoma cell is not required. Antibodies capable of binding to the target antigens as described herein may be isolated from a suitable antibody library via routine practice, for example, using the phage display, yeast display, ribosomal display, or mammalian display technology known in the art. Accordingly, monoclonal antibodies can be obtained, for example, by a process comprising the steps of:

a) cloning into vectors, especially into phages and more particularly filamentous bacteriophages, DNA or cDNA sequences obtained from lymphocytes especially peripheral blood lymphocytes of an animal (suitably previously immunized with determined antigens),

b) transforming prokaryotic cells with the above vectors in conditions allowing the production of the antibodies,

c) selecting the antibodies by subjecting them to antigen-affinity selection,

d) recovering the antibodies having the desired specificity.

Pharmaceutical compositions

According to a further aspect of the invention, there is provided a composition comprising the Vδ1 T cell population obtained by a method as defined herein. In one embodiment the Vδ1 T cell population is the expanded Vδ1 T cell population. In such embodiments, the composition may comprise the cells, optionally in combination with other excipients. Also included are compositions comprising one or more additional active agents (*e.g.* active agents suitable for treating the diseases mentioned herein).

Pharmaceutical compositions may include Vδ1 T cells, in particular expanded Vδ1 T cells, as described herein in combination with one or more pharmaceutically or physiologically acceptable carrier, diluents, or excipients. Such compositions may include buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (*e.g.*, aluminium hydroxide); and preservatives. Cryopreservation solutions which may be used in

the pharmaceutical compositions of the invention include, for example, DMSO. Compositions can be formulated, *e.g.,* for intravenous administration.

In one embodiment, the pharmaceutical composition is substantially free of, *e.g.*, there are no detectable levels of a contaminant, *e.g.*, of endotoxin or mycoplasma.

The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular, intrathecal). In a preferred embodiment, the composition is administered by intravenous infusion or injection. In another preferred embodiment, the composition is administered by intramuscular or subcutaneous injection.

It is within the scope of the invention to use the pharmaceutical composition of the invention in therapeutic methods for the treatment of diseases as described herein as an adjunct to, or in conjunction with, other established therapies normally used in the treatment of such diseases.

In a further aspect of the invention, the cell population, composition or pharmaceutical composition is administered sequentially, simultaneously or separately with at least one active agent.

Treatment methods using cell populations

According to a further aspect of the invention, there is provided the cell population obtained by a method as defined herein for use as a medicament. According to a further aspect of the invention, there is provided the expanded cell population as defined herein for use as a medicament. References herein to a cell population “for use” as a medicament or in therapy are limited to administration of the cell population to a subject. Such uses do not include administration of the antibody or fragment thereof direct to a patient *i.e.* wherein said antibody is used as the therapeutic.

In one embodiment, the cell population is for use in the treatment of cancer, an infectious disease or an inflammatory disease. In a further embodiment, the cell population is for use in the treatment of cancer.

In one embodiment, the cell population for use as a medicament comprises more than 50% Vδ1 T cells, such as more than 60%, more than 70%, more than 80%, more than 90%, more than 95% or more than 99% Vδ1 T cells. In a further embodiment, the cell population for use as a medicament consists of Vδ1 T cells.

In one embodiment, the cell population for use as a medicament comprises less than 10% αβ T cells, such as less than 8%, less than 7%, less than 6%, less than 5%, less than 4% or less than 3% αβ T cells. In one embodiment, the cell population for use as a medicament comprises less than 10% Vδ2 T cells, such as less than 8%, less than 7%, less than 6%, less than 5%, less than 4% or less than 3% Vδ2 T cells. In one embodiment, the cell population for use as a medicament comprises less than 50% NK cells, such as less than 40%, less than 30%, less than 20%, less than 10% or less than 5% NK cells. In one embodiment, less than 50% of the cells present in the cell population for use as a medicament express CD56, such as less than 40%, less than 30%, less than 20%, less than 10% or less than 5% express CD56.

According to a further aspect of the invention, there is provided the pharmaceutical composition comprising the cell population as defined herein for use as a medicament. In one embodiment, the pharmaceutical composition comprising the cell population is for use in the treatment of cancer, an infectious disease or an inflammatory disease. In a further embodiment, the pharmaceutical composition comprising the cell population is for use in the treatment of cancer.

According to a further aspect of the invention, there is provided a method of modulating an immune response in a subject in need thereof comprising administering a therapeutically effective amount of the cell population as defined herein.

According to a further aspect of the invention, there is provided a method of treating a cancer, an infectious disease or an inflammatory disease in a subject in need thereof, comprising administering a therapeutically effective amount of the cell population as defined herein. Alternatively, a therapeutically effective amount of the pharmaceutical composition comprising the cell population is administered.

According to further aspects of the invention, there is provided the use of the cell population as defined herein for the manufacture of a medicament, for example in the treatment of cancer, an infectious disease or an inflammatory disease.

Adoptive T cell therapy

Gamma delta T cells obtained by the expansion methods of the invention may be used as a medicament, for example for adoptive T cell therapy. This involves the transfer of γδ T cells into a patient. The therapy may be autologous, *i.e.* the γδ T cells may be transferred back into

the same patient from which they were obtained, or the therapy may be allogeneic, *i.e.* the γδ T cells from one person may be transferred into a different patient. In instances involving allogeneic transfer, the γδ T cells may be substantially free of αβ T cells. For example, αβ T cells may be depleted from the γδ T cell population, *e.g.*, after expansion, using any suitable means known in the art (*e.g.*, by negative selection, *e.g.,* using magnetic beads). A method of treatment may include: providing a sample (*e.g.* a non-haematopoietic tissue sample) obtained from a donor individual; culturing γδ T cells obtained from the sample as described herein, *e.g.* to produce an expanded population; and administering the population of γδ T cells to a recipient individual.

The patient or subject to be treated is preferably a human cancer patient (*e.g.*, a human cancer patient being treated for a solid tumour) or a virus-infected patient (*e.g.*, a CMV-infected or HIV infected patient). In some instances, the patient has and/or is being treated for a solid tumour. Because they are normally resident in non-haematopoietic tissues, tissue-resident Vδ1 T are also more likely to home to and be retained within tumour masses than their systemic blood-resident counterparts and adoptive transfer of these cells is likely to be more effective at targeting solid tumours and potentially other non-haematopoietic tissue-associated immunopathologies.

As γδ T cells are non-MHC restricted, they do not recognize a host into which they are transferred as foreign, which means that they are less likely to cause graft-versus-host disease. This means that they can be used “off the shelf” and transferred into any recipient, *e.g.*, for allogeneic adoptive T cell therapy.

γδ T cells obtained by methods described herein may express NKG2D and respond to a NKG2D ligand (*e.g.* MICA), which is strongly associated with malignancy. They may also express a cytotoxic profile in the absence of any activation and are therefore likely to be effective at killing tumour cells. For example, the γδ T cells obtained as described herein may express one or more, preferably all of IFN-γ, TNF-α, GM-CSF, CCL4, IL-13, Granulysin, Granzyme A and B, and Perforin in the absence of any activation. IL-17A may not be expressed.

In some embodiments, a method of treatment of an individual with a tumour may include; providing a sample of said tumour obtained from a donor individual, culturing the γδ T cells obtained from the sample as described above, and; administering the population of γδ T cells to the individual with the tumour. In a further embodiment, a method of treatment of an individual with a tumour in a non-haematopoietic tissue may include; providing a sample of

said non-haematopoietic tissue obtained from a donor individual, culturing the γδ T cells obtained from the sample as described above, and; administering the population of γδ T cells to the individual with the tumour.

5 In some instances, a therapeutically effective amount of γδ T cells obtained by the any of the methods described above can be administered in a therapeutically effective amount to a subject (*e.g.*, for treatment of cancer, *e.g.* for treatment of a solid tumour). In some cases, the therapeutically effective amount of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) is less than 10 x 10^{12} cells per dose (*e.g.*, less than 9 x 10^{12} cells per dose, less than 8 x 10^{12}
10 cells per dose, less than 7 x 10^{12} cells per dose, less than 6 x 10^{12} cells per dose, less than 5 x 10^{12} cells per dose, less than 4 x 10^{12} cells per dose, less than 3 x 10^{12} cells per dose, less than 2 x 10^{12} cells per dose, less than 1 x 10^{12} cells per dose, less than 9 x 10^{11} cells per dose, less than 8 x 10^{11} cells per dose, less than 7 x 10^{11} cells per dose, less than 6 x 10^{11} cells per dose, less than 5 x 10^{11} cells per dose, less than 4 x 10^{11} cells per dose, less than 3 x 10^{11}
15 cells per dose, less than 2 x 10^{11} cells per dose, less than 1 x 10^{11} cells per dose, less than 9 x 10^{10} cells per dose, less than 7.5 x 10^{10} cells per dose, less than 5 x 10^{10} cells per dose, less than 2.5 x 10^{10} cells per dose, less than 1 x 10^{10} cells per dose, less than 7.5 x 10^{9} cells per dose, less than 5 x 10^{9} cells per dose, less than 2.5 x 10^{9} cells per dose, less than 1 x 10^{9} cells per dose, less than 7.5 x 10^{8} cells per dose, less than 5 x 10^{8} cells per dose, less than
20 2,5 x 10^{8} cells per dose, less than 1 x 10^{8} cells per dose, less than 7.5 x 10^{7} cells per dose, less than 5 x 10^{7} cells per dose, less than 2,5 x 10^{7} cells per dose, less than 1 x 10^{7} cells per dose, less than 7.5 x 10^{6} cells per dose, less than 5 x 10^{6} cells per dose, less than 2,5 x 10^{6} cells per dose, less than 1 x 10^{6} cells per dose, less than 7.5 x 10^{5} cells per dose, less than 5 x 10^{5} cells per dose, less than 2,5 x 10^{5} cells per dose, or less than 1 x 10^{5} cells per dose).
25

In some embodiments, the therapeutically effective amount of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) is less than 10 x 10^{12} cells over the course of treatment (*e.g.*, less than 9 x 10^{12} cells, less than 8 x 10^{12} cells, less than 7 x 10^{12} cells, less than 6 x 10^{12} cells, less than 5 x 10^{12} cells, less than 4 x 10^{12} cells, less than 3 x 10^{12} cells, less than 2 x 10^{12} cells,
30 less than 1 x 10^{12} cells, less than 9 x 10^{11} cells, less than 8 x 10^{11} cells, less than 7 x 10^{11} cells, less than 6 x 10^{11} cells, less than 5 x 10^{11} cells, less than 4 x 10^{11} cells, less than 3 x 10^{11} cells, less than 2 x 10^{11} cells, less than 1 x 10^{11} cells, less than 9 x 10^{10} cells, less than 7.5 x 10^{10} cells, less than 5 x 10^{10} cells, less than 2.5 x 10^{10} cells, less than 1 x 10^{10} cells, less than 7.5 x 10^{9} cells, less than 5 x 10^{9} cells, less than 2.5 x 10^{9} cells, less than 1 x 10^{9} cells, less than
35 7.5 x 10^{8} cells, less than 5 x 10^{8} cells, less than 2.5 x 10^{8} cells, less than 1 x 10^{8} cells, less than 7.5 x 10^{7} cells, less than 5 x 10^{7} cells, less than 2.5 x 10^{7} cells, less than 1 x 10^{7} cells, less than 7.5 x 10^{6} cells, less than 5 x 10^{6} cells, less than 2.5 x 10^{6} cells, less than 1 x 10^{6}

cells, less than 7.5 x 10^5 cells, less than 5 x 10^5 cells, less than 2.5 x 10^5 cells, or less than 1 x 10^5 cells over the course of treatment).

In some embodiments, a dose of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) as described herein comprises about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) comprises up to about 1 x 10^6, 1.1 x 10^6, 2 x 10^6, 3.6 x 10^6, 5 x 10^6, 1 x 10^7, 1.8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, or 5 x 10^8 cells/kg. In some embodiments, a dose of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) comprises about 1.1 x 10^6- 1.8 x 10^7 cells/kg. In some embodiments, a dose of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) comprises about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells. In some embodiments, a dose of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) comprises at least about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells. In some embodiments, a dose of γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) comprises up to about 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9, or 5 x 10^9 cells.

In one embodiment, the subject is administered 10^4 to 10^6 γδ T cells (*e.g.*, skin-derived γδ T cells and/or Vδ1 T cells) per kg body weight of the subject. In one embodiment, the subject receives an initial administration of a population of γδ T cells (*e.g.*, an initial administration of 10^4 to 10^6 γδ T cells per kg body weight of the subject, *e.g.*, 10^4 to 10^5 γδ T cells per kg body weight of the subject), and one or more (*e.g.*, 2, 3, 4, or 5) subsequent administrations of γδ T cells (*e.g.*, one or more subsequent administration of 10^4 to 10^6 γδ T cells per kg body weight of the subject, *e.g.*, 10^4 to 10^5 γδ T cells per kg body weight of the subject). In one embodiment, the one or more subsequent administrations are administered less than 15 days, *e.g.*, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2 days after the previous administration, *e.g.*, less than 4, 3, or 2 days after the previous administration. In one embodiment, the subject receives a total of about 10^6 γδ T cells per kg body weight of the subject over the course of at least three administrations of a population of γδ T cells, *e.g.*, the subject receives an initial dose of 1 x 10^5 γδ T cells, a second administration of 3 x 10^5 γδ T cells, and a third administration of 6 x 10^5 γδ T cells, and, *e.g.*, each administration is administered less than 4, 3, or 2 days after the previous administration.

In some embodiments, one or more additional therapeutic agents can be administered to the subject. The additional therapeutic agent may be selected from the group consisting of an immunotherapeutic agent, a cytotoxic agent, a growth inhibitory agent, a radiation therapy agent, an anti-angiogenic agent, or a combination of two or more agents thereof. The

additional therapeutic agent may be administered concurrently with, prior to, or after administration of the γδ T cells. The additional therapeutic agent may be an immunotherapeutic agent, which may act on a target within the subject's body (*e.g.*, the subject's own immune system) and/or on the transferred γδ T cells.

The administration of the compositions may be carried out in any convenient manner. The compositions described herein may be administered to a patient transarterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous injection, or intraperitoneally, *e.g.*, by intradermal or subcutaneous injection. The compositions of γδ T cells may be injected directly into a tumour, lymph node, or site of infection.

Gene Engineering

The γδ T cells obtained by the method of the invention may also be gene engineered for enhanced therapeutic properties, such as for Chimeric Antigen Receptor T cell (CAR-T) therapy. This involves the generation of engineered T cell receptors (TCRs) to re-program the T cell with a new specificity, *e.g.* the specificity of a monoclonal antibody. The engineered TCR may make the T cells specific for malignant cells and therefore useful for cancer immunotherapy. For example, the T cells may recognize cancer cells expressing a tumour antigen, such as a tumour associated antigen that is not expressed by normal somatic cells from the subject tissue. Thus, the CAR-modified T cells may be used for adoptive T cell therapy of, for example, cancer patients.

Other uses of the antibodies or fragments thereof

According to a further aspect of the invention, there is provided the use of an anti-Vδ1 antibody or fragment thereof as described herein to study antigen recognition, activation, signal transduction or function of γδ T cells (in particular Vδ1 T cells). As described herein, the antibodies have been shown to be active in assays which can be used to investigate γδ T cell function. Such antibodies may also be useful for inducing the proliferation of γδ T cells, therefore may be used in methods of expanding γδ T cells (such as Vδ1 T cells).

Antibodies which bind to the Vδ1 chain can be used to detect γδ T cells (i.e. as a label). Preferably, antibodies used as a label will not stimulate cell proliferation so that the target Vδ1 T cell is not affected upon antibody binding. For example, the antibody may be labelled with a detectable label or reporter molecule or used as a capture ligand to selectively detect and/or

isolate Vδ1 T cells in a sample. Labelled antibodies find use in many methods known in the art, for example immunohistochemistry and ELISA.

The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Fluorescent labels applied to antibodies of the invention may then be used in fluorescence-activated cell sorting (FACS) methods.

Polynucleotides and expression vectors

Also provided are polynucleotides encoding the anti-Vδ1 antibody or fragments of the invention. In one embodiment, the anti-Vδ1 antibody or fragment is encoded by a polynucleotide which comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with SEQ ID NO: 99-110. In one embodiment, the anti-Vδ1 antibody or fragment is encoded by an expression vector which comprises the VH region of SEQ ID NO: 99-110. In another embodiment, the anti-Vδ1 antibody or fragment is encoded by an expression vector which comprises the VL region of SEQ ID NO: 99-110. In a further embodiment the polynucleotide comprises or consists of SEQ ID NO: 99-110. In a further aspect there is provided a cDNA comprising said polynucleotide.

In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with SEQ ID NO: 99-110. In one embodiment, the expression vector comprises the VH region of SEQ ID NO: 99-110. In another embodiment, the expression vector comprises the VL region of SEQ ID NO: 99-110. In a further embodiment the polynucleotide comprises or consists of SEQ ID NO: 99-110. In a further aspect there is provided a cDNA comprising said polynucleotide.

In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with SEQ ID NO: 99-101 or 105-108. In one embodiment, the expression vector comprises the VH region of SEQ ID NO: 99-101 or 105-108. In another embodiment, the expression vector comprises the VL region of SEQ ID NO: 99-101 or 105-108. In a further embodiment the polynucleotide comprises or consists of SEQ ID NO: 99-101 or 105-108. In a further aspect there is provided a cDNA comprising said polynucleotide.

In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with SEQ ID NO: 99-101. In one embodiment, the expression vector comprises the VH region of SEQ ID NO: 99-101. In another embodiment, the expression vector comprises the VL region of SEQ ID NO: 99-101. In a further embodiment the polynucleotide comprises or consists of SEQ ID NO: 99-101. In a further aspect there is provided a cDNA comprising said polynucleotide.

In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with any one of the portions of SEQ ID NO: 99-110 which encodes CDR1, CDR2 and/or CDR3 of the encoded immunoglobulin chain variable domain. In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with any one of the portions of SEQ ID NO: 99-101 or 105-108 which encodes CDR1, CDR2 and/or CDR3 of the encoded immunoglobulin chain variable domain. In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with any one of the portions of SEQ ID NO: 99-101 which encodes CDR1, CDR2 and/or CDR3 of the encoded immunoglobulin chain variable domain.

In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with any one of the portions of SEQ ID NO: 99-110 which encodes FR1, FR2, FR3 and/or FR4 of the encoded immunoglobulin chain variable domain. In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with any one of the portions of SEQ ID NO: 99-101 or 105-108 which encodes FR1, FR2, FR3 and/or FR4 of the encoded immunoglobulin chain variable domain. In one embodiment, the polynucleotide comprises or consists of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with any one of the portions of SEQ ID NO: 99-101 which encodes FR1, FR2, FR3 and/or FR4 of the encoded immunoglobulin chain variable domain.

The polynucleotides and expression vectors of the invention may also be described in reference to the amino acid sequence encoded. Therefore, in one embodiment, the polynucleotide comprises or consists of a sequence encoding the amino acid sequence of any

one of SEQ ID NOs: 62 to 85. In one embodiment, the expression vector comprises a sequence encoding the amino acid sequence of any one of SEQ ID NOs: 62 to 73. In another embodiment, the expression vector comprises a sequence encoding the amino acid sequence of any one of SEQ ID NOs: 74 to 85.

5

To express the antibodies, or fragments thereof, polynucleotides encoding partial or full-length light and heavy chains, as described herein, are inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. Therefore, in one aspect of the invention there is provided an expression vector comprising the
10 polynucleotide sequence as defined herein. In one embodiment, the expression vector comprises the VH region of SEQ ID NO: 99-110, such as SEQ ID NO: 99, 100, 101, 105, 106, 107 or 108. In another embodiment, the expression vector comprises the VL region of SEQ ID NO: 99-110, such as SEQ ID NO: 99, 100, 101, 105, 106, 107 or 108.

15 It will be understood that the nucleotide sequences described herein comprise additional sequences encoding amino acid residues to aid with translation, purification and detection, however alternative sequences may be used depending upon the expression system used. For example, the initial (5'-end) nine nucleotides of SEQ ID NOs: 99-110 and the final (3'-end) 36 nucleotides of SEQ ID NOs: 99-100, 102-103, 105-110, or the final (3'-end) 39 nucleotides
20 of SEQ ID NOs: 101 and 104 are optional sequences. These optional sequences can be removed, modified or substituted if alternate design, translation, purification or detection strategies are adopted.

Mutations can be made to the DNA or cDNA that encode polypeptides which are silent as to
25 the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, *e.g.*, *E. coli* and *S. cerevisiae*, as well as mammalian, specifically human, are known.

Mutation of polypeptides can be achieved for example by substitutions, additions or deletions
30 to a nucleic acid encoding the polypeptide. The substitutions, additions or deletions to a nucleic acid encoding the polypeptide can be introduced by many methods, including for example error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, gene
35 reassembly, artificial gene synthesis, Gene Site Saturation Mutagenesis (GSSM), synthetic ligation reassembly (SLR) or a combination of these methods. The modifications, additions or deletions to a nucleic acid can also be introduced by a method comprising recombination,

recursive sequence recombination, phosphothioate-modified DNA mutagenesis, uracil-containing template mutagenesis, gapped duplex mutagenesis, point mismatch repair mutagenesis, repair-deficient host strain mutagenesis, chemical mutagenesis, radiogenic mutagenesis, deletion mutagenesis, restriction-selection mutagenesis, restriction-purification mutagenesis, ensemble mutagenesis, chimeric nucleic acid multimer creation, or a combination thereof.

In particular, artificial gene synthesis may be used. A gene encoding a polypeptide of the invention can be synthetically produced by, for example, solid-phase DNA synthesis. Entire genes may be synthesized *de novo*, without the need for precursor template DNA. To obtain the desired oligonucleotide, the building blocks are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, deprotected, and collected. Products can be isolated by high-performance liquid chromatography (HPLC) to obtain the desired oligonucleotides in high purity.

Expression vectors include, for example, plasmids, retroviruses, cosmids, yeast artificial chromosomes (YACs) and Epstein-Barr virus (EBV) derived episomes. The polynucleotide is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the polynucleotide. Expression and/or control sequences can include promoters, enhancers, transcription terminators, a start codon (i.e. ATG) 5′ to the coding sequence, splicing signals for introns and stop codons. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. SEQ ID NOs: 99-110 comprise the nucleotide sequences encoding single chain variable fragments of the invention, comprising a VH region and a VL region joined by a synthetic linker (e.g. encoding SEQ ID NO: 98). It will be understood that polynucleotides or expression vectors of the invention may comprise the VH region, the VL region or both (optionally including the linker). Therefore, polynucleotides encoding the VH and VL regions can be inserted into separate vectors, alternatively sequences encoding both regions are inserted into the same expression vector. The polynucleotide(s) are inserted into the expression vector by standard methods (*e.g.*, ligation of complementary restriction sites on the polynucleotide and vector, or blunt end ligation if no restriction sites are present).

A convenient vector is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, as described herein. The expression vector

can also encode a signal peptide that facilitates secretion of the antibody (or fragment thereof) from a host cell. The polynucleotide may be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (*i.e.,* a signal peptide from a non-immunoglobulin protein).

A host cell may comprise a first vector encoding the light chain of the antibody or fragment thereof, and a second vector encoding the heavy chain of the antibody or fragment thereof. Alternatively, the heavy and light chains both encoded on the same expression vector introduced into the host cell. In one embodiment, the polynucleotide or expression vector encodes a membrane anchor or transmembrane domain fused to the antibody or fragment thereof, wherein the antibody or fragment thereof is presented on an extracellular surface of the host cell.

Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors.

Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, inter alia, Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and fungal cells. Antigen-binding fragments of antibodies such as the scFv and Fv fragments can be isolated and expressed in *E. coli* using methods known in the art.

The antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody

into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Antibodies (or fragments) of the invention can be obtained and manipulated using the techniques disclosed for example in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (2012) 4th Edition Cold Spring Harbour Laboratory Press.

Monoclonal antibodies can be produced using hybridoma technology, by fusing a specific antibody-producing B cell with a myeloma (B cell cancer) cell that is selected for its ability to grow in tissue culture and for an absence of antibody chain synthesis.

A monoclonal antibody directed against a determined antigen can, for example, be obtained by:

a) immortalizing lymphocytes obtained from the peripheral blood of an animal previously immunized with a determined antigen, with an immortal cell and preferably with myeloma cells, in order to form a hybridoma,

b) culturing the immortalized cells (hybridoma) formed and recovering the cells producing the antibodies having the desired specificity.

Alternatively, the use of a hybridoma cell is not required. Antibodies capable of binding to the target antigens as described herein may be isolated from a suitable antibody library via routine practice, for example, using the phage display, yeast display, ribosomal display, or mammalian display technology known in the art. Accordingly, monoclonal antibodies can be obtained, for example, by a process comprising the steps of:

a) cloning into vectors, especially into phages and more particularly filamentous bacteriophages, DNA or cDNA sequences obtained from lymphocytes especially peripheral blood lymphocytes of an animal (suitably previously immunized with determined antigens),

b) transforming prokaryotic cells with the above vectors in conditions allowing the production of the antibodies,

c) selecting the antibodies by subjecting them to antigen-affinity selection,

d) recovering the antibodies having the desired specificity.

It will be understood that all embodiments described herein may be applied to all aspects of the invention.

Other features and advantages of the present invention will be apparent from the description provided herein. It should be understood, however, that the description and the specific

examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications will become apparent to those skilled in the art. The invention will now be described using the following, non-limiting examples:

EXAMPLES

EXAMPLE 1. Materials and Methods

Human Antibody Discovery

Human phage display was employed to generate the human anti-human variable Vδ1+ domain antibodies as described herein. The library was constructed as described in Schofield et al (*Genome biology* 2007, **8**(11): R254) and comprised a single chain fragment variable (scFv) displaying library of ~40 billion human clones. This library was screened using antigens, methods, selections, deselection, screening, and characterization strategies as described herein.

Antigen preparation

The design of the soluble γδ TCR heterodimers comprising the TCRα and TCR β constant regions used in the below Examples were generated according to Xu *et al.* (2011) *PNAS* 108: 2414-2419. Vγ or Vδ domains were fused in-frame to a TCRα or TCRβ constant region lacking the transmembrane domain, followed by a leucine zipper sequence or an Fc sequence, and a histidine tag/linker.

The expression construct was transiently transfected in mammalian EXPI HEK293 suspension cells (either as single or co-transfections for heterodimer). Secreted recombinant proteins were recovered and purified from culture supernatant by affinity chromatography. To ensure good recovery of monomer antigen, samples were further purified using preparative size exclusion chromatography (SEC). Purified antigens were analysed for purity by SDS-PAGE and aggregation state by analytical SEC.

Antigen functional validation

The specificity of the antigens containing delta variable 1 (Vδ1) chain was confirmed in DELFIA immunoassay (Perkin Elmer) and in flow-based assay in competition with γδ T cells using REA173-Miltenyi Biotec anti-Vδ1 antibody.

Dissociation-enhanced lanthanide fluorescence immunoassay (DELFIA)

For the confirmation of antigen's specificity, DELFIA immunoassay was performed with the antigen directly coated to the plate (3 µg/mL of antigen in 50 µL PBS at 4 °C overnight (Nunc #437111) and serial dilution of primary antibodies starting at 300nM. For detection DELFIA Eu-N1 Anti-Human IgG (Perkin Elmer # 1244-330) was used as secondary antibody at 1/500 dilution in 50 µL of 3 % of MPBS (PBS + 3 % (w/V) skimmed milk powder). Development was with 50 µL of DELFIA enhancement solution (Perkin Elmer #4001-0010).

Affinity ranking of antibody of interest were performed using DELFIA immunoassay in which antibodies were captured via protein G coated on the plate and soluble biotinylated L1 (DV1-GV4) antigen was added at 5nM in 50 µL (3MPBS). For detection 50 µL of streptavidin-Eu (1:500 in assay buffer, Perkin Elmer) was used and signal was developed with DELFIA enhancement solution. D1.3 hIgG1 (described in England *et al.* (1999) *J. Immunol.* 162: 2129-2136) was used as a negative control.

Phage display selection outputs were subcloned into the scFv expression vector pSANG10 (Martin *et al.* (2006) *BMC Biotechnol.* 6: 46). Soluble scFv were expressed and screened for binding in DELFIA on directly immobilised targets. Hits were defined as a DELFIA signal above 3000 fluorescence units.

<u>Antibody preparation</u>

Selected scFvs were subcloned into IgG1 frameworks using commercially available plasmids. expi293F suspension cells were transfected with said plasmids for antibody expression. For convenience, unless otherwise noted, the antibodies characterised in these Examples refer to IgG1 formatted antibodies selected from phage display as scFv. However, the antibodies of the invention may be in any antibody format as previously discussed.

<u>Antibody purification</u>

IgG antibodies were batch purified from supernatants using protein A chromatography. Concentrated protein A eluates were then purified using Size Exclusion Chromatography (SEC). Quality of purified IgG was analysed using ELISA, SDS-PAGE and SEC-HPLC.

<u>γδ T cell preparation</u>

Populations of enriched γδ T cells were prepared according to the methods described in WO2016/198480 (i.e. blood-derived γδ T cells) or WO2020/095059 (i.e. skin-derived γδ T cells). Briefly, for blood-derived γδ T cells PBMCs were obtained from blood and subjected to magnetic depletion of αβ T cells. The αβ-depleted PBMCs were then cultured in CTS OpTmiser media (ThermoFisher) in the presence of OKT-3 (or respective anti-Vδ1 antibody),

IL-4, IFN-γ, IL-21 and IL-1β for 7 days. At day 7 of culture, the media was supplemented with OKT-3 (or respective anti-Vδ1 antibody), IL-21 and IL-15 for a further 4 days. At day 11 of culture, the media was supplemented with OKT-3 (or respective anti-Vδ1 antibody) and IL-15 for a further 3 days. At day 14 of culture, half of the media was replaced with fresh complete OpTmiser and supplemented with OKT-3 (or respective anti-Vδ1 antibody), IL-15 and IFN-γ. From day 17 of culture onwards, the culture was supplemented with OKT-3 (or respective anti-Vδ1 antibody) and IL-15 every 3 to 4 days; half of the media was replaced with fresh media every 7 days.

For skin-derived γδ T cells, skin samples were prepared by removing subcutaneous fat and a 3mm biopsy punch is used to make multiple punches. Punches were placed on carbon matrix grids and placed in the well of a G-REX6 (Wilson Wolf). Each well was filled with complete isolation medium containing AIM-V media (Gibco, Life Technologies), CTS Immune Serum Replacement (Life Technologies), IL-2 and IL-15. For the first 7 days of culture, complete isolation medium containing Amphotericin B (Life Technologies) was used ("+AMP"). Media was changed every 7 days by gently aspirating the upper media and replacing with 2X complete isolation medium (without AMP), trying not to disturb the cells at the bottom of the plate or bioreactor. Beyond three weeks in culture, the resulting egressed cells were then passaged into fresh tissue culture vessels and fresh media (e.g. AIM-V media or TexMAX media (Miltenyi)) plus recombinant IL-2, IL-4, IL-15 and IL-21 before harvest. Optionally, αβ T cells also present within the culture are then removed with aid of αβ T cell depletion kits and associated protocols, such as those provided by Miltenyi. For further reference see WO2020/095059.

γδ T cell binding assay

The binding of antibodies to γδ T cells was tested by incubating a fixed concentration of purified antibodies with 250000 γδ T cells. This incubation was performed under blocking conditions to prevent unspecific binding of antibodies via the Fc receptor. Detection was performed by addition of a secondary, fluorescent dye-conjugated antibody against human IgG1. For negative controls, cells were prepared with a) an isotype antibody only (recombinant human IgG), b) the fluorescent dye-conjugated anti-human IgG antibody only and c) a combination of a) and b). A control well of completely unstained cells was also prepared and analysed. As positive controls, a purified murine monoclonal IgG2 anti-human CD3 antibody and a purified murine monoclonal IgG1 anti-human TCR Vδ1 antibody were used in two different concentrations and stained with a fluorescent dye-conjugated goat anti-mouse secondary antibody. The assay was accepted if the lower concentration positive controls'

mean fluorescence intensity in the FITC channel was at least tenfold as high as the highest negative control.

SPR Analysis

5 A MASS-2 instrument with an amine high capacity chip (both from Sierra Sensors, Germany) was used to perform SPR analysis. 15 nM IgG were captured via protein G to an amine high capacity chip (100 nM for TS8.2). L1 (DV1-GV4) antigen was flown over the cell at a 1:2 dilution series from 2000 nM to 15.625 nM with the following parameters: 180 s association, 600 s dissociation, flowrate 30 µL/min, running buffer PBS + 0.02 % Tween 20. All experiments 10 were performed at room temperature on MASS-2 instrument. Steady state fitting was determined according to Langmuir 1:1 binding using software Sierra Analyzer 3.2.

Comparator antibodies

Antibodies were compared to commercially available antibodies in test assays as described.

15

Antibody	**Source**	**Catalogue No.**
Ultra-LEAF™ Purified anti-human CD3 Antibody (OKT3), functional	Biolegend	317326
Ultra-LEAF™ Purified anti-human IgG2a Antibody (isotype control for OKT3)	Biolegend	400264
Human TCR Vδ1 purified mAb (functional TS8.2)	ThermoFisher	TCR1730
Ultra-LEAF™ Purified Mouse IgG1, κ Isotype Ctrl Antibody for TS8.2	Biolegend	400166
Anti-human CD107a BV421 (clone H4A3)	BD Biosciences	562623
BV421 Mouse IgG1, k Isotype Control Clone X40 (RUO)	BD Biosciences	562438
Anti-TCR Vδ1-PE-Vio770, human (flow, discontinued)	Miltenyi	130-100-540

γδ TCR downregulation and degranulation assay

THP-1 (TIB-202™, ATCC) target cells loaded or not with test antibodies were labelled with CellTracker™ Orange CMTMR (ThermoFisher, C2927) and incubated with γδ T cells at 2:1 20 ratio in the presence of CD107a antibody (Anti-human CD107a BV421 (clone H4A3) BD

Biosciences 562623). After 2 hours of incubation, the surface expression of γδ TCR (to measure TCR downregulation) and expression of CD107a (to measure degranulation) on γδ T cells was evaluated using flow cytometry.

5 Killing assay

Gamma delta T cell killing activity and effect of test antibodies on the killing activity of γδ T cells was accessed by flow cytometry. After 4 hours of *in vitro* co-culture at 20:1 ratio of γδ T cells and CellTracker™ Orange CMTMR (ThermoFisher, C2927) labelled THP-1 cells (loaded or not with the antibody) were stained with Viability Dye eFluor™ 520 (ThermoFisher, 520 65-
10 0867-14) to distinguish between live and dead target THP-1 cells. During sample acquisition, target cells were gated on the CellTracker™ Orange CMTMR positivity and examined for cell death based on the uptake of Viability Dye. CMTMR and eFluor™ 520 double positive cells were recognized as the dead target cells. The killing activity of γδ T cells was presented as a % of the dead target cells.

15

Epitope mapping

All protein samples (antigen L1 (DV1-GV4) and antibodies 1245_P01_E07, 1245_P02_G04, 1252_P01_C08, 1251_P02_C05 and 1141_P01_E01) used for epitope mapping were analyzed for protein integrity and aggregation level using a high-mass MALDI.

20

In order to determine the epitope of L1(DV1-GV4)/1245_P01_E07, L1(DV1-GV4)/1245_P02_G04, L1(DV1-GV4)/1252_P01_C08, L1(DV1-GV4)/1251_P02_C05, and L1(DV1-GV4)/1141_P01_E01 complexes with high resolution, the protein complexes were incubated with deuterated cross-linkers and subjected to multi-enzymatic proteolysis using
25 trypsin, chymotrypsin, Asp-N, elastase and thermolysin. After enrichment of the cross-linked peptides, the samples were analyzed by high resolution mass spectrometry (nLC-LTQ-Orbitrap MS) and the data generated were analyzed using XQuest and Stavrox software.

SYTOX-flow killing assay

30 The SYTOX assay allows the quantification of T cell mediated cytolysis of target cells using flow cytometry. Dead/dying cells are detected by a dead cell stain (SYTOX® AADvanced™, Life Technologies, S10274) which only penetrates into cells with compromised plasma membranes but cannot not cross intact cell membranes of healthy cells. NALM-6 target cells were labelled with CTV dye (Cell Trace Violet™, Life Technologies, C34557) and were thus
35 distinguishable from the unlabelled effector T cells. Dead/dying target cells are identified through double staining of the dead cell dye and the cell trace dye.

After 16 hours *in vitro* co-culture of effector and CTV labelled target cells at indicated Effector-to-Target ratios (E:T, 1:1 or 10:1) the cells were stained with SYTOX® AADvanced™ and acquired on a FACSLyric™ (BD). The killing results are presented as % target cell reduction which is calculated by taking into account the number of live target cells (sample counts) in
5 the test samples over the live target cells in the control wells without added effector cells (maximum counts):

$$\%\, target\, reduction = 100 - \left(\frac{sample\ counts}{maximum\ counts}\right) x100$$

EXAMPLE 2. Antigen design

10 Gamma delta (γδ) T cells are polyclonal with CDR3 polyclonality. In order to avoid a situation where generated antibodies would be selected against the CDR3 sequence (as the CDR3 sequence will differ from TCR clone to TCR clone), the antigen design involved maintaining a consistent CDR3 in different formats. This design aimed to generate antibodies recognising a sequence within the variable domain, which is germline encoded and therefore the same in all
15 clones, thus providing antibodies which recognise a wider subset of γδ T cells.

Another important aspect of the antigen preparation process was to design antigens which are suitable for expression as a protein. The γδ TCR is a complex protein involving a heterodimer with inter-chain and intra-chain disulphide bonds. A leucine zipper (LZ) format and Fc format
20 were used to generate soluble TCR antigens to be used in the phage display selections. Both the LZ and Fc formats expressed well and successfully displayed the TCR (particularly heterodimeric TCRs, *e.g.* Vδ1Vγ4).

It was found that the CDR3 sequence from a public database entry for the γδ TCR expressed
25 well as proteins (RCSB Protein Data Bank entries: 3OMZ). This was therefore selected for antigen preparation.

Antigens containing the delta variable 1 chain were expressed in LZ formats as a heterodimer (*i.e.* in combination with different gamma variable chains – “L1”, “L2”, “L3”) and in Fc format
30 either as a heterodimer (“F1”, “F2”, “F3”) or as a homodimer (*i.e.* in combination with another delta variable 1 chain – “Fc1/1”). All delta variable 1 chains of the antigens contained the 3OMZ CDR3. Another series of γδ TCR antigens using similar formats were designed containing different delta variable chains (such as delta variable 2 and delta variable 3) and used to deselect antibodies with non-specific or off target binding (“L4”, “F9”, “Fc4/4”, “Fc8/8”).
35 These antigens were also designed to include the 3OMZ CDR3 to ensure that antibodies binding in the CDR3 region were also deselected.

Antigen functional validation was performed to confirm that the designed antigens would be suitable to generate anti-TRDV1 (TCR delta variable 1) antibodies. Detection was seen only with antigens containing the δ1 domain (**Figure 1**).

5

EXAMPLE 3. Phage Display

Phage display selections were performed against libraries of human scFvs using either heterodimeric LZ TCR format in round 1 and 2, with deselections on heterodimeric LZ TCR in both rounds. Or round 1 was performed using homodimeric Fc fusion TCR with deselection

10 on human IgG1 Fc followed by round 2 on heterodimeric LZ TCR with deselection on heterodimeric LZ TCR (see **Table 1**).

Table 1. Overview phage display selections

Target	Round 1 selection	Round 1 deselection	Round 2 selection	Round 2 deselection
DV1	bt-L1 (DV1-GV4)	L4 (DV2-GV4)	bt-L3 (DV1-GV8)	L4 (DV2-GV4)
DV1	bt-Fc1/1 (DV1-DV1)	Fc	bt-L1 (DV1-GV4)	L4 (DV2-GV4)

bt = biotin.

15

Selections were performed in solution phase using 100 nM biotinylated proteins. Deselections were performed using 1 µM non-biotinylated proteins.

Success of the phage display selections was analysed by polyclonal phage ELISA (DELFIA).

20 All DV1 selection outputs showed the desired binding to the targets Fc 1/1, L1, L2, L3, F1 and F3. Varying degrees of binding to non-targets L4, F9, Fc 4/4, Fc 8/8 and Fc were detected (see **Figure 2A** and **B**).

EXAMPLE 4. Antibody selection

25 Hits obtained in Example 3 were sequenced (using standard methods known in the art). 130 unique clones were identified, which showed a unique combination of VH and VL CDR3. Of these 130 unique clones, 125 showed a unique VH CDR3 and 109 showed a unique VL CDR3.

Unique clones were re-arrayed and specificity was analysed by ELISA (DELFIA). A panel of

30 94 unique human scFv binders which bind TRDV1 (L1, L2, L3, F1, F2, F3) but not TRDV2 (L4), were identified from the selections.

Affinity ranking of the selected binders was included to aid the choice of clones going forward. A large number of binders showed affinities in the nanomolar range, reacting with 25 to 100 nM biotinylated antigen. A handful of binders showed a strong reaction with 5 nM antigen, indicating possible single digit nanomolar affinities. Some binders showed no reaction with 100 nM antigen, indicating affinities in the micromolar range.

For the selection of clones to proceed with to IgG conversion, the aim was to include as many germline lineages and as many different CDR3s as possible. Further, sequence liabilities like glycosylation, integrin binding sites, CD11c/CD18 binding sites, unpaired cysteines were avoided. In addition, a variety of affinities was included.

Selected clones were screened for binding to natural, cell-surface expressed γδTCR using skin derived γδ T cells obtained from different donors. The clones chosen to be converted to IgG are shown in **Table 2**.

Table 2. DV1 binders for IgG conversion

Clone ID	Heavy CDR1	SEQ ID NO.	Heavy CDR2	SEQ ID NO.	Heavy CDR3	SEQ ID NO.	Light CDR1	SEQ ID NO.	Light CDR2	SEQ	Light CDR3	SEQ ID NO.	100 nM L1
1245_P01_E07	GFTFSDYY	38	ISSSGSTI	26	VDYADAFDI	2	QSIGTY	50	VAS	A1	QQSYSTLLT	14	162591
1252_P01_C08	GFTVSSNY	39	IYSGGST	27	PIELGAFDI	3	NIGSQS	51	YDS	A2	QVWDSSSDHVV	15	1977
1245_P02_G04	GDSVSSKSAA	40	TYYRSKWST	28	TWSGYVDV	4	QDINDW	52	DAS	A3	QQSYSTPQVT	16	5896
1245_P01_B07	GFTFSDYY	41	ISSSGSTI	29	ENYLNAFDI	5	QSLSNY	53	AAS	A4	QQSYSTPLT	17	64271
1251_P02_C05	GFTFSSYA	42	ISGGGGTT	30	DSGVAFDI	6	QNIRTW	54	DAS	A5	QQFKRYPPT	18	65269
1141_P01_E01	GYSFTSYW	43	IYPGDSDT	31	HQVDTRTADY	7	RSDVGGYNY	55	EVS	A6	SSYTSTSTLV	19	136780
1139_P01_E04	GDSVSSNSAA	44	TYYRSKWYN	32	SWNDAFDI	8	QSISTW	56	DAS	A7	QQSYSTPLT	20	23786
1245_P02_F07	GDSVSSNSAA	45	TYYRSKWYN	33	DYYYSMDV	9	QSISSW	57	DAS	A8	QQSHSHPPT	21	10450
1245_P01_G06	GFTFSDYY	46	ISSSGSTI	34	HSWNDAFDV	10	QSISSY	58	AAS	A9	QQSYSTPDT	22	22474
1245_P01_G09	GDSVSSNSAA	47	TYYGSKWYN	35	DYYYSMDV	11	QSISTW	59	DAS	A10	QQSYSTPVT	23	18430
1138_P01_B09	GFTFSDYY	48	ISSSGSTI	36	HSWSDAFDI	12	QDISNY	60	DAS	A11	QQSYSTPLT	24	29193
1251_P02_G10	GFTFSDYY	49	ISSSGSTI	37	HSWNDAFDI	13	QSISSH	61	AAS	A12	QQSYSTLLT	25	17053

EXAMPLE 5: Antibody SPR analysis

Prepared IgG antibodies were passed through a γδ cell binding assay, and the 5 best binders were selected for further functional and biophysical characterization. SPR analysis was performed to determine the equilibrium dissociation constants (K_D). Sensorgrams of the
5 interaction of the tested antibody with the analyte, along with steady state fits (if available), are presented in **Figure 3**. No binding was detected for TS8.2 with 80 RU of IgG captured on the chip. Results are summarised in **Table 3**.

Table 3. Results of IgG capture

Analyte	Clone ID	K_D (nM)	K_D (M)
L1 (DV1-GV4)	**1245_P01_E07**	12.4	1.24e-08
L1 (DV1-GV4)	**1252_P01_C08**	100	1.00e-07
L1 (DV1-GV4)	**1245_P02_G04**	126	1.26e-07
L1 (DV1-GV4)	**1245_P01_B07**	341	3.41e-07
L1 (DV1-GV4)	**1251_P02_C05**	1967*	1.97e-06
L1 (DV1-GV4)	**1139_P01_E04**	251	2.51e-07
L1 (DV1-GV4)	**1245_P02_F07**	193	1.93e-07
L1 (DV1-GV4)	**1245_P01_G06**	264	2.64e-07
L1 (DV1-GV4)	**1245_P01_G09**	208	2.08e-07
L1 (DV1-GV4)	**1138_P01_B09**	290	2.90e-07
L1 (DV1-GV4)	**1251_P02_G10**	829	8.29e-07
L1 (DV1-GV4)	**TS8.2** (commercial anti-Vδ1 antibody)	44	4.40e-08

10 *Binding of 1252_P02_C05 did not reach saturation, therefore data was extrapolated

EXAMPLE 6: TCR engagement assay

The inventors designed several assays to be used for functional characterization of the selected antibodies. The first assay assessed γδ TCR engagement by measuring
15 downregulation of the γδ TCR upon antibody binding. Selected antibodies were tested against commercial anti-CD3 and anti-Vδ1 antibodies which were used as positive controls or against 1252_P01_C08 as a positive control (for 1139_P01_E04, 1245_P02_F07, 1245_P01_G06 and 1245_P01_G09). Commercial anti-panγδ was used as a negative control because it is a panγδ antibody, recognising all γδ T cells irrespective of variable chain, and therefore is likely
20 to have a different mode of action.

The assay was performed using skin-derived γδ T cells obtained from three different donor samples (samples with 94%, 80% and 57% purity). Results are shown in **Figure 4**. EC50 values are summarised in **Table 4**, below.

5 **EXAMPLE 7: T cell degranulation assay**

A second assay assessed the degranulation of γδ T cell. It is thought γδ T cells may mediate target cell killing by perforin-granzyme-mediated activation of apoptosis. Lytic granules within the cytoplasm of the γδ T cell may be released toward the target cell upon T cell activation. Therefore, labelling target cells with antibodies to CD107a and measuring the expression by 10 flow cytometry can be used to identify degranulating γδ T cells.

As for **Example 6**, selected antibodies were tested against commercial anti-CD3 and anti-Vδ1 antibodies as positive controls or against 1252_P01_C08 as a positive control (for 1139_P01_E04, 1245_P02_F07, 1245_P01_G06 and 1245_P01_G09). IgG2a, IgG1 and 15 D1.3 antibodies were used as negative controls. The assay was performed using skin-derived γδ T cells obtained from three different donor samples (samples with 94%, 80% and 57% purity). Results are shown in **Figure 5**. EC50 values are summarised in **Table 4**, below.

EXAMPLE 8: Killing assay

20 A third assay assessed the ability of γδ T cells activated with the selected antibodies to kill target cells.

As for **Example 6**, selected antibodies were tested against commercial anti-CD3 and anti-Vδ1 antibodies as positive controls or against 1252_P01_C08 as a positive control (for 25 1139_P01_E04, 1245_P02_F07, 1245_P01_G06 and 1245_P01_G09) and anti-panγδ as a negative control. IgG2a, IgG1 and D1.3 antibodies were also used as isotype controls. The assay was performed using skin-derived γδ T cells obtained from two donors (94% and 80% purity) and the results are shown in **Figure 6**.

30 Results from the three functional assays tested in **Examples 6-8** are summarised in **Table 4**.

Table 4. Summary of results obtained from functional assays

Clone ID	TCR downregulation (EC50 µg/ml – 3 donors)	T cell degranulation (EC50 µg/ml – 3 donors)	Killing assay (EC50 µg/ml – 2 or 3 donors)
1245_P01_E07	0.04-0.11	0.007-0.004	0.06

1252_P01_C08	0.02-0.03	0.001-0.0006	0.02
1245_P02_G04	0.01-0.05	0.002	0.10
1245_P01_B07	Positive; 0.35 (1 donor only)	Positive; 0.1 (1 donor only)	0.13
1251_P02_C05	Positive; N/D	Positive; N/D	N/D*
1139_P01_E04	0.027-0.057	0.005	0.005-0.019
1245_P02_F07	0.032-0.043	0.001-0.002	0.006-0.018
1245_P01_G06	0.042-0.055	0.001	0.007-0.051
1245_P01_G09	0.029-0.040	0.001	0.003-0.008
1138_P01_B09	0.078-0.130	N/D	0.055-0.199
1251_P02_G10	0.849; N/D	N/D	N/D**
OKT3 (anti-CD3 antibody)	0.03-0.04	0.001-0.008	0.05
TS8.2 (anti-Vδ1 antibody)	0.48-0.8	0.07-0.16	N/D*

N/D: could not be determined; N/D*: could not be determined, titration curve did not reach plateau; N/D**: Reduced killing profile, EC50 not established.

EXAMPLE 9: Epitope mapping

5 In order to determine the epitope of antigen/antibody complexes with high resolution, the protein complexes were incubated with deuterated cross-linkers and subjected to multi-enzymatic cleavage. After enrichment of the cross-linked peptides, the samples were analysed by high resolution mass spectrometry (nLC-LTQ-Orbitrap MS) and the data generated were analysed using XQuest (version 2.0) and Stavrox (version 3.6) software.

10

After trypsin, chymotrypsin, Asp-N, elastase and thermolysin proteolysis of the protein complex L1(DV1-GV4)/1245_P01_E07 with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 13 cross-linked peptides between L1(DV1-GV4) and the antibody 1245_P01_E07. Results are presented in **Figure 7**.

15

After trypsin, chymotrypsin, Asp-N, elastase and thermolysin proteolysis of the protein complex L1(DV1-GV4)/1252_P01_C08 with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 5 cross-linked peptides between L1(DV1-GV4) and the antibody 1252_P01_C08. Results are presented in **Figure 8**.

20

After trypsin, chymotrypsin, Asp-N, elastase and thermolysin proteolysis of the protein complex L1(DV1-GV4)/1245_P02_G04 with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 20 cross-linked peptides between L1(DV1-GV4) and the antibody 1245_P02_G04. Results are presented in **Figure 9**.

5

After trypsin, chymotrypsin, Asp-N, elastase and thermolysin proteolysis of the protein complex L1(DV1-GV4)/1251_P02_C05 with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 5 cross-linked peptides between L1(DV1-GV4) and the antibody 1251_P02_C05. Results are presented in **Figure 10**.

10

Epitope binding with another antibody, Clone ID 1141_P01_E01, was also tested. After trypsin, chymotrypsin, Asp-N, elastase and thermolysin proteolysis of the protein complex L1(DV1-GV4)/1141_P01_E01 with deuterated d0d12, the nLC-orbitrap MS/MS analysis detected 20 cross-linked peptides between L1(DV1-GV4) and the antibody 1141_P01_E01.
15 Results are presented in **Figure 11**.

A summary of the epitope mapping results is presented in **Table 5**.

Table 5. Results of epitope mapping for antigen/antibody complexes

Clone ID	**Epitope mapping, amino acid numbering of SEQ ID NO: 1**
1245_P01_E07	5, 9, 16, 20, 62, 64, 72, 77
1252_P01_C08	50, 53, 59, 62, 64
1245_P02_G04	37, 42, 50, 53, 59, 64, 68, 69, 72, 73, 77
1251_P02_C05	59, 60, 68, 72
1141_P01_E01	3, 5, 9, 10, 12, 16, 17, 62, 64, 68, 69

20

EXAMPLE 10: Expansion of Vδ1 T cells

Expansion of isolated γδ T cells was investigated in the presence of selected antibodies and comparator antibodies. Comparator antibodies were selected from: OKT3 anti-CD3 antibody as a positive control, no antibody as a negative control or IgG1 antibody as an isotype control.
25 Commercially available anti-Vδ1 antibodies, TS-1 and TS8.2 were also tested for comparison.

Experiment 1:

An initial investigation was conducted by seeding 70,000 cells/well with Complete Optimizer and cytokines as described in the "γδ T cell preparation" for blood-derived γδ T cells of

Example 1. Selected and comparator antibodies were tested at various concentrations ranging from 4.2 ng/ml to 420 ng/ml. This experiment was conducted using tissue culture plates which allow the binding/immobilisation of the antibodies to the plastic.

5 Cells were harvested on days 7, 14 and 18 and the total cell count was determined using a cell counter (NC250, ChemoMetec). The results are shown in **Figure 12**. Cell viability of Vδ1 T cells was also measured on each harvest and all antibodies were shown to maintain cell viability throughout the experiments (data not shown). On day 18, the percentage, cell count and fold change of Vδ1 T cells was also analysed. The results are shown in **Figure 13**.

10

As can be seen in **Figure 12**, the total number of cells produced in cultures with antibodies increased steadily throughout the culture and were comparable or better than the commercial anti-Vδ1 antibodies. At day 18, the proportion of Vδ1 positive cells in the presence of 1245_P02_G04 ("G04"), 1245_P01_E07 ("E07"), 1245_P01_B07 ("B07") and 1252_P01_C08
15 ("C08") antibodies at most concentrations tested was greater than in cultures where OKT3, TS-1 or TS8.2 control antibodies were present (see **Figure 13A**).

Experiment 2:

A subsequent experiment was performed on isolated cells in a culture vessel with cytokines
20 as described in the "γδ T cell preparation" of Example 1. Compared to Experiment 1, a different culture vessel was used whose surface does not facilitate antibody binding/immobilisation. Selected and comparator antibodies were tested at various concentrations ranging from 42 pg/ml to 42 ng/ml. During Experiment 2, results were obtained from experiments run in triplicates.

25

Cells were harvested on days 7, 11, 14 and 17 and the total cell count was determined using a cell counter as before. The results are shown in **Figure 14**. On day 17, the percentage, cell count and fold change of Vδ1 T cells was also analysed. The results are shown in **Figure 15**.

30 The cell composition, including non-Vδ1 cells, were also measured during Experiment 2. Day 17 cells were harvested and analysed by flow cytometry for surface expression of Vδ1, Vδ2 and αβTCR. The proportions of each cell type in each culture are shown graphically in **Figure 16** and the percentage values are provided in **Table 6**.

35

Table 6. Cell composition at day 17 - Percentage of live cells of each subset

	αβ- γδ-	Vδ1	Vδ2	non Vδ1/Vδ2	αβ
no AB	63.00	18.17	0.86	7.10	0.37
OKT-3	25.63	50.43	0.25	20.13	1.13
IgG1	65.77	15.59	1.11	6.91	0.42
TS8.2 42ng/ml	30.60	53.57	3.59	7.46	0.14
TS-1 42ng/ml	18.77	65.90	0.91	9.51	0.12
C08 42ng/ml	0.79	96.43	0.08	2.51	0.05
C08 4.2ng/ml	1.91	94.67	0.18	2.63	0.05
C08 420pg/ml	8.47	80.57	0.28	8.42	0.04
C08 42pg/ml	35.97	25.93	3.04	19.50	0.31
B07 42ng/ml	0.94	95.57	0.46	2.73	0.05
B07 4.2ng/ml	1.79	94.10	0.40	3.28	0.01
B07 420pg/ml	3.08	91.80	0.29	3.94	0.02
B07 42pg/ml	17.93	62.90	0.85	9.16	0.07
E07 42ng/ml	2.29	85.13	0.19	11.65	0.04
E07 4.2ng/ml	2.15	91.23	0.13	5.77	0.04
E07 420pg/ml	9.25	73.90	0.42	13.05	0.02
E07 42pg/ml	49.23	18.67	2.17	7.70	0.43
G04 42ng/ml	1.90	88.53	0.47	8.09	0.05
G04 4.2ng/ml	4.25	89.67	0.93	3.98	0.02
G04 420pg/ml	25.97	50.60	1.45	12.72	0.11
G04 42pg/ml	44.00	13.77	2.33	26.30	0.32
C05 42ng/ml	25.00	42.03	3.75	13.67	1.32
C05 4.2ng/ml	46.87	22.03	2.58	16.46	0.38
C05 420pg/ml	33.53	44.60	2.23	11.13	0.22
C05 42pg/ml	36.83	25.23	6.16	18.00	0.30

As can be seen from these results, the proportion of Vδ1 positive cells is greater in cultures with B07, C08, E07 and G04 present compared to OKT3, TS-1 or TS8.2 controls. Therefore, 5 the tested antibodies produce and expand Vδ1 positive cells more efficiently than commercially available antibodies, even when present at low concentrations in culture.

Cells from day 17 of Experiment 2 were also analysed for additional cell markers, including CD3-CD56+ to identify the presence of Natural Killer (NK) cells and Vδ1 T cells which express CD27 (i.e. CD27+). The results are summarised in **Table 7**.

5 Table 7. Cell composition at day 17 - Percentage of NK and CD27+ cells

	% CD56+CD3-		%CD27+ of Vδ1	
	Mean	SEM	Mean	SEM
no AB	66.33	8.49	92.43	1.58
OKT-3	7.90	1.04	99.03	0.14
IgG1	70.67	6.41	87.87	0.81
TS8.2 42ng/ml	31.63	1.99	66.73	5.55
TS-1 42ng/ml	22.97	1.75	94.40	1.14
C08 42ng/ml	1.00	0.15	98.17	0.31
C08 4.2ng/ml	2.06	0.07	95.07	1.23
C08 420pg/ml	8.63	1.64	88.43	3.65
C08 42pg/ml	45.10	3.44	91.50	2.50
B07 42ng/ml	1.40	0.39	95.47	1.37
B07 4.2ng/ml	1.70	0.16	96.70	0.43
B07 420pg/ml	3.47	0.38	95.17	0.86
B07 42pg/ml	22.03	4.66	88.03	3.00
E07 42ng/ml	2.59	0.93	92.27	2.10
E07 4.2ng/ml	1.98	0.09	95.77	0.52
E07 420pg/ml	8.72	1.33	92.43	0.14
E07 42pg/ml	67.73	1.23	93.60	1.16
G04 42ng/ml	2.20	0.32	93.80	0.36
G04 4.2ng/ml	3.53	0.51	91.63	1.80
G04 420pg/ml	30.53	5.00	81.37	3.11
G04 42pg/ml	51.13	8.90	94.20	0.93
C05 42ng/ml	37.17	6.53	93.80	0.87
C05 4.2ng/ml	52.27	8.16	85.40	4.46
C05 420pg/ml	37.93	1.57	90.83	2.01
C05 42pg/ml	43.40	8.64	92.17	2.02

SEM: Standard error of the mean

EXAMPLE 11: Functionality of Vδ1 T cells

Vδ1 T cells expanded in the presence of the selected antibodies retained a polyclonal repertoire of CDR3 regions and were also tested for functionality using the SYTOX-flow killing assay. The results are presented for cells obtained during Experiment 1 at day 14 using cells in a 10:1 Effector-to-Target (E:T) ratio (**Figure 17A**) and for cells obtained during Experiment 2 at day 17 (post freeze-thaw) using cells at a 1:1 and 10:1 E:T ratio (**Figure 17B**).

As can be seen in **Figure 17**, Vδ1 positive cells expanded in the presence of all antibodies effectively lysed target cells, indicating that they are functional even after freezing and thawing the cells.

EXAMPLE 12: Functionality of cells after storage

The functionality of cells after a storage step of freezing and then thawing was also investigated. A portion of cells was removed from culture at day 17 of Experiment 2 and frozen. Cells were then thawed and further expanded in culture with IL-15. **Figure 18** shows the total cell counts after 7 days of culturing cells post freeze-thaw for cultures contacted with B07, C08, E07, G04 or OKT-3 antibodies prior to freezing. All cultures showed the ability to proliferate after storage. Culturing was continued until day 42 and total cell counts were monitored during this period (results shown in **Figure 19**). Total cell numbers were maintained or increased in the cultures previously exposed to selected antibodies.

EXAMPLE 13: Anti-Vδ1 antibody conferred modulation and proliferation of immune cells in TILs

Studies were undertaken to explore anti-Vδ1 antibody conferred modulation and proliferation of human tumour infiltrating lymphocytes (TILs). For these studies, human renal cell carcinoma (RCC) tumour biopsies were shipped fresh and processed upon receipt. Specifically, the tissue was chopped into ~2mm^2. Up to 1g of tissue was placed into each Miltenyi C tube along with 4.7mL RPMI and enzymes from Miltenyi's Tumour Dissociation Kit at concentrations recommended by the manufacturer aside from Enzyme R which was used at 0.2 x concentration to prevent cleavage of pertinent cell surface molecules. C-Tubes were placed on the gentleMACS™ Octo Dissociator with Heaters. Program 37C_h_TDK_1 for the dissociation of soft tumours was selected. The digest was then filtered through a 70mM filter to generate a single cell suspension. RPMI containing 10% FBS was added to the digest to quench enzymatic activity. The cells are washed 2 x with RPMI/10%FBS and resuspended for counting. Derived cells were then seeded in TC wells (24-well G-REX, Wilson Wolf) at 2.5x10e6 per well. Cells were then incubated without or without cytokines and with or without antibodies for 18 days. Antibodies included in the study are outlined in **Figure 20**. These

include OKT3 (to 50ng/ml) and 1252_P01_C08 aka "C08" herein (to 500ng/ml). When included, bolus additions of these antibodies were added on day 0, 7, 11 and 14. During said incubation, media was replaced with fresh media on days 11 and day 14. Flow cytometry analysis was performed on day 0 and day 18 to determine the lymphocyte phenotype as well as fold change in cell number. Cells were first gated on live CD45+ cells and then as indicated. In arms where recombinant cytokines were included these were added as follows. Day 0: IL-4, IFN-γ, IL-21, IL-1β. Additional IL-15 was included on day 7, 11, 14. Additional IL-21 and IFN-γ were included on day 7 and day 14 respectively. **Figure 20 (A)** shows the fold-increase in TIL Vδ1+ cells following 18 days culture in the presence of C08 or OKT3 with and without cytokine support (CK) where indicated. These results show substantial fold increases in TIL Vδ1+ cells with the application of either the C08 or comparator OKT3 antibody in the presence of cytokines, as compared to antibody or cytokines alone. **Figure 20 (B)** shows increases in total Vδ1 cell number at harvest following . These results show substantial increases in TIL Vδ1+ cell number following culture with C08 or comparator OKT3 antibody in the presence of cytokines, as compared to antibody or cytokines alone. **Figure 20 (C)** presents an example gating strategy used in the flow cytometric analysis of the cells. From the live CD45+ cell population cells were gated on lymphocytes based on their forward and side scatter properties (not shown), γδ T cells were then separated from αβ T cells by staining for the T cell receptors. Finally, the proportion of Vδ1 cells within the total γδ T cell population was determined. Example data for day 18 is shown for 2 conditions as indicated (+/-1252_P01_C08): 64.3% cells were CD45+, of those CD45% cells, 53.1% were γδ+, and of the γδ cells, 89.7 were Vδ1+. **Figure 20 (D)** presents a cell-surface phenotypic profile of TIL Vδ1+ cells at harvest. Higher levels of CD69 were observed following culture with the C08 antibody. **Figure 20 (E)** presents analysis of the TIL γδ-negative, CD8-positive lymphocyte fraction within the live CD45-positive gate at harvest. In summary, the combined results highlight the modulatory effects conferred by anti-Vδ1 antibody of the invention described herein on TIL populations.

CLAIMS

1. An *ex vivo* method of modulating Vδ1 T cells comprising administering a human, anti-TCR delta variable 1 (anti-Vδ1) antibody or fragment thereof, which binds to an epitope of a variable delta 1 (Vδ1) chain of a γδ T cell receptor (TCR) comprising one or more amino acid residues within amino acid regions:
   (i) 3-20 of SEQ ID NO: 1; and/or
   (ii) 37-77 of SEQ ID NO: 1

to a cell population comprising Vδ1 T cells.

2. The method as defined in claim 1, wherein the epitope comprises one or more amino acid residues within amino acid regions: 5-20 and 62-77; 50-64; 37-53 and 59-72; 59-77; or 3-17 and 62-69, of SEQ ID NO: 1.

3. The method as defined in claim 1 or claim 2, wherein the epitope is an activating epitope of a γδ T cell.

4. The method as defined in any one of claims 1 to 3, which only binds to an epitope in the V region of a Vδ1 chain of a γδ TCR.

5. The method as defined in any one of claims 1 to 4, which does not bind to an epitope found in CDR3 of a Vδ1 chain of a γδ TCR.

6. An *ex vivo* method of modulating Vδ1 T cells comprising administering an anti-Vδ1 antibody or fragment thereof which comprises one or more of:
   a CDR3 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 2-25;
   a CDR2 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 26-37 and SEQUENCES: A1-A12 (of Table 2); and/or
   a CDR1 comprising a sequence having at least 80% sequence identity with any one of SEQ ID NOs: 38-61,

to a cell population comprising Vδ1 T cells.

7. The method as defined in claim 6, wherein the antibody or fragment thereof comprises a VH region comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 62-73, such as SEQ ID NO: 63, 62 or 64.

8. The method as defined in claim 6, wherein the antibody or fragment thereof comprises a VL region comprising an amino acid sequence having at least 80% sequence identity with any one of SEQ ID NOs: 74-85, such as SEQ ID NO: 75, 74 or 76.

9. The method as defined in any one of claims 6 to 8, wherein the antibody or fragment thereof comprises an amino acid sequence of any one of SEQ ID NOs: 86-97, such as SEQ ID NO: 87, 86 or 88.

10. The method as defined in any one of claims 6 to 9, wherein the antibody or fragment thereof binds to the same, or essentially the same, epitope as, or competes with, an antibody or fragment thereof as defined in any one of claims 6 to 9.

11. The method as defined in any one of claims 1 to 10, wherein the antibody or fragment thereof binds a variable delta 1 (Vδ1) chain of a γδ T cell receptor (TCR) with a binding affinity (KD) as measured by surface plasmon resonance of less than 1.5×10^{-7} M.

12. The method as defined in any one of claims 1 to 11, wherein the antibody or fragment thereof is an scFv, Fab, Fab’, F(ab')2, Fv, variable domain (*e.g.* VH or VL), diabody, minibody or full length antibody.

13. The method as defined in any one of claims 1 to 12, wherein the modulation comprises expansion of Vδ1 T cells.

14. The method as defined in claim 13, wherein the method provides an expanded population of Vδ1 T cells which contains greater than about 85% Vδ1 T cells, such as greater than about 90% Vδ1 T cells.

15. The method as defined in any one of claims 1 to 14, wherein the method comprises culturing the cell population for at least 5 days.

16. The method as defined in any one of claims 1 to 15, wherein the method comprises culturing the cell population in the presence of at least one cytokine.

17. The method as defined in claim 16, wherein the cytokine is selected from: interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-7 (IL-7), interleukin-9 (IL-9), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-21 (IL-21) or mixtures thereof.

18. The method as defined in any one of claims 1 to 17, wherein the method comprises culturing the cell population in the presence of IL-2, IL-9 and/or IL-15.

19. The method as defined in any one of claims 1 to 18, wherein the method comprises culturing the cell population in the presence of IL-21.

20. The method as defined in any one of claims 1 to 19, wherein the method comprises culturing the cell population in the presence of IL-4.

21. The method as defined in any one of claims 1 to 17, wherein the method comprises culturing the cell population in a first culture medium comprising IL-4 and then culturing the cell population in a second culture medium comprising IL-15.

22. The method as defined in claim 21, wherein the first culture medium is in the absence of IL-15, IL-2 and/or IL-7.

23. The method as defined in claim 21, wherein the second culture medium is in the absence of IL-4.

24. The method as defined in any one of claims 21 to 23, wherein the first or second culture medium, or both culture media, comprises one or more additional cytokines.

25. The method as defined in claim 24, wherein the additional cytokines are selected from the group consisting of: IL-21, IFN-γ and IL-1β.

26. The method as defined in any one of claims 15 to 25, wherein the cell population is not in direct contact with stromal and/or epithelial cells during culture.

27. The method as defined in claim 26, wherein the cell population is not in direct contact with fibroblasts during culture.

28. The method as defined in any one of claims 15 to 27, wherein the cell population is not in direct contact with tumour cells and/or feeder cells during culture.

29. The method as defined in any one of claims 1 to 28, wherein the method comprises culturing the cell population in serum-free media.

30. The method as defined in any one of claims 1 to 29, wherein the cell population is enriched for T cells prior to administration of the antibody or fragment thereof.

31. The method as defined in any one of claims 1 to 30, wherein the cell population is enriched for γδ T cells prior to administration of the antibody or fragment thereof.

32. The method as defined in any one of claims 1 to 31, wherein the cell population is depleted of αβ T cells or NK cells prior to administration of the antibody or fragment thereof.

33. The method as defined in any one of claims 1 to 32, wherein the cell population is obtained from a haematopoietic sample or a fraction thereof.

34. The method as defined in claim 33, wherein the haematopoietic sample is selected from peripheral blood, umbilical cord blood, lymphoid tissue, thymus, bone marrow, lymph node tissue or fractions thereof.

35. The method as defined in claim 33 or claim 34, wherein the haematopoietic sample consists of low density mononuclear cells (LDMCs) or peripheral blood mononuclear cells (PBMCs).

36. The method as defined in any one of claims 1 to 32, wherein the cell population is obtained from a non-haematopoietic tissue sample, such as a skin, colon, gut, mammary gland, lung, prostate, liver, spleen, pancreas, uterus, vagina or other cutaneous, mucosal or serous membrane sample.

37. The method as defined in claim 36, wherein the cell population is obtained from the non-haematopoietic tissue sample by culturing the non-haematopoietic tissue sample on a synthetic scaffold configured to facilitate cell egress from the non-haematopoietic tissue sample.

38. The method as defined in any one of claims 1 to 37, wherein the cell population is obtained from a cancer tissue sample.

39. The method as defined in any one of claims 1 to 38, wherein the cell population is obtained from human or non-human animal tissue.

40. The method as defined in any one of claims 1 to 39, wherein the cell population is isolated from a sample prior to administering the anti-Vδ1 antibody or fragment thereof.

41. A Vδ1 T cell population obtained by the *ex vivo* method as defined in any one of claims 1 to 40.

42. A composition comprising the Vδ1 T cell population as defined in claim 41.

43. A pharmaceutical composition comprising the Vδ1 T cell population as defined in claim 41.

44. The pharmaceutical composition as defined in claim 43, for use as a medicament.

45. The pharmaceutical composition as defined in claim 43, for use in the treatment of cancer, an infectious disease or an inflammatory disease.

46. A method of treating a cancer, an infectious disease or an inflammatory disease in a subject in need thereof, comprising administering a therapeutically effective amount of the Vδ1 T cell population as defined in claim 41 or the pharmaceutical composition as defined in claim 43.

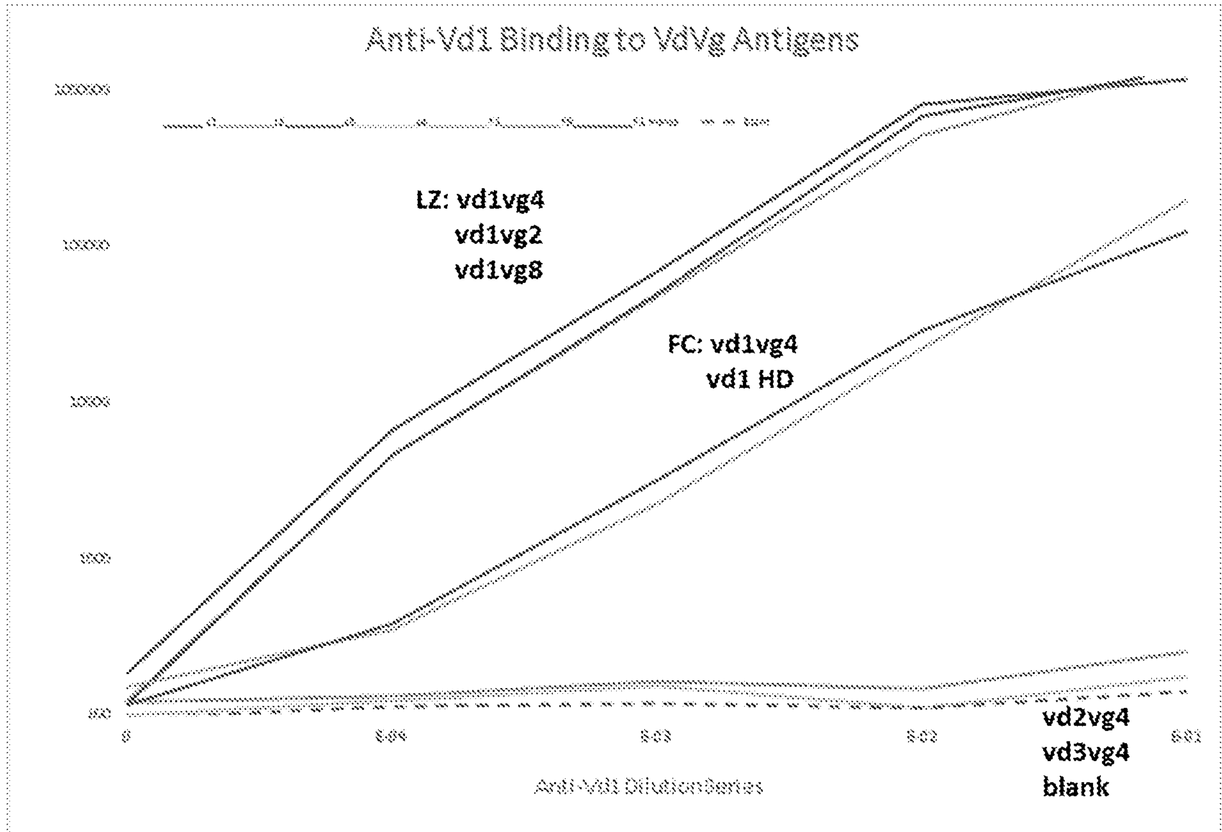

FIGURE 1

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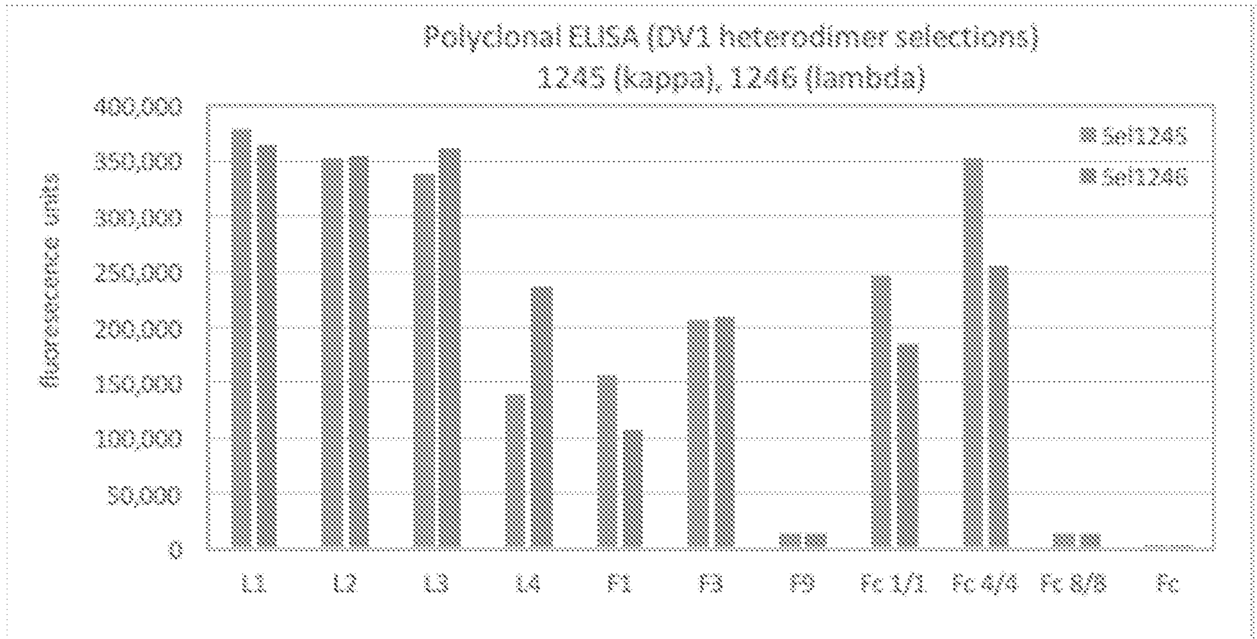

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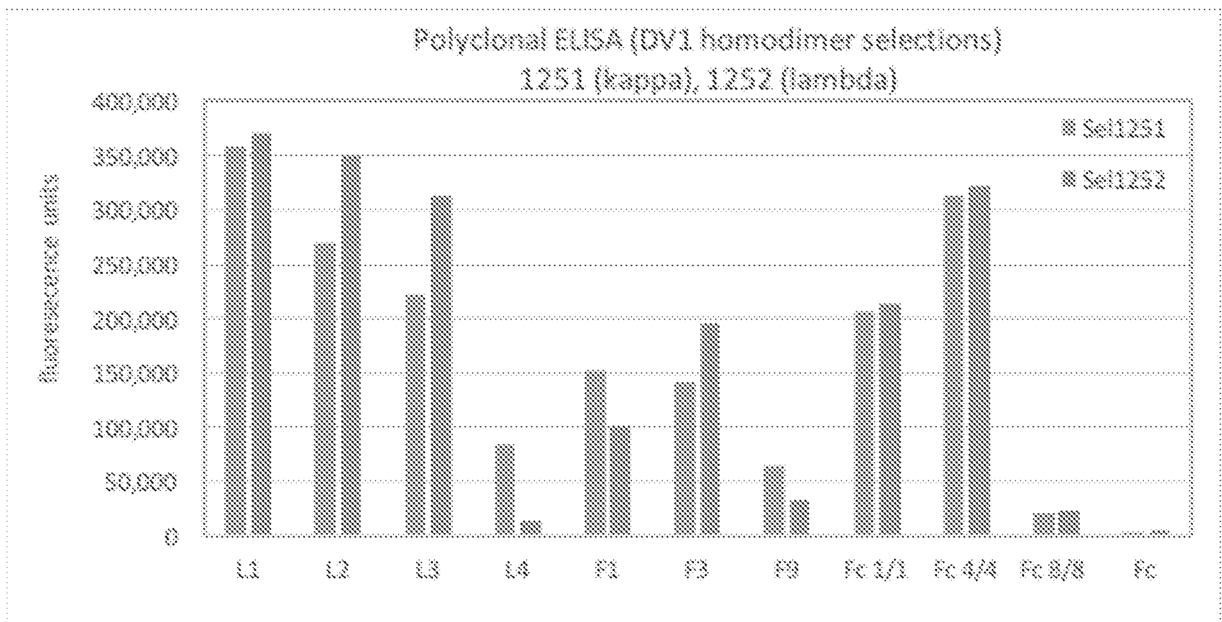

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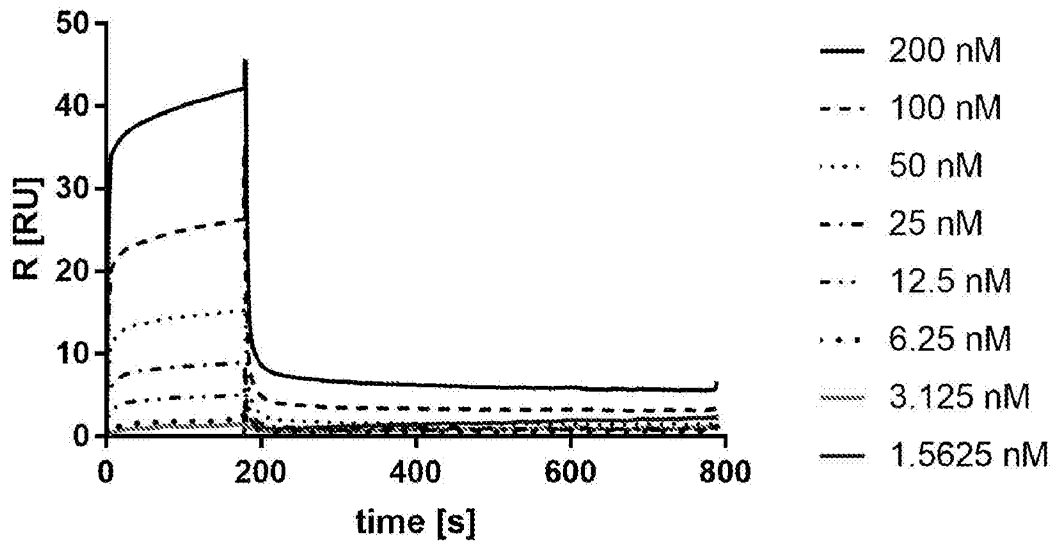

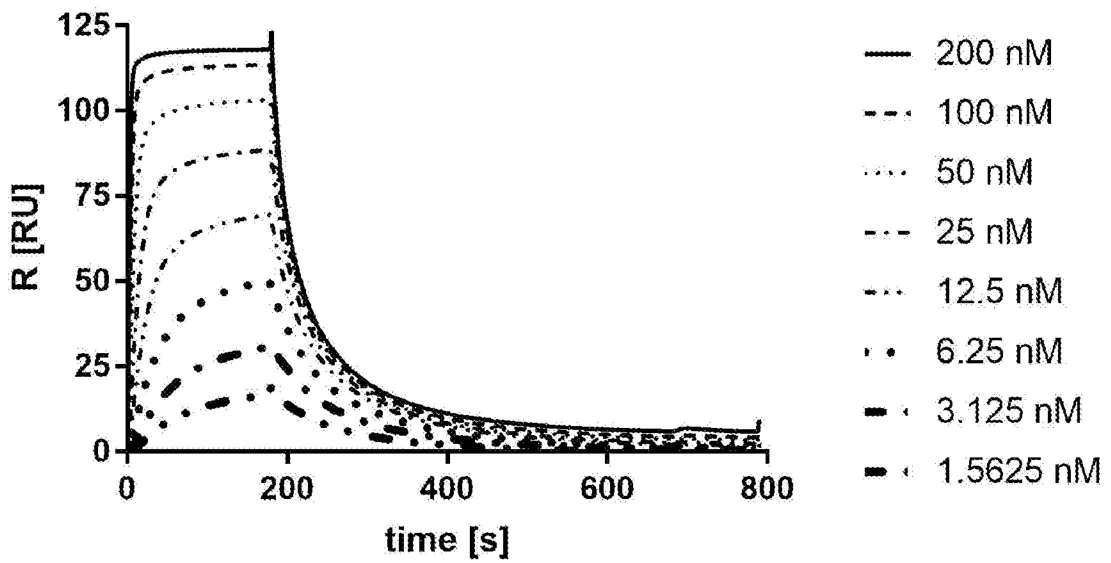

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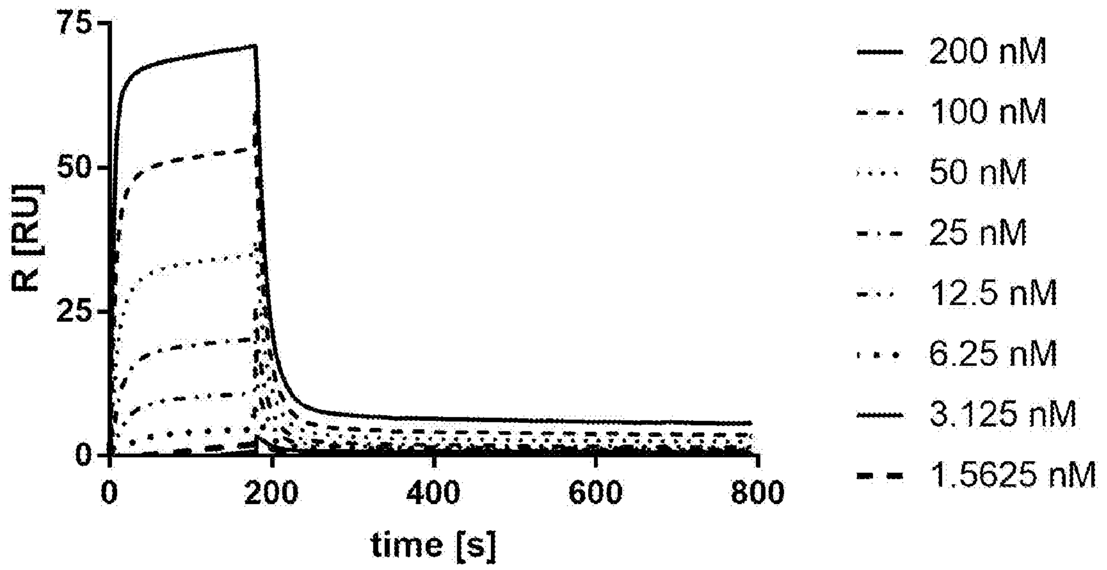

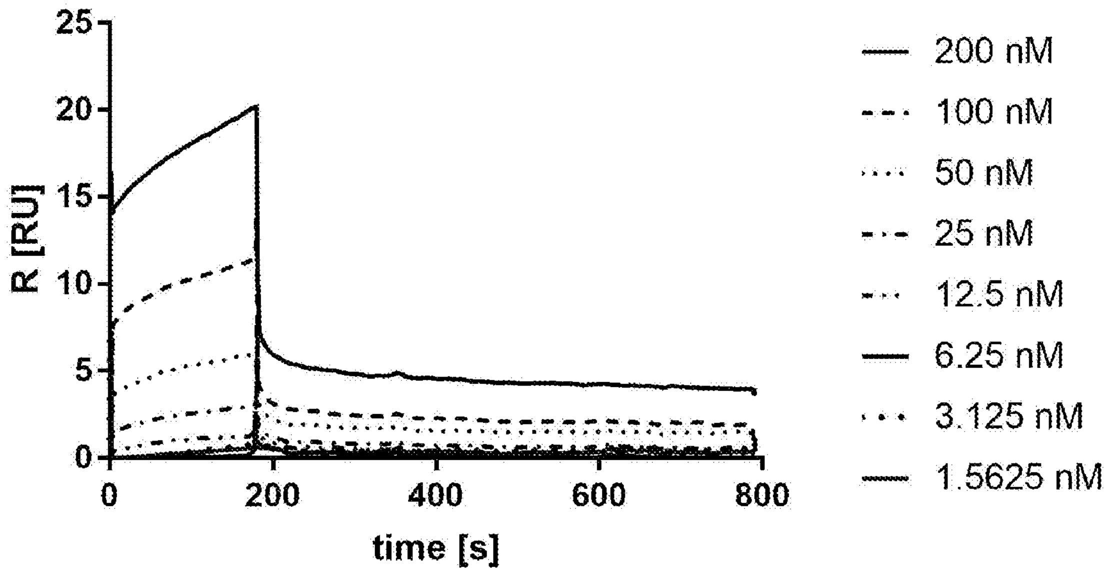

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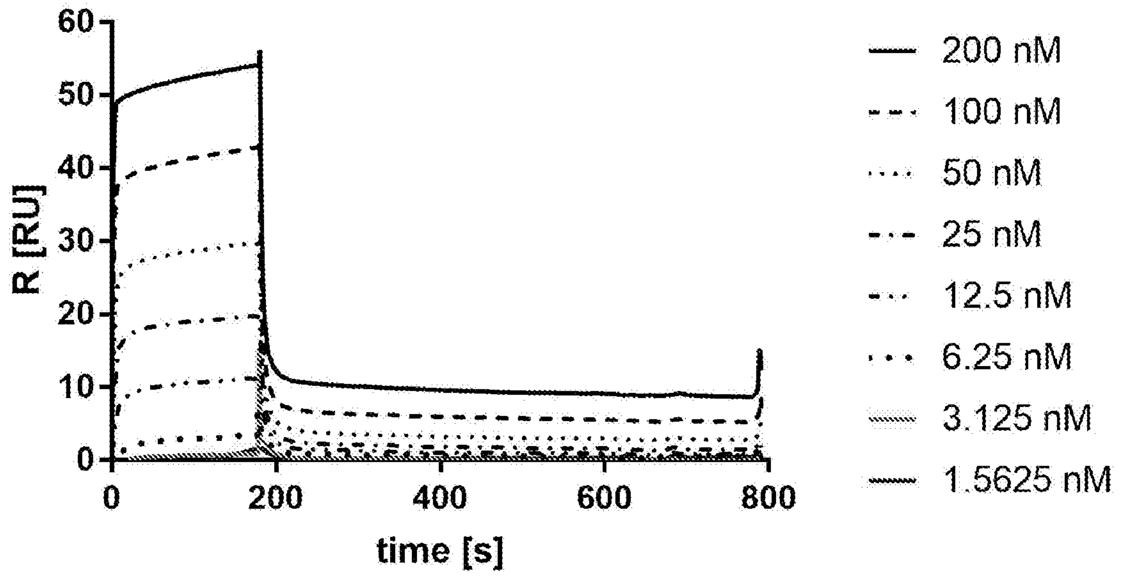

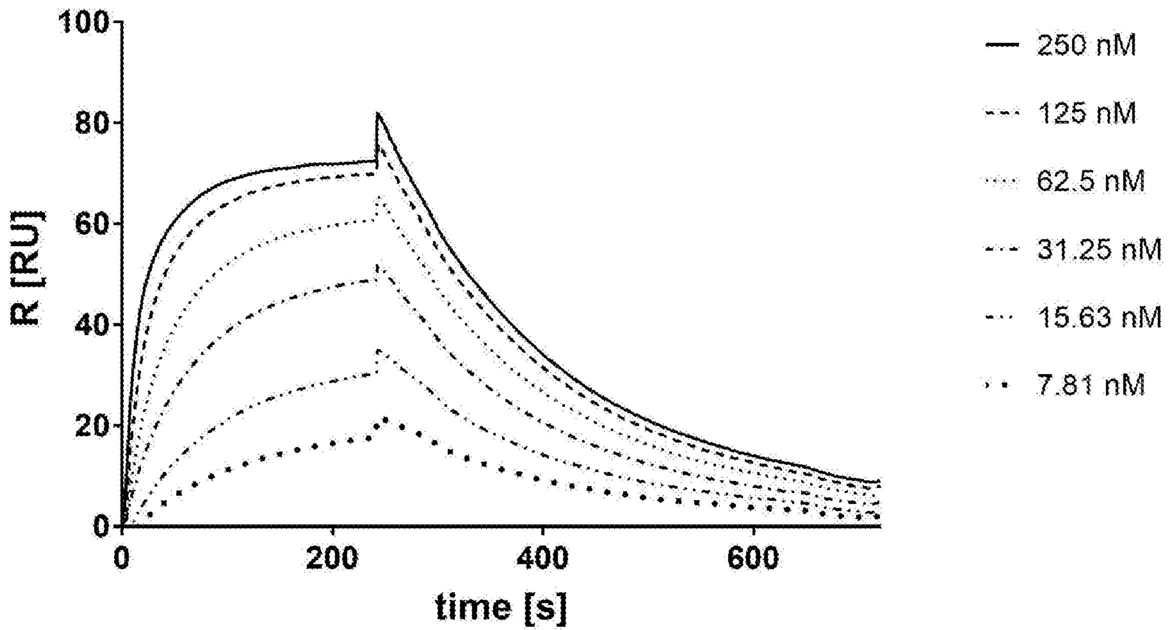

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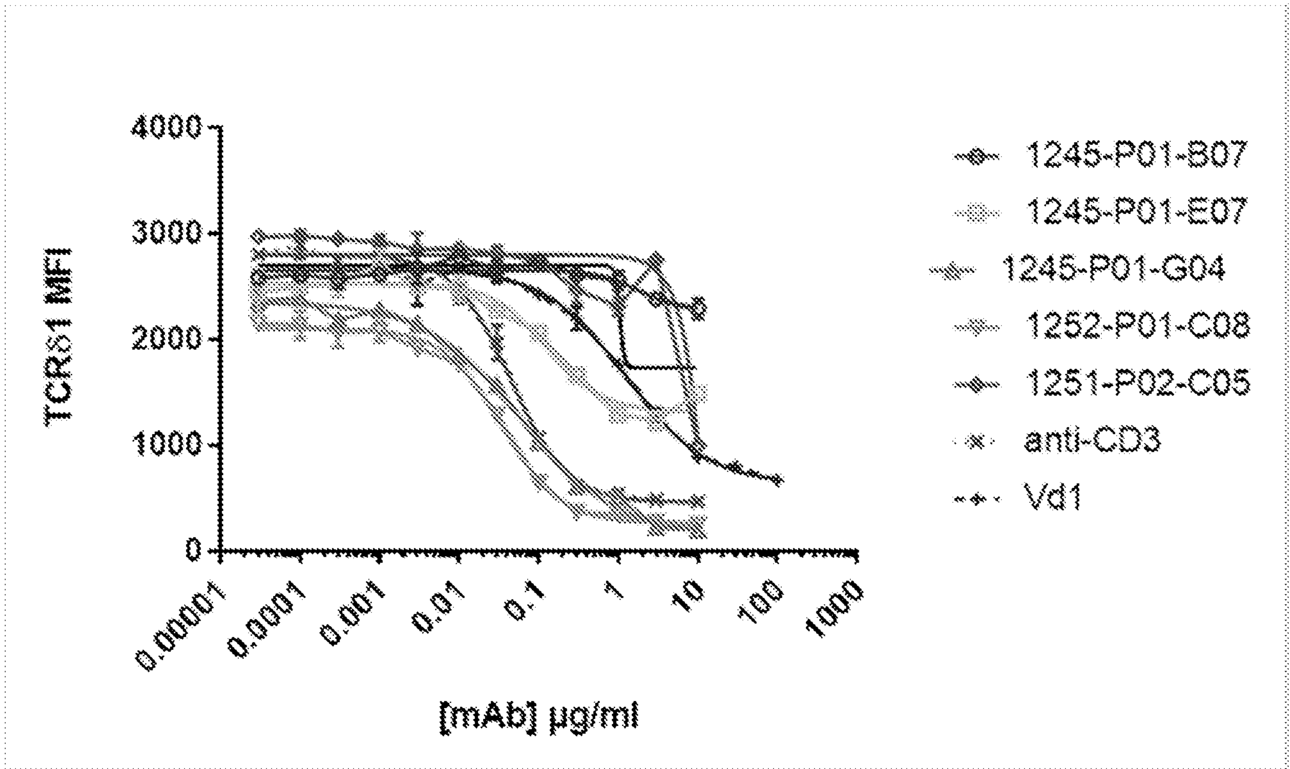

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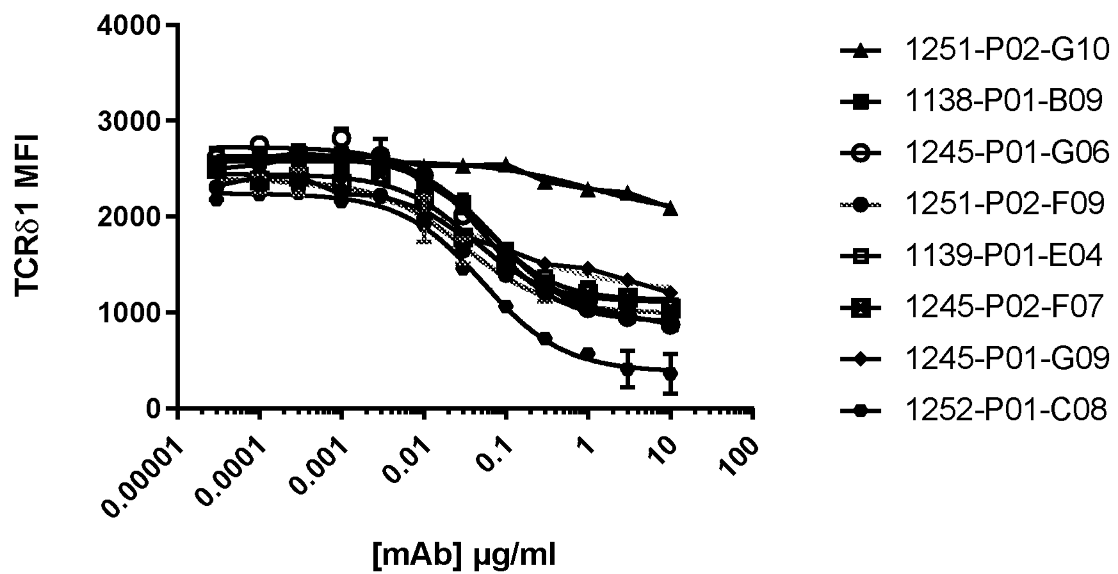

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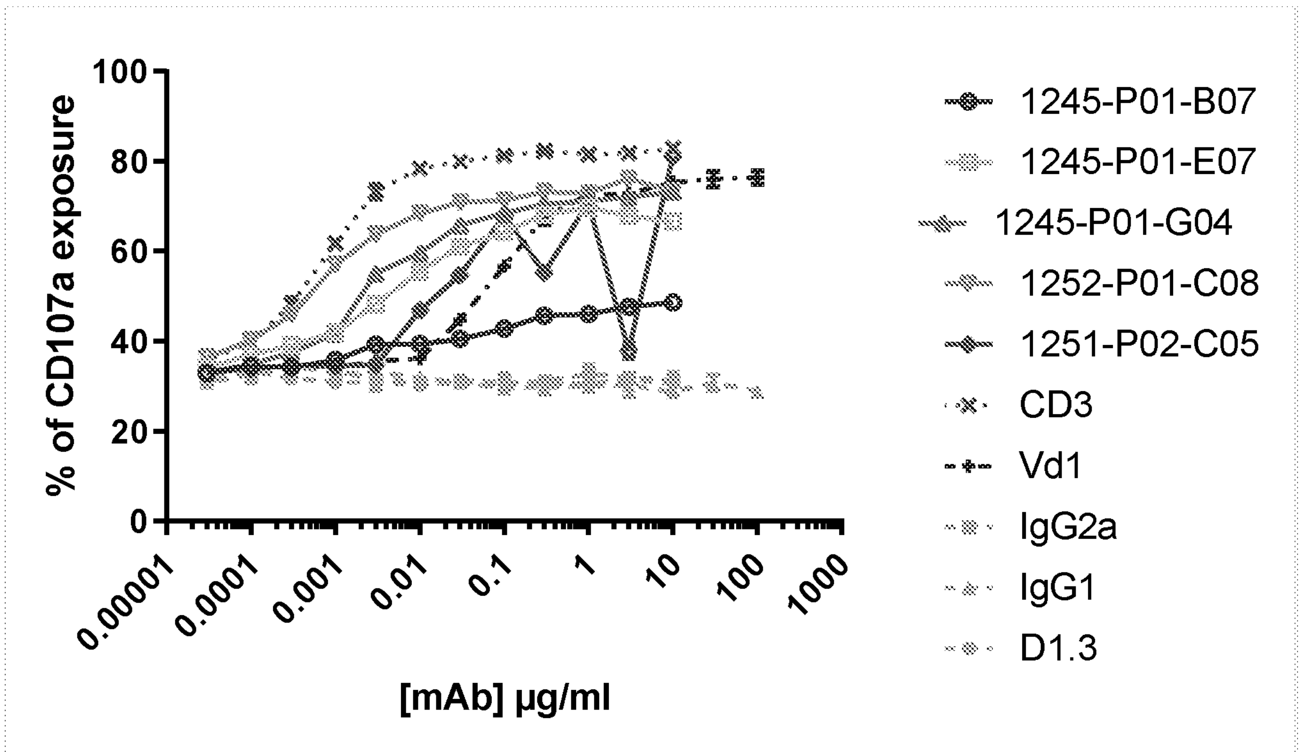

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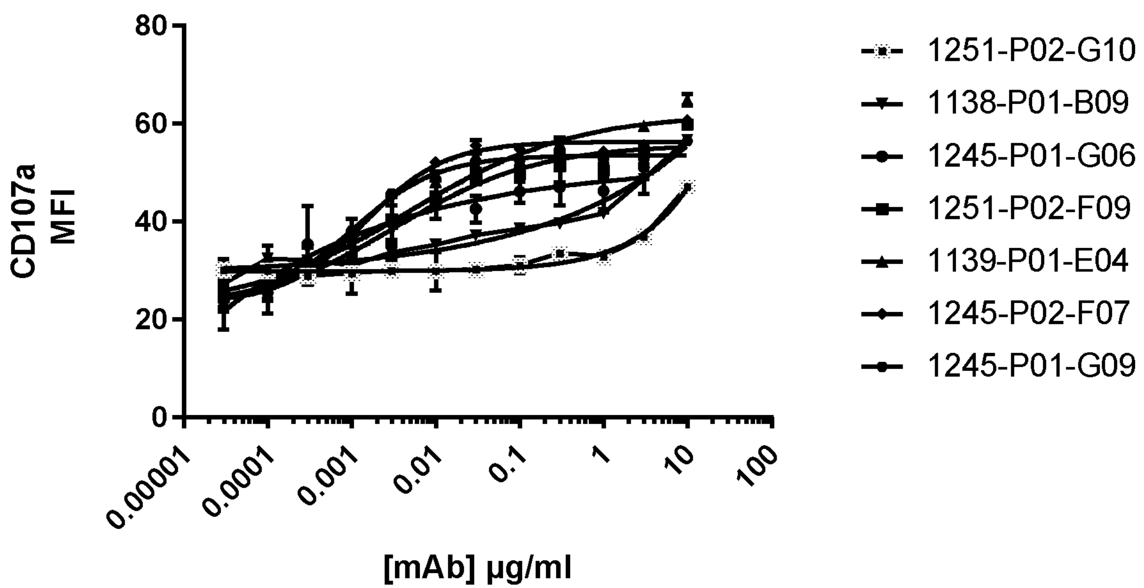

FIGURE 5

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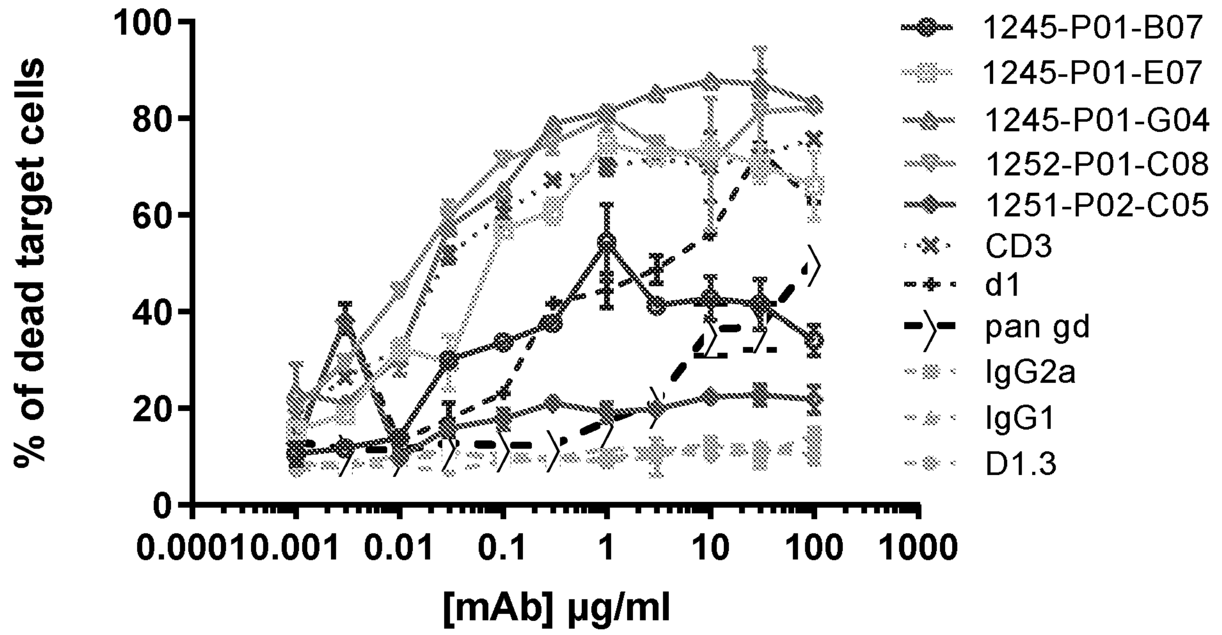

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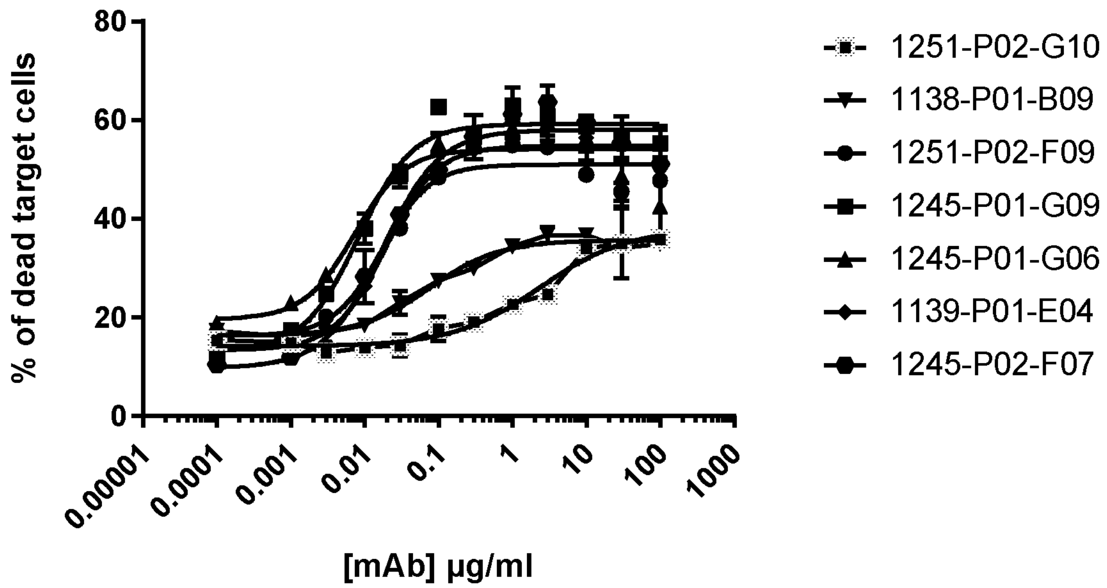

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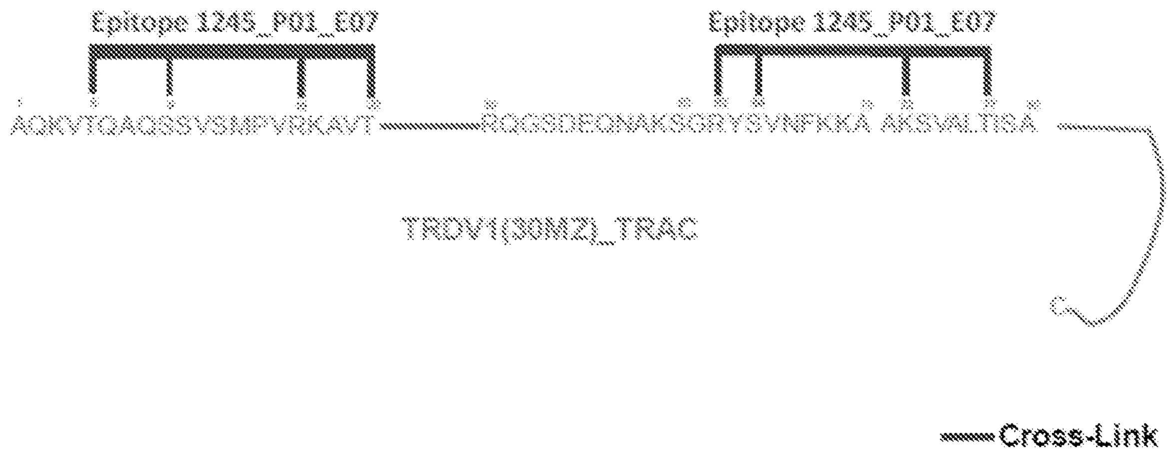

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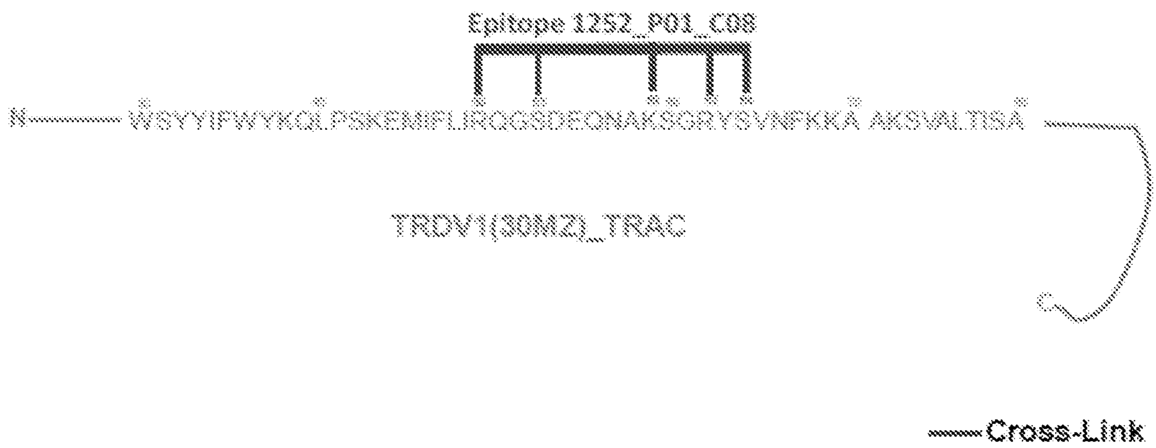


FIGURE 8

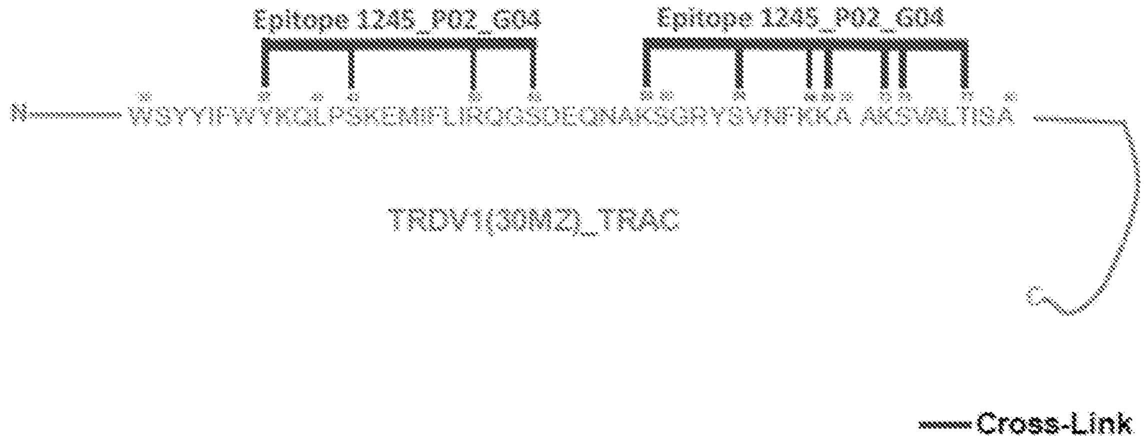


FIGURE 9

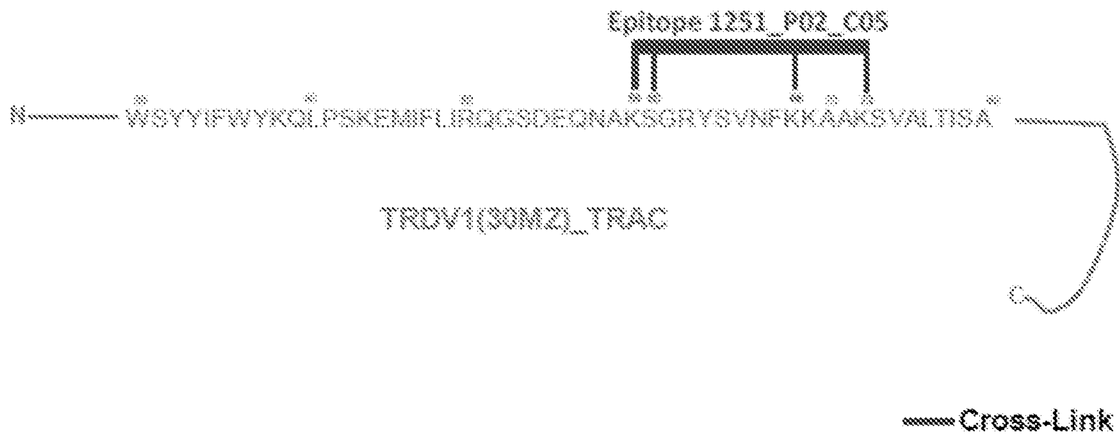
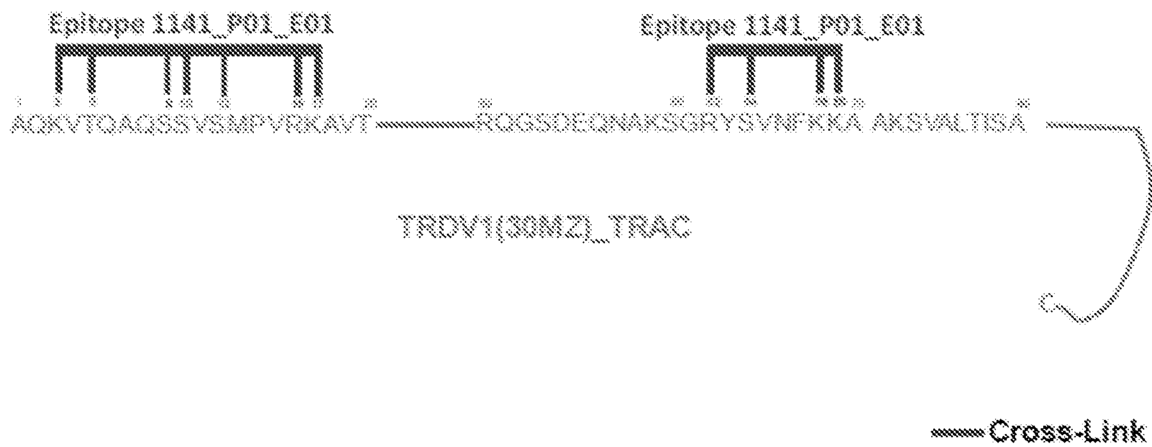


FIGURE 10



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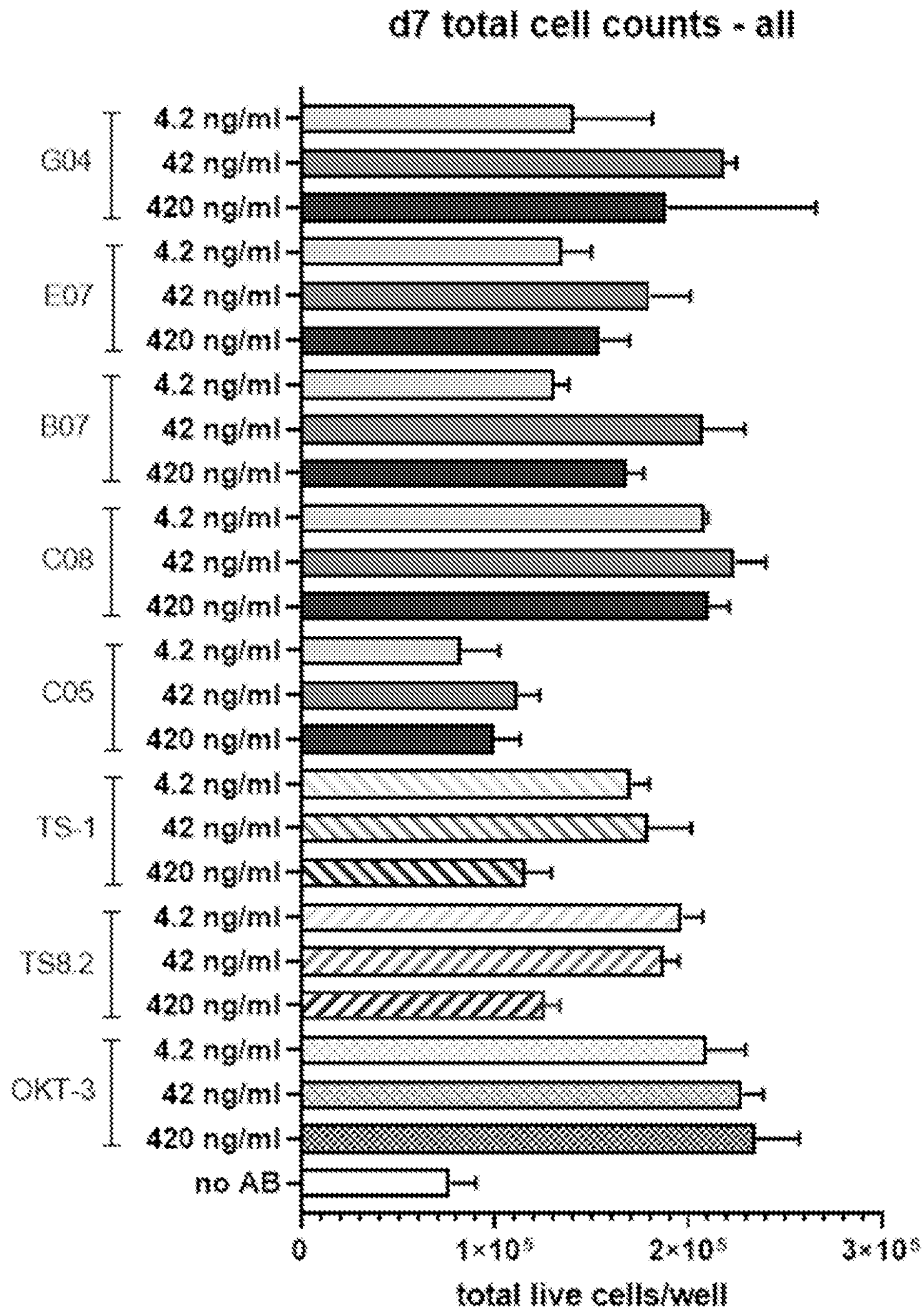

FIGURE 12

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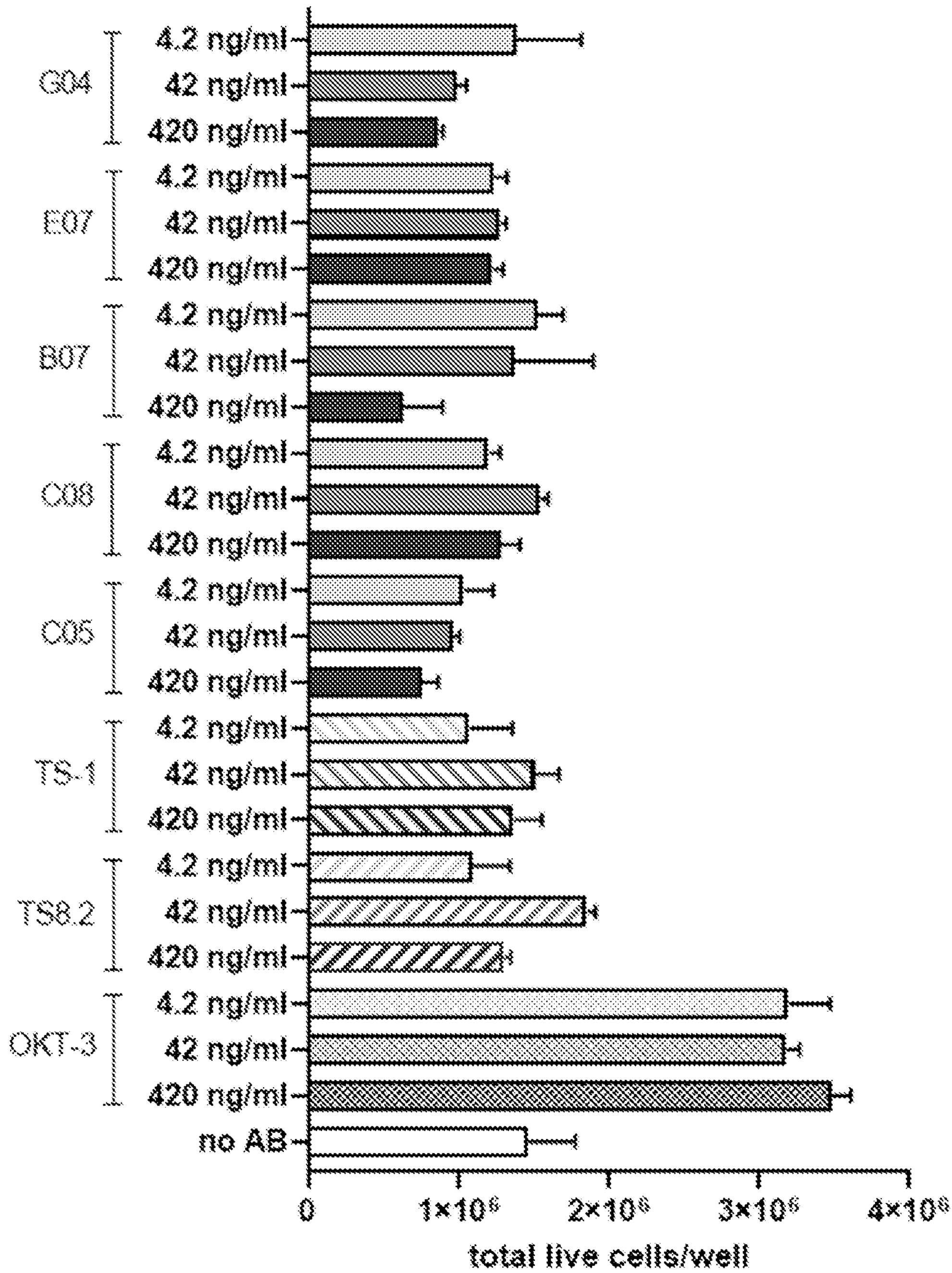

FIGURE 12 (contd.)

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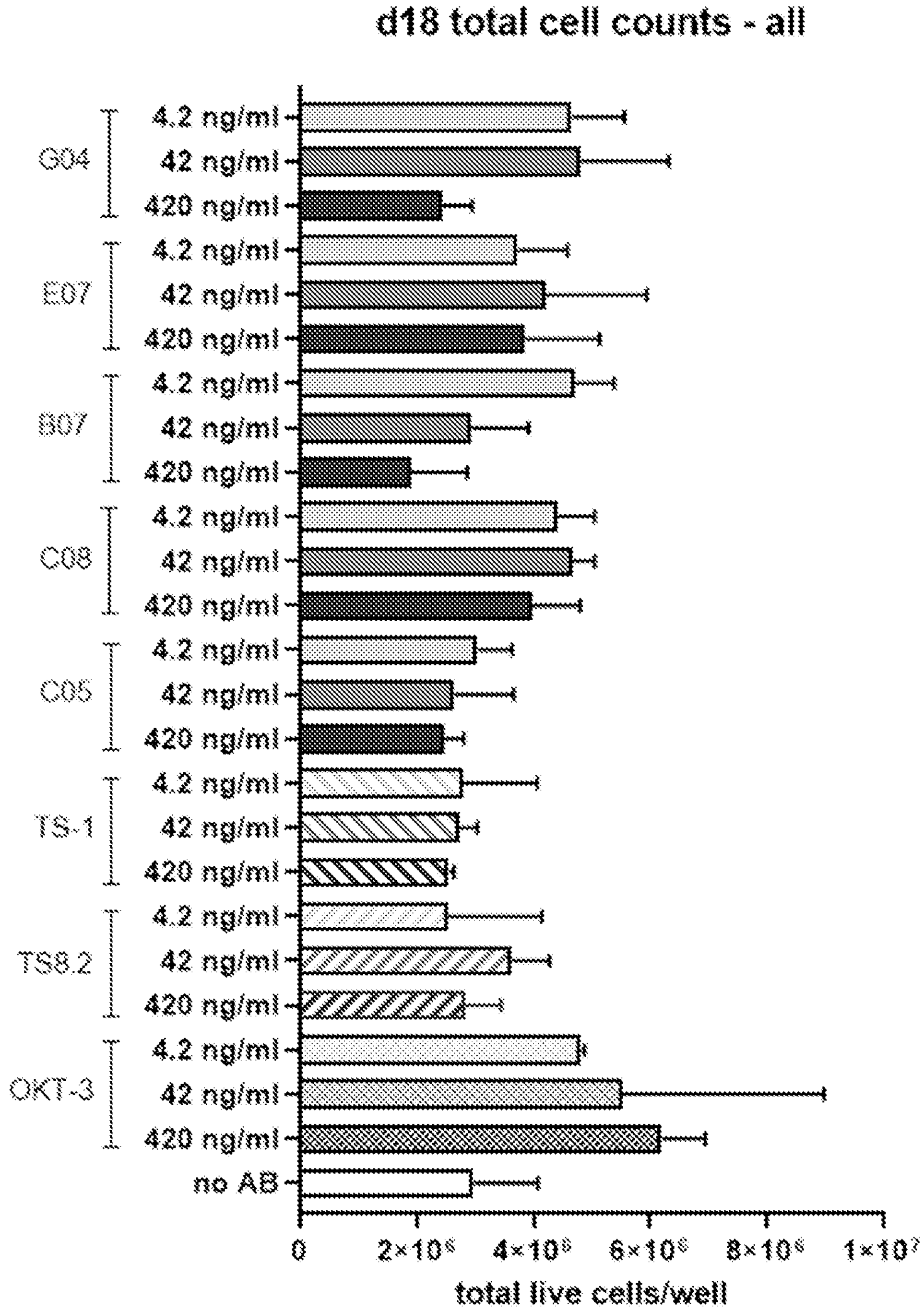

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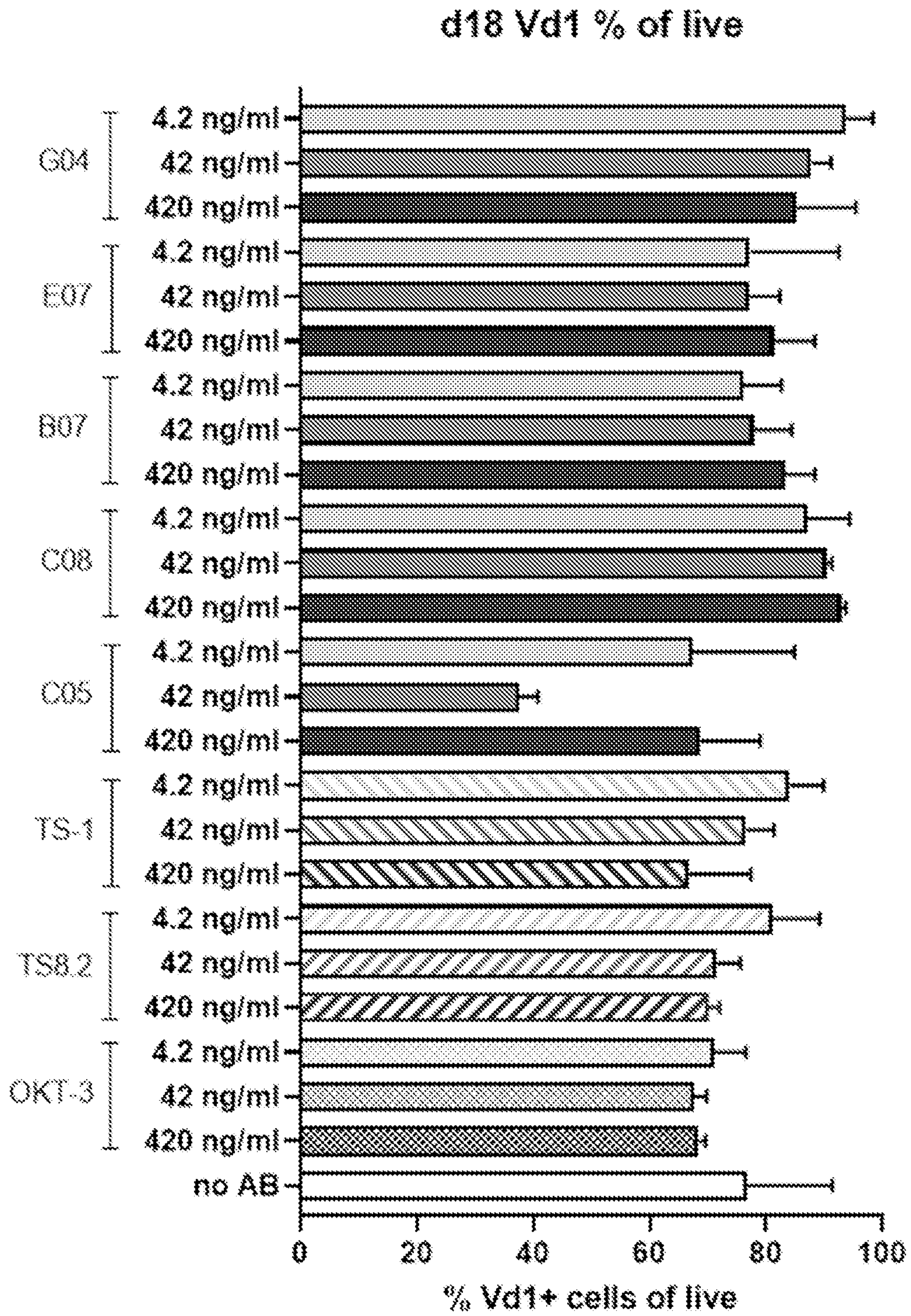

FIGURE 13

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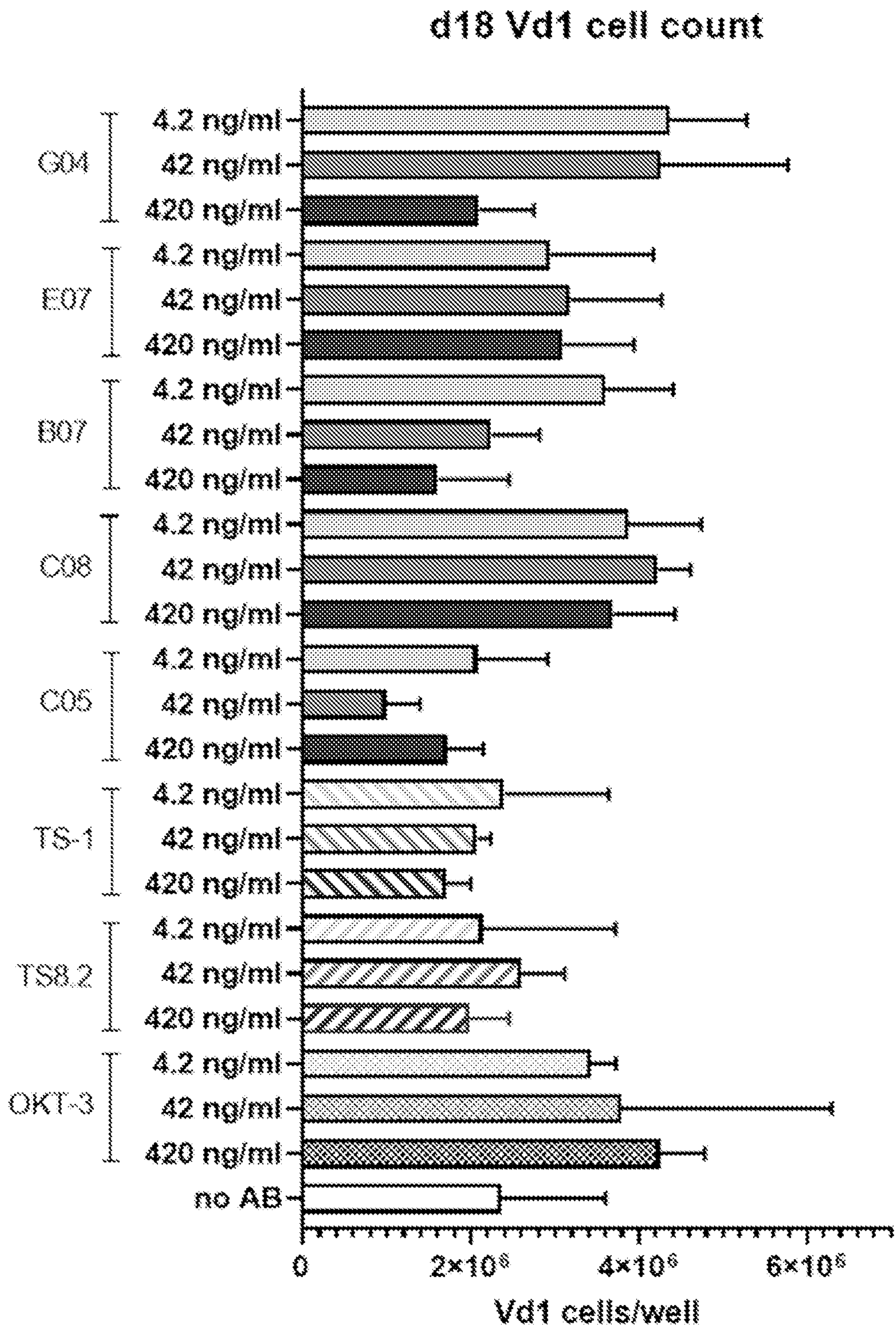

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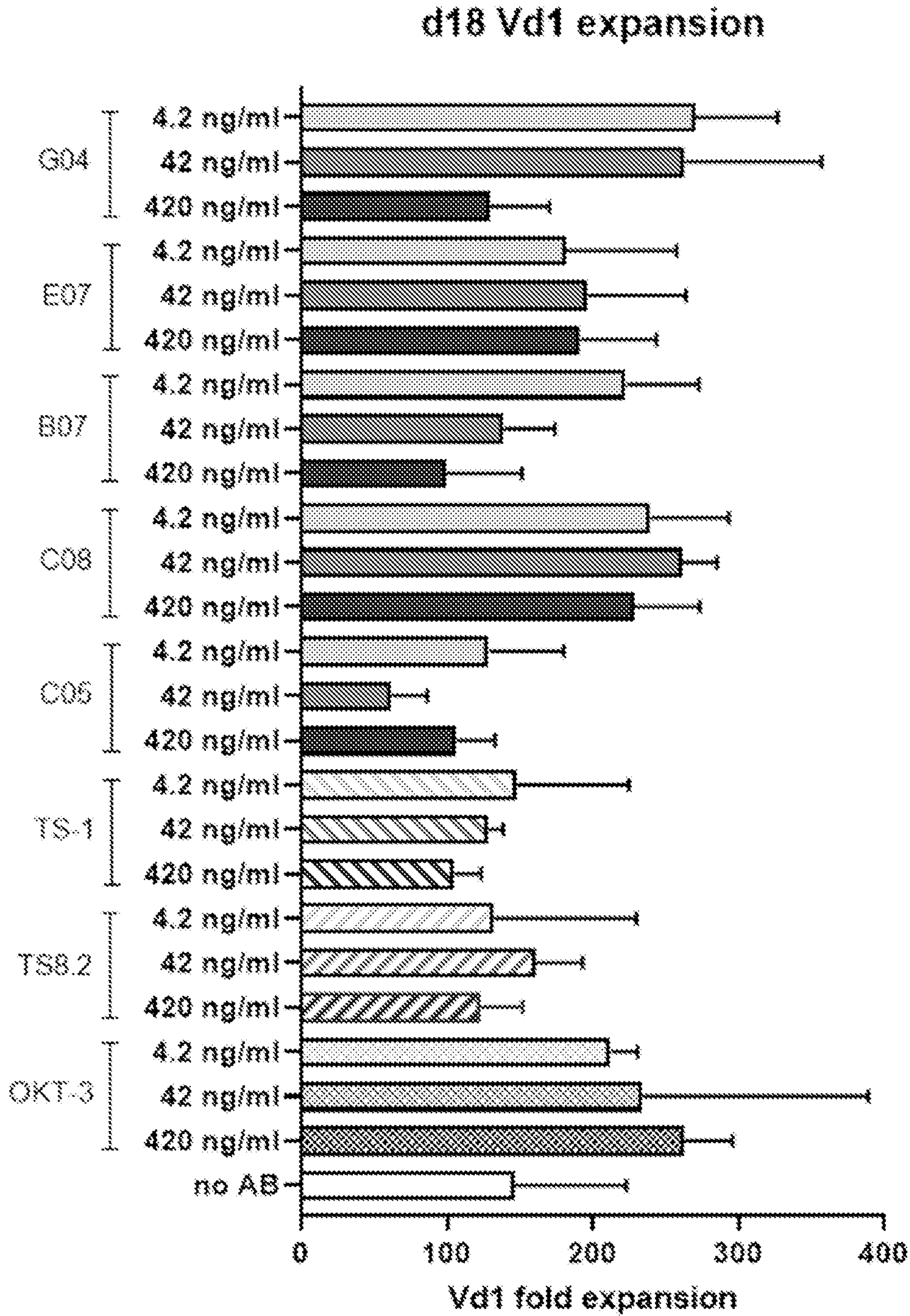

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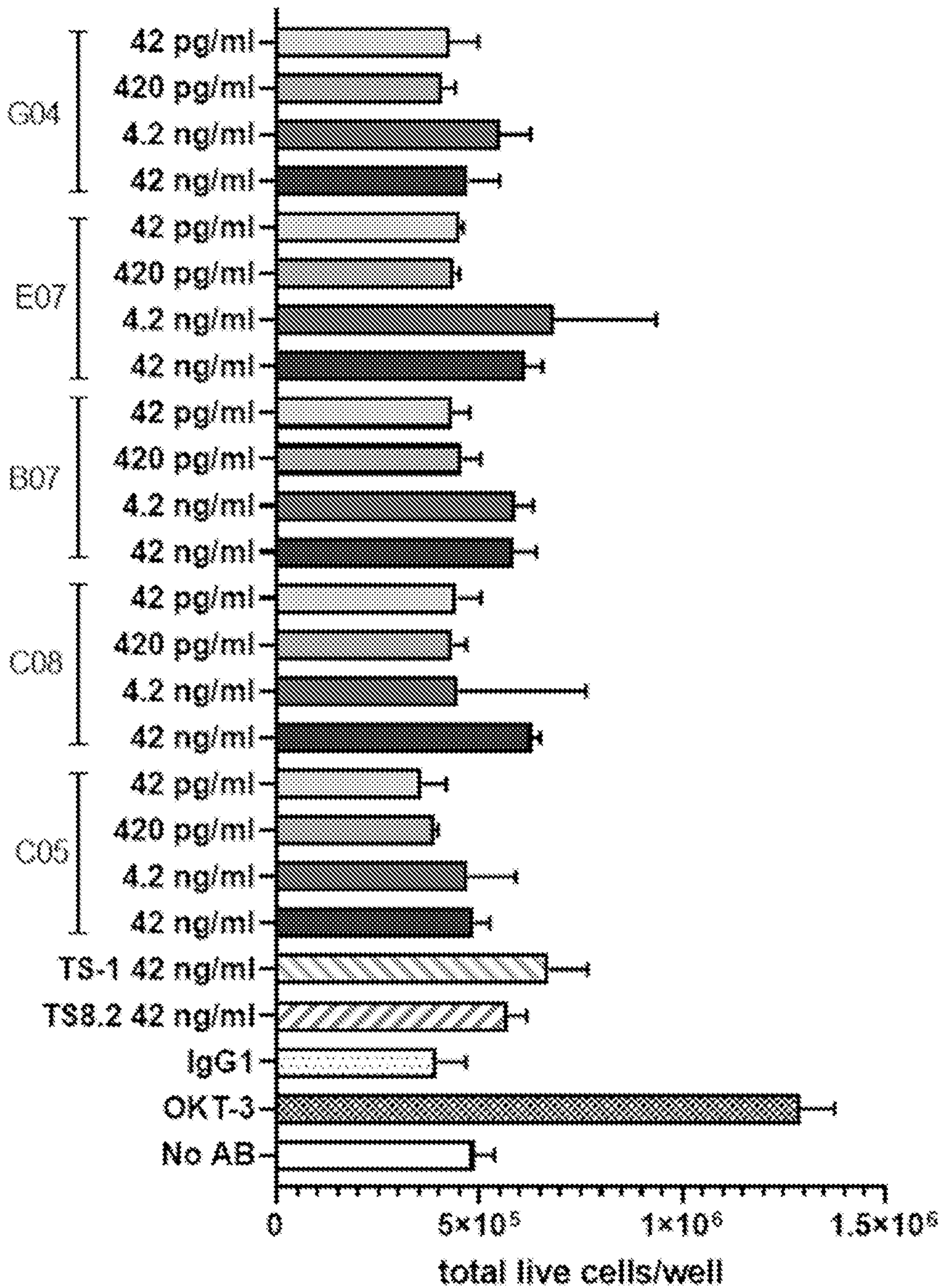

FIGURE 14

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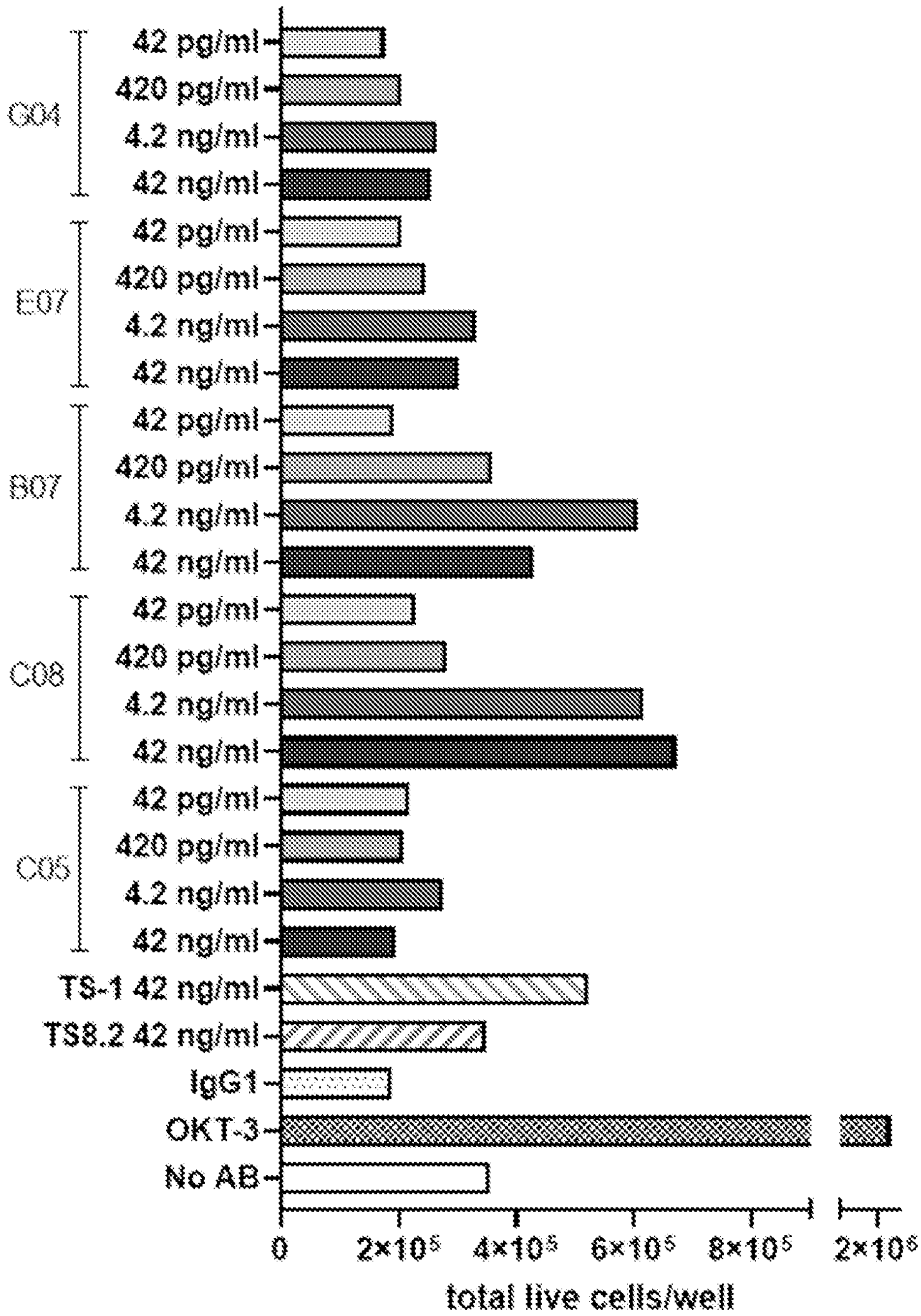

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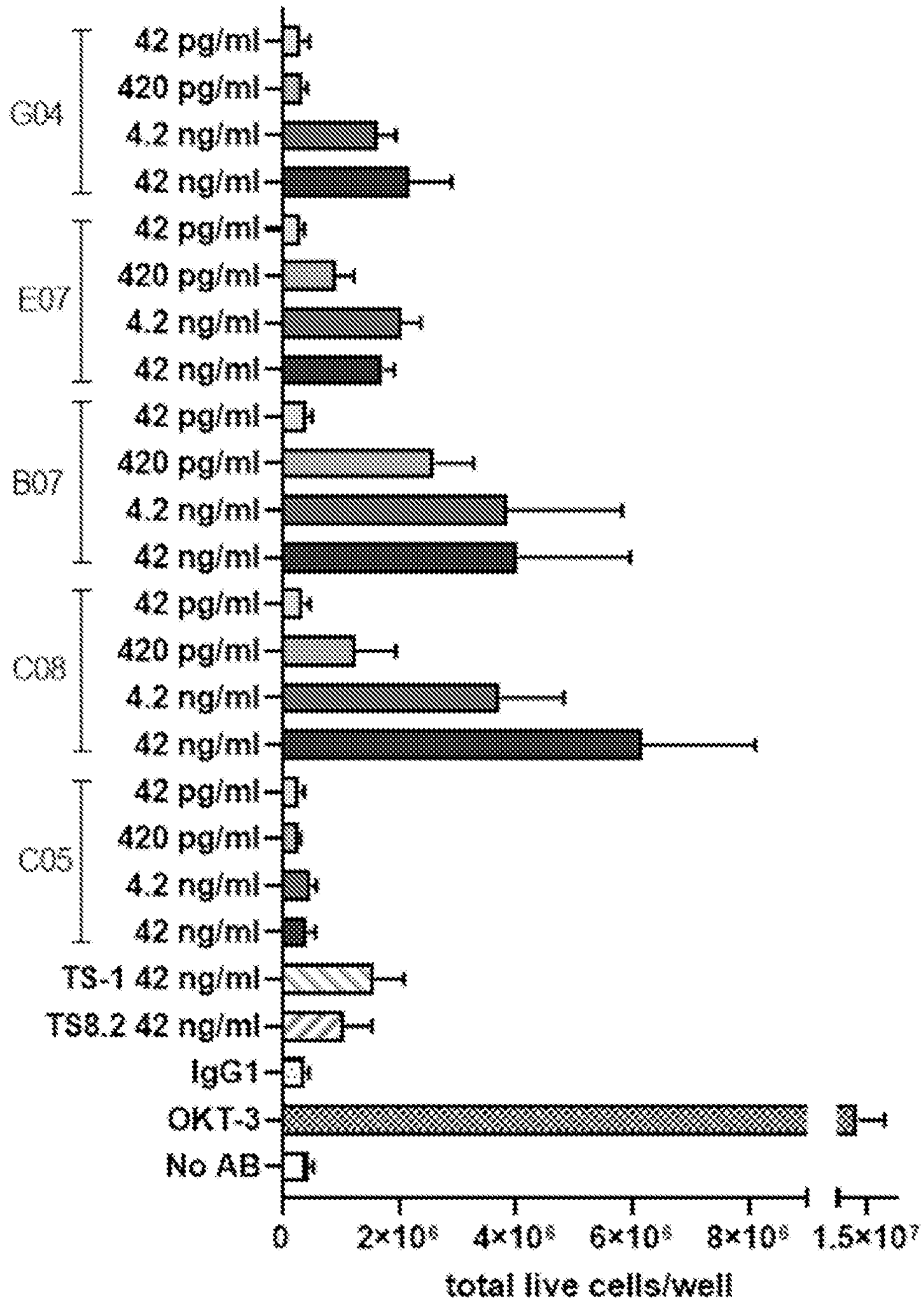

FIGURE 14 (contd.)

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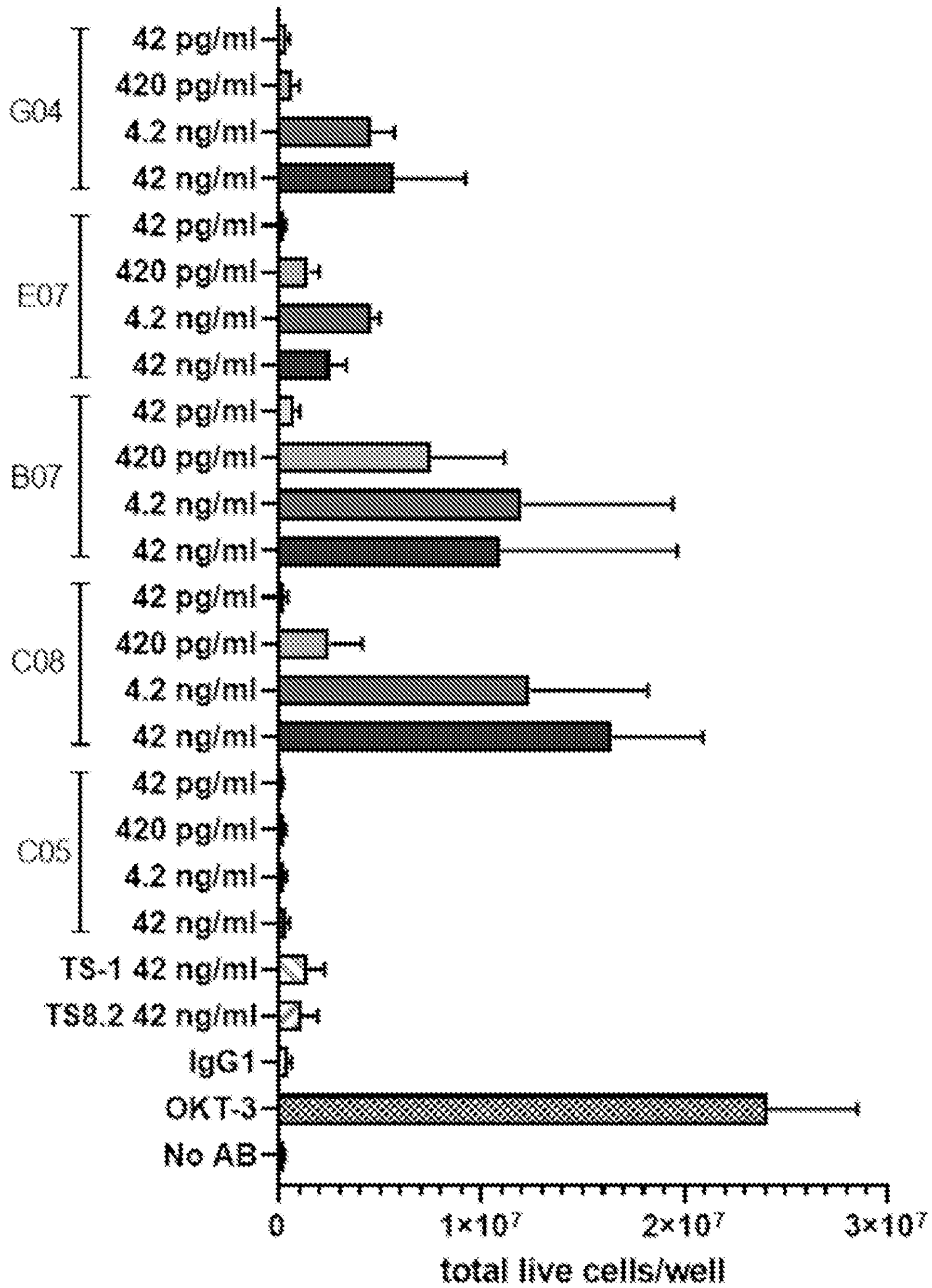

FIGURE 14 (contd.)

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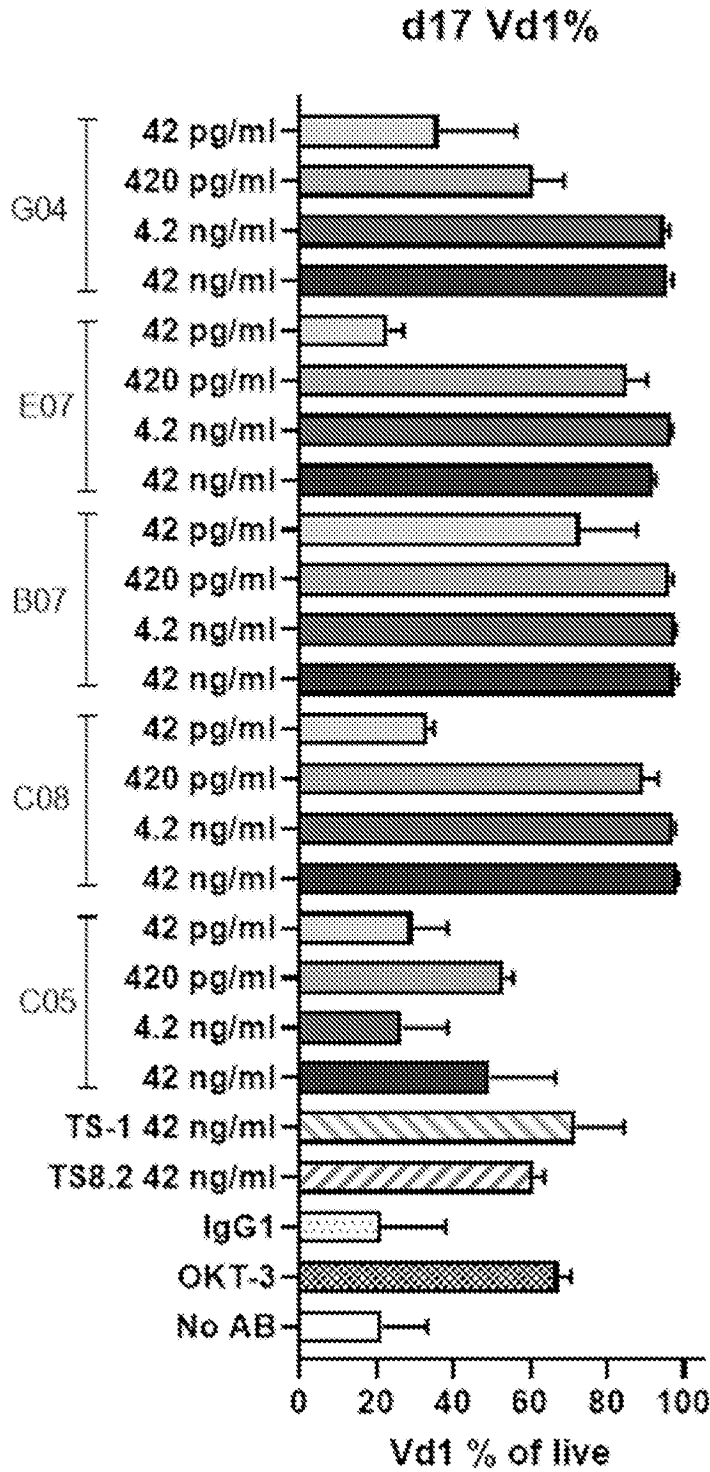

FIGURE 15

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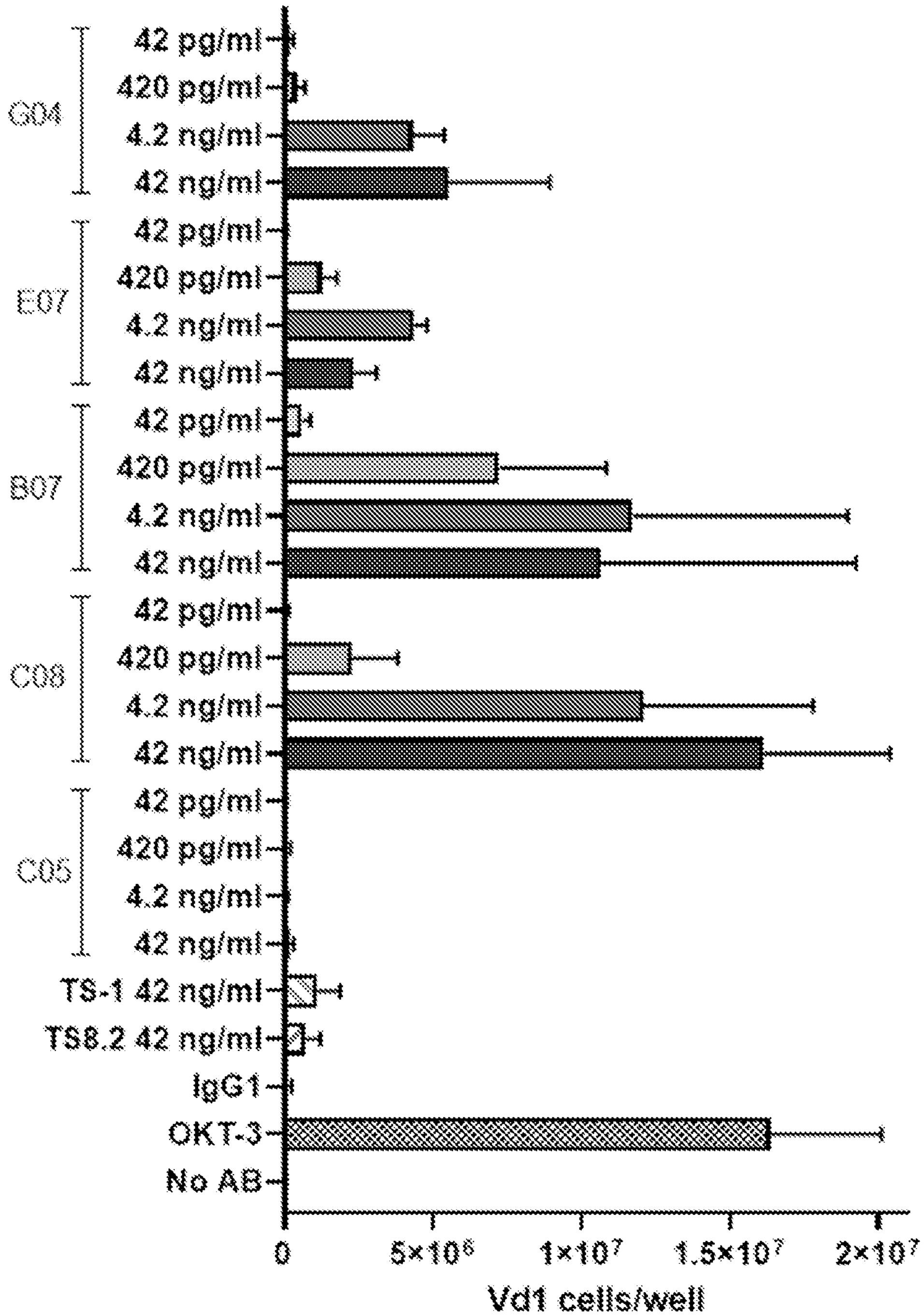

FIGURE 15 (contd.)

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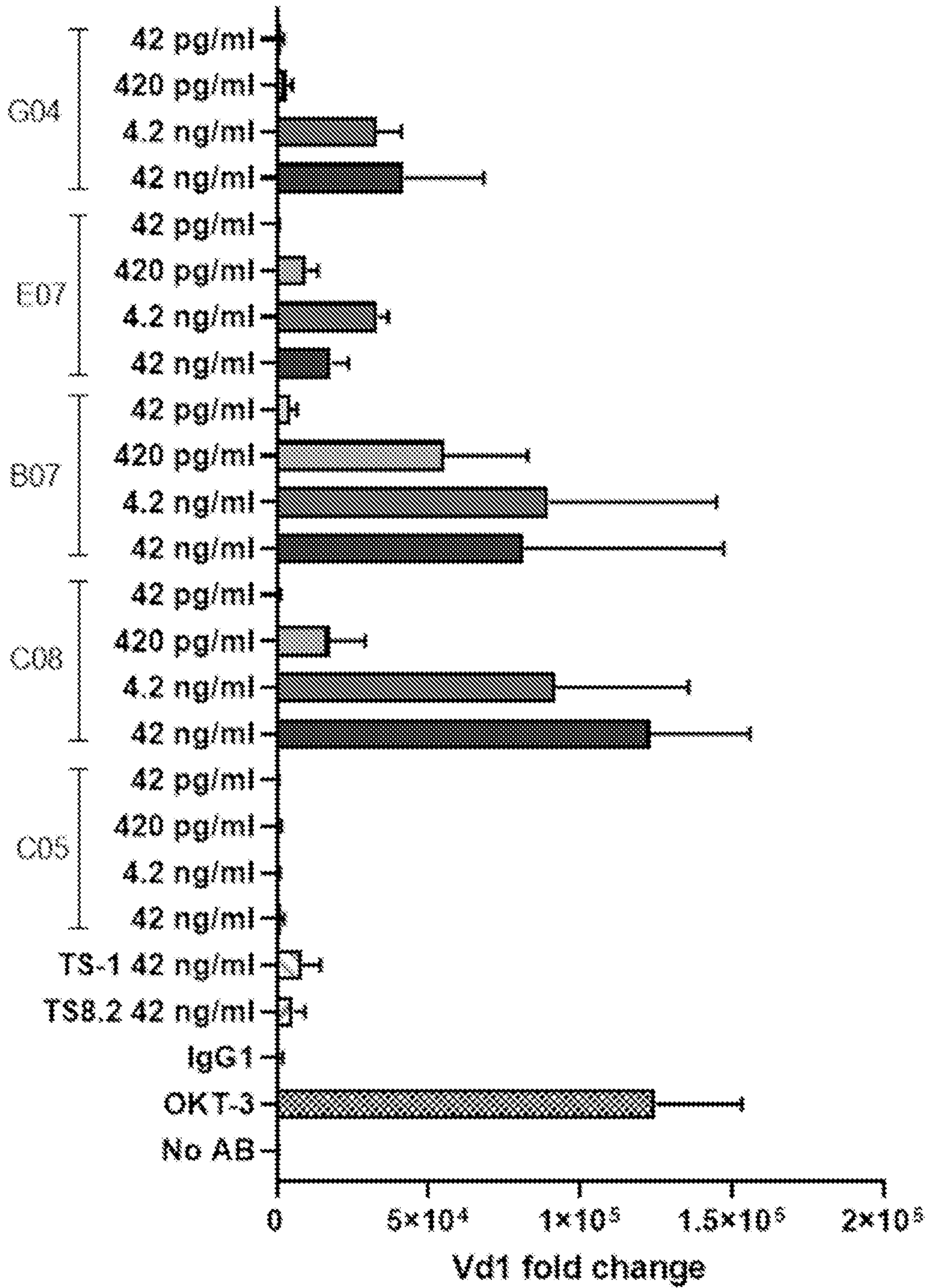

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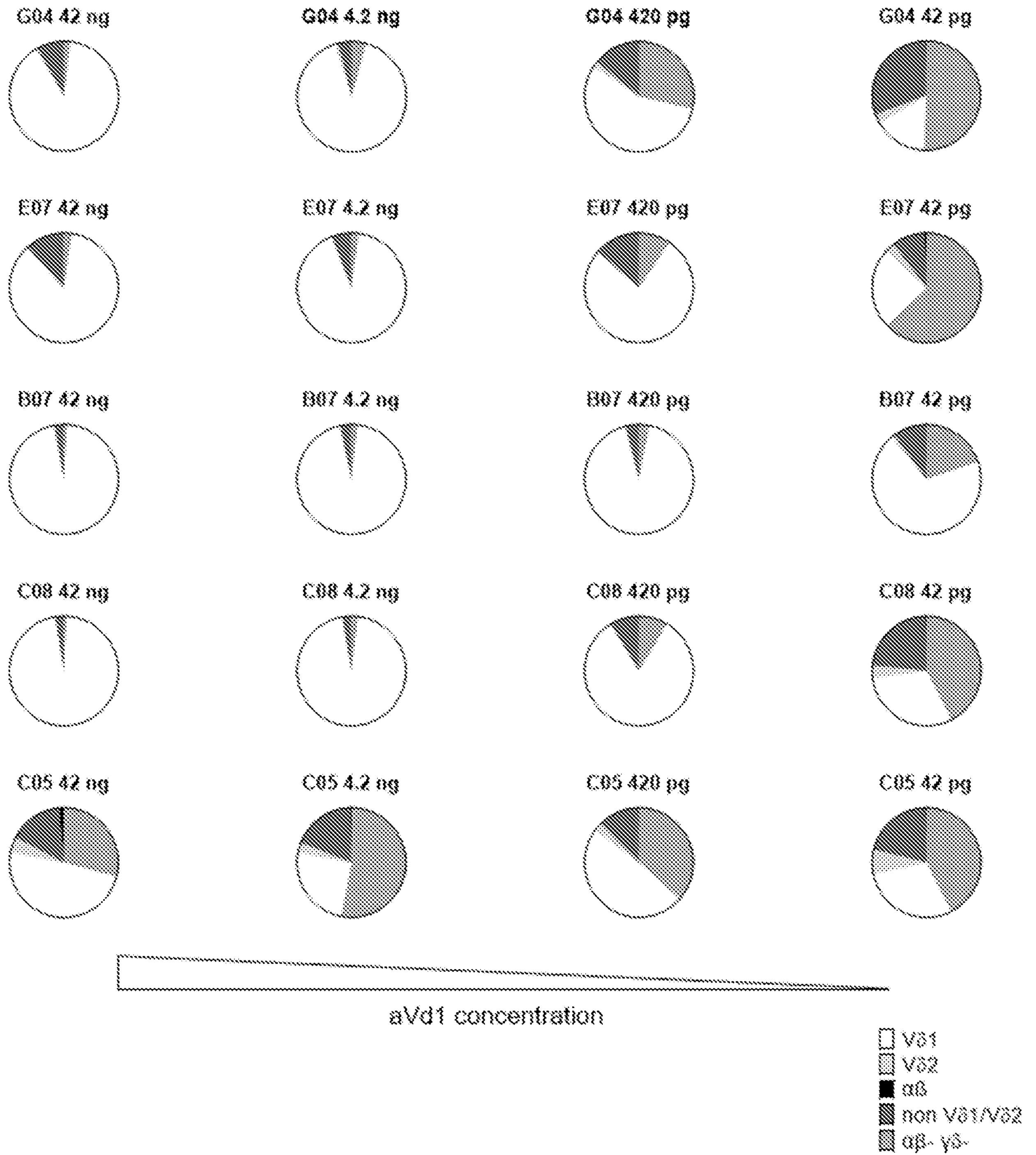

FIGURE 16

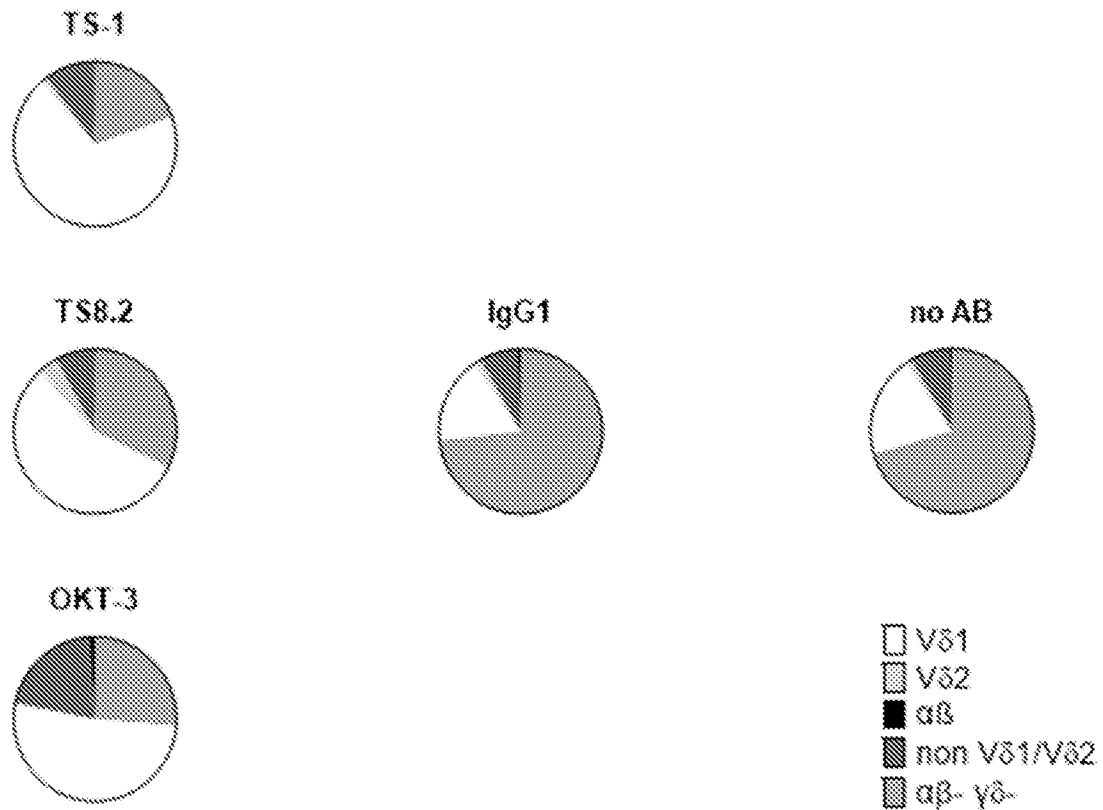

FIGURE 16 (contd.)

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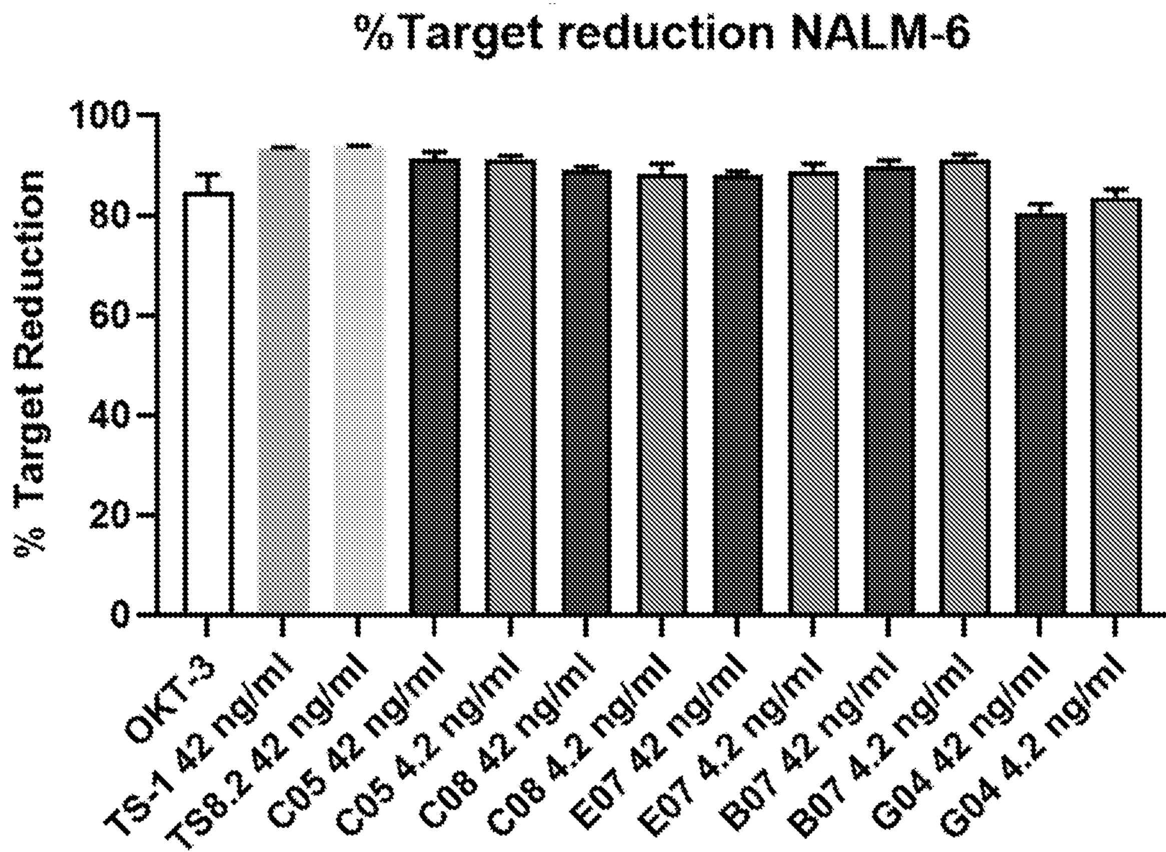

FIGURE 17

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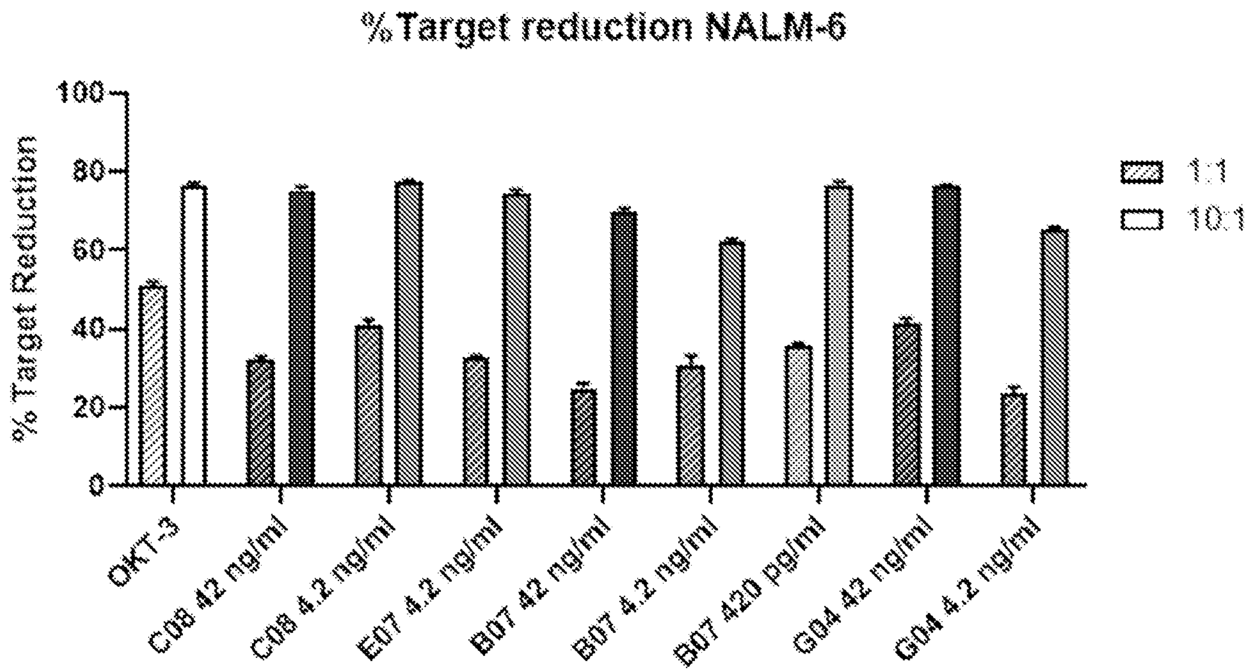

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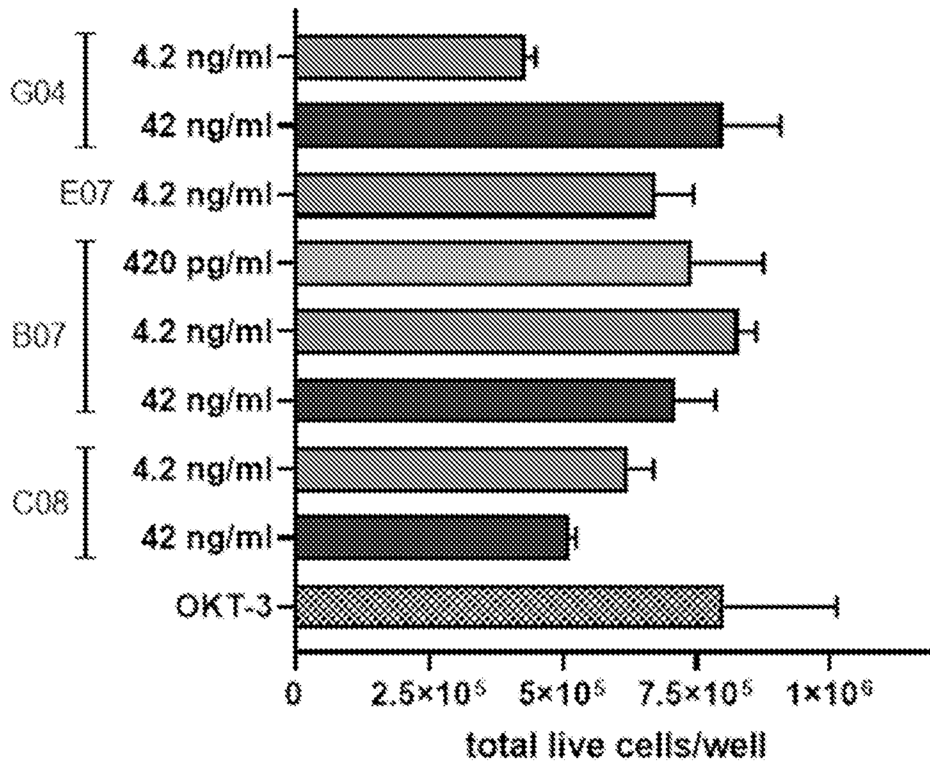
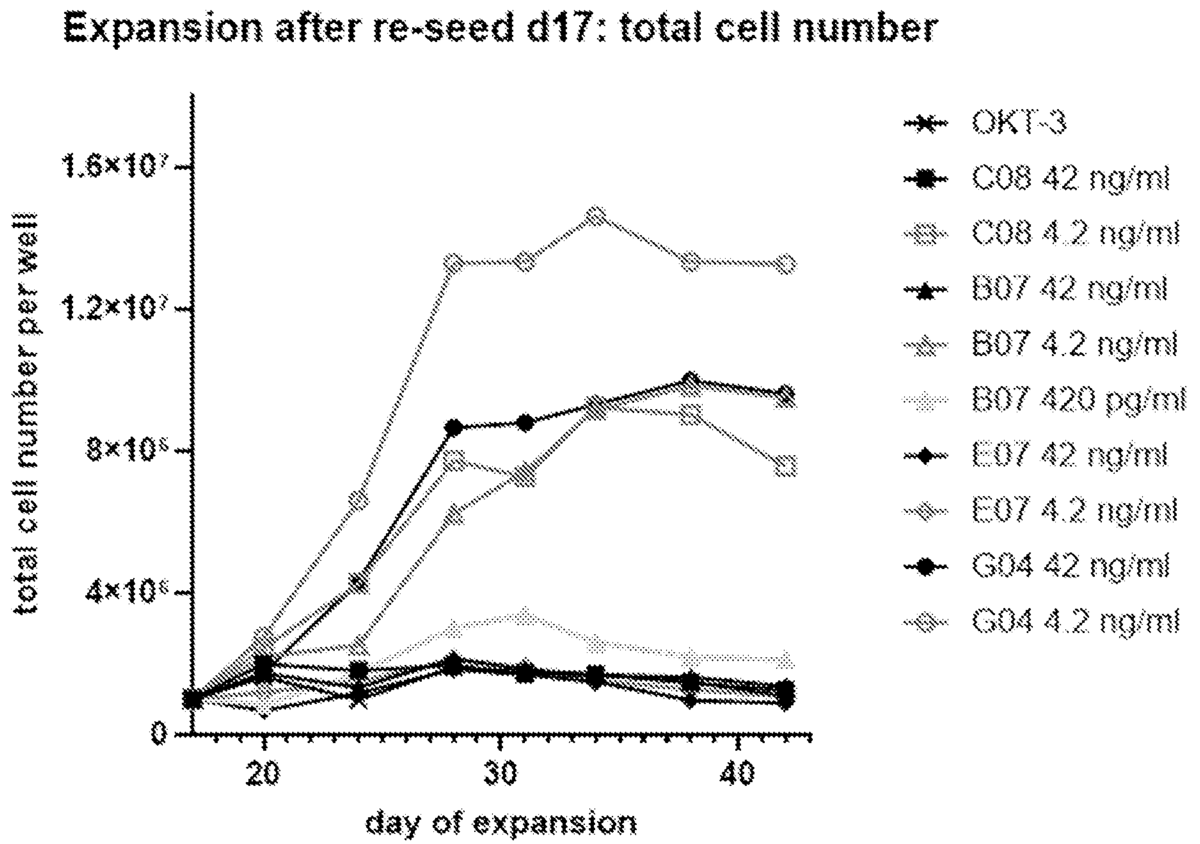


FIGURE 18



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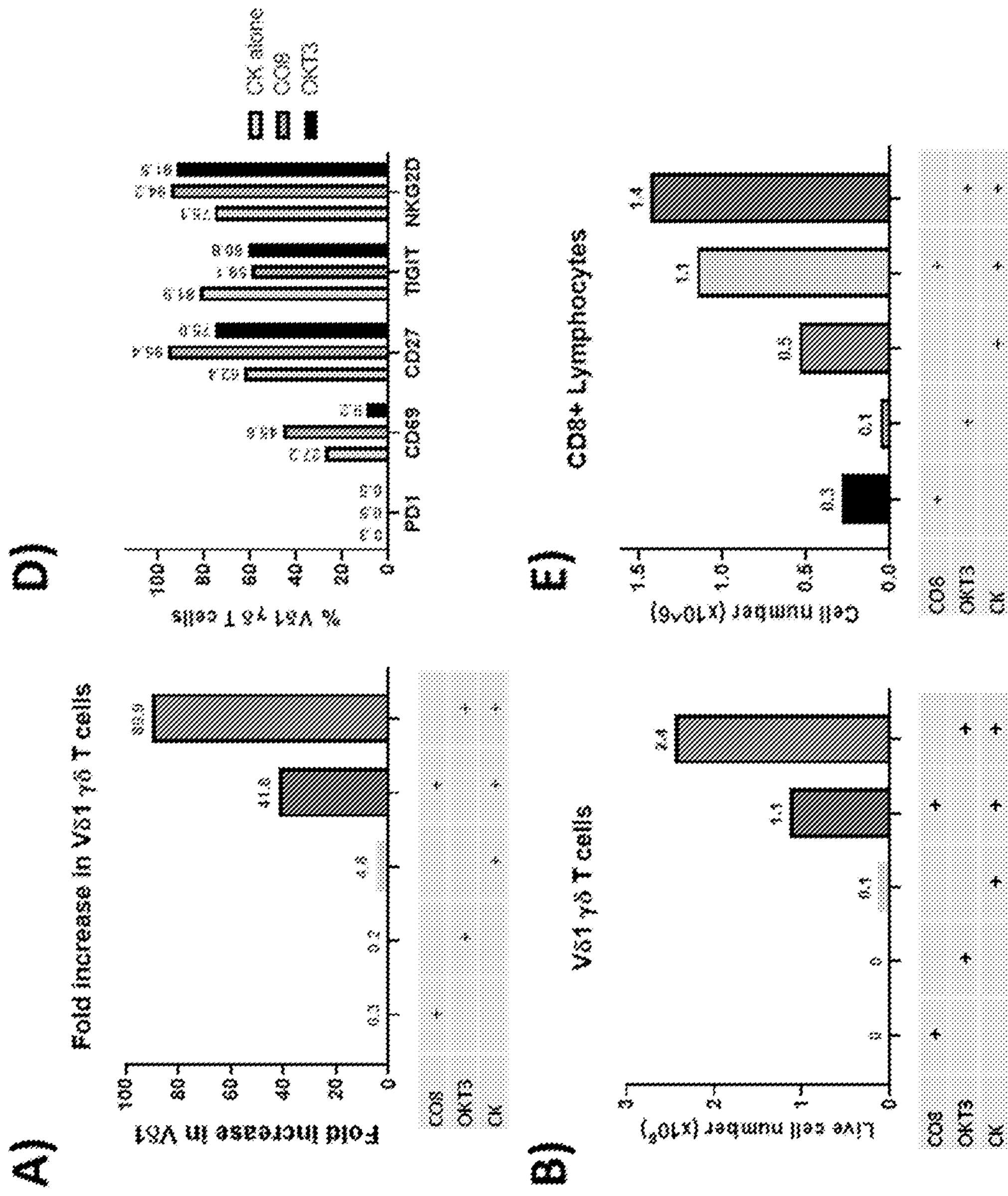

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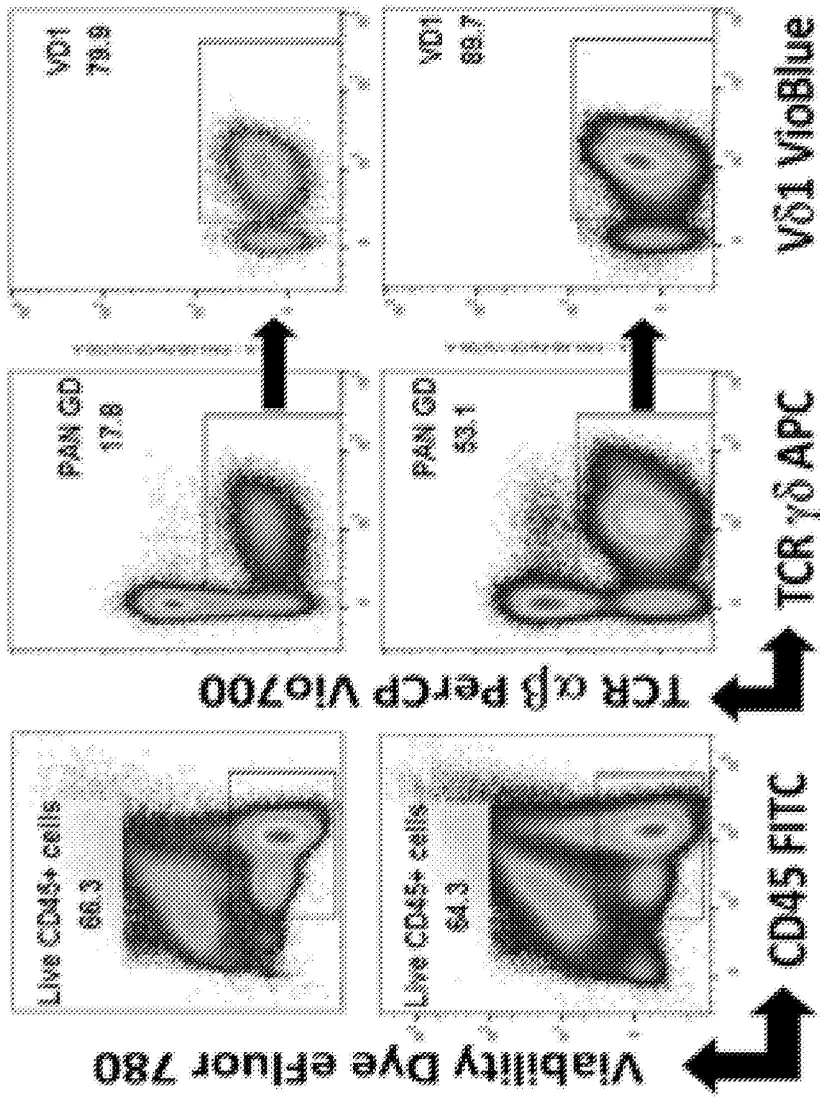

FIGURE 20 (contd.)

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<213> Homo sapiens

<400> 35

Thr Tyr Tyr Gly Ser Lys Trp Tyr Asn
1   5

<210> 36
<211> 8
<212> PRT
<213> Homo sapiens

<400> 36

Ile Ser Ser Ser Gly Ser Thr Ile
1   5

<210> 37
<211> 8
<212> PRT
<213> Homo sapiens

<400> 37

Ile Ser Ser Ser Gly Ser Thr Ile
1   5

<210> 38
<211> 8
<212> PRT
<213> Homo sapiens

<400> 38

Gly Phe Thr Phe Ser Asp Tyr Tyr
1   5

<210> 39
<211> 8
<212> PRT
<213> Homo sapiens

<400> 39

Gly Phe Thr Val Ser Ser Asn Tyr
1   5

<210> 40
<211> 10
<212> PRT
<213> Homo sapiens

<400> 40

Gly Asp Ser Val Ser Ser Lys Ser Ala Ala
1   5   10

<210> 41
<211> 8
<212> PRT
<213> Homo sapiens

<400> 41

Gly Phe Thr Phe Ser Asp Tyr Tyr
1   5

<210> 42
<211> 8
<212> PRT
<213> Homo sapiens

<400> 42

Gly Phe Thr Phe Ser Ser Tyr Ala
1   5

<210> 43
<211> 8
<212> PRT
<213> Homo sapiens

<400> 43

Gly Tyr Ser Phe Thr Ser Tyr Trp
1   5

<210> 44
<211> 10
<212> PRT
<213> Homo sapiens

<400> 44

Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1   5   10

<210> 45
<211> 10
<212> PRT
<213> Homo sapiens

<400> 45

Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1   5   10

<210> 46
<211> 8
<212> PRT
<213> Homo sapiens

<400> 46

Gly Phe Thr Phe Ser Asp Tyr Tyr
1   5

<210> 47
<211> 10
<212> PRT
<213> Homo sapiens

<400> 47

Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1   5   10

<210> 48
<211> 8
<212> PRT
<213> Homo sapiens

<400> 48

Gly Phe Thr Phe Ser Asp Tyr Tyr
1   5

<210> 49
<211> 8
<212> PRT
<213> Homo sapiens

<400> 49

Gly Phe Thr Phe Ser Asp Tyr Tyr
1   5

<210> 50
<211> 6
<212> PRT
<213> Homo sapiens

<400> 50

Gln Ser Ile Gly Thr Tyr
1   5

<210> 51
<211> 6
<212> PRT
<213> Homo sapiens

<400> 51

Asn Ile Gly Ser Gln Ser
1   5

<210> 52
<211> 6
<212> PRT
<213> Homo sapiens

<400> 52

Gln Asp Ile Asn Asp Trp
1   5

<210> 53
<211> 6
<212> PRT

<213> Homo sapiens

<400> 53

Gln Ser Leu Ser Asn Tyr
1   5

<210> 54
<211> 6
<212> PRT
<213> Homo sapiens

<400> 54

Gln Asn Ile Arg Thr Trp
1   5

<210> 55
<211> 9
<212> PRT
<213> Homo sapiens

<400> 55

Arg Ser Asp Val Gly Gly Tyr Asn Tyr
1   5

<210> 56
<211> 6
<212> PRT
<213> Homo sapiens

<400> 56

Gln Ser Ile Ser Thr Trp
1   5

<210> 57
<211> 6
<212> PRT
<213> Homo sapiens

<400> 57

Gln Ser Ile Ser Ser Trp
1   5

<210> 58
<211> 6

<212> PRT
<213> Homo sapiens

<400> 58

Gln Ser Ile Ser Ser Tyr
1   5

<210> 59
<211> 6
<212> PRT
<213> Homo sapiens

<400> 59

Gln Ser Ile Ser Thr Trp
1   5

<210> 60
<211> 6
<212> PRT
<213> Homo sapiens

<400> 60

Gln Asp Ile Ser Asn Tyr
1   5

<210> 61
<211> 6
<212> PRT
<213> Homo sapiens

<400> 61

Gln Ser Ile Ser Ser His
1   5

<210> 62
<211> 118
<212> PRT
<213> Homo sapiens

<400> 62

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Asp Tyr Ala Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 63
<211> 117
<212> PRT
<213> Homo sapiens

<400> 63

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Ser Pro Ile Glu Leu Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 64
<211> 120
<212> PRT
<213> Homo sapiens

<400> 64

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Lys
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Ser Thr Asp Tyr Ala
    50   55   60

Ala Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65   70   75   80

Gln Leu Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85   90   95

Tyr Tyr Cys Ala Arg Thr Trp Ser Gly Tyr Val Asp Val Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 65
<211> 118
<212> PRT

<213> Homo sapiens

<400> 65

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30


Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Asn Tyr Leu Asn Ala Phe Asp Ile Trp Gly Arg Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115
```

<210> 66
<211> 117
<212> PRT
<213> Homo sapiens

<400> 66

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

Ser Ala Ile Ser Gly Gly Gly Gly Thr Thr Tyr Ser Ser Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Ser Gly Val Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 67
<211> 119
<212> PRT
<213> Homo sapiens

<400> 67

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Arg His Gln Val Asp Thr Arg Thr Ala Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 68
<211> 120
<212> PRT
<213> Homo sapiens

<400> 68

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50   55   60

Val Ser Val Arg Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65   70   75   80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85   90   95

Tyr Tyr Cys Ala Arg Ser Trp Asn Asp Ala Phe Asp Ile Trp Gly Gln
            100   105   110

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 69
<211> 120
<212> PRT
<213> Homo sapiens

<400> 69

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Val Ile Ser Gly Asp Ser Val Ser Ser Asn
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50   55   60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65   70   75   80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85   90   95

Tyr Tyr Cys Ala Arg Asp Tyr Tyr Tyr Ser Met Asp Val Trp Gly Gln
            100   105   110

Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 70
<211> 118
<212> PRT
<213> Homo sapiens

<400> 70

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Ser Trp Asn Asp Ala Phe Asp Val Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 71
<211> 120
<212> PRT
<213> Homo sapiens

<400> 71

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Gly Ser Lys Trp Tyr Asn Glu Tyr Ala
    50   55   60

Leu Ser Val Lys Ser Arg Ile Ile Ile Asn Pro Asp Thr Ser Lys Asn
65   70   75   80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85   90   95

Tyr Tyr Cys Ala Arg Asp Tyr Tyr Tyr Ser Met Asp Val Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 72
<211> 118
<212> PRT
<213> Homo sapiens

<400> 72

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Ser Trp Ser Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 73
<211> 118
<212> PRT
<213> Homo sapiens

<400> 73

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Ser Trp Asn Asp Ala Phe Asp Ile Trp Gly Arg Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 74
<211> 109
<212> PRT
<213> Homo sapiens

<400> 74

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Thr Ile Ala Cys Arg Ala Gly Gln Ser Ile Gly
            20   25   30

Thr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85   90   95

```
Leu Leu Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  75
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  75

Ala Ser Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro
1               5                   10                  15


Gly Lys Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Gln
            20                  25                  30


Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Met Leu Val
        35                  40                  45


Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser
    50                  55                  60


Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu
65                  70                  75                  80


Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser
                85                  90                  95


Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210>  76
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  76

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Pro Ala Leu Ser Ala Ser
1               5                   10                  15


Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn
            20                  25                  30
```

Asp Trp Leu Ala Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85   90   95

Pro Gln Val Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105   110

<210> 77
<211> 109
<212> PRT
<213> Homo sapiens

<400> 77

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Ser Leu Ser
            20   25   30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85   90   95

Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 78
<211> 109
<212> PRT
<213> Homo sapiens

<400> 78

```
Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser
1               5                   10                  15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Arg
            20                  25                  30

Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe
    50                  55                  60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Lys Arg Tyr
                85                  90                  95

Pro Pro Thr Phe Gly Leu Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 79
<211> 112
<212> PRT
<213> Homo sapiens

<400> 79

```
Ala Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro
1               5                   10                  15

Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Arg Ser Asp Val Gly
            20                  25                  30

Gly Tyr Asn Tyr Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro
        35                  40                  45
```

Lys Leu Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn
    50   55   60

Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser
65   70   75   80

Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr
                85   90   95

Ser Thr Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105   110

<210> 80
<211> 109
<212> PRT
<213> Homo sapiens

<400> 80

Ala Ser Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1   5   10   15

Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Ser Ile Ser
            20   25   30

Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Leu Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85   90   95

Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 81

<211> 109
<212> PRT
<213> Homo sapiens

<400> 81

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
            20   25   30

Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Leu Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser His
                85   90   95

Pro Pro Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100   105

<210> 82
<211> 109
<212> PRT
<213> Homo sapiens

<400> 82

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
            20   25   30

Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe

50 55 60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
85 90 95

Pro Asp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 83
<211> 109
<212> PRT
<213> Homo sapiens

<400> 83

Ala Ser Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1 5 10 15

Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Ser Ile Ser
20 25 30

Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Leu Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Ala Ile Ser Ser Leu
65 70 75 80

Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
85 90 95

Pro Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 84
<211> 109
<212> PRT
<213> Homo sapiens

<400> 84

```
Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1               5                   10                  15


Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser
            20                  25                  30


Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe
    50                  55                  60


Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80


Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95


Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 85
<211> 109
<212> PRT
<213> Homo sapiens

<400> 85

```
Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1               5                   10                  15


Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
            20                  25                  30


Ser His Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50                  55                  60
```

Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85   90   95

Leu Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 86
<211> 240
<212> PRT
<213> Homo sapiens

<400> 86

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Val Asp Tyr Ala Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115   120   125

Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130   135   140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ala Cys Arg Ala Gly Gln
145   150   155   160

Ser Ile Gly Thr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                165   170   175

Pro Lys Leu Leu Ile Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro
            180   185   190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
        195   200   205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
    210   215   220

Tyr Ser Thr Leu Leu Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys
225   230   235   240

<210> 87
<211> 240
<212> PRT
<213> Homo sapiens

<400> 87

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
            20   25   30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50   55   60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65   70   75   80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85   90   95

Ser Pro Ile Glu Leu Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115   120   125

Gly Gly Ala Ser Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val
    130   135   140

Ala Pro Gly Lys Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly
145   150   155   160

Ser Gln Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Met
                165   170   175

Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg
            180   185   190

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg
        195   200   205

Val Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser
    210   215   220

Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225   230   235   240

<210> 88
<211> 243
<212> PRT
<213> Homo sapiens

<400> 88

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Lys
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu

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        35                  40                  45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Ser Thr Asp Tyr Ala
    50                  55                  60

Ala Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Leu Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Thr Trp Ser Gly Tyr Val Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Pro
    130                 135                 140

Ala Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Asp Ile Asn Asp Trp Leu Ala Trp Tyr Gln His Lys Pro Gly
                165                 170                 175

Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

Gln Ser Tyr Ser Thr Pro Gln Val Thr Phe Gly Gln Gly Thr Arg Leu
225                 230                 235                 240

Glu Ile Lys
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<210> 89
<211> 240
<212> PRT
<213> Homo sapiens

<400> 89

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Asn Tyr Leu Asn Ala Phe Asp Ile Trp Gly Arg Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130                 135                 140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln
145                 150                 155                 160

Ser Leu Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                165                 170                 175

Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
            180                 185                 190
```

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195   200   205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
    210   215   220

Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
225   230   235   240

<210> 90
<211> 239
<212> PRT
<213> Homo sapiens

<400> 90

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20   25   30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Ala Ile Ser Gly Gly Gly Gly Thr Thr Tyr Ser Ser Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Ser Gly Val Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115   120   125

Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser

    130   135   140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn
145   150   155   160

Ile Arg Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro
                165   170   175

Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser
            180   185   190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195   200   205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Lys
    210   215   220

Arg Tyr Pro Pro Thr Phe Gly Leu Gly Thr Lys Val Glu Ile Lys
225   230   235

<210> 91
<211> 244
<212> PRT
<213> Homo sapiens

<400> 91

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20   25   30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

Ala Arg His Gln Val Asp Thr Arg Thr Ala Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115   120   125

Ser Gly Gly Gly Ala Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val
    130   135   140

Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Arg
145   150   155   160

Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln His His Pro
                165   170   175

Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Asn Arg Pro Ser
            180   185   190

Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
        195   200   205

Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210   215   220

Ser Ser Tyr Thr Ser Thr Ser Thr Leu Val Phe Gly Gly Gly Thr Lys
225   230   235   240

Leu Thr Val Leu

<210> 92
<211> 242
<212> PRT
<213> Homo sapiens

<400> 92

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

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Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60

Val Ser Val Arg Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Ser Trp Asn Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Ala Ser Asp Ile Val Met Thr Gln Ser Pro Ser
    130                 135                 140

Thr Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Gly Gln Ser Ile Ser Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly
            180                 185                 190

Val Pro Leu Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

Gln Ser Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
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225   230   235   240

Ile Lys

<210> 93
<211> 242
<212> PRT
<213> Homo sapiens

<400> 93

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Val Ile Ser Gly Asp Ser Val Ser Ser Asn
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50   55   60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65   70   75   80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85   90   95

Tyr Tyr Cys Ala Arg Asp Tyr Tyr Tyr Ser Met Asp Val Trp Gly Gln
            100   105   110

Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115   120   125

Gly Ser Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130   135   140

Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145   150   155   160

Ser Gln Ser Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly
                165   170   175

Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly
            180   185   190

Val Pro Leu Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
        195   200   205

Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln
    210   215   220

Gln Ser His Ser His Pro Pro Thr Phe Gly Pro Gly Thr Lys Val Asp
225   230   235   240

Ile Lys

<210> 94
<211> 240
<212> PRT
<213> Homo sapiens

<400> 94

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Ser Trp Asn Asp Ala Phe Asp Val Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115   120   125

Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130   135   140

Ser Ala Ser Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln
145   150   155   160

Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                165   170   175

Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
            180   185   190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195   200   205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
    210   215   220

Tyr Ser Thr Pro Asp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225   230   235   240

<210> 95
<211> 242
<212> PRT
<213> Homo sapiens

<400> 95

Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20   25   30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

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Trp Leu Gly Arg Thr Tyr Tyr Gly Ser Lys Trp Tyr Asn Glu Tyr Ala
    50                  55                  60

Leu Ser Val Lys Ser Arg Ile Ile Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Tyr Tyr Tyr Ser Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Ala Ser Asp Ile Val Met Thr Gln Ser Pro Ser
    130                 135                 140

Thr Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Gly Gln Ser Ile Ser Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly
            180                 185                 190

Val Pro Leu Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
        195                 200                 205

Ala Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

Gln Ser Tyr Ser Thr Pro Val Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys
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<210> 96
<211> 240
<212> PRT
<213> Homo sapiens

<400> 96

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Ser Trp Ser Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115   120   125

Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130   135   140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln
145   150   155   160

Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                165   170   175

Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro
            180   185   190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195   200   205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
    210   215   220

Tyr Ser Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225   230   235   240

<210> 97
<211> 240
<212> PRT
<213> Homo sapiens

<400> 97

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Ser Trp Asn Asp Ala Phe Asp Ile Trp Gly Arg Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115   120   125

Gly Gly Gly Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130   135   140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
145   150   155   160

Ser Ile Ser Ser His Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                165   170   175

Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
            180   185   190

Ser Arg Phe Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195   200   205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
    210   215   220

Tyr Ser Thr Leu Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225   230   235   240

<210> 98
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic linker

<400> 98

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
1   5   10

<210> 99
<211> 765
<212> DNA
<213> Homo sapiens

<400> 99
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ctgagactct cctgtgcagc ctctggattc accttcagtg actactacat gagctggatc   120

cgccaggctc cagggaaggg gctggagtgg gtttcataca ttagtagtag tggtagtacc   180

atatactacg cagactctgt gaagggccga ttcaccatct ccagggacaa cgccaagaac   240

tcactgtatc tgcaaatgaa cagcctgaga gccgaggaca cggctgtgta ttactgtgca 300

agggtggact acgctgatgc atttgatatc tggggccagg gcaccctggt caccgtctcg 360

agtggtggag gcggttcagg cggaggtggc tctggcggtg gcgctagcga catccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cgcttgccgg 480

gcaggtcaga gcattggcac ctatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aaactcctga tctatgttgc atccagtttg caaagtgggg tcccgtcacg gttcagtggc 600

agtggatctg ggacagaatt cactctcacc atcagcagtc tgcaacctga agattttgca 660

acttactact gtcaacagag ttacagtacc ctcctcactt tcggcagagg gaccaaggtg 720

gaaatcaaac gtaccgcggc cgcatccgca catcatcatc accat 765

<210> 100
<211> 768
<212> DNA
<213> Homo sapiens

<400> 100
gccatggccg aggtgcagct gttggagtct gggggaggct tggtacagcc tggcaggtcc 60

ctgagactct cctgtgcagc ctctgggttc accgtcagta gcaactacat gagctgggtc 120

cgccaggctc cagggaaggg gctggagtgg gtctcagtta tttatagcgg tggtagcaca 180

tactacgcag actccgtgaa gggccgattc accatctcca gagacaattc caagaacacg 240

ctgtatcttc aaatgaacag cctgagagcc gaggacacgg ctgtgtatta ctgtgcgagc 300

cccatagagc tgggtgcttt tgatatctgg ggccaaggaa ccctggtcac cgtctcgagt 360

ggtggaggcg gttcaggcgg aggtggctct ggcggtggcg ctagctccta tgagctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggcca ggattacctg tgggggaaac 480

aacattggaa gtcaaagtgt gcactggtac cagcagaagc caggccaggc ccctatgctg 540

gtcatctatt atgatagcga ccggccctca gggatccctg agcgattctc tggctccaac 600

tctgggaaca cggccaccct gaccatcagc agggtcgaag ccggggatga ggccgactat 660

tactgtcagg tgtgggatag tagtagtgat catgtggtat tcggcggcgg gaccaagctg 720

accgtcctag gtcagcccgc ggccgcatcc gcacatcatc atcaccat 768

<210> 101
<211> 774

<212> DNA
<213> Homo sapiens

<400> 101
gccatggccc aggtacagct gcagcagtca ggtccaggac tggtgaagcc ctcgcagacc 60

ctctcactca cctgtgccat ctccggggac agtgtctcca gcaaaagtgc tgcttggaac 120

tggatcaggc agtccccatc gagaggcctt gagtggctgg gaaggacata ctacaggtcc 180

aagtggtcta ctgattatgc agcatctgtg aaaagtcgaa taaccatcaa cccagacaca 240

tccaagaacc agctctccct gcagttaaac tctgtgactc ccgaggacac ggctgtgtat 300

tactgtgcaa gaacgtggag tggttatgtg gacgtctggg gccaaggaac cctggtcacc 360

gtctcgagtg gtggaggcgg ttcaggcgga ggtggctctg gcggtggcgc tagcgacatc 420

cagatgaccc agtcccctcc cgccctgtct gcatctgtgg gagacagagt caccatcact 480

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gcccctaagc tcctgatcta tgatgcctcc agtttggaaa gtggggtccc atcaaggttc 600

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tttgcaactt actactgtca acagagttac agtacccctc aggtcacttt tggccagggg 720

acacgactgg agatcaaacg taccgcggcc gcatccgcac atcatcatca ccat 774

<210> 102
<211> 765
<212> DNA
<213> Homo sapiens

<400> 102
gccatggccg aggtgcagct gttggagtct gggggaggct tggtcaagcc tggagggtcc 60

ctgagactct cctgtgcggc ctctggattc accttcagtg actactacat gagctggatc 120

cgccaggctc cagggaaggg gctggagtgg gtttcataca ttagtagtag tggtagtacc 180

atatactacg cagactctgt gaagggccga ttcaccatct ccagggacaa cgccaagaac 240

tcactgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtgta ttactgtgcg 300

agagaaaact atctaaatgc ttttgatatc tggggccgtg gcaccctggt caccgtctcg 360

agtggtggag gcggttcagg cggaggtggc tctggcggtg gcgctagcga catccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480

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aagctcctga tctatgctgc atccagtttg caaagtgggg tcccatcaag gttcagtggc 600

agtggatctg ggacagattt cactctcacc atcagcagtc tgcaacctga agattttgcg 660

acttactact gtcaacagag ttacagtacc cctctcactt tcggcggagg gaccaagcta 720

gagatcaaac gtaccgcggc cgcatccgca catcatcatc accat 765

<210> 103
<211> 762
<212> DNA
<213> Homo sapiens

<400> 103
gccatggccg aggtgcagct gttggagtct gggggaggct tggtacagcc tggggggtcc 60

ctgagactct cctgtgcagc ctctggattc acctttagca gctatgccat gagctgggtc 120

cgccaggctc cagggaaggg gctggagtgg gtctcagcta ttagtggtgg tggtggtacc 180

acatactcct cagactccgt gaagggccgg ttcaccatct ccagagacaa ttccaagaac 240

acgctgtatc tgcaaatgaa cagcctgaga gccgaggaca cggctgtgta ttactgtgcg 300

agagattcag ggttgcttt tgatatctgg ggccaaggaa ccctggtcac cgtctcgagt 360

ggtggaggcg gttcaggcgg aggtggctct ggcggtggcg ctagcgacat ccagatgacc 420

cagtctccat ccttcctgtc tgcatctgta ggagacagag tcaccatcac ttgccgggcc 480

agtcagaata tacgtacctg gttggcctgg tatcagcaga aaccagggag agcccctaag 540

ctcctgatct atgatgcctc cagtttggaa agtggggtcc catcaaggtt cagcggcagt 600

ggatctggga ctgatttcac tctcaccatc agcagcctgc agcctgaaga ttttgcaact 660

tattactgtc aacagtttaa acgttaccct ccgacgtttg gcctggggac caaggtggag 720

atcaaacgta ccgcggccgc atccgcacat catcatcacc at 762

<210> 104
<211> 780
<212> DNA
<213> Homo sapiens

<400> 104
gccatggccc aggtccagct ggtacagtct ggagcagagg tgaaaaagcc cggggagtct 60

ctgaagatct cctgtaaggg ttctggatac agctttacca gctactggat cggctgggtg 120

cgccagatgc ccgggaaagg cctggagtgg atggggatca tctatcctgg tgactctgat 180

accagataca gcccgtcctt ccaaggccag gtcaccatct cagccgacaa gtccatcagc   240

accgcctacc tgcagtggag cagcctgaag gcctcggaca ccgccatgta ttattgtgcg   300

agacatcagg ttgatacacg gacggctgat tactggggcc agggaaccct ggtcaccgtc   360

tcgagtggtg gaggcggttc aggcggaggt ggctctggcg gtggcgctag ccagtctgcg   420

ctgactcagc ctgcctccgt gtctgggtct cctggacagt cggtcaccat ctcctgcact   480

ggaaccagga gtgacgttgg tggttataac tatgtctcct ggtaccaaca ccacccaggc   540

aaagccccca aactcatgat ttatgaggtc agtaatcggc cctcaggggt ttctaatcgc   600

ttctctggct ccaagtctgg caacacggcc tccctgacca tctctgggct ccaggctgag   660

gacgaggctg attattactg cagctcatat acaagcacca gcactctggt attcggcgga   720

gggaccaagc tgaccgtcct aggtcagccc gcggccgcat ccgcacatca tcatcaccat   780

<210> 105
<211> 771
<212> DNA
<213> Homo sapiens

<400> 105
gccatggccc aggtacagct gcagcagtca ggtccaggac tggtgaagcc ctcgcagacc   60

ctctcactca cctgtgccat ctccggggac agtgtctcta gcaacagtgc tgcttggaac   120

tggatcaggc agtccccatc gagaggcctt gagtggctgg gaaggacata ctacaggtcc   180

aagtggtata atgattatgc agtatctgtg agaagtcgaa taaccatcaa cccagacaca   240

tccaagaacc agttctccct gcagctgaac tctgtgactc ccgaggacac ggctgtgtat   300

tactgtgcaa gaagctggaa tgatgctttt gatatctggg ggcaagggac cacggtcacc   360

gtctcgagtg gtggaggcgg ttcaggcgga ggtggctctg gcggtggcgc tagcgatatt   420

gtgatgacac agtctccttc caccctgtct gcatctatag gagacagagt caccatcact   480

tgccgggccg gtcagagtat tagtacctgg ttggcctggt atcagcagaa accagggaaa   540

gcccctaagc tcctgatcta tgatgcctcc agtttggaaa gtggggtccc attaaggttc   600

agcggcagtg gatctgggac agatttcact ctcaccatca gcagtctgca acctgaagat   660

tttgcaactt actactgtca acagagttac agtaccccgc tcactttcgg cggagggacc   720

aaggtggaga tcaaacgtac cgcggccgca tccgcacatc atcatcacca t   771

<210> 106
<211> 771
<212> DNA
<213> Homo sapiens

<400> 106
gccatggccc aggtacagct gcagcagtca ggtccaggcc tggtgaagcc ctcgcagacc   60

ctctcactca cctgtgtcat ctccggggac agtgtctcta gcaacagtgc tgcttggaac   120

tggatcaggc agtccccatc gcgaggcctt gagtggctgg gaaggacata ctacaggtcc   180

aagtggtata atgattatgc agtatctgtg aaaagtcgaa taaccatcaa cccagacaca   240

tccaagaacc agttctccct gcagctgaac tctgtgactc ccgaggacac ggctgtctat   300

tattgtgcaa gagactacta ctacagtatg gacgtctggg gccaagggac aatggtcacc   360

gtctcgagtg gtggaggcgg ttcaggcgga ggtggctctg gcggtggcgc tagcgacatc   420

cagatgaccc agtctccctc caccctgtct gcatctgtag gagacagagt caccatcact   480

tgccgggcca gtcagagtat tagtagctgg ttggcctggt atcagcagaa accagggaaa   540

gcccctaagc tcctgatcta tgatgcctcc agtttggaaa gtggggtccc attaaggttc   600

agcggcagtg gatctgggac agaattcact ctcaccatca gcagcctgca gcctgatgat   660

tttgcaactt attactgtca acagagtcac agtcaccccc ctactttcgg ccctgggacc   720

aaagtggata tcaaacgtac cgcggccgca tccgcacatc atcatcacca t   771

<210> 107
<211> 765
<212> DNA
<213> Homo sapiens

<400> 107
gccatggccc aggtgcagct ggtggagtct gggggaggct tggtcaagcc tggagggtcc   60

ctgagactct cctgtgcagc ctctggattc accttcagtg actactacat gagctggatc   120

cgccaggctc cagggaaggg gctggagtgg gtttcataca ttagtagtag tggtagtacc   180

atatactacg cagactctgt gaagggccga ttcaccatct ccagggacaa cgccaagaac   240

tcactgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtgta ttactgtgcg   300

agacatagct ggaatgatgc ttttgatgtc tggggccagg gaaccctggt caccgtctcg   360

agtggtggag gcggttcagg cggaggtggc tctggcggtg gcgctagcga catccagatg   420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtctccat cacctgccgg 480

gcaagtcaga gcattagcag ctatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aagctcctga tctatgctgc atccagtttg caaagtgggg tcccatcaag gttcagtggc 600

agtggatctg ggacagattt cactctcacc atcagcagtc tgcaacctga agattttgca 660

acttactact gtcagcagag ttacagtacc cccgacactt tcggcggagg gaccaaggtg 720

gaaatcaaac gtaccgcggc cgcatccgca catcatcatc accat 765

<210> 108
<211> 771
<212> DNA
<213> Homo sapiens

<400> 108
gccatggccc aggtacagct gcagcagtca ggtccaggac tggtgaagcc ctcgcagacc 60

ctctcactca cctgtgccat ctccggggac agtgtctcta gcaacagtgc tgcttggaac 120

tggatcaggc agtccccatc gagaggcctt gagtggctgg gaaggacata ctacgggtcc 180

aagtggtata atgagtatgc actatctgtg aaaagtcgaa taatcatcaa cccagacaca 240

tccaagaacc agttctccct gcagctgaac tctgtgactc ccgaggacac ggctgtctat 300

tattgtgcaa gagactacta ctacagtatg gacgtctggg gccagggaac cctggtcacc 360

gtctcgagtg gtggaggcgg ttcaggcgga ggtggctctg gcggtggcgc tagcgatatt 420

gtgatgactc agtctccttc caccctgtct gcatctatag gagacagagt caccatcact 480

tgccgggccg gtcagagtat tagtacctgg ttggcctggt atcagcagaa accagggaaa 540

gcccctaagc tcctgatcta tgatgcctcc agtttggaaa gtggggtccc attaaggttc 600

agcggcagtg gatctgggac agaattcact ctcgccatca gcagcctgca gcctgatgat 660

tttgcaactt actactgtca acagagttac agtaccccgg taacttttgg ccaggggacc 720

aaggtggaga tcaaacgtac cgcggccgca tccgcacatc atcatcacca t 771

<210> 109
<211> 765
<212> DNA
<213> Homo sapiens

<400> 109
gccatggccg aggtgcagct gttggagtct gggggaggct tggtcaagcc tggagggtcc 60

ctgagactct cctgtgcagc ctctggattc accttcagtg actactacat gagctggatc 120

cgccaggctc cagggaaggg gctggagtgg gtttcataca ttagtagtag tggtagtacc 180

atatactacg cagactctgt gaagggccga ttcaccatct ccagggacaa cgccaagaac 240

tcactgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtgta ttactgtgcg 300

agacatagct ggagtgatgc ttttgatatc tggggccaag gaaccctggt caccgtctcg 360

agtggtggag gcggttcagg cggaggtggc tctggcggtg gcgctagcga catccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccag 480

gcgagtcagg acattagcaa ctatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aagctcctga tctacgatgc atccaatttg gaaacagggg tcccatcaag gttcagtgga 600

agtggatctg ggacagattt cactctcacc atcagcagtc tgcaacctga agattttgca 660

acttactact gtcaacagag ttacagtact cctctcactt tcggcggagg gaccaaggtg 720

gagatcaaac gtaccgcggc cgcatccgca catcatcatc accat 765

<210> 110
<211> 765
<212> DNA
<213> Homo sapiens

<400> 110
gccatggccg aagtgcagct ggtggagtcc gggggaggct tagttcagcc tggggggtcc 60

ctgagactct cctgtgcagc ctctggattc accttcagtg actactacat gagctggatc 120

cgccaggctc cagggaaggg gctggagtgg gtttcataca ttagtagtag tggtagtacc 180

atatactacg cagactctgt gaagggccga ttcaccatct ccagggacaa cgccaagaac 240

tcactgtatc tgcaaatgaa cagcctgaga gccgaggaca cggccgtgta ttactgtgcg 300

agacatagct ggaatgatgc ttttgatatc tggggccgtg gcaccctggt caccgtctcg 360

agtggtggag gcggttcagg cggaggtggc tctggcggtg gcgctagcga catccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480

gcaagtcaga gcattagcag ccatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aagctcctga tctatgctgc atccagtttg caaagtgggg tcccatccag gttcagtgcc 600

agtggatctg ggacagattt cactctcacc atcagcagcc tgcagcctga agattttgca 660

acttactact gtcaacagag ttacagtacc ctgctcactt tcggcggagg gaccaaggtg 720

gaaatcaaac gtaccgcggc cgcatccgca catcatcatc accat   765

<210> 111
<211> 664
<212> PRT
<213> Homo sapiens

<400> 111

```
Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1               5                   10                  15

Val Gly Asp Arg Val Thr Ile Ala Cys Arg Ala Gly Gln Ser Ile Gly
            20                  25                  30

Thr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50                  55                  60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95

Leu Leu Thr Phe Gly Arg Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175
```

```
Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Val Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240

Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala
                245                 250                 255

Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser
            260                 265                 270

Thr Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
        275                 280                 285

Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
    290                 295                 300

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val Asp Tyr Ala Asp Ala
305                 310                 315                 320

Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
                325                 330                 335

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
            340                 345                 350

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
        355                 360                 365

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
    370                 375                 380

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
```

385   390   395   400

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
                405   410   415

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
            420   425   430

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        435   440   445

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    450   455   460

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
465   470   475   480

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
                485   490   495

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            500   505   510

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
        515   520   525

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
    530   535   540

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
545   550   555   560

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
                565   570   575

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
            580   585   590

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        595   600   605

```
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
    610                 615                 620


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
625                 630                 635                 640


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                645                 650                 655


Ser Leu Ser Leu Ser Pro Gly Lys
            660


<210>  112
<211>  667
<212>  PRT
<213>  Homo sapiens

<400>  112

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Pro Ala Leu Ser Ala Ser
1               5                   10                  15


Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn
            20                  25                  30


Asp Trp Leu Ala Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe
    50                  55                  60


Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80


Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95


Pro Gln Val Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr
            100                 105                 110


Ala Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
        115                 120                 125
```

```
Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
    130                 135                 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145                 150                 155                 160

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
                165                 170                 175

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
            180                 185                 190

Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
        195                 200                 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Gln Gln Ser
    210                 215                 220

Gly Pro Gly Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala
225                 230                 235                 240

Ile Ser Gly Asp Ser Val Ser Ser Lys Ser Ala Ala Trp Asn Trp Ile
                245                 250                 255

Arg Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr
            260                 265                 270

Arg Ser Lys Trp Ser Thr Asp Tyr Ala Ala Ser Val Lys Ser Arg Ile
        275                 280                 285

Thr Ile Asn Pro Asp Thr Ser Lys Asn Gln Leu Ser Leu Gln Leu Asn
    290                 295                 300

Ser Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Thr Trp
305                 310                 315                 320

Ser Gly Tyr Val Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
                325                 330                 335
```

```
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
            340                 345                 350

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
        355                 360                 365

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
    370                 375                 380

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
385                 390                 395                 400

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
                405                 410                 415

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
            420                 425                 430

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
        435                 440                 445

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    450                 455                 460

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
465                 470                 475                 480

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                485                 490                 495

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
            500                 505                 510

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
        515                 520                 525

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    530                 535                 540

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
545                 550                 555                 560
```

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
                565   570   575

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            580   585   590

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        595   600   605

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    610   615   620

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
625   630   635   640

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                645   650   655

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            660   665

<210> 113
<211> 664
<212> PRT
<213> Homo sapiens

<400> 113

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Ser Leu Ser
            20   25   30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu

```
65                  70                  75                  80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95

Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Leu Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240

Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala
                245                 250                 255

Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser
            260                 265                 270

Thr Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
        275                 280                 285
```

```
Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
    290                 295                 300

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Asn Tyr Leu Asn Ala
305                 310                 315                 320

Phe Asp Ile Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser
                325                 330                 335

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
            340                 345                 350

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
        355                 360                 365

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
    370                 375                 380

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
385                 390                 395                 400

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
                405                 410                 415

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
            420                 425                 430

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        435                 440                 445

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    450                 455                 460

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
465                 470                 475                 480

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
                485                 490                 495

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
```

500 505 510

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
515 520 525

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
530 535 540

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
545 550 555 560

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
565 570 575

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
580 585 590

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
595 600 605

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
610 615 620

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
625 630 635 640

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
645 650 655

Ser Leu Ser Leu Ser Pro Gly Lys
660

<210> 114
<211> 663
<212> PRT
<213> Homo sapiens

<400> 114

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser
1 5 10 15

```
Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Arg
            20                  25                  30

Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe
    50                  55                  60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Lys Arg Tyr
                85                  90                  95

Pro Pro Thr Phe Gly Leu Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Leu Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240
```

```
Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala
                245                 250                 255

Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Gly Gly Gly
            260                 265                 270

Thr Thr Tyr Ser Ser Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
        275                 280                 285

Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
    290                 295                 300

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Ser Gly Val Ala Phe
305                 310                 315                 320

Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
                325                 330                 335

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
            340                 345                 350

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
        355                 360                 365

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
    370                 375                 380

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
385                 390                 395                 400

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
                405                 410                 415

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
            420                 425                 430

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        435                 440                 445
```

```
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    450                 455                 460

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
465                 470                 475                 480

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                485                 490                 495

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            500                 505                 510

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        515                 520                 525

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    530                 535                 540

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
545                 550                 555                 560

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
                565                 570                 575

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            580                 585                 590

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        595                 600                 605

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    610                 615                 620

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
625                 630                 635                 640

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
                645                 650                 655

Leu Ser Leu Ser Pro Gly Lys
            660
```

<210> 115
<211> 667
<212> PRT
<213> Homo sapiens

<400> 115

```
Ala Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro
1               5                   10                  15

Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Arg Ser Asp Val Gly
            20                  25                  30

Gly Tyr Asn Tyr Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro
        35                  40                  45

Lys Leu Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn
    50                  55                  60

Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser
65                  70                  75                  80

Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr
                85                  90                  95

Ser Thr Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110

Gly Gln Pro Ala Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
        115                 120                 125

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
    130                 135                 140

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
145                 150                 155                 160

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
                165                 170                 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
```

```
            180                 185                 190

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
        195                 200                 205

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser Gln Val Gln Leu Val Gln
    210                 215                 220

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
225                 230                 235                 240

Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr Trp Ile Gly Trp Val Arg
                245                 250                 255

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Tyr Pro Gly
            260                 265                 270

Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile
        275                 280                 285

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
    290                 295                 300

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Gln Val Asp
305                 310                 315                 320

Thr Arg Thr Ala Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
                325                 330                 335

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
            340                 345                 350

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
        355                 360                 365

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
    370                 375                 380

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
385                 390                 395                 400
```

```
Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
                405                 410                 415

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
            420                 425                 430

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
        435                 440                 445

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    450                 455                 460

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
465                 470                 475                 480

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                485                 490                 495

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
            500                 505                 510

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
        515                 520                 525

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    530                 535                 540

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
545                 550                 555                 560

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
                565                 570                 575

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            580                 585                 590

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        595                 600                 605

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
```

    610   615   620

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
625   630   635   640

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                645   650   655

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            660   665

<210> 116
<211> 663
<212> PRT
<213> Homo sapiens

<400> 116

Ala Ser Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro
1   5   10   15

Gly Lys Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Gln
            20   25   30

Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Met Leu Val
        35   40   45

Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser
    50   55   60

Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu
65   70   75   80

Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser
                85   90   95

Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100   105   110

Pro Ala Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115   120   125

```
Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser Glu Val Gln Leu Leu Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240

Ser Gly Phe Thr Val Ser Ser Asn Tyr Met Ser Trp Val Arg Gln Ala
                245                 250                 255

Pro Gly Lys Gly Leu Glu Trp Val Ser Val Ile Tyr Ser Gly Gly Ser
            260                 265                 270

Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
        275                 280                 285

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
    290                 295                 300

Asp Thr Ala Val Tyr Tyr Cys Ala Ser Pro Ile Glu Leu Gly Ala Phe
305                 310                 315                 320

Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
                325                 330                 335

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
            340                 345                 350
```

```
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
        355                 360                 365

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
    370                 375                 380

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
385                 390                 395                 400

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
                405                 410                 415

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
            420                 425                 430

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        435                 440                 445

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    450                 455                 460

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
465                 470                 475                 480

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                485                 490                 495

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            500                 505                 510

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        515                 520                 525

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    530                 535                 540

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
545                 550                 555                 560
```

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
                565   570   575

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            580   585   590

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        595   600   605

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    610   615   620

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
625   630   635   640

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
                645   650   655

Leu Ser Leu Ser Pro Gly Lys
            660

<210> 117
<211> 666
<212> PRT
<213> Homo sapiens

<400> 117

Ala Ser Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1   5   10   15

Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Ser Ile Ser
            20   25   30

Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Leu Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

```
Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95

Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Gln Gln Ser Gly
    210                 215                 220

Pro Gly Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile
225                 230                 235                 240

Ser Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg
                245                 250                 255

Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg
            260                 265                 270

Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val Arg Ser Arg Ile Thr
        275                 280                 285

Ile Asn Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser
```

```
    290                 295                 300

Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Trp Asn
305                 310                 315                 320

Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
                325                 330                 335

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
            340                 345                 350

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
        355                 360                 365

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
    370                 375                 380

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
385                 390                 395                 400

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
                405                 410                 415

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
            420                 425                 430

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
        435                 440                 445

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510
```

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515   520   525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530   535   540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545   550   555   560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565   570   575

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            580   585   590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595   600   605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610   615   620

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625   630   635   640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645   650   655

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            660   665

<210> 118
<211> 666
<212> PRT
<213> Homo sapiens

<400> 118

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
            20   25   30

```
Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Leu Arg Phe
    50                  55                  60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80

Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser His Ser His
                85                  90                  95

Pro Pro Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Gln Gln Ser Gly
    210                 215                 220

Pro Gly Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Val Ile
225                 230                 235                 240
```

```
Ser Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg
                245                 250                 255

Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg
            260                 265                 270

Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr
        275                 280                 285

Ile Asn Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser
    290                 295                 300

Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Tyr Tyr
305                 310                 315                 320

Tyr Ser Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
                325                 330                 335

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
            340                 345                 350

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
        355                 360                 365

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
    370                 375                 380

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
385                 390                 395                 400

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
                405                 410                 415

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
            420                 425                 430

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
        435                 440                 445

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460
```

```
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515                 520                 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530                 535                 540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545                 550                 555                 560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565                 570                 575

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            580                 585                 590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595                 600                 605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610                 615                 620

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625                 630                 635                 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645                 650                 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            660                 665
```

<210> 119
<211> 664
<212> PRT
<213> Homo sapiens

<400> 119

```
Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1               5                   10                  15

Val Gly Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
            20                  25                  30

Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50                  55                  60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95

Pro Asp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190
```

```
Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Val Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240

Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala
                245                 250                 255

Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser
            260                 265                 270

Thr Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
        275                 280                 285

Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
    290                 295                 300

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg His Ser Trp Asn Asp Ala
305                 310                 315                 320

Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
                325                 330                 335

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
            340                 345                 350

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
        355                 360                 365

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
    370                 375                 380

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
385                 390                 395                 400

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
```

```
                405                 410                 415

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
            420                 425                 430

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        435                 440                 445

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    450                 455                 460

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
465                 470                 475                 480

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
                485                 490                 495

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            500                 505                 510

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
        515                 520                 525

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
    530                 535                 540

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
545                 550                 555                 560

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
                565                 570                 575

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
            580                 585                 590

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        595                 600                 605

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
    610                 615                 620
```

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
625   630   635   640

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                645   650   655

Ser Leu Ser Leu Ser Pro Gly Lys
            660

<210> 120
<211> 666
<212> PRT
<213> Homo sapiens

<400> 120

Ala Ser Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1   5   10   15

Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Ser Ile Ser
            20   25   30

Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Leu Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Ala Ile Ser Ser Leu
65   70   75   80

Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85   90   95

Pro Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100   105   110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115   120   125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130   135   140

```
Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Gln Gln Ser Gly
    210                 215                 220

Pro Gly Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile
225                 230                 235                 240

Ser Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg
                245                 250                 255

Gln Ser Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Gly
            260                 265                 270

Ser Lys Trp Tyr Asn Glu Tyr Ala Leu Ser Val Lys Ser Arg Ile Ile
        275                 280                 285

Ile Asn Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser
    290                 295                 300

Val Thr Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Tyr Tyr
305                 310                 315                 320

Tyr Ser Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
                325                 330                 335

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
            340                 345                 350
```

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
        355   360   365

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
    370   375   380

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
385   390   395   400

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
                405   410   415

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
            420   425   430

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
        435   440   445

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
    450   455   460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465   470   475   480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485   490   495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500   505   510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515   520   525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530   535   540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545   550   555   560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565   570   575

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            580   585   590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595   600   605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610   615   620

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625   630   635   640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645   650   655

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            660   665

<210> 121
<211> 664
<212> PRT
<213> Homo sapiens

<400> 121

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1   5   10   15

Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser
            20   25   30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe
    50   55   60

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65   70   75   80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr

```
                85                  90                  95

Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Leu Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240

Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala
                245                 250                 255

Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser
            260                 265                 270

Thr Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
        275                 280                 285

Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
    290                 295                 300
```

```
Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg His Ser Trp Ser Asp Ala
305                 310                 315                 320

Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
                325                 330                 335

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
            340                 345                 350

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
        355                 360                 365

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
    370                 375                 380

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
385                 390                 395                 400

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
                405                 410                 415

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
            420                 425                 430

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        435                 440                 445

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    450                 455                 460

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
465                 470                 475                 480

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
                485                 490                 495

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            500                 505                 510

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
```

515 520 525

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
530 535 540

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
545 550 555 560

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
565 570 575

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
580 585 590

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
595 600 605

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
610 615 620

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
625 630 635 640

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
645 650 655

Ser Leu Ser Leu Ser Pro Gly Lys
660

<210> 122
<211> 664
<212> PRT
<213> Homo sapiens

<400> 122

Ala Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
1 5 10 15

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
20 25 30

```
Ser His Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe
    50                  55                  60

Ser Ala Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
65                  70                  75                  80

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr
                85                  90                  95

Leu Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Ala
            100                 105                 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
        115                 120                 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
                165                 170                 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
            180                 185                 190

Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu Val Glu Ser Gly
    210                 215                 220

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
225                 230                 235                 240

Ser Gly Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala
                245                 250                 255
```

```
Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser
            260                 265                 270

Thr Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
        275                 280                 285

Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
    290                 295                 300

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg His Ser Trp Asn Asp Ala
305                 310                 315                 320

Phe Asp Ile Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser
                325                 330                 335

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
            340                 345                 350

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
        355                 360                 365

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
    370                 375                 380

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
385                 390                 395                 400

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
                405                 410                 415

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
            420                 425                 430

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
        435                 440                 445

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    450                 455                 460
```

```
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
465                 470                 475                 480

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
                485                 490                 495

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            500                 505                 510

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
        515                 520                 525

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
    530                 535                 540

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
545                 550                 555                 560

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
                565                 570                 575

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
            580                 585                 590

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        595                 600                 605

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
    610                 615                 620

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
625                 630                 635                 640

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                645                 650                 655

Ser Leu Ser Leu Ser Pro Gly Lys
            660

<210>  123
<211>  254
```

<212> PRT
<213> Artificial Sequence

<220>
<223> TRDV1(3OMZ) TRAC antigen sequence

<400> 123

```
Ala Gln Lys Val Thr Gln Ala Gln Ser Ser Val Ser Met Pro Val Arg
1               5                   10                  15


Lys Ala Val Thr Leu Asn Cys Leu Tyr Glu Thr Ser Trp Trp Ser Tyr
            20                  25                  30


Tyr Ile Phe Trp Tyr Lys Gln Leu Pro Ser Lys Glu Met Ile Phe Leu
        35                  40                  45


Ile Arg Gln Gly Ser Asp Glu Gln Asn Ala Lys Ser Gly Arg Tyr Ser
    50                  55                  60


Val Asn Phe Lys Lys Ala Ala Lys Ser Val Ala Leu Thr Ile Ser Ala
65                  70                  75                  80


Leu Gln Leu Glu Asp Ser Ala Lys Tyr Phe Cys Ala Leu Gly Glu Ser
                85                  90                  95


Leu Thr Arg Ala Asp Lys Leu Ile Phe Gly Lys Gly Thr Arg Val Thr
            100                 105                 110


Val Glu Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg
        115                 120                 125


Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp
    130                 135                 140


Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr
145                 150                 155                 160


Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser
                165                 170                 175


Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe
            180                 185                 190
```

```
Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser
        195                 200                 205

Ser Cys Thr Thr Ala Pro Ser Ala Gln Leu Lys Lys Lys Leu Gln Ala
    210                 215                 220

Leu Lys Lys Lys Asn Ala Gln Leu Lys Trp Lys Leu Gln Ala Leu Lys
225                 230                 235                 240

Lys Lys Leu Ala Gln Gly Ser Gly His His His His His His
                245                 250


<210>  124
<211>  12
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Optional scFv tag sequence (kappa sequence + His tag)

<400>  124

Arg Thr Ala Ala Ala Ser Ala His His His His His
1               5                   10


<210>  125
<211>  37
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Optional scFv tag sequence (kappa sequence + His and FLAG tag)

<400>  125

Arg Thr Ala Ala Ala Ser Ala His His His His His His Lys Leu Asp
1               5                   10                  15

Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile Asp Tyr Lys
            20                  25                  30

Asp Asp Asp Asp Lys
        35
```

<210> 126
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Optional scFv tag sequence (lambda sequence + His tag)

<400> 126

```
Gly Gln Pro Ala Ala Ala Ser Ala His His His His His
1               5                   10
```

<210> 127
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Optional scFv tag sequence (lambda sequence + His and FLAG tag)

<400> 127

```
Gly Gln Pro Ala Ala Ala Ser Ala His His His His His His Lys Leu
1               5                   10                  15


Asp Tyr Lys Asp His Asp Gly Asp Tyr Lys Asp His Asp Ile Asp Tyr
            20                  25                  30


Lys Asp Asp Asp Asp Lys
        35
```

<210> 128
<211> 254
<212> PRT
<213> Homo sapiens

<400> 128

```
Ala Gln Lys Val Thr Gln Ala Gln Ser Ser Val Ser Met Pro Val Arg
1               5                   10                  15


Lys Ala Val Thr Leu Asn Cys Leu Tyr Glu Thr Ser Trp Trp Ser Tyr
            20                  25                  30


Tyr Ile Phe Trp Tyr Lys Gln Leu Pro Ser Lys Glu Met Ile Phe Leu
        35                  40                  45
```

```
Ile Arg Gln Gly Ser Asp Glu Gln Asn Ala Lys Ser Gly Arg Tyr Ser
    50                  55                  60

Val Asn Phe Lys Lys Ala Val Lys Ser Val Ala Leu Thr Ile Ser Ala
65                  70                  75                  80

Leu Gln Leu Glu Asp Ser Ala Lys Tyr Phe Cys Ala Leu Gly Glu Ser
                85                  90                  95

Leu Thr Arg Ala Asp Lys Leu Ile Phe Gly Lys Gly Thr Arg Val Thr
            100                 105                 110

Val Glu Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg
        115                 120                 125

Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp
    130                 135                 140

Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr
145                 150                 155                 160

Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser
                165                 170                 175

Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe
            180                 185                 190

Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser
        195                 200                 205

Ser Cys Thr Thr Ala Pro Ser Ala Gln Leu Lys Lys Lys Leu Gln Ala
    210                 215                 220

Leu Lys Lys Lys Asn Ala Gln Leu Lys Trp Lys Leu Gln Ala Leu Lys
225                 230                 235                 240

Lys Lys Leu Ala Gln Gly Ser Gly His His His His His His
                245                 250
```

<210> 129

<211> 20
<212> PRT
<213> Homo sapiens

<400> 129

```
Met Leu Phe Ser Ser Leu Leu Cys Val Phe Val Ala Phe Ser Tyr Ser
1               5                   10                  15


Gly Ser Ser Val
            20
```

<210> 130
<211> 95
<212> PRT
<213> Homo sapiens

<400> 130

```
Ala Gln Lys Val Thr Gln Ala Gln Ser Ser Val Ser Met Pro Val Arg
1               5                   10                  15


Lys Ala Val Thr Leu Asn Cys Leu Tyr Glu Thr Ser Trp Trp Ser Tyr
            20                  25                  30


Tyr Ile Phe Trp Tyr Lys Gln Leu Pro Ser Lys Glu Met Ile Phe Leu
        35                  40                  45


Ile Arg Gln Gly Ser Asp Glu Gln Asn Ala Lys Ser Gly Arg Tyr Ser
    50                  55                  60


Val Asn Phe Lys Lys Ala Ala Lys Ser Val Ala Leu Thr Ile Ser Ala
65                  70                  75                  80


Leu Gln Leu Glu Asp Ser Ala Lys Tyr Phe Cys Ala Leu Gly Glu
                85                  90                  95
```

<210> 131
<211> 16
<212> PRT
<213> Homo sapiens

<400> 131

```
Thr Asp Lys Leu Ile Phe Gly Lys Gly Thr Arg Val Thr Val Glu Pro
1               5                   10                  15
```

<210> 132
<211> 17
<212> PRT
<213> Homo sapiens

<400> 132

Leu Thr Ala Gln Leu Phe Phe Gly Lys Gly Thr Gln Leu Ile Val Glu
1   5   10   15

Pro

<210> 133
<211> 19
<212> PRT
<213> Homo sapiens

<400> 133

Ser Trp Asp Thr Arg Gln Met Phe Phe Gly Thr Gly Ile Lys Leu Phe
1   5   10   15

Val Glu Pro

<210> 134
<211> 15
<212> PRT
<213> Homo sapiens

<400> 134

Arg Pro Leu Ile Phe Gly Lys Gly Thr Tyr Leu Glu Val Gln Gln
1   5   10   15

<210> 135
<211> 153
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa can be any naturally occurring amino acid

<400> 135

```
Xaa Ser Gln Pro His Thr Lys Pro Ser Val Phe Val Met Lys Asn Gly
1               5                   10                  15


Thr Asn Val Ala Cys Leu Val Lys Glu Phe Tyr Pro Lys Asp Ile Arg
            20                  25                  30


Ile Asn Leu Val Ser Ser Lys Lys Ile Thr Glu Phe Asp Pro Ala Ile
        35                  40                  45


Val Ile Ser Pro Ser Gly Lys Tyr Asn Ala Val Lys Leu Gly Lys Tyr
    50                  55                  60


Glu Ser Asn Ser Val Thr Cys Ser Val Gln His Asp Asn Lys Thr Val
65                  70                  75                  80


His Ser Thr Asp Phe Glu Val Lys Thr Asp Ser Thr Asp His Val Lys
                85                  90                  95


Pro Lys Glu Thr Glu Asn Thr Lys Gln Pro Ser Lys Ser Cys His Lys
            100                 105                 110


Pro Lys Ala Ile Val His Thr Glu Lys Val Asn Met Met Ser Leu Thr
        115                 120                 125


Val Leu Gly Leu Arg Met Leu Phe Ala Lys Thr Val Ala Val Asn Phe
    130                 135                 140


Leu Leu Thr Ala Lys Leu Phe Phe Leu
145                 150
```