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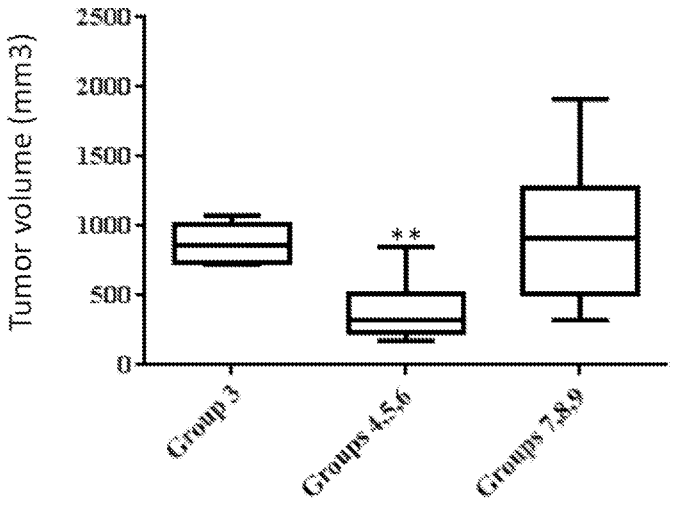
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(54) Title: Single Domain Antibodies that Bind to CD137

Figure 7



(57) Abstract: The disclosure relates to CD137 binding agents and the use of such binding agents in the treatment, prevention and detection of disease.

[Continued on next page]

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Single Domain Antibodies that bind to CD137

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 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.

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 multimerisation of the receptor and recruitment of signalling molecules such as the TRAF family of proteins leading to kinase modulation and activation of the Nf-KB pathway. Thus, multimerisation 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, 2014). 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.

Development of a CD137 binding molecule that possess minimal agonistic and internalising activity would therefore provide a building block for the generation of bispecific molecules that co-target CD137 and other molecules, for example tumour associated antigens expressed within the tumour microenvironment. In such molecules dual, e.g. simultaneous engagement of both targets may result in CD137 activation thus restricting the site of action to the tumor microenvironment and potentially minimising undesirable effects of CD137 therapy.

Summary

The invention relates to novel binding molecules with specificity for CD137. The inventors have identified single variable heavy chain domain antibodies that bind to CD137, but 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 an agonistic response. Thus, whilst the single variable heavy chain domain antibodies that bind to CD137 do not induce clusterisation 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.

In one aspect, there is provided an isolated single variable heavy chain domain antibody which binds to human CD137 but does not elicit CD137 signalling when bound to CD137 as a monospecific entity. In one embodiment, said single variable heavy chain domain antibody inhibits the binding of CD137L to CD137.

In one embodiment, the single variable heavy chain domain antibody comprises a CDR1 comprising a SEQ ID NO. selected from table 1, a CDR2 comprising a SEQ ID NO. selected from table 1 and a CDR3 comprising a SEQ ID NO. selected from table 1. Preferably, the CDRs are defined using Kabat nomenclature.

In one embodiment, the single variable heavy chain domain antibody 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. Preferably, the CDRs are defined using Kabat nomenclature.

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

In one embodiment, the single variable heavy chain domain antibody comprises SEQ ID NO. 4 or 428 or a sequence with at least 50% homology thereto.

In one embodiment, the single variable heavy chain domain antibody is selected from SEQ ID NOs. 4, 312, 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 50% homology thereto. In one embodiment, the single variable heavy chain domain antibody is capable of binding CD137 with an affinity with a KD of about 0.4nM or of about 3nM. In one embodiment, the single variable heavy chain domain antibody is obtained or obtainable from a transgenic rodent, e.g. mouse, that expresses a transgene comprising human V, D and J regions.

In one embodiment, the said rodent does not produce functional endogenous light and heavy chains.

Also provided in another aspect is a binding molecule comprising

a) a single variable heavy chain domain antibody that binds to CD137 described herein and

b) a moiety that binds to a tumor specific antigen.

In one embodiment, the moiety that binds to a tumor specific antigen is a single variable heavy chain domain antibody. In one embodiment of the binding molecule, the single variable heavy chain domain antibody that binds to CD137 is linked to the single variable heavy chain domain antibody that binds to a tumor specific antigen by a peptide linker. In one embodiment, said linker is selected from a (G4S)n linker wherein n is 1 to 10. In one embodiment, the tumor specific antigen is selected from PSMA, Her2, CD123,

CD19, CD20, CD22, CD23, CD74, BCMA, CD30, CD33, CD52, EGRF CECAM6, CAXII, CD24, CEA, Mesothelin, cMet, TAG72, MUC1, MUC16, STEAP, EphvIII, FAP, GD2, IL-13Ra2, L1-CAM, PSCA,GPC3, Her3, gpA33, 5T4 and ROR1. In one embodiment, the isolated single variable heavy chain domain antibody or the binding molecule is conjugated to a toxin, enzyme, radioisotope, half-life extending moiety, label, therapeutic molecule or other chemical moiety. In one embodiment, the said half-life extending moiety is selected from 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, or an albumin binding peptide or single domain antibody that binds to human serum albumin.

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

In another aspect, we provide the single variable heavy chain domain antibody, binding molecule pharmaceutical composition described above for use in the treatment of disease, for example wherein said disease is selected from cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency or other immune system-related disorder.

Also provided is a method for treating a cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency or other immune system-related disorder comprising administering a therapeutically effective amount of the single variable heavy chain domain antibody, binding molecule or a pharmaceutical composition described above.

In another aspect, we provide a kit comprising a single variable heavy chain domain antibody, binding molecule or a pharmaceutical composition as described herein.

In another aspect, we provide a nucleic acid molecule comprising a nucleic acid sequence encoding a single variable heavy chain domain antibody as described herein, for example a nucleic acid molecule comprising SEQ ID NO. 629 or 735 or a nucleic acid molecule having at least 50% homology thereto. In another aspect, we provide a vector or host cell comprising a nucleic acid molecule according to the above.

In another aspect, we provide methods for producing a single variable heavy chain domain antibody that binds to human CD137. We also provide a single V_H domain antibody obtained or obtainable by the method. In another aspect, we provide a transgenic rodent, e.g. mouse, that produces a heavy chain only antibody that binds to CD137 produced upon immunisation with a CD137 antigen. We also provide a heavy chain only antibody comprising a V_H domain that binds to human CD137 obtained or obtainable from a transgenic rodent.

In another aspect, we provide a method for promoting CD8+ T cell expansion, inducing activation of cytotoxic T lymphocytes (CTL) and/or cytokine release comprising administering to a subject a single variable heavy chain domain antibody, a binding molecule or a pharmaceutical composition as described herein.

In another aspect, we provide a use of a single variable heavy chain domain antibody as described herein in a binding molecule that further comprises a single heavy variable chain domain antibody which binds to a tumor specific antigen.

Figures

The invention is further described in the following non-limiting figures. The single domain antibody as used in the figures is listed in tables 2 and 3.

Figure 1. Binding kinetics of monovalent, bivalent and trivalent Humabody® V_H. Association and dissociation kinetics of **(A)** Monovalent, **(B)** Bivalent and **(C)** trivalent versions of Humabody® V_H 1.1 (SEQ ID No. 4) and **(D)** monovalent, **(E)** bivalent and **(F)** trivalent Humabody® V_H 2.1 (SEQ ID NO. 428) were measured for binding to human CD137huFc tagged protein captured onto Protein G sensors using biolayer interferometry. Multivalent formats show enhanced binding compare to monovalent Humabody® V_H.

Figure 2: 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 showed increased binding signal confirming dual target binding.

Figure 3. Activation of CD137 signalling in the Jurkat NF-kB Luciferase Reporter Assay. PSMA expressing cells **(A and B)** or non-expressing parental cells **(C and D)** were co-cultured with Jurkat human CD137 NF-kB-luciferase reporter cells. **(E)** CHO PSMA cells, **(F)** DU145 PSMA cells or **(G)** 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, bivalent, trivalent and bispecific versions of Humabody® V_H 1.1 (SEQ ID No. 4) and monovalent, bivalent, trivalent and bispecific versions of Humabody® V_H 2.1 (SEQ ID NO. 428) were tested for the potential to agonise CD137 to result in signalling via NF-kB. Monovalent PSMA Humabody® V_{Hs} were included as controls. Monovalent, bivalent and trivalent molecules did not act as agonists in the assay. Bispecific molecules in the presence of PSMA expressing cells were able to effectively stimulate CD137 signalling.

Figure 4. Enhancement of IL-2 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 (SEQ ID No. 4) monovalent and bispecific molecules, Humabody® V_H 2.1 (SEQ ID No. 428) monovalent and bispecific molecules, anti CD137 benchmark antibody and anti PSMA antibody were added at a concentration of 10nM. Supernatants were harvested after 48 hours and levels of IL-2 determined. **(A)** Enhancement of IL-2 responses for 3 different T-cell donors in the presence of PSMA expressing cells. **(B)** Representative data for measurement of IL-2 levels in the presence of parental cells. Monovalent Humabody® V_H did not stimulate IL2 production in the assay. **(C)** Bispecific molecules in the presence of PSMA expressing cells were able to effectively enhance IL-2 production. The anti CD137 antibody (soluble, non-cross linked) enhanced IL-2 production in a PSMA independent response. **(D and E)** Concentration dependence of IL-2 response. **(F)** Bispecific molecules induce interferon gamma.

Figure 5. CD137 mediated Internalisation

(A) V_H 1.1 (SEQ ID No. 4), (B) trivalent V_H and (C) anti CD137 antibody were incubated with CHO CD137 cells at 4°C to allow binding them at 37°C for internalisation. Cells were co- stained with anti-human Ig AF488 antibody or anti His/anti Mouse Ig AF488 antibody followed by anti LAMP1/anti rabbit Ig AF488 for detection of lysosomes. Monovalent V_H showed minimal internalisation remaining predominantly cell surface bound with no co-localisation to lysosomes. Multivalent monospecific V_H showed increased internalisation as indicated by presence of clusters inside the cell but were not co-localised to lysosomes. CD137 antibody co-localised with the lysosome staining demonstrating this molecule is internalised.

Figure 6. Mode of action of a bispecific molecule. This figure illustrates the mode of action of a binding molecule that binds simultaneously to CD137 and a tumor specific antigen, such as PSMA, leading to tumor selective T cell agonism.

Figure 7: 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, n=5 mice per donor) were treated on days 33-45 with 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.

The T cell costimulatory receptor CD137 is an important regulator of immune responses and therefore an important target in cancer therapy. 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 multimerisation 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.

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 multimerisation 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. CD137 signalling is activated only when the single variable heavy chain domain antibodies are provided together with another moiety specific to a second antigen, for example as a multispecific , e.g. 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.

A monovalent molecule has one antigen binding site and binds to a single target. A bivalent molecule has two antigen binding sites and binds to a single target. A bispecific molecule binds to two different targets (antigens). A trispecific molecule binds to three different targets (antigens) and so forth.

When a single variable heavy chain domain antibody as described herein is provided as part of a fusion protein together with a second moiety, for example a molecule that binds specifically to a tumor specific antigen, dual binding to both the second target moiety and to CD137 results in multimerisation of the CD137 receptor and CD137 signalling. Induction of CD137 signalling thus requires dual engagement of both targets, i.e. CD137 and the tumor specific antigen. This leads to localised CD137 signalling in the tumor microenvironment. Only dual, e.g. simultaneous engagement of both targets by the multispecific molecule results in CD137 activation. Target specific activation in the vicinity of the tumor 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 potentially avoiding unwanted liver toxicity.

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.

In particular, as explained below, the single domain antibodies described herein can be used in a multivalent or multispecific format. Thus, the single domain antibodies described herein are can be used as building blocks for multispecific molecules and the invention also relates to multifunctional binding agents comprising a single domain antibody as described herein.

The properties of the single domain antibodies of the invention as described above can be exploited in therapeutic methods and uses as well as in pharmaceutical formulations as described herein.

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
ACCATTTATGAGACCAGTACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAG
AAGAAGGAGGATGTGAACTGTGA (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 single domain antibody or binding molecule of the invention, including a multispecific, e.g. bispecific or trispecific, 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 single domain antibody is useful as a therapeutic agent in targeting a cell or tissue expressing the antigen CD137 as described herein. Binding is to the extracellular domain of CD137.

Binding molecules of the invention, including the single domain antibodies and multispecific binding agents described herein, bind specifically to human CD137. In other words, binding to the CD137 antigen is measurably different from a non-specific interaction. As demonstrated in the examples, the single domain antibodies of the invention do not cross react with mouse CD137. Preferably, the single domain antibodies of the invention bind to human CD137 and also bind to monkey (e.g., cynomolgus) CD137.

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

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 is comprised of 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 a F(ab')2, Fab, Fv, scFv, heavy chain, light chain, variable 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 variable heavy (V_H) or 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 “immunoglobulin single variable domain”. A single domain antibody (~12 to 15 kDa) has thus either the V_H or V_L domain. 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” (for single domain antibody) generally refers to a single immunoglobulin variable domain (V_H, V_{HH} or V_L) polypeptide that specifically binds antigen. For use in therapy, human single domain antibodies are preferred over camelid derived V_{HH}, primarily because they are not as likely to provoke an immune response when administered to a patient.

The terms “single domain antibody”, “single variable domain antibody”, “single variable heavy chain domain antibod”, “single V_H domain antibody”, “immunoglobulin single variable domain (ISV)” or “immunoglobulin single variable domain antibody” are 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, e.g. “single heavy chain domain antibody”, “single variable heavy chain domain antibody, “immunoglobulin single heavy chain variable domain”, “single V_H single domain antibody” ,“V_H single domain antibody”, “single heavy chain domain”, “single variable heavy chain domain”, “single V_H single domain” ,“V_H single domain” describe the single heavy chain variable fragment of an antibody which retains binding specificity to the antigen in the absence of light chain or other antibody fragments. A single variable “heavy chain domain antibody, single variable heavy chain domain, immunoglobulin single heavy chain variable domain (ISV), human V_H single domain” etc as used herein therefore does not comprise any other parts of a full antibody, but the antigen binding V_H domain only; e.g. it only includes the V_H domain and does not comprise constant heavy chain domains and does not comprise a light chain. A single variable heavy chain domain antibody is capable of binding to an antigen in the absence of light chain.

In one aspect, the invention relates to an isolated single variable heavy chain domain antibody that binds to human CD137.

As explained below, the embodiments relate to single variable heavy chain domain antibodies /immunoglobulin single variable heavy chain domains which bind a CD137 antigen. Thus, the single variable heavy chain domain antibody 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.

Thus, in some embodiments, the isolated binding agents/molecules comprise or consist of at least one single domain antibody wherein said domain is a human variable heavy chain domain; they are devoid of V_L domains and V_H constant domains and bind to the target antigen. In other embodiments, the isolated binding agents/molecules comprise or consist of two or more single domain antibodies.

The term "isolated" refers to a moiety that is isolated form its natural environment. For example, the term "isolated" refers to a single domain antibody that is substantially free of other single domain antibodies, 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). 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. (G4S)n linkers wherein n= 1 to 15, e.g. one of SEQ ID NO. 790-797.

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 by 1 to 5 amino acids.

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 percent homology, and not considering any conservative substitutions as part of the sequence identity. Thus, the percent homology between two amino acid sequences is equivalent to the percent 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 percent 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 V_H domain, a V_{HH} domain, a humanised V_{HH} domain, a camelized V_H domain or 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 human variable domain (V_H). The term single V_H domain antibody as used herein designates a single human variable heavy chain domain antibody.

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 germline 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. a 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.

In some embodiments, the single domain antibody is a single domain antibody wherein the domain is a human variable heavy chain (V_H) domain. Thus, in preferred embodiments, the invention provides isolated single domain antibodies that bind human CD137, wherein the domain is a variable heavy chain domain, preferably a V_H domain and wherein said single domain antibodies bind to human CD137.

In one aspect, the invention relates to a single variable heavy chain domain antibody (i.e. a monovalent binding molecule, that is a molecule that has one binding entity only), wherein the single domain antibody exhibits one or more of the following properties:

(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 as shown in example 6;

(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 as shown in example 6;

(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 9;

(g) does not bind to mouse CD137;
(h) provides good stability as shown in the examples;
(i) does not increase reporter gene activity and thus does not have agonistic CD137 activity. This can be measured as shown in example 9;
(j) binds to cynomolgus CD137 and/or
(k) inhibits tumor growth in vivo when linked to a V_H that binds to PSMA. This can for example be measured as in the examples, e.g. in example 10.

In one embodiment the single variable heavy chain domain antibody has more than one feature selected from a) to jk, for example a combination of 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 features. In one embodiment, the single variable heavy chain domain antibody inhibits the interaction between CD137 ligand and CD137 expressed on the surface of cells. In one embodiment, the single variable heavy chain domain antibody inhibits the interaction between CD137 ligand and CD137 expressed on the surface of cells and also shows one or more of the features listed in a, b, c, e to k.

Exemplary sequence features

In one aspect, the single variable heavy chain domain antibody comprises a CDR1, CDR2 and/or CDR3 as shown for one of the single domain antibodies as shown in Table 1. In one aspect, the single variable heavy chain domain antibody comprises a set of CDR1, CDR2 or CDR3 selected form the set of CDRs as shown for one of the single domain antibodies as shown Table 1. In one embodiment, the CDR1, CDR2, CDR3 with at least 40%, at least 75% or at least 80% homology to one of the CDRs in Table 1. In one aspect, the single variable heavy chain domain antibody comprises a CDR1 comprising SEQ ID NO. 1 or a sequence with at least 40% at least 75% or at least 80% homology thereto, a CDR2 comprising SEQ ID NO. 2 or a sequence with at least 40%, at least 75%, at least 80% or at least 90% homology thereto and a CDR3 comprising SEQ ID NO. 3 or a sequence with at least 40%, at least 75%, at least 80% or at least 90% homology, or a CDR1 comprising SEQ ID NO. 5 or a sequence with at least 40%, at least 75%, at least 80% or at least 90% homology thereto, a CDR2 comprising SEQ ID NO. 6 or a sequence with at least 40% homology thereto and a CDR3 comprising SEQ ID NO. 7 and so forth. In one embodiment, the single variable heavy chain domain antibody comprises a CDR1, CDR2 or CDR3 as shown in SEQ IDs 309, 310 and 311 or sequences with at least 75% homology thereto. In one embodiment, the single variable heavy chain domain antibody comprises a CDR1, CDR2 or CDR3 as shown in SEQ IDs 873, 874 and 875 or sequences with at least 40%, at least 75%, at least 80% or at least 90% homology thereto. The CDRs are defined according to Kabat.

Sequence homology as defined above and generally as defined 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 one aspect, the single variable heavy chain domain antibody comprises or consists of a full length sequence as shown in Table 1 or a sequence with at least 50%, 60%, 70%, 80%, 90% homology thereto. For example, the single variable heavy chain domain antibody comprising a full length sequence that comprises or consists of a sequence selected from the sequences listed in Table 1, 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 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 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 1.90 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 is selected from V_H 1.78 or a variant thereof. In one embodiment, the single variable heavy chain domain antibody comprises CDR1, 2, and 3 as shown for a V_H single domain antibody selected from V_H 1.107 to 1.114 or a sequence with at least 75% homology thereto (e.g. 90% or 95%). In one embodiment, the single variable heavy chain domain antibody is selected from V_H 1.107 to 1.114 as shown in table 1, that is SEQ ID No. 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 75% homology thereto (e.g. 90% or 95%). In one embodiment, the single variable heavy chain domain antibody is selected from V_H 1.113 as shown in table 1 or a sequence with at least 75%, 80%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence homology thereto.

Table 1 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 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.2	SEQ ID NO: 5 SYWMT	SEQ ID NO: 6 HIKEDGSEKY YVDSVEG	SEQ ID NO: 7 GGDGYSDSHY GVDV	SEQ ID NO: 8 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWFRQAPGKGL EWVAHIKEDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAEDT AVYYCARGGDGYSDSHYGVDVWGQGTTVTVSS
1.3	SEQ ID NO: 9 SYWMT	SEQ ID NO: 10 NINQDGSEK YYVDSVEG	SEQ ID NO: 11 GGLGYGDSHY GMDV	SEQ ID NO: 12 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMTWFRQAPGRGL EWVANINQDGSEKYYVDSVEGRFTVSRDNAKNSLYLQMNSLRAED TAVYYCARGGLGYGDSHYGMDVWGQGTTVTVSS
1.4	SEQ ID NO: 13 NYWMT	SEQ ID NO: 14 NINQDGSEK YYVDSVEG	SEQ ID NO: 15 GGLGYGDSHY GMDV	SEQ ID NO: 16 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMTWFRQAPGGG LEWVANINQDGSEKYYVDSVEGRFTVSRDNAKNSLYLQMNSLRAE DTAVYYCARGGLGYGDSHYGMDVWGQGTTVTVSS
1.5	SEQ ID NO: 17 NYWMI	SEQ ID NO: 18 NINQDGSEK YYVDSVEG	SEQ ID NO: 19 GGDGYSGSHH GTDV	SEQ ID NO: 20 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWFRQAPGKGL EWVANINQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGDGYSGSHHGTDVWGQGTTVTVSS

1.6	SEQ ID NO: 21 SYWMS	SEQ ID NO: 22 NIKQDGSEKY YVDSVKG	SEQ ID NO: 23 GGEGYSTSHYG MDV	SEQ ID NO: 24 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGL EWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGEGYSTSHYGMDVWGQGTTVTVSS
1.7	SEQ ID NO: 25 SYWML	SEQ ID NO: 26 NINQDGSEK YYVDSVKG	SEQ ID NO: 27 GGDGYSDSHF GTDV	SEQ ID NO: 28 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGKGL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNTLRAEDT AIYYCARGGDGYSDSHFGTDVWGQGTTVTVSS
1.8	SEQ ID NO: 29 SYWMF	SEQ ID NO: 30 NINQDGSEK YYVDSVEG	SEQ ID NO: 31 GGDGYSDSHY GTDV	SEQ ID NO: 32 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMFWFRQAPGEGL EWVANINQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDT AIYYCARGGDGYSDSHYGTDVWGQGTTVTVSS
1.9	SEQ ID NO: 33 NYWMT	SEQ ID NO: 34 NINQDGSEK YYVDSVEG	SEQ ID NO: 35 GGLGYGDSHY GMDV	SEQ ID NO: 36 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMTWFRQAPGGG LEWVANINQDGSEKYYVDSVEGRFTVSRDNAKNSLDLQMNSLRAE DTAVYYCARGGLGYGDSHYGMDVWGQGTTVTVSS
1.10	SEQ ID NO: 37 DYWMN	SEQ ID NO: 38 NIKEDGSEKY YVDSVEG	SEQ ID NO: 39 GGAGYSMSHY GMDV	SEQ ID NO: 40 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYWMNWARQAPGKG LEWVANIKEDGSEKYYVDSVEGRFTISRDNAKNSTYLQMNSLRVEDT AVYYCARGGAGYSMSHYGMDVWGQGTTVTVSS
1.11	SEQ ID NO: 41 DYWMN	SEQ ID NO: 42 NIKEDGSEKY YVDSVEG	SEQ ID NO: 43 GGAGYSMSHY GMDV	SEQ ID NO: 44 EVQLVESGGGLVQPGGSLRLSCEASGFTFSDYWMNWARQAPGKG LEWVANIKEDGSEKYYVDSVEGRFTISRDNAKNSTYLQMNSLRAEDT AVYYCARGGAGYSMSHYGMDVWGQGTTVTVSS
1.12	SEQ ID NO: 45 SYWML	SEQ ID NO: 46 NINQDGSEK YYVDSVKG	SEQ ID NO: 47 GGDGYSNSHF GTDV	SEQ ID NO: 48 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGKGL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNTLRAEDT AIYYCARGGDGYSNSHFGTDVWGQGTTVTVSS
1.13	SEQ ID NO: 49 SYWMF	SEQ ID NO: 50 NINQDGSEK YYVDSVEG	SEQ ID NO: 51 GGDGYSDSHY GTDV	SEQ ID NO: 52 EVQLVESGGGLVKPGGSLRLSCGASGFTFSSYWMFWFRQAPGEGL EWVANINQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAEDT AIYYCARGGDGYSDSHYGTDVWGQGTTVTVSS
1.14	SEQ ID NO: 53 NYWMN	SEQ ID NO: 54 NIKEDGSENY YVDSVKG	SEQ ID NO: 55 GGEGYSTSHYG MDV	SEQ ID NO: 56 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKG LEWVANIKEDGSENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYSTSHYGMDVWGQGTTVTVSS
1.15	SEQ ID NO: 57 TYWML	SEQ ID NO: 58 NINQDGSEK YYVDSVKG	SEQ ID NO: 59 GGDGYSDSHF GTDV	SEQ ID NO: 60 EVQLVESGGGLVQPGGSLRLSCGASGFTFSTYWMLWFRQAPGKGL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLSLQMNSLRAEDT ATYYCARGGDGYSDSHFGTDVWGQGTTVTVSS
1.16	SEQ ID NO: 61 NYWMM	SEQ ID NO: 62 NINQDGSEK YFVDSVEG	SEQ ID NO: 63 GGDGYSSSHY GTDV	SEQ ID NO: 64 EVQLVESGGGLVQPGGSLRLSCVASGFTFSNYWMMWFRQAPGKG LEWVANINQDGSEKYFVDSVEGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGDGYSSSHYGTDVWGQGTTVTVSS
1.17	SEQ ID NO: 65 SYWMN	SEQ ID NO: 66 NIKEDGSEKY YVDSVKG	SEQ ID NO: 67 GGDSYGYRDY GMDV	SEQ ID NO: 68 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKG LEWVANIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.18	SEQ ID NO: 69 THWMN	SEQ ID NO: 70 NINQDGSEK YYVDSVEG	SEQ ID NO: 71 GGVGYGDSHF GMDV	SEQ ID NO: 72 EVQLVESGGGLVQPGGSLRLSCAASGFTFSTHWMNWARQAPGKE LEWVANINQDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAED TAVYYCARGGVGYGDSHFGMDVWGLGTTVTVSS
1.19	SEQ ID NO: 73 SYWMI	SEQ ID NO: 74 NINQDGSEK	SEQ ID NO: 75 GGDDYSNSHY GMDV	SEQ ID NO: 76 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMIWVRQAPGKGL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT

		YYVDSVKG		AVYYCARGGDDYSNSHYGMDVSGQGTTVTVSS
1.20	SEQ ID NO: 77 SYWMN	SEQ ID NO: 78 NINQDGSEK YYVDSVQG	SEQ ID NO: 79 GGFGYGDSHY GMDV	SEQ ID NO: 80 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKG LEWVANINQDGSEKYYVDSVQGRFTISRDNANNSLYLQMNSLRAE DTAVYYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.21	SEQ ID NO: 81 SYWMF	SEQ ID NO: 82 NVNQDGSEK YYVDSVEG	SEQ ID NO: 83 GGEGYSDSHY GTDV	SEQ ID NO: 84 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMFWFRQAPGKEL EWVANVNQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAED TAIYYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.22	SEQ ID NO: 85 NYWMN	SEQ ID NO: 86 NIKEDGSEKY YVDSVEG	SEQ ID NO: 87 GGEGYGDSHY GMDV	SEQ ID NO: 88 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKG LEWVANIKEDGSEKYYVDSVEGRFTISRDNARNSLYLQMNSLRAEDT AVYYCARGGEGYGDSHYGMDVSGQGTTVTVSS
1.23	SEQ ID NO: 89 SYWMN	SEQ ID NO: 90 NIKQDGSEKY YVDSVKG	SEQ ID NO: 91 GGEGYGDDHY GMDV	SEQ ID NO: 92 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLTAED TAVYYCARGGEGYGDDHYGMDVWGQGTTVTVSS
1.24	SEQ ID NO: 93 SYWMS	SEQ ID NO: 94 NIKQDGSEKY YVDSVKG	SEQ ID NO: 95 GGEGYGDYHY GLDV	SEQ ID NO: 96 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYGDYHYGLDVSGQGTTVTVSS
1.25	SEQ ID NO: 97 SYWMN	SEQ ID NO: 98 NIKQDGSEKY YVDSVKG	SEQ ID NO: 99 GGDSYGYRDY GMDV	SEQ ID NO: 100 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.26	SEQ ID NO: 101 THWMN	SEQ ID NO: 102 NINQDGSEK YYVDSVEG	SEQ ID NO: 103 GGVGYGDSHF GMDV	SEQ ID NO: 104 EVQLVESGGGLVQPGGSLRLSCVASGFTFSTHWMNWARQAPGKE LEWVANINQDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAED TAVYYCARGGVGYGDSHFGMDVWGLGTTVTVSS
1.27	SEQ ID NO: 105 SYWML	SEQ ID NO: 106 NINQDGSEK YYVDSVEG	SEQ ID NO: 107 GGEGYSDSHH GTDV	SEQ ID NO: 108 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGEGL EWVANINQDGSEKYYVDSVEGRLTISRDNAKNALYLQMNSLRAEDT AIYYCARGGEGYSDSHHGTDVWGQGTTVTVSS
1.28	SEQ ID NO: 109 NYWMN	SEQ ID NO: 110 NIKQDGSEKY YVDSVKG	SEQ ID NO: 111 GGDNYAYRDF GMDV	SEQ ID NO: 112 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGDNYAYRDFGMDVWGQGTTVTVSS
1.29	SEQ ID NO: 113 NYWMF	SEQ ID NO: 114 NVNQDGSEK YYVDSVEG	SEQ ID NO: 115 GGEGYSDSHY GTDV	SEQ ID NO: 116 EVQLVESGGGLVQPGGSLRLSCGASGFTFSNYWMFWFRQAPGKEL EWVANVNQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAED TAIYYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.30	SEQ ID NO: 117 SYWMN	SEQ ID NO: 118 NINQDGSEK YYVDSVKG	SEQ ID NO: 119 GGEEYGSSHYG MDV	SEQ ID NO: 120 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKG LEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEEYGSSHYGMDVWGLGTTVTVSS
1.31	SEQ ID NO: 121 SYWMN	SEQ ID NO: 122 NINQDGSEK YYVDSVKG	SEQ ID NO: 123 GGDSYGYRDY GMDV	SEQ ID NO: 124 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKG LEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.32	SEQ ID NO: 125 SYWMN	SEQ ID NO: 126 NINQNGSEK YYVDSVEG	SEQ ID NO: 127 GGFGYGDSHY GMDV	SEQ ID NO: 128 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQTPGKGL EWVANINQNGSEKYYVDSVEGRFNISRDNAKNSLYLQMSSLRAEDT AVYYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.33	SEQ ID NO: 129	SEQ ID NO: 130	SEQ ID NO: 131	SEQ ID NO: 132 EVQLVESGGGLVQAGGSLRLSCVASGFTFSNYWMTWFRQAPGKGL

	NYWMT	NINQDESEEY YVDSVKG	GGDGYSDSHY GTDV	EWVANINQDESEEYYVDSVKGRFTISRDNAKNSLFLQMNSLRAEDT AIYYCARGGDGYSDSHYGTDVWGQGTTVTVSS
1.34	SEQ ID NO: 133 NYWMN	SEQ ID NO: 134 NIKEDGSENY YVDSVKG	SEQ ID NO: 135 GGEGYSTSHYG MDV	SEQ ID NO: 136 QVQLQESGGGLVQPGGSLRLSCTASGFTFSNYWMNWVRQAPGKG LEWVANIKEDGSENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYSTSHYGMDVWGQGTTVTVSS
1.35	SEQ ID NO: 137 NYWMN	SEQ ID NO: 138 NIKQDGSEKY YVDSVEG	SEQ ID NO: 139 GGEGYGESHY GMDV	SEQ ID NO: 140 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKG LEWVANIKQDGSEKYYVDSVEGRFTISRDNAKNSLYLQMDSLRAED TAVYYCARGGEGYGESHYGMDVSGQGTTVTVSS
1.36	SEQ ID NO: 141 TYWMN	SEQ ID NO: 142 NIKQDGSEKY YVDSVKG	SEQ ID NO: 143 GGDSYGYRDY GMDV	SEQ ID NO: 144 EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYWMNWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGDSYGYRDYGMDVWGQGTTVTVSS
1.37	SEQ ID NO: 145 YYWMI	SEQ ID NO: 146 NINQDGSEK YYVDSVKG	SEQ ID NO: 147 GGDGYSNSHF GMDV	SEQ ID NO: 148 EVQLVESGGGLVQPGGSLRLSCAASGFTFSYYWMIWFRQAPGEELE WVANINQDGSEKYYVDSVKGRFIISRDNATNSLFLQMNSLRAEDTA VYYCARGGDGYSNSHFGMDVWGQGTTVTVSS
1.38	SEQ ID NO: 149 NYWMI	SEQ ID NO: 150 NINQDGSEK YYVDSVKG	SEQ ID NO: 151 GGEGYSDSHY GTDV	SEQ ID NO: 152 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWYRQAPGEEL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AIYYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.39	SEQ ID NO: 153 NYWMN	SEQ ID NO: 154 NINQDESEKY YVDSVKG	SEQ ID NO: 155 GGFGYGDSHF GMDV	SEQ ID NO: 156 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKE LEWVANINQDESEKYYVDSVKGRFTVSRDNAKNSLFLQMNSLRAD DTAVYYCARGGFGYGDSHFGMDVWGQGTTVTVSS
1.40	SEQ ID NO: 157 NYWMF	SEQ ID NO: 158 NVNQDGSEK YYVDSVEG	SEQ ID NO: 159 GGEGYSDSHY GTDV	SEQ ID NO: 160 EVQLVESGGGLVQPGGSLRLSCGASGFTFSNYWMFWFRQAPGKEL EWVANVNQDGSEKYYVDSVEGRFTISRDDAKNSLYLQMNSLRAED TAIYYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.41	SEQ ID NO: 161 NYWMF	SEQ ID NO: 162 NVNQNGSEK YYVDSVEG	SEQ ID NO: 163 GGEGYSDSHY GTDV	SEQ ID NO: 164 EVQLVESGGGLVQPGGSLRLSCGASGFTFSNYWMFWFRQAPGKEL EWVANVNQNGSEKYYVDSVEGRFTISRDNAKNSLYLQMNSLRAED TAIYYCARGGEGYSDSHYGTDVWGQGTTVTVSS
1.42	SEQ ID NO: 165 NYWMN	SEQ ID NO: 166 NIKQDGSEKY YVDSVKG	SEQ ID NO: 167 GGEGYGDSHY GMDV	SEQ ID NO: 168 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKDSLYLQMNSLRAED TAIYYCARGGEGYGDSHYGMDVSGQGTTVTVSS
1.43	SEQ ID NO: 169 NYWMI	SEQ ID NO: 170 NINQDGSEK YYVDSVKG	SEQ ID NO: 171 GGDGYSNSHY GMDV	SEQ ID NO: 172 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWYRQAPGEEL EWVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDT AVYYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.44	SEQ ID NO: 173 DYWMI	SEQ ID NO: 174 NINQDGSEK YYVDSVKG	SEQ ID NO: 175 GGDGYSNSHY GMDV	SEQ ID NO: 176 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYWMIWYRQAPGEEL EWVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDT AVYYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.45	SEQ ID NO: 177 KYWMI	SEQ ID NO: 178 NINQDGSEK YYVDSVEG	SEQ ID NO: 179 GGDDYSNSHY GMDV	SEQ ID NO: 180 EVQLVESGGGLVQPGGSLRLSCAASGFTFSKYWMIWVRQAPEKGL EWVANINQDGSEKYYVDSVEGRFTISRDNVNNSLYLQMNSLRAEDT AVYYCARGGDDYSNSHYGMDVSGQGTTVTVSS
1.46	SEQ ID NO: 181 NYWMS	SEQ ID NO: 182 NINQDGSEK YYVDSVKG	SEQ ID NO: 183 GGEEYSSSHYG MDV	SEQ ID NO: 184 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMSWVRQAPGRG LEWVANINQDGSEKYYVDSVKGRFTISRDNAKSSLYLQMNSLRAED TAVYYCARGGEEYSSSHYGMDVWGQGTTVTVSS
1.47	SEQ ID NO:	SEQ ID NO:	SEQ ID NO:	SEQ ID NO: 188

	185 NYWMN	186 NIKQDGSEN YYVDSVKG	187 GGEGYSTSHYG MDV	EVQLVESGGGLVQPGGSLRLSCIASGFSFSNYWMNWVRQAPGKGL EWVANIKQDGSENYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGEGYSTSHYGMDVWGQGTAVTVSS
1.48	SEQ ID NO: 189 SYWMS	SEQ ID NO: 190 NIKQDGSEKY YVDSVKG	SEQ ID NO: 191 GGEGYGVDHY GLDV	SEQ ID NO: 192 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKG LEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDT AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.49	SEQ ID NO: 193 SYWML	SEQ ID NO: 194 NVNQDGSEN YYVDSVEG	SEQ ID NO: 195 GGEDYGNSHF GMDV	SEQ ID NO: 196 EVQLVESGGGLVQPGGSLRLSCGASGFTFSSYWMLWFRQAPGKEL EWVANVNQDGSENYYVDSVEGRFTISRDNAKNSLYLQMHSLRAED TAVYYCARGGEDYGNSHFGMDVWGQGTMVTVSS
1.50	SEQ ID NO: 197 NYWMI	SEQ ID NO: 198 NINQDGSEK YYVDSVKG	SEQ ID NO: 199 GGDGYSNSHY GMDV	SEQ ID NO: 200 EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTA VYYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.51	SEQ ID NO: 201 NYWMI	SEQ ID NO: 202 NINQDGSEK YYVDSVKG	SEQ ID NO: 203 GGDGYSNSHY GMDV	SEQ ID NO: 204 EVQLVESGGGLVKPGGSLRLSCAASGFTFSNYWMIWYRQAPGEELE WVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDTA VYYCARGGDGYSNSHYGMDVWGQGTTVTVSS
1.52	SEQ ID NO: 205 KYWMI	SEQ ID NO: 206 NINQDGSEK YYVDSVEG	SEQ ID NO: 207 GGDDYSISHFG MDV	SEQ ID NO: 208 EVQLVESGGGLVQIGGSLRLSCAASGFTFSKYWMIWVRQAPEKGLE WVANINQDGSEKYYVDSVEGRFTISRDNANNSLFLQMNSLRAEDT AVYYCARGGDDYSISHFGMDVSGQGTRVTVSS
1.53	SEQ ID NO: 209 KYWMI	SEQ ID NO: 210 NINQDGSEK YYVDSVEG	SEQ ID NO: 211 GGDDYSHSHY GMDV	SEQ ID NO: 212 EVQLVESGGGLVQIGGSLRLSCVASGFTFSKYWMIWVRQAPEKGLE WVANINQDGSEKYYVDSVEGRFTISRDNANNSLYLQMNSLRAEDT AVYYCARGGDDYSHSHYGMDVSGQGTTVTVSS
1.54	SEQ ID NO: 213 NYWMN	SEQ ID NO: 214 NINQDGSEK YYVDSVKG	SEQ ID NO: 215 GGFGYGDSHY GMDV	SEQ ID NO: 216 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYWMNWVRQAPGKE LEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRADD TAVYYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.55	SEQ ID NO: 217 SYWLN	SEQ ID NO: 218 NINQDGSEN YYVDSVEG	SEQ ID NO: 219 GGEDYGNSHF GMDV	SEQ ID NO: 220 EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYWLNWVRQAPGKGL EWVANINQDGSENYYVDSVEGRFTISRDNAKNSLYLQMHSLRAEDT AVYYCARGGEDYGNSHFGMDVWGQGTMVTVSS
1.56	SEQ ID NO: 221 SYWMS	SEQ ID NO: 222 NIKQDGSEKY YVDSVKG	SEQ ID NO: 223 GGEGYGVDHY GLDV	SEQ ID NO: 224 QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGL EWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDT AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.57	SEQ ID NO: 225 DYWMN	SEQ ID NO: 226 NIKEDGSEKY YVDSVEG	SEQ ID NO: 227 GGEGYGDNHY GMDV	SEQ ID NO: 228 QVQLVESGGGLVQPGGSLRLSCTASGFTFSDYWMNWVRQAPGKG LEWVANIKEDGSEKYYVDSVEGRFTISRDNARNSLYLQMTSLREEDT AMYYCARGGEGYGDNHYGMDVSGQGTTVTVSS
1.58	SEQ ID NO: 229 SYWMN	SEQ ID NO: 230 NINQDGSEK YYVDSVEG	SEQ ID NO: 231 GGPDYGDLHY GMDV	SEQ ID NO: 232 EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYWMNWVRQAPGKE AEWVANINQDGSEKYYVDSVEGRFTISRDNAKNSLFLQMNSLRDED TAVYYCARGGPDYGDLHYGMDVWGQGTTVTVSS
1.59	SEQ ID NO: 233 RYWMS	SEQ ID NO: 234 NINQDGREK YYVDSVKG	SEQ ID NO: 235 GGEGYGDYHY GMDV	SEQ ID NO: 236 QVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKG LERVANINQDGREKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYGDYHYGMDVSGQGTTVTVSS
1.60	SEQ ID NO: 237 NYWMI	SEQ ID NO: 238 NINQDGSEK YYVDSVKG	SEQ ID NO: 239 GGDGYSNSHY GMDV	SEQ ID NO: 240 EVQLVESGGGLVQPGGSPRLSCAASGFTLSNYWMIWYRQAPGEKL EWVANINQDGSEKYYVDSVKGRFTISRDNATNSLFLQMNSLRAEDT AVYYCARGGDGYSNSHYGMDVWGQGTTVTVSS

1.61	SEQ ID NO: 241 NYWMN	SEQ ID NO: 242 NINQDESEKY YVDSVKG	SEQ ID NO: 243 GGFGYGDSHF GMDV	SEQ ID NO: 244 EVQLVESGGGLVQPGGSLRLSCVASGFNFSNYWMNWVRQAPGKE LEWVANINQDESEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRADD TAVYYCARGGFGYGDSHFGMDVWGQGTTVTVSS
1.62	SEQ ID NO: 245 NYWMN	SEQ ID NO: 246 NINQDESEKY YVDSVKG	SEQ ID NO: 247 GGFGYGDSHF GMDV	SEQ ID NO: 248 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYWMNWVRQAPGKE LEWVANINQDESEKYYVDSVKGRFTIFRDNAKNSLFLQMNSLRADD TAVYYCARGGFGYGDSHFGMDVWGQGTTVTVSS
1.63	SEQ ID NO: 249 SFWMN	SEQ ID NO: 250 NINQDGSEK YYVDSVKG	SEQ ID NO: 251 GGPDYGDLHY GMDV	SEQ ID NO: 252 EVQLVESGGGLVQPGGSLSLSCAASGFTFRSFWMNWVRQAPGKE AEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRAED TAVYYCARGGPDYGDLHYGMDVWGQGTTVTVSS
1.64	SEQ ID NO: 253 SYWMN	SEQ ID NO: 254 NINQDGSEK YYVDSVKG	SEQ ID NO: 255 GGPDYGDLHY GMDV	SEQ ID NO: 256 EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYWMNWVRQAPGKE AEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRDED TAVYYCARGGPDYGDLHYGMDVWGQGTTVTVSS
1.65	SEQ ID NO: 257 NYWMI	SEQ ID NO: 258 NINQDGSEK YYVDSVKG	SEQ ID NO: 259 GGEDYGNSHY GMDV	SEQ ID NO: 260 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWYRQAPGEEL EWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMHSLRAEDT AVYYCARGGEDYGNSHYGMDVWGQGTMVTVSS
1.66	SEQ ID NO: 261 NYWMN	SEQ ID NO: 262 NINQDGSER YYVDSVKG	SEQ ID NO: 263 GGEGYGIDHY GLDV	SEQ ID NO: 264 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMNSLRAED TAVYFCARGGEGYGIDHYGLDVSGQGTTVTVSS
1.67	SEQ ID NO: 265 SYWMS	SEQ ID NO: 266 NINQDGSER YYVDSVKG	SEQ ID NO: 267 GGEGYGVDHY GLDV	SEQ ID NO: 268 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDT AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.68	SEQ ID NO: 269 NYWMI	SEQ ID NO: 270 NINQDGSEK YYVDSVEG	SEQ ID NO: 271 GGEGYGVDHY GLDV	SEQ ID NO: 272 QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMIWVRQAPGKGL EWVANINQDGSEKYYVDSVEGRFTISRDNAKSSLYLQMSNLRAEDT AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.69	SEQ ID NO: 273 NYWMN	SEQ ID NO: 274 NINQDGSEK YYVDSVKG	SEQ ID NO: 275 GGTGYGSDHY GMDV	SEQ ID NO: 276 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSLRAED TAVYYCARGGTGYGSDHYGMDVSGQGTTVTVSS
1.70	SEQ ID NO: 277 NYWMN	SEQ ID NO: 278 NINQDGSEN YYVDSVKG	SEQ ID NO: 279 GGFGYGDSHY GMDV	SEQ ID NO: 280 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYWMNWVRQAPGKE LEWVANINQDGSENYYVDSVKGRFTISRDNVKNSLFLQMNRLRAD DTAVYYCARGGFGYGDSHYGMDVWGQGTTVTVSS
1.71	SEQ ID NO: 281 NYWMI	SEQ ID NO: 282 NINQNGSER YYVDSVQG	SEQ ID NO: 283 GGADYSNSHY GMDV	SEQ ID NO: 284 EVQLVESGGGLVQPGGSLRLSCAASGFTFGNYWMIWVRQAPGKEL EWLANINQNGSERYYVDSVQGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGADYSNSHYGMDVSGQGTTVTVSS
1.72	SEQ ID NO: 285 SYWMS	SEQ ID NO: 286 NINQDGSER YYVDSVKG	SEQ ID NO: 287 GGEGYGVDHY GLDV	SEQ ID NO: 288 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNANNSLHLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.73	SEQ ID NO: 289 SYWMN	SEQ ID NO: 290 NINPDGSEKY YVDSVQG	SEQ ID NO: 291 GGPGYGDLHY GMDV	SEQ ID NO: 292 EVQLVESGGGLVQPGGSLRLSCAASGFTFRSYWMNWVRQAPGKE AEWVANINPDGSEKYYVDSVQGRHTISRDNAKNSLFLEMNSLRVED TALYYCARGGPGYGDLHYGMDVWGQGTTVTVSS
1.74	SEQ ID NO: 293 NYWMN	SEQ ID NO: 294 NINQDGSEK	SEQ ID NO: 295 GGEGYGVDHY	SEQ ID NO: 296 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSEKYYVDSVEGRFTISRDNAKSSLYLQMSSLRAEDT

		YYVDSVEG	GLDV	AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.75	SEQ ID NO: 297 DYYMS	SEQ ID NO: 298 NINQDGSER YYVDSVKG	SEQ ID NO: 299 GGEGYGVDHY GLDV	SEQ ID NO: 300 QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLE WVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.76	SEQ ID NO: 301 NYWMN	SEQ ID NO: 302 NINQDGSER YYVDSVKG	SEQ ID NO: 303 GGEGYGVDHY GLDV	SEQ ID NO: 304 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.77	SEQ ID NO: 305 NYWMN	SEQ ID NO: 306 NINQDGSER YYVDSVKG	SEQ ID NO: 307 GGEGYGVDHY GLDV	SEQ ID NO: 308 QVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.78	SEQ ID NO: 309 NYWMN	SEQ ID NO: 310 NINQDGSER YYVDSVKG	SEQ ID NO: 311 GGEGYGVDHY GLDV	SEQ ID NO: 312 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.79	SEQ ID NO: 313 NYWMN	SEQ ID NO: 314 NINQDGSER YYVDSVKG	SEQ ID NO: 315 GGEGYGVNHY GLDV	SEQ ID NO: 316 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVNHYGLDVSGQGTTVTVSS
1.80	SEQ ID NO: 317 DYYMS	SEQ ID NO: 318 NIKQDGSERY YVDSVKG	SEQ ID NO: 319 GGEGYGVDHY GLDV	SEQ ID NO: 320 QVQLVESGGGLVKPGGSLRLSCVASGFTFSDYYMSWIRQAPGKGLE WVANIKQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDTA VYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.81	SEQ ID NO: 321 NYWMN	SEQ ID NO: 322 NINQDGSER YYVDSVEG	SEQ ID NO: 323 GGEGYGVDHY GLDV	SEQ ID NO: 324 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVEGRFTISRDNAKSSLYLQMSNLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.82	SEQ ID NO: 325 NYWMN	SEQ ID NO: 326 NINQDGSER YYVDSVKG	SEQ ID NO: 327 GGEGYGVDHY GLDV	SEQ ID NO: 328 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDT AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.83	SEQ ID NO: 329 NYWMN	SEQ ID NO: 330 NINQDGSER YYVDSVKG	SEQ ID NO: 331 GGEGYGVDHY GLDV	SEQ ID NO: 332 QVQLQESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGK GLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAE DTAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.84	SEQ ID NO: 333 NYWMN	SEQ ID NO: 334 NINQDGSER YYVDSVKG	SEQ ID NO: 335 GGEGYGVDHY GLDV	SEQ ID NO: 336 QVQLVESGGGLVKPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.85	SEQ ID NO: 337 NYWMN	SEQ ID NO: 338 NINQDGSER YYVDSVKG	SEQ ID NO: 339 GGEGYGVDHY GLDV	SEQ ID NO: 340 QVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNANNSLHLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.86	SEQ ID NO: 341 NYWMN	SEQ ID NO: 342 NINQDGSER YYVDSVEG	SEQ ID NO: 343 GGEGYGVDHY GLDV	SEQ ID NO: 344 QVQLGESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGK GLEWVANINQDGSERYYVDSVEGRFTISRDNAKSSLYLQMSNLRAE DTAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.87	SEQ ID NO: 345 NYWMN	SEQ ID NO: 346 NINQDGSER YYVDSVKG	SEQ ID NO: 347 GGEGYGVDHY GLDV	SEQ ID NO: 348 QVQLVESGGGLVQPGGSLKLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKSSLYLQMSSLRAEDT AVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.88	SEQ ID NO: 349	SEQ ID NO: 350	SEQ ID NO: 351	SEQ ID NO: 352 QVQLQESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGK

	NYWMN	NINQDGSER YYVDSVKG	GGEGYGVDHY GLDV	GLEWVANINQDGSERYYVDSVKGRFTISRGNAKNSLYLQMSSLRAE DTAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.89	SEQ ID NO: 353 DYGMS	SEQ ID NO: 354 NINQDGSER YYVDSVKG	SEQ ID NO: 355 GGEGYGVDHY GLDV	SEQ ID NO: 356 QVQLVESGGGVVQPGRSLRLSCAASGFTFDDYGMSWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.90	SEQ ID NO: 357 SHWMT	SEQ ID NO: 358 HIKEDGSEKY YEDSVEG	SEQ ID NO: 359 GGDGYSDSHF GVDV	SEQ ID NO: 360 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGL EWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.91	SEQ ID NO: 361 SHWMT	SEQ ID NO: 362 HIKEDGSEKY YVDSVKG	SEQ ID NO: 363 GGDGYSDSHF GVDV	SEQ ID NO: 364 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYVDSVKGRFTVSRDNAKNSVYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.92	SEQ ID NO: 365 SHWMT	SEQ ID NO: 366 HIKEDGSEKY YEDSVKG	SEQ ID NO: 367 GGDGYSDSHF GVDV	SEQ ID NO: 368 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYEDSVKGRFTVSRDNAKNSVYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.93	SEQ ID NO: 369 SHWMT	SEQ ID NO: 370 HIKEDGSEKY YEDSVEG	SEQ ID NO: 371 GGDGYSDSHF GVDV	SEQ ID NO: 372 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYEDSVEGRFTISRDNAKNSVYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.94	SEQ ID NO: 373 SHWMT	SEQ ID NO: 374 HIKEDGSEKY YEDSVEG	SEQ ID NO: 375 GGDGYSDSHF GVDV	SEQ ID NO: 376 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSLYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.95	SEQ ID NO: 377 SHWMT	SEQ ID NO: 378 HIKEDGSEKY YVDSVKG	SEQ ID NO: 379 GGDGYSDSHF GVDV	SEQ ID NO: 380 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGL EWVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.96	SEQ ID NO: 381 SHWMT	SEQ ID NO: 382 HIKEDGSEKY YVDSVKG	SEQ ID NO: 383 GGDGYSDSHF GVDV	SEQ ID NO: 384 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.97	SEQ ID NO: 385 SHWMT	SEQ ID NO: 386 HIKEDESEKY YVDSVKG	SEQ ID NO: 387 GGVGYSISHFG VDV	SEQ ID NO: 388 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGL EWVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGVGYSISHFGVDVWGQGTTVTVSS
1.98	SEQ ID NO: 389 SHWMT	SEQ ID NO: 390 HIKEDESEKY YVDSVKG	SEQ ID NO: 391 GGEGYSISHFG VDV	SEQ ID NO: 392 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWVRQAPGKGL EWVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGEGYSISHFGVDVWGQGTTVTVSS
1.99	SEQ ID NO: 393 SHWMT	SEQ ID NO: 394 HIKEDESEKY YVDSVKG	SEQ ID NO: 395 GGDGYSDSHF GVDV	SEQ ID NO: 396 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.100	SEQ ID NO: 397 SHWMT	SEQ ID NO: 398 HIKEDESEKY YVDSVKG	SEQ ID NO: 399 GGDGYSISHFG VDV	SEQ ID NO: 400 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGDGYSISHFGVDVWGQGTTVTVSS
1.101	SEQ ID NO: 401 SHWMT	SEQ ID NO: 402 HIKEGGSEKY YVDSVKG	SEQ ID NO: 403 GGDGYSDSHF GVDV	SEQ ID NO: 404 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEGGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.102	SEQ ID NO:	SEQ ID NO:	SEQ ID NO:	SEQ ID NO: 408

	405 SHWMT	406 HIKEEGSEKY YVDSVKG	407 GGDGYSDSHF GVDV	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEEGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGDGYSDSHFGVDVWGQGTTVTVSS
1.103	SEQ ID NO: 409 SHWMT	SEQ ID NO: 410 HIKEDGSEKY YVDSVKG	SEQ ID NO: 411 GGEGYSDSHF GVDV	SEQ ID NO: 412 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGEGYSDSHFGVDVWGQGTTVTVSS
1.104	SEQ ID NO: 413 SHWMT	SEQ ID NO: 414 HIKEDGSEKY YVDSVKG	SEQ ID NO: 415 GGVGYSDSHF GVDV	SEQ ID NO: 416 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGGVGYSDSHFGVDVWGQGTTVTVSS
1.105	SEQ ID NO: 417 SHWMT	SEQ ID NO: 418 HIKEDESEKY YVDSVKG	SEQ ID NO: 419 GGVGYSISHFG VDV	SEQ ID NO: 420 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGVGYSISHFGVDVWGQGTTVTVSS
1.106	SEQ ID NO: 421 SHWMT	SEQ ID NO: 422 HIKEDESEKY YVDSVKG	SEQ ID NO: 423 GGEGYSISHFG VDV	SEQ ID NO: 424 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGL EWVAHIKEDESEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA VYYCARGGEGYSISHFGVDVWGQGTTVTVSS
1.107	SEQ ID NO: 849 NYWMN	SEQ ID NO: 850 NINQDGSER YYVDSVKG	SEQ ID NO: 851 GGEGYGVDHY GLDV	SEQ ID NO: 852 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.108	SEQ ID NO: 853 NYWMN	SEQ ID NO: 854 NINQDGSER YYVDSVKG	SEQ ID NO: 855 GGEGYGVDHY GLDV	SEQ ID NO: 856 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYFCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.109	SEQ ID NO: 857 NYWMN	SEQ ID NO: 858 NINQDGSER YYVDSVKG	SEQ ID NO: 859 GGEGYGVDHY GLDV	SEQ ID NO: 860 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.110	SEQ ID NO: 861 NYWMN	SEQ ID NO:862 NINQDGSER YYVDSVKG	SEQ ID NO: 863 GGEGYGVDHY GLDV	SEQ ID NO: 864 EVQLVESGGGLVQPGGSLRLSCAASGFTLS NYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYFCARGGEGYGVDHYGLDVSGQGTT VTVSS
1.111	SEQ ID NO: 865 NYWMN	SEQ ID NO: 866 NINQDGSER YYVDSVKG	SEQ ID NO: 867 GGEGYGVDHY GLDV	SEQ ID NO: 868 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMSSLRAED TAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.112	SEQ ID NO: 869 NYWMN	SEQ ID NO: 870 NINQDGSER YYVDSVKG	SEQ ID NO: 871 GGEGYGVDHY GLDV	SEQ ID NO: 872 EVQLVESGGGLVQPGGSLRLSCAATGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.113	SEQ ID NO: 873 NYWMN	SEQ ID NO: 874 NINQDGSER YYVDSVKG	SEQ ID NO: 875 GGEGYGVDHY GLDV	SEQ ID NO: 876 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKG LEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSS
1.114	SEQ ID NO: 877 NYWMN	SEQ ID NO: 878 NINQDESERY YVDSVKG	SEQ ID NO: 879 GGEGYGVDHY GLDV	SEQ ID NO: 880 EVQLVESGGGLVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKG LEWVANINQDESERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSS

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 comprising a CDR1, CDR2, CDR3 with at least 40% or 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. The CDRs are defined according to Kabat. 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).

Sequence homology 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 one embodiment, the single variable heavy chain domain antibody comprises or consists of a full length sequence as shown in Table 2 or a sequence with at least 70% homology thereto. For example, the single variable heavy chain domain antibody comprises a full length sequence comprising or consisting of a sequence selected from those shown in Table 2, e.g. SEQ ID NO. 428, 432, 436, 440 and so forth or a sequence with at least 50% homology thereto. Sequence homology as mentioned above an be at least 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.

Table 2 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 YISGSGDIIDYADSVKG	SEQ ID NO: 427 EDSRLTGTTDFDN	SEQ ID NO: 428 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.2	SEQ ID NO: 429 DYYMS	SEQ ID NO: 430 YISGSGDIIDYADSVKG	SEQ ID NO: 431 EDSRIPGTTDFDN	SEQ ID NO: 432 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.3	SEQ ID NO: 433 DYYMS	SEQ ID NO: 434 YISGSGDIIDYADSVKG	SEQ ID NO: 435 EDSRIPGTTDFDN	SEQ ID NO: 436 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWISYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.4	SEQ ID NO:	SEQ ID NO: 438	SEQ ID NO:	SEQ ID NO: 440

	437 DYYMS	YISGSGDVIDYAD SVKG	439 EDSRIPGTTDF DN	EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDVIDYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.5	SEQ ID NO: 441 DYYMS	SEQ ID NO: 442 YISGSGDIIDYADS VKG	SEQ ID NO: 443 EDSRIPGTTDF DN	SEQ ID NO: 444 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYHCAKEDSRIPGTTDFDNWGQGTLVTVSS
2.6	SEQ ID NO: 445 DYYMS	SEQ ID NO: 446 YISGSGDIIDYADS VKG	SEQ ID NO: 447 EDSRIPGTTDF DS	SEQ ID NO: 448 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYHCAKEDSRIPGTTDFDSWGQGTMVTVSS
2.7	SEQ ID NO: 449 DYYMS	SEQ ID NO: 450 YISGSGTTIDYADS VKG	SEQ ID NO: 451 EDIRMTGTTDF DN	SEQ ID NO: 452 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGTTIDYADSVKGRFTISRDNARNSLYLQMNSLRA EDTAVYYCAREDIRMTGTTDFDNWGQGTLVTVSS
2.8	SEQ ID NO: 453 DYYMS	SEQ ID NO: 454 HISGSGTTIDYAD SVKG	SEQ ID NO: 455 EDSRMPGTTD FDN	SEQ ID NO: 456 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYHCAREDSRMPGTTDFDNWGQGTLVTVSS
2.9	SEQ ID NO: 457 DYYMT	SEQ ID NO: 458 YISGSGDTIDYAES VKG	SEQ ID NO: 459 EDSRIAGTTDF DN	SEQ ID NO: 460 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAPGK GLEWISYISGSGDTIDYAESVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYHCAREDSRIAGTTDFDNWGPGTLVTVSS
2.10	SEQ ID NO: 461 DYYMT	SEQ ID NO: 462 YISSSGSNIDYADS VKG	SEQ ID NO: 463 EDSRLSGTTDF DY	SEQ ID NO: 464 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAPGK GLEWVSYISSSGSNIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDSRLSGTTDFDYWGQGTLVTVSS
2.11	SEQ ID NO: 465 DYYMT	SEQ ID NO: 466 YISGSGDTIDYAES VKG	SEQ ID NO: 467 EDSRIAGTTDF DN	SEQ ID NO: 468 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWFRQAPGK GLEWISYISGSGDTIDYAESVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYHCAREDSRIAGTTDFDNWGPGTLVTVSS
2.12	SEQ ID NO: 469 DYYMS	SEQ ID NO: 470 HISGSGTTIDYAD SVKG	SEQ ID NO: 471 EDIRMTGTTDF DH	SEQ ID NO: 472 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNARKSLYLQMNSLR AEDTAVYYCAREDIRMTGTTDFDHWGQGTLVTVSS
2.13	SEQ ID NO: 473 DYYMS	SEQ ID NO: 474 HISSSGNTIDYAD SVKG	SEQ ID NO: 475 EDPRLPGTTDF DY	SEQ ID NO: 476 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSHISSSGNTIDYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCAREDPRLPGTTDFDYWGQGTLVTVSS
2.14	SEQ ID NO: 477 DYYMT	SEQ ID NO: 478 YISGSGDTIDYAES VKG	SEQ ID NO: 479 EDIRMPGTTDF DH	SEQ ID NO: 480 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAPGK GLEWISYISGSGDTIDYAESVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.15	SEQ ID NO: 481 DYYMS	SEQ ID NO: 482 HISGSGTTIDYAD SVKG	SEQ ID NO: 483 EDIRMPGTTDF DH	SEQ ID NO: 484 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.16	SEQ ID NO: 485 DYYMS	SEQ ID NO: 486 HISSSGSTIDYADS VKG	SEQ ID NO: 487 EDPRLTGTTDF DY	SEQ ID NO: 488 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSHISSSGSTIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRLTGTTDFDYWGQGALVTVSS
2.17	SEQ ID NO: 489 DYYMS	SEQ ID NO: 490 YISSSGSTISYADS VKG	SEQ ID NO: 491 EDPRISGTTDF DN	SEQ ID NO: 492 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSYISSSGSTISYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRISGTTDFDNWGQGTLVTVSS

2.18	SEQ ID NO: 493 DYYMS	SEQ ID NO: 494 HISSSGNTIDYAD SVKG	SEQ ID NO: 495 EDPRLPGTTDF DY	SEQ ID NO: 496 QVQLQESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSHISSSGNTIDYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCAREDPRLPGTTDFDYWGQGTLVTVSS
2.19	SEQ ID NO: 497 DYYMS	SEQ ID NO: 498 YISGTGITTDYADS VKG	SEQ ID NO: 499 EDPRLPGTSEF DN	SEQ ID NO: 500 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGTGITTDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRLPGTSEFDNWGQGTLVTVSS
2.20	SEQ ID NO: 501 DYYMS	SEQ ID NO: 502 HISSSGSTIDYADS VKG	SEQ ID NO: 503 EDPRMPGTFD FDN	SEQ ID NO: 504 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSHISSSGSTIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRMPGTFDFDNWGQGTLVTVSS
2.21	SEQ ID NO: 505 DYYMS	SEQ ID NO: 506 HISGSGTTIDYAD SVKG	SEQ ID NO: 507 EDIRMPGTTDF DH	SEQ ID NO: 508 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.22	SEQ ID NO: 509 DYYMS	SEQ ID NO: 510 HISGSGTTIDYAD SVKG	SEQ ID NO: 511 EDIRMPGTTDF DH	SEQ ID NO: 512 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNARDSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.23	SEQ ID NO: 513 DYYMS	SEQ ID NO: 514 HISGSGTTIDYAD SVKG	SEQ ID NO: 515 EDIRMPGTTDF DH	SEQ ID NO: 516 EVQLVESGGGLVTPGGSLRLSCAVSGFTFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.24	SEQ ID NO: 517 DYYMS	SEQ ID NO: 518 HISGSGTTIDYAD SVKG	SEQ ID NO: 519 EDIRMPGTTDF DH	SEQ ID NO: 520 EVQLVESGGGLVKPGGSLRLSCAVSGFTFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKGRFTISRDNARNSLYLQMNSLR AEDTAMYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.25	SEQ ID NO: 521 DYYMS	SEQ ID NO: 522 HISGSGTTIDYAD SVKD	SEQ ID NO: 523 EDIRMPGTTDF DH	SEQ ID NO: 524 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKDRFTISRDNARNSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.26	SEQ ID NO: 525 DYYMS	SEQ ID NO: 526 HISSSGTTIDYADS VKG	SEQ ID NO: 527 EDIRMPGTTDF DN	SEQ ID NO: 528 EVQLVESGGGLVKPGGSLRLSCTASGFTFTDYYMSWFRQAPGK GLEWVSHISSSGTTIDYADSVKGRFTISRDNAKNSLYLQMNSLRA DDTAVYYCAREDIRMPGTTDFDNWGQGTLVTVSS
2.27	SEQ ID NO: 529 DYYMT	SEQ ID NO: 530 YISSSGSTISYADS VKG	SEQ ID NO: 531 EDIRMSGTTDF DY	SEQ ID NO: 532 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWFRQAPGK GLEWVSYISSSGSTISYADSVKGRFTISRDNANNSLYLQMNSLRA EDTAVYHCAREDIRMSGTTDFDYWGQGTLVTVSS
2.28	SEQ ID NO: 533 DYYMS	SEQ ID NO: 534 HISSSGSSIDYADS VKG	SEQ ID NO: 535 EDPRLSGTIDF DS	SEQ ID NO: 536 QVQLVESGGGLVKPGGSLRLSCAASGFIFSDYYMSWFRQAPGK GLEWVSHISSSGSSIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRLSGTIDFDSWGQGTLVTVSS
2.29	SEQ ID NO: 537 DYYMS	SEQ ID NO: 538 HIGGSGTTIDYAD SVKG	SEQ ID NO: 539 EDIRMPGTTDF DH	SEQ ID NO: 540 EVQLVESGGGLVKPGGSLRLSCAASGFAFSDYYMSWFRQAPGK GLEWVSHIGGSGTTIDYADSVKGRFTISRDNARNSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.30	SEQ ID NO: 541 DYYMS	SEQ ID NO: 542 YISSSGSTIYYADS VKG	SEQ ID NO: 543 EDPRVPGTTNF DY	SEQ ID NO: 544 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRVPGTTNFDYWGQGTLVTVSS
2.31	SEQ ID NO: 545 DYYMT	SEQ ID NO: 546 YISGSGSTIDYADS VKG	SEQ ID NO: 547 EDGRIPGTTDF	SEQ ID NO: 548 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWMRQAPG KGLEWVSYISGSGSTIDYADSVKGRFTISRDNAKNSLYLQMNSLR

			DH	PEDTAVYYCAKEDGRIPGTTDFDHWGQGTLVTVSS
2.32	SEQ ID NO: 549 DYYMS	SEQ ID NO: 550 HISGSGTTIDYAD SVKD	SEQ ID NO: 551 EDIRMPGTTDF DH	SEQ ID NO: 552 EVQLVESGGGLVQPGGSLRLSCAASGFAFSDYYMSWFRQAPGK GLEWVSHISGSGTTIDYADSVKDRFTISRDNARNSLYLQMNSLR AEDTAVYYCAREDIRMPGTTDFDHWGQGTLVTVSS
2.33	SEQ ID NO: 553 DYFMS	SEQ ID NO: 554 HISSSGNSIDYAD SVKG	SEQ ID NO: 555 EDPRLPGTTDF DY	SEQ ID NO: 556 QVQLVESGGGLVKPGGSLRLSCAASGFPFSDYFMSWFRQAPGK GLEWVSHISSSGNSIDYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCAKEDPRLPGTTDFDYWGQGTLVTVSS
2.34	SEQ ID NO: 557 DSYMS	SEQ ID NO: 558 HISNSGSTISYADS VKG	SEQ ID NO: 559 EDPRLPGTSDF DY	SEQ ID NO: 560 QVQLVESGGGLVKPGGSLRLSCAASGFTFSDSYMSWIRQAPGK GLEWVSHISNSGSTISYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRLPGTSDFDYWGQGTLVTVSS
2.35	SEQ ID NO: 561 DYYMS	SEQ ID NO: 562 HISSSGSSIDYADS VKG	SEQ ID NO: 563 EDPRLSGTTDF DQ	SEQ ID NO: 564 QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSHISSSGSSIDYADSVKGRFTISRDNAKNSLYLQMNSLRD EDTAVYYCAREDPRLSGTTDFDQWGQGTLVTVSS
2.36	SEQ ID NO: 565 SYWMS	SEQ ID NO: 566 HISSSGSTIDYAES VKG	SEQ ID NO: 567 EDPRMTGTTD FDY	SEQ ID NO: 568 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPG KGLEWVSHISSSGSTIDYAESVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCAREDPRMTGTTDFDYWGQGTLVTVSS
2.37	SEQ ID NO: 569 NYFMS	SEQ ID NO: 570 HISSSGNTIDYAD SVKG	SEQ ID NO: 571 EDPRLPGTTDF DY	SEQ ID NO: 572 QVQLQESGGGLVKPGGSLRLSCAASGFTFSNYFMSWIRQAPGK GLEWVSHISSSGNTIDYADSVKGRFTISRDNAKNSLYLQMDSLR AEDTAVYYCSREDPRLPGTTDFDYWGQGTLVTVSS
2.38	SEQ ID NO: 573 DYYMT	SEQ ID NO: 574 YISSGGSTIHYADS VKG	SEQ ID NO: 575 ENPRLPGTMD FDY	SEQ ID NO: 576 EVQLVESGGGVVKPGGSLRLSCAASGFTFSDYYMTWIRQGPGK GQEWISYISSGGSTIHYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCARENPRLPGTMDFDYWGQGTLVTVSS
2.39	SEQ ID NO: 577 DHFMS	SEQ ID NO: 578 NIKQDGSEKYYVD SVKG	SEQ ID NO: 579 EDPRLTGTTDF DN	SEQ ID NO: 580 QVQLVESGGGLVQPGGSLRLSCAASGFTFSDHFMSWFRQAPG KGLEWVANIKQDGSEKYYVDSVKGRFTISRDNAKNSLFLQMNSL RAEDTAMYYCAREDPRLTGTTDFDNWGQGTLVTVSS
2.40	SEQ ID NO: 581 NYWMT	SEQ ID NO: 582 HISSTGSTIDYADS VKG	SEQ ID NO: 583 EDPRLPGTMD FDY	SEQ ID NO: 584 EVQLVESGGGLVQAGGSLRLSCVASGFTFSNYWMTWFRQAPG RGLEWVSHISSTGSTIDYADSVKGRFTISRDNAENSLYLQMNSLR AEDTAVYYCAREDPRLPGTMDFDYWGQGTLVTVSS
2.41	SEQ ID NO: 585 DYYMS	SEQ ID NO: 586 YISGSGDIIDYADS VKG	SEQ ID NO: 587 EDSRLTGTTDF DN	SEQ ID NO: 588 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLR AEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.42	SEQ ID NO: 589 DYYMS	SEQ ID NO: 590 YISGSGDIIDYADS VKG	SEQ ID NO: 591 EDSRLTGTTDF DN	SEQ ID NO: 592 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWIRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLR AEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.43	SEQ ID NO: 593 DYYMS	SEQ ID NO: 594 YISGSGDIIDYADS VKG	SEQ ID NO: 595 EDSRLTGTTDF DN	SEQ ID NO: 596 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLR AEDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.44	SEQ ID NO: 597 DYYMS	SEQ ID NO: 598 YISGSGDIIDYADS VKG	SEQ ID NO: 599 EDSRLTGTTDF DN	SEQ ID NO: 600 EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSS
2.45	SEQ ID NO: 601	SEQ ID NO: 602 YISGSGDIIDYADS	SEQ ID NO: 603	SEQ ID NO: 604 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK

	DYYMS	VKG	EDSRLTGTTDF DN	GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLR AEDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.46	SEQ ID NO: 605 DYYMS	SEQ ID NO: 606 YISGSGDIIDYADS VKG	SEQ ID NO: 607 EDSRLTGTTDF DN	SEQ ID NO: 608 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.47	SEQ ID NO: 609 DYYMS	SEQ ID NO: 610 YISGSGDIIDYADS VKG	SEQ ID NO: 611 EDSRLTGTTDF DN	SEQ ID NO: 612 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDSRLTGTTDFDNWGQGTLVTVSS
2.48	SEQ ID NO: 613 DYYMS	SEQ ID NO: 614 YISGSGDIIDYADS VKG	SEQ ID NO: 615 EDARLTGTTDF DN	SEQ ID NO: 616 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDARLTGTTDFDNWGQGTLVTVSS
2.49	SEQ ID NO: 617 DYYMS	SEQ ID NO: 618 YISGSGDIIDYADS VKG	SEQ ID NO: 619 EDPRLTGTTDF DN	SEQ ID NO: 620 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRLTGTTDFDNWGQGTLVTVSS
2.50	SEQ ID NO: 621 DYYMS	SEQ ID NO: 622 YISGSGDIIDYADS VKG	SEQ ID NO: 623 EDARLTGTTDF DN	SEQ ID NO: 624 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDARLTGTTDFDNWGQGTLVTVSS
2.51	SEQ ID NO: 625 DYYMS	SEQ ID NO: 626 YISGSGDIIDYADS VKG	SEQ ID NO: 627 EDPRLTGTTDF DN	SEQ ID NO: 628 EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWFRQAPGK GLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTAVYYCAREDPRLTGTTDFDNWGQGTLVTVSS

In some embodiments, there is provided a single V_H domain antibody that is a variant of any of the above single V_H domain antibodies shown in Table 1 or Table 2 and having one or more amino acid substitutions, deletions, insertions or other modifications, and which retains a biological function of the single domain antibody, that is binding to CD137 and, for example, blocking the binding of CD137L to CD137. Thus, variant single V_H 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 single V_H 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, 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 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% sequence homology to the non-variant molecule, for example at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% or at least 95%, 96%, 97%, 98% or 99% sequence homology. In one embodiment, there is provided a variant selected from SEQ ID Nos. 4, 312, 428, 624, 852, 856, 860, 864, 868, 872, 876 or 880

wherein said variant has 1 to 20, e.g. 1 to 10 amino acid substitutions compared to one of these sequences.

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 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 3 below.

Table 3. 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 invention provides a V_H single domain antibody that is a variant of a single domain antibody selected from those shown in Table 1 or 2 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 sequences 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, 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, 5 or more 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.

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.

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 features

Single V_H domain antibodies described herein have shown excellent stability. Furthermore, V_H single domain antibodies described herein show specificity for human CD137. V_H single domain antibodies described herein also inhibit binding of CD137L to CD137.

The single V_H domain antibodies of the invention preferably have KD, IC50 and/or EC50 values as further described herein and as shown in the examples. For example, the KD can be least about 0.4nM or about 3nM. IC50 and/or EC50 values can be as shown in the examples.

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.

In one embodiment, a monovalent single V_H domain antibody as described herein is not internalised or substantially not internalised. Internalisation can be measured as in the examples.

Exemplary nucleic acids

The present invention further provides an isolated nucleic acid encoding a single domain antibody of the present invention. 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 full length single V_H domain antibody of the invention as shown above.

In one aspect, the invention thus also relates to a nucleic acid sequences comprising or consisting of a sequence selected from those shown in table 4 or table 5.

Table 4 Nucleic acids encoding V_H 1.1 to 1.114

Name	Nucleotide Sequence

1.1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGA ACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGC TACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 629
1.2	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGTTATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATA AAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAATAA CTCGCTGTATCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTGACTCCCACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 630
1.3	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGTTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGATTAGGCT ACGGTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 631
1.4	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGGGGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAA CTCACTGTATCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGATTAGGCT ACGGTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 632
1.5	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGATCTGGTTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTGGCTCCCACCACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 633
1.6	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAAGGC TATAGCACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 634
1.7	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACACCCTGAGAGCCGAGGACACGGCTATTTATTATTGTGCGAGAGGGGGTGATGGCT ACAGTGACTCCCACTTCGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 635
1.8	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCTCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 636
1.9	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGGGGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGGAGTGAGAAGTACTATGTGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAA CTCACTGGATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGATTAGGCT ACGGTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 637
1.10	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG

	GATTCACCTTTAGTGACTATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGGAGGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATATCCAGAGACAACGCCAAGA ACTCAACGTATCTGCAAATGAACAGCCTGAGAGTCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGGGCCGG GTATAGCATGTCTCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 638
1.11	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGAAGCCTCTG GATTCACCTTTAGTGACTATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGGAGGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATATCCAGAGACAACGCCAAGA ACTCAACGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGGGCCGG GTATAGTATGTCTCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 639
1.12	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACACCCTGCGAGCCGAGGACACGGCTATTTATTATTGTGCGAGAGGGGGTGATGGCTA CAGTAACTCCCACTTCGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 640
1.13	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCTCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 641
1.14	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAATTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGGAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAAGGCT ATAGCACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 642
1.15	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTACCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTCTCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCAACTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTGACTCCCACTTCGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 643
1.16	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGATGTGGTTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAGAAATACTTTGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTA CAGTAGCTCTCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 644
1.17	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGGAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAGCT ATGGTTACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 645
1.18	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTACCCATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGAGCTGGAATGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAA TTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTATATTACTGTGCGAGAGGGGGGGTTGGCT ACGGTGACTCCCACTTCGGTATGGACGTCTGGGGCCTAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 646
1.19	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGATCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA

	AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGACT ACAGTAACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 647
1.20	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGCAGGGCCGATTCACCATCTCCAGAGACAATGCCAATAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCT ACGGTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 648
1.21	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGTTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTA CAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 649
1.22	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAATATAA AGGAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAGGAA CTCACTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAGGGC TACGGTGACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 650
1.23	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGTTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTTTATCTGCAAATGAACAGCCTGACAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGGGGGGGAGGGCTA CGGTGACGACCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.651
1.24	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAGGGCT ACGGTGACTACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 652
1.25	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAGCT ATGGTTACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 653
1.26	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG ATTCACCTTTAGTACCCATTGGATGAACTGGGCCCGCCAGGCTCCAGGGAAGGAGCTGGAATGGGTGGCCAACATAA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAAT TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAAGACACGGCTGTATATTACTGTGCGAGAGGGGGGGTTGGCTA CGGTGACTCCCACTTCGGTATGGACGTCTGGGGCCTAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 654
1.27	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGTTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGAGAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGACTCACCATCTCCAGAGACAACGCCAAGAA CGCTCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAAGGCT ACAGTGATTCCCACCACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 655
1.28	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA

	CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAACT ATGCTTACAGGGACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.656
1.29	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAATTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTA CAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 657
1.30	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAAGAG TATGGGAGCTCGCACTACGGTATGGACGTCTGGGGCCTGGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 658
1.31	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGGGGGGGACAGCT ATGGTTACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 659
1.32	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTAAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAGTTATTGGATGAACTGGGTCCGCCAGACTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AATCAAAATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCAACATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTACAAATGAGTAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCT ACGGTGATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 660
1.33	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGGCGGGGGGGTCCCTAAGACTCTCCTGTGTAGCCTCTG GATTCACCTTTAGTAATTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGAAAGTGAGGAATACTATGTGGACTCTGTGAAGGGCCGTTTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTGACTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 661
1.34	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTG GATTCACCTTTAGTAATTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAGGAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAAGGCT ATAGCACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 662
1.35	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATTA AGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGGACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAGGGCT ACGGTGAATCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 663
1.36	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTACCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AAACAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGACAGCT ATGGTTACAGGGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 664
1.37	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTTACTATTGGATGATCTGGTTCCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCATTATCTCCAGAGACAACGCCACGAAC TCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTA

	CAGTAATTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 665
1.38	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCT ACAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAGGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 666
1.39	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGAAAGTGAAAAATACTATGTTGACTCTGTGAAGGGCCGTTTCACCGTCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTATATTACTGTGCGAGAGGGGGGTTTGGCT ACGGTGACTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO.667
1.40	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAATTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACGACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTA CAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.668
1.41	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAATTATTGGATGTTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTA ACCAAAATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTACTGTGCGAGAGGAGGTGAGGGCTA CAGTGATTCCCACTACGGTACGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 669
1.42	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGGAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATTTATTATTGTGCGAGAGGGGGGGAGGGTTA CGGTGACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 670
1.43	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTAATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 671
1.44	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTGACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTAATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 672
1.45	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAAATATTGGATGATCTGGGTCCGCCAGGCTCCAGAAAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATTTCCAGAGACAATGTCAATAA CTCATTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTACTACTGTGCGAGAGGAGGTGATGACT ACAGTAACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 673
1.46	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAG CTCACTGTATCTGCAAATGAACAGCCTTAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGGGGGGAAGAAT ATAGCAGCTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA

	SEQ ID NO. 674
1.47	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTATAGCCTCTGG ATTCAGCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGGGAAGGGT ATAGCACCTCGCACTACGGTATGGACGTCTGGGGCCAAGGGACCGCGGTCACTGTCTCTTCA SEQ ID NO. 675
1.48	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 676
1.49	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGGAGCCTCTG GATTCACCTTTAGTAGCTATTGGATGCTCTGGTTCCGCCAGGCTCCAGGAAAGGAGCTGGAGTGGGTGGCCAATGTTA ACCAAGATGGCAGTGAGAATTACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGGTGAAGACTA CGGTAACTCCCACTTCGGCATGGACGTCTGGGGCCAAGGGACCATGGTCACCGTCTCCTCA SEQ ID NO. 677
1.50	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGCAGATCCCTGAGACTCTCTTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAAC TCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCTA CAGTAATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 678
1.51	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTAATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 679
1.52	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGATTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCCG GATTCACCTTTAGTAAATATTGGATGATCTGGGTCCGCCAGGCTCCAGAAAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATTTCCAGAGACAACGCCAATAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTACTACTGTGCGAGAGGAGGTGATGACT ACAGTATCTCCCACTTCGGTATGGACGTCTCGGGCCAAGGGACCAGGGTCACCGTCTCCTCA SEQ ID NO. 680
1.53	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGATTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG ATTCACCTTTAGTAAATATTGGATGATCTGGGTCCGCCAGGCTCCAGAAAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATTTCCAGAGACAACGCCAATAAT TCATTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTACTACTGTGCGAGAGGAGGTGATGACTA CAGTCACTCCCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 681
1.54	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCAACTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCT ACGGTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 682
1.55	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTGGTAGTTATTGGCTGAATTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGCAGTGAGAATTACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGGTGAAGACT ACGGTAACTCCCACTTCGGCATGGACGTCTGGGGCCAAGGGACCATGGTCACTGTCTCTTCA SEQ ID NO. 683

1.56	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 684
1.57	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTACAGCCTCTGG ATTCACCTTTAGTGACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGTAAGGGGCTGGAGTGGGTGGCCAATATAA AGGAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAGGAA CTCACTGTATCTGCAAATGACCAGCCTGAGAGAAGAAGACACGGCTATGTATTACTGTGCGAGAGGGGGGGAGGGC TACGGTGACAACCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 685
1.58	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGAAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGGCGGAATGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATATTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGCCCCGACT ACGGTGACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 686
1.59	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTAAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGGTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGCGGGTGGCCAACATAA ACCAAGATGGACGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGGGGGGGAGGGCT ACGGTGACTACCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 687
1.60	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCCGAGACTCTCCTGTGCAGCCTCTG GATTCACCCTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGAAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCACGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGTGATGGCT ACAGTAATTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 688
1.61	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG ATTCAACTTCAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATAA ACCAAGATGAAAGTGAAAAATACTATGTAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCTA CGGTGACTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 689
1.62	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCAATTTTAGTAACTATTGGATGAACTGGGTCCGTCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGAAAGTGAAAAATACTATGTAGACTCTGTGAAGGGCCGATTCACCATTTTCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCT ACGGTGACTCCCACTTCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 690
1.63	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGTCTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGAAGCTTTTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGGCGGAATGGGTGGCCAACATAA ATCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGCCCCGACTAC GGTGACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 691
1.64	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGAAGCTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGGCGGAATGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATATTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTTTATTACTGTGCGAGAGGAGGCCCCGACT ACGGTGACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 692
1.65	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG

	GATTCACCTTTAGTAACTATTGGATGATCTGGTACCGCCAGGCTCCAGGTGAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGCACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGAGGTGAAGACT ACGGTAACTCCCACTACGGCATGGACGTCTGGGGCCAAGGGACCATGGTCACCGTCTCTTCA SEQ ID NO. 693
1.66	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAG CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTATCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 694
1.67	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA ATCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGC TCACTGTATCTGCAAATGAGTAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCTA TGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 695
1.68	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAACTATTGGATGATCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGC TCACTGTATCTGCAAATGAGCAACCTGAGAGCCGAGGACACGGCTGTATATTTCTGTGCGAGAGGGGGGGAAGGCTA TGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 696
1.69	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGGGAACAGGCT ATGGTTCCGACCACTACGGTATGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 697
1.70	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCAATTTTAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGAGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAGAATTACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGTCAAGAA CTCACTGTTTCTGCAAATGAACCGCCTGAGAGCCGACGACACGGCTGTGTATTACTGTGCGAGAGGGGGGTTTGGCT ACGGTGACTCCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 698
1.71	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTGGTAACTATTGGATGATCTGGGTCCGCCAGGCTCCAGGCAAGGAGTTGGAGTGGCTGGCCAACATA AACCAAAATGGAAGTGAGAGATACTATGTGGACTCTGTGCAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTATATTACTGTGCGAGAGGGGGTGCTGACT ACAGTAACTCCCACTACGGTATGGACGTCAGCGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 699
1.72	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAAC TCACTGCATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 700
1.73	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTAGAAGTTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAAGAGGCGGAATGGGTGGCCAACATA AACCCAGATGGAAGTGAGAAATACTATGTGGACTCTGTGCAGGGCCGACACACCATCTCCAGAGACAACGCCAAGAA CTCACTGTTTCTGGAAATGAACAGCCTGAGAGTCGAGGACACGGCTCTTTATTACTGTGCGAGAGGAGGCCCCGGCTA CGGTGACCTCCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 701
1.74	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA

	AATCAAGATGGAAGTGAAAAATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAG CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCCTCA SEQ ID NO. 702
1.75	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 703
1.76	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 704
1.77	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 705
1.78	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 706
1.79	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCAACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCTTCA SEQ ID NO. 707
1.80	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG ATTCACCTTCAGTGACTACTATATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AGCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGC TCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO.708
1.81	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAG CTCACTGTATCTGCAAATGAGCAACCTGAGAGCCGAGGACACGGCTGTATATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 709
1.82	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATTTCCAGAGACAACGCCAAGAG CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 710
1.83	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA

	CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 711
1.84	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO.712
1.85	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAACAA CTCACTGCATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGC TATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 713
1.86	CAGGTGCAGCTGGGGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAG CTCACTGTATCTGCAAATGAGCAACCTGAGAGCCGAGGACACGGCTGTATATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 714
1.87	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAAACTCTCCTGTGCAGCCACTGG ATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA ACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATTTCCAGAGACAACGCCAAGAGC TCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 715
1.88	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCACTG GATTCACCTTAAGTAACTATTGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGGCAACGCCAAGAA CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 716
1.89	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATA AACCAAGATGGAAGTGAAAGATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCACTGTATCTGCAAATGAGCAGCCTGAGAGCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGGGGGGGAAGGCT ATGGTGTCGACCACTACGGTTTGGACGTCTCGGGCCAAGGGACCACGGTCACTGTCTCTTCA SEQ ID NO. 717
1.90	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCAC ATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCC AAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGT GATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 718
1.91	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCGTCTCCAGAGACAACGCCA AGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 719
1.92	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGAAGGGCCGATTCACCGTCTCCAGAGACAACGCCA AGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG

	ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 720
1.93	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 721
1.94	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 722
1.95	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCAC ATAAAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGT GATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 723
1.96	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 724
1.97	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCAC ATAAAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGT GTTGGCTACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 725
1.98	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCAC ATAAAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGT GAGGGCTACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 726
1.99	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 727
1.100	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 728
1.101	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGGCGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

	SEQ ID NO. 729
1.102	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGAGGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG ATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 730
1.103	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG AGGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 731
1.104	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGT TGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 732
1.105	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGT TGGCTACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO.733
1.106	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACA TAAAGGAAGACGAAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCA AGAACTCGTTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTG AGGGCTACAGTATCTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA SEQ ID NO. 734
1.107	GAGGTGCAATTAGTCGAATCGGGGGGGTGGACTGGTTCAGCCGGGAGGTAGCCTGCGCCTGTCCTGTGCCGCATCT GGTTTTACATTAAGTAACTACTGGATGAATTGGGTTCGTCAAGCGCCTGGAAAGGGCTTAGAGTGGGTGGCTAATA TTAACCAGGACGGGTCAGAGCGCTACTATGTGGATTCAGTAAAAGGTCGCTTCACTATCAGCCGCGATAATGCTAA AAATTCGCTGTACCTTCAGATGTCATCACTTCGTGCAGAGGATACAGCTGTGTATTTCTGCGCGCGTGGAGGCGAG GGGTACGGGGTAGACCACTATGGGTTGGATGTCTCGGGACAAGGCACGACCGTCACTGTCAGTAGC SEQ ID NO. 881
1.108	GAGGTCCAGTTGGTTGAGTCCGGCGGCGGCTTGGTCCAACCAGGGGGGTCGCTTCGCTTATCTTGCGCTGCCACAG GGTTTACCCTGAGCAACTACTGGATGAACTGGGTGCGCCAAGCGCCTGGGAAGGGGTTAGAGTGGGTCGCCAACA TCAACCAAGACGGTTCGGAGCGTTACTATGTCGACAGCGTGAAGGGCCGTTTCACGATCTCCCGCGATAACGCTAA GAACTCCCTGTATTTGCAAATGAATAGCCTTCGTGCGGAGGATACTGCGGTTTATTTCTGTGCTCGTGGCGGTGAAG GATATGGGGTTGACCATTATGGGTTGGATGTCTCCGGGCAAGGGACAACGGTGACCGTGTCATCC SEQ ID NO. 882
1.109	GAGGTTCAACTTGTTGAATCGGGTGGCGGATTAGTACAACCCGGCGGCTCGCTGCGTTTATCGTGTGCGGCAACCG GATTTACTTTATCAAACTATTGGATGAATTGGGTGCGCCAGGCTCCAGGGAAAGGTCTGGAATGGGTAGCGAATAT CAACCAAGACGGCTCAGAACGCTACTACGTGGACTCCGTAAAAGGTCGTTTCACCATCTCTCGTGACAATGCTAAAA ATTCTTTGTATTTGCAAATGAGTTCACTTCGTGCTGAGGATACTGCGGTCTATTACTGTGCTCGCGGGGGGGAAGGC TACGGAGTAGACCACTACGGGTTGGATGTTTCTGGACAGGGAACGACGGTTACTGTAAGCAGC SEQ ID NO. 883
1.110	GAGGTTCAGTTAGTTGAGTCCGGCGGGGGATTAGTTCAACCTGGCGGAAGCCTTCGTCTGAGTTGTGCCGCGAGC GGGTTTACCCTTAGCAATTACTGGATGAACTGGGTACGTCAAGCTCCAGGTAAAGGTTTAGAATGGGTCGCTAACA TTAATCAAGATGGTTCTGAACGCTATTATGTAGACTCGGTAAAGGGTCGTTTTACAATTTCTCGCGACAACGCCAAA AACTCTTTGTACCTTCAAATGAATTCCTTACGCGCTGAGGACACTGCTGTCTATTTCTGTGCGCGTGGAGGGGAGGG ATACGGAGTTGACCACTATGGGCTGGACGTTTCAGGACAGGGCACTACGGTAACTGTGTCTTCG SEQ ID NO. 884

1.111	GAGGTTCAGTTAGTAGAGTCCGGGGGAGGACTGGTACAACCTGGGGGTAGTTTGCGTCTGTCTTGTGCAGCCAGC GGTTTCACATTGTCTAACTATTGGATGAATTGGGTTCGTCAAGCGCCTGGCAAGGGACTGGAGTGGGTTGCAAACA TTAATCAAGATGGCAGCGAGCGTTATTACGTGGACTCAGTAAAAGGGCGCTTCACGATTAGCCGCGATAATGCTAA GAACTCCTTATATCTGCAGATGTCATCTTTGCGTGCCGAGGACACGGCAGTTTACTATTGCGCACGTGGTGGCGAG GGATACGGCGTGGATCACTATGGTTTGGACGTATCGGGCCAAGGGACTACCGTGACTGTGTCCTCT SEQ ID NO. 885
1.112	GAGGAGGTACAGCTTGTCGAGTCTGGCGGTGGCCTTGTGCAACCGGGGGGTTCTTTACGTTTATCCTGTGCCGCTA CAGGATTTACGTTAAGCAACTATTGGATGAACTGGGTACGTCAAGCTCCGGGGAAGGGGCTGGAATGGGTTGCCA ATATCAATCAGGATGGGTCTGAACGCTACTACGTTGATTCTGTTAAGGGTCGCTTTACTATTTCACGTGACAATGCC AAGAACAGTCTTTACCTTCAAATGAACTCGTTACGCGCTGAGGATACTGCTGTGTACTACTGTGCGCGCGGCGGAG AGGGATACGGTGTCGATCATTATGGGCTTGACGTAAGCGGGCAGGGTACGACGGTGACGGTATCATCA SEQ ID NO. 556
1.113	GAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCG GGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACA TTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAA AAATTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAG GATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCC SEQ ID NO. 887
1.114	GAGGTGCAGTTGGTAGAGAGTGGGGGTGGCCTGGTCCAACCAGGTGGGTCCCTTCGTTTGTCTTGCGCCGCCTCTG GGTTTACTCTGTCAAATTATTGGATGAACTGGGTGCGCCAAGCTCCCGGCAAGGGGTTGGAGTGGGTTGCCAACAT TAATCAGGACGAATCCGAGCGTTACTATGTTGATTCTGTAAAAGGGCGCTTCACTATCTCTCGTGATAATGCTAAGA ACAGTTTGTACCTGCAAATGAATTCACTGCGTGCCGAGGATACCGCGGTGTACTATTGTGCCCGTGGAGGAGAGGG ATACGGGGTCGATCACTATGGCTTAGACGTATCGGGCCAGGGAACAACCGTCACC GTATCCTCA SEQ ID NO. 888

Table 5 Nucleic acids encoding V_H 2.1 to 2.51

Name	Nucleotide Sequence
2.1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTA ACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 735
2.2	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTA GTGGTAGTGGTGATATCATAGACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTAT ACCTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 736
2.3	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTATATGAGTTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGATTTCGTACATTA GTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTAT ACCTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 737
2.4	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTA GTGGTAGTGGTGATGTCATTGACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAATT CACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATA CCTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 738
2.5	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTAG TGGTAGTGGTGATATCATAGACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTC

	ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTATAC CTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 739
2.6	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCGTACATTA GTGGTAGTGGTGATATCATAGACTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAAAGAAGATTCCCGTAT ACCTGGAACTACGGACTTTGACAGTTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA SEQ ID NO. 740
2.7	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCAGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTGGTAGTGGTACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAAC TCACTATATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGAT GACTGGAACTACGGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 741
2.8	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTATATCTACAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGCAT GCCTGGAACTACGGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 742
2.9	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTATATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGATTTCATACATTA GTGGTAGTGGTGATACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAT TCACTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCGCGTAT AGCCGGAACTACGGACTTTGACAACTGGGGCCCGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 743
2.10	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTAGTAGTGGTAGTAACATAGATTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCTAGGGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCCCGTTTA AGTGGAACTACGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 744
2.11	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTATATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGATTTCATACATTA GTGGTAGTGGTGATACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAT TCACTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCGCGTAT AGCCGGAACTACGGACTTTGACAACTGGGGCCCGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 745
2.12	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTGGTAGTGGTACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAAG TCACTATATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTCTATTACTGTGCCAGAGAAGATATCAGGAT GACTGGAACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 746
2.13	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TAGTAGTGGTAATACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTC ACTTTATCTGCAAATGAATAGTCTGAGAGCCGAGGACACGGCCGTTTATTACTGTGCGAGAGAAGATCCTCGTTTACC TGGAACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 747
2.14	GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTATATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGATTTCATACATTAG TGGTAGTGGTGATACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAATT CACTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATG

	CCTGGAACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 748
2.15	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGC CTGGAACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 749
2.16	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TAGTAGTGGGAGTACCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACT CACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTA ACTGGAACTACAGATTTTGACTACTGGGGCCAGGGAGCCCTGGTCACTGTCTCCTCA SEQ ID NO. 750
2.17	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAG TAGTAGTGGTAGTACCATATCCTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTATAA GTGGAACTACAGATTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 751
2.18	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTAGTAGTGGTAATACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACT CACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTTTATTACTGTGCGAGAGAAGATCCTCGTTTAC CTGGAACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 752
2.19	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAG TGGTACTGGTATTACCACAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTACC TGGAACTTCAGAATTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 753
2.20	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTAGTAGTGGTAGTACCATAGATTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACT CACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTCTATTACTGTGCGAGAGAAGATCCCCGTATG CCTGGAACTTTTGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 754
2.21	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAAT TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGAT GCCTGGAACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 755
2.22	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGGATT CACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATG CCTGGAACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 756
2.23	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCACGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGC CTGGAACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA

	SEQ ID NO. 757
2.24	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGTCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAATTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCATGTATTACTGTGCCAGAGAAGATATCAGGATGC CTGGAACTACGGATTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 758
2.25	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTTAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGACCGCTTCACCATCTCCAGGGACAACGCCAGGAATTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGATGC CTGGAACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 759
2.26	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTACAGCCTCTGG ATTCACCTTCACTGACTATTATATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTTTCACACATTAG TAGTAGTGGTACTACAATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGACGACACGGCCGTATATTACTGTGCGAGAGAAGATATCAGGATGC CTGGAACTACGGACTTTGACAACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO.760
2.27	CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGACCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA GTAGTAGTGGTAGTACCATTTCCTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAACAACT CACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTATATCACTGTGCGAGAGAAGATATACGTATG AGTGGGACTACGGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 761
2.28	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCATCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TAGTAGTGGTAGTTCCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATTTCGAGGGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTAA GTGGAACTATAGATTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 762
2.29	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATT GGTGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAGGAA TTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGA TGCCTGGAACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 763
2.30	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAG TAGTAGTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTGTGC CTGGAACTACGAACTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO. 764
2.31	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTACTACATGACCTGGATGCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAG TGGCAGTGGTAGTACCATTGACTATGCAGACTCTGTGAAGGGCCGATTCACGATCTCCAGGGACAACGCCAAGAACT CACTGTACCTGCAAATGAACAGCCTGAGACCCGAGGACACGGCCGTGTATTACTGTGCGAAAGAAGATGGCCGTATA CCTGGAACTACGGACTTTGACCACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 765
2.32	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCGCCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCGGGGAAGGGGCTGGAGTGGGTTTCACACATT AGTGGTAGTGGAACTACCATAGACTACGCAGACTCTGTGAAGGACCGCTTCACCATCTCCAGGGACAACGCCAGGAA TTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCCAGAGAAGATATCAGGA TGCCTGGAACTACGGACTTTGACCACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 766

2.33	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCCCCTTCAGTGACTACTTCATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTAG TAGTAGTGGTAATTCCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTTTATTACTGTGCGAAAGAAGATCCTCGTTTACC TGGAACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 767
2.34	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACTCCTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACATATTAG TAATTCTGGTAGTACCATAAGCTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTC ACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTACC TGGAACTTCAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 768
2.35	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTAGTAGTGGTAGTTCCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATTTCGAGGGACAACGCCAAGAATT CACTGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTTTA AGTGGAACTACAGATTTTGACCAGTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 769
2.36	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTTAGTAGCTATTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTAGTAGTGGTAGTACCATAGACTACGCAGAGTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCTCGTAT GACTGGAACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCTTCA SEQ ID NO. 770
2.37	CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACCTTCAGTAACTACTTCATGAGTTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCACACATTA GTAGTAGTGGTAATACCATAGACTACGCAGACTCTGTGAAGGGCCGCTTCACCATCTCCAGGGACAACGCCAAGAACT CACTTTATCTGCAAATGGATAGTCTGAGAGCCGAGGACACGGCCGTTTATTACTGTTCGAGAGAAGATCCTCGTTTAC CTGGAACTACAGATTTTGACTACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 771
2.38	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTG GATTCACTTTCAGTGACTACTACATGACCTGGATCCGCCAGGGTCCAGGGAAGGGACAGGAATGGATTTCATACATTA GTAGTGGTGGTAGCACCATACACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAAATCCCCGTTTA CCTGGAACTATGGACTTTGACTATTGGGGCCAGGGAACCCTGGTCACTGTCTCCTCA SEQ ID NO.772
2.39	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG ATTCACCTTCAGTGACCACTTCATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATAA AACAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC TCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTATGTATTACTGTGCGAGAGAGGATCCTCGTTTA ACTGGAACTACAGATTTTGACAACTGGGGCCAGGGAACCCTGGTCACTGTCTCTTCA SEQ ID NO. 773
2.40	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGGCGGGGGGGTCCCTAAGACTCTCCTGTGTAGCCTCTG GATTCACCTTTAGTAATTATTGGATGACCTGGTTCCGCCAGGCTCCAGGGAGGGGGCTGGAGTGGGTTTCACACATTA GTAGTACTGGATCTACCATAGACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCGAGAACT CACTATATTTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCCCGTTTAC CTGGAACTATGGACTTTGACTATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 774
2.41	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 775
2.4	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCT

2	GGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 776
2.43	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 777
2.44	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 778
2.45	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 779
2.46	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 780
2.47	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATTCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 781
2.48	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATGCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 782
2.49	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 783
2.50	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATGCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO. 784
2.51	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA

	TTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAA GAACTCTCTGTATCTGCAGATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGAAGATCCC CGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA 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 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 of SEQ ID Nos. 629, 706, 881, 882, 883, 884, 885, 996, 887 or 735 or a sequence with at least 75% homology thereto.

A nucleic acid according to the present invention 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 an anti- CD137 single domain antibody as described herein is provided, wherein the method comprises culturing the host cell under conditions suitable for expression of the polynucleotide encoding the single domain antibody, and isolating the single domain antibody.

In another aspect, there are provided binding molecules, e.g. antibodies, antibody fragments or antibody mimetics that bind at or near the same epitope or an overlapping epitope on human CD137 as any of the CD137 single domain antibodies of the invention (i.e., antibodies that have the ability to cross-compete for binding to CD137 with any of the single domain antibodies of the invention. The single domain antibodies of the invention can thus be used as a reference antibody). In some embodiments, the reference antibody for cross-competition studies is single domain antibody 1.1 (SEQ ID No. 4). Such cross-competing antibodies can be identified based on their ability to cross-compete with a single domain antibody described herein in standard CD137 binding assays. For example, BIAcore® analysis, ELISA assays or flow cytometry may be used to demonstrate cross-competition with the single domain antibodies.

In one embodiment, there is provided a binding agent capable of binding human CD137 wherein any one of the single domain antibodies described above displaces the binding agent in a competitive assay. In one

embodiment, said single domain antibody is V_H 1.1 (SEQ ID No. 4), V_H V_H 1.78 (SEQ ID No. 312), V_H 1.113 (SEQ ID No. 876) or V_H 2.1 (SEQ ID No. 428) or a sequence with at least 75% homology thereto. In some embodiments, the binding agent is an antibody, a functional fragment thereof, for example a single domain antibody, an antibody mimetic protein or a protein that mimics the natural ligand of CD137. In another aspect, there is provided a binding agent capable of binding human CD137 wherein the binding agent displaces any one of the single domain antibodies described above in a competitive assay. In one embodiment, said single domain antibody is V_H 1.1 (SEQ ID No. 4), V_H 1.78 (SEQ ID No. 312), V_H 1.113 (SEQ ID No. 876) or V_H 2.1 (SEQ ID No. 428) or a sequence with at least 75% homology thereto. In another aspect, invention provides a binding agent capable of binding human CD137 wherein the binding agent binds to essentially the same epitope as the single domain antibody of the invention.

In another aspect, we provide an isolated heavy chain only antibody comprising a V_H domain as described herein or with at least 70%, 80% or 90% homology thereto. A heavy chain only antibody may be isolated from a transgenic mammal expressing human V, D and J regions as described herein.

The single variable heavy chain domain antibody described herein can be used as a building block in a multispecific, for example bispecific, binding agent that provides dual targeting of a CD137 expressing cell and a cell that, for example, expresses a tumor specific antigen. Accordingly, we provide the use of a single variable heavy chain domain antibody described herein in a binding molecule for dual, e.g. simultaneous engagement of CD137 and a second antigen, for example a tumor specific antigen. Such binding molecule simultaneously binds to at least two different targets. As described below, in some embodiments, there is provided a method for making binding agents that provide dual targeting of a CD137 expressing cell and a cell that, for example, expresses a tumor specific antigen. A nucleic acid encoding a single variable heavy chain domain antibody described herein, for example as listed above, is linked to nucleic acid encoding a linker peptide which in turn is linked to a nucleic acid encoding, for example, a single variable heavy chain domain antibody encoding a tumor specific antigen. The nucleic acid construct can be expressed in a host cell, for example a bacterial, mammalian or yeast cell.

Exemplary multispecific binding molecules

In one aspect, there is provided a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 described herein and at least a second moiety that binds to a second antigen, for example a tumor specific antigen. The terms binding agent and binding molecule are used interchangeably herein. The binding molecule may be a fusion protein.

In one embodiment, the at least second moiety is a binding molecule, for example selected from an antibody or antibody fragment (e.g., a Fab, F(ab')2, Fv, a single chain Fv fragment (scFv) or single domain antibody, for example a V_H or V_{HH} domain) or antibody mimetic protein. In one embodiment, the single domain antibody of the invention can be linked to an antibody Fc region or fragment thereof, comprising

one or both of C_H2 and C_H3 domains, and optionally a hinge region. In one embodiment, the at least second moiety is a V_H domain.

The binding agent may be multispecific, for example bispecific. In one embodiment, the binding molecule comprises a first V_H single domain antibody that binds to CD137 as described herein (V_H (A)) and a second V_H single domain antibody (V_H (B)) that binds to another antigen and thus has the following formula: V_H (A)-L-V_H (B). V_H (A) is conjugated to V_H (B), i.e. linked to V_H (B), 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(BA)-FR3(B)-CDR3(B)-FR4(B). The order of the single VH 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.

In one embodiment, the binding molecule is bispecific. Thus, in one aspect, the invention relates to a bispecific molecule comprising a single domain antibody described herein linked to a second functional moiety having a different binding specificity than said single domain antibody.

The term "peptide linker" 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) and GGSG (SEQ ID NO: 797).

In one embodiment, the second moiety binds to a tumor specific antigen. In one embodiment, there is provided a binding molecule comprising

a) a single variable heavy chain domain antibody that binds to CD137 as described herein and

b) a single variable heavy chain domain antibody that binds to a tumor specific antigen.

The tumor specific antigen as used herein may be selected from a list including, but not limited to PSMA, Her2, CD123, CD19, CD20, CD22, CD23, CD74, BCMA, CD30, CD33, CD52, EGRF CECAM6, CAXII, CD24, CEA, Mesothelin, cMet, TAG72, MUC1, MUC16, STEAP, EphvIII, FAP, GD2, IL-13Ra2, L1-CAM, PSCA,GPC3, Her3, gpA33, 5T4 and ROR1. Exemplary binding molecules that bind to CD137 and PSMA are shown in the examples.

In one aspect, the invention relates to a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 as described herein linked to another moiety that binds to a tumor specific antigen, for example a single variable heavy chain domain antibody that binds to tumor specific antigen, 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 CD137 ligand. This can be measured as shown in example 6.

(c) does not bind to mouse CD137;

(d) binds to cells expressing CD137 but does not bind to cells that do not express CD137. This can be measured as shown in example 6;

(e) increases reporter gene activity. This can be measured as shown in example 9.

(f) inhibits tumor cell growth in vivo as shown in example 10;

(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 9;

(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 via CD137 positive NK cell activation;

(r) binds simultaneously to CD137 and a tumor specific antigen, such as PSMA, when linked to a moiety that binds such tumor specific antigen;

(s) binds to cyno CD137;

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

(u) activates NK cells;

(v) recruits T-cells to tumour cells.

In one embodiment, the binding molecule exhibits more than 1 of the properties above, for example a combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 properties or all properties selected from the above list, including any combination of properties.

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 a tumor specific antigen. 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. Examples of such linker are set out above. The

single variable heavy chain domain antibody that binds to CD137 can be linked to the other polypeptide via its N or C terminus.

The fusion protein described above is capable of simultaneous binding to CD137 on the surface of effector cells and to the tumor specific antigen displayed on the cell surface of tumor cells.

The dual, e.g. simultaneous binding leads to multimerisation of the CD137 receptor thus resulting in CD137 signalling. This leads to T cell activation. In some embodiments, co-engagement of the two targets, i.e. simultaneous binding to those targets, 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 at least similar, comparable or 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 may be capable of co-stimulating T cell responses in a functional T cell activation essentially as described 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.

In another aspect, a nucleic acid encoding a fusion protein described herein is provided. Also provided is a vector comprising such nucleic acid and a host cell expressing such vector.

In one embodiment, a binding molecule as described herein binds to CD137 with a KD of about 0.4nM or of about 3nM as measured according to the methods shown in the examples. Binding can be measured as in the examples.

Simultaneous targeting of CD137 and a tumor associated antigen 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.

Exemplary modifications

In one embodiment, the single domain antibody or binding agent described above comprises further binding molecules. Thus, the binding agent can for example be trispecific or tetraspecific. Additional specificities are also envisaged. Any combination of the aforesaid molecules can be made in a multispecific binding agent, for example, a trispecific binding agent that includes a single domain antibody that binds to CD137 as described herein and a second and third binding specificity.

In one embodiment, the binding molecule comprises a first V_H single domain antibody that binds to CD137 (V_H (A)) as described herein and a second, third, fourth, fifth etc moiety each binding to another antigen. This moiety can be a V_H single domain antibody (V_H (B), V_H (C), V_H (D), V_H (E)() that binds to another antigen and the agent thus has the following formula: 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 VH(B) bind to and wherein n 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. The linker can be a peptide linker with GS residues such as (Gly4Ser)n as described above. In one embodiment, the order of the V_H domains is reversed. In other words, a single variable heavy chain domain antibody that binds to CD137 is linked to another entity via either its C or N terminus.

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 an antibody, or part thereof that binds a serum albumin, e.g., human serum albumin (HSA) or mouse serum albumin (MSA). The further moiety may comprise a V_H domain that binds serum albumin, e.g., human serum albumin (HSA) or mouse serum albumin (MSA), for example as shown in SEQ ID NO. 901.

The further moiety may comprise a serum albumin, e.g. a human serum albumin (HSA) or a variant thereof such as HSA C34S. Further provided is a binding molecule as described herein comprising a VH domain as described herein and an Fc domain, e.g., wherein the VH domain is fused to an Fc domain. Further provided is a binding molecule that comprises a second variable domain that specifically binds a second antigen, where the second antigen is an antigen other than human CD137. The second antigen may be a cluster of differentiation (CD) molecule or a Major Histocompatibility Complex (MHC) Class II molecule.

In one embodiment, the anti-CD137 single domain antibodies or multivalent 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, the anti-CD137 single domain antibodies or multivalent 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 anti-CD137 single domain antibodies or multivalent 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 an antibody fragment, for example a V_H domain that increases half life.

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).

To generate multivalent binding agents and fusion proteins as described above, two or more polypeptides 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, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

Exemplary methods for making the single domain antibody

A single domain antibody described herein can be obtained from a transgenic mammal, for example a rodent, that expresses heavy chain only antibodies upon stimulation with a CD137 antigen. 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, for example a mouse, 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.

One aspect also relates to a method for producing a human heavy chain only antibodies capable of binding human CD137 said method comprising

a) immunising a transgenic rodent, e.g. mouse, with an CD137 antigen 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 form 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.

Another aspect also relates to a method for producing a single V_H domain antibody capable of binding human CD137 said method comprising

a) immunising a transgenic rodent with an CD137 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 human CD137, 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 CD137 and

c) isolating the amino acid sequence(s) that can bind to / have affinity for CD137.

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.

Another aspect also relates to an isolated V_H single domain antibody or an isolated heavy chain only antibody comprising a V_H domain binding to CD137 comprising an amino acid product of or derived from a human V_H germline sequence. The heavy chain only antibody may be fully human or comprise mouse sequences.

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.

The invention also relates to a rodent, preferably a mouse which expresses a human heavy chain locus and which has been immunized with a CD137 antigen. The invention also relates to a rodent as described above, preferably a mouse which expresses a heavy chain only antibody comprising a human V_H domain that binds to human CD137. Preferably, said rodent is not capable of making functional endogenous kappa and lambda light and/or heavy chains. The human heavy chain locus is located on a transgene which can be as described above.

The invention also relates to an anti-human CD137 single V_H domain antibody or an anti-human CD137 heavy chain only antibody comprising a human V_H domain or obtained or obtainable from a rodent, preferably a mouse, immunised with a human CD137 antigen and which expresses a human heavy chain locus. Preferably, said rodent is not capable of making functional endogenous kappa and lambda light and/or heavy chains. The human heavy chain locus is located on a transgene which can be as described above.

Exemplary therapeutic applications

In one aspect, we provide single variable heavy chain domain antibodies described herein and the binding agents described herein for use as an anti-cancer agent or immune modulator.

In another aspect, there is provided a pharmaceutical composition comprising a single variable heavy chain domain antibody that binds to CD137 as described herein or comprising a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 as described herein and optionally a pharmaceutically acceptable carrier. A single domain antibody, a binding molecule or composition comprising a single variable heavy chain domain antibody that binds to CD137 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 conjugate 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 conjugates 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 injeciton, intravenous injection or infusion. In one embodiment, the composition is part of a device which includes an injector pen. The composition may be provided as a pre-filled syringe or other self-administration device.

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.

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 animal's body weight, and more preferably about 1 mg/kg to about 10 mg/kg of the animal'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.

The invention provides methods of treating CD137-mediated diseases or disorders in a mammal, e.g., a human patient, comprising administering an effective amount of an antibody of the present invention to a mammal in need thereof. In particular, the invention furthermore relates to a method for the prevention and/or treatment of a disorder selected from cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency and other immune system-related disorder said method comprising administering, to a subject in need thereof, a pharmaceutically active amount of a single variable heavy chain domain antibody that binds to CD137, binding molecule composition comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition of the invention, or of a pharmaceutical composition of the invention.

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 an anti-CD137 antibody, 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 also relates to a single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition of the invention for use in the treatment or prevention of a disease.

In another aspect, the invention relates to a single variable heavy chain domain antibody that binds to CD137, a binding molecule that comprises single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition of the invention for use in the treatment or prevention of cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency, and other immune system-related disorder.

In another aspect, the invention relates to the use of a single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition of the invention in the treatment or prevention of a disease.

In another aspect, the invention relates to the use of a single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition of the invention in the manufacture of a medicament for the treatment or prevention of cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency, and other immune system-related disorder.

The cancer can be selected from a solid or non-solid tumor. For example, the cancer may be selected from bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, breast cancer, brain cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, kidney cancer, sarcoma of soft tissue, cancer of the urethra, cancer of the bladder, renal cancer, lung cancer, non-small cell lung cancer, thymoma, urothelial carcinoma leukemia, prostate cancer, mesothelioma, adrenocortical carcinoma, lymphomas, such as such as Hodgkin's disease, non-Hodgkin's, gastric cancer, and multiple myelomas.

In one embodiment, the tumor is a solid tumor. Examples of solid tumors which may be accordingly treated include breast carcinoma, lung carcinoma, colorectal carcinoma, pancreatic carcinoma, glioma and lymphoma. Some examples of such tumors include epidermoid tumors, squamous tumors, such as head and neck tumors, colorectal tumors, prostate tumors, breast tumors, lung tumors, including small cell and non-small cell lung tumors, pancreatic tumors, thyroid tumors, ovarian tumors, and liver tumors. Other examples include Kaposi's sarcoma, CNS, neoplasms, neuroblastomas, capillary hemangioblastomas, meningiomas and cerebral metastases, melanoma, gastrointestinal and renal carcinomas and sarcomas, rhabdomyosarcoma, glioblastoma, preferably glioblastoma multiforme, and leiomyosarcoma. Examples of vascularized skin cancers for which the antagonists of this invention are effective include squamous cell carcinoma, basal cell carcinoma and skin cancers that can be treated by suppressing the growth of malignant keratinocytes, such as human malignant keratinocytes.

In one embodiment, the tumor is a non-solid tumor. Examples of non-solid tumors include leukemia, multiple myeloma and lymphoma.

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

Preferred cancers whose growth may be inhibited using the antibodies of the invention include cancers typically responsive to immunotherapy. Non-limiting examples of preferred cancers for treatment include melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), breast cancer, colon cancer and lung cancer (e.g. non-small cell lung cancer).

In one embodiment, the cancer has progressed after another treatment, for example chemotherapy.

The competitive CD137 binders described herein inhibit CD137 ligand binding to CD137.This leads to a suppression of the signal received by the CD137 receptor. This can be advantageous for the treatment of inflammatory and autoimmune diseases and the monovalent binding molecules described herein therefore find application in the treatment of such diseases.

The immune disorder can be selected from graft vs. host disease, arthritis, alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune diseases of the adrenal gland, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune oophoritis and orchitis, autoimmune thrombocytopenia, Behcet's disease, bullous pemphigoid, cardiomyopathy, celiac sprue-dermatitis, chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, cicatrical pemphigoid, CREST syndrome, cold agglutinin disease, Crohn's disease, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, glomerulonephritis, Graves' disease, Guillain-Barre, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), IgA neuropathy, juvenile arthritis, lichen planus, lupus erthematosus, Meniere's disease, mixed connective tissue disease, multiple sclerosis, Neuromyelitis optica (NMO), type 1 or immune -mediated diabetes mellitus, myasthenia gravis, pemphigus vulgaris, pernicious anemia, polyarteritis nodosa, polychrondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, Raynauld's phenomenon, Reiter's syndrome, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, stiff-man syndrome, systemic lupus erythematosus, lupus erythematosus, takayasu arteritis, temporal arteristis/ giant cell arteritis, transverse myelitis, ulcerative colitis, uveitis, vasculitides such as dermatitis herpetiformis vasculitis, vitiligo, and Wegener's granulomatosis. The neurological disease can be selected from Alzheimer's disease, epilepsy, Parkinson's disease, dementia, multiple sclerosis, peripheral neuropathy or post-herpetic neuralgia.

Exemplary combinations with other agents

The molecules or pharmaceutical composition of the invention 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, or antibody mimetic protein.

In one embodiment, the single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition described herein is used in combination with an existing therapy or therapeutic agent, for example an anti-cancer therapy. Thus, in another aspect, the invention also relates to a combination therapy comprising administration of a single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition described herein and an anti-cancer therapy.

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

In a specific embodiment of the present invention, the single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition described herein is administered concurrently with a chemotherapeutic agent or with radiation therapy. In another specific embodiment, the chemotherapeutic agent or radiation therapy is administered prior or subsequent to administration of the composition of the present invention, preferably at least an hour, five hours, 12 hours, a day, a week, a month, more preferably several months (e. g. up to three months), prior or subsequent to administration of composition of the present invention.

In some embodiments, the single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical

composition described herein may be administered with two or more therapeutic agents. In some embodiments, the binding agents of the invention may be administered with two or more therapeutic agents.

The single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or a pharmaceutical composition as described herein may be administered at the same time or at a different time as the other therapy or therapeutic compound or 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 single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 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 in a subject, comprising administering to a subject a therapeutically effective amount of a single variable heavy chain domain antibody that binds to CD137, 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 method for activating the downstream signalling pathway of CD137 comprising administering to a subject a single variable heavy chain domain antibody that binds to CD137, 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 method for inducing T lymphocyte activation and /or proliferation comprising administering to a subject a single variable heavy chain domain antibody that binds to CD137, 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 method for dual targeting of a CD137 expressing cell and a tumor antigen 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 expressing cell.

Immunoconjugates and other agents

In another aspect, there is provided an immunoconjugate comprising a single variable heavy chain domain antibody that binds to CD137 or a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 described herein conjugated to at least one therapeutic and/or diagnostic agent.

The invention also relates to the use of a single variable heavy chain domain antibody that binds to CD137 or a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 described herein for use a diagnostic agent. The invention also relates to the use of a single variable heavy chain domain antibody that binds to CD137 or a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 described herein conjugated to a label.

Exemplary kits

In another aspect, the invention provides a kit for the treatment or prevention of a disease for example as listed herein or an immune response and/or for detecting CD137 for diagnosis, prognosis or monitoring disease comprising a single domain antibody of the invention. Such a kit may contain other components, packaging, instructions, or material to aid in the detection of CD137 protein. The kit may include a labeled single variable heavy chain domain antibody that binds to CD137 or a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 and one or more compounds for detecting the label.

The invention in another aspect provides a single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or pharmaceutical composition described herein packaged in lyophilized form, or packaged in an aqueous medium.

Exemplary non therapeutic applications

In another aspect, a single variable heavy chain domain antibody that binds to CD137 described herein is used for non-therapeutic purposes, such as diagnostic tests and assays. A method for detecting the presence of human CD137 in a test sample comprises contacting said sample with a single domain antibody described herein and at least one detectable label and detecting binding of said single domain antibody to human CD137.

Modifications of antibodies for diagnostic purposes are well known in the art. For example, antibodies may be modified with a ligand group such as biotin, or a detectable marker group such as a fluorescent group, a radioisotope, or an enzyme. Compounds of the invention can be used for diagnostic purposes and e.g. labelled using conventional techniques. Suitable detectable labels include but are not limited to fluorophores, chromophores, radioactive atoms, electron-dense reagents, enzymes, and ligands having specific binding partners.

Also provided is a single variable heavy chain domain antibody that binds to CD137, a binding molecule comprising a single variable heavy chain domain antibody that binds to CD137 or a 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. Construction of Tg/TKO mice

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). In summary, 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.

The transgenic founder mice were back crossed with animals that lacked endogenous immunoglobulin expression to create the Tg/TKO lines used in the immunisation studies described below.

EXAMPLE 2. Immunisation Protocol

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.

EXAMPLE 3. Serum ELISA

Serum was 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.

Whole blood samples were centrifuged at 13000rpm for 5 mins to separate blood from serum. Serial dilutions of serum were prepared in 3% Marvel®/PBS in polypropylene tubes or plates, pre-incubated for at least one hour at room temperature then transferred to the blocked ELISA plate and incubated for at least one hour. Unbound protein was removed by repetitive washing with PBS/Tween®-20 followed by PBS. A 1:10,000 solution of biotin-conjugated, goat anti-mouse IgG, Fcgamma subclass 1 specific antibody (Jackson ImmunoResearch cat. no.115-065-205), prepared in PBS/3% Marvel® was added to each well and incubated at room temperature for at least one hour. Unbound detection antibody was removed by repeated washing using PBS/Tween® 20 and PBS. Neutravidin-HRP solution (Pierce cat. no. 31030) in 3% Marvel®/PBS was added to the ELISA plates and allowed to bind for 30 minutes, then washed as above. The ELISA was developed using TMB substrate (Sigma cat. no. T0440) and the reaction was stopped by the addition of 50ul 0.5M H_2SO_4 solution (Sigma cat. no. 320501). Absorbance at 450nm was measured using the BMG Pherastar.

EXAMPLE 4. Generation of Libraries from Immunised Mice

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. 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. V_H/phagemid PCR products were pooled by animal-of-origin or V_H germline

families and purified using Fermentas PCR purification kit (cat. no. K0702) according to the manufacturer's instructions. The eluted DNA was transformed into TG1 *E. coli* (Lucigen, cat. no. 60502-2) by electroporation using the Bio-Rad GenePulser Xcell pulsed at 2500V, 25uF, 200W. Electroporated cells were pooled. Libraries were harvested.

EXAMPLE 5. Selection strategies for isolation of CD137 binding V_H isolation and optimisation

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).

EXAMPLE 6: Screening of Periplasmic Extracts for Binding to CHO human CD137 Cells and Inhibition of human CD137 Ligand Binding to human CD137

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. Small-scale bacterial periplasmic extracts were prepared from 1ml cultures, grown in deep well plates according to standard techniques. 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). Fluorescence emission was 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.

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. Total binding controls containing diluted periplasmic extract sample 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. 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.

EXAMPLE 7. Sequencing

Table 1 shows the sequences of Family 1 VHs and table 2 those of Family 2 VHs.

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.

EXAMPLE 8. Preparation Purified V_H

a) Preparation of purified V_H

Purified V_H were obtained by using the V_H C-terminal 6xHIS tag for nickel-agarose affinity chromatographic purification of the periplasmic extracts according to standard procedures. Yields of purified V_H were estimated spectrophotometrically and purity was assessed using SDS PAGE. Alternatively, V_H were purified from the supernatants of W3110 *E coli* with pJExpress vector according to standard procedures. Yields of purified V_H were estimated spectrophotometrically and purity was assessed using SDS PAGE. If required, samples were concentrated using Vivaspin 20, 3 kDa MWCO PES, concentrator (Sartorius, # VS2092) and endotoxin depleted using Etoxiclear resin (Prometic, # 3250-00010).

b) Generation of multivalent constructs

DNA sequences encoding Humabody® V_H specific for CD137 and a V_H specific for PSMA were amplified by PCR. They were assembled into larger fragments, with the V_H sequences flanked by linkers encoding glycine/serine-rich sequences, and ligated into an expression vector by a restriction enzyme-based method. Plasmids were transformed into microbial expression systems as per standard techniques. The presence of Humabody® V_H sequences was verified by a standard colony PCR technique. Insert sequences were then confirmed by Sanger sequencing using vector-specific and internal primers to ensure complete sequence coverage. Sequences for exemplary constructs are shown below.

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 6c PSMA binding single VH 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

Table 6d Exemplary nucleic acids

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

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

Table 7: exemplary multivalent constructs

SEQ ID NO:798 1.1-6GS-1.1 Protein EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMN SLRAEDTAVYYCARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQ PGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCAR GGDGYSDSHFGVDVWGQGTTVTVSS
SEQ ID NO:799 1.1-6GS-1.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGG AAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAA TGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGT GGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGG TTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTT GGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCA GGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGG GCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTG TATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGT CTCTTCA
SEQ ID NO:800 2.1-6GS-2.1 Protein EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLR AEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKPGGSL RVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCAREDSRLTG TTDFDNWGQGTLVTVSS
SEQ ID NO:801 2.1-6GS-2.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCA CCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGT GATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATG AACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAA TTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGG AGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCA AGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTC CAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATT CACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACT GTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
SEQ ID NO: 802 1.1-6GS-1.1-6GS-1.1 Protein

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMN SLRAEDTAVYYCARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQ PGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCAR GGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGF TFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCARGGDGYSDSHFGVD VWGQGTTVTVSS
SEQ ID NO: 803 1.1-6GS-1.1-6GS-1.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA CCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGG AAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAA TGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGT GGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGG TTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTT GGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCA GGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGG GCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTG TATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGT CTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATC GGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCC ACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAA CTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGT GACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCA
SEQ ID NO: 804 2.1-6GS-2.1-6GS-2.1 Protein EVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLR AEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKPGGSL RVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCAREDSRLTG TTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVKPGGSLRVSCAASGFTFSDYYMS WFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCAREDSRLTGTTDFDNWGQGTLVTVS S
SEQ ID NO: 805 2.1-6GS-2.1-6GS-2.1 Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCA CCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGT GATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATG AACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAA TTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGG AGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCA AGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTC CAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATT CACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACT GTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGT GGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGG TGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCT GGATTCACCTTCAGTGACTACTACATGAGCTGGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGG TAGTGGTGATATCATAGACTACGCAGACTCTGTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCT GCAGATGAACAACCTGAGAGCCGAGGACACGGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGAC TTTGACAATTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA
SEQ ID NO: 806 4.1(PSMA-binding VH)-6GS-1.1 Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG 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 LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG 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
SEQ ID NO. 843 4.1-6GS-1.1-6GS-VH (MSA) Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGG GGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTT GGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACT CTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAGAACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGAC ACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACAGTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCA CGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGG CGGTGGATCGGGTGGAGGTGGTAGTCAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCTGA

GACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGTTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTCGCAACTATTAGTGATAGTGGTAGTAGTGCAGACTACGCAGATTCCGTGAAGGGACGGTTCACCATCTCCAGAGACAA CTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCTGAAGACACGGCCGTGTATTACTGTGCGAGAGGCCGGTATA ACTGGAACCCCCGAGCTTTGGGTATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA
SEQ ID NO. 844 4.1-6GS-1.1-6GS-MSA Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG LVQPGGSLRLSCAASGFTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYY CARGGDGYSDSHFGVDVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCA ASGFTFSSYAMSWVRQAPGKGLEWVATISDSGSSADYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRYNWNPRAL GIWGQGTMVTVSS
SEQ ID NO. 845 4.1-6GS-2.1-6GS-MSA Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGG GGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGAGTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACATGAGCT GGTTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTGGTAGTGGTGATATCATAGACTACGCAGACTCT GTAAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCTCTGTATCTGCAGATGAACAACCTGAGAGCCGAGGACAC GGCCGTGTATCACTGTGCGAGAGAAGATTCCCGTCTAACTGGAACTACGGACTTTGACAATTGGGGCCAGGGAACCCTGGTCA CCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTG GATCGGGTGGAGGTGGTAGTCAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCTGAGACTCT CCTGTGCAGCCTCTGGATTCACCTTTAGTAGTTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTC GCAACTATTAGTGATAGTGGTAGTAGTGCAGACTACGCAGATTCCGTGAAGGGACGGTTCACCATCTCCAGAGACAACTCCAA GAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCTGAAGACACGGCCGTGTATTACTGTGCGAGAGGCCGGTATAACTGGA ACCCCCGAGCTTTGGGTATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCA
SEQ ID NO. 846 4.1-6GS-2.1-6GS-MSA Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG LVKPGGSLRVSCAASGFTFSDYYMSWFRQAPGKGLEWVSYISGSGDIIDYADSVKGRFTISRDNAKNSLYLQMNNLRAEDTAVYHCA REDSRLTGTTDFDNWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFT FSSYAMSWVRQAPGKGLEWVATISDSGSSADYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRYNWNPRALGIWG QGTMVTVSS
SEQ ID NO. 847 3.8-6GS-1.1-6GS-MSA nucleotide GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA GTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAATGAT GGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGCAAAT GAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGA TCGGGTGGAGGTGGTAGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCGGGGGGGTCCCTGAGACTCTCC TGTGCAGCCTCTGGATTCACCTTTAGTAGCCATTGGATGACTTGGTTCCGTCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGC CCACATAAAGGAAGACGGAAGTGAGAAATACTATGAGGACTCTGTGGAGGGCCGATTCACCGTCTCCAGAGACAACGCCAAG AACTCGGTATATCTGCAAATGAACAGTCTGAGAGCCGAAGACACGGCTGTGTATTACTGTGCGAGAGGAGGTGATGGCTACA GTGACTCCCACTTCGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACTGTCTCTTCAGGTGGTGGCGGTTCAGGCGGAGG TGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTCAGGTGCAGCTGGT GGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGTTATG CCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCGCAACTATTAGTGATAGTGGTAGTAGTGCAGACTA CGCAGATTCCGTGAAGGGACGGTTCACCATCTCCAGAGACAACTCCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAG CTGAAGACACGGCCGTGTATTACTGTGCGAGAGGCCGGTATAACTGGAACCCCCGAGCTTTGGGTATCTGGGGCCAAGGGAC AATGGTCACCGTCTCCTCA
SEQ ID NO. 848 3.8-6GS-1.1-6GS-MSA Protein EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNSLR VEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG

FTFSSHWMTWFRQAPGKGLEWVAHIKEDGSEKYYEDSVEGRFTVSRDNAKNSVYLQMNSLRAEDTAVYYCARGGDGYSDSHFGV
DVWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSQVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVR
QAPGKGLEWVATISDSGSSADYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRYNWNPRALGIWGQGTMVTVSS

SEQ ID NO. 889 4.1-6GS-1.113-4GS Nucleotide
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT
CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA
AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG
AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT
CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA
GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGG
AGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTG
GGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCGAACATTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCG
GTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAATTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACC
GCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCGTCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGT
TACCGTCTCTTCCGGCGGAGGTGGCTCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGCGGCGGTGGTAGT

SEQ ID NO. 890 4.1-6GS-1.113-4GS Protein
EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS
LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG
LVQPGGSLRLSCAASGFTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYY
CARGGEGYGVDHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGG

SEQ ID NO. 891 3.8-6GS-1.113-4GS Nucleotide
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA
GTTTTAGCAGCTATGCCCTCAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAAGTATTGGTGAGAATGAT
GGTACCACAGACTACGCAGACGCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGCAAAT
GAACAGCCTGAGAGTCGAGGACACGGCCGTCTATTACTGTGTGAAAGATGGTGTCCACTGGGGCCAGGGAACCCTGGTCACC
GTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGAGGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGA
TCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGT
GCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGCG
AACATTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAAA
TTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCGT
CGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGC
TCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGCGGCGGTGGTAGT

SEQ ID NO. 892 3.8-6GS-1.113-4GS Protein
EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNSLR
VEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG
FTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKN
SLYLQMNSLRAEDTAVYYCARGGEGYGVDHYGLDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGS

SEQ ID NO. 893 4.1-6GS-1.113-6GS-VH (HSA)-4GS Nucleotide
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT
CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA
AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG
AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT
CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA
GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGG
AGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCGTGCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTG
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SEQ ID NO. 894 4.1-6GS-1.113-6GS- VH (HSA)-4GS Protein

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SEQ ID NO.895 3.8-6GS- VH (HSA)-1.113-4GS Nucleotide

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SEQ ID NO. 896 3.8-6GS- VH (HSA)-1.113-4GS Protein

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

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SEQ ID NO. 898 Protein 3.8-6GS-1.113-6GS- VH (HSA)-4GS EVQLLESGGGLVQPGGSLRLSCAASGFSFSSYALSWVRQAPGKGLEWVSSIGENDGTTDYADAVKGRFTISRDNSKNTLYLQMNSLR VEDTAVYYCVKDGVHWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG FTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGGEGYGVDHYG LDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGRSLRLSCAASGFTFHHYAMHWVR QAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCVRDSSLFIVGAPTFEHWGRGTLVTVSSG GGGSGGGGSGGGGSGGGGS
SEQ ID NO.899 4.1-6GS- VH (HSA)-1.113-4GS Nucleotide GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCT CCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGACTGGAGTGGGTGGCATATATATCATATGATGGA AGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATG AACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATCCGGCCTGGGGATTACGTTTGGGGGAGTCATCGT CCTATGATTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGTGGCGGTTCAGGCGGAGGTGGCTCTGGA GGTGGAGGTTCAGGAGGTGGTGGTTCTGGCGGCGGTGGATCGGGTGGAGGTGGTAGTGAAGTACAACTGGTTGAATCGGGT GGTGGATTGGTCCAACCTGGAAGATCATTGAGGCTTTCTTGTGCAGCTTCCGGATTCACCTTTCATCACTATGCTATGCACTGG GTGAGACAAGCCCCTGGTAAGGGCTTGGAATGGGTGTCCGGAATCTCCTGGAATGGTAACAAAATAACATATGCAGATTCCGT TAAGGGTAGATTTACTATTAGCCGTGATAATGCAAAAAACAGTTTATACTTGCAGATGAATTCCTTGAGGGCTGAGGATACAGC TCTTTACTATTGTGTGCGTGACTCATCGTTGTTCATTGTCGGAGCCCCAACTTTCGAACATTGGGGTAGAGGTACCCTAGTTACG GTTAGCTCAGGCGGAGGTGGCTCTGGAGGAGGAGGTTCAGGAGGTGGTGGATCTGGAGGAGGCGGATCGGGGGGTGGAGG AAGTGGCGGCGGTGGTAGTGAGGTGCAGTTAGTTGAGAGCGGAGGTGGTTTAGTTCAGCCGGGGGGCTCGCTTCGCCTGTCG TGCGCCGCCTCGGGATTCACATTATCAAACTACTGGATGAATTGGGTCCGCCAGGCTCCGGGCAAAGGTCTTGAGTGGGTGGC GAACATTAATCAGGACGGGAGCGAGCGTTATTACGTTGATTCGGTAAAAGGACGTTTCACTATCAGTCGTGACAACGCTAAAA ATTCCTTGTACTTACAGATGAACTCACTTCGTGCTGAGGACACCGCAGTGTACTACTGTGCTCGCGGTGGTGAAGGATACGGCG TCGATCACTACGGCCTTGATGTATCAGGACAGGGGACTACAGTTACCGTCTCTTCCGGCGGAGGTGGCTCTGGAGGAGGCGG ATCGGGGGGTGGAGGAAGTGGCGGCGGTGGTAGT
SEQ ID NO. 900 4.1-6GS- VH (HSA)-1.113-4GS Protein EVQLVESGGGVVQPGRSLRLSCAASGFSFSGYGMHWVRQAPGKGLEWVAYISYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNS LRAEDTAVYYCAKDPAWGLRLGESSSYDFDIWGQGTMVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGG LVQPGRSLRLSCAASGFTFHHYAMHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYY CVRDSSLFIVGAPTFEHWGRGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASG FTLSNYWMNWVRQAPGKGLEWVANINQDGSERYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGGEGYGVDHYG LDVSGQGTTVTVSSGGGGSGGGGSGGGGSGGGGS
SEQ ID NO. 901 VH that binds to HSA as used in constructs above protein EVQLVESGGGLVQPGRSLRSCAASGFTFHHYAMHWVRQAPGKGLEWVSGISWNGNKITYADSVKGRFTISRDNAKNSLYLQMNS LRAEDTALYYCVRDSSLFIVGAPTFEHWGRGTLVTVSS

SEQ ID NO. 902 VH that binds to HSA as used in constructs above nucleotide

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EXAMPLE 9. Testing of Purified V_H

b) Binding Assays

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.

Binding to human CD137Fc recombinant protein (Acro Biosystems 41B-H5258), rhesus CD137Fc recombinant protein (Sino Biologicals cat no. 90847-K02H) and mouse CD137Fc protein (Acro Biosystems 41B-M5258) was measured using an HTRF Binding assay format. All reagents and serially diluted V_H were prepared in assay buffer containing PBS, 0.1% BSA and 0.4M Potassium Fluoride. Samples or assay buffer (non-specific binding) were incubated with 0.5nM human, rhesus or mouse CD137, 1nM Anti human-Fc Cryptate PAb (Cisbio cat. no. 61HFCKLB) and 20nM anti His-D2 (CisBio cat no 61HISDLA) in black 384-shallow well assay plates for a minimum of 3 hours at room temperature. Time-resolved fluorescent emission at 620nm and 665nm was measured following excitation at 337nm on the BMG PHERAstar plate reader. The HTRF ratio were calculated ((665nm emission/620nm emission)*10000) and the data corrected for (non-specific binding) to give the specific binding signal. Molar EC_{50} values for binding to human CD137, rhesus CD137 and mouse CD137 protein are shown in Table 8. V_H bound to human and rhesus CD137 but not to mouse CD137 protein.

Table 8: Binding of V_H to CD137

Humabody® ID	HTRF			ELISA		
	Human CD137	Rhesus CD137	Mouse CD137	Human CD137	Human GITR	Human OX40
1.78	2.1E-10	1.4E-10	-	+	-	-
1.1	2.6E-10	1.1E-09	-	+	-	-
1.18	4.5E-10	5.1E-09	-	+	-	-

1.11	5.8E-10	6.8E-09	-	+	-	-
1.52	4.8E-10	4.5E-10	-	+	-	-
2.9	1.3E-09	1.2E-09	-	+	-	-
2.2	9.1E-10	5.6E-10	-	+	-	-
2.1	3.7E-09	4.9E-09	-	+	-	-
2.8	3.1E-09	1.6E-09	-	+	-	-
2.14	1.2E-09	1.3E-09	-	+	-	-
2.26	nd	nd	nd	nd	nd	nd

No binding (-), Binding measured (+), not determined (nd)

Table 9

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
1.18	3.1E-10	-				1.9E-09
1.11	2.7E-10	-				8.9E-10
1.52	3.7E-10	-				8.8E-10
2.9	1.8E-10	-				6.0E-10
2.2	1.8E-10	-				7.4E-10
2.1	6.5E-10	-				2.4E-09
2.8	1.9E-10	-				6.5e-09
2.14	3.1E-10	-				6.1E-10
2.26	1.8E-10					2.8E-09
1.113	9.0E-11					nd
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

Specificity of binding for CD137 over the tumour necrosis factor receptor family members OX40 and GITR (Glucocorticoid-induced TNFR-related) was determined using an ELISA assay. Nunc Maxisorp plates were coated with 1ug/ml human CD137 -Fc recombinant protein (Acro Biosystems 41B-H5258), human GITR-Fc (R&D Systems cat no. 689-GR) human OX40-Fc (R&D Systems cat no. 3388-OX) in sodium carbonate buffer overnight at 4°C then washed twice with PBS. Non-specific protein interactions were blocked by incubation with 1% (w/v) skimmed milk powder (Marvel®) in PBS/0.1% Tween-20 for 1 hour at room temperature. Plates were washed twice with PBS then VH or antibody control (1ug/ml) added for 1 hour at room temperature. Following three washes with PBS/0.1% Tween-20 a 1:1000 dilution of anti His-HRP (V_H detection) or anti mouse-HRP (positive control mouse monoclonal antibody detection) was added in 1% Marvel/PBS/0.1% Tween-20. The detection antibodies were allowed to bind for 1 hour at room temperature then the plates were washed twice in PBS/0.1% Tween-20 and once in PBS. The ELISA was developed using TMB substrate and the reaction was stopped by the addition of 50ul 0.5M H_2SO_4 solution. The absorbance at 450nm was measured using the BMG Pherastar. All V_H tested bound to CD137 but did not bind to GITR or OX40 (Table 8).

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 9. 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.

Binding 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). 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 molar 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.

Binding kinetics of purified V_H, bivalent V_H and trivalent V_H molecules were measured on a ForteBio Octet RED 384 instrument. CD137-Fc tagged protein was diluted to 3µg/ml in kinetics buffer (0.1% BSA, 0.02% Tween, 1x PBS) and coupled to Protein G biosensors (ForteBio cat no. 18-5082) via the Fc tag. V_H were serially diluted (typically 1:2 dilution series starting with 50nM, V_H at the highest concentration) and binding to the CD137-Fc-coupled Protein G biosensors measured. Binding kinetics were determined from the (blank subtracted) sensor gram trace using 1:1 binding models and ForteBio Octet Data Analysis 9.0 software. Example kinetic and binding affinity data obtained is shown Table 10 (monovalent $V_{H)}$ and Figure 1 (bivalent and trivalent molecules). In this assay format monomer V_H bound CD137-Fc with affinities of between 91pM and 5.3nM. Bivalent and trivalent formats showed enhanced binding compared to the monovalent V_H.

Table 10: Kinetics of binding of V_H to human CD137

Humabody® ID	KD (M)	kon(1/Ms)	kdis(1/s)
1.78	7.2E-10	3.04E+05	2.19E-04
1.75	7.5E-10	4.74E+05	3.53E-04
1.1	3.4E-10	9.89E+05	3.40E-04
1.39	9.0E-10	5.59E+05	5.05E-04
1.18	1.2E-10	5.18E+06	6.25E-04
1.11	2.5E-09	5.96E+05	1.48E-03
1.71	9.1E-11	3.13E+05	2.84E-05
1.16	2.4E-09	6.10E+05	1.45E-03
1.52	3.2E-09	3.00E+05	9.63E-04
1.63	2.8E-09	2.17E+05	5.96E-04
1.81	1.6E-10	1.06E+06	1.71E-04
2.20	1.2E-09	1.64E+06	2.00E-03
2.1	2.9E-09	1.35E+06	3.88E-03
2.8	5.3E-09	1.17E+06	6.16E-03
2.14	9.6E-10	1.63E+06	1.57E-03
2.26	4.7E-09	1.80E+06	8.42E-03

The kinetics of monovalent and bispecific Humabody V_H 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 11.

Table 11

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 sdAb 1.113 in table 2 for binding to human CD137Fc were ka 3.6E+06 ± 1.6E+06 (1/Ms), Kdis 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.

sdAb 1.113 demonstrated superior cyno binding compared to other molecules tested. sdAb 1.113 also demonstrated better overall developability characteristics (stability and/or expression).

Dual target engagement of CD137 and PSMA by the bispecific molecules was assessed using an ELISA format. 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 2 shows representative data demonstrating that bispecific molecules can simultaneously bind both human CD137 and human PSMA.

a) Inhibition of CD137 Ligand binding to CD137

The ability of purified Humabody V_H to inhibit the binding of CD137 Ligand to CHO human CD137 cells was measured in the FMAT ligand inhibition assay essentially as described in Example 6. IC_{50} values determined from serially diluted V_H are shown in table 12. V_H inhibited the binding of human CD137 Ligand to human CD137.

Table 12: Inhibition of CD137L Binding. Values shown are an average of 2-6 determinations

CD137 Ligand Inhibition					
Humabody® V_H	**IC_{50} (M)**	**Humabody® V_H**	**IC_{50} (M)**	**Humabody® V_H**	**IC_{50} (M)**
1.78	1.5E-09	1.102	1.7E-09	1.125	1.7E-09
1.1	1.1E-09	1.103	1.3E-09	1.126	8.4E-10
1.18	1.2E-09	1.104	1.1E-09	1.128	8.8E-10
1.11	1.6E-09	1.105	2.8E-09	1.129	2.0E-10
1.52	1.2E-09	1.106	2.1E-09	1.130	1.9E-09
2.9	2.0E-09	1.107	5.5E-10	1.131	3.3E-10
2.20	1.7E-09	1.108	5.0E-10	2.41	1.6E-08
2.1	5.7E-09	1.109	9.0E-10	2.42	2.0E-07
2.8	1.9E-08	1.110	8.1E-10	2.43	1.9E-08
2.14	2.0E-09	1.111	7.5E-10	2.44	5.7E-09
2.26	8.5E-09	1.112	4.7E-10	2.45	5.3E-09
1.90	7.8E-09	1.113	7.3E-10	2.46	7.8E-08
1.91	1.9E-09	1.114	2.7E-10	2.47	8.8E-09
1.92	2.9E-09	1.115	3.5E-10	2.48	8.6E-08
1.93	7.0E-10	1.116	2.5E-09	2.49	4.2E-08
1.94	8.0E-10	1.117	1.5E-09	2.50	1.4E-08
1.95	2.4E-08	1.118	3.4E-09	2.51	2.7E-08
1.96	2.7E-09	1.119	1.3E-09	1.1-6GS-1.1	2.8E-10
1.97	3.8E-09	1.120	2.5E-10	2.1-6GS-2.1	4.3E-10
1.98	4.7E-09	1.121	1.4E-09	1.1-6GS-1.1-6GS-1.1	2.0E-10
1.99	1.5E-09	1.122	1.3E-09	2.1-6GS-2.1-6GS-2.1	4.2E-10
1.100	1.4E-09	1.123	7.8E-10	4.1-6GS-1.1	2.5E-09
1.101	7.9E-09	1.124	1.6E-09	4.1-6GS-2.1	1.3E-08
		4.1	-	4.1-6GS-1.78	3.7E-09
		3.8	-	1.78-6GS-4.1	2.8E-09
				3.8-6GS-1.1	1.7E-09
				1.1-6GS-3.8	1.3E-09

b) Stability

Purified Humabody® V_H were subjected to size exclusion chromatography. Briefly, purified V_H were stored at between 8.98 and 9.26 mg/ml in PBS buffer for 0-14 days at either 4°C or 40°C, and then analysed at various time points using a Waters H-Class Bio UPLC containing a PDA detector (detection at 280nm) with separation on a Waters ACQUITY BEH 125Å SEC column. Samples were injected in 10µl volumes and were run in a mobile phase containing 200 mM NaCl, 100 mM sodium phosphate, pH 7.4 + 5% propan-1-ol at a flow rate of 0.4ml/min. Data were collected for 6 minutes and the percentage of the sample comprising monomer after storage was calculated (Table 13 for representative data). It should be noted that these data were collected under non-optimised buffer conditions.

Table 13

		%Area T0 Monomer 4°C				% Area T0 Monomer 40°C				
Humabody® ID	**Conc. mg/ml**	**Day 1**	**Day 4**	**Day 7**	**Day 14**	**Day 0**	**Day 1**	**Day 4**	**Day 7**	**Day 14**
1.1	9.02	99.85	99.87	99.84	97.50	99.85	99.66	91.10	99.31	97.20
1.78	9.63	99.70	99.64	99.45	99.43	99.70	98.86	98.73	98.75	98.66
2.1	8.98	100.00	98.41	99.89	98.22	100.00	98.91	96.86	98.04	97.17
2.14	9.26	99.92	99.19	99.92	98.06	99.92	97.88	95.15	95.50	93.69

c) Serum Stability

Serum stability of Humabody® V_H was assessed by measurement of their activity following incubation for 0, 1, 3/4 or 7 days in mouse serum (Sigma M5905) or human serum (Sigma H4522). The pre-incubated samples were serially diluted and tested in the FMAT CHO CD137 Ligand inhibition and CHO CD137 Binding assays as previously described in Example 6. Minimal loss of activity was observed following incubation with serum (Table 14 for representative data).

Table 14

Humabody® ID	**Serum**	**CD137 Ligand Inhibition**				**CD137 Binding**			
		Day 0	**Day 1**	**Day 3/4**	**Day 7**	**Day 0**	**Day 1**	**Day 3/4**	**Day 7**
1.1	**Mouse**	1.2E-9	1.2E-9	1.0E-9	1.1E-9	1.5E-10	1.7E-10	1.6E-10	2.0E-10
	Human	1.7E-9	1.0E-9	1.1E-9	1.1E-9	1.8E-10	1.5E-10	1.8E-10	1.8E-10
2.1	**Mouse**	9.4E-9	1.4E-8	7.8E-9	1.1E-8	3.6E-10	5.5E-10	3.1E-10	4.3E-10
	Human	6.9E-9	5.0E-9	5.2E-9	4.0E-9	3.4E-10	2.6E-10	2.6E-10	1.8E-10

d) Functional Activity

The ability of monovalent V_H, 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.

PSMA expressing cells or parental (non PSMA) expressing (5000/well) were plated overnight in media (RPMI 1640 supplemented with 10% FBS, 2mM L-Glutamine, 1X Pen/Strep) into 384 well, white flat bottomed tissue culture treated plates. Serially diluted monovalent V_H, multivalent V_H and PSMA/CD137 targeting bispecific molecules were prepared in media and added to the wells followed by Jurkat human CD137 NF-kB luciferase reporter gene cells (Promega). 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 3 shows that monovalent V_H, and exemplified multivalent CD137 binding molecules did not increase reporter gene activity and thus do not have agonistic CD137 activity in this assay. Bispecific molecules activated the Jurkat reporter cells in the presence of the PSMA expressing cells (Figure 3A and 3BC) but not when co-cultured with parental non PSMA expressing cells (Figures 3A, 3B, 3E and 3F). This demonstrates that dual target engagement of PSMA and CD137 with a monovalent CD137 binding arm results in agonistic CD137 activity.

Humabody® V_H were further tested for their ability to induce IL-2 release in a co-culture assay using PSMA expressing cells or parental cells and human CD8+ T cells. PSMA or parental 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 IL2 levels quantified using a human IL-2 assay kit according to the manufacturer's instructions. (Cisbio Cat no. 64IL2PEB) IFNgamma levels were quantified using a human IFNgamma assay kit according to the manufacturer's instructions (Cisbio Cat no. 62HIFNGPEH).

Figure 4A shows that monovalent CD137 targeting V_H do not stimulate IL-2 production from CD8+ T cells. Bispecific molecules with monovalent CD137 and PSMA binding arms increase IL-2 production from T-cells in the presence of PSMA expressing cells. This stimulation is not observed when parent cells are used in the co-culture assay with CD8+ T cells confirming the requirement for dual target engagement of CD137

and PSMA by the bispecific molecules (representative data shown in Figure 4B). Benchmark anti CD137 antibody stimulated IL-2 production in a PSMA cell line independent response (Figure 4B and 4C). Stimulation of IL-2 production by CD8+ T cells was concentration dependent (Figure 4D). Maximum responses levels were T cell donor dependent for both antibody and bispecific molecules (Figure 4E). Interferon gamma was also produced in response to the bispecific molecules (Figure 4F).

e) Internalisation

CHO human CD137 cells were plated on poly-L-lysine coated coverslips and allowed to adhere overnight. Monovalent V_H (500nM), trivalent V_H (500nM) and anti CD137 benchmark antibody (100nM) were prepared in RPMI supplemented with 10% FBS/0.5% fatty acid free BSA and incubated with the cells for 30mins at 4°C. Samples were then incubated either at 37°C for 2 hours followed by fixing with 4% PFA for 10 mins at room and washing three times with PBS or were fixed immediately following the 4°C incubation (control samples). After the wash steps samples were permeabilised with 0.5% saponin in PBS for 10 mins at room temperature, washed three times with PBS and blocked with PBS containing 1% BSA/10% FBS/0.05% Tween-20 for 45 mins. Antibody was detected by staining with anti-human Alexa Fluor-488 antibody (1:2000 dilution) in staining buffer containing PBS/0.5% BSA/0.05% Tween-20 for 1hr. Humabody® V_H were detected by staining with anti His antibody (1:500 dilution) followed by anti-mouse Alexa Fluor-488 secondary antibody (1:2000 dilution). Samples were washed with PBS/0.05% Tween-20 (PBS-T) then lysosomes stained for 1 hour using a primary antibody against LAMP-1 (1:200 dilution in staining buffer). Following three washes with PBS-T samples were stained with anti-rabbit Alexa Fluor-647(1:500 dilution in stating buffer) then washed again. Coverslips were mounted into slides and imaged using a NILON A1R confocal system, laser line 488nm and 640nm) with Apo 60x Oil λS DIC N2 objective.

Figure 5 exemplifies the reduced potential for monomer V_H to internalise compared to a multivalent V_H molecule or an anti CD137 antibody. Monovalent V_H showed no co-localisation with lysosomes and remained predominantly cell surface bound. Multivalent V_H showed increased internalisation as indicated by the observed clustering and antibody co-localised with the lysosomal staining.

EXAMPLE 10. 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 compared to the controls group (Figure 7).

EXMAPLE 11: 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.

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Claims

1. An isolated single variable heavy chain domain antibody which binds to human CD137 but does not elicit CD137 signalling when bound to CD137 as a monospecific entity.
2. The single variable heavy chain domain antibody according to claim 1 wherein said single variable heavy chain domain antibody inhibits the binding of CD137L to CD137.
3. The single variable heavy chain domain antibody according to claim 1 or 2 comprising a CDR1 comprising a SEQ ID NO. selected from table 1, a CDR2 comprising a SEQ ID NO. selected from table 1 and a CDR3 comprising a SEQ ID NO. selected from table 1.
4. The single variable heavy chain domain antibody according to claim 3 comprising human framework regions.
5. The single variable heavy chain domain antibody according to a preceding claim comprising SEQ ID NO. 4, or a sequence with at least 70%, 80% or 90% homology thereto.
6. The single variable heavy chain domain antibody according to claim 1 or 2 comprising a CDR1 comprising a SEQ ID NO. selected from table 2, a CDR2 comprising a SEQ ID NO. selected from table 2 and a CDR3 comprising a SEQ ID NO. selected from table 2.
7. The single variable heavy chain domain antibody according to claim 6 comprising human framework regions.
8. The single variable heavy chain domain antibody according to claim 5 or 6 comprising SEQ ID NO. 428, 852, 856, 860, 864, 868, 872, 876 or 880 or a sequence with at least 70% homology thereto.
9. The single variable heavy chain domain antibody according to any preceding claim capable of binding CD137 with an affinity with a KD of about 0.4nM or of about 3nM.
10. The single variable heavy chain domain antibody according to any preceding claim obtained or obtainable from a transgenic rodent that expresses a transgene comprising human V, D and J regions.
11. The single variable heavy chain domain antibody according to claim 10 wherein said rodent does not produce functional endogenous light and heavy chains.
12. A binding molecule comprising
    a) a single variable heavy chain domain antibody that binds to CD137 according to any of claims 1 to 11 and
    b) a moiety that binds to a tumor specific antigen.
13. The binding molecule according to claim 12 wherein the moiety that binds to a tumor specific antigen is selected from a F(ab')2, Fab, Fv, scFv, heavy chain, light chain, a single variable domain antibody or a single variable heavy chain domain antibody.
14. The binding molecule according to any of claims 12 or 13 wherein the single variable heavy chain domain antibody that binds to CD137 is linked to the single variable heavy chain domain antibody that binds to a tumor specific antigen by a peptide linker.
15. The binding molecule according to claim 14 wherein said linker is selected from a (G4S)n linker wherein n is 1 to 10.

16. The binding molecule according to any of claim 12 to 15 wherein the tumor specific antigen is selected from PSMA, Her2, CD123, CD19, CD20, CD22, CD23, CD74, BCMA, CD30, CD33, CD52, EGRF CECAM6, CAXII, CD24, CEA, Mesothelin, cMet, TAG72, MUC1, MUC16, STEAP, EphvIII, FAP, GD2, IL-13Ra2, L1-CAM, PSCA,GPC3, Her3, gpA33, 5T4 and ROR1.
17. The isolated single variable heavy chain domain antibody according to any of claims 1 to 11 or a binding molecule according to any of claim 12 to 16 wherein said variable heavy chain single domain antibody or binding molecule is conjugated to one or more moiety selected from a a toxin, enzyme, radioisotope, half-life extending moiety, label, therapeutic molecule or other chemical moiety.
18. The isolated single variable heavy chain domain antibody or a 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 or single domain antibody that binds to human serum albumin.
19. A pharmaceutical composition comprising a single variable heavy chain domain antibody according to any of claims 1 to 11 or a binding molecule according to any of claims 12 to 18 and a pharmaceutical carrier.
20. The single variable heavy chain domain antibody according to any of claims 1 to 11, or a binding molecule according to any of claims 12 to 18 or a pharmaceutical composition according to claim 19 for use in the treatment of disease.
21. The single variable heavy chain domain antibody according to any of claims 1 to 11, or a binding molecule according to any of claims 12 to 18 or a pharmaceutical composition according to claim 19 for use according to claim 20, wherein said disease is selected from cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency or other immune system-related disorder.
22. A method for treating a cancer, an immune disorder, neurological disease, inflammatory disorder, allergy, transplant rejection, viral infection, immune deficiency or other immune system-related disorder comprising administering a therapeutically effective amount of a single variable heavy chain domain antibody according to any of claims 1 to 11, or a binding molecule according to any of claims 12 to 18 or a pharmaceutical composition according to claim 19.
23. The single variable heavy chain domain antibody according to any of claims 1 to 11, or a binding molecule according to any of claims 12 to 18 or a pharmaceutical composition according to claim 19 for a use according to claim 20 or 21 or a method according to claim 22 wherein said cancer is selected from bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, breast cancer, brain cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the

adrenal gland, kidney cancer, sarcoma of soft tissue, cancer of the urethra, cancer of the bladder, renal cancer, lung cancer, non-small cell lung cancer, thymoma, urothelial carcinoma leukemia, prostate cancer, mesothelioma, adrenocortical carcinoma, lymphomas, such as such as Hodgkin's disease, non-Hodgkin's, gastric cancer, and multiple myelomas.

24. A kit comprising single variable heavy chain domain antibody according to any of claims 1 to 11, or a binding molecule according to any of claims 12 to 18 or a pharmaceutical composition according to claim 19 optionally together with a reagent and/or instructions for use.
25. A nucleic acid molecule comprising a nucleic acid sequence encoding a single variable heavy chain domain antibody of any of claims 1 to 11.
26. The nucleic acid molecule according to claim 25 comprising SEQ ID NO. 629 or 735 or a nucleic acid molecule having 70% homology thereto.
27. A vector comprising nucleic acid molecule according to any of claims 25 or 26.
28. A host cell comprising a nucleic acid molecule according to any of claims 25 or 26 or a vector according to claim 27.
29. The host cell according to claim 28 wherein said host cell is a bacterial, yeast, viral or mammalian cell.
30. A method for producing a single domain antibody according to any of claims 1 to 11 comprising expressing a nucleic acid encoding said binding molecule in a host cell and isolating the binding molecule from the host cell.
31. A method for producing a single V_H domain antibody that binds to human CD137 comprising immunising a transgenic animal that expresses a nucleic acid construct comprising human heavy chain V genes and that is not capable of making functional endogenous light or heavy chains with an CD137 antigen, generating a library from said animal, isolating single V_H domain antibodies from said libraries and identifying a single V_H domain antibody that binds to human CD137 and isolating said antibody.
32. A single V_H domain obtained or obtainable by the method of claim 31.
33. A transgenic rodent that produces a heavy chain only antibody that comprises the V_H domain of claim 32.
34. A heavy chain only antibody comprising a V_H domain, for example according to any of claims 1 to 11, that binds to human CD137 obtained or obtainable from a transgenic mouse following immunisation with CD137 wherein said mouse expresses human V, D and J loci and does not produce functional endogenous lambda and kappa light chains and heavy chain.
35. A method for promoting CD8+ T cell expansion, inducing activation of cytotoxic T lymphocytes (CTL) and/or cytokine release comprising administering to a subject a single variable heavy chain domain antibody according to any of claims 1 to 11, or a binding molecule according to any of claims 12 to 18 or a pharmaceutical composition according to claim 19.
36. A use of a single variable heavy chain domain antibody according to any of claims 1 to 11 in a binding molecule that comprises a single heavy variable chain domain antibody which binds to a tumor specific antigen.

Figure 1

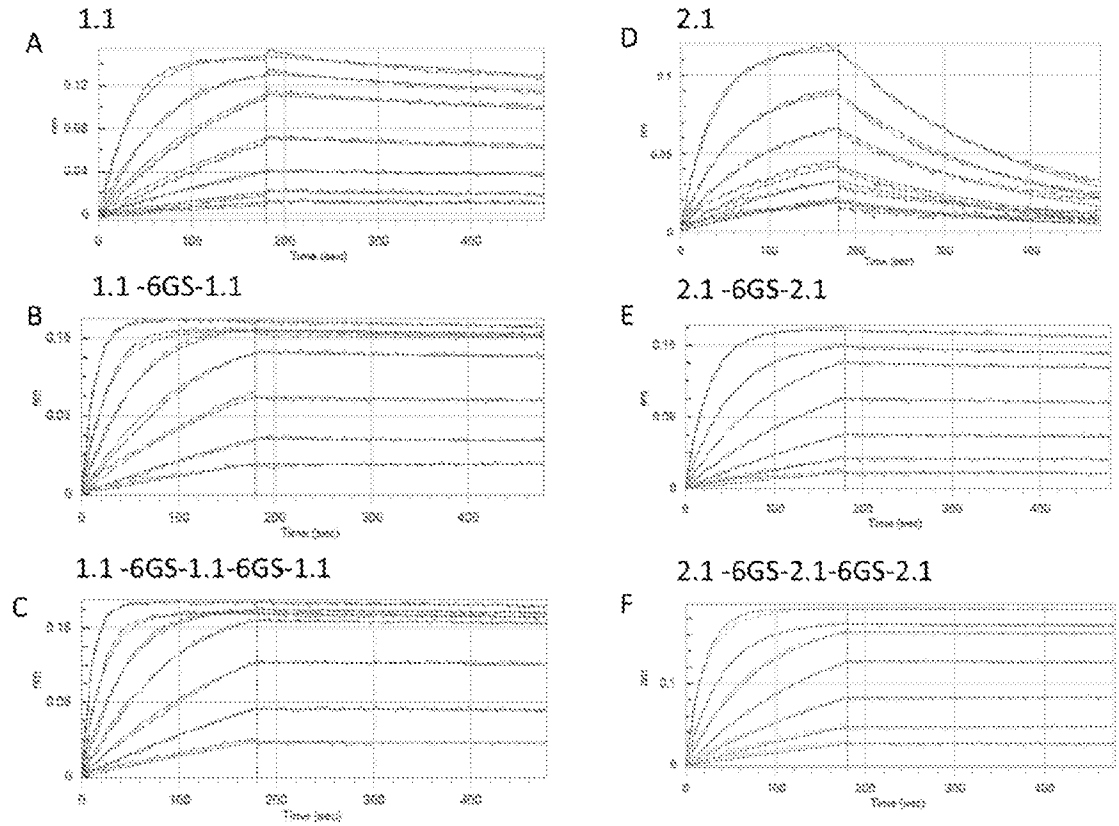


Figure 2

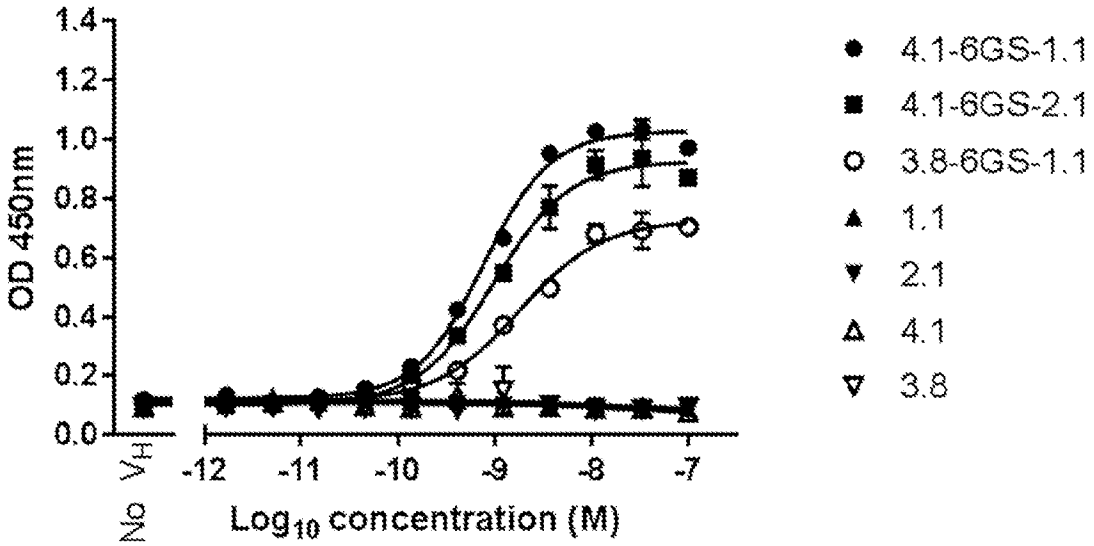
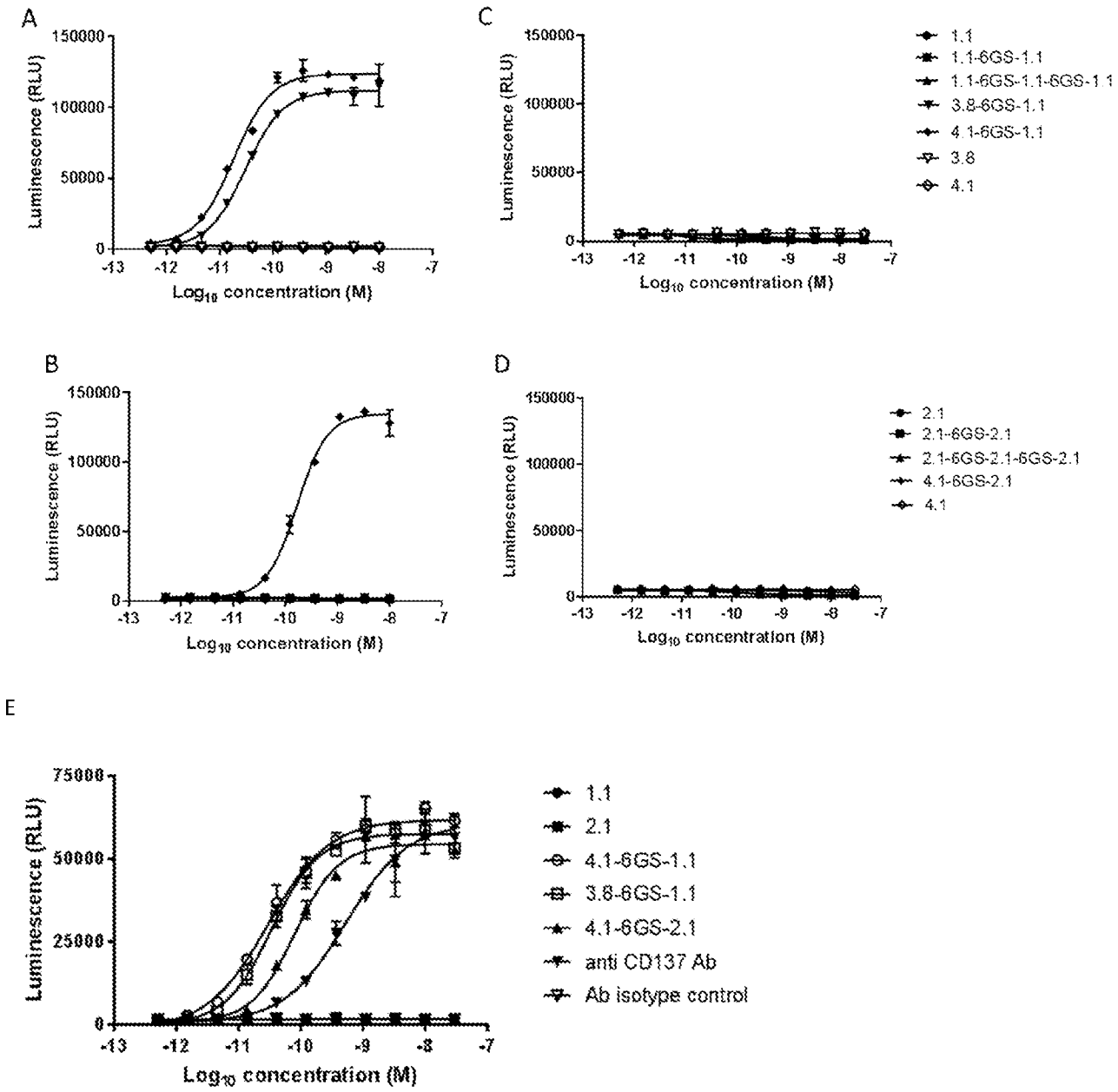
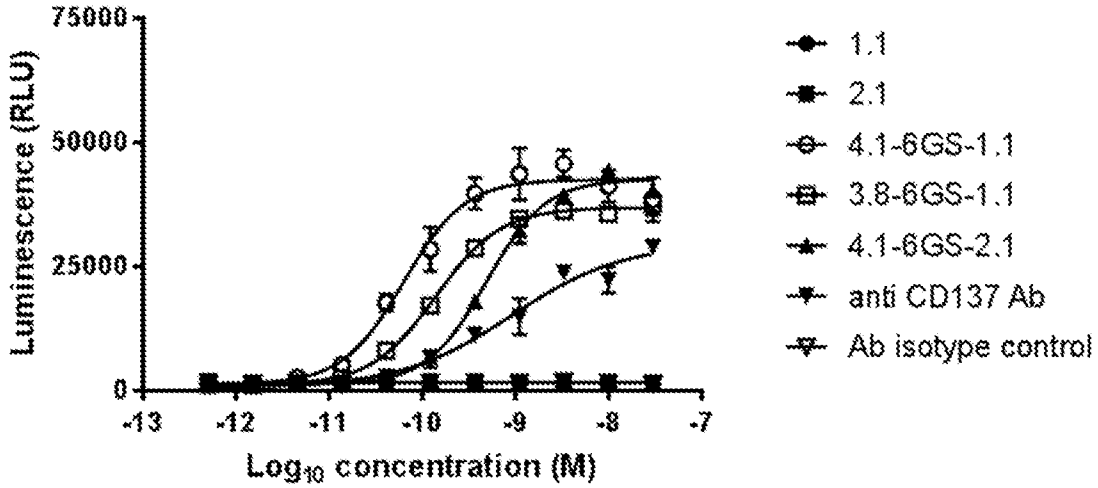


Figure 3


A
B
C
D
E
Luminescence (RLU)
Log10 concentration (M)
1.1
1.1-6GS-1.1
1.1-6GS-1.1-6GS-1.1
3.8-6GS-1.1
4.1-6GS-1.1
3.8
4.1
2.1
2.1-6GS-2.1
2.1-6GS-2.1-6GS-2.1
4.1-6GS-2.1
anti CD137 Ab
Ab isotype control

F


75000
50000
25000
0
Luminescence (RLU)
-13
-12
-11
-10
-9
-8
-7
Log10 concentration (M)
1.1
2.1
4.1-6GS-1.1
3.8-6GS-1.1
4.1-6GS-2.1
anti CD137 Ab
Ab isotype control

G

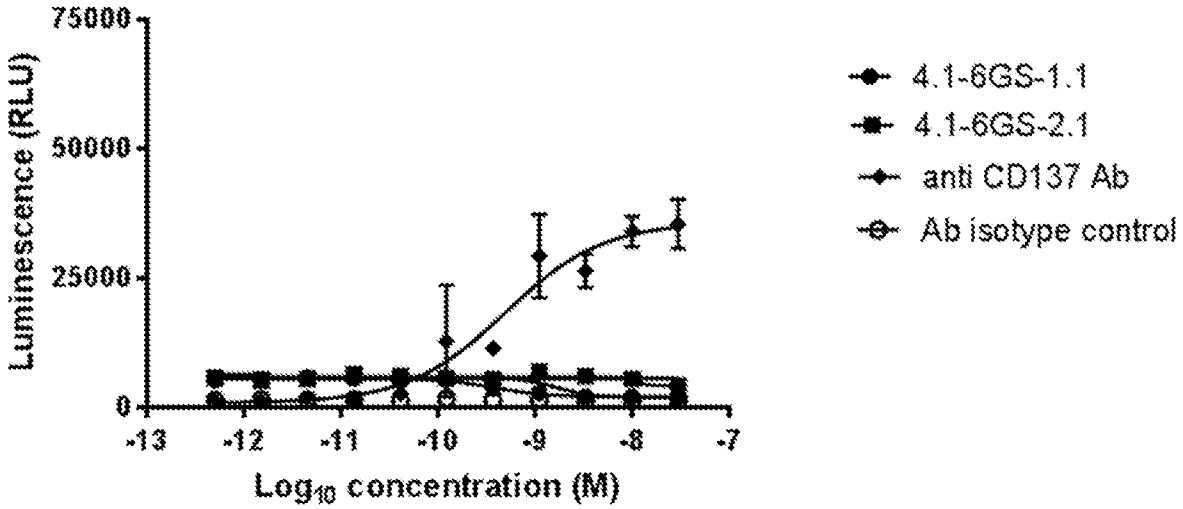
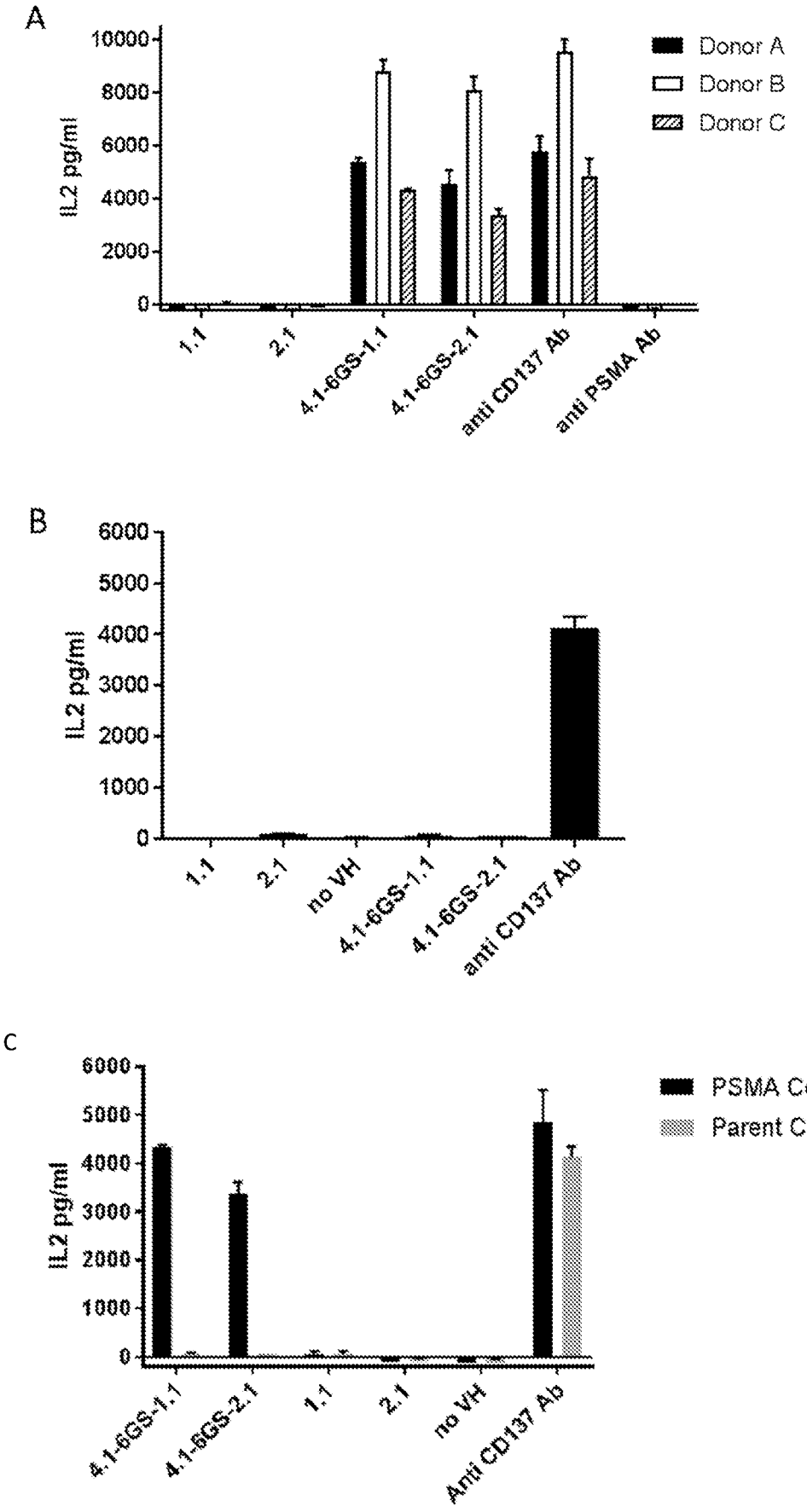
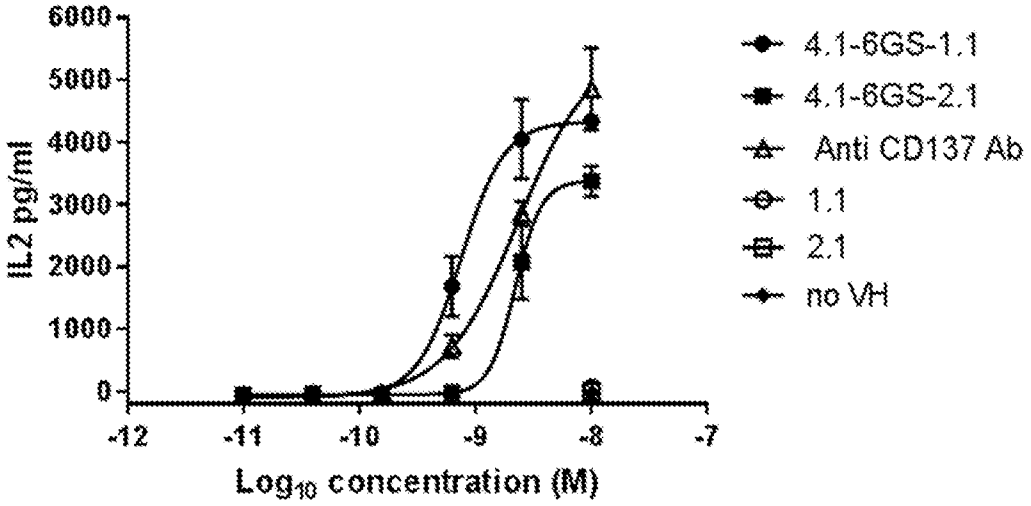

75000
50000
25000
0
Luminescence (RLU)
-13
-12
-11
-10
-9
-8
-7
Log10 concentration (M)
4.1-6GS-1.1
4.1-6GS-2.1
anti CD137 Ab
Ab isotype control

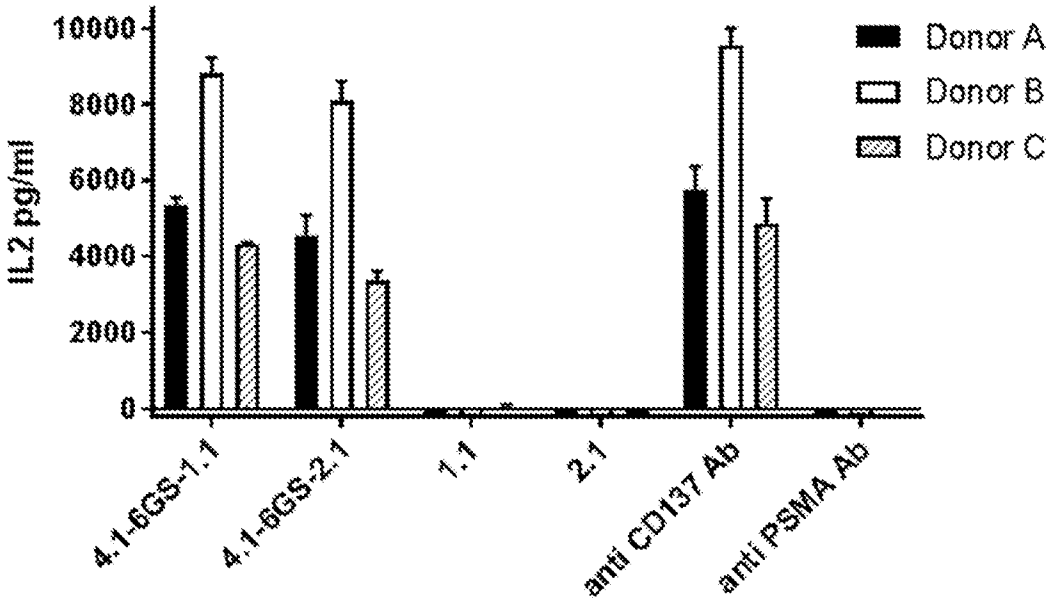
Figure 4


A
IL2 pg/ml
10000
8000
6000
4000
2000
0
Donor A
Donor B
Donor C
1.1
2.1
4.1-6GS-1.1
4.1-6GS-2.1
anti CD137 Ab
anti PSMA Ab
B
IL2 pg/ml
6000
5000
4000
3000
2000
1000
0
1.1
2.1
no VH
4.1-6GS-1.1
4.1-6GS-2.1
anti CD137 Ab
C
IL2 pg/ml
6000
5000
4000
3000
2000
1000
0
PSMA Cells
Parent Cells
4.1-6GS-1.1
4.1-6GS-2.1
1.1
2.1
no VH
Anti CD137 Ab

D


6000
5000
4000
3000
2000
1000
0
IL2 pg/ml
-12
-11
-10
-9
-8
-7
Log10 concentration (M)
4.1-6GS-1.1
4.1-6GS-2.1
Anti CD137 Ab
1.1
2.1
no VH

E


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

F

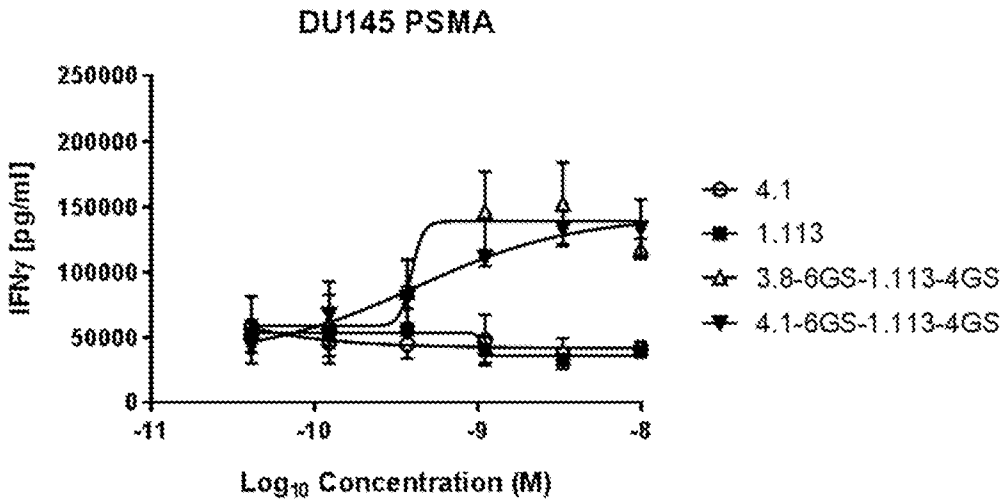
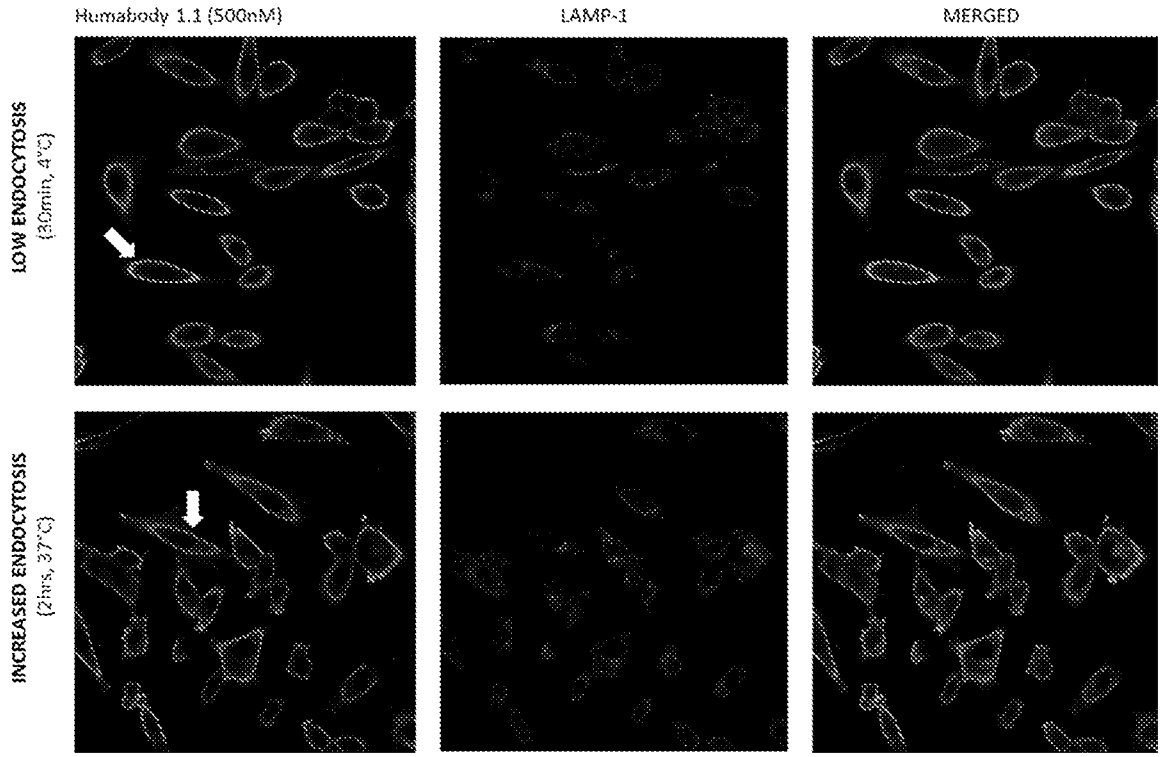
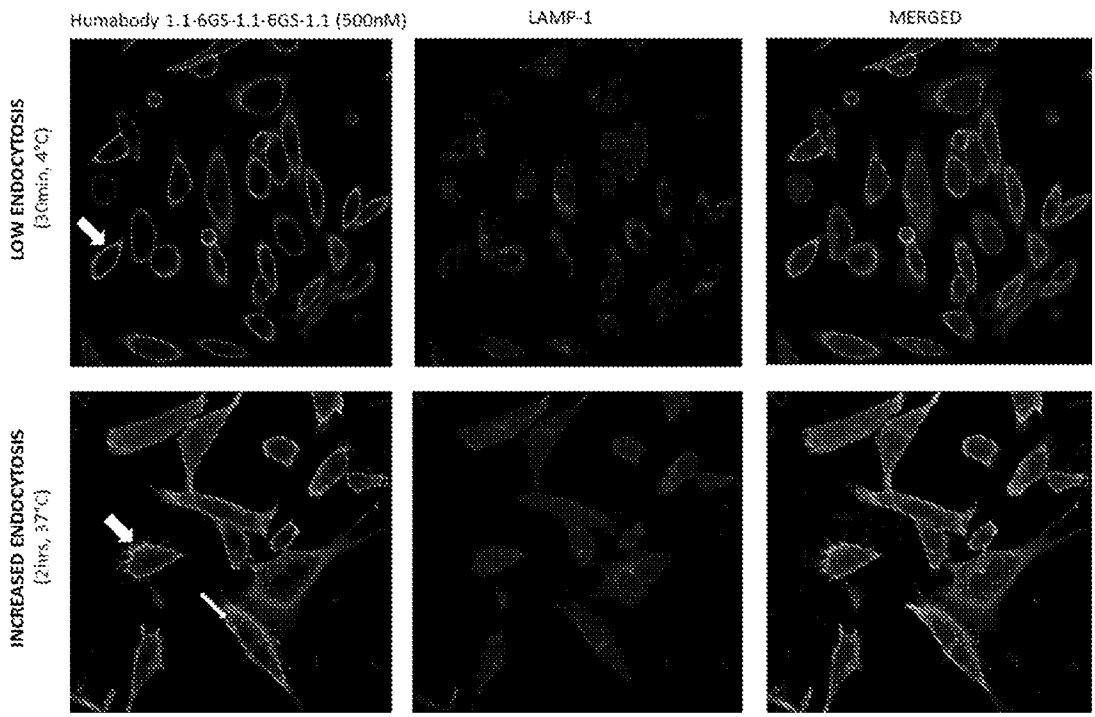

DU145 PSMA
250000
200000
150000
100000
50000
0
IFNγ [pg/ml]
-11
-10
-9
-8
Log10 Concentration (M)
4.1
1.113
3.8-6GS-1.113-4GS
4.1-6GS-1.113-4GS

Figure 5

A


Humabody 1.1 (500nM)
LAMP-1
MERGED
LOW ENDOCYTOSIS
(30min, 4°C)
INCREASED ENDOCYTOSIS
(2hrs, 37°C)

B


Humabody 1.1-6G5-1.1-6G5-1.1 (500nM)
LAMP-1
MERGED
LOW ENDOCYTOSIS
(30min, 4°C)
INCREASED ENDOCYTOSIS
(2hrs, 37°C)

C

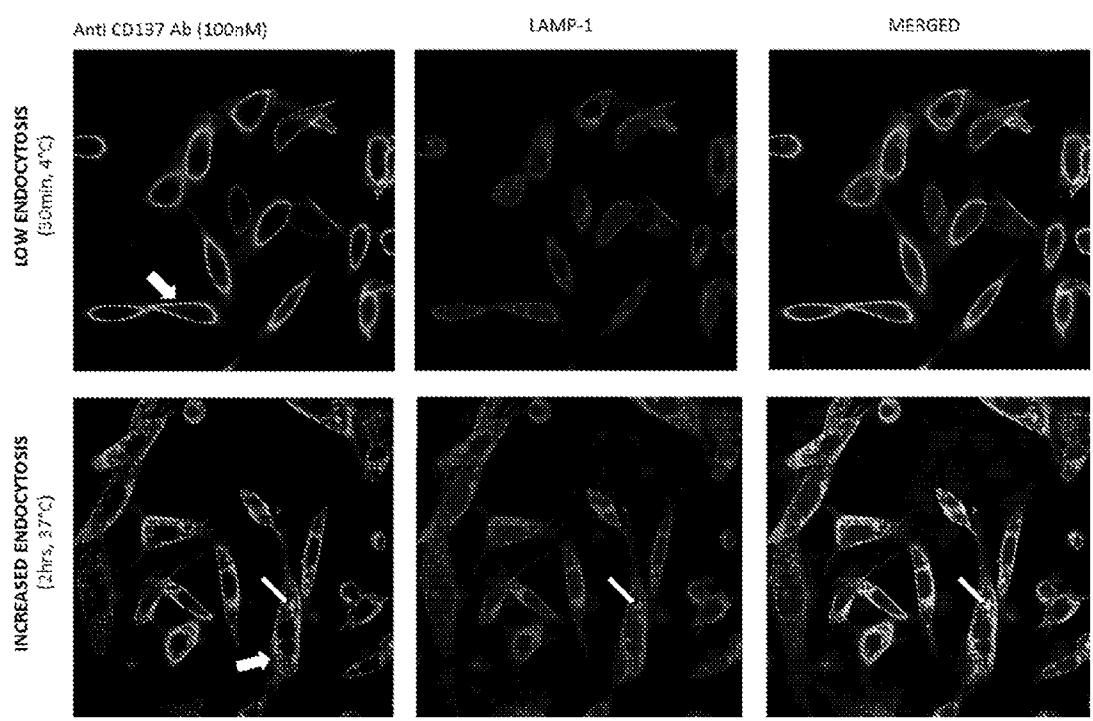

Anti CD137 Ab (100nM)
LAMP-1
MERGED
LOW ENDOCYTOSIS
(30min, 4°C)
INCREASED ENDOCYTOSIS
(2hrs, 37°C)

Figure 6

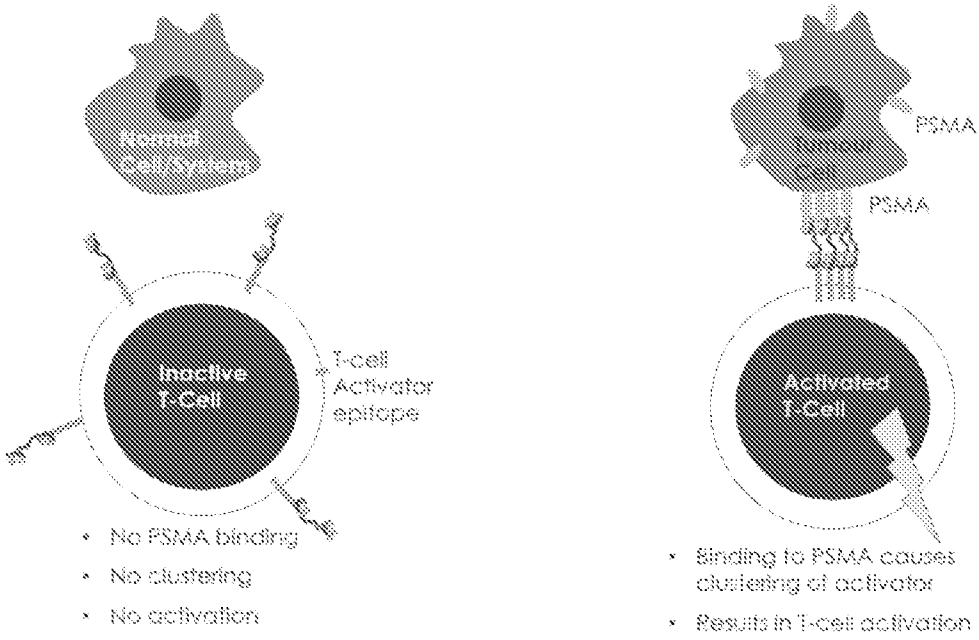
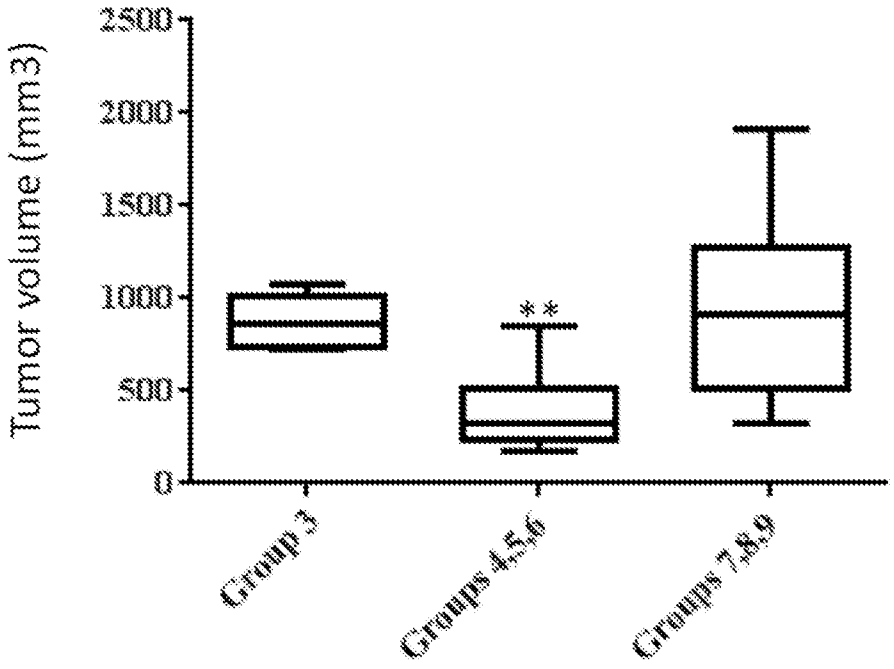


Figure 7



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/053279

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 C07K16/30
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.
X	WO 2017/123650 A2 (INHIBRX LP [US]) 20 July 2017 (2017-07-20)	1-17, 19-30, 32,34-36
Y	paragraph [0173] - paragraph [0174] paragraph [0211]; example 1 paragraph [0212] - paragraph [0213]; example 2 figure 21 paragraph [0229]	18,31,33

Y	WO 2016/062990 A1 (CRESCENDO BIOLOG LTD [GB]) 28 April 2016 (2016-04-28) the whole document	31,33

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2019	01/02/2019

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2018/053279

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No
PCT/GB2018/053279

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