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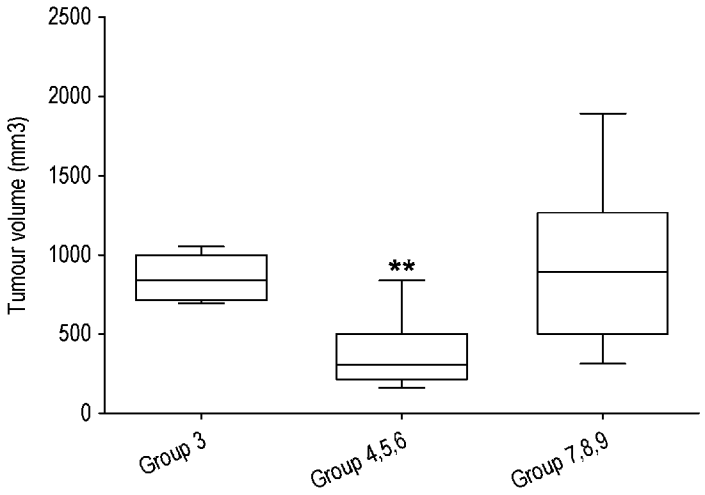

FIG. 6

(57) Abstract: The disclosure relates to agents that simultaneously bind CD137 and PSMA and which comprise a single domain antibody specific to CD137 and a moiety that binds PSMA. The disclosure also relates to therapeutic and diagnostic applications of such agents, for example in the treatment or detection of a cancer.

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Molecules that bind to CD137 and PSMA

Introduction

Cancer remains one of the leading causes of death in the world. Recent studies have shown an estimated 12.7 million cancer cases worldwide. This number is expected to increase to 21 million by 2030 (Vinay and Kwon 2014).

CD137 (4-1BB, TNFRS9) is a type 1 transmembrane glycoprotein belonging to the TNF receptor superfamily. It was originally cloned by Kwon et al (1989) from the cDNA of activated murine T cells. It has subsequently been shown to have a broad immune cell expression pattern found on T cells, B cells, NK and NK T cells, dendritic cells (DC), macrophages, neutrophils and eosinophils. Expression has also been reported on non-haematopoetic cells, for example epithelial, endothelial and smooth muscle cells and on tumour cell lines. CD137 expression is mainly activation induced, although low level constitutive expression has been demonstrated on some cell types including Tregs and DC's.

The 255 amino acid human CD137 protein (Genbank accession NP_001552) consists of a 17 amino acid signal peptide sequence, an extracellular region containing four cysteine rich domains, a 27 amino acid transmembrane region and a short 42 amino acid intracellular domain. It exists as both a monomer and dimer on the cell surface. The main ligand for CD137 is CD137 ligand (CD137L, 4-1BB-L, TNFS9), although interactions with galectin-9 which facilitates receptor aggregation (Madireddi et al 2014) and matrix proteins such as fibronectin (Chalupny et al, 1992) have also been reported. CD137 ligand is predominantly expressed on activated antigen presenting cells such as dendritic cells, B-cells and macrophages.

Interaction of the trimeric CD137 ligand with CD137 results in clustering of the receptor and recruitment of signalling molecules such as the TRAF family of proteins leading to kinase modulation and activation of the NfKB pathway. Thus, clustering of CD137 is crucial for initiation and regulation of downstream signalling.

Studies using agonist anti CD137 monoclonal antibodies in vitro and in vivo have shown that upon activation CD137 is rapidly internalised into an endosomal compartment termed the 'signalosome' from which it keeps signalling (reviewed in Sanchez-Paulete et al 2016).

Co-stimulatory TNFR family members such as CD137, CD27, OX40 (CD134), HVEM, CD30, and GITR are involved in sustaining the T cell responses after initial T-cell activation. In CD4+ and CD8+ T cells, CD137 acts as a costimulatory receptor that modulates T-cell receptor (TCR) mediated signalling. Ligation of CD137 together with TCR activation promotes proliferation, cytokine production, and inhibits apoptosis through induction of anti-apoptotic B-cell lymphoma-extra large (Bcl-xl) and B-cell lymphoma 2 (Bcl-2) pathways. Cross-linking of CD137 on NK cells has been shown to stimulate IFN-gamma secretion and

proliferation. Dendritic cell responses to CD137 stimulation include enhanced maturation and antigen presentation and secretion of cytokines IL-6, IL12 –and IL-27 and enzymes such as indoleamine-2,3-dioxygenase (IDO) which can modulate T-cell function. CD137 can also upregulate intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) on tumor vascular endothelium, thus inducing effector cell migration and retention of the activated T-cells in the tumor microenvironment.

Cross linking of CD137 by anti CD137 antibodies has been shown to have potent anti-tumour effects in vivo in a number of models including sarcoma, mastocytoma, glioma, lymphoma, myeloma, and hepatocellular carcinoma. CD8+ cell depletion studies have demonstrated that this effect primarily involves cytolytic T cell expansion and infiltration resulting in tumour cell lysis. However, contributions of other types of cells such as DCs, NK-cells or CD4+ T-cells have been reported in some tumour models. Furthermore, anti CD137 therapy has been shown to trigger an immunologic memory response and to inhibit autoimmune reactions (reviewed in Vinay et al 2012).

It has been shown that existing agonistic therapies result in systemic CD137 effects leading to unwanted side effects. Activation of CD137 signalling has been associated with severe toxicity in murine models. Clinical trials of a fully human IgG4 anti CD137 agonistic antibody (Urelumab®, BMS-663513) reported neutropenia, elevated liver enzymes and at high doses severe hepatic toxicity resulting in trial termination. This severe toxicity has not been observed for a fully human IgG2 (PF-05082566) that is also in clinical trials both as a monotherapy and in combination therapy approaches.

Agonistic antibodies targeting co-stimulatory TNFRs have been shown to require engagement of FcγRs (Bulliard et al). Thus, non-targeted clustering via FcγRs may influence the mechanism by which agonistic antibodies act on these targets.

In light of the toxicity profile observed with existing therapies, there is a need for alternative cancer therapies based on the use of alternative CD137 binding molecules that have reduced toxicity. In particular, there is a clinical need for targeted CD137 agonists that effectively engage CD137 on the surface of cells and have reduced toxicity, including liver toxicity.

Prostate cancer is the most commonly diagnosed non-skin-related malignancy in males in developed countries. It is estimated that one in six males will be diagnosed with prostate cancer.

Current treatments for prostate cancer include surgery, radiation, and adjuvant hormonal therapy. Although these therapies are relatively effective in the early stages of disease, the majority of patients initially diagnosed with localized prostate cancer ultimately relapse. Whilst chemotherapy is one of the most widely used approaches in combating advanced prostate cancer, its therapeutic efficacy is usually insufficient due to lack of specificity and associated toxicity. Lack of targeted delivery to prostate cancer cells is one of the

primary obstacles in achieving feasible therapeutic effect. Consequently, there remains a critical need for strategies to increase the selectivity of anti-prostate cancer agents (Barve et al).

The diagnosis of prostate cancer has greatly improved following the use of serum-based markers such as the prostate specific antigen (PSA). In addition, prostate tumour-associated antigens offer targets for tumour imaging, diagnosis, and targeted therapies. The prostate specific membrane antigen (PSMA), a prostate tumour associated marker, is such a target.

PSMA is a 750-residue type II transmembrane glycoprotein highly restricted to prostate secretory epithelial cell membranes. It is highly expressed in prostate cancer cells and in nonprostatic solid tumor neovasculature and other solid tumors and expressed at lower levels in other tissues, including healthy prostate, kidney, liver, small intestine, and brain. PSMA expression increases with prostate disease progression and metastasis and its expression level has thus been correlated with tumour aggressiveness. Various immunohistological studies have demonstrated increased PSMA levels in virtually all cases of prostatic carcinoma compared to those levels in benign prostate epithelial cells. Intense PSMA staining is found in all stages of the disease, including prostatic intraepithelial neoplasia, late stage androgen-independent prostate cancer and secondary prostate tumours localized to lymph nodes, bone, soft tissue, and lungs. PSMA is thus widely used as a biomarker for prostate cancer cells.

PSMA has a 3-part structure: a 19-amino-acid internal portion, a 24-amino-acid transmembrane portion, and a 707-amino-acid external portion. It forms a noncovalent homodimer that possesses glutamate carboxypeptidase activity based on its ability to process the neuropeptide N-acetylaspartylglutamate and glutamate-conjugated folate derivatives. PSMA is rapidly and efficiently internalized by an endocytic pathway and rapidly recycles back to the membrane.

The invention addresses the need for alternative antibody-based treatments for use in the treatment of a cancer.

Summary

The invention relates to novel binding molecules with specificity for both CD137 and PSMA. The inventors have identified single variable heavy chain domain antibodies that bind to CD137 and inhibit binding of CD137L to CD137. They do not cause CD137 signalling when bound to CD137 in monospecific format, that is without being linked to another moiety that binds a second target. However, when linked to a moiety that binds a tumor specific antigen, the single variable heavy chain domain antibodies elicit CD137 signalling. Thus, whilst the single variable heavy chain domain antibodies that bind to CD137 do not induce clustering of the receptor and do not have agonistic activity when bound to CD137 without a binding partner that targets a second antigen, the dual engagement of CD137 and a tumor specific antigen in a bispecific molecule leads to CD137 agonism. The single variable heavy chain domain antibodies that bind to CD137

can therefore be used as a subunit in a multispecific binding molecule that simultaneously engages CD137 and PSMA.

Bi- and multispecific molecules described herein bind to CD137 and PSMA and simultaneously engage both targets. This dual engagement results in CD137 activation, thus restricting the site of action to the tumor microenvironment and potentially minimising undesirable effects of existing CD137 therapies.

In one aspect, there is provided an isolated binding molecule comprising or consisting of
a) a single variable heavy chain domain antibody that binds to CD137 and
b) a moiety that binds to PSMA.

In one embodiment, the single variable heavy chain domain antibody that binds to CD137 comprises a CDR1 comprising SEQ ID NO. 1 or a sequence with at least 40% homology thereto, a CDR2 comprising SEQ ID NO. 2 or a sequence with at least 40% homology thereto and a CDR3 comprising SEQ ID NO. 3 or a sequence with at least 40% homology thereto or a CDR1 comprising SEQ ID NO. 425 or a sequence with at least 40% homology thereto, a CDR2 comprising SEQ ID NO. 426 or a sequence with at least 40% homology thereto and a CDR3 comprising SEQ ID NO. 427 or a sequence with at least 40% homology thereto.
In one embodiment, the single variable heavy chain domain antibody that binds to CD137 comprises human framework regions.
In one embodiment, the single variable heavy chain domain antibody that binds to CD137 comprises a full length sequence as listed in table 2 or 3 or a sequence with at least 75% homology thereto.
In one embodiment, the single variable heavy chain domain antibody that binds to CD137 comprises or consists of one of the following sequences: SEQ ID NO. 4, 312, 428, 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 50% homology thereto.
In one embodiment, the moiety that binds to PSMA is selected from an antibody, an antibody fragment, an antibody mimetic, a protein that mimics the natural ligand of CD137 or other polypeptide.
In one embodiment, said antibody fragment is selected from a Fab, F(ab')2, Fv, a single chain Fv fragment (scFv), a single domain antibody or fragment thereof.
In one embodiment, said single domain antibody is a single V_H domain antibody.
In one embodiment, said single V_H domain antibody comprises a CDR1 comprising SEQ ID NO. 812 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 813 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 814 or a sequence with at least 75% homology thereto or wherein said V_H single domain antibody comprises a CDR1 comprising SEQ ID NO. 837 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 838 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 839 or a sequence with at least 75% homology thereto.
In one embodiment, the single variable heavy chain domain antibody that binds to PSMA comprises a full length sequence as listed in table 6 or 7 or a sequence with at least 50% homology thereto.

In one embodiment, the single variable heavy chain domain antibody moiety that binds to PSMA comprises SEQ ID NO. 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825 or 840 or a sequence with at least 50% homology thereto.

In one embodiment, a single domain antibody 1.1 or 2.1 having one of SEQ ID No. 4, 312, 852, 856, 860, 864, 868, 872, 876, 880 or 428 or a variant t(e.g. a molecules with 1 to 10 or 1 to 20 amino acid substitutions) hereof is linked to a single domain antibody 3.1, 3.8 or 4.1 having SEQ ID No. 815, 822 or 840 respectively.

In one embodiment, the isolated binding molecule is capable of binding CD137 with an affinity with a Kd of about of at least about 10-6 M, alternatively at least about 10-7 M, alternatively at least about 10-8 M, alternatively at least about 10-9 M, alternatively at least about 10-10 M, alternatively at least about 10-11 M, alternatively at least about 10-12 M, or greater affinity.

In one embodiment, the isolated binding molecule is capable of binding PSMA with an affinity with a Kd of about of at least about 10-6 M, alternatively at least about 10-7 M, alternatively at least about 10-8 M, alternatively at least about 10-9 M, alternatively at least about 10-10 M, alternatively at least about 10-11 M, alternatively at least about 10-12 M, or greater affinity.

In one embodiment, the single variable heavy chain domain antibody that binds to CD137 is linked to the moiety that binds PSMA by a peptide linker.

In one embodiment, said linker is selected from a (G4S)n linker wherein n is 1 to 10.

An isolated binding molecule of the invention may comprise a single variable heavy chain domain antibody that binds to CD137 linked to a moiety that binds PSMA. In one embodiment, the isolated binding molecule is conjugated to a toxin, enzyme, radioisotope, half-life extending moiety, label, therapeutic molecule or other chemical moiety.

In one embodiment, said half-life extending moiety is selected from the group consisting of an albumin binding moiety, a transferrin binding moiety, a polyethylene glycol molecule, a recombinant polyethylene glycol molecule, human serum albumin, a fragment of human serum albumin, and an albumin binding peptide or single domain antibody that binds to human serum albumin.

Generally, the single variable heavy chain domain antibody which binds to human CD137 does not cause CD137 signalling when bound to CD137 as a monospecific entity.

In one embodiment, the single variable heavy chain domain antibody which binds to human CD137 is obtained or obtainable from a transgenic rodent that expresses a transgene comprising human V, D and J regions.

In one embodiment, said rodent, e.g. a mouse, does not produce functional endogenous light and heavy chains.

Also provided is a pharmaceutical composition comprising a binding molecule as described herein, e.g. comprising a single variable heavy chain domain antibody as described herein and a pharmaceutical carrier.

Also provided is a binding molecule or a pharmaceutical composition as described herein for use in the treatment of disease such as cancer, prostate cancer or a PSMA positive tumor.

Also provided is a method for treating cancer comprising administering a therapeutically effective amount of a binding molecule or a pharmaceutical composition as described herein.

In one embodiment, said cancer is prostate cancer lung cancer, glioblastoma, renal, bladder, testicular, neuroendocrine, colon, and breast cancer.

Also provided is a nucleic acid molecule comprising a nucleic acid sequence encoding the binding molecule as described herein.

Also provided is a vector comprising a nucleic acid molecule as described herein.

Also provided is a host cell comprising a nucleic acid molecule or a vector as described herein.

In one embodiment, the host cell is a bacterial, yeast, viral, plant or mammalian cell.

Also provided is a method for producing a binding molecule described herein comprising expressing a nucleic acid encoding said binding molecule in a host cell and isolating the binding molecule from the host cell.

Also provided is a method for promoting CD8+ T cell expansion, inducing activation of cytotoxic T lymphocytes (CTL) and/or cytokine release comprising administering a binding molecule or a pharmaceutical composition as described herein.

Also provided is an in vivo or in vitro method for reducing human PSMA activity comprising contacting human PSMA with a binding molecule as described above.

Also provided is a kit comprising a binding molecule as described herein or a pharmaceutical composition as described herein.

Also provided is a use of a binding molecule or a pharmaceutical composition as described above for activating, e.g. simultaneously activating, downstream signalling pathways of CD137 and PSMA.

Also provided is a method for activating, e.g. simultaneously activating, downstream signalling pathways of CD137 and PSMA comprising administering a binding molecule or a pharmaceutical composition as described herein.

Also provided is a method for dual engagement of CD137 and PSMA comprising administering a binding molecule or a pharmaceutical composition as described herein.

Also provided is a use of a binding molecule or a pharmaceutical composition as described herein for inducing a local T cell response in the vicinity of a PSMA positive tumor cell or tissue.

Also provided is a method for inducing a local T cell response in the vicinity of a PSMA positive tumor cell or tissue comprising administering a binding molecule or a pharmaceutical composition as described herein.

Figures

The invention is further described in the following non-limiting figures.

Figure 1: Dual Binding Cell based ELISA.

CHO human PSMA expressing cells were seeded onto plates and monovalent V_H or bispecific molecules added. CD137huFc was subsequently added and binding detected using anti human Fc-HRP. Only bispecific molecule sshowed increased binding signal confirming dual target binding.

Figure 2: Activation of CD137 signalling in the Jurkat NF-kB Luciferase Reporter Assay.

(A) CHO PSMA cells, **(B)** DU145 PSMA cells or **(C)** DU145 parental cells (bispecific testing)/media only (antibody testing) were cultured with Jurkat human CD137 NF-kB-luciferase reporter cells. Relative luminescence signal (RLU) was measured as a readout of the luciferase reporter gene activity resulting from CD137 mediated activation of the NF-kB signalling pathway. Monovalent Humabody® V_H 1.1 and 2.1 were unable to stimulate a response. Bispecific Humabody ® V_H stimulated CD137 signalling in a PSMA dependent and concentration dependent manner. The level of response was PSMA expression level dependent with higher maximal response observed in the presence of higher expression of PSMA. Anti CD137 antibody responses were PSMA expression independent. Bispecific molecules in the presence of PSMA expressing cells were able to effectively stimulate CD137 signalling.

Figure 3. Enhancement of cytokine production in T-cells.

Human CD8+ T cells were co-cultured with PSMA expressing cells or non-expressing parental cells in the presence of plate bound anti CD3 antibody. Humabody® V_H 1.1 monovalent and bispecific molecules, Humabody® V_H 2.1 monovalent and bispecific molecules, anti CD137 comparator antibody and anti PSMA antibody. Supernatants were harvested after 48 hours and levels of IL-2 determined. **(A)** Enhancement of IL-2 responses in the presence of PSMA expressing and non-PSMA expressing cells **(B)** IL-2 responses for 3 different T-cell donors in the presence of PSMA expressing cells. **(C and D)** Concentration dependence of IL-2 response. **(E)** Interferon-gamma production in the presence of PSMA expressing cells. Monovalent Humabody® V_H did not stimulate IL2 or IFN-gamma production in the assay. Bispecific molecules in the presence of PSMA expressing cells were able to effectively enhance cytokineIL-2 production. The anti CD137 antibody (soluble/non-cross linked) enhanced IL-2 production in a PSMA independent response.

Figure 4. Mode of action of bispecific molecule. This figure illustrates the mode of action of a binding molecule that binds both CD137 and PSMA, leading to tumor selective T cell agonism.

Figure 5: Enhancement of TNF alpha production. SEB Pre-stimulated PBMCs were treated for 3 days with 1ng/ml SEB and Humabody constructs 4.1-6GS-1.1, 3.8-6GS-1.1 or a control V_H in the presence of either **(A)** CHO PSMA cells or **(B)** CHO parent cells and 1ng/ml SEB. TNF-alpha concentrations (Mean ± standard deviation) were determined from 3 replicate wells.

Figure 6: In vivo experiment: Effect of Humabody® in DU145 PSMA/hu PBMC engrafted NCG Mice

Pooled tumour volume data from HuPBMC engrafted NCG mice implanted with DU145 PSMA prostate cell lines. Groups 4-6 (3 huPBMC donors, each group n=5 mice per donor) were treated on days 9-32 with PBS (BIW) and on days 33-45 with 4.1-6GS-1.1-V_H (MSA) (3mg/kg, daily). Groups 7-9 (3 huPBMC donors, n=5 mice per donor) were treated with control anti CD137 antibody (3mg/kg, BIW) on days 9-32. Group 3 (non hPBMC engrafted group, n=5 mice) were untreated. Tumor volumes were measured at day 46 post-tumor implant. Statistical Significance (Mann-Whitney U test): ** = $P < 0.01$, compared to group 3.

Detailed description of the embodiments

The embodiments of the invention will now be further described. In the following passages, different embodiments are described. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or

advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, pathology, oncology, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. The methods and techniques of the present disclosure are generally performed according to conventional methods well-known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Green and Sambrook et al., Molecular Cloning: A Laboratory Manual, 4th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2012); Therapeutic Monoclonal Antibodies: From Bench to Clinic, Zhiqiang An (Editor), Wiley, (2009); and Antibody Engineering, 2nd Ed., Vols 1 and 2, Ontermann and Dubel, eds., Springer-Verlag, Heidelberg (2010).

Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Suitable assays to measure the properties as set out above are also described in the examples.

The term "antibody" as used herein broadly refers to any immunoglobulin (Ig) molecule, or antigen binding portion thereof, comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivation thereof, which retains the essential epitope binding features of an Ig molecule.

In a full-length antibody, each heavy chain is comprised of a heavy chain variable region or domain (abbreviated herein as HCVR) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, C_H1, C_H2 and C_H3. Each light chain has a light chain variable region or domain (abbreviated herein as LCVR) and a light chain constant region. The light chain constant region is comprised of one domain, C_L.

The heavy chain and light chain variable regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each heavy chain and light chain variable region 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.

Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG 1, IgG2, IgG 3, IgG4, IgAl and IgA2) or subclass.

The term "CDR" refers to the complementarity-determining region within antibody variable sequences. There are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs can be defined differently according to different systems known in the art.

The Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (Kabat et al., (1971) Ann. NY Acad. Sci. 190:382-391 and Kabat, et al., (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Chothia refers instead to the location of the structural loops (Chothia and Lesk J. Mol. Biol. 196:901 -917 (1987)). The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1 -113 of the heavy chain). Another system is the ImMunoGeneTics (IMGT) numbering scheme. The IMGT numbering scheme is described in Lefranc et al., Dev. Comp. Immunol., 29, 185-203 (2005).

The system described by Kabat is used herein. The terms "Kabat numbering", "Kabat definitions" and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (i.e., hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion.

A chimeric antibody is a recombinant protein that contains the variable domains including the complementarity determining regions (CDRs) of an antibody derived from one species, preferably a rodent antibody, while the constant domains of the antibody molecule are derived from those of a human antibody.

A humanized antibody is a recombinant protein in which the CDRs from an antibody from one species; e.g., a rodent antibody, are transferred from the heavy and light variable chains of the rodent antibody into human heavy and light variable domains (e.g., framework region sequences). The constant domains of the antibody molecule are derived from those of a human antibody. In certain embodiments, a limited number of framework region amino acid residues from the parent (rodent) antibody may be substituted into the human antibody framework region sequences.

The term "antigen binding site" refers to the part of the antibody or antibody fragment that comprises the area that specifically binds to an antigen. An antigen binding site may be provided by one or more antibody variable domains. An antigen binding site is typically comprised within the associated V_H and V_L of an antibody or antibody fragment.

An antibody fragment is a portion of an antibody, for example as F(ab')2, Fab, Fv, scFv, heavy chain, light chain, heavy (V_H), variable light (V_L) chain domain and the like. Functional fragments of a full length antibody retain the target specificity of a full antibody. Recombinant functional antibody fragments, such as Fab (Fragment, antibody), scFv (single chain variable chain fragments) and single domain antibodies (dAbs) have therefore been used to develop therapeutics as an alternative to therapeutics based on mAbs.

scFv fragments (~25kDa) consist of the two variable domains, V_H and V_L. Naturally, V_H and V_L domain are non-covalently associated via hydrophobic interaction and tend to dissociate. However, stable fragments can be engineered by linking the domains with a hydrophilic flexible linker to create a single chain Fv (scFv).

The smallest antigen binding fragment is the single variable fragment, namely the single variable heavy (V_H) or single variable light (V_L) chain domain. V_H and V_L domains respectively are capable of binding to an antigen. Binding to a light chain/heavy chain partner respectively or indeed the presence of other parts of the full antibody is not required for target binding. The antigen-binding entity of an antibody, reduced in size to one single domain (corresponding to the V_H or V_L domain), is generally referred to as a “single domain antibody” or “single immunoglobulin variable domain”. A single domain antibody (~12 to 15 kDa) thus consists of either the V_H or V_L domain, but it does not comprise other parts of a full length antibody. Single domain antibodies derived from camelid heavy chain only antibodies that are naturally devoid of light chains as well as single domain antibodies that have a human heavy chain domain have been described (Muyldermans 2001, Holliger 2005). Antigen binding single V_H domains have also been identified from, for example, a library of murine V_H genes amplified from genomic DNA from the spleens of immunized mice and expressed in *E. coli* (Ward et al., 1989, Nature 341: 544-546). Ward et al. named the isolated single V_H domains "dAbs" for "domain antibodies." The term "dAb" or “sdAb” generally refers to a single immunoglobulin variable domain (V_H, V_{HH} or V_L) polypeptide that specifically binds antigen. Such a molecule only has the V_H or V_L binding domain respectively, but does not comprise other parts of a full length antibody. Unless otherwise specified, as used herein, the term refers to a single domain antibody that has a V_H domain. For use in therapy, human single domain antibodies are preferred, primarily because they are not as likely to provoke an immune response when administered to a patient.

The terms “single domain antibody”, “V_H domain antibody”, “single V_H domain antibody”, “V_H single domain antibody”, “single variable domain“, “single variable domain antibody“, “single variable heavy chain domain antibody“ or immunoglobulin single variable domain (ISV)” are thus all well known in the art and describe the single variable fragment of an antibody that binds to a target antigen. These terms are used interchangeably herein. These terms above and specifically “single heavy chain domain antibody”, “single variable heavy chain domain antibody” “single V_H domain antibody”, “ISV”, and “V_H single domain” as used herein describe a part of an antibody, i.e. the single heavy chain variable fragment of an antibody, e.g. the V_H domain, which retains binding specificity to the antigen in the absence of light chain or other antibody fragments. Such a molecule, e.g. a single variable heavy chain domain antibody is capable of binding to an

antigen in the absence of light chain. A single variable heavy chain domain antibody does not comprise other parts of a full length antibody; it only includes the V_H domain. Thus, as used herein, these terms and specifically a single domain antibody, specify a binding moiety that is solely made up of the V_H domain and does not have other parts of an antibody. As explained herein, the CD137 binding entity illustrated below is a V_H single domain antibody and in preferred embodiments, the PSMA binding entity is also a V_H single domain antibody.

As explained below, the embodiments relate to isolated binding molecules which comprise or consist of a single variable heavy chain domain antibody /immunoglobulin single variable heavy chain domain which bind a CD137 antigen and also comprise a moiety that binds to PSMA. Thus, the single variable heavy chain domain antibody (i.e. a V_H domain) is capable of binding to CD137 in the absence of light chain. Human single variable heavy chain domain antibodies ("V_H domain antibody") are particularly preferred. Such binding molecules are also termed Humabody® herein. Humabody® is a registered trademark of Crescendo Biologics Ltd.

The term "isolated" refers to a moiety that is isolated from its natural environment. For example, the term "isolated" refers to a single domain antibody or binding molecule that is substantially free of other single domain antibodies or binding molecule, antibodies or antibody fragments. Moreover, an isolated single domain antibody may be substantially free of other cellular material and/or chemicals.

Each V_H domain antibody comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. Thus, in one embodiment of the invention, the domain is a human variable heavy chain (V_H) domain with the following formula FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4.

Modifications to the C or N-terminal V_H framework sequence may be made to the single domain antibodies of the invention to improve their properties. For example, the V_H domain may comprise C or N-terminal extensions. C-terminal extensions can be added to the C- terminal end of a V_H domain which terminates with the residues VTVSS (SEQ ID No. 788).

In one embodiment, the single domain antibodies of the invention comprise C-terminal extensions of from 1 to 50 residues, for example 1 to 10, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, 1-20, 1-30 or 1-40 additional amino acids. In one embodiment, the single domain antibodies of the invention comprise additional amino acids of the human C_H1 domain thus that the C terminal end extends into the C_H1 domain. For example, C-terminal extensions may comprise neutral, nonpolar amino acids, such as A, L, V, P, M, G, I, F or W or neutral polar amino acids, such as S or T. C-terminal extensions may also be selected from peptide linkers or tags, e.g. SEQ ID Nos. 790-797.

Additional C or N-terminal residues can be peptide linkers that are for example used to conjugate the single domain antibodies of the invention to another moiety, or tags that aid the detection of the molecule. Such tags are well known in the art and include for, example linker His tags, e.g., hexa-His (HHHHHH, SEQ ID No. 789) or myc tags.

As used herein, the term "homology" or “identity” generally refers to the percentage of amino acid residues in a sequence that are identical with the residues of the reference polypeptide with which it is compared, after aligning the sequences and in some embodiments after introducing gaps, if necessary, to achieve the maximum percentage homology, and not considering any conservative substitutions as part of the sequence identity. Thus, the percentage homology between two amino acid sequences is equivalent to the percentage identity between the two sequences. Neither N- or C-terminal extensions, tags or insertions shall be construed as reducing identity or homology. Methods and computer programs for the alignment are well known. The percentage identity between two amino acid sequences can be determined using well known mathematical algorithms.

According to some embodiments of the various aspects of the invention, the variable domain of the single domain antibodies as described herein is a human variable domain (as used herein V_H refers to a human domain), a camelid variable domain (V_{HH}), a humanised V_{HH} domain, a camelized V_H domain, a sequence modified V_H or V_{HH} domain. In one embodiment, the variable domain of the single domain antibodies as described herein is a V_H domain.

As used herein, a human V_H domain includes a fully human or substantially fully human V_H domain. As used herein, the term human V_H domain also includes V_H domains that are isolated from heavy chain only antibodies made by transgenic mice expressing fully human immunoglobulin heavy chain loci, in particular in response to an immunisation with an antigen of interest, for example as described in WO2016/062990 and in the examples below. In one embodiment, a human V_H domain can also include a V_H domain that is derived from or based on a human V_H domain amino acid or produced from a human V_H nucleic acid sequence. Thus, the term human V_H domain includes variable heavy chain regions derived from or encoded by human germline immunoglobulin sequences and for example obtained from heavy chain only antibodies produced in transgenic mice expressing fully human V_H genes. In some embodiments, a substantially human V_H domain or V_H domain that is derived from or based on a human V_H domain may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced in vitro, e.g. by random or site-specific mutagenesis, or introduced by somatic mutation in vivo). The term “human V_H domain” therefore also includes a substantially human V_H domain, i.e. human V_H domain wherein one or more amino acid residue has been modified, for example to remove sequence liabilities. For example, a substantially human V_H domain the V_H domain may include up to 10, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or up to 20 amino acid modifications compared to a germline human sequence.

However, the term "human V_H domain" or "substantially human V_H domain", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. In one embodiment, the term "human V_H domain", as used herein, is also not intended to include camelized V_H domains, that is human V_H domains that have been specifically modified, for example in vitro by conventional mutagenesis methods to select predetermined positions in the V_H domains sequence and introduce one or more point mutation at the predetermined position to change one or more predetermined residue to a specific residue that can be found in a camelid V_{HH} domain.

The term "KD" refers to the "equilibrium dissociation constant" and refers to the value obtained in a titration measurement at equilibrium, or by dividing the dissociation rate constant (Koff) by the association rate constant (Kon). “KA” refers to the affinity constant. The association rate constant, the dissociation rate constant and the equilibrium dissociation constant are used to represent the binding affinity of an antibody to an antigen. Methods for determining association and dissociation rate constants are well known in the art. Using fluorescence-based techniques offers high sensitivity and the ability to examine samples in physiological buffers at equilibrium. Other experimental approaches and instruments such as a BIAcore® assay can be used.

The term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used in this disclosure can be exhibited, for example, by a molecule having a KD for the target of at least about 10-6 M, alternatively at least about 10-7 M, alternatively at least about 10-8 M, alternatively at least about 10-9 M, alternatively at least about 10-10 M, alternatively at least about 10-11 M, alternatively at least about 10-12 M, or greater affinity. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

In some embodiments, there is provided binding molecule that comprises a V_H single domain antibody that is a variant of any of the single V_H domain antibodies described herein having one or more amino acid substitutions, deletions, insertions or other modifications, and which retains a biological function of the single domain antibody. Thus, variant V_H single domain antibody can be sequence engineered. Modifications may include one or more substitution, deletion or insertion of one or more codons encoding the single domain antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence V_H single domain antibody or polypeptide. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 25, for example 1 to 5, 1 to 10, 1 to 15 or 1 to 20 amino acids, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence. A

variant of a V_H single domain antibody described herein has at least 50%, for example at least 70%, 71%, 72%, 73%, 74%,75%, 76%, 77%, 78%, 79%, 8 0%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology to the non-variant molecule, preferably at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology.

In one embodiment, the modification is a conservative sequence modification. As used herein, the term "conservative sequence modifications" is intended to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an sdAb of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the CDR regions of a single domain antibody of the invention can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for retained function (i.e., CD137 binding) using the functional assays described herein.

Thus, these amino acid changes can typically be made without altering the biological activity, function, or other desired property of the polypeptide, such as its affinity or its specificity for antigen. In some instances these changes are made to improve the affinity of the antibody, e.g., single V_H domain antibody, for its target antigen. In general, single amino acid substitutions in nonessential regions of a polypeptide do not substantially alter biological activity. Furthermore, substitutions of amino acids that are similar in structure or function are less likely to disrupt the polypeptides' biological activity. Abbreviations for the amino acid residues that comprise polypeptides and peptides described herein, and conservative substitutions for these amino acid residues are shown in Table 1 below.

Table 1. Amino Acid Residues and Examples of Conservative Amino Acid Substitutions

Original residue **Three letter code, single letter code**	**Conservative substitution**
Alanine, Ala, A	Gly, Ser
Arginine, Arg, R	Lys, His
Asparagine, Asn, N	Gln, His
Aspartic acid Asp, D	Glu, Asn

Cysteine, Cys, C	Ser, Ala
Glutamine, Gln, Q	Asn
Glutamic acid, Glu, E	Asp, Gln
Glycine, Gly, G	Ala
Histidein, His, H	Asn, Gln
Isoleucine, Ile, I	Leu, Val
Leucine, Leu, L	Ile, Val
Lysine, lys, K	Ar, His
Methionine, Met, M	Leu, Ile, Tyr
Phenylalanine, Phe, F	Tyr, Met, Leu
Proline, Pro, P	Ala
Serine, Ser, S	Thr
Threonine, Thr, T	Ser
Tryptophan, Trp, W	Tyr, Phe
Tyrosine, Tyr, Y	Try, Phe
Valine, Val, V	Ile, Leu

In some embodiments, the binding molecule includes a V_H single domain antibody that is a variant of a single domain antibody selected from those shown in Tables 2, 3 and 4 that comprises one or more sequence modification and has improvements in one or more of a property such as binding affinity, specificity, thermostability, expression level, effector function, glycosylation, reduced immunogenicity, or solubility as compared to the unmodified single domain antibody.

A skilled person will know that there are different ways to identify, obtain and optimise the antigen binding molecules as described herein, including in vitro and in vivo expression libraries. This is further described in the examples. Optimisation techniques known in the art, such as display (e.g., ribosome and/or phage display) and / or mutagenesis (e.g., error-prone mutagenesis) can be used. The invention therefore also comprises sequence optimised variants of the single domain antibodies described herein.

In one embodiment, modifications can be made to decrease the immunogenicity of the single domain antibody. For example, one approach is to revert one or more framework residues to the corresponding human germline sequence. More specifically, a single domain antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the single domain antibody is derived. Such residues can be identified by comparing the single domain antibody framework sequences to the germline sequences from which the single domain antibody is derived. In one embodiment, all framework residues are germline sequence.

To return one or more of the amino acid residues in the framework region sequences to their germline configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis or PCR-mediated mutagenesis.

Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T cell epitopes to thereby reduce the potential immunogenicity of the antibody.

In still another embodiment, the glycosylation is modified. For example, an aglycoslated antibody can be made (i.e., the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for the antigen.

In one embodiment, the one or more substitution is in the CDR1, 2 or 3 region. For example, there may be 1, 2, 3, 4 or 5 amino acid substitutions in the CDR1, 2 or 3. In another example, there may be 1 or 2 amino acid deletions. In one embodiment, the one or more substitution is in the framework region. For example, there may be 1 to 10 or more amino acid substitutions in the CDR1, 2 or 3. In another example, there may be 1 to 10 or more amino acid deletions.

The term “epitope” or “antigenic determinant” refers to a site on the surface of an antigen (e.g., PSMA or CD137) to which an immunoglobulin, antibody or antibody fragment, including a V_H single domain antibody specifically binds. Generally, an antigen has several or many different epitopes and reacts with many different antibodies. The term specifically includes linear epitopes and conformational epitopes. Epitopes within protein antigens can be formed both from contiguous amino acids (usually a linear epitope) or non-contiguous amino acids juxtaposed by tertiary folding of the protein (usually a conformational epitope). Epitopes formed from contiguous amino acids are typically, but not always, retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in a unique spatial conformation. Methods for determining what epitopes are bound by a given antibody or antibody fragment (i.e., epitope mapping) are well known in the art and include, for example, immunoblotting and immunoprecipitation assays, wherein overlapping or contiguous peptides from are tested for reactivity with a given antibody or antibody fragment. An antibody binds "essentially the same epitope" as a reference antibody, when the two antibodies recognize identical or sterically overlapping epitopes. The most widely used and rapid methods for determining whether two epitopes bind to identical or sterically overlapping epitopes are competition assays, which can be configured in different formats, using either labelled antigen or labelled antibody.

The inventors have surprisingly identified single variable heavy chain domain antibodies that, when targeted to CD137 in a monospecific format, that is without being linked to another moiety specific to a second antigen, bind specifically to CD137, but do not induce clustering of the CD137 receptor. Binding of the single variable heavy chain domain antibodies described herein in a monovalent or monospecific format does therefore not activate CD137 signalling and does not lead to CD137 signalling. Binding of the single variable heavy chain domain antibodies described herein does not agonise CD137 signalling unless they are provided together with another moiety specific to a second antigen, for example as a bispecific fusion protein wherein a single variable heavy chain domain antibody described herein is linked to a moiety that binds to a tumor specific antigen, for example a single variable heavy chain domain antibody that binds to a tumor specific antigen.

When a single variable heavy chain domain antibody as described herein is provided as part of a binding molecule, for example as fusion protein together with a moiety that binds to PSMA, such as a single variable heavy chain domain antibody that binds to PSMA, binding to CD137 and the target moiety results in clustering of the CD137 receptor and CD137 signalling. Induction of CD137 signalling thus requires dual engagement of both targets, i.e. CD137 and PSMA. This leads to localised CD137 signalling in the tumor microenvironment. Only simultaneous engagement of both targets by the bispecific molecule results in CD137 activation. Target specific activation in the vicinity of the tumor potentially avoids systemic CD137 effects leading to uncontrollable side effects. The binding molecules effectively engage CD137 on the surface of cells through mechanisms other than binding to Fc-receptors thus also avoiding unwanted liver toxicity. Simultaneously, they engage cells that express PSMA.

We describe a binding molecule that binds to both CD137 and PSMA. The terms “binding molecule” and “binding agent” are used interchangeably herein. A binding molecule as used herein refers to a binding molecule that specifically binds at least two targets, i.e. CD137 and PSMA, wherein one subunit/entity/moiety that binds to CD137 is conjugated/linked a second subunit/entity/moiety that binds PSMA. As described herein, in some embodiments, the binding molecule is a fusion protein wherein one polypeptide that binds to CD137 is conjugated/linked to a second polypeptide that binds to PSMA.

In one aspect, the invention relates to an isolated multispecific binding molecule that binds to both CD137 and PSMA and comprises a single variable heavy chain domain antibody that binds to CD137. In some embodiments, the single variable heavy chain domain antibody that binds to CD137 is as described herein.

The properties of the multispecific binding molecules of the invention can be exploited in therapeutic methods and uses as well as in pharmaceutical formulations as described herein.

In one aspect, the invention relates an isolated binding molecule comprising or consisting of
a) a single variable heavy chain domain antibody that binds to CD137 and

b) a moiety that binds to PSMA.

Thus, the entity that binds to CD137 is not a full antibody that comprises light and heavy chains, but a single variable heavy chain domain, i.e. a V_H domain only. In some embodiments, the single variable heavy chain domain antibody that binds to CD137 is selected from one of the single variable heavy chain domain antibodies that bind to CD137 having a SEQ ID No. as described herein as listed in the tables below (tables 2 and 3) wherein the CDRs are defined according to Kabat.

The single variable heavy chain domain antibody that binds to CD137 and the moiety that binds to PSMA are linked, for example by a peptide linker. For example, the single variable heavy chain domain antibody that binds to CD137 can be linked at its N or C terminus to the moiety that binds to PSMA.

The moiety that binds PSMA can be selected from an antibody, antibody mimetic, antibody scaffold, antibody fragment or other polypeptide. An antibody fragment can be selected from a portion of an antibody, for example a F(ab')2, Fab, Fv, scFv, heavy chain, light chain, heavy or variable light chain domain heavy or variable light chain domain, or part thereof, such as a CDR.

In one embodiment, the entity that binds PSMA is a single variable heavy chain domain antibody that binds to PSMA, such as a human V_H domain antibody. In some embodiments, the single variable heavy chain domain antibody that binds to PSMA is selected from one of the single variable heavy chain domain antibodies that bind to PSMA having a SEQ ID No. as described herein and in the tables below.

In one embodiment, there is provided a binding molecule comprising or consisting of
a) a single variable heavy chain domain antibody that binds to CD137 and
b) a single variable heavy chain domain antibody that binds to PSMA.

Thus, the binding molecule has two single variable heavy chain domains, one that binds to CD137 and one that binds to PSMA. No other domains/chains of a full antibody are present. In some embodiments, the single variable heavy chain domain antibody that binds CD137 and the single variable heavy chain domain antibody that binds PSMA is a human V_H domain antibody.

In one aspect, we provide a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137, for example having a SEQ ID No. as described herein (e.g. as set out in table 2 or 3), linked to another moiety that binds to PSMA, for example having a SEQ ID No. as described herein wherein the binding molecule exhibits one or more of the following properties:

(a) binds to human CD137 with a KD as measured in the examples;
(b) inhibits the interaction between human CD137 ligand and human CD137 expressed on the surface of cells. This can be measured as shown in example 4;

(c) does not bind to mouse CD137;

(d) binds to cells expressing CD137 and simultaneously binds to cells expressing PSMA. This can be measured as shown in example 5;

(e) increases reporter gene activity. This can be measured as shown in example 5;

(f) inhibits tumor cell growth in vivo;

(g) promotes CD8+ T cell expansion;

(h) induces activation of cytotoxic T lymphocytes (CTL);

(i) stimulates IL-2 production from CD8+ cells. This can be measured as shown in example 5;

(j) induces tumor specific T cell activation;

(k) activates CD137 signalling in T cells as measured in the examples;

(l) inhibits activation induced cell death;

(m) enhances T cell survival;

(n) limits systemic T cell activation;

(o) enhances the cytotoxic effector function of T cells;

(p) promotes local activation of anti-tumor cells in tumor antigen positive tumors;

(q) enhances of antibody-dependent cellular cytotoxicity;

(r) binds simultaneously to CD137 and PSMA;

(s) binds to cyno CD137;

(t) reverses the regulator function of T-reg cells;

(u) activates NK cells and/or

(v) reduces tumour volume compared to control groups in mice as shown in example 6.

In one embodiment, the binding molecule exhibits more than 1 of the properties above, for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or all of the properties selected from the above list, including any combination of properties. In one embodiment, the binding agent inhibits the interaction between human CD137 ligand and human CD137 expressed on the surface of cells.

In one embodiment, the binding molecule is a fusion protein comprising at least two subunits, i.e. a CD137-binding subunit fused to a PSMA-binding subunit wherein the CD137-binding subunit is a single variable heavy chain domain antibody that binds to CD137. In one embodiment, the binding molecule is a fusion protein comprising a single variable heavy chain domain antibody that binds to CD137 linked to a single variable heavy chain domain antibody that binds to PSMA. The linker is, for example, a peptide linker with GS residues such as (Gly4Ser)n, where n=from 1 to 10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 as further described below.

The binding agent is multispecific, for example bispecific or trispecific. A bispecific molecule binds to 2 different targets. A trispecific molecule binds to 2 different targets. A monovalent molecule has one binding entity. A bivalent molecule has two binding entities which bind to the same or different target.

In one embodiment, the binding molecule comprises a first V_H single domain antibody that binds to CD137 (V_H (A)) and a second V_H single domain antibody (V_H (B)) that binds to PSMA and thus has the following formula: V_H (A)- L-V_H (B). V_H (A) is conjugated to V_H (B), that is linked, for example with a peptide linker. L denotes a linker.

Each V_H comprises CDR and FR regions. Thus, the binding molecule may have the following formula: FR1(A)-CDR1(A)-FR2(A)-CDR2(A)-FR3(A)-CDR3(A)-FR4(A)-L-FR1(B)-CDR1(B)-FR2(B)-CDR2(B)-FR3(B)-CDR3(B)-FR4(B). The order of the single V_H domains A and B is not particularly limited, so that, within a polypeptide of the invention, single variable domain A may be located N-terminally and single variable domain B may be located C-terminally, or vice versa.

The term "peptide linker" as used in the various embodiments described herein refers to a peptide comprising one or more amino acids. A peptide linker comprises 1 to 44 amino acids, more particularly 2 to 20 amino acids. Peptide linkers are known in the art or are described herein. Suitable, non-immunogenic linker peptides are, for example, linkers that include G and/or S residues, (G4S)n, (SG4)n or G4(SG4)n peptide linkers, wherein "n" is generally a number between 1 and 10, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. In one embodiment, the peptide is for example selected from the group consisting of GGGGS (SEQ ID NO: 790), GGGGSGGGGS (SEQ ID NO:791), SGGGGSGGGG (SEQ ID NO:792), GGGGSGGGGSGGGG (SEQ ID NO:793), GSGSGSGS (SEQ ID NO:794), GGSGSGSG (SEQ ID NO:795), GGSGSG (SEQ ID NO:796), GGSG (SEQ ID NO:797).

The fusion protein described above is capable of dual, e.g. simultaneous, engagement/binding to CD137 on the surface of effector cells and to PSMA displayed on the cell surface of tumor cells. The dual, e.g. simultaneous binding leads to clustering of the CD137 receptor resulting in CD137 signalling. This leads to T cell activation. In some embodiments, dual, e.g. simultaneous binding leads to tumor antigen specific effector cell activation and results in tumor cell killing.

In some embodiments, the fusion protein is capable of binding CD137 with an EC50 value that is similar or at least equivalent to the EC50 value by which the monovalent single heavy chain domain antibody binds to CD137. In some embodiments, the fusion protein binds CD137 with an EC50 value as shown in the examples.

In some embodiments, the fusion protein described herein may be capable of co-stimulating T cell responses in a functional T cell activation essentially described as in the examples. In some embodiments, the fusion protein described herein may be able to induce IL-2 and/or IFN gamma secretion and T cell proliferation in a functional T cell activation. The fusion polypeptide as described herein is, in some embodiments, also capable of local induction of IL-2 and/or IFN gamma secretion in the vicinity of the targeted tumor that is cells that are positive for the tumor antigen to which the fusion protein binds.

In some embodiments, the fusion protein may be capable of producing a synergistic effect through dual targeting of the CD137 expressing cell and the tumor antigen expressing cell.

Dual, e.g. simultaneous targeting of CD137 and PSMA in the microenvironment of the tumor may enhance anti-tumor activity and reduce tumor growth. Moreover, by eliciting CD137 signalling locally, side effects may be reduced. CD137 signalling results in the recruitment of TRAF family members and activation of kinases. T cell mediated signalling protects CD8+ cells from activation induced death. Also provided is the use of the fusion protein as described herein for co-stimulating T cells.

In one embodiment, a binding molecule as described herein binds to CD137 with a KD of at least about 10-6 M, alternatively at least about 10-7 M, alternatively at least about 10-8 M, alternatively at least about 10-9 M, alternatively at least about 10-10 M, alternatively at least about 10-11 M, alternatively at least about 10-12 M, or greater affinityas measured according to the methods shown in the examples. In one embodiment, a binding molecule as described herein binds to PSMA with a KD of at least about 10-6 M, alternatively at least about 10-7 M, alternatively at least about 10-8 M, alternatively at least about 10-9 M, alternatively at least about 10-10 M, alternatively at least about 10-11 M, alternatively at least about 10-12 M, or greater affinity as measured according to the methods shown in the examples. Binding can be measured as in the examples. In some embodiments, the binding molecules of the invention have IC50 and/or EC50 values as further described herein and as shown in the examples. Binding molecules described herein have shown excellent stability.

In another aspect, a nucleic acid molecule encoding a fusion protein described herein is provided.
For example, the nucleic acid molecule comprises a nucleic acid encoding a single variable heavy chain domain antibody that binds to CD137 as specified herein and a nucleic acid encoding a single variable heavy chain domain antibody that binds to PSMA as specified herein.
A nucleic acid may comprise DNA or RNA and may be wholly or partially synthetic or recombinantly produced. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

Furthermore, the invention relates to a nucleic acid construct comprising at least one nucleic acid as defined above. The construct may be in the form of a plasmid, vector, transcription or expression cassette.

The invention also relates to an isolated recombinant host cell comprising one or more nucleic acid construct as described above. The host cell may be a bacterial, viral, plant, mammalian or other suitable host cell. In one embodiment, the cell is an E. coli cell. In another embodiment, the cell is a yeast cell. In another embodiment, the cell is a Chinese Hamster Ovary (CHO) cell.

In one embodiment, a method of making the fusion protein as described herein is provided, wherein the method comprises culturing the host cell under conditions suitable for expression of the polynucleotide encoding the fusion protein, and isolating the single domain antibody.

Exemplary immunoglobulins included in the binding molecule

As described above, the binding molecules comprise a single variable heavy chain domain antibody that binds CD137 (CD137-binding subunit) and a moiety that binds PSMA (PSMA binding subunit). For example, the binding molecule can be a fusion protein wherein a single variable heavy chain domain antibody that binds CD137 is linked to another polypeptide that binds to PSMA. The below provides examples of the CD137-binding subunit and the PSMA binding subunit.

Exemplary immunoglobulins included in the binding molecule and which bind CD137

Examples of single variable heavy chain domain antibodies that bind to CD137 and that may form one of the subunits of the binding molecule that bind to both, CD137 and PSMA, are described and can be used in the various embodiments of the invention.

CD137 is an important regulator of immune responses and therefore an important target in cancer therapy. The T cell costimulatory receptor CD137 is induced on activated T cells and plays a variety of crucial roles: preventing activation-induced cell death (AICD), promoting cell cycle progression, enhancing cytotoxicity and the production of type 1 cytokines such as IL-2, IFN-γ, and TNF-α, and increasing the memory CD8+ T cells. In vivo CD137 triggering with agonistic antibodies enhances CD8+ T cell responses against tumors. CD137 mediated anti-cancer effects are based on its ability to induce activation of cytotoxic T lymphocytes (CTL), and among others, high amounts of IFN-γ. CD137/CD137L interactions are also considered positive regulators of CD8+ T cell responses against viruses such as influenza virus, lymphocytic choriomeningitis virus (LCMV), and herpes simplex virus (HSV). CD137 is involved in sustaining the T cell responses after initial T-cell activation.

Importantly, CD137 signalling requires clustering of the CD137 receptor. Such clustering is mediated by the interaction of the trimeric CD137 ligand with the CD137 receptor resulting in recruitment of signalling molecules such as the TRAF family of proteins. This in turn leads to kinase modulation and activation of the Nf-KB signalling pathway. The NF-κB family of transcription factors has an essential role in inflammation and innate immunity. Furthermore, NF-κB is increasingly recognized as a crucial player in many steps of cancer initiation and progression.

Single domain antibodies described herein bind specifically to wild type human CD137 (UniProt Accession No. Q07011, GenBank Accession No. NM_001561). The amino acid sequence (SEQ ID No. 786) and nucleotide sequences for wild type human CD137 are shown below (SEQ ID No. 787).

MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTFCDNNRNQICSPCPPNSFSSAGGQRTCDICRQCKG
VFRTRKECSSTSNAECDCTPGFHCLGAGCSMCEQDCKQGQELTKKGCKDCCFGTFNDQKRGICRPWTN
CSLDGKSVLVNGTKERDVVCGPSPADLSPGASSVTPPAPAREPGHSPQIISFFLALTSTALLFLLFFLTLRFS
VVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ ID No. 786)
ATGGGAAACAGCTGTTACAACATAGTAGCCACTCTGTTGCTGGTCCTCAACTTTGAGAGGACAAGATC
ATTGCAGGATCCTTGTAGTAACTGCCCAGCTGGTACATTCTGTGATAATAACAGGAATCAGATTTGCAG
TCCCTGTCCTCCAAATAGTTTCTCCAGCGCAGGTGGACAAAGGACCTGTGACATATGCAGGCAGTGTA
AAGGTGTTTTCAGGACCAGGAAGGAGTGTTCCTCCACCAGCAATGCAGAGTGTGACTGCACTCCAGG
GTTTCACTGCCTGGGGGCAGGATGCAGCATGTGTGAACAGGATTGTAAACAAGGTCAAGAACTGACA
AAAAAAGGTTGTAAAGACTGTTGCTTTGGGACATTTAACGATCAGAAACGTGGCATCTGTCGACCCTG
GACAAACTGTTCTTTGGATGGAAAGTCTGTGCTTGTGAATGGGACGAAGGAGAGGGACGTGGTCTGT
GGACCATCTCCAGCCGACCTCTCTCCGGGAGCATCCTCTGTGACCCCGCCTGCCCCTGCGAGAGAG
CCAGGACACTCTCCGCAGATCATCTCCTTCTTTCTTGCGCTGACGTCGACTGCGTTGCTCTTCCTGCT
GTTCTTCCTCACGCTCCGTTTCTCTGTTGTTAAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACA
CCATTTATGAGACCAGTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGA
AGAAGGAGGATGTGAACTGTGA (SEQ ID No. 787)

Unless otherwise specified, the term CD137 as used herein refers to human CD137. CD137 is also known as “4-1BB”, “TNF receptor superfamily member 9”, “TNFRS9”, “induced by lymphocyte activation” and “ILA” these terms are used interchangeably, and include variants, isoforms of human CD137.

The terms "CD137 binding molecule/protein/polypeptide/agent/moiety”, "CD137 antigen binding molecule molecule/protein/polypeptide/agent/moiety”, “anti-CD137 single domain antibody”, “anti-CD137 single immunoglobulin variable domain”, “anti-CD137 heavy chain only antibody” or “anti-CD137 antibody” all refer to a molecule capable of specifically binding to the human CD137 antigen. The binding reaction may be shown by standard methods, for example with reference to a negative control test using an antibody of unrelated specificity.

A multispecific binding agent described herein, "which binds" or is “capable of binding” an antigen of interest, e.g. human CD137, is one that binds the antigen with sufficient affinity such that the antibody is useful as a therapeutic agent in targeting a cell or tissue expressing the antigen CD137. Binding is to the extracellular domain of CD137.

Binding molecules of the invention bind specifically to human CD137. In other words, binding to the CD137 antigen is measurably different from a non-specific interaction. They do not cross react with mouse CD137. In one embodiment, the sdAb binds to human CD137 and also binds to monkey (e.g., cynomolgous) CD137.

In one aspect, the monovalent single domain antibody used in the multispecific molecule exhibits one or more of the following properties as a monovalent entity (i.e. when it is not provided in a multispecific format together with an entity that binds to PSMA):

(a) binds to human CD137 with a KD as measured in the examples;

(b) binds to cells expressing CD137, but does not bind to cells that do not express CD137. This can be measured in a FMAT assay;

(c) shows minimal cell internalisation. This can be measured as shown in the examples;

(d) inhibits the interaction between CD137 ligand and CD137 expressed on the surface of cells. This can be measured in a FMAT assay.

(e) does not activate CD137 signalling in T cells. This can be measured as shown in the examples;

(f) does not stimulate IL-2 production from CD8+ cells. This can be measured as shown in example 5;

(g) does not bind to mouse CD137;

(h) provides good stability as shown in the examples and/or

(i) does not increase reporter gene activity and thus does not elicit CD137 signalling. This can be measured as shown in example 5.

Exemplary sequence features

In one aspect, the single variable heavy chain domain antibody comprises a CDR1, CDR2 or CDR3 as shown for one of the single domain antibodies as shown in Table 2 or a set of CDRs (i.e. CDR1, CDR2, CDR3) wherein said set is as shown for one of the single domain antibodies as shown in Table 2. In one aspect, it comprises a CDR1, CDR2, CDR3 at least 40% or 75% homology thereto. For example, the single variable heavy chain domain antibody comprises a CDR1 comprising SEQ ID NO. 1 or a sequence with at least 40%, 75% or 80% homology thereto, a CDR2 comprising SEQ ID NO. 2 or a sequence with at least 40%, 75% or 80% homology thereto and a CDR3 comprising SEQ ID NO. 3 or a sequence with at least 40%, 75% or 80% homology, or a CDR1 comprising SEQ ID NO. 5 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 6 or a sequence with at least 40%, 75% or 80% homology thereto and a CDR3 comprising SEQ ID NO. 7 or a sequence with at least 40% , 75% or 80% homology thereto and so forth.

Sequence homology as above and as used generally herein can be at least 40%, 50%, 60%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology.

In one embodiment, the single variable heavy chain domain antibody comprises human framework regions.

In another aspect, the single variable heavy chain domain antibody according to the invention comprises or consists of a full length sequence as shown in Table 2 or a sequence with at least 50% homology thereto. For example, the single variable heavy chain domain antibody has a sequence selected from the

sequences listed in Table 2, i.e. SEQ ID NO. 4, 8, 12, 16, 20 and so forth or a sequence with at least 50% homology thereto. Sequence homology can be at least 50%, 60%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology. In one embodiment, the single variable heavy chain domain antibody comprises a CDR1, 2, and 3 as shown for V_H single domain antibodies 1.1 to 1.89 or 1.90 to 1.106 or comprises or consists of a full length sequence as shown for V_H single domain antibodies 1.1 to 1.89 or 1.90 to 1.106 (i.e. SEQ ID NOs. 364, 368, 372, 376, 380, 384, 388, 392, 396, 400, 404, 408, 412, 416, 420 or 424). In one embodiment, the single variable heavy chain domain antibody comprises a CDR1, 2, and 3 as shown for V_H single domain antibodies V_H 1.107 to 1.114 as shown in table 2, e.g. SEQ ID No. 873, 874, 875) or a sequence with at least 75%, 80% or 90% homology thereto. In one embodiment, the single variable heavy chain domain antibody is selected from V_H 1.107 to 1.114 as shown in table 2, i.e. V_H 1.107, 1.108, 1.109, 1.110, 1.111, 1.112, 1.113 or 1.114, that is SEQ ID NOs. 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 75%, 80% or 90% homology thereto. In one embodiment, the single variable heavy chain domain antibody is V_H 1.113 or a sequence with at least 75%, 80% or 90% homology thereto.

Table 2 Full length sequences and CDR sequences of V_H single domain antibodies (Family 1)

Name	CDR1	CDR2	CDR3	Full Length
1.1	SEQ ID NO: 1 SHWMT	SEQ ID NO: 2 HIKEDGSEKY YEDSVEG	SEQ ID NO: 3 GGDGYSDSHF GVDV	SEQ ID NO: 4 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAV YYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.2	SEQ ID NO: 5 SYWMT	SEQ ID NO: 6 HIKEDGSEKY YVDSVEG	SEQ ID NO: 7 GGDGYSDSHY GVDV	SEQ ID NO: 8 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWFRQAPGKGLE WVAHIKEDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAEDTAV YYCARGGDGYSDSHYGVDVWGQGTTVTVSS
1.3	SEQ ID NO: 9 SYWMT	SEQ ID NO: 10 NINQDGSEK YYVDSVEG	SEQ ID NO: 11 GGLGYGDSHY GMDV	SEQ ID NO: 12 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWFRQAPGRGLE WVANINQDGSEKYYVDSVEGRFTVSRDNAKNSLYLQMNSLRAEDTA VYYCARGGLGYGDSHYGMDVWGQGTTVTVSS
1.4	SEQ ID NO: 13 NYWMT	SEQ ID NO: 14 NINQDGSEK YYVDSVEG	SEQ ID NO: 15 GGLGYGDSHY GMDV	SEQ ID NO: 16 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMTWFRQAPGGGLE WVANINQDGSEKYYVDSVEGRFTVSRDNAKNSLYLQMNSLRAEDTA VYYCARGGLGYGDSHYGMDVWGQGTTVTVSS
1.5	SEQ ID NO: 17 NYWMI	SEQ ID NO: 18 NINQDGSEK YYVDSVEG	SEQ ID NO: 19 GGDGYSGSHH GTDV	SEQ ID NO: 20 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWFRQAPGKGLE WVANINQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGDGYSGSHHGTDVWGQGTTVTVSS
1.6	SEQ ID NO: 21 SYWMS	SEQ ID NO: 22 NIKQDGSEKY YVDSVKG	SEQ ID NO: 23 GGEGYSTSHYG MDV	SEQ ID NO: 24 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYSTSHYGMDVWGQGTTVTVSS
1.7	SEQ ID NO: 25 SYWML	SEQ ID NO: 26 NINQDGSEK YYVDSVKG	SEQ ID NO: 27 GGDGYSDSHF GTDV	SEQ ID NO: 28 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGKGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNTLRAEDTAI YYCARGGDGYSDSHFGTDVWGQGTTVTVSS
1.8	SEQ ID NO: 29	SEQ ID NO: 30	SEQ ID NO: 31 GGDGYSDSHY	SEQ ID NO: 32 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMFWFRQAPGEGLE

	SYWMF	NINQDGSEK YYVDSVEG	GTDV	WVANINQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTAIY YCARGGDGYSDSHYGTDVWGQGTTVTVSS
1.9	SEQ ID NO: 33 NYWMT	SEQ ID NO: 34 NINQDGSEK YYVDSVEG	SEQ ID NO: 35 GGLGYGDSHY GMDV	SEQ ID NO: 36 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMTWFRQAPGGGLE WVANINQDGSEKYYVDSVEGRFTVSRDNAKNSLDLQMNSLRAEDTA VYYCARGGLGYGDSHYGMDVWGQGTTVTVSS
1.10	SEQ ID NO: 37 DYWMN	SEQ ID NO: 38 NIKEDGSEKY YVDSVEG	SEQ ID NO: 39 GGAGYSMSHY GMDV	SEQ ID NO: 40 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYWMNWARQAPGKGLE WVANIKEDGSEKYYVDSVEGRFTISRDNAKNSTYLQMNSLRVEDTAV YYCARGGAGYSMSHYGMDVWGQGTTVTVSS
1.11	SEQ ID NO: 41 DYWMN	SEQ ID NO: 42 NIKEDGSEKY YVDSVEG	SEQ ID NO: 43 GGAGYSMSHY GMDV	SEQ ID NO: 44 EVQLVESGGGLVQPGGSLRLSCEASGFTFSDYWMNWARQAPGKGLE WVANIKEDGSEKYYVDSVEGRFTISRDNAKNSTYLQMNSLRAEDTAV YYCARGGAGYSMSHYGMDVWGQGTTVTVSS
1.12	SEQ ID NO: 45 SYWML	SEQ ID NO: 46 NINQDGSEK YYVDSVKG	SEQ ID NO: 47 GGDGYSNSHF GTDV	SEQ ID NO: 48 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGKGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNTLRAEDTAI YYCARGGDGYSNSHFGTDVWGQGTTVTVSS
1.13	SEQ ID NO: 49 SYWMF	SEQ ID NO: 50 NINQDGSEK YYVDSVEG	SEQ ID NO: 51 GGDGYSDSHY GTDV	SEQ ID NO: 52 EVQLVESGGGLVKPGGSLRLSCGASGFTFSSYWMFWFRQAPGEGLE WVANINQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTAIY YCARGGDGYSDSHYGTDVWGQGTTVTVSS
1.14	SEQ ID NO: 53 NYWMN	SEQ ID NO: 54 NIKEDGSENY YVDSVKG	SEQ ID NO: 55 GGEGYSTSHYG MDV	SEQ ID NO: 56 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLE WVANIKEDGSENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYSTSHYGMDVWGQGTTVTVSS
1.15	SEQ ID NO: 57 TYWML	SEQ ID NO: 58 NINQDGSEK YYVDSVKG	SEQ ID NO: 59 GGDGYSDSHF GTDV	SEQ ID NO: 60 EVQLVESGGGLVQPGGSLRLSCGASGFTFSTYWMLWFRQAPGKGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLSLQMNSLRAEDTAT YYCARGGDGYSDSHFGTDVWGQGTTVTVSS
1.16	SEQ ID NO: 61 NYWMM	SEQ ID NO: 62 NINQDGSEK YFVDSVEG	SEQ ID NO: 63 GGDGYSSSHY GTDV	SEQ ID NO: 64 EVQLVESGGGLVQPGGSLRLSCVASGFTFSNYWMMWFRQAPGKGL EWVANINQDGSEKYFVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGDGYSSSHYGTDVWGQGTTVTVSS
1.17	SEQ ID NO: 65 SYWMN	SEQ ID NO: 66 NIKEDGSEKY YVDSVKG	SEQ ID NO: 67 GGDSYGYRDY GMDV	SEQ ID NO: 68 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLE WVANIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.18	SEQ ID NO: 69 THWMN	SEQ ID NO: 70 NINQDGSEK YYVDSVEG	SEQ ID NO: 71 GGVGYGDSHF GMDV	SEQ ID NO: 72 EVQLVESGGGLVQPGGSLRLSCAASGFTFSTHWMNWARQAPGKELE WVANINQDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAEDTAV YYCARGGVGYGDSHFGMDVWGLGTTVTVSS
1.19	SEQ ID NO: 73 SYWMI	SEQ ID NO: 74 NINQDGSEK YYVDSVKG	SEQ ID NO: 75 GGDDYSNSHY GMDV	SEQ ID NO: 76 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMIWVRQAPGKGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGDDYSNSHYGMDVSGQGTTVTVSS
1.20	SEQ ID NO: 77 SYWMN	SEQ ID NO: 78 NINQDGSEK YYVDSVQG	SEQ ID NO: 79 GGFGYGDSHY GMDV	SEQ ID NO: 80 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLE WVANINQDGSEKYYVDSVQGRFTISRDNANNSLYLQMNSLRAEDTA VYYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.21	SEQ ID NO: 81 SYWMF	SEQ ID NO: 82 NVNQDGSEK YYVDSVEG	SEQ ID NO: 83 GGEGYSDSHY GTDV	SEQ ID NO: 84 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMFWFRQAPGKELE WVANVNQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTAI YYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.22	SEQ ID NO:	SEQ ID NO:	SEQ ID NO: 87	SEQ ID NO: 88

	85 NYWMN	86 NIKEDGSEKY YVDSVEG	GGEGYGDSHY GMDV	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGL EWVANIKEDGSEKYYVDSVEGRFTISRDNARNSLYLQMNSLRAEDTAV YYCARGGEGYGDSHYGMDVSGQGTTVTVSS
1.23	SEQ ID NO: 89 SYWMN	SEQ ID NO: 90 NIKQDGSEKY YVDSVKG	SEQ ID NO: 91 GGEGYGDDHY GMDV	SEQ ID NO: 92 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLTAEDTAV YYCARGGEGYGDDHYGMDVWGQGTTVTVSS
1.24	SEQ ID NO: 93 SYWMS	SEQ ID NO: 94 NIKQDGSEKY YVDSVKG	SEQ ID NO: 95 GGEGYGDYHY GLDV	SEQ ID NO: 96 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYGDYHYGLDVSGQGTTVTVSS
1.25	SEQ ID NO: 97 SYWMN	SEQ ID NO: 98 NIKQDGSEKY YVDSVKG	SEQ ID NO: 99 GGDSYGYRDY GMDV	SEQ ID NO: 100 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.26	SEQ ID NO: 101 THWMN	SEQ ID NO: 102 NINQDGSEK YYVDSVEG	SEQ ID NO: 103 GGVGYGDSHF GMDV	SEQ ID NO: 104 EVQLVESGGGLVQPGGSLRLSCVASGFTFSTHWMNWARQAPGKELE WVANINQDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAEDTAV YYCARGGVGYGDSHFGMDVWGLGTTVTVSS
1.27	SEQ ID NO: 105 SYWML	SEQ ID NO: 106 NINQDGSEK YYVDSVEG	SEQ ID NO: 107 GGEGYSDSHH GTDV	SEQ ID NO: 108 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGEGLE WVANINQDGSEKYYVDSVEGRLTISRDNAKNALYLQMNSLRAEDTAI YYCARGGEGYSDSHHGTDVWGQGTTVTVSS
1.28	SEQ ID NO: 109 NYWMN	SEQ ID NO: 110 NIKQDGSEKY YVDSVKG	SEQ ID NO: 111 GGDNYAYRDF GMDV	SEQ ID NO: 112 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGDNYAYRDFGMDVWGQGTTVTVSS
1.29	SEQ ID NO: 113 NYWMF	SEQ ID NO: 114 NVNQDGSEK YYVDSVEG	SEQ ID NO: 115 GGEGYSDSHY GTDV	SEQ ID NO: 116 EVQLVESGGGLVQPGGSLRLSCGASGFTFSNYWMFWFRQAPGKELE WVANVNQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTAI YYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.30	SEQ ID NO: 117 SYWMN	SEQ ID NO: 118 NINQDGSEK YYVDSVKG	SEQ ID NO: 119 GGEEYGSSHYG MDV	SEQ ID NO: 120 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEEYGSSHYGMDVWGLGTTVTVSS
1.31	SEQ ID NO: 121 SYWMN	SEQ ID NO: 122 NINQDGSEK YYVDSVKG	SEQ ID NO: 123 GGDSYGYRDY GMDV	SEQ ID NO: 124 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.32	SEQ ID NO: 125 SYWMN	SEQ ID NO: 126 NINQNGSEK YYVDSVEG	SEQ ID NO: 127 GGFGYGDSHY GMDV	SEQ ID NO: 128 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQTPGKGLE WVANINQNGSEKYYVDSVEGRFNISRDNAKNSLYLQMSSLRAEDTAV YYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.33	SEQ ID NO: 129 NYWMT	SEQ ID NO: 130 NINQDESEEY YVDSVKG	SEQ ID NO: 131 GGDGYSDSHY GTDV	SEQ ID NO: 132 EVQLVESGGGLVQAGGSLRLSCVASGFTFSNYWMTWFRQAPGKGLE WVANINQDESEEYYVDSVKGRFTISRDNAKNSLFLQMNSLRAEDTAIY YCARGGDGYSDSHYGTDVWGQGTTVTVSS
1.34	SEQ ID NO: 133 NYWMN	SEQ ID NO: 134 NIKEDGSENY YVDSVKG	SEQ ID NO: 135 GGEGYSTSHYG MDV	SEQ ID NO: 136 QVQLQESGGGLVQPGGSLRLSCTASGFTFSNYWMNWVRQAPGKGL EWVANIKEDGSENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGEGYSTSHYGMDVWGQGTTVTVSS
1.35	SEQ ID NO: 137 NYWMN	SEQ ID NO: 138 NIKQDGSEKY YVDSVEG	SEQ ID NO: 139 GGEGYGESHY GMDV	SEQ ID NO: 140 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGL EWVANIKQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMDSLRAEDTA VYYCARGGEGYGESHYGMDVSGQGTTVTVSS

1.36	SEQ ID NO: 141 TYWMN	SEQ ID NO: 142 NIKQDGSEKY YVDSVKG	SEQ ID NO: 143 GGDSYGYRDY GMDV	SEQ ID NO: 144 EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYWMNWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.37	SEQ ID NO: 145 YYWMI	SEQ ID NO: 146 NINQDGSEK YYVDSVKG	SEQ ID NO: 147 GGDGYSNSHF GMDV	SEQ ID NO: 148 EVQLVESGGGLVQPGGSLRLSCAASGFTFSYYWMIWFRQAPGEELE WVANINQDGSEKYYVDSVKGRFIISRDNATNSLFLQMNSLRAEDTAVY YCARGGDGYSNSHFGMDVWGQGTTVTVSS
1.38	SEQ ID NO: 149 NYWMI	SEQ ID NO: 150 NINQDGSEK YYVDSVKG	SEQ ID NO: 151 GGEGYSDSHY GTDV	SEQ ID NO: 152 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAIY YCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.39	SEQ ID NO: 153 NYWMN	SEQ ID NO: 154 NINQDESEKY YVDSVKG	SEQ ID NO: 155 GGFGYGDSHF GMDV	SEQ ID NO: 156 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKELE WVANINQDESEKYYVDSVKGRFTVSRDNAKNSLFLQMNSLRADDTA VYYCARGGFGYGDSHFGMDVWGQGTTVTVSS
1.40	SEQ ID NO: 157 NYWMF	SEQ ID NO: 158 NVNQDGSEK YYVDSVEG	SEQ ID NO: 159 GGEGYSDSHY GTDV	SEQ ID NO: 160 EVQLVESGGGLVQPGGSLRLSCGASGFTFSNYWMFWFRQAPGKELE WVANVNQDGSEKYYVDSVEGRFTISRDDAKNSLYLQMNSLRAEDTAI YYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.41	SEQ ID NO: 161 NYWMF	SEQ ID NO: 162 NVNQNGSEK YYVDSVEG	SEQ ID NO: 163 GGEGYSDSHY GTDV	SEQ ID NO: 164 EVQLVESGGGLVQPGGSLRLSCGASGFTFSNYWMFWFRQAPGKELE WVANVNQNGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDTAI YYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.42	SEQ ID NO: 165 NYWMN	SEQ ID NO: 166 NIKQDGSEKY YVDSVKG	SEQ ID NO: 167 GGEGYGDSHY GMDV	SEQ ID NO: 168 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGL EWVANIKQDGSEKYYVDSVKGRFTISRDNAKDSLYLQMNSLRAEDTAI YYCARGGEGYGDSHYGMDVSGQGTTVTVSS
1.43	SEQ ID NO: 169 NYWMI	SEQ ID NO: 170 NINQDGSEK YYVDSVKG	SEQ ID NO: 171 GGDGYSNSHY GMDV	SEQ ID NO: 172 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTAV YYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.44	SEQ ID NO: 173 DYWMI	SEQ ID NO: 174 NINQDGSEK YYVDSVKG	SEQ ID NO: 175 GGDGYSNSHY GMDV	SEQ ID NO: 176 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTAV YYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.45	SEQ ID NO: 177 KYWMI	SEQ ID NO: 178 NINQDGSEK YYVDSVEG	SEQ ID NO: 179 GGDDYSNSHY GMDV	SEQ ID NO: 180 EVQLVESGGGLVQPGGSLRLSCAASGFTFSKYWMIWVRQAPEKGLE WVANINQDGSEKYYVDSVEGRFTISRDNVNNSLYLQMNSLRAEDTAV YYCARGGDDYSNSHYGMDVSGQGTTVTVSS
1.46	SEQ ID NO: 181 NYWMS	SEQ ID NO: 182 NINQDGSEK YYVDSVKG	SEQ ID NO: 183 GGEEYSSSHYG MDV	SEQ ID NO: 184 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMSWVRQAPGRGLE WVANINQDGSEKYYVDSVKGRFTISRDNAKSSLYLQMNSLRAEDTAV YYCARGGEEYSSSHYGMDVWGQGTTVTVSS
1.47	SEQ ID NO: 185 NYWMN	SEQ ID NO: 186 NIKQDGSEN YYVDSVKG	SEQ ID NO: 187 GGEGYSTSHYG MDV	SEQ ID NO: 188 EVQLVESGGGLVQPGGSLRLSCIASGFSFSNYWMNWVRQAPGKGLE WVANIKQDGSENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYSTSHYGMDVWGQGTAVTVSS
1.48	SEQ ID NO: 189 SYWMS	SEQ ID NO: 190 NIKQDGSEKY YVDSVKG	SEQ ID NO: 191 GGEGYGVDHY GLDV	SEQ ID NO: 192 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAVY FCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.49	SEQ ID NO: 193 SYWML	SEQ ID NO: 194 NVNQDGSEN	SEQ ID NO: 195 GGEDYGNSHF	SEQ ID NO: 196 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGKELE WVANVNQDGSENYYVDSVEGRFTISRDNAKNSLYLQMHSLRAEDTA

		YYVDSVEG	GMDV	VYYCARGGEDYGNSHFGMDVWGQGTMVTVSS
1.50	SEQ ID NO: 197 NYWMI	SEQ ID NO: 198 NINQDGSEK YYVDSVKG	SEQ ID NO: 199 GGDGYSNSHY GMDV	SEQ ID NO: 200 EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTAV YYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.51	SEQ ID NO: 201 NYWMI	SEQ ID NO: 202 NINQDGSEK YYVDSVKG	SEQ ID NO: 203 GGDGYSNSHY GMDV	SEQ ID NO: 204 EVQLVESGGGLVKPGGSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTAV YYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.52	SEQ ID NO: 205 KYWMI	SEQ ID NO: 206 NINQDGSEK YYVDSVEG	SEQ ID NO: 207 GGDDYSISHFG MDV	SEQ ID NO: 208 EVQLVESGGGLVQIGGSLRLSCAASGFTFSKYWMIWVRQAPEKGLEW VANINQDGSEKYYVDSVEGRFTISRDNANNSLFLQMNSLRAEDTAVYY CARGGDDYSISHFGMDVSGQGTRVTVSS
1.53	SEQ ID NO: 209 KYWMI	SEQ ID NO: 210 NINQDGSEK YYVDSVEG	SEQ ID NO: 211 GGDDYSHSHY GMDV	SEQ ID NO: 212 EVQLVESGGGLVQIGGSLRLSCVASGFTFSKYWMIWVRQAPEKGLEW VANINQDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAEDTAVYY CARGGDDYSHSHYGMDVSGQGTTVTVSS
1.54	SEQ ID NO: 213 NYWMN	SEQ ID NO: 214 NINQDGSEK YYVDSVKG	SEQ ID NO: 215 GGFGYGDSHY GMDV	SEQ ID NO: 216 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYWMNWVRQAPGKELE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRADDTAV YYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.55	SEQ ID NO: 217 SYWLN	SEQ ID NO: 218 NINQDGSEN YYVDSVEG	SEQ ID NO: 219 GGEDYGNSHF GMDV	SEQ ID NO: 220 EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWLNWVRQAPGKGLE WVANINQDGSENYYVDSVEGRFTISRDNAKNSLYLQMHSLRAEDTAV YYCARGGEDYGNSHFGMDVWGQGTMVTVSS
1.56	SEQ ID NO: 221 SYWMS	SEQ ID NO: 222 NIKQDGSEKY YVDSVKG	SEQ ID NO: 223 GGEGYGVDHY GLDV	SEQ ID NO: 224 QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE WVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAVY FCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.57	SEQ ID NO: 225 DYWMN	SEQ ID NO: 226 NIKEDGSEKY YVDSVEG	SEQ ID NO: 227 GGEGYGDNHY GMDV	SEQ ID NO: 228 QVQLVESGGGLVQPGGSLRLSCTASGFTFSDYWMNWVRQAPGKGL EWVANIKEDGSEKYYVDSVEGRFTISRDNARNSLYLQMTSLREEDTA MYYCARGGEGYGDNHYGMDVSGQGTTVTVSS
1.58	SEQ ID NO: 229 SYWMN	SEQ ID NO: 230 NINQDGSEK YYVDSVEG	SEQ ID NO: 231 GGPDYGDLHY GMDV	SEQ ID NO: 232 EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYWMNWVRQAPGKEAE WVANINQDGSEKYYVDSVEGRFTISRDNAKNSLFLQMNSLRDEDTAV YYCARGGPDYGDLHYGMDVWGQGTTVTVSS
1.59	SEQ ID NO: 233 RYWMS	SEQ ID NO: 234 NINQDGREK YYVDSVKG	SEQ ID NO: 235 GGEGYGDYHY GMDV	SEQ ID NO: 236 QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLE RVANINQDGREKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYGDYHYGMDVSGQGTTVTVSS
1.60	SEQ ID NO: 237 NYWMI	SEQ ID NO: 238 NINQDGSEK YYVDSVKG	SEQ ID NO: 239 GGDGYSNSHY GMDV	SEQ ID NO: 240 EVQLVESGGGLVQPGGSPRLSCAASGFTLSNYWMIWYRQAPGEKLE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTAV YYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.61	SEQ ID NO: 241 NYWMN	SEQ ID NO: 242 NINQDESEKY YVDSVKG	SEQ ID NO: 243 GGFGYGDSHF GMDV	SEQ ID NO: 244 EVQLVESGGGLVQPGGSLRLSCVASGFNFSNYWMNWVRQAPGKELE WVANINQDESEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRADDTAV YYCARGGFGYGDSHFGMDVWGQGTTVTVSS
1.62	SEQ ID NO: 245 NYWMN	SEQ ID NO: 246 NINQDESEKY YVDSVKG	SEQ ID NO: 247 GGFGYGDSHF GMDV	SEQ ID NO: 248 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYWMNWVRQAPGKELE WVANINQDESEKYYVDSVKGRFTIFRDNAKNSLFLQMNSLRADDTAV YYCARGGFGYGDSHFGMDVWGQGTTVTVSS
1.63	SEQ ID NO: 249	SEQ ID NO: 250	SEQ ID NO: 251	SEQ ID NO: 252 EVQLVESGGGLVQPGGSLSLSCAASGFTFRSFWMNWVRQAPGKEAE

	SFWMN	NINQDGSEK YYVDSVKG	GGPDYGDLHY GMDV	WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRAEDTAV YYCARGGPDYGDLHYGMDVWGQGTTVTVSS
1.64	SEQ ID NO: 253 SYWMN	SEQ ID NO: 254 NINQDGSEK YYVDSVKG	SEQ ID NO: 255 GGPDYGDLHY GMDV	SEQ ID NO: 256 EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYWMNWVRQAPGKEAE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRDEDTAV YYCARGGPDYGDLHYGMDVWGQGTTVTVSS
1.65	SEQ ID NO: 257 NYWMI	SEQ ID NO: 258 NINQDGSEK YYVDSVKG	SEQ ID NO: 259 GGEDYGNSHY GMDV	SEQ ID NO: 260 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMHSLRAEDTAV YYCARGGEDYGNSHYGMDVWGQGTMVTVSS
1.66	SEQ ID NO: 261 NYWMN	SEQ ID NO: 262 NINQDGSER YYVDSVKG	SEQ ID NO: 263 GGEGYGIDHY GLDV	SEQ ID NO: 264 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMNSLRAEDTAV YFCARGGEGYGIDHYGLDVSGQGTTVTVSS
1.67	SEQ ID NO: 265 SYWMS	SEQ ID NO: 266 NINQDGSER YYVDSVKG	SEQ ID NO: 267 GGEGYGVDHY GLDV	SEQ ID NO: 268 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDTAVY FCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.68	SEQ ID NO: 269 NYWMI	SEQ ID NO: 270 NINQDGSEK YYVDSVEG	SEQ ID NO: 271 GGEGYGVDHY GLDV	SEQ ID NO: 272 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWVRQAPGKGLE WVANINQDGSEKYYVDSVEGRFTISRDNAKSSLYLQMSNLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.69	SEQ ID NO: 273 NYWMN	SEQ ID NO: 274 NINQDGSEK YYVDSVKG	SEQ ID NO: 275 GGTGYGSDHY GMDV	SEQ ID NO: 276 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRAEDTA VYYCARGGTGYGSDHYGMDVSGQGTTVTVSS
1.70	SEQ ID NO: 277 NYWMN	SEQ ID NO: 278 NINQDGSEN YYVDSVKG	SEQ ID NO: 279 GGFGYGDSHY GMDV	SEQ ID NO: 280 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYWMNWVRQAPGKELE WVANINQDGSENYYVDSVKGRFTISRDNVKNSLFLQMNRLRADDTA VYYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.71	SEQ ID NO: 281 NYWMI	SEQ ID NO: 282 NINQNGSER YYVDSVQG	SEQ ID NO: 283 GGADYSNSHY GMDV	SEQ ID NO: 284 EVQLVESGGGLVQPGGSLRLSCAASGFTFGNYWMIWVRQAPGKELE WLANINQNGSERYYVDSVQGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGADYSNSHYGMDVSGQGTTVTVSS
1.72	SEQ ID NO: 285 SYWMS	SEQ ID NO: 286 NINQDGSER YYVDSVKG	SEQ ID NO: 287 GGEGYGVDHY GLDV	SEQ ID NO: 288 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNANNSLHLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.73	SEQ ID NO: 289 SYWMN	SEQ ID NO: 290 NINPDGSEKY YVDSVQG	SEQ ID NO: 291 GGPGYGDLHY GMDV	SEQ ID NO: 292 EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYWMNWVRQAPGKEAE WVANINPDGSEKYYVDSVQGRHTISRDNAKNSLFLEMNSLRVEDTAL YYCARGGPGYGDLHYGMDVWGQGTTVTVSS
1.74	SEQ ID NO: 293 NYWMN	SEQ ID NO: 294 NINQDGSEK YYVDSVEG	SEQ ID NO: 295 GGEGYGVDHY GLDV	SEQ ID NO: 296 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSEKYYVDSVEGRFTISRDNAKSSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.75	SEQ ID NO: 297 DYYMS	SEQ ID NO: 298 NINQDGSER YYVDSVKG	SEQ ID NO: 299 GGEGYGVDHY GLDV	SEQ ID NO: 300 QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.76	SEQ ID NO: 301 NYWMN	SEQ ID NO: 302 NINQDGSER YYVDSVKG	SEQ ID NO: 303 GGEGYGVDHY GLDV	SEQ ID NO: 304 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.77	SEQ ID NO:	SEQ ID NO:	SEQ ID NO:	SEQ ID NO: 308

	305 NYWMN	306 NINQDGSER YYVDSVKG	307 GGEGYGVDHY GLDV	QVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.78	SEQ ID NO: 309 NYWMN	SEQ ID NO: 310 NINQDGSER YYVDSVKG	SEQ ID NO: 311 GGEGYGVDHY GLDV	SEQ ID NO: 312 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.79	SEQ ID NO: 313 NYWMN	SEQ ID NO: 314 NINQDGSER YYVDSVKG	SEQ ID NO: 315 GGEGYGVNHY GLDV	SEQ ID NO: 316 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVNHYGLDVSGQGTTVTVSS
1.80	SEQ ID NO: 317 DYYMS	SEQ ID NO: 318 NIKQDGSERY YVDSVKG	SEQ ID NO: 319 GGEGYGVDHY GLDV	SEQ ID NO: 320 QVQLVESGGGLVKPGGSLRLSCVASGFTFSDYYMSWIRQAPGKGLEW VANIKQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDTAVYFC ARGGEGYGVDHYGLDVSGQGTTVTVSS
1.81	SEQ ID NO: 321 NYWMN	SEQ ID NO: 322 NINQDGSER YYVDSVEG	SEQ ID NO: 323 GGEGYGVDHY GLDV	SEQ ID NO: 324 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVEGRFTISRDNAKSSLYLQMSNLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.82	SEQ ID NO: 325 NYWMN	SEQ ID NO: 326 NINQDGSER YYVDSVKG	SEQ ID NO: 327 GGEGYGVDHY GLDV	SEQ ID NO: 328 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.83	SEQ ID NO: 329 NYWMN	SEQ ID NO: 330 NINQDGSER YYVDSVKG	SEQ ID NO: 331 GGEGYGVDHY GLDV	SEQ ID NO: 332 QVQLQESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.84	SEQ ID NO: 333 NYWMN	SEQ ID NO: 334 NINQDGSER YYVDSVKG	SEQ ID NO: 335 GGEGYGVDHY GLDV	SEQ ID NO: 336 QVQLVESGGGLVKPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.85	SEQ ID NO: 337 NYWMN	SEQ ID NO: 338 NINQDGSER YYVDSVKG	SEQ ID NO: 339 GGEGYGVDHY GLDV	SEQ ID NO: 340 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNANNSLHLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.86	SEQ ID NO: 341 NYWMN	SEQ ID NO: 342 NINQDGSER YYVDSVEG	SEQ ID NO: 343 GGEGYGVDHY GLDV	SEQ ID NO: 344 QVQLGESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVEGRFTISRDNAKSSLYLQMSNLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.87	SEQ ID NO: 345 NYWMN	SEQ ID NO: 346 NINQDGSER YYVDSVKG	SEQ ID NO: 347 GGEGYGVDHY GLDV	SEQ ID NO: 348 QVQLVESGGGLVQPGGSLKLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.88	SEQ ID NO: 349 NYWMN	SEQ ID NO: 350 NINQDGSER YYVDSVKG	SEQ ID NO: 351 GGEGYGVDHY GLDV	SEQ ID NO: 352 QVQLQESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGL EWVANINQDGSERYYVDSVKGRFTISRGNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.89	SEQ ID NO: 353 DYGMS	SEQ ID NO: 354 NINQDGSER YYVDSVKG	SEQ ID NO: 355 GGEGYGVDHY GLDV	SEQ ID NO: 356 QVQLVESGGGVVQPGRSLRLSCAASGFTFDDYGMSWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.90	SEQ ID NO: 357 SHWMT	SEQ ID NO: 358 HIKEDGSEKY YEDSVEG	SEQ ID NO: 359 GGDGYSDSHF GVDV	SEQ ID NO: 360 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGLE WVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAV YYCARGGDGYSDSHFGVDVWGQGTTVTVSS

1.91	SEQ ID NO: 361 SHWMT	SEQ ID NO: 362 HIKEDGSEKY YVDSVKG	SEQ ID NO: 363 GGDGYSDSHF GVDV	SEQ ID NO: 364 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYVDSVKGRFTVSRDNAKNSVYLQMNSLRAEDTAV YYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.92	SEQ ID NO: 365 SHWMT	SEQ ID NO: 366 HIKEDGSEKY YEDSVKG	SEQ ID NO: 367 GGDGYSDSHF GVDV	SEQ ID NO: 368 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYEDSVKGRFTVSRDNAKNSVYLQMNSLRAEDTAV YYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.93	SEQ ID NO: 369 SHWMT	SEQ ID NO: 370 HIKEDGSEKY YEDSVEG	SEQ ID NO: 371 GGDGYSDSHF GVDV	SEQ ID NO: 372 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYEDSVEGRFTISRDNAKNSVYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.94	SEQ ID NO: 373 SHWMT	SEQ ID NO: 374 HIKEDGSEKY YEDSVEG	SEQ ID NO: 375 GGDGYSDSHF GVDV	SEQ ID NO: 376 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSLYLQMNSLRAEDTAV YYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.95	SEQ ID NO: 377 SHWMT	SEQ ID NO: 378 HIKEDGSEKY YVDSVKG	SEQ ID NO: 379 GGDGYSDSHF GVDV	SEQ ID NO: 380 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGLE WVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.96	SEQ ID NO: 381 SHWMT	SEQ ID NO: 382 HIKEDGSEKY YVDSVKG	SEQ ID NO: 383 GGDGYSDSHF GVDV	SEQ ID NO: 384 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.97	SEQ ID NO: 385 SHWMT	SEQ ID NO: 386 HIKEDESEKY YVDSVKG	SEQ ID NO: 387 GGVGYSISHFG VDV	SEQ ID NO: 388 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGLE WVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGVGYSISHFGVDVWGQGTTVTVSS
1.98	SEQ ID NO: 389 SHWMT	SEQ ID NO: 390 HIKEDESEKY YVDSVKG	SEQ ID NO: 391 GGEGYSISHFG VDV	SEQ ID NO: 392 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGLE WVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGEGYSISHFGVDVWGQGTTVTVSS
1.99	SEQ ID NO: 393 SHWMT	SEQ ID NO: 394 HIKEDESEKY YVDSVKG	SEQ ID NO: 395 GGDGYSDSHF GVDV	SEQ ID NO: 396 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.100	SEQ ID NO: 397 SHWMT	SEQ ID NO: 398 HIKEDESEKY YVDSVKG	SEQ ID NO: 399 GGDGYSISHFG VDV	SEQ ID NO: 400 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDGYSISHFGVDVWGQGTTVTVSS
1.101	SEQ ID NO: 401 SHWMT	SEQ ID NO: 402 HIKEGGSEKY YVDSVKG	SEQ ID NO: 403 GGDGYSDSHF GVDV	SEQ ID NO: 404 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEGGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.102	SEQ ID NO: 405 SHWMT	SEQ ID NO: 406 HIKEEGSEKY YVDSVKG	SEQ ID NO: 407 GGDGYSDSHF GVDV	SEQ ID NO: 408 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEEGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.103	SEQ ID NO: 409 SHWMT	SEQ ID NO: 410 HIKEDGSEKY YVDSVKG	SEQ ID NO: 411 GGEGYSDSHF GVDV	SEQ ID NO: 412 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGEGYSDSHFGVDVWGQGTTVTVSS
1.104	SEQ ID NO: 413 SHWMT	SEQ ID NO: 414 HIKEDGSEKY	SEQ ID NO: 415 GGVGYSDSHF	SEQ ID NO: 416 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY

		YVDSVKG	GVDV	YCARGGVGYSDSHFGVDVWGQGTTVTVSS
1.105	SEQ ID NO: 417 SHWMT	SEQ ID NO: 418 HIKEDESEKY YVDSVKG	SEQ ID NO: 419 GGVGYSISHFG VDV	SEQ ID NO: 420 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGVGYSISHFGVDVWGQGTTVTVSS
1.106	SEQ ID NO: 421 SHWMT	SEQ ID NO: 422 HIKEDESEKY YVDSVKG	SEQ ID NO: 423 GGEGYSISHFG VDV	SEQ ID NO: 424 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLE WVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARGGEGYSISHFGVDVWGQGTTVTVSS
1.107	SEQ ID NO: 849 NYWMN	SEQ ID NO: 850 NINQDGSER YYVDSVKG	SEQ ID NO: 851 GGEGYGVDHY GLDV	SEQ ID NO: 852 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.108	SEQ ID NO: 853 NYWMN	SEQ ID NO: 854 NINQDGSER YYVDSVKG	SEQ ID NO: 855 GGEGYGVDHY GLDV	SEQ ID NO: 856 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.109	SEQ ID NO: 857 NYWMN	SEQ ID NO: 858 NINQDGSER YYVDSVKG	SEQ ID NO: 859 GGEGYGVDHY GLDV	SEQ ID NO: 860 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAV YYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.110	SEQ ID NO: 861 NYWMN	SEQ ID NO:862 NINQDGSER YYVDSVKG	SEQ ID NO: 863 GGEGYGVDHY GLDV	SEQ ID NO: 864 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.111	SEQ ID NO: 865 NYWMN	SEQ ID NO: 866 NINQDGSER YYVDSVKG	SEQ ID NO: 867 GGEGYGVDHY GLDV	SEQ ID NO: 868 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTAV YYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.112	SEQ ID NO: 869 NYWMN	SEQ ID NO: 870 NINQDGSER YYVDSVKG	SEQ ID NO: 871 GGEGYGVDHY GLDV	SEQ ID NO: 872 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.113	SEQ ID NO: 873 NYWMN	SEQ ID NO: 874 NINQDGSER YYVDSVKG	SEQ ID NO: 875 GGEGYGVDHY GLDV	SEQ ID NO: 876 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.114	SEQ ID NO: 877 NYWMN	SEQ ID NO: 878 NINQDESERY YVDSVKG	SEQ ID NO: 879 GGEGYGVDHY GLDV	SEQ ID NO: 880 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLE WVANINQDESERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGGEGYGVDHYGLDVSGQGTTVTVSS

In one aspect, the single variable heavy chain domain antibody comprises a CDR1, CDR2 or CDR3 as shown for one of the single domain antibodies as shown in Table 3 or comprising a CDR1, CDR2, CDR3 at least 75% homology thereto. For example, the single variable heavy chain domain antibody comprises a CDR1 comprising SEQ ID NO. 425 or a sequence with at least 80% homology thereto, a CDR2 comprising SEQ ID NO. 426 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 427 or a sequence with at least 75% homology, or a CDR1 comprising SEQ ID NO. 429 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 430 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 431 and so forth.

Sequence homology can be at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology.

In one embodiment, the single variable heavy chain domain antibody comprises human framework regions.

In one embodiment, the single variable heavy chain domain antibody comprising or consisting of a full length sequence as shown in Table 3 or a sequence with at least 50% homology thereto. For example, the single variable heavy chain domain antibody has a sequence selected from those shown in Table 3, e.g. SEQ ID NO. 428, 432, 436, 440 and so forth or a sequence with at least 50% homology thereto. Sequence homology can be at least 50%, 60%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology.

In one embodiment, the single variable heavy chain domain antibody comprises CDR1, 2, and 3 as shown for V_H single domain antibodies 2.41 to 2.51 or comprises or consists of a full length sequence as shown for V_H single domain antibodies 2.41 to 2.51 (i.e. SEQ ID NOs. 588, 592, 596, 600, 604, 608, 612, 616, or 620).

Table 3 Full length sequences and CDR sequences of V_H single domain antibodies (Family 2)

Name	CDR1	CDR2	CDR3	Full Length
2.1	SEQ ID NO: 425 DYYMS	SEQ ID NO: 426 YISGSGDIIDYA DSVKG	SEQ ID NO: 427 EDSRLTGTTDFD N	SEQ ID NO: 428 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NNLRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.2	SEQ ID NO: 429 DYYMS	SEQ ID NO: 430 YISGSGDIIDYA DSVKG	SEQ ID NO: 431 EDSRIPGTTDFD N	SEQ ID NO: 432 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.3	SEQ ID NO: 433 DYYMS	SEQ ID NO: 434 YISGSGDIIDYA DSVKG	SEQ ID NO: 435 EDSRIPGTTDFD N	SEQ ID NO: 436 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWISYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.4	SEQ ID NO: 437 DYYMS	SEQ ID NO: 438 YISGSGDVIDYA DSVKG	SEQ ID NO: 439 EDSRIPGTTDFD N	SEQ ID NO: 440 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDVIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.5	SEQ ID NO: 441 DYYMS	SEQ ID NO: 442 YISGSGDIIDYA DSVKG	SEQ ID NO: 443 EDSRIPGTTDFD N	SEQ ID NO: 444 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.6	SEQ ID NO: 445 DYYMS	SEQ ID NO: 446 YISGSGDIIDYA DSVKG	SEQ ID NO: 447 EDSRIPGTTDFDS	SEQ ID NO: 448 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYHCAKEDSRIPGTTDFDSWGQGTMVTVSS
2.7	SEQ ID NO:	SEQ ID NO: 450	SEQ ID NO: 451	SEQ ID NO: 452

	449 DYYMS	YISGSGTTIDYA DSVKG	EDIRMTGTTDFD N	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGTTIDYADSVKGRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMTGTTDFDNWGQGTLVTVSS
2.8	SEQ ID NO: 453 DYYMS	SEQ ID NO: 454 HISGSGTTIDYA DSVKG	SEQ ID NO: 455 EDSRMPGTTDFD N	SEQ ID NO: 456 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYHCAREDSRMPGTTDFDNWGQGTLVTVSS
2.9	SEQ ID NO: 457 DYYMT	SEQ ID NO: 458 YISGSGDTIDYA ESVKG	SEQ ID NO: 459 EDSRIAGTTDFD N	SEQ ID NO: 460 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAP GKGLEWISYISGSGDTIDYAESVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYHCAREDSRIAGTTDFDNWGPGTLVTVSS
2.10	SEQ ID NO: 461 DYYMT	SEQ ID NO: 462 YISSSGSNIDYA DSVKG	SEQ ID NO: 463 EDSRLSGTTDFDY	SEQ ID NO: 464 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAP GKGLEWVSYISSSGSNIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDSRLSGTTDFDYWGQGTLVTVSS
2.11	SEQ ID NO: 465 DYYMT	SEQ ID NO: 466 YISGSGDTIDYA ESVKG	SEQ ID NO: 467 EDSRIAGTTDFD N	SEQ ID NO: 468 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWFRQAP GKGLEWISYISGSGDTIDYAESVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYHCAREDSRIAGTTDFDNWGPGTLVTVSS
2.12	SEQ ID NO: 469 DYYMS	SEQ ID NO: 470 HISGSGTTIDYA DSVKG	SEQ ID NO: 471 EDIRMTGTTDFD H	SEQ ID NO: 472 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNARKSLYLQM NSLRAEDTAVYYCAREDIRMTGTTDFDHWGQGTLVTVSS
2.13	SEQ ID NO: 473 DYYMS	SEQ ID NO: 474 HISSSGNTIDYA DSVKG	SEQ ID NO: 475 EDPRLPGTTDFD Y	SEQ ID NO: 476 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSHISSSGNTIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLPGTTDFDYWGQGTLVTVSS
2.14	SEQ ID NO: 477 DYYMT	SEQ ID NO: 478 YISGSGDTIDYA ESVKG	SEQ ID NO: 479 EDIRMPGTTDFD H	SEQ ID NO: 480 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAP GKGLEWISYISGSGDTIDYAESVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.15	SEQ ID NO: 481 DYYMS	SEQ ID NO: 482 HISGSGTTIDYA DSVKG	SEQ ID NO: 483 EDIRMPGTTDFD H	SEQ ID NO: 484 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.16	SEQ ID NO: 485 DYYMS	SEQ ID NO: 486 HISSSGSTIDYA DSVKG	SEQ ID NO: 487 EDPRLTGTTDFD Y	SEQ ID NO: 488 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSHISSSGSTIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLTGTTDFDYWGQGALVTVSS
2.17	SEQ ID NO: 489 DYYMS	SEQ ID NO: 490 YISSSGSTISYAD SVKG	SEQ ID NO: 491 EDPRISGTTDFD N	SEQ ID NO: 492 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTISYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAREDPRISGTTDFDNWGQGTLVTVSS
2.18	SEQ ID NO: 493 DYYMS	SEQ ID NO: 494 HISSSGNTIDYA DSVKG	SEQ ID NO: 495 EDPRLPGTTDFD Y	SEQ ID NO: 496 QVQLQESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSHISSSGNTIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLPGTTDFDYWGQGTLVTVSS
2.19	SEQ ID NO: 497 DYYMS	SEQ ID NO: 498 YISGTGITTDYA DSVKG	SEQ ID NO: 499 EDPRLPGTSEFD N	SEQ ID NO: 500 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGTGITTDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLPGTSEFDNWGQGTLVTVSS
2.20	SEQ ID NO: 501 DYYMS	SEQ ID NO: 502 HISSSGSTIDYA DSVKG	SEQ ID NO: 503 EDPRMPGTFDFD N	SEQ ID NO: 504 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSHISSSGSTIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRMPGTFDFDNWGQGTLVTVSS

2.21	SEQ ID NO: 505 DYYMS	SEQ ID NO: 506 HISGSGTTIDYA DSVKG	SEQ ID NO: 507 EDIRMPGTTDFD H	SEQ ID NO: 508 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.22	SEQ ID NO: 509 DYYMS	SEQ ID NO: 510 HISGSGTTIDYA DSVKG	SEQ ID NO: 511 EDIRMPGTTDFD H	SEQ ID NO: 512 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNARDSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.23	SEQ ID NO: 513 DYYMS	SEQ ID NO: 514 HISGSGTTIDYA DSVKG	SEQ ID NO: 515 EDIRMPGTTDFD H	SEQ ID NO: 516 EVQLVESGGGLVTPGGSLRLSCAVSGFTFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.24	SEQ ID NO: 517 DYYMS	SEQ ID NO: 518 HISGSGTTIDYA DSVKG	SEQ ID NO: 519 EDIRMPGTTDFD H	SEQ ID NO: 520 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQM NSLRAEDTAMYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.25	SEQ ID NO: 521 DYYMS	SEQ ID NO: 522 HISGSGTTIDYA DSVKD	SEQ ID NO: 523 EDIRMPGTTDFD H	SEQ ID NO: 524 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKDRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.26	SEQ ID NO: 525 DYYMS	SEQ ID NO: 526 HISSSGTTIDYA DSVKG	SEQ ID NO: 527 EDIRMPGTTDFD N	SEQ ID NO: 528 EVQLVESGGGLVKPGGSLRLSCTASGFTFTDYYMSWFRQAP GKGLEWVSHISSSGTTIDYADSVKGRFTISRDNAKNSLYLQM NSLRADDTAVYYCAREDIRMPGTTDFDNWGQGTLVTVSS
2.27	SEQ ID NO: 529 DYYMT	SEQ ID NO: 530 YISSSGSTISYAD SVKG	SEQ ID NO: 531 EDIRMSGTTDFD Y	SEQ ID NO: 532 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAP GKGLEWVSYISSSGSTISYADSVKGRFTISRDNANNSLYLQM NSLRAEDTAVYHCAREDIRMSGTTDFDYWGQGTLVTVSS
2.28	SEQ ID NO: 533 DYYMS	SEQ ID NO: 534 HISSSGSSIDYA DSVKG	SEQ ID NO: 535 EDPRLSGTIDFDS	SEQ ID NO: 536 QVQLVESGGGLVKPGGSLRLSCAASGFIFSDYYMSWFRQAP GKGLEWVSHISSSGSSIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLSGTIDFDSWGQGTLVTVSS
2.29	SEQ ID NO: 537 DYYMS	SEQ ID NO: 538 HIGGSGTTIDYA DSVKG	SEQ ID NO: 539 EDIRMPGTTDFD H	SEQ ID NO: 540 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAP GKGLEWVSHIGGSGTTIDYADSVKGRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.30	SEQ ID NO: 541 DYYMS	SEQ ID NO: 542 YISSSGSTIYYAD SVKG	SEQ ID NO: 543 EDPRVPGTTNFD Y	SEQ ID NO: 544 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAREDPRVPGTTNFDYWGQGTLVTVSS
2.31	SEQ ID NO: 545 DYYMT	SEQ ID NO: 546 YISGSGSTIDYA DSVKG	SEQ ID NO: 547 EDGRIPGTTDFD H	SEQ ID NO: 548 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWMRQA PGKGLEWVSYISGSGSTIDYADSVKGRFTISRDNAKNSLYLQ MNSLRPEDTAVYYCAKEDGRIPGTTDFDHWGQGTLVTVSS
2.32	SEQ ID NO: 549 DYYMS	SEQ ID NO: 550 HISGSGTTIDYA DSVKD	SEQ ID NO: 551 EDIRMPGTTDFD H	SEQ ID NO: 552 EVQLVESGGGLVQPGGSLRLSCAASGFAFSDYYMSWFRQAP GKGLEWVSHISGSGTTIDYADSVKDRFTISRDNARNSLYLQM NSLRAEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.33	SEQ ID NO: 553 DYFMS	SEQ ID NO: 554 HISSSGNSIDYA DSVKG	SEQ ID NO: 555 EDPRLPGTTDFD Y	SEQ ID NO: 556 QVQLVESGGGLVKPGGSLRLSCAASGFPFSDYFMSWFRQAP GKGLEWVSHISSSGNSIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAKEDPRLPGTTDFDYWGQGTLVTVSS
2.34	SEQ ID NO: 557 DSYMS	SEQ ID NO: 558 HISNSGSTISYA DSVKG	SEQ ID NO: 559 EDPRLPGTSDFD Y	SEQ ID NO: 560 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDSYMSWIRQAP GKGLEWVSHISNSGSTISYADSVKGRFTISRDNAKNSLYLQM

				NSLRAEDTAVYYCAREDPRLPGTSDFDYWGQGTLVTVSS
2.35	SEQ ID NO: 561 DYYMS	SEQ ID NO: 562 HISSSGSSIDYA DSVKG	SEQ ID NO: 563 EDPRLSGTTDFD Q	SEQ ID NO: 564 QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSHISSSGSSIDYADSVKGRFTISRDNAKNSLYLQM NSLRDEDTAVYYCAREDPRLSGTTDFDQWGQGTLVTVSS
2.36	SEQ ID NO: 565 SYWMS	SEQ ID NO: 566 HISSSGSTIDYAE SVKG	SEQ ID NO: 567 EDPRMTGTTDFD Y	SEQ ID NO: 568 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQA PGKGLEWVSHISSSGSTIDYAESVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRMTGTTDFDYWGQGTLVTVSS
2.37	SEQ ID NO: 569 NYFMS	SEQ ID NO: 570 HISSSGNTIDYA DSVKG	SEQ ID NO: 571 EDPRLPGTTDFD Y	SEQ ID NO: 572 QVQLQESGGGLVKPGGSLRLSCAASGFTFSNYFMSWIRQAP GKGLEWVSHISSSGNTIDYADSVKGRFTISRDNAKNSLYLQM DSLRAEDTAVYYCSREDPRLPGTTDFDYWGQGTLVTVSS
2.38	SEQ ID NO: 573 DYYMT	SEQ ID NO: 574 YISSGGSTIHYA DSVKG	SEQ ID NO: 575 ENPRLPGTMDFD Y	SEQ ID NO: 576 EVQLVESGGGVVKPGGSLRLSCAASGFTFSDYYMTWIRQGP GKGQEWISYISSGGSTIHYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCARENPRLPGTMDFDYWGQGTLVTVSS
2.39	SEQ ID NO: 577 DHFMS	SEQ ID NO: 578 NIKQDGSEKYY VDSVKG	SEQ ID NO: 579 EDPRLTGTTDFD N	SEQ ID NO: 580 QVQLVESGGGLVQPGGSLRLSCAASGFTFSDHFMSWFRQA PGKGLEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLFLQ MNSLRAEDTAMYYCAREDPRLTGTTDFDNWGQGTLVTVSS
2.40	SEQ ID NO: 581 NYWMT	SEQ ID NO: 582 HISSTGSTIDYA DSVKG	SEQ ID NO: 583 EDPRLPGTMDFD Y	SEQ ID NO: 584 EVQLVESGGGLVQAGGSLRLSCVASGFTFSNYWMTWFRQA PGRGLEWVSHISSTGSTIDYADSVKGRFTISRDNAENSLYLQ MNSLRAEDTAVYYCAREDPRLPGTMDFDYWGQGTLVTVSS
2.41	SEQ ID NO: 585 DYYMS	SEQ ID NO: 586 YISGSGDIIDYA DSVKG	SEQ ID NO: 587 EDSRLTGTTDFD N	SEQ ID NO: 588 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NNLRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.42	SEQ ID NO: 589 DYYMS	SEQ ID NO: 590 YISGSGDIIDYA DSVKG	SEQ ID NO: 591 EDSRLTGTTDFD N	SEQ ID NO: 592 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NNLRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.43	SEQ ID NO: 593 DYYMS	SEQ ID NO: 594 YISGSGDIIDYA DSVKG	SEQ ID NO: 595 EDSRLTGTTDFD N	SEQ ID NO: 596 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NNLRAEDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.44	SEQ ID NO: 597 DYYMS	SEQ ID NO: 598 YISGSGDIIDYA DSVKG	SEQ ID NO: 599 EDSRLTGTTDFD N	SEQ ID NO: 600 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.45	SEQ ID NO: 601 DYYMS	SEQ ID NO: 602 YISGSGDIIDYA DSVKG	SEQ ID NO: 603 EDSRLTGTTDFD N	SEQ ID NO: 604 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NNLRAEDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.46	SEQ ID NO: 605 DYYMS	SEQ ID NO: 606 YISGSGDIIDYA DSVKG	SEQ ID NO: 607 EDSRLTGTTDFD N	SEQ ID NO: 608 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.47	SEQ ID NO: 609 DYYMS	SEQ ID NO: 610 YISGSGDIIDYA DSVKG	SEQ ID NO: 611 EDSRLTGTTDFD N	SEQ ID NO: 612 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.48	SEQ ID NO: 613	SEQ ID NO: 614 YISGSGDIIDYA	SEQ ID NO: 615 EDARLTGTTDFD	SEQ ID NO: 616 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP

	DYYMS	DSVKG	N	GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDARLTGTTDFDNWGQGTLVTVSS
2.49	SEQ ID NO: 617 DYYMS	SEQ ID NO: 618 YISGSGDIIDYA DSVKG	SEQ ID NO: 619 EDPRLTGTTDFD N	SEQ ID NO: 620 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLTGTTDFDNWGQGTLVTVSS
2.50	SEQ ID NO: 621 DYYMS	SEQ ID NO: 622 YISGSGDIIDYA DSVKG	SEQ ID NO: 623 EDARLTGTTDFD N	SEQ ID NO: 624 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDARLTGTTDFDNWGQGTLVTVSS
2.5 1	SEQ ID NO: 625 DYYMS	SEQ ID NO: 626 YISGSGDIIDYA DSVKG	SEQ ID NO: 627 EDPRLTGTTDFD N	SEQ ID NO: 628 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAP GKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQM NSLRAEDTAVYYCAREDPRLTGTTDFDNWGQGTLVTVSS

In one embodiment, the binding molecule may comprise one or more single domain antibodies that bind to CD137, for example one or two single domain antibodies as described above in Tables 2 and 3.

In some embodiments, there is provided a V_H single domain antibody that is a variant of any of the above single V_H domain antibodies shown in Table 2 or Table 3 having one or more amino acid substitutions, deletions, insertions or other modifications, and which retains a biological function of the single domain antibody. Thus, variant V_H single domain antibodies can be sequence engineered. Modifications are described elsewhere herein. In one embedment, there is provided a variant of V_{Hs} 1.07 to 1.113, for example V_H1.113 which has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 substitutions.

Examples of substitutions

In one embodiment, the variant comprises one or more the following substitutions with reference to SEQ ID NO. 4 (V_H1.1) or combinations thereof:

- F37V
- E61V + E65K
- E65K
- V70I
- V79L
- F37V + E61V + E65K + V70I +V79L
- E61V + E65K + V70I +V79L
- F37V + E61V + E65K + V70I + V79L + G55E + D101V + D105I
- F37V + E61V + E65K + V70I +V79LFGL + G55E + D101E + D105I
- E61V + E65K + V70I +V79L + G55E
- E61V + E65K + V70I +V79L + G55E + D105I
- E61V + E65K + V70I +V79L + D54G, E61V + E65K + V70I + V79L + D54E,
- E61V + E65K + V70I + V79L + D101E
- E61V + E65K + V70I +V79L + D101V or

- E61V + E65K + V70I +V79L + G55E + D101V + D105I, E61V + E65K + V70I +V79L + G55E + D101E + D105I

In one embodiment, the variant comprises one or more the following substitutions with reference to SEQ ID NO. 4 (V_H1.1) or combinations thereof:

a) E61V + E65K + V70I + V79L + G55E + D101→any amino acid selected from the following F, L, I, M, V, S, P, T, A, Y, H, Q, K, D, W, R, G;

b) E61V + E65K + V70I + V79L + G55E + D105→any amino acid selected from the following F, L, M, S, P, T, A, Y, H, Q, N, K, D, E, W, R, G or

c) E61V + E65K + V70I + V79L + G55E, D101→any amino acid selected from the following F, L, I, M, V, S, P, T, A, Y, H, Q, K, D, W, R, G+ D105→ any amino acid selected from the following F, L, M, S, P, T, A, Y, H, Q, N, K, D, E, W, R, G.

In one embodiment, the variant comprises one or more the following substitutions with reference to SEQ ID NO. 312 (V_H1.78) or combinations thereof:

- Q1E + T25S
- Q1E + S84N
- Q1E + F95Y
- Q1E + T25S + S84N
- Q1E + T25S + F95Y
- Q1E + S84N + F95Y
- Q1E + T25S + S84N + F95Y or
- Q1E + T25S + G55E + S84N + F95Y

In one embodiment, the variant comprises one or more the following substitutions with reference to SEQ ID NO. 428 (V_H2.1) or combinations thereof:

- V20L,
- F37I,
- N85S,
- N95Y,
- V20L + H95Y,
- V20L + F37I + N85S + H95Y, V20L + N85S + H95Y,
- V20L + F37I + N85S + H95Y + S101A,
- V20L + F37I + N85S + H95Y + S101P or
- V20L + N85S + H95Y + S101A, V20L + N85S + H95Y +S101A.

In one embodiment, the variant comprises one or more the following substitutions with reference to SEQ ID NO. 624 (V_H2.50) or combinations thereof:

- S35T + V48I + I57T + L103M + T104R + T107I

- S35T + A101T + L103V + T104R + T107V
- S35T + V48I + I57T + A101E + L103L + T104W + T107V
- S35T + V48I + L103T + T104R + T107V
- Y32H + S35T + V48I + S52G + S54D + D56A + I58L + A101L + T104P + T107I + N111H
- S35T + A101T + L103V + T104R + T107V + N111S
- A28T + S30T + Y33W + S35T + V48I + G53S + S54D + D56K + I57T + L103M + T104P + T107I + N111Y
- S35T + V48I + L103T + T104R + T107V + N111S
- S35T + V48I + I57T + S101E + T104W + T107V + N111S or
- S35T + V48I + I57T + L103M + T104R + T107I + N111S

Exemplary nucleic acids encoding CD137 polypeptide

An isolated nucleic acid encoding a single domain antibody as shown above is set out below. Nucleic acid may include DNA and/or RNA. In one aspect, the present invention provides a nucleic acid that codes for a CDR, for example CDR3, a set of two or three CDRs or a V_H single domain antibody of the invention as shown above.

Table 4 Nucleic acids encoding V_H 1.1 to 1.114

Name	Nucleotide Sequence
1.1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAA GGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTC GGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAG TGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 629
1.2	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGTTATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAG GAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAATAACTCG CTGTATCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGT GACTCCCACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 630
1.3	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGTTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGATTAGGCTACGGTG ACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 631
1.4	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGGGGGGGCTGGAGTGGGTGGCCAACATAAA CCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTC ACTGTATCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGATTAGGCTACGG TGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 632
1.5	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGTTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTG

	GCTCCCACCACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 633
1.6	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAAGGCTATAG CACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 634
1.7	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACACCCTGAGAGCCGAGGACACGGCTATTTATTATTGTGCGAGAGGGGGTGATGGCTACAGTGA CTCCCACTTCGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 635
1.8	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCTCT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGA TTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 636
1.9	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGGGGGGGCTGGAGTGGGTGGCCAACATAAA CCAAGATGGGAGTGAGAAGTACTATGTGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTC ACTGGATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGATTAGGCTACG GTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 637
1.10	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTGACTATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG GAGGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATATCCAGAGACAACGCCAAGAACTCA ACGTATCTGCAAATGAACAGCCTGAGAGTCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGGGCCGGGTATAG CATGTCTCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 638
1.11	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGAAGCCTCTGGA TTCACCTTTAGTGACTATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG GAGGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATATCCAGAGACAACGCCAAGAACTCA ACGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGGGCCGGGTATAG TATGTCTCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 639
1.12	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACACCCTGCGAGCCGAGGACACGGCTATTTATTATTGTGCGAGAGGGGGTGATGGCTACAGTAA CTCCCACTTCGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 640
1.13	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCTC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTG ATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 641
1.14	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAATTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG GAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAAGGCTATAGC ACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA

	SEQ ID NO. 642
1.15	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTACCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTCTCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCAACTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGA CTCCCACTTCGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 643
1.16	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATGTGGTTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTTTGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAG CTCTCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 644
1.17	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG GAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAGCTATGGT TACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 645
1.18	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTACCCATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGAGCTGGAATGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAATTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTATATTACTGTGCGAGAGGGGGGGTTGGCTACGGTG ACTCCCACTTCGGTATGGACGTCTGGGGCCTAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 646
1.19	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGATCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGACTACAGT AACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 647
1.20	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGCAGGGCCGATTCACCATCTCCAGAGACAATGCCAATAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTACGGTG ACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 648
1.21	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAGTTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTACAGTG ATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 649
1.22	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAATATAAAG GAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAGGAACTCA CTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAGGGCTACGG TGACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 650
1.23	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGTTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTTTATCTGCAAATGAACAGCCTGACAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGGGGGGGAGGGCTACGGT GACGACCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.651

1.24	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAGGGCTACGG TGACTACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 652
1.25	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAGCTATGGT TACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 653
1.26	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA TTCACCTTTAGTACCCATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGAGCTGGAATGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAATTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTATATTACTGTGCGAGAGGGGGGGTTGGCTACGGTG ACTCCCACTTCGGTATGGACGTCTGGGGCCTAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 654
1.27	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAGTTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGACTCACCATCTCCAGAGACAACGCCAAGAACGCTC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAAGGCTACAGTG ATTCCCACCACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 655
1.28	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAACTATGCT TACAGGGACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.656
1.29	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAATTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTACAGTG ATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 657
1.30	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAAGAGTATGG GAGCTCGCACTACGGTATGGACGTCTGGGGCCTGGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 658
1.31	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGGGGGGGACAGCTATGGT TACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 659
1.32	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTAAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGTTATTGGATGAACTGGGTCCGCCAGACTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAT CAAAATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCAACATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTACAAATGAGTAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTACGGT GATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 660
1.33	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGGCGGGGGGGTCCCTAAGACTCTCCTGTGTAGCCTCTGG

	ATTCACCTTTAGTAATTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGAAAGTGAGGAATACTATGTGGACTCTGTGAAGGGCCGTTTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTG ACTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 661
1.34	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGA TTCACCTTTAGTAATTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG GAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAAGGCTATAGC ACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 662
1.35	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATTAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGGACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAGGGCTACGG TGAATCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 663
1.36	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTACCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAA CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAGCTATGGT TACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 664
1.37	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTTACTATTGGATGATCTGGTTCCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCATTATCTCCAGAGACAACGCCACGAACTCACT GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAA TTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 665
1.38	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTACAGTGA TTCCCACTACGGTACGGACGTCTGGGGCCAGGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 666
1.39	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATAAAC CAAGATGAAAGTGAAAAATACTATGTTGACTCTGTGAAGGGCCGTTTCACCGTCTCCAGAGACAACGCCAAGAACTCAC TGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTATATTACTGTGCGAGAGGGGGGTTTGGCTACGGTG ACTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO.667
1.40	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAATTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACGACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTACAGTG ATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.668
1.41	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAATTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTAACC AAAATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTACAGTGA TTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 669
1.42	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG

	CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGGACTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTATTGTGCGAGAGGGGGGGAGGGTTACGGT GACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 670
1.43	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAACTCACT GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAA TTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 671
1.44	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTGACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAACTCACT GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAA TTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 672
1.45	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAAATATTGGATGATCTGGGTCCGCCAGGCTCCAGAAAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATTTCCAGAGACAATGTCAATAACTCATT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTACTACTGTGCGAGAGGAGGTGATGACTACAGTAA CTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 673
1.46	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAACAGCCTTAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGGAAGAATATAGC AGCTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 674
1.47	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTATAGCCTCTGGA TTCAGCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAAGGGTATAGC ACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCGCGGTCACTGTCTCTTCA SEQ ID NO. 675
1.48	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 676
1.49	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTAACC AAGATGGCAGTGAGAATTACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGGTGAAGACTACGGTAA CTCCCACTTCGGCATGGACGTCTGGGGCCAAGGGACCATGGTCACCGTCTCCTCA SEQ ID NO. 677
1.50	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGCAGATCCCTGAGACTCTCTTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAACTCACT GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAA TTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 678
1.51	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAACTCACT

	GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAA TTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 679
1.52	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGATTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCCGGA TTCACCTTTAGTAAATATTGGATGATCTGGGTCCGCCAGGCTCCAGAAAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATTTCCAGAGACAACGCCAATAACTCACT GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTACTACTGTGCGAGAGGAGGTGATGACTACAGTAT CTCCCACTTCGGTATGGACGTCTCGGGCCAAGGGACCAGGGTCACCGTCTCCTCA SEQ ID NO. 680
1.53	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGATTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA TTCACCTTTAGTAAATATTGGATGATCTGGGTCCGCCAGGCTCCAGAAAAGGGGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATTTCCAGAGACAACGCCAATAATTCATT GTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTACTACTGTGCGAGAGGAGGTGATGACTACAGTCA CTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 681
1.54	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCAACTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTACGGT GACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 682
1.55	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTGGTAGTTATTGGCTGAATTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGCAGTGAGAATTACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGGTGAAGACTACGGTA ACTCCCACTTCGGCATGGACGTCTGGGGCCAAGGGACCATGGTCACTGTCTCTTCA SEQ ID NO. 683
1.56	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 684
1.57	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGA TTCACCTTTAGTGACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGTAAGGGGCTGGAGTGGGTGGCCAATATAAAG GAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAGGAACTCA CTGTATCTGCAAATGACCAGCCTGAGAGAAGAAGACACGGCTATGTATTACTGTGCGAGAGGGGGGGAGGGCTACGG TGACAACCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 685
1.58	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGAAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGGCGGAATGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATATTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTTTCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGCCCCGACTACGGT GACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 686
1.59	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTAAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGGTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGCGGGTGGCCAACATAAAC CAAGATGGACGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGGGGGGGAGGGCTACGGT GACTACCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 687
1.60	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCCGAGACTCTCCTGTGCAGCCTCTGGA TTCACCCTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGAAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAACTCACT GTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTACAGTAA

	TTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 688
1.61	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA TTCAACTTCAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATAAAC CAAGATGAAAGTGAAAAATACTATGTAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTACGGTG ACTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 689
1.62	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCAATTTTAGTAACTATTGGATGAACTGGGTCCGTCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATAAAC CAAGATGAAAGTGAAAAATACTATGTAGACTCTGTGAAGGGCCGATTCACCATTTTCAGAGACAACGCCAAGAACTCAC TGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTACGGTG ACTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 690
1.63	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGTCTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGAAGCTTTTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGGCGGAATGGGTGGCCAACATAAAT CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGCCCCGACTACGGT GACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 691
1.64	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGAAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGGCGGAATGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATATTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTTTCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGCCCCGACTACGGTG ACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 692
1.65	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAAACC AAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGGTGAAGACTACGGTAA CTCCCACTACGGCATGGACGTCTGGGGCCAAGGGACCATGGTCACCGTCTCTTCA SEQ ID NO. 693
1.66	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT ATCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 694
1.67	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAT CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGTAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 695
1.68	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAACTATTGGATGATCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGCAACCTGAGAGCCGAGGACACGGCTGTATATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 696
1.69	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCAC TGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGAACAGGCTATGGTT CCGACCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA

	SEQ ID NO. 697
1.70	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCAATTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGTCAAGAACTCAC TGTTTCTGCAAATGAACCGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTACGGTG ACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 698
1.71	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTGGTAACTATTGGATGATCTGGGTCCGCCAGGCTCCAGGCAAGGAGTTGGAGTGGCTGGCCAACATAAACC AAAATGGAAGTGAGAGATACTATGTGGACTCTGTGCAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGGGGTGCTGACTACAGTAA CTCCCACTACGGTATGGACGTCAGCGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 699
1.72	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAACTCAC TGCATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 700
1.73	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGAAGTTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAAGAGGCGGAATGGGTGGCCAACATAAA CCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGCAGGGCCGACACACCATCTCCAGAGACAACGCCAAGAACTC ACTGTTTCTGGAAATGAACAGCCTGAGAGTCGAGGACACGGCTCTTTATTACTGTGCGAGAGGAGGCCCCGGCTACGG TGACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 701
1.74	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAT CAAGATGGAAGTGAAAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 702
1.75	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 703
1.76	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 704
1.77	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 705
1.78	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 706

1.79	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCAACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 707
1.80	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA TTCACCTTCAGTGACTACTATATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAG CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.708
1.81	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGCAACCTGAGAGCCGAGGACACGGCTGTATATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 709
1.82	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATTTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 710
1.83	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGG ATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAA CCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTC ACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATG GTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 711
1.84	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO.712
1.85	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAACTCAC TGCATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 713
1.86	CAGGTGCAGCTGGGGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGG ATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAA CCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTC ACTGTATCTGCAAATGAGCAACCTGAGAGCCGAGGACACGGCTGTATATTTCTGTGCGAGAGGGGGGGAAGGCTATGG TGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 714
1.87	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAAACTCTCCTGTGCAGCCACTGGA TTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATTTCCAGAGACAACGCCAAGAGCTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 715
1.88	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTGG

	ATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAA CCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGGCAACGCCAAGAACTC ACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATG GTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 716
1.89	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAC CAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTATGGT GTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 717
1.90	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGA ACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 718
1.91	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGA ACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 719
1.92	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGAAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGA ACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 720
1.93	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 721
1.94	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 722
1.95	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 723
1.96	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 724
1.97	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA

	AAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGTTGGC TACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 725
1.98	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGAGGGC TACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 726
1.99	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 727
1.100	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 728
1.101	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGGCGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 729
1.102	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGAGGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 730
1.103	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGAGGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 731
1.104	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGTTGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 732
1.105	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGTTGGC TACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO.733
1.106	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGA

	ACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGAGGGC TACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 734
1.107	GAGGTGCAATTAGTCGAATCGGGGGGGTGGACTGGTTCAGCCGGGAGGTAGCCTGCGCCTGTCCTGTGCCGCATCTG GTTTTACATTAAGTAACTACTGGATGAATTGGGTTCGTCAAGCGCCTGGAAAGGGCTTAGAGTGGGTGGCTAATATT AACCAGGACGGGTCAGAGCGCTACTATGTGGATTCAGTAAAAGGTCGCTTCACTATCAGCCGCGATAATGCTAAAAA TTCGCTGTACCTTCAGATGTCATCACTTCGTGCAGAGGATACAGCTGTGTATTTCTGCGCGCGTGGAGGCGAGGGGT ACGGGGTAGACCACTATGGGTTGGATGTCTCGGGACAAGGCACGACCGTCACTGTCAGTAGC SEQ ID NO. 881
1.108	GAGGTCCAGTTGGTTGAGTCCGGCGGCGGCTTGGTCCAACCAGGGGGGTCGCTTCGCTTATCTTGCGCTGCCACAGG GTTTACCCTGAGCAACTACTGGATGAACTGGGTGCGCCAAGCGCCTGGGAAGGGGTTAGAGTGGGTCGCCAACATC AACCAAGACGGTTCGGAGCGTTACTATGTCGACAGCGTGAAGGGCCGTTTCACGATCTCCCGCGATAACGCTAAGAA CTCCCTGTATTTGCAAATGAATAGCCTTCGTGCGGAGGATACTGCGGTTTATTTCTGTGCTCGTGGCGGTGAAGGATA TGGGGTTGACCATTATGGGTTGGATGTCTCCGGGCAAGGGACAACGGTGACCGTGTCATCC SEQ ID NO. 882
1.109	GAGGTTCAACTTGTTGAATCGGGTGGCGGATTAGTACAACCCGGCGGCTCGCTGCGTTTATCGTGTGCGGCAACCGG ATTTACTTTATCAAACTATTGGATGAATTGGGTGCGCCAGGCTCCAGGGAAAGGTCTGGAATGGGTAGCGAATATCA ACCAAGACGGCTCAGAACGCTACTACGTGGACTCCGTAAAAGGTCGTTTCACCATCTCTCGTGACAATGCTAAAAATT CTTTGTATTTGCAAATGAGTTCACTTCGTGCTGAGGATACTGCGGTCTATTACTGTGCTCGCGGGGGGGAAGGCTACG GAGTAGACCACTACGGGTTGGATGTTTCTGGACAGGGAACGACGGTTACTGTAAGCAGC SEQ ID NO. 883
1.110	GAGGTTCAGTTAGTTGAGTCCGGCGGGGGATTAGTTCAACCTGGCGGAAGCCTTCGTCTGAGTTGTGCCGCGAGCG GGTTTACCCTTAGCAATTACTGGATGAACTGGGTACGTCAAGCTCCAGGTAAAGGTTTAGAATGGGTCGCTAACATTA ATCAAGATGGTTCTGAACGCTATTATGTAGACTCGGTAAAGGGTCGTTTTACAATTTCTCGCGACAACGCCAAAAACT CTTTGTACCTTCAAATGAATTCCTTACGCGCTGAGGACACTGCTGTCTATTTCTGTGCGCGTGGAGGGGAGGGATACG GAGTTGACCACTATGGGCTGGACGTTTCAGGACAGGGCACTACGGTAACTGTGTCTTCG SEQ ID NO. 884
1.111	GAGGTTCAGTTAGTAGAGTCCGGGGGAGGACTGGTACAACCTGGGGGTAGTTTGCGTCTGTCTTGTGCAGCCAGCG GTTTCACATTGTCTAACTATTGGATGAATTGGGTTCGTCAAGCGCCTGGCAAGGGACTGGAGTGGGTTGCAAACATT AATCAAGATGGCAGCGAGCGTTATTACGTGGACTCAGTAAAAGGGCGCTTCACGATTAGCCGCGATAATGCTAAGAA CTCCTTATATCTGCAGATGTCATCTTTGCGTGCCGAGGACACGGCAGTTTACTATTGCGCACGTGGTGGCGAGGGATA CGGCGTGGATCACTATGGTTTGGACGTATCGGGCCAAGGGACTACCGTGACTGTGTCCTCT SEQ ID NO. 885
1.112	GAGGAGGTACAGCTTGTCGAGTCTGGCGGTGGCCTTGTGCAACCGGGGGGTTCTTTACGTTTATCCTGTGCCGCTAC AGGATTTACGTTAAGCAACTATTGGATGAACTGGGTACGTCAAGCTCCGGGGAAGGGGCTGGAATGGGTTGCCAAT ATCAATCAGGATGGGTCTGAACGCTACTACGTTGATTCTGTTAAGGGTCGCTTTACTATTTCACGTGACAATGCCAAG AACAGTCTTTACCTTCAAATGAACTCGTTACGCGCTGAGGATACTGCTGTGTACTACTGTGCGCGCGGCGGAGAGGG ATACGGTGTCGATCATTATGGGCTTGACGTAAGCGGGCAGGGTACGACGGTGACGGTATCATCA SEQ ID NO. 886
1.113	GAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCGG GATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACATT AATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAA TTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATA CGGCGTCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCC SEQ ID NO. 887
1.114	GAGGTGCAGTTGGTAGAGAGTGGGGGTGGCCTGGTCCAACCAGGTGGGTCCCTTCGTTTGTCTTGCGCCGCCTCTGG GTTTACTCTGTCAAATTATTGGATGAACTGGGTGCGCCAAGCTCCCGGCAAGGGGTTGGAGTGGGTTGCCAACATTA ATCAGGACGAATCCGAGCGTTACTATGTTGATTCTGTAAAAGGGCGCTTCACTATCTCTCGTGATAATGCTAAGAACA GTTTGTACCTGCAAATGAATTCACTGCGTGCCGAGGATACCGCGGTGTACTATTGTGCCCGTGGAGGAGAGGGATAC GGGGTCGATCACTATGGCTTAGACGTATCGGGCCAGGGAACAACCGTCACC GTATCCTCA SEQ ID NO. 888

Table 5 Nucleic acids encoding V_H 2.1 to 2.51

Name	Nucleotide Sequence
2.1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTG GTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCT GTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGG AACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 735
2.2	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTAGTG GTAGTGGTGATATCATAGACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATACCTGG AACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 736
2.3	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTATATGAGTTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATTTCGTACATTAGTG GTAGTGGTGATATCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATACCTGG AACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 737
2.4	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTAGTG GTAGTGGTGATGTCATTGACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATACCTGG AACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 738
2.5	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTAGTG GTAGTGGTGATATCATAGACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATACCTGG AACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 739
2.6	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTAGTG GTAGTGGTGATATCATAGACTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATACCTGG AACTACGGACTTTGACAGTTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA SEQ ID NO. 740
2.7	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCAGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTG GTAGTGGTACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAACTCACT ATATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGACTGG AACTACGGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 741
2.8	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT ATATCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGCATGCCTGG AACTACGGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 742
2.9	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTATATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGATTTCATACATTAGTG GTAGTGGTGATACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAATTCACT GTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCGCGTATAGCCGG

	AACTACGGACTTTGACAACTGGGGCCCGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 743
2.10	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTA GTAGTGGTAGTAACATAGATTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCTAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCCCGTTTAAGTGG AACTACGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 744
2.11	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTATATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGATTTCATACATTAGTG GTAGTGGTGATACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAATTCACT GTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCGCGTATAGCCGG AACTACGGACTTTGACAACTGGGGCCCGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 745
2.12	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGTACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAAGTCACT ATATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTCTATTACTGTGCCAGAGAAGATATCAGGATGACTGG AACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 746
2.13	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAATACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTCACT TTATCTGCAAATGAATAGTCTGAGAGCCGAGGACACGGCCGTTTATTACTGTGCGAGAGAAGATCCTCGTTTACCTGGA ACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 747
2.14	GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTATATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGATTTCATACATTAGTG GTAGTGGTGATACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAATTCACT GTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 748
2.15	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 749
2.16	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGGAGTACCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTAACTGG AACTACAGATTTTGACTACTGGGGCCAGGGAGCCCTGGTCACTGTCTCCTCA SEQ ID NO. 750
2.17	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTA GTAGTGGTAGTACCATATCCTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTATAAGTGG AACTACAGATTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 751
2.18	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAATACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTTTATTACTGTGCGAGAGAAGATCCTCGTTTACCTGGA ACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

	SEQ ID NO. 752
2.19	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTG GTACTGGTATTACCACAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTACCTGG AACTTCAGAATTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 753
2.20	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAGTACCATAGATTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTCTATTACTGTGCGAGAGAAGATCCCCGTATGCCTGG AACTTTTGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 754
2.21	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 755
2.22	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGGATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 756
2.23	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCACGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 757
2.24	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCATGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 758
2.25	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTTAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGACCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 759
2.26	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTACAGCCTCTGGA TTCACCTTCACTGACTATTATATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTTTCACACATTAGTA GTAGTGGTACTACAATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCCGTATATTACTGTGCGAGAGAAGATATCAGGATGCCTGG AACTACGGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO.760
2.27	CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTA GTAGTGGTAGTACCATTTCCTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAACAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATCACTGTGCGAGAGAAGATATACGTATGAGTGG GACTACGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 761

2.28	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCATCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAGTTCCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATTTCGAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTAAGTGG AACTATAGATTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 762
2.29	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTGGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 763
2.30	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTA GTAGTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTGTGCCTGG AACTACGAACTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 764
2.31	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGACCTGGATGCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTG GCAGTGGTAGTACCATTGACTATGCAGACTCTGTGAAGGGCCGATTCACGATCTCCAGGGACAACGCCAAGAACTCACT GTACCTGCAAATGAACAGCCTGAGACCCGAGGACACGGCCGTGTATTACTGTGCGAAAGAAGATGGCCGTATACCTGG AACTACGGACTTTGACCACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 765
2.32	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCGGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTG GTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGACCGCTTCACCATCTCCAGGGACAACGCCAGGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGCCTGG AACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 766
2.33	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCCCCTTCAGTGACTACTTCATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAATTCCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTTTATTACTGTGCGAAAGAAGATCCTCGTTTACCTGGA ACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 767
2.34	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTCCTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACATATTAGTA ATTCTGGTAGTACCATAAGCTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTACCTGG AACTTCAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 768
2.35	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAGTTCCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATTTCGAGGGACAACGCCAAGAATTCACT GTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTAAGTGG AACTACAGATTTTGACCAGTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 769
2.36	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAGTACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACT GTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTATGACTGG AACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 770
2.37	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA

	TTCACCTTCAGTAACTACTTCATGAGTTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAGTA GTAGTGGTAATACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTCACT TTATCTGCAAATGGATAGTCTGAGAGCCGAGGACACGGCCGTTTATTACTGTTCGAGAGAAGATCCTCGTTTACCTGGA ACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 771
2.38	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACTTTCAGTGACTACTACATGACCTGGATCCGCCAGGGTCCAGGGAAGGGACAGGAATGGATTTCATACATTAGT AGTGGTGGTAGCACCATACACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAAATCCCCGTTTACCTGG AACTATGGACTTTGACTATTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO.772
2.39	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGA TTCACCTTCAGTGACCACTTCATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAAAA CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCA CTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATGTATTACTGTGCGAGAGAGGATCCTCGTTTAACTG GAACTACAGATTTTGACAACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 773
2.40	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGGCGGGGGGGTCCCTAAGACTCTCCTGTGTAGCCTCTGG ATTCACCTTTAGTAATTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGGTTTCACACATTAGT AGTACTGGATCTACCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCGAGAACTCAC TATATTTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCCCGTTTACCTGG AACTATGGACTTTGACTATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 774
2.41	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 775
2.42	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATT AGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAA CTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 776
2.43	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 777
2.44	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCCCGTCTA ACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 778
2.45	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCCCGTCTA ACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 779
2.46	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATT

	AGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAA CTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 780
2.47	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 781
2.48	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATT AGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAA CTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATGCCCGTC TAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 782
2.49	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATT AGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAA CTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCCCGTC TAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 783
2.50	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATGCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 784
2.51	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCCCGTCT AACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 785

In one embodiment, the nucleic acid sequence has at least 50% sequence homology to one of the sequences selected above. In one embodiment, said sequence homology is at least 50%, 60%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%. In one embodiment, the nucleic acid is selected from one SEQ ID Nos. 629, 706, 881, 882, 883, 884, 885, 886, 887 or 735.

Exemplary immunoglobulins included in the binding molecule and which bind PSMA

Examples of moieties for example, single variable heavy chain domain antibodies, that bind to PSMA and that may form one of the subunits of the binding molecules that bind to both, CD137 and PSMA, are described and can be used in the various embodiments of the invention.

The PSMA binding molecules bind to wild type human PSMA (UniProt Accession NO. Q04609). The sequence for the monomer is shown below (SEQ ID No. 842).

1 MWNLLHETDS AVATARRPRW LCAGALVLAG GFFLLGFLFG WFIKSSNEAT NITPKHNMKA

61 FLDELKAENI KKFLYNFTQI PHLAGTEQNF QLAKQIQSQW KEFGLDSVEL AHYDVLLSYP
121 NKTHPNYISI INEDGNEIFN TSLFEPPPPG YENVSDIVPP FSAFSPQGMP EGDLVYVNYA
181 RTEDFFKLER DMKINCSGKI VIARYGKVFR GNKVKNAQLA GAKGVILYSD PADYFAPGVK
241 SYPDGWNLPG GGVQRGNILN LNGAGDPLTP GYPANEYAYR RGIAEAVGLP SIPVHPIGY
301 DAQKLLEKMG GSAPPDSSWR GSLKVPYNVG PGFTGNFSTQ KVKMHIHSTN EVTRIYNVIG
361 TLRGAVEPDR YVILGGHRDS WVFGGIDPQS GAAVVHEIVR SFGTLKKEGW RPRRTILFAS
421 WDAEEFGLLG STEWAEENSR LLQERGVAYI NADSSIEGNY TLRVDCTPLM YSLVHNLTKE
481 LKSPDEGFEG KSLYESWTKK SPSPEFSGMP RISKLGSGND FEVFFQRLGI ASGRARYTKN
541 WETNKFSGYP LYHSVYETYE LVEKFYDPMF KYHLTVAQVR GGMVFELANS IVLPFDCRDY
601 AVVLRKYADK IYSISMKHPQ EMKTYSVSFD SLFSAVKNFT EIASKFSERL QDFDKSNPIV
661 LRMMNDQLMF LERAFIDPLG LPDRPFYRHV IYAPSSHNKY AGESFPGIYD ALFDIESKVD
721 PSKAWGEVKR QIYVAAFTVQ AAAETLSEVA

In one embodiment, the PSMA binding molecules of the invention bind to wild type human PSMA and/or cyno PSMA. The terms "PSMA binding molecule", “PSMA binding protein” “anti-PSMA single domain antibody” or “anti-PSMA antibody” as used herein all refer to a molecule capable of binding to the human PSMA antigen. The term "PSMA binding molecule" includes a PSMA binding protein. The binding reaction may be shown by standard methods (qualitative assays) including, for example, a binding assay, competition assay or a bioassay for determining the inhibition of PSMA binding to its receptor or any kind of binding assays, with reference to a negative control test in which an antibody of unrelated specificity. Suitable assays are shown in the examples.

A binding molecule of the invention, including a single domain antibody and multivalent or multispecific binding agent described herein, "which binds" or is “capable of binding” an antigen of interest, e.g. PSMA, is one that binds, i.e. targets, the PSMA antigen with sufficient affinity such that it is useful in therapy in targeting a cell or tissue expressing the antigen.

Exemplary sequences

A single V_H domain antibody that binds to PSMA may be as described in WO2017/122017 incorporated herein by reference. In one embodiment, the single variable heavy chain domain antibody comprises a CDR1 comprising SEQ ID NO. 812 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 813 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 814 or a sequence with at least 75% homology thereto. In one embodiment, the single variable heavy chain domain antibody comprises a CDR1 comprising SEQ ID NO. 837 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 838 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 839 or a sequence with at least 75% homology thereto.

Sequence homology can be 75, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology.

In one embodiment, the single variable heavy chain domain antibody comprises human framework regions. In one embodiment, the single variable heavy chain domain antibody is selected from single variable heavy chain domain antibody as shown in table 6 or 7, or from a sequence with at least 80% homology thereto. The PSMA binding entity can also be selected form a part thereof, such as a CDR3.

In one embodiment, the single variable heavy chain domain antibody comprises a sequence selected from SEQ ID NOs. 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, or 840. In one embodiment, the sequence is SEQ ID NO. 822 or from a sequence with at least 50%, 60%, 70% or 75% homology thereto. Sequence homology can be 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology. In one embodiment, the single variable heavy chain domain antibody comprises a sequence selected from SEQ ID NOs. 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, or 840 or a variant thereof, e.g. a variant with 1 to 10 or 1 to 20 substitutions.

Table 6a PSMA binding single V_H domain antibodies

Name	CDR1	CDR2	CDR3	SEQ ID full VH
3.1	SEQ ID NO. 812 SYAMS	SEQ ID NO. 813 SIGENDGTTDY ADSVKG	SEQ ID NO. 814 DGVH	SEQ ID NO. 815 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYAMSWV RQAPGKGLEWVSSIGENDGTTDYADSVKGRFTISRDN SKSMLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLV TVSS

Table 6b PSMA binding single V_H domain antibodies

Clone number	V_H Full length sequence
3.2	SEQ ID NO. 816 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADFVKGRFTISRDNSK NTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.3	SEQ ID NO. 817 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADNVKGRFTISRDNS KNTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.4	SEQ ID NO. 818 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYAADVKGRFTISRDNS KNTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.5	SEQ ID NO. 819 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADVVKGRFTISRDNS KNTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.6	SEQ ID NO. 820 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYAAFVKGRFTISRDNSK NTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS

3.7	SEQ ID NO. 821 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADTVKGRFTISRDNSK NTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.8	SEQ ID NO. 822 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNS KNTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.9	SEQ ID NO. 823 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYAASVKGRFTISRDNSK NTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.10	SEQ ID NO. 824 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYAAYVKGRFTISRDNSK NTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS
3.11	SEQ ID NO. 825 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYAATVKGRFTISRDNSK NTLYLQMNSLRVEDTAVYYCVKDGVHWGQGTLVTVSS

Table 7 PSMA binding single V_H domain antibody

4.1	SEQ ID NO. 837 GYGMH	SEQ ID NO. 838 YISYDGSN KYYADSVK G	SEQ ID NO. 839 DPAWGLRLGESS SYDFDI	SEQ ID NO. 840 EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQA PGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGT MVTVSS

In one embodiment, the variant comprises substitutions. Typical modifications are explained elsewhere herein.

Exemplary nucleic acids

Nucleic acids that encode the single domain antibodies shown above are set out below in table 7b.

3.1 SEQ ID NO. 826 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAGTATGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.2 SEQ ID NO. 827 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT AACGCTACCACAGACTACGCAGACTTCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.3 SEQ ID NO. 828 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.4 SEQ ID NO. 829 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGCCGACGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA

3.5 SEQ ID NO. 830 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACGTCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.6 SEQ ID NO. 831 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGCCTTCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.7 SEQ ID NO. 832 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACACCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.8 SEQ ID NO. 833 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.9 SEQ ID NO. 834 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGCCTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.10 SEQ ID NO. 835 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGCCTACGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
3.11 SEQ ID NO. 836 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGCCACCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCA
4.1 SEQ ID NO. 841 GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC TCCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATG GAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTC ATCGTCCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACTGTCTCTTCA

In one embodiment, the binding molecule may comprise one or more single domain antibodies that bind to PSMA, for example one or two single domain antibodies as described above.

In one embodiment, the binding molecule may comprise one or more single domain antibodies that bind to PSMA, for example one or two single domain antibodies as described above. In one embodiment the binding molecule comprises two single domain antibodies that bind to PSMA wherein each binds to a different epitope of PSMA hus providing a biparatopic PSMA binder.

Exemplary binding molecules

Any combination of the aforesaid single variable heavy chain domain antibodies that bind to CD137 and PSMA respectively can be used in a binding agent for dual engagement of CD137 and PSMA expressing cells. Thus, in one embodiment, any of the single variable heavy chain domain antibodies disclosed above, for example as listed in any of Tables 2 or 3 can be combined in a fusion protein with any of the single variable heavy chain domain antibodies as listed in any of Tables 6a, 6b or 7.

Thus, in one embodiment, the fusion protein comprises a single domain antibody having a sequence selected from SEQ ID Nos 4, 8, 12, 16, 20, 24, 28, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 272, 276, 280, 284, 288, 292, 296, 300, 304, 308, 312, 316, 320, 324, 328,332, 336, 340, 344, 448, 352, 356, 360, 364, 368, 372, 376, 380, 384, 388, 392, 396, 400, 404, 408, 412, 416, 420, 424, 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 75% homology thereto and a single domain antibody having a sequence selected from SEQ ID Nos 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825 or 840 or a sequence with at least 75% homology thereto. In one embodiment, the sequence is selected from SEQ ID Nos 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 75% homology thereto.

In another embodiment, the fusion protein comprises a single domain antibody having a sequence selected from SEQ ID Nos 428, 432, 436, 440, 444, 448, 452, 456, 460, 464, 468, 472, 476, 480, 484, 488, 492, 496, 500, 508, 512, 516, 520, 524, 528, 532, 536, 540, 544, 548, 552, 556, 560, 564, 568, 572, 576, 580, 584, 588, 592, 596, 600,604, 608, 612, 616, 620, 624 or 628 or a sequence with at least 75% homology thereto and a single domain antibody having a sequence selected from SEQ ID Nos 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825 or 840 or a sequence with at least 75% homology thereto. In one embodiment, a single domain antibody 1.1 or 2.1 having SEQ ID No. 4 or 428 or a single domain antibody having SEQ ID No. 312, 852, 856, 860, 864, 868, 872, 876, 880 or 428 is linked to a single domain antibody 3.1, 3.8 or 4.1 having SEQ ID No. 815, 822 or 840 respectively. In one embodiment, a single domain 1.113 having SEQ ID No. 876 is linked to a single domain antibody 3.1, 3.8 or 4.1 having SEQ ID No. 815, 822 or 840 respectively. In one embodiment, a single domain 1.113 having SEQ ID No. 876 is linked to a single domain antibody 4.1 having SEQ ID No. 840. In one embodiment, the fusion protein comprises or consists of single domain antibody 1.113 linked to single domain antibody 4.1 or 3.8 and single domain antibody as shown in SEQ ID No. 901. The order of the single domain antibodies can vary, for example the CD137 binding single domain antibody can located be 3' or 5' of the PSMA binding

molecule. The single domain antibody as shown in SEQ ID No. 901 is preferably located at the C terminal end.

The two single domain antibodies can be linked in the fusion protein with a peptide linker, such as a G4S linker as described herein. In one embodiment the invention relates to one of the fusion proteins and nucleic acids encoding such fusion proteins as listed in table 8 below (i.e. selected from one of the protein and (i.e. selected from one of the protein and nucleic acid constructs of SEQ ID NO. 806-811) or fusion proteins and nucleic acids encoding such fusion proteins as listed in table 10 in the examples (i.e. selected from one of the protein and nucleic acid constructs of SEQ ID NO. 889-900). In one embodiment, the protein comprises the single domain antibodies defined as 4.1 or 1.113 as described herein linked with a (G4S)n peptide linker wherein n is as defined herein, e.g. 1, 2,3, 4, 5, 6, 7, 8, 9 or 10 (i.e. 4.1-(G4S)n-1.113). In one embodiment, the protein is selected from SEQ ID Nos. 844, 846, 890 or 894. In one embodiment, the protein comprises or consists of SEQ ID NO. 890 optionally including a HSA binding sdAb. In one embodiment, the protein is encoded by the nucleic acid sequence of SEQ ID NO. 891.

Table 8

SEQ ID NO: 806 4.1(PSMA-binding VH)-6GS-1.1 Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG LVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYY CARGGDGYSDSHFGVDVWGQGTTVTVSS
SEQ ID NO: 807 4.1(PSMA-binding VH)-6GS-1.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGG GGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTT GGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACT CTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGAC ACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCA CGGTCACTGTCTCTTCA
SEQ ID NO: 808 4.1(PSMA-binding VH)-6GS-2.1 EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG LVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCA REDSRLTGTTDFDNWGQGTLVTVSS
SEQ ID NO: 809 4.1(PSMA-binding VH)-6GS-2.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGG GGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCT GGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCT GTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACAC GGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCA CCGTCTCCTCA

SEQ ID NO: 810 Protein 3.8-6GS-1.1 EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNSLR VEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG FTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCARGGDGYSDSHFGV DVWGQGTTVTVSS
SEQ ID NO: 811 3.8-6GS-1. Nucleotide GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA GTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAATGAT GGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGCAAAT GAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGA TCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCC TGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGC CCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAG AACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACA GTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA

Exemplary modifications of the binding molecule

In one embodiment, a binding agent described above comprises further binding molecules. Thus, the binding agent can, for example, be trispecific or tetraspecific.

In one embodiment, the binding molecule comprises a first V_H single domain antibody that binds to CD137 (V_H (A)) and a second moiety, for example a V_H single domain antibody, that binds to PSMA (V_H (B)). It further comprises a third, fourth, fifth etc moiety, for example a V_H single domain antibody (i.e. V_H (C), V_H (D), V_H (E)) that binds to another antigen. Thus, in one embodiment, the binding molecule has the following formula (wherein V_H stands for a single domain antibody as defined herein, that is the single V_H domain that does not comprise other parts of a full antibody and retains binding to the antigen): V_H (A)-L- V_H (B)-L-V_H (X)n wherein X denotes a V_H binding to a target other than the target V_H (A) and V_H (B) bind to and wherein X is 1 to 10, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. L denotes a linker, for example a peptide linker. As explained elsewhere, a moiety that binds to PSMA or another target can be selected from an antibody or fragment thereof or other polypeptide.

In another embodiment, the further moiety may serve to prolong the half-life of the binding molecule. The further moiety may comprise a protein, for example a peptide, antibody, or part thereof, such as a V_H or CDR, that binds a serum albumin, e.g., human serum albumin (HSA) or mouse serum albumin (MSA). In one embodiment, the further moiety may comprise a V_H domain that binds serum albumin, e.g., human serum albumin (HSA) or mouse serum albumin (MSA). In one embodiment, the V_H domain that binds HSA is SEQ ID NO. 901 or a sequence with at least 90% sequence homology thereto. The further moiety may comprise a serum albumin, e.g. a HSA or a variant thereof such as HSA C34S. Further provided is a binding molecule as described herein comprising a V_H domain and an Fc domain, e.g., wherein the V_H domain is fused to an Fc domain.

The term "half-life" as used herein refers to the time taken for the serum concentration of the amino acid sequence, compound or polypeptide to be reduced by 50%, in vivo, for example due to degradation of the

sequence or compound and/or clearance or sequestration of the sequence or compound by natural mechanisms. Half-life may be increased by at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding V_H single domain antibodies of the invention. For example, increased half-life may be more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding V_H single domain antibodies or fusion protein of the invention. The in vivo half-life of an amino acid sequence, compound or polypeptide of the invention can be determined in any manner known per se, such as by pharmacokinetic analysis. Suitable techniques will be clear to the person skilled in the art. Half life can for example be expressed using parameters such as the t1/2-alpha t1/2-beta and the area under the curve (AUC).

In one embodiment, the binding agents are labelled with a detectable or functional label. A label can be any molecule that produces or can be induced to produce a signal, including but not limited to fluorophores, fluorescers, radiolabels, enzymes, chemiluminescers, a nuclear magnetic resonance active label or photosensitizers. Thus, the binding may be detected and/or measured by detecting fluorescence or luminescence, radioactivity, enzyme activity or light absorbance.

In still other embodiments binding agents are coupled to at least one therapeutic moiety, such as a drug, an enzyme or a toxin. In one embodiment, the therapeutic moiety is a toxin, for example a cytotoxic radionuclide, chemical toxin or protein toxin.

In another aspect, the binding agents of the invention are modified to increase half-life, for example by a chemical modification, especially by PEGylation, or by incorporation in a liposome or using a serum albumin protein. Increased half life can also be conferred by conjugating the molecule to a n antibody fragment, for example a V_H domain that increases half life.

To generate multivalent binding agents as described above, two binding molecules can be connected by a linker, for example a polypeptide linker. Suitable linkers include for example a linker with GS residues such as (Gly4Ser)n, where n=from 1 to 10 or more, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and specific sequences of examples are provided elsewhere.

Exemplary methods for making single domain antibody and binding molecules

A single domain antibody described herein for use in the multispecifc molecule can be obtained from a transgenic rodent that expresses heavy chain only antibodies upon stimulation with a CD137 or PSMA antigen respectively. The transgenic rodent, for example a mouse, preferably has a reduced capacity to express endogenous antibody genes. Thus, in one embodiment, the rodent has a reduced capacity to express endogenous light and/or heavy chain antibody genes. The rodent may therefore comprise modifications to disrupt expression of endogenous kappa and lambda light and/or heavy chain antibody genes so that no functional light and/or heavy chains are produced, for example as further explained below.

A method for producing a human heavy chain only antibody capable of binding the target antigen comprises

a) immunising a transgenic rodent, e.g. a mouse, with target antigen (i.e. PSMA or CD137) wherein said rodent expresses a nucleic acid construct comprising unrearranged human heavy chain V genes and is not capable of making functional endogenous light or heavy chains,
b) isolating human heavy chain only antibodies.

Further steps can include isolating a V_H domain from said heavy chain only antibody, for example by generating a library of sequences comprising V_H domain sequences from said rodent, e.g. mouse, and isolating sequences comprising V_H domain sequences from said libraries.

A method for producing a single V_H domain antibody capable of binding to the target antigen comprises

a) immunising a transgenic rodent, e.g. a mouse with a target antigen wherein said rodent, e.g. mouse, expresses a nucleic acid construct comprising unrearranged human heavy chain V genes and is not capable of making functional endogenous light or heavy chains,
b) generating a library of sequences comprising V_H domain sequences from said rodent, e.g. mouse, and
c) isolating sequences comprising V_H domain sequences from said libraries.

Further steps may include identifying a single V_H domain antibody or heavy chain only antibody that binds to the target antigen, for example by using functional assays as shown in the examples.

Methods for preparing or generating the polypeptides, nucleic acids, host cells, products and compositions described herein using in vitro expression libraries can comprise the steps of:

a) providing a set, collection or library of nucleic acid sequences encoding amino acid sequences; and

b) screening said set, collection or library for amino acid sequences that can bind to / have affinity for the target antigen and

c) isolating the amino acid sequence(s) that can bind to / have affinity for target antigen.

In the above method, the set, collection or library of amino acid sequences may be displayed on a phage, phagemid, ribosome or suitable micro-organism (such as yeast), such as to facilitate screening. Suitable methods, techniques and host organisms for displaying and screening (a set, collection or library of) amino acid sequences will be clear to the person skilled in the art (see for example Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press; 1st edition (October 28, 1996) Brian K. Kay, Jill Winter, John McCafferty).

Libraries, for example phage libraries, are generated by isolating a cell or tissue expressing an antigen-specific, heavy chain-only antibody, cloning the sequence encoding the V_H domain(s) from mRNA derived from the isolated cell or tissue and displaying the encoded protein using a library. The V_H domain(s) can be expressed in bacterial, yeast or other expression systems.

In the various aspects and embodiments as out herein, the term rodent may relate to a mouse or a rat. In one embodiment, the rodent is a mouse. The mouse may comprise a non-functional endogenous lambda light chain locus. Thus, the mouse does not make a functional endogenous lambda light chain. In one embodiment, the lambda light chain locus is deleted in part or completely or rendered non-functional through insertion, inversion, a recombination event, gene editing or gene silencing. For example, at least the constant region genes C1, C2 and C3 may be deleted or rendered non-functional through insertion or other modification as described above. In one embodiment, the locus is functionally silenced so that the mouse does not make a functional lambda light chain.

Furthermore, the mouse may comprise a non-functional endogenous kappa light chain locus. Thus, the mouse does not make a functional endogenous kappa light chain. In one embodiment, the kappa light chain locus is deleted in part or completely or rendered non-functional through insertion, inversion, a recombination event, gene editing or gene silencing. In one embodiment, the locus is functionally silenced so that the mouse does not make a functional kappa light chain.

The mouse having functionally-silenced endogenous lambda and kappa L-chain loci may, for example, be made as disclosed in WO 2003/000737, which is hereby incorporated by reference in its entirety.

Furthermore, the mouse may comprise a non-functional endogenous heavy chain locus. Thus, the mouse does not make a functional endogenous heavy chain. In one embodiment, the heavy chain locus is deleted in part or completely or rendered non-functional through insertion, inversion, a recombination event, gene editing or gene silencing. In one embodiment, the locus is functionally silenced so that the mouse does not make a functional heavy chain.

For example, as described in WO 2004/076618 (hereby incorporated by reference in its entirety), all 8 endogenous heavy chain constant region immunoglobulin genes (μ, δ, $\gamma3$, $\gamma1$, $\gamma2a$, $\gamma2b$, ε and α) are absent in the mouse, or partially absent to the extent that they are non-functional, or genes δ, $\gamma3$, $\gamma1$, $\gamma2a$, $\gamma2b$ and ε are absent and the flanking genes μ and α are partially absent to the extent that they are rendered non-functional, or genes μ, δ, $\gamma3$, $\gamma1$, $\gamma2a$, $\gamma2b$ and ε are absent and α is partially absent to the extent that it is rendered non-functional, or δ, $\gamma3$, $\gamma1$, $\gamma2a$, $\gamma2b$, ε and α are absent and μ is partially absent to the extent that it is rendered non-functional. By deletion in part is meant that the endogenous locus gene sequence has been deleted or disrupted, for example by an insertion, to the extent that no functional endogenous gene product is encoded by the locus, *i.e.*, that no functional product is expressed from the locus. In another embodiment, the locus is functionally silenced.

In one embodiment, the mouse comprises a non-functional endogenous heavy chain locus, a non-functional endogenous lambda light chain locus and a non-functional endogenous kappa light chain locus. The mouse therefore does not produce any functional endogenous light or heavy chains. Thus, the mouse is a triple knockout (TKO) mouse.

The transgenic mouse may comprise a vector, for example a Yeast Artificial Chromosome (YAC) for expressing a heterologous, preferably a human, heavy chain locus. YACs are vectors that can be employed for the cloning of very large DNA inserts in yeast. As well as comprising all three cis-acting structural elements essential for behaving like natural yeast chromosomes (an autonomously replicating sequence (ARS), a centromere (CEN) and two telomeres (TEL)), their capacity to accept large DNA inserts enables them to reach the minimum size (150 kb) required for chromosome-like stability and for fidelity of transmission in yeast cells. The construction and use of YACs is well known in the art (*e.g.*, Bruschi, C.V. and Gjuracic, K. Yeast Artificial Chromosomes, Encyclopedia of Life Sciences, 2002 Macmillan Publishers Ltd, Nature Publishing Group).

For example, the YAC may comprise a plethora of unrearranaged human V_H, D and J genes in combination with mouse immunoglobulin constant region genes lacking C_H1 domains, mouse enhancer and regulatory regions. The human V_H, D and J genes are human V_H, D and J loci and they are unrearranged genes that are fully human.

Alternative methods known in the art may be used for deletion or inactivation of endogenous mouse or rat immunoglobulin genes and introduction of human V_H, D and J genes in combination with mouse immunoglobulin constant region genes lacking C_H1 domains, mouse enhancer and regulatory regions.

Transgenic mice can be created according to standard techniques as illustrated in the examples. The two most characterised routes for creating transgenic mice are via pronuclear microinjection of genetic material into freshly fertilised oocytes or via the introduction of stably transfected embryonic stem cells into morula or blastocyst stage embryos. Regardless of how the genetic material is introduced, the manipulated embryos are transferred to pseudo-pregnant female recipients where pregnancy continues and candidate transgenic pups are born. The main differences between these broad methods are that ES clones can be screened extensively before their use to create a transgenic animal. In contrast, pronuclear microinjection relies on the genetic material integrating to the host genome after its introduction and, generally speaking, the successful incorporation of the transgene cannot be confirmed until after pups are born.

There are many methods known in the art to both assist with and determine whether successful integration of transgenes occurs. Transgenic animals can be generated by multiple means including random integration of the construct into the genome, site-specific integration, or homologous recombination. There are various tools and techniques that can be used to both drive and select for transgene integration and

subsequent modification including the use of drug resistance markers (positive selection), recombinases, recombination-mediated cassette exchange, negative selection techniques, and nucleases to improve the efficiency of recombination. Most of these methods are commonly used in the modification of ES cells. However, some of the techniques may have utility for enhancing transgenesis mediated via pronuclear injection.

Further refinements can be used to give more efficient generation of the transgenic line within the desired background. As described above, in preferred embodiments, the endogenous mouse immunoglobulin expression is silenced to permit sole use of the introduced transgene for the expression of the heavy-chain only repertoire that can be exploited for drug discovery. Genetically-manipulated mice, for example TKO mice that are silenced for all endogenous immunoglobulin loci (mouse heavy chain, mouse kappa chain and mouse lambda chain) can be used as described above. The transfer of any introduced transgene to this TKO background can be achieved via breeding, either conventional or with the inclusion of an IVF step to give efficient scaling of the process. However, it is also possible to include the TKO background during the transgenesis procedure. For example, for microinjection, the oocytes may be derived from TKO donors. Similarly, ES cells from TKO embryos can be derived for use in transgenesis.

Triple knock-out mice into which transgenes have been introduced to express immunoglobulin loci are referred to herein as TKO/Tg. In one embodiment, the mouse is as described in WO2016/062990.

Fusion proteins as described herein can be generated by linking a nucleic acid encoding a single variable heavy chain domain antibody that binds to CD137 to a nucleic acid encoding a single variable heavy chain domain antibody that binds to PSMA, for example using a nucleic acid sequence that encodes a peptide linker. Such fusion nucleic acid molecules are then expressed in suitable host cells.

Exemplary therapeutic applications of the binding molecules

In another aspect, there is provided a pharmaceutical composition comprising a binding molecule as described herein and optionally a pharmaceutically acceptable carrier. A binding molecule as described herein or the pharmaceutical composition of the invention can be administered by any convenient route, including but not limited to oral, topical, parenteral, sublingual, rectal, vaginal, ocular, intranasal, pulmonary, intradermal, intravitreal, intramuscular, intraperitoneal, intravenous, subcutaneous, intracerebral, transdermal, transmucosal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin or by inhalation.

Parenteral administration includes, for example, intravenous, intramuscular, intraarterial, intraperitoneal, intranasal, rectal, intravesical, intradermal, topical or subcutaneous administration. Preferably, the compositions are administered parenterally.

The pharmaceutically acceptable carrier or vehicle can be particulate, so that the compositions are, for example, in tablet or powder form. The term "carrier" refers to a diluent, adjuvant or excipient, with which a

drug antibody of the present invention is administered. Such pharmaceutical carriers can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The carriers can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents can be used. In one embodiment, when administered to an animal, the single domain antibody of the present invention or compositions and pharmaceutically acceptable carriers are sterile. Water is a preferred carrier when the drug antibody of the present invention are administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical carriers also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The pharmaceutical composition of the invention can be in the form of a liquid, *e.g.*, a solution, emulsion or suspension. The liquid can be useful for delivery by injection, infusion (*e.g.*, IV infusion) or sub-cutaneously.

When intended for oral administration, the composition is preferably in solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the composition can be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition typically contains one or more inert diluents. In addition, one or more of the following can be present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, corn starch and the like; lubricants such as magnesium stearate; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin; a flavoring agent such as peppermint, methyl salicylate or orange flavoring; and a coloring agent. When the composition is in the form of a capsule (e. g. a gelatin capsule), it can contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol, cyclodextrin or a fatty oil.

The composition can be in the form of a liquid, e. g. an elixir, syrup, solution, emulsion or suspension. The liquid can be useful for oral administration or for delivery by injection. When intended for oral administration, a composition can comprise one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition for administration by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent can also be included.

Compositions can take the form of one or more dosage units.

In specific embodiments, it can be desirable to administer the composition locally to the area in need of treatment, or by intravenous injection or infusion.

The amount of the therapeutic that is effective/active in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account.

Typically, the amount is at least about 0.01% of a single domain antibody of the present invention by weight of the composition. When intended for oral administration, this amount can be varied to range from about 0.1 % to about 80% by weight of the composition. Preferred oral compositions can comprise from about 4% to about 50% of the single domain antibody of the present invention by weight of the composition.

Preferred compositions of the present invention are prepared so that a parenteral dosage unit contains from about 0.01 % to about 2% by weight of the single domain antibody of the present invention. The invention also relates to a device, such as a pre-filled syringe which comprises a binding molecule of the invention.

For administration by injection, the composition can comprise from about typically about 0.1 mg/kg to about 250 mg/kg of the subject's body weight, preferably, between about 0.1 mg/kg and about 20 mg/kg of the subject's body weight, and more preferably about 1 mg/kg to about 10 mg/kg of the subject's body weight. In one embodiment, the composition is administered at a dose of about 1 to 30 mg/kg, e.g., about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. The dosing schedule can vary from e.g., once a week to once every 2, 3, or 4 weeks.

As used herein, "treat", "treating" or "treatment" means inhibiting or relieving a disease or disorder. For example, treatment can include a postponement of development of the symptoms associated with a disease or disorder, and/or a reduction in the severity of such symptoms that will, or are expected, to develop with said disease. The terms include ameliorating existing symptoms, preventing additional symptoms, and ameliorating or preventing the underlying causes of such symptoms. Thus, the terms denote that a beneficial result is being conferred on at least some of the mammals, e.g., human patients, being treated. Many medical treatments are effective for some, but not all, patients that undergo the treatment.

The term "subject" or "patient" refers to an animal which is the object of treatment, observation, or experiment. By way of example only, a subject includes, but is not limited to, a mammal, including, but not

limited to, a human or a non-human mammal, such as a non-human primate, murine, bovine, equine, canine, ovine, or feline.

As used herein, the term "effective amount" means an amount of the binding molecule as described herein, that when administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, is effective to achieve the desired therapeutic or prophylactic effect under the conditions of administration.

The invention furthermore relates to a method for the prevention and/or treatment of cancer, in particular prostate cancer, comprising administering a binding molecule of the invention to a subject, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a binding molecule and/or of a pharmaceutical composition of the invention. In particular, the invention relates to a method for the prevention and/or treatment of cancer, in particular prostate cancer, said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a binding molecule or a pharmaceutical composition of the invention.

The invention also relates to a binding molecule of the invention for use in the treatment of a disease. The invention also relates to a binding molecule of the invention for use in the treatment of cancer, in particular prostate cancer or a prostatic disorder. "Prostate cancer" refers to all stages and all forms of cancer arising from the tissue of the prostate gland. The invention also relates to the treatment of a disease characterized by aberrant expression of PSMA.

In another aspect, the invention relates to the use of a binding molecule of the invention in the treatment of disease. In another aspect, the invention relates to the use of a binding molecule of the invention in the manufacture of a medicament for the treatment of cancer, such as prostate cancer or a prostatic disorder.

The binding molecules of the invention are also useful for the treatment, prevention, or amelioration of a disease. In one embodiment, the disease is associated with PSMA positive cells. In one embodiment, the disease is cancer. In one embodiment, the cancer associated with a PSMA positive tumor.

Expression of PSMA has been detected in other cancers, more specifically in the neovasculature associated with these cancers. A wide range of carcinomas, including conventional (clear cell) renal cell, transitional cell of the bladder, testicular-embryonal, neuroendocrine, colon, and breast, and the different types of malignancies were found consistently and strongly to express PSMA in their neovasculature. In one embodiment, the cancer to be treated is selected from a tumor in the neovasculature that expresses PSMA, for example selected from renal, bladder, testicular, neuroendocrine, colon, and breast cancer.

In one aspect, the cancer is locally advanced unresectable, metastatic, or recurrent cancer.

In one embodiment, the cancer is selected from the following non limiting list: prostate cancer, lung cancer or glioblastoma. In one embodiment, the disease is a prostatic disorder which refers to any disease that afflicts the prostate gland in the male reproductive system. The prostate gland is dependent on the hormonal secretions of the testes.

The binding molecule of the invention may be administered as the sole active ingredient or in combination with one or more other therapeutic and/or cytotoxic moiety. In one embodiment, the binding molecule may be conjugated to a toxic moiety.

In one embodiment, the single domain antibody is used in combination with surgery.

Exemplary combinations with other agents

The molecules or pharmaceutical composition of the invention, including monovalent or multivalent molecules, may be administered as the sole active ingredient or in combination with one or more other therapeutic agent. A therapeutic agent is a compound or molecule which is useful in the treatment of a disease. Examples of therapeutic agents include antibodies, antibody fragments, drugs, toxins, nucleases, hormones, immunomodulators, pro-apoptotic agents, anti-angiogenic agents, boron compounds, photoactive agents or dyes and radioisotopes. An antibody molecule includes a full antibody or fragment thereof (e.g., a Fab, F(ab')2, Fv, a single chain Fv fragment (scFv) or a single domain antibody, for example a V_H domain, antibody mimetic protein or a protein that mimics the natural ligand of CD137.

The anti-cancer therapy may include a therapeutic agent or radiation therapy and includes gene therapy, viral therapy, RNA therapy bone marrow transplantation, nanotherapy, targeted anti-cancer therapies or oncolytic drugs. Examples of other therapeutic agents include other checkpoint inhibitors, antineoplastic agents, immunogenic agents, attenuated cancerous cells, tumor antigens, antigen presenting cells such as dendritic cells pulsed with tumor-derived antigen or nucleic acids, immune stimulating cytokines (e.g., IL-2, IFNa2, GM-CSF), targeted small molecules and biological molecules (such as components of signal transduction pathways, e.g. modulators of tyrosine kinases and inhibitors of receptor tyrosine kinases, and agents that bind to tumor- specific antigens, including EGFR antagonists), an anti-inflammatory agent, a cytotoxic agent, a radiotoxic agent, or an immunosuppressive agent and cells transfected with a gene encoding an immune stimulating cytokine (e.g., GM-CSF), chemotherapy. In one embodiment, administration is in combination with surgery. The binding molecule of the invention may be administered at the same time or at a different time as the other therapy, *e.g.*, simultaneously, separately or sequentially.

Exemplary methods for modulating immune response, inhibiting tumor growth etc

In yet another aspect, there is provided a method of modulating an immune response in a subject comprising administering to the subject the binding molecule or pharmaceutical composition described

herein such that the immune response in the subject is modulated. Preferably, the binding molecule enhances, stimulates or increases the immune response in the subject.

In a further aspect, there is provided a method of inhibiting growth of tumor cells or promoting tumor regression in a subject, comprising administering to a subject a therapeutically effective amount of a binding molecule or a pharmaceutical composition described herein.

In a further aspect, there is provided a method for activating the downstream signalling pathway of CD137 comprising administering to a subject a binding molecule or a pharmaceutical composition described herein.

In a further aspect, there is provided a method for inducing T lymphocyte activation and /or proliferation comprising administering to a subject a binding molecule or a pharmaceutical composition described herein.

In a further aspect, there is provided a method for dual targeting of a CD137 expressing cell and a tumor antigen, i.e. PSMA, expressing cell comprising administering to a subject a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or a pharmaceutical composition described herein.

In a further aspect, there is provided a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or a pharmaceutical composition described herein for dual targeting of a CD137 expressing cell and a tumor antigen, i.e. PSMA, expressing cell. For example, the binding molecule comprises a single variable heavy chain domain antibody that binds to CD137 described herein and a single variable heavy chain domain antibody that binds to PSMA described herein

Exemplary immunoconjugates

In another aspect, there is provided an immunoconjugate comprising a binding molecule described herein conjugated to at least one therapeutic and/or diagnostic agent i.e. an imagining agent.

Exemplary kits

In another aspect, the invention provides a kit for detecting prostate cancer for diagnosis, treatment, prognosis or monitoring comprising a binding molecule of the invention. The kit may also comprise instructions for use. The kits may include a labeled binding molecule of the invention as described above and one or more compounds for detecting the label. Also provided is a binding molecule of the invention packaged in lyophilized form, or packaged in an aqueous medium. The kits may include reagent, (e.g. for reconstituting) and / or instructions for use and/or a device for administration.

Exemplary non-therapeutic applications

The invention also relates to detection methods using the binding molecule of the invention. Given their ability to bind to human PSMA, the human-PSMA-binding molecules as disclosed herein can be used to detect PSMA (*e.g.*, in a biological sample, such as serum or plasma), using a conventional immunoassay, such as an enzyme linked immunosorbent assays (ELISA), an radioimmunoassay (RIA) or tissue immunohistochemistry. In particular, the invention also relates to *in vitro* or *in vivo* methods for diagnosing

or monitoring progression of a cancer, in particular prostate cancer. *In vitro* methods comprise detecting the presence of a PSMA protein in a test sample and comparing this with control sample from a normal subject or with a standard value or standard value range for a normal subject. The sample may be selected from blood, plasma, serum, semen, urine or a tissue biopsy.

The method may include: (a) contacting the sample (and optionally, a reference, *e.g.*, a positive and/ or negative control sample) with a PSMA binding molecule of the invention and (b) detecting either the binding molecule bound to PSMA or unbound binding molecule in the sample, to thereby detect PSMA in the biological sample. The binding molecule can be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials.

In vivo methods may comprise detecting the presence of PSMA *in vivo*, for example by imaging in a subject. In this method, a PSMA binding molecule of the invention is labeled to detect binding. A labelled molecule of the invention may thus be used as an imaging agent.

As an alternative to labeling the binding molecule of the invention, human PSMA can be assayed in biological fluids by a competition immunoassay utilizing PSMA standards labeled with a detectable substance and an unlabeled human PSMA binding molecule. In this assay, the biological sample, the labeled PSMA standards and the human PSMA binding molecule are combined and the amount of labeled PSMA standard bound to the unlabeled binding molecule is determined. The amount of human PSMA in the biological sample is inversely proportional to the amount of labeled PSMA standard bound to the PSMA binding molecule. Similarly, human PSMA can also be assayed in biological fluids by a competition immunoassay utilizing PSMA standards labeled with a detectable substance and an unlabeled human PSMA binding molecule.

Binding molecules disclosed herein can be used to inhibit PSMA activity, *e.g.*, in a cell culture containing PSMA, in human subjects or in other mammalian subjects having PSMA with which a binding molecule disclosed herein cross-reacts. In one embodiment, a method for inhibiting or increasing PSMA activity is provided comprising contacting PSMA with a binding molecule disclosed herein such that PSMA activity is inhibited or increased. For example, in a cell culture containing, or suspected of containing PSMA, a binding molecule disclosed herein can be added to the culture medium to inhibit PSMA activity in the culture.

Therefore, in one embodiment, the invention also relates to a method of ablating or killing a cell that expresses PSMA, *e.g.*, a cancerous or non-cancerous prostatic cell. Methods of the invention include contacting the cell, with PSMA binding molecule of the invention, in an amount sufficient to ablate or kill the cell. The methods can be used on cells in culture, *e.g.*, *in vitro* or *ex vivo*.

Also provided is a binding molecule or pharmaceutical composition described herein with reference to the figures and examples. Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. While the foregoing disclosure provides a general description of the subject matter encompassed within the scope of the present disclosure, including methods, as well as the best mode thereof, of making and using this disclosure, the following examples are provided to further enable those skilled in the art to practice this disclosure. However, those skilled in the art will appreciate that the specifics of these examples should not be read as limiting on the invention, the scope of which should be apprehended from the claims and equivalents thereof appended to this disclosure. Various further aspects and embodiments of the present disclosure will be apparent to those skilled in the art in view of the present disclosure.

All documents mentioned in this specification are incorporated herein by reference in their entirety, including references to gene accession numbers, scientific publications and references to patent publications.

"and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example "A and/or B" is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein. Unless context dictates otherwise, the descriptions and definitions of the features set out above are not limited to any particular aspect or embodiment of the invention and apply equally to all aspects and embodiments which are described.

The invention is now further described in the non-limiting examples.

EXAMPLES

EXAMPLE 1. Isolation of Humabody® V_H specific for CD137 and PSMA

Humabody® V_H specific for CD137 or PSMA were generated by immunisation of the Crescendo's proprietary transgenic mouse that has silenced murine immunoglobulin loci and a transgene containing human heavy chain antibody genes.

Mice carrying a human heavy-chain antibody transgenic locus in germline configuration within a background that is silenced for endogenous heavy and light chain antibody expression (triple knock-out, or TKO) were created as previously described (WO2004/076618, WO2003/000737, Ren *et al.*, Genomics, 84, 686, 2004; Zou *et al.*, J. Immunol., 170, 1354, 2003 and WO2016/062990). Briefly, transgenic mice were derived following pronuclear microinjection of freshly fertilised oocytes with a yeast artificial chromosome (YAC) comprising a plethora of human V_H, D and J genes in combination with mouse immunoglobulin constant region genes lacking C_H1 domains, mouse enhancer and regulatory regions. The

YAC used comprised multiple human heavy chain V genes, multiple human heavy chain D and J genes, a murine C_H1 gene and a murine 3' enhancer gene. It lacks the C_H1 exon.

Mice were immunised with recombinant human CD137 or PSMA proteins. At the end of the immunisation schedule, lymph nodes and spleens were harvested for RNA extraction. Heavy chain variable domains (V_H) sequences were amplified by PCR and cloned into a phagemid vector. Standard phage display techniques were used to isolate the V_H that bound to the target proteins, including generation of libraries from immunised mice described above followed standard protocols of library generation, standard screening procedures of bacterial periplasmic extracts, optimisation, sequencing and purification methods. Amino acid and nucleic acid sequences for clones 1.1, 2.1, 3.1 and 4.1 are shown in tables 2, 3, 5, 6 and 7.

For example, the PSMA-binding subunit may be generated as disclosed in WO2017/122017. For the generation of VH that bind CD137 Tg/TKO mice aged 8-12 weeks were immunised with human CD137-human Fc chimeric protein (Acro Biosystems cat no. 41B-H5258), human CD137-His tagged protein (R&D Systems, custom product), CHO cells over-expressing human CD137 (cell line produced in-house using standard methods) or a combination of recombinant protein and CHO human CD137 expressing cells. Serum was then collected from mice before and after immunisation and checked by ELISA for the presence of serum human CD137 reactive heavy chain antibodies in response to immunisation with CD137 antigen.

Generation of libraries from immunised mice described above followed standard protocols of library generation as summarised below. Tissue, including total spleen, inguinal and brachial lymph nodes was collected into RNAlater® from several immunised mice. Total RNA was extracted from supernatants and V_H sequences were mined from the RNA samples using Superscript III RT-PCR high-fidelity kit (Invitrogen cat. no. 12574-035) according to the manufacturer's protocol. Preparation of library phage stocks and phage display selections were performed according to published methods (Antibody Engineering, edited by Benny Lo, chapter 8, p161-176, 2004). In most cases, phage display combined with a panning approach was used to isolate binding V_H domains. However, a variety of different selection methods are well described in the art, including soluble protein selections, cell based selections and selections performed under stress (e.g., heat). Following selections of the libraries, specific V_H that bound to CHO cells expressing human CD137, did not bind to CHO parental cells and inhibited the interaction between human CD137 expressed on the surface of CHO cells and recombinant human CD137 Ligand protein were identified by single point screening of bacterial periplasmic extracts. Binding of His-tagged V_H in the supernatants to CHO human CD137 cells and to CHO parent cells for determination of non CD137 specific binding was assessed using Fluorescence Microvolume Assay Technology (FMAT). In parallel to the binding assay, periplasmic extracts were tested for their ability to inhibit the interaction of human CD137 ligand protein with CHO human CD137 cells in an FMAT format. Families of V_H were identified that bound to the CHO human CD137 cells, did not bind CHO parental cells and that inhibited CD137 binding to CD137 Ligand. Each individual V_H clone as identified above was sequenced from the phagemid and grouped based on V_H germline and CDR3 amino acid similarity. Representative clones were further characterised. Further clones were generated by sequence optimisation of clone Humabody® V_H 1.1 and

Humabody® V_H 2.1 respectively to improve binding activity, revert sequence to germline or remove biophysical sequence liabilities such as isomerisation or deamidation sites. Purified V_H were obtained by using standard procedures. Table 2 shows the sequences of Family 1 V_Hs and table 3 those of Family 2 V_Hs.

Purified Humabody® V_H were tested for binding to human CD137 protein, rhesus CD137Fc recombinant protein, mouse CD137 protein, tumour necrosis factor receptor family members OX40 and GITR (Glucocorticoid-induced TNFR-related), CHO human CD137 cells, CHO parent cells and human T- cells. VH bound to human and rhesus CD137 but not to mouse CD137 protein. Binding of serially diluted V_H to CHO human CD137 cells and CHO parent cells were performed using an FMAT assay format. V_H bound to CHO human CD137 expressing cells but did not bind to CHO parental cells. Binding of monovalent single domain antibodies to primary T cells was measured using flow cytometry. Humabody® V_H as described herein bound to pre-stimulated CD8+ cells. The ability of purified Humabody V_H to inhibit the binding of CD137 Ligand to CHO human CD137 cells was also measured in the FMAT ligand inhibition assay. V_H inhibited the binding of human CD137 Ligand to human CD137. A functional assay was also carried out to assess the ability of monovalent V_H that bind to CD137, to act as CD137 agonists was assessed in a reporter gene assay using Jurkat cells expressing CD137 and an NF-kB luciferase reporter gene. Their activity was compared to bivalent and trivalent molecules which have increased potential for avid interactions and to bispecific molecules consisting of CD137 V_H linked to a V_H that bound to the tumour antigen PSMA. In the bispecific molecule, CD137 agonism resulted from co-engagement of both CD137 and the cell expressed PSMA.

EXAMPLE 2. Generation of Bispecific Constructs and Stability Testing

Multivalent constructs were generated by linking isolated Humabody® V_H nucleic acid sequences using linkers of encoding glycine/serine rich sequences $(G4S)_x$ where x is the number of G4S repeats and ranges from 2 to 12 repeat units. DNA sequences encoding each Humabody® were amplified by PCR. The products were assembled into larger fragments with the V_H single domain antibody sequences flanked by the $(G4S)_x$ linkers and ligated into an expression vector by a restriction enzyme-based method. Plasmids were transformed into microbial expression systems as per standard molecular biology techniques. The presence of inserts were verified by standard colony PCR technique and sequence confirmed by Sanger sequencing using vector-specific and internal primers to ensure complete sequence coverage. For generation of bispecific molecules the first and second sequence were not the same with one sequence corresponding to a Humabody® V_H specific for CD137 and the other to a Humabody® that binds the tumour associated antigen PSMA. In another example monovalent and bispecific binding agents were optionally linked to a half-life extending Humabody® nucleic acid sequence (MSA binder). Bispecific and trispecific constructs were expressed by microbial cell systems. For stability testing purified bispecific and trispecific V_H were subjected to size exclusion chromatography. Example data for representative constructs is shown in table 9.

Table 9

		Timepoint (days)								
		% Monomer by SEC 4°C				% Monomer by SEC 40°C				
Antibody clone	Conc.	1	4	7	14	0	1	4	7	14
4.1-6GS-2.1	5mg/ml	99.44	99.37	99.41	99.38	99.44	99.14	98.95	98.90	98.64
3.8-6GS-1.1	5mg/ml	98.58	98.53	98.55	98.52	98.58	97.54	96.83	96.63	92.66
4.1-6GS-1.1-6GS-VH (MSA)	5mg/ml	99.39	99.36	99.34	99.33	99.39	99.37	99.22	99.16	99.16

Examples of trispecific fusion proteins and nucleic acids encoding such fusion proteins are shown below. Examples of bivalent molecules are also shown below (table 10).

SEQ ID NO:798 1.1-6GS-1.1 Protein EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQM NSLRAEDTAVYYCARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL VQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSS
SEQ ID NO:799 1.1-6GS-1.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC ACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGAC GGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTG CAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTC GGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGG TGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGG GGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTT GGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGAC TCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAA GACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGG ACCACGGTCACTGTCTCTTCA
SEQ ID NO:800 2.1-6GS-2.1 Protein EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNN LRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKP GGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCARE DSRLTGTTDFDNWGQGTLVTVSS
SEQ ID NO:801 2.1-6GS-2.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTC ACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTG GTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCA GATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTT TGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAG GTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGG CTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTGGTTCC GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAA AGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGG CCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCAC CGTCTCCTCA
SEQ ID NO: 802 1.1-6GS-1.1-6GS-1.1 Protein EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQM NSLRAEDTAVYYCARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGL

VQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVY YCARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSC AASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCARGGDGYS DSHFGVDVWGQGTTVTVSS
SEQ ID NO: 803 1.1-6GS-1.1-6GS-1.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC ACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGAC GGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTG CAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTC GGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGG TGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGG GGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTT GGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGAC TCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAA GACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGG ACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCT GGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGT CCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGG CTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCC AGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGA GGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA
SEQ ID NO: 804 2.1-6GS-2.1-6GS-2.1 Protein EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNN LRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKP GGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCARE DSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKPGGSLRVSCAASGFTF SDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCAREDSRLTGTTDFDNWG QGTLVTVSS
SEQ ID NO: 805 2.1-6GS-2.1-6GS-2.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTC ACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTG GTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCA GATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTT TGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAG GTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGG CTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTGGTTCC GCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAA AGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGG CCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCAC CGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTG GATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTC TCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGG TTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCC AAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTC TAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
SEQ ID NO. 843 4.1-6GS-1.1-6GS-VH (MSA) Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC TCCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATG GAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTC ATCGTCCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGC TCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGG AGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTG GATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACT ATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAG

AGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGG CCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTG GTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTCAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCC GGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGTTATGCCATGAGCTGGGTCCGCCAGGCTCCA GGGAAGGGGCTGGAGTGGGTCGCAACTATTAGTGATAGTGGTAGTAGTGCAGACTACGCAGATTCCGTGAAGGGACGGTT CACCATCTCCAGAGACAACTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCTGAAGACACGGCCGTGTATTAC TGTGCGAGAGGCCGGTATAACTGGAACCCCCGAGCTTTGGGTATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA
SEQ ID NO. 844 4.1-6GS-1.1-6GS-MSA Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSL RLSCAASGFTFSSYAMSWVRQAPGKGLEWVATISDSGSSADYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRYN WNPRALGIWGQGTMVTVSS
SEQ ID NO. 845 4.1-6GS-1.1-6GS-MSA Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC TCCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATG GAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTC ATCGTCCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGC TCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGG AGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTA CATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTA CGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGA GCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAG GGAACCCTGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGG TTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTCAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGTTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGA AGGGGCTGGAGTGGGTCGCAACTATTAGTGATAGTGGTAGTAGTGCAGACTACGCAGATTCCGTGAAGGGACGGTTCACCA TCTCCAGAGACAACTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCTGAAGACACGGCCGTGTATTACTGTGC GAGAGGCCGGTATAACTGGAACCCCCGAGCTTTGGGTATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA
SEQ ID NO. 846 4.1-6GS-2.1-6GS-MSA Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG GGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAV YHCAREDSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSC AASGFTFSSYAMSWVRQAPGKGLEWVATISDSGSSADYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRYNWNPR ALGIWGQGTMVTVSS
SEQ ID NO. 847 3.8-6GS-1.1-6GS-MSA nucleotide GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGC GGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGA GACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGA GTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAG ACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAG GTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCG GTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAG TCAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATT CACCTTTAGTAGTTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGCAACTATTAGTGATAG TGGTAGTAGTGCAGACTACGCAGATTCCGTGAAGGGACGGTTCACCATCTCCAGAGACAACTCCAAGAACACGCTGTATCTT CAAATGAACAGCCTGAGAGCTGAAGACACGGCCGTGTATTACTGTGCGAGAGGCCGGTATAACTGGAACCCCCGAGCTTTG GGTATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA

SEQ ID NO. 848 3.8-6GS-1.1-6GS-MSA Protein EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNS LRVEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCA ASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCARGGDGYSDS HFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAM SWVRQAPGKGLEWVATISDSGSSADYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRYNWNPRALGIWGQGTM VTVSS
SEQ ID NO. 889 4.1-6GS-1.113-4GS Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC TCCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATG GAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTC ATCGTCCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGC TCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGA GAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGG ATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACATTAATCAGGACGGGAGCGAGCGTTATTAC GTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAATTCCTTGTACTTACAGATGAACTCACTTCGTGC TGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACA GGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGCTCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGCGGCGGTG GTAGT
SEQ ID NO. 890 4.1-6GS-1.113-4GS Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGEGYGVDHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGG
SEQ ID NO. 891 3.8-6GS-1.113-4GS Nucleotide GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGC GGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCG CCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAG TGGGTGGCGAACATTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACA ACGCTAAAAATTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAA GGATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGC TCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGCGGCGGTGGTAGT
SEQ ID NO. 892 3.8-6GS-1.113-4GS Protein EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNS LRVEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCA ASGFTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGS
SEQ ID NO. 893 4.1-6GS-1.113-6GS-VH (HSA)-4GS Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC TCCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATG GAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTC ATCGTCCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGC TCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGA GAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGG ATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACATTAATCAGGACGGGAGCGAGCGTTATTAC GTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAATTCCTTGTACTTACAGATGAACTCACTTCGTGC TGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACA GGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGCTCTGGAGGAGGCGGATCGGGGGGTGGAGGAAGTGGCGGCGGT

GGTAGTGGAGGAGGTGGTTCTGGAGGCGGTGGCTCTGAAGTACAACTGGTTGAATCGGGTGGTGGATTGGTCCAACCTGG AAGATCATTGAGGCTTTCTTGTGCAGCTTCCGGATTCACCTTTCATCACTATGCTATGCACTGGGTGAGACAAGCCCCTGGTA AGGGCTTGGAATGGGTGTCCGGAATCTCCTGGAATGGTAACAAAATAACATATGCAGATTCCGTTAAGGGTAGATTTACTAT TAGCCGTGATAATGCAAAAAACAGTTTATACTTGCAGATGAATTCCTTGAGGGCTGAGGATACAGCTCTTTACTATTGTGTGC GTGACTCATCGTTGTTCATTGTCGGAGCCCCAACTTTCGAACATTGGGGTAGAGGTACCCTAGTTACGGTTAGCTCAGGCGG AGGTGGCTCTGGAGGAGGCGGATCGGGGGGTGGAGGAAGTGGCGGCGGTGGTAGT
SEQ ID NO. 894 4.1-6GS-1.113-6GS- VH (HSA)-4GS Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGEGYGVDHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLR LSCAASGFTFHHYAMHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCVRDSSLFI VGAPTFEHWGRGTLVTVSSGGGGSGGGGSGGGGSGGGGS
SEQ ID NO.895 3.8-6GS- VH (HSA)-1.113-4GS Nucleotide GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCAAGTATTGGTGAGAAT GATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTAC AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG TCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGC GGTGGATCGGGTGGAGGTGGTAGTGAAGTACAACTGGTTGAATCGGGTGGTGGATTGGTCCAACCTGGAAGATCATTGAG GCTTTCTTGTGCAGCTTCCGGATTCACCTTTCATCACTATGCTATGCACTGGGTGAGACAAGCCCCTGGTAAGGGCTTGGAAT GGGTGTCCGGAATCTCCTGGAATGGTAACAAAATAACATATGCAGATTCCGTTAAGGGTAGATTTACTATTAGCCGTGATAA TGCAAAAAACAGTTTATACTTGCAGATGAATTCCTTGAGGGCTGAGGATACAGCTCTTTACTATTGTGTGCGTGACTCATCGT TGTTCATTGTCGGAGCCCCAACTTTCGAACATTGGGGTAGAGGTACCCTAGTTACGGTTAGCTCAGGCGGAGGTGGCTCTGG AGGAGGAGGTTCAGGAGGTGGTGGATCTGGAGGAGGCGGATCGGGGGGTGGAGGAAGTGGCGGCGGTGGTAGTGAGGT GCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCGGGATTCACATTA TCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACATTAATCAGGACGGGAGC GAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAATTCCTTGTACTTACAGATGAA CTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCGTCGATCACTACGGCCTTGAT GTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGCTCTGGAGGAGGCGGATCGGGGGGTGGAGGAAG TGGCGGCGGTGGTAGTGAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCT GTGCAGCCTCTGGATTCAGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTC AAGTATTGGTGAGAATGATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAA GAATACGCTGTATCTACAAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGG GGCCAGGGAACCCTGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGG TGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAAGTACAACTGGTTGAATCGGGTGGTGGATTGGTCCAAC CTGGAAGATCATTGAGGCTTTCTTGTGCAGCTTCCGGATTCACCTTTCATCACTATGCTATGCACTGGGTGAGACAAGCCCCT GGTAAGGGCTTGGAATGGGTGTCCGGAATCTCCTGGAATGGTAACAAAATAACATATGCAGATTCCGTTAAGGGTAGATTTA CTATTAGCCGTGATAATGCAAAAAACAGTTTATACTTGCAGATGAATTCCTTGAGGGCTGAGGATACAGCTCTTTACTATTGT GTGCGTGACTCATCGTTGTTCATTGTCGGAGCCCCAACTTTCGAACATTGGGGTAGAGGTACCCTAGTTACGGTTAGCTCAGG CGGAGGTGGCTCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGAGGAGGCGGATCGGGGGGTGGAGGAAGTGGCGG CGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGC CTCGGGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACATT AATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAATTCCT TGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCGTCGA TCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGCTCTGGAGGAGGCGGATC GGGGGGTGGAGGAAGTGGCGGCGGTGGTAGT
SEQ ID NO. 896 3.8-6GS- VH (HSA)-1.113-4GS Protein EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNS LRVEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCA ASGFTFHHYAMHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCVRDSSLFIVGA PTFEHWGRGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMN WVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGGEGYGVDHYGLDVSGQGT

TVTVSSGGGGSGGGGSGGGGSGGGGS

SEQ ID NO. 897 3.8-6GS-1.113-6GS- VH (HSA)-4GS Nucleotide

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC
AGTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCAAGTATTGGTGAGAAT
GATGGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTAC
AAATGAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGG
TCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGC
GGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCG
CCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAG
TGGGTGGCGAACATTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACA
ACGCTAAAAATTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAA
GGATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGCTCTG
GAGGAGGCGGATCGGGGGGTGGAGGAAGTGGCGGCGGTGGTAGTGGAGGAGGTGGTTCTGGAGGCGGTGGCTCTGAAG
TACAACTGGTTGAATCGGGTGGTGGATTGGTCCAACCTGGAAGATCATTGAGGCTTTCTTGTGCAGCTTCCGGATTCACCTTT
CATCACTATGCTATGCACTGGGTGAGACAAGCCCCTGGTAAGGGCTTGGAATGGGTGTCCGGAATCTCCTGGAATGGTAACA
AAATAACATATGCAGATTCCGTTAAGGGTAGATTTACTATTAGCCGTGATAATGCAAAAAACAGTTTATACTTGCAGATGAAT
TCCTTGAGGGCTGAGGATACAGCTCTTTACTATTGTGTGCGTGACTCATCGTTGTTCATTGTCGGAGCCCCAACTTTCGAACAT
TGGGGTAGAGGTACCCTAGTTACGGTTAGCTCAGGCGGAGGTGGCTCTGGAGGAGGCGGATCGGGGGGTGGAGGAAGTG
GCGGCGGTGGTAGT

SEQ ID NO. 898 Protein 3.8-6GS-1.113-6GS- VH (HSA)-4GS

EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNS
LRVEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCA
ASGFTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGGEGYGV
DHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCAASGFTFHHYA
MHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCVRDSSLFIVGAPTFEHWGRG
TLVTVSSGGGGSGGGGSGGGGSGGGGS

SEQ ID NO.899 4.1-6GS- VH (HSA)-1.113-4GS Nucleotide

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTC
TCCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATG
GAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCA
AATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTC
ATCGTCCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGC
TCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAAGTACAACTGGTTGA
ATCGGGTGGTGGATTGGTCCAACCTGGAAGATCATTGAGGCTTTCTTGTGCAGCTTCCGGATTCACCTTTCATCACTATGCTA
TGCACTGGGTGAGACAAGCCCCTGGTAAGGGCTTGGAATGGGTGTCCGGAATCTCCTGGAATGGTAACAAAATAACATATG
CAGATTCCGTTAAGGGTAGATTTACTATTAGCCGTGATAATGCAAAAAACAGTTTATACTTGCAGATGAATTCCTTGAGGGCT
GAGGATACAGCTCTTTACTATTGTGTGCGTGACTCATCGTTGTTCATTGTCGGAGCCCCAACTTTCGAACATTGGGGTAGAGG
TACCCTAGTTACGGTTAGCTCAGGCGGAGGTGGCTCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGAGGAGGCGGAT
CGGGGGGTGGAGGAAGTGGCGGCGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGG
CTCGCTTCGCCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAA
GGTCTTGAGTGGGTGGCGAACATTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCA
GTCGTGACAACGCTAAAAATTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGC
GGTGGTGAAGGATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGA
GGTGGCTCTGGAGGAGGCGGATCGGGGGGTGGAGGAAGTGGCGGCGGTGGTAGT

SEQ ID NO. 900 4.1-6GS- VH (HSA)-1.113-4GS Protein

EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMN
SLRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESG
GGLVQPGRSLRLSCAASGFTFHHYAMHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT
ALYYCVRDSSLFIVGAPTFEHWGRGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLS
CAASGFTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGGEGY

GVDHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGS
SEQ ID NO. 901 VH that binds to HSA as used in constructs above protein EVQLVESGGGLVQPGRSLRSCAASGFTFHHYAMHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMN SLRAEDTALYYCVRDSSLFIVGAPTFEHWGRGTLVTVSS
SEQ ID NO. 902 VH that binds to HSA as used in constructs above nucleotide GGCTTTGTGAGCGGATACAATTATAATATGTGGAATTGTGAGCGCTCACAATTCCACAACGGTTTCCCTCTAGAAATAAT TTTGTTTAACTTTTAGGAGGTAAAACATATGAAGAAAACGGCAATCGCAATCGCAGTCGCTCTGGCGGGTTTCGCAACTG TAGCGCAAGCCGAGGTGCAACTGGTCGAGTCTGGTGGTGGTTTGGTGCAACCTGGTAGAAGCTTGCGTTTGAGTTGTGCC GCTTCCGGCTTCACTTTCCATCATTATGCTATGCACTGGGTTCGTCAAGCTCCCGGAAAAGGTTTGGAGTGGGTTTCCGG AATTTCCTGGAATGGCAATAAGATTACGTACGCTGATTCAGTGAAAGGAAGGTTTACAATCAGTAGAGATAATGCTAAAA ACTCATTGTATCTACAAATGAACAGCCTAAGAGCAGAAGATACCGCTCTGTACTACTGTGTTAGAGATAGCTCGTTATTC ATTGTAGGTGCACCAACTTTTGAACATTGGGGTCGGGGTACTCTTGTGACTGTCTCATCCGCGGCCGCACACCACCATCA TCACCACTAACTCGAGCGCCTAATGAAAGCTTCCCCAAGGGCGACACCCCCTAATTAGCCCGGGCGAAAGGCCCAGTCTT TCGACTGAGCCTTTCGTTTTATTTGATGCCTGGCAGTTCCCTACTCTCGCATGGGGAGTCCCCACACTACCATCGGCGCT ACGGCGTTTCACTTCTGAGTTCGGCATGGA

EXAMPLE 3: Binding to CD137 and PSMA

3.1 Cell binding

Binding of His-tagged molecules to CHO human CD137, CHO parent, CHO human PSMA, DU145 PSMA and DU145 parent cells was assessed using Fluorescence Microvolume Assay Technology (FMAT). All reagents were prepared in FMAT assay buffer (pH 7.4) containing PBS, 0.1% Bovine Serum Albumin, 0.05% Sodium Azide. Serially diluted samples were transferred into 384 well black clear-bottomed assay plates (Costar cat. no. 3655) and incubated for a minimum of 2 hours at room temperature with 1.5nM Anti-His (Millipore cat. no. 05-949), 3nM Goat Anti-Mouse Alexa Fluor-488 (Jackson ImmunoResearch cat. no. 115-545-071) and 2000 cells/well pre-stained with DRAQ5 (Thermo Scientific cat. no. 62251). Fluorescence emission was then measured on the TTP Mirrorball plate reader in the FL2 (502nm-537nm) and FL5 (677-800nm) channels following excitation at 488nm and 640nm. Data was gated on FL5 perimeter and peak intensity and the FL2 median mean fluorescence intensity of the gated data used for determination of V_H binding. Example EC_{50} values for binding are shown in table 11. Monovalent CD137 specific Humabody® V_H, bispecific and trispecific molecules with a CD137 binding arm bound to CHO CD137 expressing cells. Monovalent PSMA specific Humabody® V_H, bispecific and trispecific molecules with a PSMA binding arm bound to PSMA expressing cells.

Table 11

Humabody®	FMAT					Flow Cytometry
	CHO huCD137	CHO Parent	CHO PSMA	DU145 PSMA	DU145 Parent	CD8+
1.78	3.2E-10	-	-	-	-	6.1E-10
1.1	2.2E-10	-	-	-	-	2.2E-10
2.1	6.5E-10	-	-	-	-	2.4E-09
4.1	-	-	1.7E-10	1.9E-10	-	nd

3.8	-	-	2.3E-10	2.9E-10	-	nd
4.1-6GS-1.1	4.3E-10	-	1.9E-10	2.1E-10	-	7.3E-10
4.1-6GS-2.1	9.7E-10	-	2.8E-10	3.9E-10	-	3.0E-09
3.8-6GS-1.1	5.6E-10	-	6.0E-10	6.8E-10	-	1.1E-09
1.1-6GS-3.8	5.6E-10		6.3E-10	8.1E-10		nd
4.1-6GS-1.1-VH (MSA)	5.8E-10	-	3.2E-10	3.6E-10	-	nd
4.1-6GS-1.1-VH (MSA)	1.9E-09	-	3.0E-10	4.2E-10	-	nd
3.8-6GS-1.1-VH (MSA)	5.9E-10	-	5.9E-10	8.2E-10	-	nd

Binding of monovalent single domain antibodies to primary T cells was measured using flow cytometry. Peripheral blood mononuclear cells (PBMCs) were isolated from human blood by density gradient centrifugation then CD8+ T cells purified using a negative selection isolation kit according to the manufacturer's protocol (Miltenyi Biotech cat no 130-042-401). CD8+ T cells were stimulated PMA/Ionomycin for 48-72 hours in RPMI media supplemented with 10% FBS, 2mM Glutamine, 1X Pen/Strep. Cells were transferred into 96 well plates, blocked for 10mins with staining buffer (PBS/1% BSA/0.05% Sodium Azide) then incubated with serially diluted V_H in staining buffer (PBS/1% BSA) for 30 mins - 1 hour at 4°C. Cells were washed by centrifugation then V_H binding detected using Anti His antibody (Millipore 05-949) and Goat Anti Mouse Alexa Fluor-488 (Jackson ImmunoResearch cat no. 115-545-071). A Live Dead near IR stain (Molecular Probes cat no. L10119) was used for discrimination of live cells. After further washing cells were fixed and fluorescence measured by flow cytometry. Average EC_{50} values for binding (2-3 donors) are shown in Table 9. Monovalent CD137 specific Humabody® V_H and bispecific molecules with a CD137 binding arm bound to pre-stimulated CD8+ cells.

3.2 Affinity kinetics

Binding kinetics of purified monovalent V_H, and PSMA-CD137 targeting bispecific molecules were determined on a ForteBio Octet RED 384 instrument. To study the interaction with the antigens, CD137-Fc tag protein (Acro Biosystems cat no. 41B-H5258) or PSMA-his (R&D Systems cat no. 4234-ZN) was immobilised onto AR2G biosensors (ForteBio cat no. 18-5082) by amine coupling. Monovalent V_H and bispecific molecules were serially diluted (typically 1:2 dilution series starting between 12-25nM, at the highest concentration) in kinetics buffer (0.1% BSA, 0.02% Tween, 1x PBS) and binding to the immobilised proteins was studied during the association and dissociation phases. PSMA binding was measured using 180 seconds association and 600 seconds dissociation phases. CD137 binding was measured 180 seconds association and 600 seconds dissociation phases. Reference subtracted data were fitted to a 1:1 binding model using the ForteBio Octet Data Analysis software. Example kinetic and binding affinity data obtained are shown in Table 12.

Table 12

Humabody®	**Human CD137**			**Human PSMA**		
	KD (M)	**Kon (1/Ms)**	**kdis (1/s)**	**KD (M)**	**kon (1/Ms)**	**kdis (1/s)**
1.1	5.2E-10	7.1E+05	3.6E-04	-	-	-

2.1	6.7E-09	7.7E+05	5.2E-03	-	-	-
4.1	-	-	-	5.3E-10	3.1E+05	1.6E-04
3.8	-	-	-	9.0E-10	3.9E+05	3.5E-04
4.1-6GS-1.1	7.3E-10	4.1E+05	3.1E-04	1.3E-09	4.3E+05	5.4E-04
4.1-6GS-2.1	4.8E-09	5.8E+05	2.6E-03	6.6E-10	5.0E+05	3.3E-04
3.8-6GS-1.1	5.6E-10	4.9E+05	2.9E-04	5.7E-09	3.0E+05	1.7E-03

The Biacore T200 instrument was used to study the interaction between VH with human and rhesus CD137-human IgG1Fc tagged protein by surface plasmon resonance (SPR). Single cycle kinetics assays used to evaluate the kinetics and affinity of the interaction. Experiments were performed at 25^{O}C in HBS-EP+ assay buffer with a flow rate of 30µl/minute. A Protein G chip was used to capture the Fc tagged recombinant CD137 diluted to 2µg/ml to one of the flow cells over 7 seconds. A second flow cell without any captured CD137 was used as the reference cell. A five point, three-fold dilution series of V_H was made with a top concentration of 60nM. The binding kinetics were followed by flowing these over the chip surface. The contact time for each of the binding steps was 180 seconds and the dissociation step was 1800 and 3600 seconds for rhesus and human CD137 respectively. After each run, the sensors were regenerated with glycine pH 1.5 to remove the captured CD137. The data was fitted to a 1:1 binding model after double reference subtraction using the Biacore T200 Evaluation software. Average kinetic constants (± Standard deviation) for Humabody® 1.113 for binding to human CD137Fc were ka 3.6E+06 ± 1.6E+06 (1/Ms), Kd is 3.0E-04 ± 1.1E-04 (1/s) and KD 8.5E-11 ± 7.8E-12 (M) and for binding to rhesus CD137Fc were ka 1.1E+06 ± 2.2E+05 (1/Ms), Kdis 2.8E-04 ± 6.8E-06 (1/s) and KD 2.7E-10 ± 5.2E-11. Average kinetic constants (± Standard deviation) for construct 4.1-6GS-1.113-6GS-V_H that binds HSA-4GS for binding to human CD137Fc were ka 5.6E+05 (1/Ms), Kdis 1.7E-05 (1/s) and KD 3.1E-11 (M) and for binding to rhesus CD137Fc were ka 4.4E+05 (1/Ms), Kdis 5.2E-05 (1/s) and KD 1.2E-10 (M). Humabody® 1.113 showed better binding to cyno compared to other molecules and also showed better developability characteristics (stability and expression) compared to other molecules.

3.3 Co-engagement

Engagement of 3 targets was also demonstrated using ForteBio Octet instrument. Association 1 - Binding of the trispecific molecule to CD137Fc captured on protein G biosensors. Association 2 - binding of Human serum Albumin, Association 3 - Binding of PSMA in the presence of Human serum albumin to minimise HSA dissociation. This demonstrated that trispecific molecules can simultaneously bind targets.

Dual target engagement of CD137 and PSMA by the bispecific molecules was assessed using an ELISA format and by flow cytometry with T cells. For ELISA, CHO-PSMA cells (20000/well) were seeded into 96 well plates (Greiner cat no. 353872) in Hams F12 supplemented with L-Glutamine + Blasticidin + Tetracycline and incubated at 37°C with 5% CO_2 overnight. All subsequent steps were performed at room temperature and included washes with PBS between each step. Plates were blocked with PBS/0.1% BSA for 1 hour then serially diluted Humabody® V_H were added and allowed to bind for 1 hour. Following removal of unbound V_H, 1nM CD137huFc (Acro Biosystems cat no. 41B-H5258) was added to the wells

and incubated for 1 hour. A 1:3000 dilution of Anti-huFc-HRP (Jackson ImmunoResearch cat no. 109-035-098) was subsequently added for 1 hour and plates developed by addition of TMB. The reaction was stopped by addition of 0.5M sulphuric acid and plates read on BMG PheraStar at Absorbance 450nm. Figure 1 shows representative data demonstrating that bispecific molecules can simultaneously bind both human CD137 and human PSMA. Human CD8+ T cells pre-stimulated for 48 hours with PMA/ionomycin were washed with FACS buffer (PBS supplemented with 10% human serum and 0.05% sodium azide) by centrifugation. Serially diluted bispecific and trispecific Humabody VH construct were added to the cells for 1 hour on ice. Plates were washed with FACS buffer then detection mix containing 5nM biotinylated-PSMA, 20nM Streptavidin AlexaFluor488 and Live/Dead NearIR cell stain dilution added. Plates were incubated at 4°C for 1 hour then washed twice with FACS buffer by centrifugation. Cells were fixed by addition 1X BD Cell fix solution, then washed twice with PBS by centrifugation and the cell pellets resuspended in PBS. Fluorescence was measured in the RL2-H channels (Live/Dead stain) and BL1-H channel (AlexaFluor488 stain) on the iQue Plus Screener (IntelliCyt). The bispecific and trispecific molecules were able to simultaneously bind human CD8+ T cells and PSMA protein.

Binding to cell lines was also measured using Fluorescence Microvolume Assay technology as per section 3.1. CD137huFc/anti humanFc-Alexa Fluor-488 was used for detection of binding to PSMA expressing cells.

ELISA data is the average EC50 (± SD) for n=3 determinations. Flow cytometry data shown is the average EC50 (± SD) for a minimum of 6 different human T-cell donors (Table 13). Construct 4.1-6GS-1.113-6GS-VH HSA -4GS bound CHO cynomolgus PSMA cells in the FMAT assay (Average EC_{50} ± SD (M) 5.7E-10 ± 4.6E-11, 0.57nM n=3).

Table 13

	ELISA EC50 ± SD	Flow Cytometry
3.8-6GS-VH HSA-6GS-1.113-4GS	2.5E-09 ± 9.6E-10	4.0E-09 ± 1.5E-09
3.8-6GS-1.113-6GS- VH HSA 4GS	1.6E-09 ± 4.2E-10	3.4E-09 ± 1.8E-09
3.8-6GS-1.113	1.3E-09 ± 2.6E-10	8.7E-10 ± 4.5E-10
4.1-6GS- VH HSA 6GS-1.113-4GS	1.1E-09 ± 3.4E-10	3.7E-09 ± 1.7E-09
4.1-6GS-1.113-6GS- VH HSA 4GS	2.2E-09 ± 2.0E-10	4.2E-09 ± 1.3E-09
4.1-6GS-1.113	5.7E-10 ± 2.0E-10	1.3E-09 ± 8.8E-10

EXAMPLE 4. Inhibition of CD137L Binding

Humabody® V_{Hs} were tested for their ability to inhibit the interaction of human CD137-ligand protein with CHO human CD137 cells in an FMAT format. Serially diluted V_H in FMAT assay buffer were incubated for a minimum of 2 hours at room temperature with 0.2nM – 0.4nM CD137L-huFc (Sino Biologicals cat no. 15693-101H), 3nM Alexa Fluor® 488 Goat Anti-Human IgG, Fc gamma fragment specific goat anti human IgG (Jackson ImmunoResearch cat no. 109-545-098) and 2000 cells pre-stained with DRAQ5. Total binding controls containing FMAT assay buffer and non-specific binding controls containing excess non-Fc tagged competitor were set up on each plate for data normalisation. Fluorescence signal was measured

using the TTP Mirrorball and the FL2 median mean fluorescence intensity of gated used for the data normalisation. The data was expressed as a % of the total binding control (% control) after subtraction of the background signal determined from the non-specific binding control wells. V_H in monovalent and bispecific formats inhibited CD137 binding to CD137 Ligand (Table 14).

Table 14

Humabody® V_H	IC_{50} (M)
1.78	1.5E-09
1.1	1.1E-09
2.1	5.7E-09
4.1	-
3.8	-
4.1-6GS-1.1	2.5E-09
4.1-6GS-2.1	1.3E-08
4.1-6GS-1.78	3.7E-09
1.78-6GS-4.1	2.8E-09
3.8-6GS-1.1	1.7E-09
1.1-6GS-3.8	1.3E-09

EXAMPLE 5 Functional activity

5.1 Co-culture Functional Activity Assays

The ability of bispecific molecules to act as CD137 agonists was assessed in a co-culture reporter gene assay using Jurkat cells expressing CD137 and an NF-kB luciferase reporter gene and cells expressing human PSMA. Assays were performed using high PSMA expressing cells (CHO PSMA) and low PSMA expressing cells (DU145 PSMA). PSMA expressing cells or parental cells (5000/well) were plated overnight into 384 well, white clear bottomed tissue culture treated plates. For CHO cells media was removed the next day and replace by assay media (RPMI 1640 supplemented with 10% FBS, 2mM L-Glutamine, 1X Pen/Strep). Serially diluted monomer V_H, bispecific and Jurkat reporter cells were prepared in assay media (RPMI 1640 supplemented with 10% FBS, 2mM L-Glutamine, 1X Pen/Strep) and added to the wells. After a 5-6 hour incubation at 37°C in a CO_2 incubator the level of luciferase reporter expression was determined by addition of BioGlo reagent (Promega G7940) and measurement of luminescent signal on the BMG Pherastar. Figure 2 exemplifies the concentration and PSMA dependent stimulation of the NF-kB pathway by CD137-PSMA V_H bispecific molecules. The level of PSMA expression determines the maximum response with higher maximal levels obtained for the CHO PSMA high PSMA expressing cell line compared to the low expressing DU145 PSMA cells (Figure 2b). Anti CD137 antibody stimulates NF-kB driven reporter gene activity in a PSMA independent manner (Figure 2c). The experiments show that in the bispecific molecule, CD137 agonism resulted from co-engagement of both CD137 and the cell expressed PSMA.

5.2 IL-2 release

Bispecific molecules were tested for their ability to induce IL-2 release from T cells in a co-culture assay. DU145 PSMA or parental DU145 cells were resuspended in media (RPMI 1640 supplemented with 10% FBS, 2mM L-Glutamine, 1X Pen/Strep) and seeded at a density of 20000 per well onto 96 well flat bottom

plates that had been pre-coated with 5ug/ml anti CD3 antibody (e-Bioscience cat no. 14-0037-82). Cells were allowed to adhere overnight at 37°C, 5% CO_2. Peripheral blood mononuclear cells (PBMCs) were isolated from human blood by density gradient centrifugation then CD8+ T cells purified using a negative selection isolation kit according to the manufacturer's protocol (Miltenyi Biotech cat no 130-042-401). Humabody® $V_{H,}$ bispecifics and benchmark antibodies were prepared in media and added together with the T cells (100000 cells/well) to the assay plates. Supernatants were harvested after a 48 hour incubation at 37°C, 5% CO_2 and IL-2 levels quantified using a human IL-2 assay kit according to the manufacturer's instructions (Cisbio Cat no. 64IL2PEB). Stimulation of IL-2 production by CD8+ T cells was independent of PSMA for the anti CD137 benchmark antibody but was PSMA dependent (Figure 3a) and concentration dependent (Figure 3b, 3d). Maximum responses levels were T cell donor dependent for both antibody and bispecific molecules (Figure 3c). Interferon gamma was also induced (Figure 3e).

5.3. Stimulation of superantigen-activated cells

PBMC from healthy donor were stimulated with 10ng/ml SEB (Staphylococcal enterotoxin B) for 16 hours prior to treatment. CHO cells or CHO cells expressing PSMA were plated into 96-well plates at 10,000 per well. Humabody® constructs were added to a final concentration of 50nM and a 4-fold dilution series. SEB-stimulated PBMC were added at 75,000 per well in media with 1ng/ml SEB. Plates were incubated at 37°C 5% CO_2 for 3 days. Supernatants were harvested for cytokine measurement. TNF-alpha was measured using Cisbio HTRF kit (62HTNFAPEG) according to manufacturer's instructions. TNF-alpha increased in a bispecific Humabody® dependant dose-response manner in the presence of cells expressing PSMA. There was no induction in the absence of PSMA (Figure 5).

EXAMPLE 6. Effect of Humabody® in DU145 PSMA/hu PBMC engrafted NCG Mice

Male NCG mice (NOD-Prkdcem26Cd52Il2rgem26Cd22/NjuCrl, Charles River) were injected sub-cutaneously in the right flank with 1 x 10 7 DU145 PSMA cells in 50% matrigel. On Day 8, hPBMCs (HemaCare BioResearch Products) were engrafted via tail vein. Non engrafted mice were used as control groups. Mice were then treated with Humabody® or control CD137 agonist antibody administered intraperitoneally and body weights, clinical observations, and tumour volumes recorded. Study was performed at Charles River Discovery Services North Carolina (CR Discovery Services) which specifically complies with the recommendations of the Guide for Care and Use of Laboratory Animals with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care, and is accredited by AAALAC. Half-life extended bispecific Humabody® treated groups showed a reduced tumour volume compare to the controls group (Figure 6).

EXAMPLE 7 Pharmacokinetics analysis of single intravenous dose of a half life extended molecule in double transgenic humanised FcRn/HSA mouse

Experiments were conducted using a Human Neonatal Fc Receptor / Albumin Mouse model by genOway®. This double humanized neonatal Fc receptor (FcRn)/albumin mouse model maintains an autologous receptor-ligand interaction and mimics the physiological drug clearance in humans, and therefore

represents a unique and reliable tool to measure and optimize albumin-linked small molecules and conventional drug pharmacokinetics and study and predict the half-life of circulating biologics and biosimilar drugs (Viuff D, Antunes F, Evans L, Cameron J, Dyrnesli H, Thue Ravn B, Stougaard M, Thiam K, Andersen B, Kjærulff S, Howard KA. 2016. Generation of a double transgenic humanized neonatal Fc receptor (FcRn)/albumin mouse to study the pharmacokinetics of albumin-linked drugs. J Control Release).

The hFcRn/HSA humanized mouse provides more predictable "human-like" pharmacokinetic results than WT mice. This model is well suited for *in vivo* assessment of HSA-binding drugs' pharmacokinetic, distribution and toxicity.

A trispecific molecule (4.1-6GS-1.113-6GS- VH HSA -4GS) was used in these experiments to test pharmacokinetics.

Briefly, male genOway® Human HSA/ FcRn Tg mice were dosed with a single intravenous injection of trispecific (n=3) at 2mg/kg via tail vein. Blood samples were collected at Pre-dose and at 0.083h, 1h, 8h, 24h, 48h, 72h and 96h post drug administration via the saphenous vein. At 168h post dose all animals were euthanised and blood was collected. Plasma was separated and stored at -80°C until an assay was carried out. Plasma samples were analysed on Gyrolab immunoassay platform, using biotinylated human PSMA as capture and human CD137Dylight650 as detection. Data was analysed using Gyros to obtain concentrations in plasma. Pharmacokinetic analysis of data was done using PK Solver 2.0.

Results of study show that the molecule has a half-life of 18.13 ± 0.412 hours (n=3) when dosed at 2mg/kg intravenously in human HSA/FcRn Tg mice.

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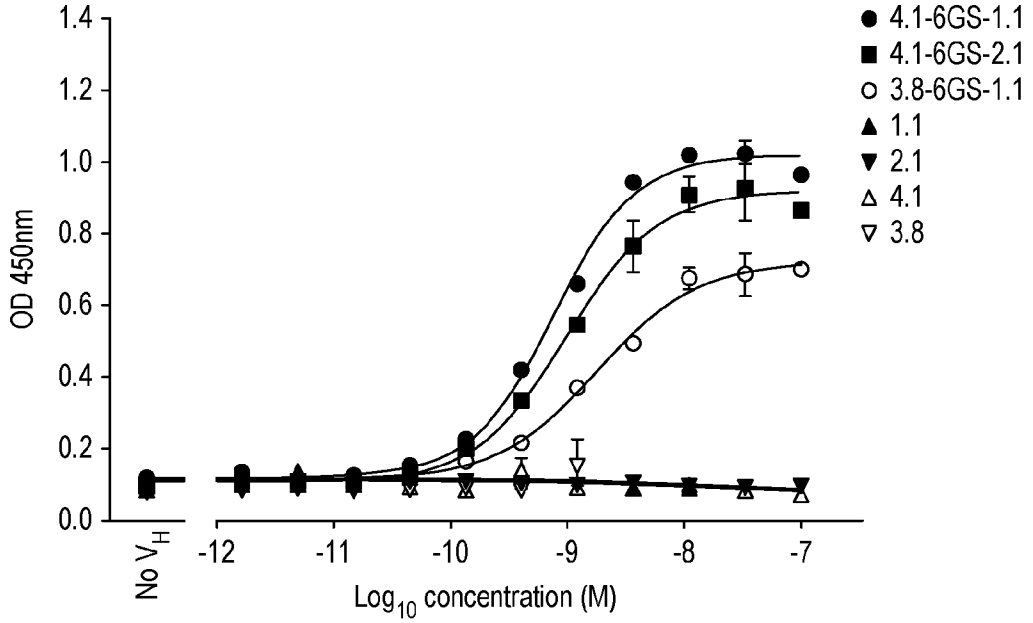
Claims

1. An isolated binding molecule comprising
   a) a single variable heavy chain domain antibody that binds to CD137 and
   b) a moiety that binds to PSMA.
2. The isolated binding molecule according to claim 1 wherein the single variable heavy chain domain antibody that binds to CD137 comprises a CDR1 comprising SEQ ID NO. 1 or a sequence with at least 40% homology thereto, a CDR2 comprising SEQ ID NO. 2 or a sequence with at least 40% homology thereto and a CDR3 comprising SEQ ID NO. 3 or a sequence with at least 40% homology thereto or a CDR1 comprising SEQ ID NO. 425 or a sequence with at least 40% homology thereto, a CDR2 comprising SEQ ID NO. 426 or a sequence with at least 40% homology thereto and a CDR3 comprising SEQ ID NO. 427 or a sequence with at least 40% homology thereto or a sequence with at least 40% homology thereto and a CDR3 comprising SEQ ID NO. 427 or a sequence with at least 75% homology thereto.
3. The isolated binding molecule according to claim 2 wherein the single variable heavy chain domain antibody that binds to CD137 comprises human framework regions.
4. The isolated binding molecule according to a preceding claim wherein the single variable heavy chain domain antibody that binds to CD137 comprises a full length sequence as listed in table 2 or 3 or a sequence with at least 75% homology thereto.
5. The isolated binding molecule according to a preceding claim wherein the single variable heavy chain domain antibody that binds to CD137 comprises SEQ ID NO. 4, 312, 852, 856, 860, 864, 868, 872, 876, 880 or 428 or a sequence with at least 75% homology thereto.
6. The isolated binding molecule according to a preceding claim wherein the moiety that binds to PSMA is selected from an antibody, an antibody fragment, an antibody mimetic or other polypeptide.
7. The isolated binding molecule according to claim 6 wherein said antibody fragment is selected from a Fab, F(ab')2, Fv, a single chain Fv fragment (scFv), a single domain antibody or fragment thereof.
8. The isolated binding molecule according to claim 7 wherein said single domain antibody is a V_H single domain antibody.
9. The isolated binding molecule according to claim 8 wherein said V_H single domain antibody comprises a CDR1 comprising SEQ ID NO. 812 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 813 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 814 or a sequence with at least 75% homology thereto or wherein said V_H single domain antibody comprises a CDR1 comprising SEQ ID NO. 837 or a sequence with at least 75% homology thereto, a CDR2 comprising SEQ ID NO. 838 or a sequence with at least 75% homology thereto and a CDR3 comprising SEQ ID NO. 839 or a sequence with at least 75% homology thereto.

10. The isolated binding molecule according to any preceding claim wherein the single variable heavy chain domain antibody that binds to PSMA comprises a full length sequence as listed in table 6 or 7 or a sequence with at least 75% homology thereto.
11. The isolated binding molecule according to any preceding claim wherein the single variable heavy chain domain antibody that binds to PSMA comprises SEQ ID NO. 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825 or 840 or a sequence with at least 75% homology thereto.
12. The isolated binding molecule according to any preceding claim wherein a single domain antibody 1.1 or 2.1 having SEQ ID No. 4 or 428, or a single domain antibody having SEQ ID No 312, 852, 856, 860, 864, 868, 872 or 876 or a sequence with at least 75% sequence homology thereto is linked to a single domain antibody 3.1, 3.8 or 4.1 having SEQ ID No. 815, 822 or 840 respectively.
13. The isolated binding molecule according to any preceding claim capable of binding CD137 with an affinity with a Kd of at least about 10-6 M to about 10-12M.
14. The isolated binding molecule according to any preceding claim capable of binding PSMA with an affinity with a Kd of about 10-6 M to about 10-12M.
15. The isolated binding molecule according to any preceding claim wherein the single variable heavy chain domain antibody that binds to CD137 is linked to the moiety that binds PSMA by a peptide linker.
16. The binding molecule according to claim 15 wherein said linker is selected from a (G4S)n linker wherein n is an integer selected from 1 to 10.
17. The isolated binding molecule according to any preceding claim conjugated to one or more moiety selected from a toxin, enzyme, radioisotope, half-life extending moiety, label, therapeutic molecule and other chemical moiety.
18. The isolated binding molecule according to claim 17 wherein said half-life extending moiety is selected from the group consisting of an albumin binding moiety, a transferrin binding moiety, a polyethylene glycol molecule, a recombinant polyethylene glycol molecule, human serum albumin, a fragment of human serum albumin, and an albumin binding peptide and single domain antibody that binds to human serum albumin.
19. The isolated binding molecule according to any preceding claim wherein the single variable heavy chain domain antibody which binds to human CD137 does not cause CD137 signalling when bound to CD137 as a monospecific entity.
20. The isolated binding molecule according to any preceding claim wherein the single variable heavy chain domain antibody which binds to human CD137 is obtained or obtainable from a transgenic rodent that expresses a transgene comprising human V, D and J regions.
21. The single variable heavy chain domain antibody according to claim 20 wherein said rodent does not produce functional endogenous light and heavy chains.
22. A pharmaceutical composition comprising a binding molecule according to preceding claim and a pharmaceutical carrier.
23. A binding molecule according to any of claims 1 to 21 or a pharmaceutical composition according to claim 23 for use in the treatment of disease.

24. A binding molecule according to any of claims 1 to 21 or a pharmaceutical composition according to claim 22 wherein said disease is a cancer.
25. A method for treating prostate cancer or a prostatic disorder comprising administering a therapeutically effective amount of a binding molecule according to any of claims 1 to 21 or a pharmaceutical composition according to claim 22.
26. A binding molecule according to claim 24 or a method according to claim 25 wherein said cancer is prostate cancer lung cancer, glioblastoma, renal, bladder, testicular, neuroendocrine, colon, and breast cancer.
27. A nucleic acid molecule comprising a nucleic acid sequence encoding the binding molecule according to any of claims 1 to 21.
28. A vector comprising nucleic acid molecule according to claim 27.
29. A host cell comprising a nucleic acid molecule according to claim 27 or a vector according to claim 28.
30. The host cell according to claim 29 wherein said host cell is a bacterial, yeast, viral or mammalian cell.
31. A method for producing a binding molecule according to any of claims 1 to 21 comprising expressing a nucleic acid encoding said binding molecule in a host cell and isolating the binding molecule from the host cell.
32. A method for promoting CD8+ T cell expansion, inducing activation of cytotoxic T lymphocytes (CTL) and/or cytokine release comprising administering to a binding molecule according to any of claims 1 to 21 or a pharmaceutical composition according to claim 22.
33. An *in vivo* or *in vitro* method for reducing human PSMA activity comprising contacting human PSMA with a binding molecule according to any of claims 1 to 21.
34. A kit comprising a binding molecule according to any one of claims 1 to 21 or a pharmaceutical composition according to claim 22.
35. A use of a binding molecule according to any one of claims 1 to 21 or a pharmaceutical composition according to claim 22 for simultaneously activating downstream signalling pathways of CD137 and PSMA.
36. A method for co-stimulating downstream signalling pathways of CD137 and PSMA comprising administering a binding molecule according to any of claims 1 to 21 or a pharmaceutical composition according to claim 22.
37. A use of a binding molecule according to any of claims 1 to 21 or a pharmaceutical composition according to claim 22 for inducing a local T cell response in the vicinity of a PSMA positive tumor cell or tissue.
38. A method for inducing a local T cell response in the vicinity of a PSMA positive tumor cell or tissue comprising administering a binding molecule according to any one of claims 1 to 21 or a pharmaceutical composition according to claim 22.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No V_H
-12
-11
-10
-9
-8
-7
Log_{10} concentration (M)
4.1-6GS-1.1
4.1-6GS-2.1
3.8-6GS-1.1
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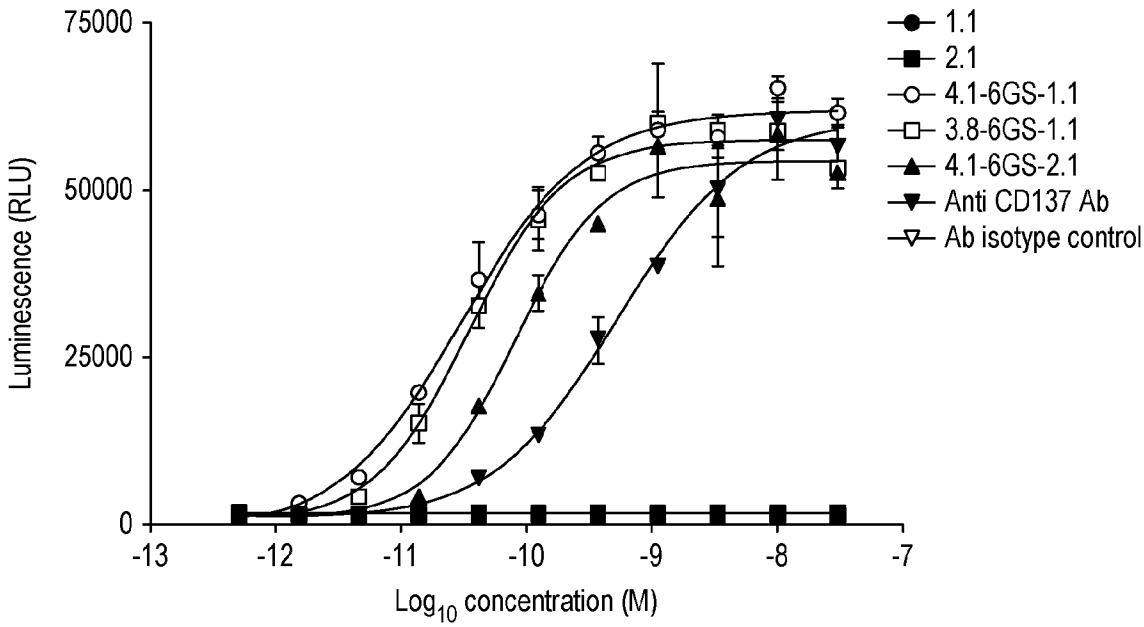
2.1
4.1
3.8

FIG. 1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Log_{10} concentration (M)
1.1
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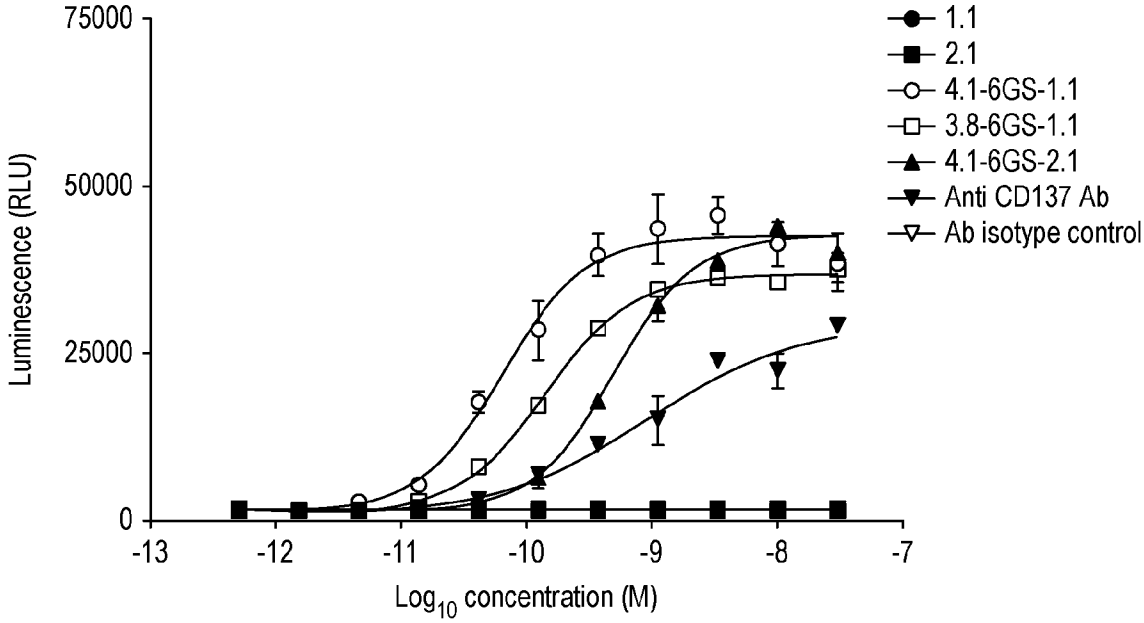
3.8-6GS-1.1
4.1-6GS-2.1
Anti CD137 Ab
Ab isotype control

FIG. 2A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Luminescence (RLU)
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-8
-7
Log10 concentration (M)
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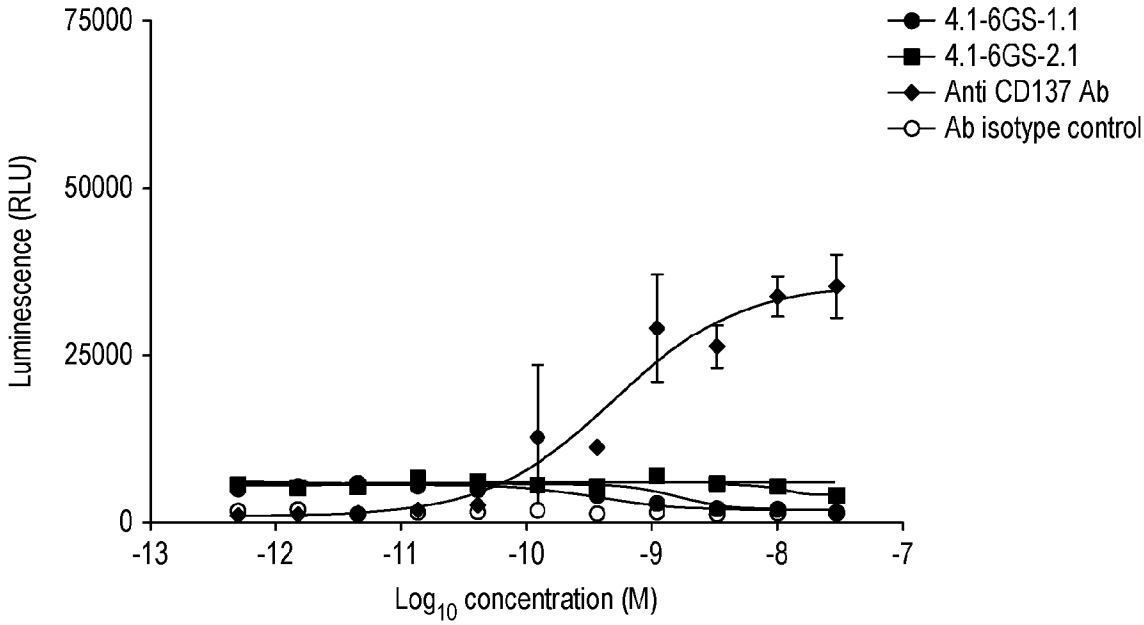
2.1
4.1-6GS-1.1
3.8-6GS-1.1
4.1-6GS-2.1
Anti CD137 Ab
Ab isotype control

FIG. 2B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Luminescence (RLU)
-13
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-10
-9
-8
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Log10 concentration (M)
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4.1-6GS-2.1
Anti CD137 Ab
Ab isotype control

FIG. 2C

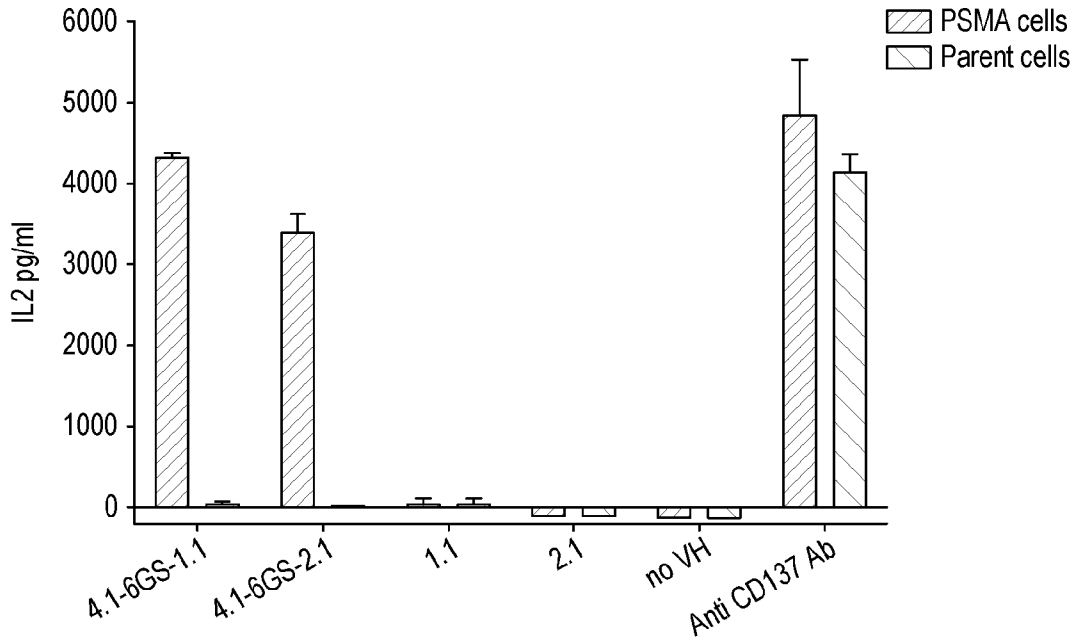
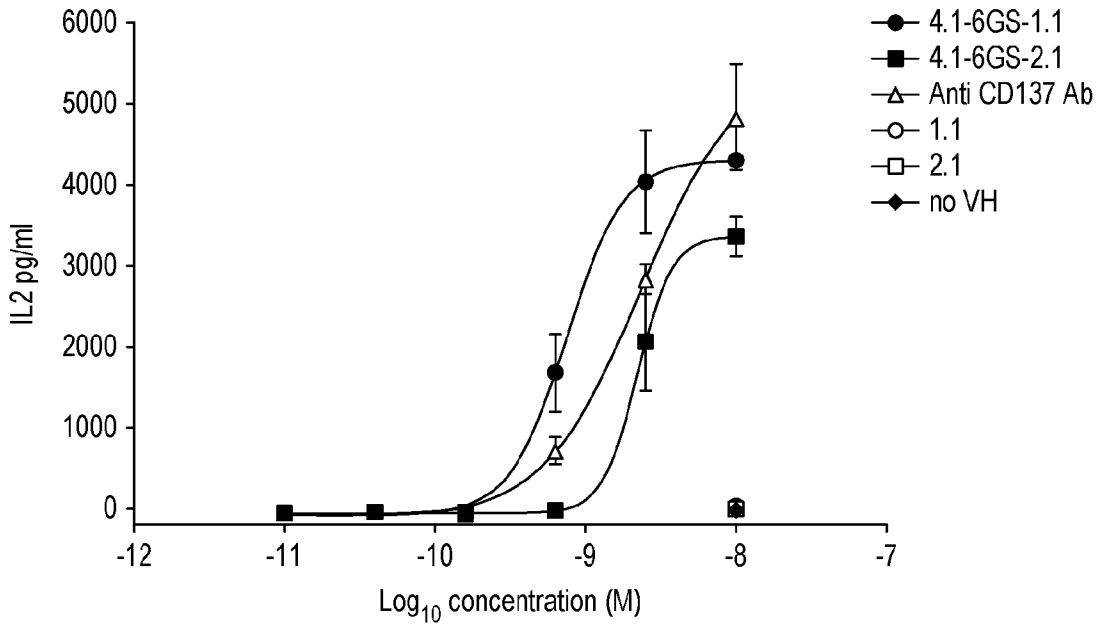

PSMA cells
Parent cells
IL2 pg/ml
6000
5000
4000
3000
2000
1000
0
4.1-6GS-1.1
4.1-6GS-2.1
1.1
2.1
no VH
Anti CD137 Ab

FIG. 3A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4.1-6GS-2.1
Anti CD137 Ab
1.1
2.1
no VH
IL2 pg/ml
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5000
4000
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2000
1000
0
-12
-11
-10
-9
-8
-7
Log10 concentration (M)

FIG. 3B

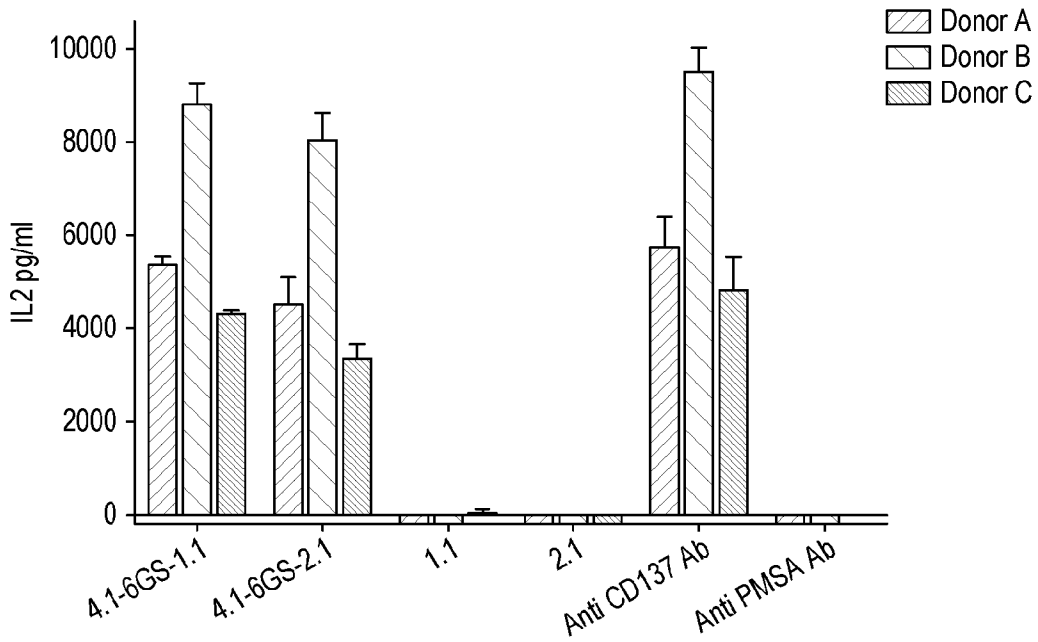
Donor A
Donor B
Donor C
IL2 pg/ml
10000
8000
6000
4000
2000
0
4.1-6GS-1.1
4.1-6GS-2.1
1.1
2.1
Anti CD137 Ab
Anti PMSA Ab

FIG. 3C

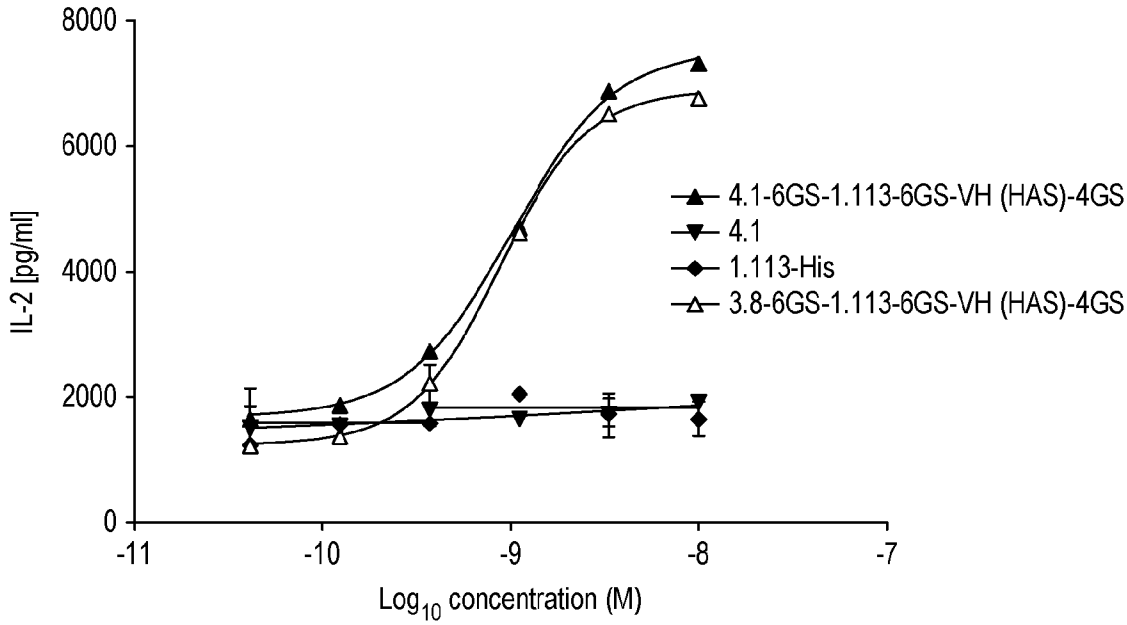
IL-2 [pg/ml]
8000
6000
4000
2000
0
-11
-10
-9
-8
-7
Log10 concentration (M)
4.1-6GS-1.113-6GS-VH (HAS)-4GS
4.1
1.113-His
3.8-6GS-1.113-6GS-VH (HAS)-4GS

FIG. 3D

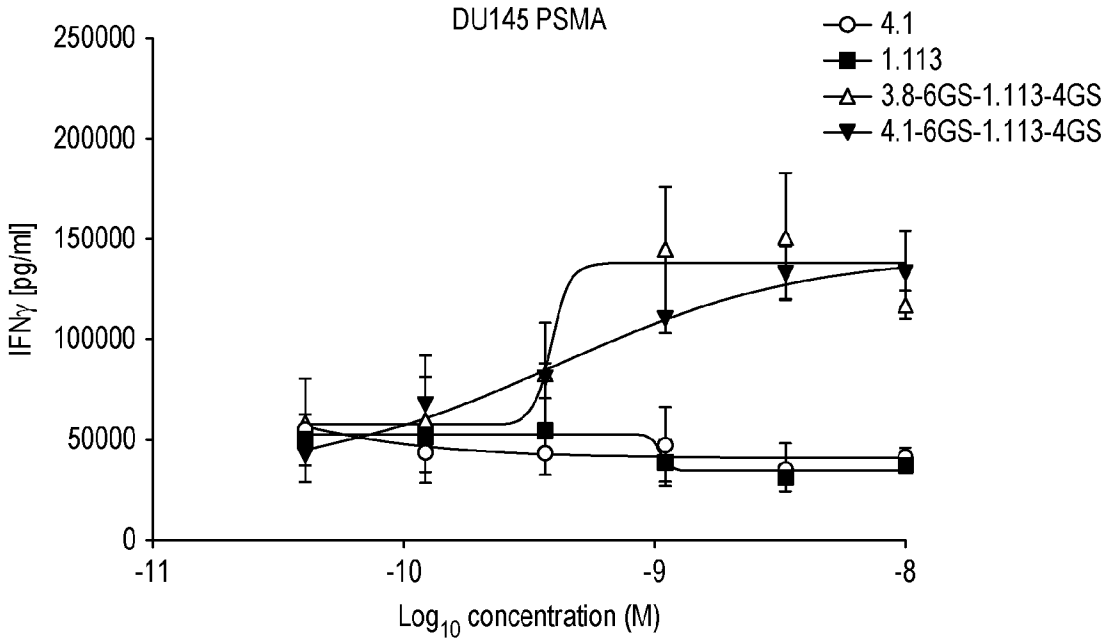
DU145 PSMA
4.1
1.113
3.8-6GS-1.113-4GS
4.1-6GS-1.113-4GS
IFNγ [pg/ml]
250000
200000
150000
100000
50000
0
-11
-10
-9
-8
Log10 concentration (M)

FIG. 3E

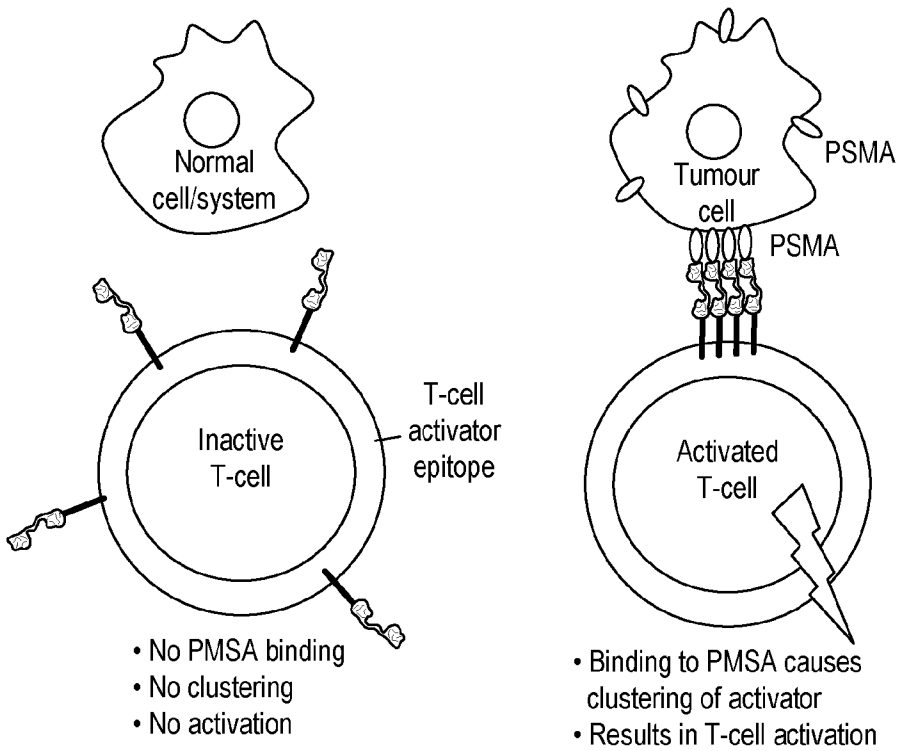
Normal cell/system
Tumour cell
PSMA
PSMA
Inactive T-cell
T-cell activator epitope
Activated T-cell
• No PMSA binding
• No clustering
• No activation
• Binding to PMSA causes clustering of activator
• Results in T-cell activation

FIG. 4

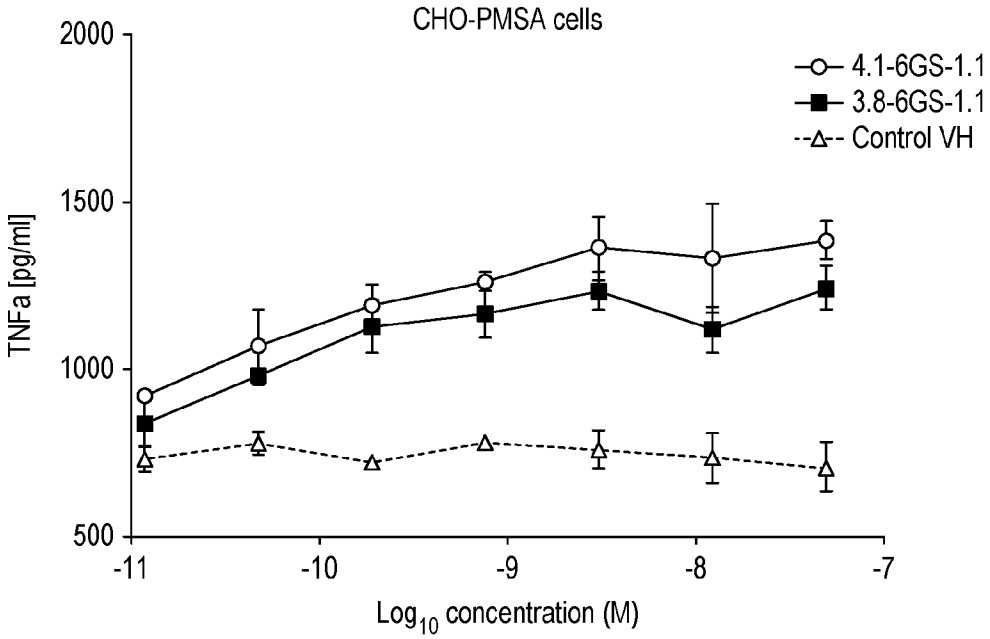
CHO-PMSA cells
4.1-6GS-1.1
3.8-6GS-1.1
Control VH
TNFa [pg/ml]
2000
1500
1000
500
-11
-10
-9
-8
-7
Log10 concentration (M)

FIG. 5A

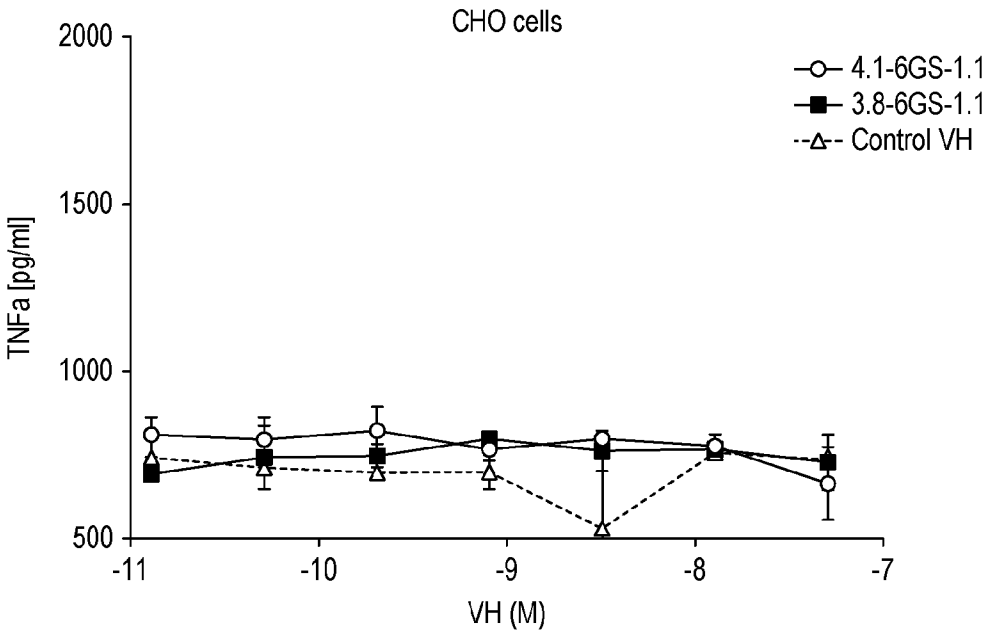
CHO cells
4.1-6GS-1.1
3.8-6GS-1.1
Control VH
TNFa [pg/ml]
2000
1500
1000
500
-11
-10
-9
-8
-7
VH (M)

FIG. 5B

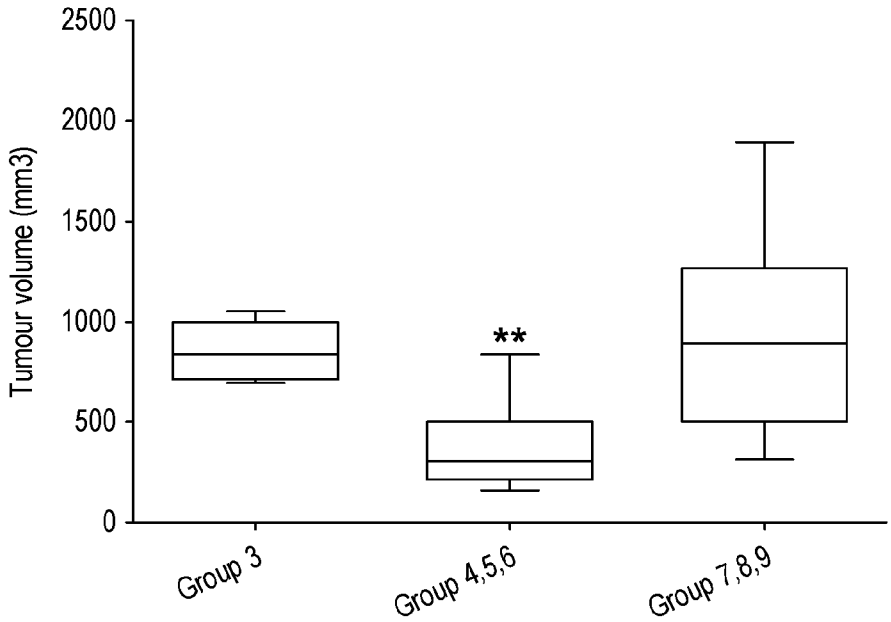
2500
2000
1500
1000
500
0
Tumour volume (mm3)
**
Group 3
Group 4,5,6
Group 7,8,9

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/053280

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 C07K16/30 A61P35/00 C07K16/46
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/123650 A2 (INHIBRX LP [US]) 20 July 2017 (2017-07-20) paragraph [0173] - paragraph [0174] paragraph [0211]; example 1 paragraph [0212] - paragraph [0213]; example 2 figure 21 paragraph [0229]	1-38
Y	WO 2016/062990 A1 (CRESCENDO BIOLOG LTD [GB]) 28 April 2016 (2016-04-28) the whole document	1-38
A	WO 2016/184882 A1 (PIERIS PHARMACEUTICALS GMBH [DE]) 24 November 2016 (2016-11-24) paragraph [0219] - paragraph [0224]; example 20	1-38

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2019	11/02/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Irion, Andrea

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2018/053280

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

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

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☒ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/053280

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2017/060144 A1 (F HOFFMANN-LA ROCHE AG [CH]; HOFFMANN-LA ROCHE INC [US]) 13 April 2017 (2017-04-13) page 4, lines 10-15 page 4, lines 20-24 page 248, line 14 - page 277, line 15	1-38
A	JUAN DUBROT ET AL: "Treatment with anti-CD137 mAbs causes intense accumulations of liver T cells without selective antitumor immunotherapeutic effects in this organ", CANCER IMMUNOLOGY, IMMUNOTHERAPY, SPRINGER, BERLIN, DE, vol. 59, no. 8, 25 March 2010 (2010-03-25), pages 1223-1233, XP019842192, ISSN: 1432-0851 the whole document	1-38
A	TIMOTHY S. FISHER ET AL: "Targeting of 4-1BB by monoclonal antibody PF-05082566 enhances T-cell function and promotes anti-tumor activity", CANCER IMMUNOLOGY, IMMUNOTHERAPY, vol. 61, no. 10, 11 March 2012 (2012-03-11), pages 1721-1733, XP055391951, Berlin/Heidelberg ISSN: 0340-7004, DOI: 10.1007/s00262-012-1237-1 page 1725, left-hand column, paragraph 3 - page 1727, right-hand column	1-38
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/053280

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DASS S VINAY ET AL: "Therapeutic potential of anti-CD137 (4-1BB) monoclonal antibodies", EXPERT OPINION ON THERAPEUTIC TARGETS, vol. 20, no. 3, 1 October 2015 (2015-10-01), pages 361-373, XP055447708, UK ISSN: 1472-8222, DOI: 10.1517/14728222.2016.1091448 abstract page 368, right-hand column, paragraph 1 the whole document -----	1-38
A	HOLT L J ET AL: "Anti-serum albumin domain antibodies for extending the half lives of short lived drugs", PROTEIN ENGINEERING, DESIGN AND SELECTION, OXFORD JOURNAL, LONDON, GB, vol. 21, no. 5, 1 May 2008 (2008-05-01), pages 283-288, XP002591536, ISSN: 1741-0126, DOI: 10.1093/PROTEIN/GZM067 [retrieved on 2008-04-02] abstract -----	1-38
Y	WO 2017/122017 A1 (CRESCENDO BIOLOGICS LTD [GB]) 20 July 2017 (2017-07-20) page 19; table 1 page 26; table 2 page 75, line 25 - page 76, line 36 -----	1-38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2018/053280

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		WO 2016184882 A1	24-11-2016
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		AU 2016334623 A1	15-02-2018
		BR 112018002128 A2	11-09-2018
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		CO 2018000967 A2	19-04-2018
		CR 20180171 A	03-05-2018
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