TREATMENT OF PD-L1 NEGATIVE OR LOW EXPRESSING CANCER WITH ANTI-ICOS ANTIBODIES

Field of the Invention

This invention relates to compositions and methods for the treatment of cancer, in particular difficult-to-treat cancers. More specifically, the present invention relates to compositions and methods for the treatment of PD-L1 negative or PD-L1 low expressing cancers using an anti-ICOS antibody, either alone or in combination with other agents, such as an anti-PD-L1 antibody.

Background

ICOS (Inducible T cell Co-Stimulator) is a member of the CD28 gene family involved in regulating immune responses, in particular humoral immune responses, first identified in 1999 [1]. It is a 55 kDa transmembrane protein, existing as a disulphide linked homodimer with two differentially glycosylated subunits. ICOS is exclusively expressed on T lymphocytes, and is found on a variety of T cell subsets. It is present at low levels on naïve T lymphocytes but its expression is rapidly induced upon immune activation, being upregulated in response to pro-inflammatory stimuli such as on engagement of TCR and co-stimulation with CD28 [2, 3]. ICOS plays a role in the late phase of T cell activation, memory T cell formation and importantly in the regulation of humoral responses through T cell dependent B cell responses [4, 5]. Intracellularly, ICOS binds PI3K and activates the kinases phophoinositide-dependent kinase 1 (PDK1) and protein kinase B (PKB). Activation of ICOS prevents cell death and upregulates cellular metabolism. In the absence of ICOS (ICOS knock-out) or in the presence of anti-ICOS neutralising antibodies there would be a suppression of pro-inflammatory responses.

ICOS binds to ICOS ligand (ICOSL) expressed on B-cells and antigen presenting cells (APC) [6, 7]. As a co-stimulatory molecule it serves to regulate TCR mediated immune responses and antibody responses to antigen. The expression of ICOS on T regulatory cells may be important, as it has been suggested that this cell type plays a negative role in immunosurveillance of cancer cells - there is emerging evidence for this in ovarian cancer [8]. Importantly, ICOS expression has been reported to be higher on intratumoural regulatory T cells (TRegs) compared with CD4+ and CD8+ effector cells that are present in the tumour microenvironment. Depletion of TRegs using antibodies with Fc-mediated cellular effector function has demonstrated strong anti-tumour efficacy in a pre-clinical model [9]. Mounting evidence implicates ICOS in an anti-tumour effect in both animal models as well as patients treated with immune-checkpoint inhibitors. In mice deficient in ICOS or ICOSL the anti-tumor effect of anti-CTLA4 therapy is diminished [10] while in normal mice ICOS ligand increases the effectiveness of anti-CTLA4 treatment in melanoma and prostate cancer [11]. Furthermore, in

humans a retrospective study of advanced melanoma patients showed increased levels of ICOS following ipilimumab (anti-CTLA4) treatment [12]. In addition, ICOS expression is upregulated in bladder cancer patients treated with anti-CTLA4 [13]. It has also been observed that in cancer patients treated with anti-CTLA4 therapy the bulk of tumour specific IFNγ producing CD4 T-cells are ICOS positive while sustained elevation of ICOS positive CD4 T cells correlates with survival [12, 13, 14].

WO2016/120789 described anti-ICOS antibodies and proposed their use for activating T cells and for treating cancer, infectious disease and/or sepsis. A number of murine anti-ICOS antibodies were generated, of which a sub-set were reported to be agonists of the human ICOS receptor. The antibody "422.2" was selected as the lead anti-ICOS antibody and was humanised to produce a human "IgG4PE" antibody designated "H2L5". H2L5 was reported to have an affinity of 1.34 nM for human ICOS and 0.95 nM for cynomolgus ICOS, to induce cytokine production in T cells, and to upregulate T cell activation markers in conjunction with CD3 stimulation. However, mice bearing implanted human melanoma cells were reported to show only minimal tumour growth delay or increase in survival when treated with H2L5 hIgG4PE, compared with control treated group. The antibody also failed to produce significant further inhibition of tumour growth in combination experiments with ipilimumab (anti-CTLA-4) or pembrolizumab (anti-PD-1), compared with ipilimumab or pembrolizumab monotherapy. Finally, In mice bearing implanted colon cancer cells (CT26), low doses of a mouse cross reactive surrogate of H2L5 in combination with a mouse surrogate of ipilimumab or pembrolizumab only mildly improved overall survival compared with anti-CTL4 and anti-PD1 therapy alone. A similar lack of strong therapeutic benefit was shown in mice bearing implanted EMT6 cells.

WO2016/154177 described further examples of anti-ICOS antibodies. These antibodies were reported to be agonists of CD4+ T cells, including effector CD8 + T cells (TEff), and to deplete T regulator cells (TRegs). Selective effects of the antibodies on TEff vs TReg cells were described, whereby the antibodies could preferentially deplete TRegs while having minimal effect on TEffs that express a lower level of ICOS. The anti-ICOS antibodies were proposed for use in treating cancer, and combination therapy with anti-PD-1 or anti-PD-L1 antibodies was described.

Programmed death-1 (PD-1) is a 50-55 kDa type I transmembrane receptor that is a member of the CD28 family. PD-1 is involved in the regulation of T-cell activation and is expressed on T-cells, B cells, and myeloid cells. Two ligands for PD-1, PD ligand 1 (PD-L1) and ligand 2 (PD-L2) have been identified and have co-stimulatory features.

Programmed cell death 1 ligand 1 (PD-L1), also known as cluster of differentiation (CD274) or B7 homolog 1 (B7-H1), is a member of the B7 family that modulates activation or inhibition of the PD-1 receptor. The open reading frame of PD-L1 encodes a putative type 1 transmembrane protein of 290 amino acids, which includes two extracellular Ig domains (a N-

terminal V-like domain and a Ig C-like domain), a hydrophobic transmembrane domain and a cytoplasmic tail of 30 amino acids. The 30 amino acid intracellular (cytoplasmic) domain contains no obvious signalling motifs, but does have a potential site for protein kinase C phosphorylation.

The complete amino acid sequence for PD-L1 can be found in NCBI Reference Sequence: NP_054862.1 (SEQ ID NO: 1), which refers to many journal articles, including, for example, Dong, H., *et al.* (1999), "PD-L1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion," Nat. Med. 5 (12), 1365-1369. The PD-L1 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, and zebrafish. The murine form of PD-L1 bears 69% amino acid identity with the human form of PD-L1, and also shares a conserved structure.

In humans, PD-L1 is expressed on a number of immune cell types including activated and anergic/exhausted T-cells, on naive and activated B-cells, as well as on myeloid dendritic cells (DC), monocytes and mast cells. It is also expressed on non-immune cells including islets of the pancreas, Kupffer cells of the liver, vascular endothelium and selected epithelia, for example airway epithelia and renal tubule epithelia, where its expression is enhanced during inflammatory episodes. PD-L1 expression is also found at increased levels on a number of tumours including, but not limited to breast (including but not limited to triple negative breast cancer and inflammatory breast cancer), ovarian, cervical, colon, colorectal, lung, including non-small cell lung cancer, renal, including renal cell carcinoma, gastric, oesophageal, bladder, hepatocellular cancer, squamous cell carcinoma of the head and neck (SCCHN) and pancreatic cancer, melanoma and uveal melanoma.

PD-1/PD-L1 signalling is believed to serve a critical non-redundant function within the immune system by negatively regulating T-cell responses. This regulation is involved in T-cell development in the thymus, in regulation of chronic inflammatory responses and in maintenance of both peripheral tolerance and immune privilege. It appears that upregulation of PD-L1 may allow cancers to evade the host immune system and, in many cancers, the expression of PD-L1 is associated with reduced survival and an unfavourable prognosis. Therapeutic monoclonal antibodies that are able to block the PD-1/PD-L1 pathway may enhance anti-tumoural immune responses in patients with cancer. Published clinical data suggest a correlation between clinical responses with tumoural membranous expression of PD-L1 (Brahmer *et al.*, Journal of Clinical Oncology, 2010, Topalian *et al.*, NEJM, 2012) and a stronger correlation between lack of clinical responses and a lack of PD-L1 protein localized to the membrane (Brahmer *et al.*, Journal of Clinical Oncology, 2010, Topalian *et al.*, NEJM, 2012). Thus, PD-L1 expression in tumours or tumour-infiltrating leukocytes (Herbst RS, *et al.*, “Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients”, Nature, 2014, Nov 27, 515(7528):563-7, doi: 10.1038/nature14011) is a candidate molecular marker for use in selecting patients for

immunotherapy, for example, immunotherapy using anti-PD-L1 antibodies. Patient enrichment based on surface expression of PD-L1 may significantly enhance the clinical success of treatment with drugs targeting the PD-1/PD-L1 pathway. There is also evidence of an on-going immune response, such as the tumour infiltrating $CD8^+$ T-cells, or the presence of signature of cytokine activation, such as IFNγ.

Further evidence of PD-L1 expression and correlation to disease will emerge from the numerous ongoing clinical trials. Atezolizumab is the most advanced, and recent data from Phase II trials shows therapeutic effects in metastatic urothelial carcinoma and NSCLC, particularly in patients with PD-$L1^+$ immune cells in the tumour microenvironment (see Fehrenbacher *et al.*, 2016, The Lancet, http://doi.org/10.1016/S0140-6736(16)00587-0; Rosenberg *et al.*, 2016, The Lancet, http://doi.org/10.1016/S0140-6736(16)00561-4). Recent results from a Phase III trial of 1225 patients with NSCLC showed improved survival in patients taking atezolizumab, compared with chemotherapy, regardless of tumour expression of PD-L1 (Rittmeyer *et al.*, 2017, The Lancet, 389(10066), 255–265).

WO2018/029474 describes exemplary anti-ICOS antibodies. WO2017/220990 described exemplary anti-PD-L1 antibodies.

PD-L1 expression is often used as a predictive marker for whether a tumour will respond treatment, such as a PD-L1 antibody. PD-L1 acts as a "brak on the immune system, in a negative feedback loop, to modulate the immune response. Although a suppressive signal, its presence in tumours is therefore indicative of an anti-tumour immune response. PD-L1 negative tumours are immunologicall "cold", their PD-L1 negative status indicating that the cells have not been exposed to inflammation. In general, higher PD-L1 expression is associated with greater inflammation and these PD-L1 high tumours are more likely to respond to immunotherapy, since there are pre-existing immune cells which are capable of "seeing" and attacking the tumour. Existing anti-PD-L1 antibodies that have been approved for treatment are approved only for PD-L1 expression tumours. It has previously been considered unlikely that PD-L1 low expressing tumours would response to immunotherapy, such as with an anti-ICOS antibody, an anti-PD-L1 antibody, or a combination of anti-ICOS and anti-PD-L1 antibodies.

Summary of the Invention

The present inventors have discovered that immunotherapy can successfully treat PD-L1-negative or PD-L1 low expressing tumours. More specifically, the present inventors have discovered that PD-L1-negative or PD-L1 low expressing tumours can be successfully treated with an inhibitor of ICOS (for example an anti-ICOS antibody or antigen binding fragment thereof) or with a combination of an ICOS inhibitor (for example an anti-ICOS antibody or antigen binding fragment thereof) and a PD-L1 inhibitor (for example an anti-PD-L1 antibody or antigen binding fragment thereof or an anti-PD-1 antibody or antigen binding fragment thereof).

These treatments are suprising, as it was not previously considered possible to treat a PD-L1 negative or low PD-L1 expressing cancer with immunotherapy, in particular immunotherapy comprising administration of a PD-L1 inhibitor, such as an anti-PD-L1 antibody and/or comprising administration of an ICOS inhibitor, such as an anti-ICOS antibody. The present invention results in a surprising new mechanism for the treatment of cancers, including difficult-to-treat cancers, such as those with low levels of PD-L1 expression on the tumour cells and tumour-infiltrating lymphocytes, or PD-L1 negative cancers.

An antibody to ICOS that acts to increase effector T cell activity represents a therapeutic approach in immunooncology and in other medical contexts where a CD8+ T cell response is beneficial, including various diseases and conditions and in vaccination regimens. In many diseases and conditions involving an immune component, a balance exists between effector T cells (TEff) which exert the CD8+ T cell immune response, and regulatory T cells (TReg) which suppress that immune response by downregulating TEffs. The present invention relates to antibodies that modulate this TEff/TReg balance in favour of effector T cell activity. Antibodies that trigger the depletion of ICOS highly positive regulatory T cells would relieve the suppression of TEffs, and thus have a net effect of promoting the effector T cell response. An additional or complementary mechanism for an anti-ICOS antibody is via agonistic activity at the ICOS receptor level, to stimulate the effector T cell response.

The relative expression of ICOS on effector T cells (TEff) compared with regulatory T cells (TReg), and the relative activities of these cell populations, will influence the overall effect of an anti-ICOS antibody *in vivo*. An envisaged mode of action combines agonism of effector T cells with depletion of ICOS positive regulatory T cells. Differential and even opposing effects on these two different T cell populations may be achievable due to their different levels of ICOS expression. Dual-engineering of the variable and constant regions respectively of an anti-ICOS antibody can provide a molecule that exerts a net positive effect on effector T cell response by affecting the CD8/TReg ratio. An antigen-binding domain of an agonist antibody, which activates the ICOS receptor, may be combined with an antibody constant (Fc) region that promotes downregulation and/or clearance of highly expressing cells to which the antibody is bound. An effector positive constant region may be used to recruit cellular effector functions against the target cells (TRegs), e.g., to promote antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody dependent cell phagocytosis (ADCP). The antibody may thus act both to promote effector T cell activation and to downregulate immunosuppressive T Regulatory cells. Since ICOS is more highly expressed on TRegs than on TEffs, a therapeutic balance may be achieved whereby Teff function is promoted while TRegs are depleted, resulting in a net increase in the T cell immune response (e.g, anti-tumour response or other therapeutically beneficial T cell response).

Several pre-clinical and clinical studies have shown a strong positive correlation between high effector T-cell to T-reg cell ratio in the tumour microenvironment (TME) and overall survival. In ovarian cancer patients the ratio of CD8:T-reg cells has been reported to be an indicator of good clinical outcome [15]. A similar observation was made in metastatic melanoma patients after receiving ipilumumab [16]. In pre-clinical studies, it has also been shown that high effector cell:T-reg ratio in TME is associated with anti-tumour response.

This invention uses antibodies that bind human ICOS. The antibodies target the ICOS extracellular domain and thereby bind to T cells expressing ICOS. Examples are provided of antibodies that have been designed to have an agonistic effect on ICOS, thus enhancing the function of effector T cells, as indicated by an ability to increase IFNγ expression and secretion. As noted, anti-ICOS antibodies may also be engineered to deplete cells to which they bind, which should have the effect of preferentially downregulating regulatory T cells, lifting the suppressive effect of these cells on the effector T cell response and thus promoting the effector T cell response overall. Regardless of their mechanism of action, it is demonstrated empirically that anti-ICOS antibodies according to the present invention do stimulate T cell response and have anti-tumour effects *in vivo*, as shown in the Examples. Through selection of appropriate antibody formats such as those including constant regions with a desired level of Fc effector function, or absence of such effector function where appropriate, the anti-ICOS antibodies may be tailored for use in a variety of medical contexts including treatment of diseases and conditions in which an effector T cell response is beneficial and/or where suppression of regulatory T cells is desired.

Exemplary anti-ICOS antibodies include STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009, the sequences of which are set out herein.

The present invention provides a method of treating cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression, comprising administering to the patient an modulator of ICOS.

The present invention also provides a method of treating cancer in a patient who has previously received treatment for the cancer, wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor and the patient did not respond to the previous treatment or ceased responding to the previous treatment, comprising administering to the patient a modulator of ICOS.

The present invention also provides an ICOS modulator for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

The present invention also provides an ICOS modulator for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor.

The present invention also provides use of an ICOS modulator in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

The present invention also provides use of an ICOS modulator in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor.

Generally, the modulator of ICOS is an ICOS agonist. The modulator of ICOS may be an anti-ICOS antibody. In preferred embodiments, the modulator of ICOS is an agonistic anti-ICOS antibody.

In some embodiments, the methods or uses may involve a combination therapy with a PD-L1 inhibitor, for example a PD-L1 inhibitor that prevents the binding of PD-L1 to PD-1, such as an anti-PD-L1 or and anti-PD-1 antibody.

An anti-ICOS antibody used in the invention may be one that competes for binding to human ICOS with an antibody (e.g., human IgG1, or an scFv) comprising the heavy and light chain complementarity determining regions (CDRs) of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, optionally an antibody comprising the VH and VL domains of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

An anti-ICOS antibody according to the present invention may comprise one or more CDRs of any of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 (e.g., all 6 CDRs of any such antibody, or a set of HCDRs and/or LCDRs) or variants thereof as described herein.

The anti-ICOS antibody may comprise an antibody VH domain comprising CDRs HCDR1, HCDR2 and HCDR3 and an antibody VL domain comprising CDRs LCDR1, LCDR2 and LCDR3, wherein the HCDR3 is an HCDR3 of an antibody selected from STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 or comprises that HCDR3 with 1, 2, 3, 4 or 5 amino acid alterations. The HCDR2 may be the HCDR2 of the selected antibody or it may comprise that HCDR2 with 1, 2, 3, 4 or 5 amino acid alterations. The HCDR1 may be the HCDR1 of the selected antibody or it may comprise that HCDR1 with 1, 2, 3, 4 or 5 amino acid alterations.

The anti-ICOS antibody may comprise an antibody VL domain comprising CDRs HCDR1, HCDR2 and HCDR3 and an antibody VL domain comprising CDRs LCDR1, LCDR2 and LCDR3, wherein the LCDR3 is an LCDR3 of an antibody selected from STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 or comprises that LCDR3 with 1, 2, 3, 4 or 5 amino acid alterations. The LCDR2 may be the LCDR2 of the selected antibody or it may comprise that LCDR2 with 1, 2, 3, 4 or 5 amino acid alterations. The LCDR1 may be the LCDR1 of the selected antibody or it may comprise that LCDR1 with 1, 2, 3, 4 or 5 amino acid alterations.

An anti-ICOS antibody may comprise:

an antibody VH domain comprising complementarity determining regions HCDR1, HCDR2 and HCDR3, and

an antibody VL domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3,

wherein the heavy chain complementarity determining regions are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004 or STIM005, STIM006, STIM007, STIM008 or STIM009 heavy chain complementarity determining regions with 1, 2, 3, 4 or 5 amino acid alterations; and/or

wherein the light chain complementarity determining regions are those of antibody STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 light chain complementarity determining regions with 1, 2, 3, 4 or 5 amino acid alterations.

An anti-ICOS antibody may comprise a VH domain comprising a set of heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3, wherein

HCDR1 is the HCDR1 of STIM003,

HCDR2 is the HCDR2 of STIM003,

HCDR3 is the HCDR3 of STIM003,

or comprising that set of HCDRs with 1, 2, 3, 4, 5 or 6 amino acid alterations.

An anti-ICOS antibody may comprise a VL domain comprising a set of light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3, wherein

LCDR1 is the LCDR1 of STIM003,

LCDR2 is the LCDR2 of STIM003,

LCDR3 is the LCDR3 of STIM003,

or comprising that set of LCDRs with 1, 2, 3 or 4 amino acid alterations.

Amino acid alterations (e.g., substitutions) may be at any residue position in the CDRs. Examples of amino acid alterations are those illustrated in Figure 10, Figure 11 and Figure 12,

which show alignments of variant sequences of anti-ICOS antibodies. Thus, an amino acid alteration in a STIM003 CDR may be a substitution of the residue present at the corresponding position in antibody CL-74570 or antibody CL-71642 as indicated in Figure 11.

Example amino acid alterations in STIM003 CDRs are substitutions at the following residue positions, defined according to IMGT:

In HCDR1, substitution at IMGT position 28, optionally a conservative substitution, e.g., V28F.

In HCDR2, substitution at IMGT position 59, 63 and/or 64. Optionally the substitution at position 59 is N59I, the substitution at position 63 is G63D and/or the substitution at position 64 is D64N and/or D64S.

In HCDR3, substitution at IMGT position 106, 108, 109 and/or 112. Optionally the substitution at position 106 is R106A, the substitution at position 108 is F108Y, the substitution at position 109 is Y109F and/or the substitution at position 112 is H112N.

In LCDR1, substitution at position 36, e.g., R36S.

In LCDR3, substitution at position 105, 108 and/or 109. Optionally the substitution at position 105 is H105Q, the substitution at position 108 is D108G and/or the substitution at position 109 is M109N or M109S.

Anti-ICOS antibodies used in the invention may comprise VH and/or VL domain framework regions corresponding to human germline gene segment sequences. For example, it may comprise one or more framework regions of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009. The framework region or framework regions may be a FR1, FR2, FR3 and/or FR4.

As described in Example 2, Table E12-1 shows the human germline V, D and J gene segments that generated the VH domains of these antibodies through recombination and Table E12-2 shows the human germline V and J gene segments that generated the VL domains of these antibodies through recombination. Antibody VH and VL domains used in the present invention may be based on these V(D)J segments.

An antibody used in the invention may comprise an antibody VH domain which

(i) is derived from recombination of a human heavy chain V gene segment, a human heavy chain D gene segment and a human heavy chain J gene segment, wherein

the V segment is IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10);

the D gene segment is IGHD6-19 (e.g., IGHD6-19*01), IGHD3-10 (e.g., IGHD3-10*01) or IGHD3-9 (e.g., IGHD3-9*01); and/or

the J gene segment is IGHJ6 (e.g., IGHJ6*02), IGHJ4 (e.g., IGHJ4*02) or IGHJ3 (e.g., IGHJ3*02), or

(ii) comprises framework regions FR1, FR2, FR3 and FR4, wherein

FR1 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR2 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR3 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations, and/or

FR4 aligns with human germline J gene segment IGJH6 (e.g., JH6*02), IGJH4 (e.g., JH4*02) or IGJH3 (e.g., JH3*02), optionally with 1, 2, 3, 4 or 5 amino acid alterations.

FR1, FR2 and FR3 of the VH domain typically align with the same germline V gene segment. Thus, for example, the antibody may comprise a VH domain derived from recombination of human heavy chain V gene segment IGHV3-20 (e.g., VH3-20*d01), a human heavy chain D gene segment and a human heavy chain J gene segment IGJH4 (e.g., JH4*02). An antibody may comprise VH domain framework regions FR1, FR2, FR3 and FR4, wherein FR1, FR2 and FR3 each align with human germline V gene segment IGHV3-20 (e.g., IGVH3-20*d01) with up to 1, 2, 3, 4 or 5 amino acid alterations, and a FR4 that aligns with human germline J gene segment IGHJ4 (e.g., IGHJ4*02) with up to 1, 2, 3, 4 or 5 amino acid alterations. Alignment may be exact, but in some cases one or more residues can be mutated from germline, so there may be amino acid substitutions present, or in rarer cases deletions or insertions.

An antibody used in the invention may comprise an antibody VL domain which

(i) is derived from recombination of a human light chain V gene segment and a human light chain J gene segment, wherein

the V segment is IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), and/or

the J gene segment is IGKJ4 (e.g., IGKJ4*01), IGKJ2 (e.g., IGKJ2*04), IGLJ3 (e.g., IGKJ3*01) or IGKJ1 (e.g., IGKJ1*01); or

(ii) comprises framework regions FR1, FR2, FR3 and FR4, wherein

FR1 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR2 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR3 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations, and/or

FR4 aligns with human germline J gene segment IGKJ4 (e.g., IGKJ4*01), IGKJ2 (e.g., IGKJ2*04), IGKJ3 (e.g., IGKJ3*01) or IGKJ1 (e.g., IGKJ1*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations.

FR1, FR2 and FR3 of the VL domain typically align with the same germline V gene segment. Thus, for example, the antibody may comprise a VL domain derived from recombination of human light chain V gene segment IGKV3-20 (e.g., IGKV3-20*01) and human light chain J gene segment IGKJ3 (e.g., IGKJ3*01). An antibody may comprise VL domain framework regions FR1, FR2, FR3 and FR4, wherein FR1, FR2 and FR3 each align with human germline V gene segment IGKV3-20 (e.g., IGKV3-20*01) with up to 1, 2, 3, 4 or 5 amino acid alterations, and a FR4 that aligns with human germline J gene segment IGKJ3 (e.g., IGKJ3*01) with up to 1, 2, 3, 4 or 5 amino acid alterations. Alignment may be exact, but in some cases one or more residues can be mutated from germline, so there may be amino acid substitutions present, or in rarer cases deletions or insertions.

An antibody used in the invention may comprise an antibody VH domain which is the VH domain of STIM001, STIM002, STIM002-B, STIM003, STIM004 or STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009. The amino acid sequence identity may be at least 95 %.

The antibody may comprise an antibody VL domain which is the VL domain of STIM001, STIM002, STIM002-B, STIM003, STIM004 or STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VL domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009. The amino acid sequence identity may be at least 95 %.

An antibody VH domain having the HCDRs of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or having a variant of those CDRs, may be paired with an antibody VL domain having the LCDRs of the same antibody, or having a variant of those CDRs. Similary, the VH domain of any of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or a variant of that VH domain, may be paired with a VL domain of the same antibody, or a VL domain variant of the same antibody.

For instance, the antibody may comprise the antibody STIM001 VH domain and the STIM001 VL domain. In another example, the antibody may comprise the antibody STIM002 VH

domain and the STIM002 VL domain. In another example, the antibody may comprise the antibody STIM003 VH domain and the STIM003 VL domain.

Antibodies may include constant regions, optionally human heavy and/or light chain constant regions. An exemplary isotype is IgG, e.g., human IgG1.

Brief Description of the Drawings

Certain aspects and embodiments of the invention will now be described in more detail with reference to the accompanying drawings.

Figure 1: Dual mechanism of action of KY1044 (aka STIM003), an agonistic anti-ICOS antibody. (A) Tumour untreated prior to KY1044 treatment. (i) Supression of Effector T cells (ii) Regulatory T cell-mediated immune evasion. (B) Tumor and ICOS agonism. (iii) $ICOS^{HI}$ Regulatory T cells remain. (iv) $ICOS^{LOW}$ Effector T cells stimulated, IFNɣ expressed. (C) Tumor and depletion $ICOS^{HI}$ T_{regs}. (v) $ICOS^{HI}$ Regulatory T cells killed. This figure shows the potential for a dula mechanism of action (agnonism and depletion). One aspect of the dual mechanism of action is ICOS T_{eff} agonism, which increases activation (cytokine production) of T_{eff} cells, as shown in (B). The other aspect of the dual mechanism of action is ICOS T_{reg} depletion which releases the inhibition of T_{eff} cells, as shown in (C).

Figure 2: Schematic of a clinical trial study design. All comer patient population with preferred indications: e.g. NSCLC, HNSCC, HCC, melanoma ,cervical, gatric/esophageal, renal, pancreatic and TNBC. Dosing: Q3W I.V. (** = n=21 enrolled, n=20 treated) (i) KY1044 and enrichment pool. (ii) KY1044 + Atezolizumab and enrichment pool. Phase 1 Dose Escalation (completed) – KY1044 single agent dose escalation, and – KY1044 in combination with atezolizumab dose escalation. Phase 1 Enrichment Cohorts (ongoing). Phase 2 Expansion (ongoing) – selected indications in which anti-tumor activity was observed in Phase 1.

Figure 3: Staining of cells for PD-L1 expression

Figure 4: Threshold of the CD8 low vs high based on the median. (A) $PD\text{-}L1^{+}$ immune infiltrate in the TME and $CD8^{+}$ in the TME. (B) $PD\text{-}L1^{+}$ on tumour cells in TME and $CD8^{+}$ in the TME. Each panel (A) and (B) is divided into four quadrants: Q1= CD8 low/PD-L1 high; Q2= Hot tumor and PD-L1 high; Q3= Cold tumor; Q4= CD8 high/PD-L1 low. PR = partial response, CR = complete response, SD = stable disease, PD = progressive disease.

Figure 5: Effect of anti-ICOS treatment using KY1044 in Patient A. (A) Information table for Patient A. (B) TME analysis (as determined by IHC) at screening at C2D8 (cycle 2, day 8), (i) Minimal effect on $CD8^+$ T cells. (ii) Depletion of $ICOS^+$ Tregs. (iii) 73.6-fold improvement in $CD8^+/ICOS^+$ T_{reg} ratio. (C) PD-L1 expression in the TME (as determined by IHC) at screening at C2D8, (iv) 0% $PD\text{-}L1^+$ tumor cells. (v) Low $PD\text{-}L1^+$ immune infiltrate in TME. (D)Baseline PBMC analysis (as determined by chipcytometry), (vi) Low CD4 cells; High CD8 cells % of T cells. (vii) average T cells; above average monocytes. (viii) above average % of $ICOS^+$ cells.(E) Longitudinal PBCM and ICOS RO analysis (as determined by chipcytometry) (pre dose, cycle 1 day 8, cycle 2 day 1 (pre dose) and cycle 2 day 8). (ix) No depletion of peripheral CD4 menory cells. (x) No free ICOS on peripheral CD4 MEMs.

Figure 6: IHC analysis for Patient A at screening and at C2D8 following treatment with KY1044. (A) Depletion of $ICOS^+$ T_{regs} 75.97 to 0.7 (cells/mm^2) at screening and C2D8. (B) $CD8^+$ cells present 227.27 and 154.11 (cells/mm^2) at screening and C2D8. (C) $PD\text{-}L1^+$ tumor 0% at both timepoints, $PD\text{-}L1^+$ infiltrate 1% and 0% at screening and C2D8.

Figure 7: Effect of anti-ICOS treatment using KY1044 in Patient B. (A) Information table for Patient B. (B) TME analysis (as determined by IHC). (i) Average density of $CD8^+$ T cells at screening. (ii) Very low density of $ICOS^+$ T_{regs} at screening. (iii) Very high ratio of $CD8^+/ICOS^+$ T_{regs} at screening.(C) PD-L1 expression in the TME (as determined by IHC). (iv) 0% $PD\text{-}L1^+$ tumor cells at screening. (v) Low $PD\text{-}L1^+$ immune infiltrate in TME. (D) Longitudinal PBMC and ICOS RO analysis in patient B (as determined by chipcytometry). (vi) No depletion of peripheral CD4 memory cells. (vii) No free ICOS on peripheral CD4 MEMs. This patient reached a stable disease state following treatment with KY1044.

Figure 8: IHC analysis for Patient B at screening. (A) Very low $ICOS^+$ T_{reg} density at screening 0.07 (cells/mm^2). (B) High $CD8^+$ cell density at screening 98.65 (cells/mm^2). (C) $PD\text{-}L1^+$ tumor 0% at screening, $PD\text{-}L1^+$ infiltrate 0% at screening.

Figure 9: Patient Case Study – Patient C. Results for Patient C following treatment with KY1044, showing reduction in target lesion size at C3D8 and C10D1. Patient C information: Age/sex/diagnosis = 59years/male/HPV positive metastatic squamous cell carcinoma of the head/neck. PD-L1 status at screening (SP263): (%TC/%IC) = 3/2. Allocation = KY1044 8.0mg + atezolizumab 1,200mg Q3W. (A) Previous therapies vs times on treatment in this study. 5-FU = fluorouracil, PD = disease progression, PR = partial response, ** = patient was maintaining response of PR at the data cut for this figure (16 December 2020). (B) Target lesion change from baseline. (C) Baseline (June 2020). (D) Cycle 3/Day 8 (August 2020).

Figure 10: STIM002 VH (top) and VL (bottom) domain amino acid sequences, showing residues that differ in the corresponding sequences of STIM001, STIM002B and related antibodies CL-61091, CL-64536, CL-64837, CL-64841 and CL-64912 and/or in the human germline. Sequence numbering is according to IMGT.

Figure 11: STIM003 VH (top) and VL (bottom) domain amino acid sequences, showing residues that differ in the corresponding sequences of related antibodies CL-71642 and CL-74570 and/or in the human germline. Sequence numbering is according to IMGT. The VL domain of antibody CL-71642 obtained from sequencing is shown here without the N terminal residue. From the alignment it can be seen that the full VH domain sequence would comprise an N terminal glutamic acid.

Figure 12: STIM007 VH (top) and VL (bottom) domain amino acid sequences, showing residues that differ in the corresponding sequences of STIM008 and/or in the human germline. Sequence numbering is according to IMGT.

Detailed Description

ICOS

Anti-ICOS antibodies used in the present invention bind the extracellular domain of human ICOS. Thus, the antibodies bind ICOS-expressing T lymphocytes. “ICOS” or “the ICOS receptor” referred to herein may be human ICOS, unless the context dictates otherwise. Sequences of human, cynomolgus and mouse ICOS are shown in the appended sequence listing, and are available from NCBI as human NCBI ID: NP_036224.1, mouse NCBI ID: NP_059508.2 and cynomolgus GenBank ID: EHH55098.1.

PD-L1

Many tumour cells express surface molecules that are specific to cancer that can serve as diagnostic and/or therapeutic antibody targets. Examples of cell surface proteins expressed by tumour molecules that can be useful as biomarkers include, for example, members of the B7 family of proteins, major histocompatibility complex molecules (MHC), cytokine and growth factor receptors such as the receptor for eipdermal growth factor (EGFR). The B7 family is a group of proteins that are members of the immunoglobulin (Ig) superfamily of cell-surface proteins that bind to receptors on lymphocytes to regulate immune responses. The family includes transmembrane or glycosylphosphatidylinositol (GPI)-linked proteins characterized by extracellular Ig-like domains (IgV and IgC domains related to the variable and constant domains

of immunoglobulins). All members have short cytoplasmic domains. There are seven known members of the B7 family: B7-1, B7-2, PD-L1 (B7-H1), PD-L2, B7-H2, B7-H3, and B7-H4.

The complete amino acid sequence for PD-L1 can be found in NCBI Reference Sequence: NP 054862.1, which refers to many journal articles, including, for example, Dong, H., *et al.* (1999), "PD-L1, a third member of the B7 family, co-stimulates T- cell proliferation and interleukin-10 secretion," Nat. Med. 5 (12), 1365-1369, the disclosure of which is hereby incorporated by reference herein in its entirety. The amino acid sequence of PD-L1 includes a 30 amino acid long cytoplasmic domain that is unique to PD-L1, which shows little homology to other molecules, including other B7 family members.

PD-1

The complete amino acid sequence for PD-1 can be found UniProt accession no. Q9UMF3.

ICOS modulators

The ICOS modulators used in the present invention may be any suitable ICOS modulators. Generally, the ICOS modulator may be an ICOS agonist. In some embodiments, the ICOS modualtor is an anti-ICOS antibody. In preferred embodiments, the ICOS modulator is an agonistic anti-ICOS antibody.

The ICOS modultaors (for example agonistic anti-ICOS antibodies) may deplete ICOS+ T Cells, in particular ICOS+ Tregs.

In some embodiments, the ICOS modulators are multispecific (such as bispecific), that is they specifically bind to multiple (for example two) different antigens. In some embodiments, the ICOS modulator is a multi-specific antibody (for example a bispecific antibody) that specifically binds ICOS and PD-L1 or PD-1. In some embodiments, the ICOS modulator is a multi-specific antibody (for example a bispecific antibody) that specifically binds ICOS and is an ICOS agonist, and specifically binds PD-L1 or PD-1 and is a PD-L1 or PD-1 antagonist.

PD-L1 inhibitors

The PD-L1 inhibitors used in the present invention generally inhibit the binding of PD-L1 to PD-1 (or the binding of PD-1 to PD-L1). The PD-L1 inhibitors may be an anti-PD-L1 or anti-PD-1 binding molecule. In some embodiments, the PD-L1 or PD-1 inhibitors are anti-PD-L1 or anti-PD-1 antibodies, respectively. Generally, the PD-L1 inhibitors are antagonists of PD-L1, for example antagonistic anti-PD-L1 or anti-PD-1 antibodies.

Combinations of ICOS modulators and PD-L1 inhibitors

In some embodiments the invention uses a combination of an ICOS modulator and a PD-L1 inhibitor. The ICOS modulator and PD-L1 inhibitor may be for simulataneous, separate or

sequential administration. In some embodients, the ICOS modulator is an anti-ICOS antibody (for example an agonistic anti-ICOS antibody) and the PD-L1 inhibitor is an anti-PD-L1 antibody or an anti-PD-1 antibody. In some embodiments, the ICOS modulator is an IgG1 anti-ICOS antibody and the PD-L1 inhibitor is an IgG1 anti-PD-L1 antibody or an IgG1 anti-PD-1 antibody

Cross-reactivity

Antibodies used in the present invention are preferably cross-reactive, and may for example bind the extracellular domain of mouse ICOS as well as human ICOS. The antibodies may bind other non-human ICOS, including ICOS of primates such as cynomolgus. An anti-ICOS antibody intended for therapeutic use in humans must bind human ICOS, whereas binding to ICOS of other species would not have direct therapeutic relevance in the human clinical context. Nevertheless, the data herein indicate that antibodies that bind both human and mouse ICOS have properties that render them particularly suitable as agonist and depleting molecules. This may result from one or more particular epitopes being targeted by the cross-reactive antibodies. Regardless of the underlying theory, however, cross-reactive antibodies are of high value and are excellent candidates as therapeutic molecules for pre-clinical and clinical studies. Anti-PD-L1 and/or anti-PD-1 antibodies used in the invention may also exhibit cross-reactivity.

The STIM antibodies described here were generated using Kymouse™ technology where the mouse had been engineered to lack expression of mouse ICOS (an ICOS knock-out). ICOS knock-out transgenic animals and their use for generating cross-reactive antibodies are further aspects of the present invention.

One way to quantify the extent of species cross-reactivity of an antibody is as the fold-difference in its affinity for antigen or one species compared with antigen of another species, e.g., fold difference in affinity for human ICOS vs mouse ICOS. Affinity may be quantified as K_D, referring to the equilibrium dissociation constant of the antibody-antigen reaction as determined by SPR with the antibody in Fab format as described elsewhere herein. A species cross-reactive anti-ICOS antibody may have a fold-difference in affinity for binding human and mouse ICOS that is 30-fold or less, 25-fold or less, 20-fold or less, 15-fold or less, 10-fold or less or 5-fold or less. To put it another way, the K_D of binding the extracellular domain of human ICOS may be within 30-fold, 25-fold, 20-fold, 15-fold, 10-fold or 5-fold of the K_D of binding the extracellular domain of mouse ICOS. Antibodies can also be considered cross-reactive if the K_D for binding antigen of both species meets a threshold value, e.g., if the K_D of binding human ICOS and the K_D of binding mouse ICOS are both 10 mM or less, preferably 5 mM or less, more preferably 1 mM or less. The K_D may be 10 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less. The K_D may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less.

An alternative measure of cross-reactivity for binding human ICOS and mouse ICOS is the ability of an antibody to neutralise ICOS ligand binding to ICOS receptor, such as in an HTRF assay (see Example 8 of WO2018/029474). Examples of species cross-reactive antibodies are provided herein, including STIM001, STIM002, STIM002-B, STIM003, STIM005 and STIM006, each of which was confirmed as neutralising binding of human B7-H2 (ICOS ligand) to human ICOS and neutralising binding of mouse B7-H2 to mouse ICOS in an HTRF assay. Any of these antibodies or their variants may be selected when an antibody cross-reactive for human and mouse ICOS is desired. A species cross-reactive anti-ICOS antibody may have an IC50 for inhibiting binding of human ICOS to human ICOS receptor that is within 25-fold, 20-fold, 15-fold, 10-fold or 5-fold of the IC50 for inhibiting mouse ICOS to mouse ICOS receptor as determined in an HTRF assay. Antibodies can also be considered cross-reactive if the IC50 for inhibiting binding of human ICOS to human ICOS receptor and the IC50 for inhibiting binding of mouse ICOS to mouse ICOS receptor are both 1 mM or less, preferably 0.5 mM or less, e.g., 30 nM or less, 20 nM or less, 10 nM or less. The IC50s may be 5 nM or less, 4 nM or less, 3 nM or less or 2 nM or less. In some cases the IC50s will be at least 0.1 nM, at least 0.5 nM or at least 1 nM.

Specificity

Antibodies used according to the present invention are preferably specific for ICOS. That is, the antibody binds its epitope on the target protein, ICOS (human ICOS, and preferably mouse and/or cynomolgus ICOS as noted above), but does not show significant binding to molecules that do not present that epitope, including other molecules in the CD28 gene family. An antibody according to the present invention preferably does not bind human CD28. The antibody preferably also does not bind mouse or cynomolgus CD28.

CD28 co-stimulates T cell responses when engaged by its ligands CD80 and CD86 on professional antigen presenting cells in the context of antigen recognition via the TCR. For various *in vivo* uses of the antibodies described herein, the avoidance of binding to CD28 is considered advantageous. Non-binding of the anti-ICOS antibody to CD28 should allow CD28 to interact with its native ligands and to generate appropriate co-stimulatory signal for T cell activation. Additionally, non-binding of the anti-ICOS antibody to CD28 avoids the risk of superagonism. Over-stimulation of CD28 can induce proliferation in resting T cells without the normal requirement for recognition of a cognate antigen via the TCR, potentially leading to runaway activation of T cells and consequent cytokine-release syndrome, especially in human subjects. The non-recognition of CD28 by antibodies according to the present invention therefore represents an advantage in terms of their safe clinical use in humans.

As discussed elsewhere herein, the present invention extends to multispecific antibodies (e.g., bispecifics). A multispecific (e.g., bispecific) antibody may comprise (i) an antibody antigen

binding site for ICOS and (ii) a further antigen binding site (optionally an antibody antigen binding site, as described herein) which recognises another antigen (e.g., PD-L1). Specific binding of individual antigen binding sites may be determined. Thus, antibodies that specifically bind ICOS include antibodies comprising an antigen binding site that specifically binds ICOS, wherein optionally the antigen binding site for ICOS is comprised within an antigen-binding molecule that further includes one or more additional binding sites for one or more other antigens, e.g., a bispecific antibody that binds ICOS and PD-L1.

Some antibodies used in the invention specifcialyl bind PD-L1 or PD-1. That is, the antibody binds its epitope on the target protein, PD-L1 or PD-1 (human PD-L1 or PD-1, and preferably mouse and/or cynomolgus PD-L1 or PD-1), but does not show significant binding to molecules that do not present that epitope.

Affinity

The affinity of binding of an antibody to ICOS (or to another antigen, such as PD-L1 or PD-1) may be determined. Affinity of an antibody for its antigen may be quantified in terms of the equilibrium dissociation constant K_D, the ratio Ka/Kd of the association or on-rate (Ka) and the dissociation or off-rate (kd) of the antibody-antigen interaction. Kd, Ka and Kd for antibody-antigen binding can be measured using surface plasmon resonance (SPR).

An antibody used in the present invention may bind the EC domain of human ICOS with a K_D of 10 mM or less, preferably 5 mM or less, more preferably 1 mM or less. The K_D may be 50 nM or less, 10 nM or less, 5 nM or less, 2 nM or less, or 1 nM or less. The K_D may be 0.9 nM or less, 0.8 nM or less, 0.7 nM or less, 0.6 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, or 0.1 nM or less. The K_D may be at least 0.001 nM, for example at least 0.01 nM or at least 0.1 nM.

Quantification of affinity may be performed using SPR with the antibody in Fab format. A suitable protocol is as follows:

1. Coupling anti-human (or other antibody constant region species-matched) IgG to a biosensor chip (e.g., GLM chip) such as by primary amine coupling;
2. Exposing the anti-human IgG (or other matched species antibody) to a test antibody, e.g., in Fab format, to capture test antibody on the chip;
3. Passing the test antigen over the chip's capture surface at a range of concentrations, e.g., at 5000 nM, 1000 nM, 200 nM, 40 nM, 8 nM and 2 nM, and at 0 nM (i.e., buffer alone); and
4. Determining the affinity of binding of test antibody to test antigen using SPR at 25 °C.

Buffer may be at pH 7.6, 150 mM NaCl, 0.05 % detergent (e.g., P20) and 3 mM EDTA. Buffer may optionally contain 10 mM HEPES. HBS-EP can be used as running buffer. HBS-EP is available from Teknova Inc (California; catalogue number H8022).

Regeneration of the capture surface can be carried out with 10 mM glycine at pH 1.7. This removes the captured antibody and allows the surface to be used for another interaction. The binding data can be fitted to 1:1 model inherent using standard techniques, e.g., using a model inherent to the ProteOn XPR36TM analysis software.

A variety of SPR instruments are known, such as Biacore™, ProteOn XPR36™ (Bio-Rad®), and KinExA® (Sapidyne Instruments, Inc). Worked examples of SPR are found in Example 7 of WO2018/029474.

As described, affinity may be determined by SPR with the antibody in Fab format, with the antigen coupled to the chip surface and the test antibody passed over the chip in Fab format in solution, to determine affinity of the monomeric antibody-antigen interaction. Affinity can be determined at any desired pH, e.g., pH 5.5 or pH 7.6, and any desired temperature e.g., 25°C or 37°C. As reported in Example 7 of WO2018/029474, antibodies according to the present invention bound human ICOS with an apparent affinity of less than 2 nM, as determined by SPR using the antibody in monovalent (Fab) format.

Other ways to measure binding of an antibody to ICOS include fluorescence activated cell sorting (FACS), e.g., using cells (e.g., CHO cells) with exogenous surface expression of ICOS or activated primary T cells expressing endogenous levels of ICOS. Antibody binding to ICOS-expressing cells as measured by FACS indicates that the antibody is able to bind the extracellular (EC) domain of ICOS.

ICOS Receptor Agonism

The ICOS ligand (ICOSL, also known as B7-H2) is a cell surface expressed molecule that binds to the ICOS receptor [17]. This intercellular ligand-receptor interaction promotes multimerisation of ICOS on the T cell surface, activating the receptor and stimulating downstream signalling in the T cell. In effector T cells, this receptor activation stimulates the effector T cell response.

Anti-ICOS antibodies may act as agonists of ICOS, mimicking and even surpassing this stimulatory effect of the native ICOS ligand on the receptor. Such agonism may result from ability of the antibody to promote multimerisation of ICOS on the T cell. One mechanism for this is where the antibodies form intercellular bridges between ICOS on the T cell surface and receptors on an adjacent cell (e.g., B cell, antigen-presenting cell, or other immune cell), such as Fc receptors. Another mechanism is where antibodies having multiple (e.g., two) antigen-binding sites (e.g., two VH-VL domain pairs) bridge multiple ICOS receptor molecules and so promote multimerisation. A combination of these mechanisms may occur.

Agonism can be tested for in in vitro T cell activation assays, using antibody in soluble form (e.g., in immunoglobulin format or other antibody format comprising two spatially separated antigen-binding sites, e.g., two VH-VL pairs), either including or excluding a cross-linking agent,

or using antibody bound to a solid surface to provide a tethered array of antigen-binding sites. Agonism assays may use a human ICOS positive T lymphocyte cell line such as MJ cells (ATCC CRL-8294) as the target T cell for activation in such assays. One or more measures of T cell activation can be determined for a test antibody and compared with a reference molecule or a negative control to determine whether there is a statistically significant ($p<0.05$) difference in T cell activation effected by the test antibody compared with the reference molecule or the control. One suitable measure of T cell activation is production of cytokines, e.g., IFNγ, TNFα or IL-2. The skilled person will include suitable controls as appropriate, standardising assay conditions between test antibody and control. A suitable negative control is an antibody in the same format (e.g., isotype control) that does not bind ICOS, e.g., an antibody specific for an antigen that is not present in the assay system. A significant difference is observed for test antibody relative to a cognate isotype control within the dynamic range of the assay is indicative that the antibody acts as an agonist of the ICOS receptor in that assay.

An agonist antibody may be defined as one which, when tested in a T cell activation assay:

has a significantly lower EC50 for induction of IFNγ production compared with control antibody;

induces significantly higher maximal IFNγ production compared with control antibody;

has a significantly lower EC50 for induction of IFNγ production compared with ICOSL-Fc;

induces significantly higher maximal IFNγ production compared with ICOSL-Fc;

has a significantly lower EC50 for induction of IFNγ production compared with reference antibody C398.4A; and/or

induces significantly higher maximal IFNγ production compared with reference antibody C398.4A.

In vitro T cell assays include the bead-bound assay of Example 13 of WO2018/029474, the plate-bound assay of Example 14 of WO2018/029474 and the soluble form assay of Example 15 of WO2018/029474.

A significantly lower or significantly higher value may for example be up to 0.5-fold different, up to 0.75-fold different, up to 2-fold different, up to 3-fold different, up to 4-fold different or up to 5-fold different, compared with the reference or control value.

Thus, in one example, an antibody according to the present invention has a significantly lower, e.g., at least 2-fold lower, EC50 for induction of IFNγ in an MJ cell activation assay using the antibody in bead-bound format, compared with control.

The bead-bound assay uses the antibody (and, for control or reference experiments, the control antibody, reference antibody or ICOSL-Fc) bound to the surface of beads. Magnetic beads may be used, and various kinds are commercially available, e.g., Tosyl-activated

DYNABEADS M-450 (DYNAL Inc, 5 Delaware Drive, Lake Success, N.Y. 11042 Prod No. 140.03, 140.04). Beads may be coated as described in Example 13 of WO2018/029474, or generally by dissolving the coating material in carbonate buffer (pH 9.6, 0.2 M) or other method known in the art. Use of beads conveniently allows the quantity of protein bound to the bead surface to be determined with a good degree of accuracy. Standard Fc-protein quantification methods can be used for coupled protein quantification on beads. Any suitable method can be used, with reference to a relevant standard within the dynamic range of the assay. DELFIA is exemplified in Example 13 of WO2018/029474, but ELISA or other methods could be used.

Agonism activity of an antibody can also be measured in primary human T lymphocytes *ex vivo*. The ability of an antibody to induce expression of IFNγ in such T cells is indicative of ICOS agonism. Described herein are two T cell activation assays using primary cells – see Example 2 of WO2018/029474, T cell activation assay 1 and T cell activation assay 2. Preferably, an antibody will show significant ($p<0.05$) induction of IFNγ at 5 μg/ml compared with control antibody in T cell activation assay 1 and/or T cell activation assay 2. As noted above, an anti-ICOS antibody may stimulate T cell activation to a greater degree than ICOS-L or C398.4 in such an assay. Thus, the antibody may show significantly ($p<0.05$) greater induction of IFNγ at 5 μg/ml compared with the control or reference antibody in T cell activation assay 1 or 2. TNFα or IL-2 induction may be measured as an alternative assay readout.

Agonism of an anti-ICOS antibody may contribute to its ability to change the balance between populations of TReg and TEff cells *in vivo,* e.g., in a site of pathology such as a tumour microenvironment, in favour of TEff cells. The ability of an antibody to enhance tumour cell killing by activated ICOS-positive effector T cells may be determined, as discussed elsewhere herein.

PD-L1 or PD-1 Receptor Antagonism

PD-L1 or PD-1 inhibitors may act as PD-L1 or PD-1 antagnosist. That is, they inhibit the binding of PD-L1 to PD-1 (or the binding of PD-1 to PD-L1).

T cell dependent killing

Effector T cell function can be determined in a biologically relevant context using an *in vitro* co-culture assay where tumour cells are incubated with relevant immune cells to trigger immune cell-dependent killing, in which the effect of an anti-ICOS antibody on tumour cell killing by TEffs is observed.

The ability of an antibody to enhance tumour cell killing by activated ICOS-positive effector T cells may be determined. An anti-ICOS antibody may stimulate significantly greater ($p<0.05$) tumour cell killing compared with a control antibody. An anti-ICOS antibody may stimulate similar or greater tumour cell killing in such an assay as compared with a reference

molecule such as the ICOS ligand or the C398.4 antibody. A similar degree of tumour cell killing can be represented as the assay readout for the test antibody being less than two-fold different from that for the reference molecule.

ICOS Ligand-Receptor Neutralisation Potency

An antibody used in the present invention may be one which inhibits binding of ICOS to its ligand ICOSL.

The degree to which an antibody inhibits binding of the ICOS receptor to its ligand is referred to as its ligand-receptor neutralising potency. Potency is normally expressed as an IC50 value, in pM unless otherwise stated. In ligand-binding studies, IC50 is the concentration that reduces receptor binding by 50 % of maximal specific binding level. IC50 may be calculated by plotting % specific receptor binding as a function of the log of the antibody concentration, and using a software program such as Prism (GraphPad) to fit a sigmoidal function to the data to generate IC50 values. Neutralising potency may be determined in an HTRF assay. A detailed working example of an HTRF assay for ligand-receptor neutralising potency is set out in Example 8 of WO2018/029474.

An IC50 value may represent the mean of a plurality of measurements. Thus, for example, IC50 values may be obtained from the results of triplicate experiments, and a mean IC50 value can then be calculated.

An antibody may have an IC50 of 1 mM or less in a ligand-receptor neutralisation assay, e.g., 0.5 mM or less. The IC50 may be, 30 nM or less, 20 nM or less, 10 nM or less, 5 nM or less, 4 nM or less, 3 nM or less or 2 nM or less. The IC50 may be at least 0.1 nM, at least 0.5 nM or at least 1 nM.

Antibodies

As described in more detail in the Examples of WO2018/029474, we isolated and characterised antibodies of particular interest, designated STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009. In various aspects of the invention, unless context dictates otherwise, antibodies may be selected from any of these antibodies, or from the sub-set of STIM001, STIM002, STIM003, STIM004 and STIM005. Sequences of each of these antibodies are provided in the appended sequence listing, wherein for each antibody the following sequences are shown: nucleotide sequence encoding VH domain; amino acid sequence of VH domain; VH CDR1 amino acid sequence, VH CDR2 amino acid sequence; VH CDR3 amino acid sequence; nucleotide sequence encoding VL domain; amino acid sequence of VL domain; VL CDR1 amino acid sequence; VL CDR2 amino acid sequence; and VL CDR3 amino acid sequence, respectively. The present invention encompasses anti-ICOS antibodies having the VH and/or VL domain sequences of all

antibodies shown in the appended sequence listing and/or in the drawings, as well as antibodies comprising the HCDRs and/or LCDRs of those antibodies, and optionally having the full heavy chain and/or full light chain amino acid sequence.

STIM001 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:366, comprising the CDRH1 amino acid sequence of Seq ID No:363, the CDRH2 amino acid sequence of Seq ID No:364, and the CDRH3 amino acid sequence of Seq ID No:365. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:367. STIM001 has a light chain variable region (V_L) amino acid sequence of Seq ID No:373, comprising the CDRL1 amino acid sequence of Seq ID No:370, the CDRL2 amino acid sequence of Seq ID No:371, and the CDRL3 amino acid sequence of Seq ID No:372. The light chain nucleic acid sequence of the V_L domain is Seq ID No:374. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:368 (heavy chain nucleic acid sequence Seq ID No:369). A full length light chain amino acid sequence is Seq ID No:375 (light chain nucleic acid sequence Seq ID No:376).

STIM002 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:380, comprising the CDRH1 amino acid sequence of Seq ID No:377, the CDRH2 amino acid sequence of Seq ID No:378, and the CDRH3 amino acid sequence of Seq ID No:379. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:381. STIM002 has a light chain variable region (V_L) amino acid sequence of Seq ID No:387, comprising the CDRL1 amino acid sequence of Seq ID No:384, the CDRL2 amino acid sequence of Seq ID No:385, and the CDRL3 amino acid sequence of Seq ID No:386. The light chain nucleic acid sequence of the V_L domain is Seq ID No:388 or Seq ID No:519. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:382 (heavy chain nucleic acid sequence Seq ID No:383). A full length light chain amino acid sequence is Seq ID No:389 (light chain nucleic acid sequence Seq ID No:390 or Seq ID NO:520).

STIM002-B has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:394, comprising the CDRH1 amino acid sequence of Seq ID No:391, the CDRH2 amino acid sequence of Seq ID No:392, and the CDRH3 amino acid sequence of Seq ID No:393. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:395. STIM002-B has a light chain variable region (V_L) amino acid sequence of Seq ID No:401, comprising the CDRL1 amino acid sequence of Seq ID No:398, the CDRL2 amino acid sequence of Seq ID No:399, and the CDRL3 amino acid sequence of Seq ID No:400. The light chain nucleic acid sequence of the V_L domain is Seq ID No:402. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:396 (heavy chain nucleic acid sequence Seq ID No:397). A full length light chain amino acid sequence is Seq ID No:403 (light chain nucleic acid sequence Seq ID No:404).

STIM003 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:408, comprising the CDRH1 amino acid sequence of Seq ID No:405, the CDRH2 amino acid sequence of Seq ID No:406, and the CDRH3 amino acid sequence of Seq ID No:407. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:409 or Seq ID No:521. STIM003 has a light chain variable region (V_L) amino acid sequence of Seq ID No:415, comprising the CDRL1 amino acid sequence of Seq ID No:412, the CDRL2 amino acid sequence of Seq ID No:413, and the CDRL3 amino acid sequence of Seq ID No:414. The light chain nucleic acid sequence of the V_L domain is Seq ID No:4416. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:410 (heavy chain nucleic acid sequence Seq ID No:411 or Seq ID No:522). A full length light chain amino acid sequence is Seq ID No:417 (light chain nucleic acid sequence Seq ID No:418).

STIM004 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:422, comprising the CDRH1 amino acid sequence of Seq ID No:419, the CDRH2 amino acid sequence of Seq ID No:420, and the CDRH3 amino acid sequence of Seq ID No:421. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:423. STIM004 has a light

chain variable region (V_L) amino acid sequence of Seq ID No:429, comprising the CDRL1 amino acid sequence of Seq ID No:426, the CDRL2 amino acid sequence of Seq ID No:427, and the CDRL3 amino acid sequence of Seq ID No:428. The light chain nucleic acid sequence of the V_L domain is Seq ID No:430 or Seq ID No:431. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:424 (heavy chain nucleic acid sequence Seq ID No:425). A full length light chain amino acid sequence is Seq ID No:432 (light chain nucleic acid sequence Seq ID No:433 or Seq ID no: 434).

STIM005 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:438, comprising the CDRH1 amino acid sequence of Seq ID No:435, the CDRH2 amino acid sequence of Seq ID No:436, and the CDRH3 amino acid sequence of Seq ID No:437. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:439. STIM005 has a light chain variable region (V_L) amino acid sequence of Seq ID No:445, comprising the CDRL1 amino acid sequence of Seq ID No:442, the CDRL2 amino acid sequence of Seq ID No:443, and the CDRL3 amino acid sequence of Seq ID No:444. The light chain nucleic acid sequence of the V_L domain is Seq ID No:446. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:440 (heavy chain nucleic acid sequence Seq ID No:441). A full length light chain amino acid sequence is Seq ID No:447 (light chain nucleic acid sequence Seq ID No:448).

STIM006 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:452, comprising the CDRH1 amino acid sequence of Seq ID No:449, the CDRH2 amino acid sequence of Seq ID No:450, and the CDRH3 amino acid sequence of Seq ID No:451. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:453. STIM006 has a light chain variable region (V_L) amino acid sequence of Seq ID No:459, comprising the CDRL1 amino acid sequence of Seq ID No:456, the CDRL2 amino acid sequence of Seq ID No:457, and the CDRL3 amino acid sequence of Seq ID No:458. The light chain nucleic acid sequence of the V_L domain is Seq ID No:460. The V_H domain may be combined with any of the heavy chain

constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:454 (heavy chain nucleic acid sequence Seq ID No:455). A full length light chain amino acid sequence is Seq ID No:461 (light chain nucleic acid sequence Seq ID No:462).

STIM007 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:466, comprising the CDRH1 amino acid sequence of Seq ID No:463, the CDRH2 amino acid sequence of Seq ID No:464, and the CDRH3 amino acid sequence of Seq ID No:465. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:467. STIM007 has a light chain variable region (V_L) amino acid sequence of Seq ID No:473, comprising the CDRL1 amino acid sequence of Seq ID No:470, the CDRL2 amino acid sequence of Seq ID No:471, and the CDRL3 amino acid sequence of Seq ID No:472. The light chain nucleic acid sequence of the V_L domain is Seq ID No:474. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:468 (heavy chain nucleic acid sequence Seq ID No:469). A full length light chain amino acid sequence is Seq ID No:475 (light chain nucleic acid sequence Seq ID No:476).

STIM008 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:480, comprising the CDRH1 amino acid sequence of Seq ID No:477, the CDRH2 amino acid sequence of Seq ID No:478, and the CDRH3 amino acid sequence of Seq ID No:479. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:481. STIM008 has a light chain variable region (V_L) amino acid sequence of Seq ID No:487, comprising the CDRL1 amino acid sequence of Seq ID No:484, the CDRL2 amino acid sequence of Seq ID No:485, and the CDRL3 amino acid sequence of Seq ID No:486. The light chain nucleic acid sequence of the V_L domain is Seq ID No:488. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233,

235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:482 (heavy chain nucleic acid sequence Seq ID No:483). A full length light chain amino acid sequence is Seq ID No:489 (light chain nucleic acid sequence Seq ID No:490).

STIM009 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:494, comprising the CDRH1 amino acid sequence of Seq ID No:491, the CDRH2 amino acid sequence of Seq ID No:492, and the CDRH3 amino acid sequence of Seq ID No:493. The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:495. STIM009 has a light chain variable region (V_L) amino acid sequence of Seq ID No:501, comprising the CDRL1 amino acid sequence of Seq ID No:498, the CDRL2 amino acid sequence of Seq ID No:499, and the CDRL3 amino acid sequence of Seq ID No:500. The light chain nucleic acid sequence of the V_L domain is Seq ID No:502. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:496 (heavy chain nucleic acid sequence Seq ID No:497). A full length light chain amino acid sequence is Seq ID No:503 (light chain nucleic acid sequence Seq ID No:504).

Antibodies according to the present invention are immunoglobulins or molecules comprising immunoglobulin domains, whether natural or partly or wholly synthetically produced. Antibodies may be IgG, IgM, IgA, IgD or IgE molecules or antigen-specific antibody fragments thereof (including, but not limited to, a Fab, F(ab')2, Fv, disulphide linked Fv, scFv, single domain antibody, closed conformation multispecific antibody, disulphide-linked scfv, diabody), whether derived from any species that naturally produces an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria. Antibodies can be humanised using routine technology. The term antibody covers any polypeptide or protein comprising an antibody antigen-binding site. An antigen-binding site (paratope) is the part of an antibody that binds to and is complementary to the epitope of its target antigen (ICOS).

The term "epitope" refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl

groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

The antigen binding site is a polypeptide or domain that comprises one or more CDRs of an antibody and is capable of binding the antigen. For example, the polypeptide comprises a CDR3 (e.g., HCDR3). For example the polypeptide comprises CDRs 1 and 2 (e.g., HCDR1 and 2) or CDRs 1-3 of a variable domain of an antibody (e.g., HCDRs1-3).

An antibody antigen-binding site may be provided by one or more antibody variable domains. In an example, the antibody binding site is provided by a single variable domain, e.g., a heavy chain variable domain (VH domain) or a light chain variable domain (VL domain). In another example, the binding site comprises a VH/VL pair or two or more of such pairs. Thus, an antibody antigen-binding site may comprise a VH and a VL.

The antibody may be a whole immunoglobulin, including constant regions, or may be an antibody fragment. An antibody fragment is a portion of an intact antibody, for example comprising the antigen binding and/or variable region of the intact antibody. Examples of antibody fragments include:

(i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment including two Fab fragments linked by a disulfide bridge at the hinge region;

(iii) an Fd fragment consisting of the VH and CH1 domains;

(iv) an Fv fragment consisting of the VL and VH domains of a single arm of an antibody,

(v) a dAb fragment (Ward et al., (1989) Nature 341:544-546; which is incorporated by reference herein in its entirety), which consists of a VH or VL domain; and

(vi) an isolated complementarity determining region (CDR) that retains specific antigen-binding functionality.

Further examples of antibodies are H2 antibodies that comprise a dimer of a heavy chain (5'-VH-(optional hinge)-CH2-CH3-3') and are devoid of a light chain.

Single-chain antibodies (e.g., scFv) are a commonly used fragment. Multispecific antibodies may be formed from antibody fragments. An antibody of the invention may employ any such format, as appropriate.

Optionally, the antibody immunoglobulin domains may be fused or conjugated to additional polypeptide sequences and/or to labels, tags, toxins or other molecules. Antibody immunoglobulin domains may be fused or conjugated to one or more different antigen binding regions, providing a molecule that is able to bind a second antigen in addition to ICOS. An antibody of the present invention may be a multispecific antibody, e.g., a bispecific antibody, comprising (i) an antibody antigen binding site for ICOS and (ii) a further antigen binding site (optionally an antibody antigen binding site, as described herein) which recognises another antigen (e.g., PD-L1).

An antibody normally comprises an antibody VH and/or VL domain. Isolated VH and VL domains of antibodies are also part of the invention. The antibody variable domains are the portions of the light and heavy chains of antibodies that include amino acid sequences of complementarity determining regions (CDRs; ie., CDR1, CDR2, and CDR3), and framework regions (FRs). Thus, within each of the VH and VL domains are CDRs and FRs. A VH domain comprises a set of HCDRs, and a VL domain comprises a set of LCDRs. VH refers to the variable domain of the heavy chain. VL refers to the variable domain of the light chain. Each VH and VL is typically 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. According to the methods used in this invention, the amino acid positions assigned to CDRs and FRs may be defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991)) or according to IMGT nomenclature. An antibody may comprise an antibody VH domain comprising a VH CDR1, CDR2 and CDR3 and a framework. It may alternatively or also comprise an antibody VL domain comprising a VL CDR1, CDR2 and CDR3 and a framework. Examples of antibody VH and VL domains and CDRs according to the present invention are as listed in the appended sequence listing that forms part of the present disclosure. The CDRs shown in the sequence listing are defined according to the IMGT system [18]. All VH and VL sequences, CDR sequences, sets of CDRs and sets of HCDRs and sets of LCDRs disclosed herein represent aspects and embodiments of the invention. As described herein, a "set of CDRs" comprises CDR1, CDR2 and CDR3. Thus, a set of HCDRs refers to HCDR1, HCDR2 and HCDR3, and a set of LCDRs refers to LCDR1, LCDR2 and LCDR3. Unless otherwise stated, a "set of CDRs" includes HCDRs and LCDRs.

An antibody the invention may comprise one or more CDRs as described herein, e.g. a CDR3, and optionally also a CDR1 and CDR2 to form a set of CDRs. The CDR or set of CDRs may be a CDR or set of CDRs of any of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009, or may be a variant thereof as described herein.

The invention provides antibodies comprising an HCDR1, HCDR2 and/or HCDR3 of any of antibodies STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 and/or an LCDR1, LCDR2 and/or LCDR3 of any of these antibodies, e.g. a set of CDRs. The antibody may comprise a set of VH CDRs of one of these antibodies. Optionally it may also comprise a set of VL CDRs of one of these antibodies, and the VL CDRs may be from the same or a different antibody as the VH CDRs.

A VH domain comprising a disclosed set of HCDRs, and/or a VL domain comprising a disclosed set of LCDRs, are also provided by the invention.

Typically, a VH domain is paired with a VL domain to provide an antibody antigen-binding site, although as discussed further below a VH or VL domain alone may be used to bind

antigen. The STIM003 VH domain may be paired with the STIM003 VL domain, so that an antibody antigen-binding site is formed comprising both the STIM003 VH and VL domains. Analogous embodiments are provided for the other VH and VL domains disclosed herein. In other embodiments, the STIM003 VH is paired with a VL domain other than the STIM003 VL. Light-chain promiscuity is well established in the art. Again, analogous embodiments are provided by the invention for the other VH and VL domains disclosed herein.

Thus, the VH of any of antibodies STIM001, STIM002, STIM003, STIM004 and STIM005 may be paired with the VL of any of antibodies STIM001, STIM002, STIM003, STIM004 and STIM005. Further, the VH of any of antibodies STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 may be paired with the VL of any of antibodies STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

An antibody may comprise one or more CDRs, e.g. a set of CDRs, within an antibody framework. The framework regions may be of human germline gene segment sequences. Thus, the antibody may be a human antibody having a VH domain comprising a set of HCDRs in a human germline framework. Normally the antibody also has a VL domain comprising a set of LCDRs, e.g. in a human germline framework. An antibody "gene segment", e.g., a VH gene segment, D gene segment, or JH gene segment refers to oligonucleotide having a nucleic acid sequence from which that portion of an antibody is derived, e.g., a VH gene segment is an oligonucleotide comprising a nucleic acid sequence that corresponds to a polypeptide VH domain from FR1 to part of CDR3. Human V, D and J gene segments recombine to generate the VH domain, and human V and J segments recombine to generate the VL domain. The D domain or region refers to the diversity domain or region of an antibody chain. J domain or region refers to the joining domain or region of an antibody chain. Somatic hypermutation may result in an antibody VH or VL domain having framework regions that do not exactly match or align with the corresponding gene segments, but sequence alignment can be used to identify the closest gene segments and thus identify from which particular combination of gene segments a particular VH or VL domain is derived. When aligning antibody sequences with gene segments, the antibody amino acid sequence may be aligned with the amino acid sequence encoded by the gene segment, or the antibody nucleotide sequence may be aligned directly with the nucleotide sequence of the gene segment.

Alignments of STIM antibody VH and VL domain sequences against related antibodies and against human germline sequences are shown in Figure 10, Figure 11 and Figure 12.

An antibody of the invention may be a human antibody or a chimaeric antibody comprising human variable regions and non-human (e.g., mouse) constant regions. The antibody of the invention for example has human variable regions, and optionally also has human constant regions.

Thus, antibodies optionally include constant regions or parts thereof, e.g., human antibody constant regions or parts thereof. For example, a VL domain may be attached at its C-terminal end to antibody light chain kappa or lambda constant domains. Similarly, an antibody VH domain may be attached at its C-terminal end to all or part (e.g. a CH1 domain or Fc region) of an immunoglobulin heavy chain constant region derived from any antibody isotype, e.g. IgG, IgA, IgE and IgM and any of the isotype sub-classes, such as IgG1 or IgG4.

Examples of human heavy chain constant regions are shown in Table S1.

Constant regions of antibodies of the invention may alternatively be non-human constant regions. For example, when antibodies are generated in transgenic animals (examples of which are described elsewhere herein), chimaeric antibodies may be produced comprising human variable regions and non-human (host animal) constant regions. Some transgenic animals generate fully human antibodies. Others have been engineered to generate antibodies comprising chimaeric heavy chains and fully human light chains. Where antibodies comprise one or more non-human constant regions, these may be replaced with human constant regions to provide antibodies more suitable for administration to humans as therapeutic compositions, as their immunogenicity is thereby reduced.

Digestion of antibodies with the enzyme papain, results in two identical antigen-binding fragments, known also as "Fab" fragments, and a "Fc" fragment, having no antigen-binding activity but having the ability to crystallize. "Fab" when used herein refers to a fragment of an antibody that includes one constant and one variable domain of each of the heavy and light chains. The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. The "Fc fragment" refers to the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, the region which is also recognised by Fc receptors (FcR) found on certain types of cells. Digestion of antibodies with the enzyme pepsin, results in the a F(ab')2 fragment in which the two arms of the antibody molecule remain linked and comprise two-antigen binding sites. The F(ab')2 fragment has the ability to crosslink antigen.

"Fv" when used herein refers to the minimum fragment of an antibody that retains both antigen-recognition and antigen-binding sites. This region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent or covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognise and bind antigen, although at a lower affinity than the entire binding site.

Antibodies disclosed herein may be modified to increase or decrease serum half-life. In one embodiment, one or more of the following mutations: T252L, T254S or T256F are introduced to increase biological half-life of the antibody. Biological half-life can also be increased by altering the heavy chain constant region CH_1 domain or CL region to contain a salvage receptor binding epitope taken from two loops of a CH_2 domain of an Fc region of an IgG, as described in U.S. Patent Numbers. 5,869,046 and 6,121,022, the modifications described therein are incorporated herein by reference. In another embodiment, the Fc hinge region of an antibody or antigen-binding fragment of the invention is mutated to decrease the biological half-life of the antibody or fragment. One or more amino acid mutations are introduced into the CH_2-CH_3 domain interface region of the Fc-hinge fragment such that the antibody or fragment has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. Other methods of increasing serum half-life are known to those skilled in the art. Thus, in one embodiment, the antibody or fragment is PEGylated. In another embodiment, the antibody or fragment is fused to an albumin-biding domain, e.g. an albumin binding single domain antibody (dAb). In another embodiment, the antibody or fragment is PASylated (i.e. genetic fusion of polypeptide sequences composed of PAS (XL-Protein GmbH) which forms uncharged random coil structures with large hydrodynamic volume). In another embodiment, the antibody or fragment is XTENylated®/rPEGylated (i.e. genetic fusion of non-exact repeat peptide sequence (Amunix, Versartis) to the therapeutic peptide). In another embodiment, the antibody or fragment is ELPylated (i.e. genetic fusion to ELP repeat sequence (PhaseBio)). These various half-life extending fusions are described in more detail in Strohl, BioDrugs (2015) 29:215–239, which fusions, e.g. in Tables 2 and 6, are incorporated herein by reference.

The antibody may have a modified constant region which increases stabililty. Thus, in one embodiment, the heavy chain constant region comprises a Ser228Pro mutation. In another embodiment, the antibodies and fragments disclosed herein comprise a heavy chain hinge region that has been modified to alter the number of cysteine residues. This modification can be used to facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

The details above may apply to any ICOS modulators or PD-L1 inhibitors that are antibodies.

Fc effector functions, ADCC, ADCP and CDC

As discussed above, anti-ICOS antibodies can be provided in various isotypes and with different constant regions. Examples of human IgG antibody heavy chain constant region sequences are shown in Table S1. The Fc region of the antibody primarily determines its effector function in terms of Fc binding, antibody-dependent cell-mediated cytotoxicity (ADCC)

activity, complement dependent cytotoxicity (CDC) activity and antibody-dependent cell phagocytosis (ADCP) activity. These “cellular effector functions”, as distinct from effector T cell function, involve recruitment of cells bearing Fc receptors to the site of the target cells, resulting in killing of the antibody-bound cell. In addition to ADCC and CDC, the ADCP mechanism [19] represents a means of depleting antibody-bound T cells, and thus targeting high ICOS expressing TRegs for deletion.

Cellular effector functions ADCC, ADCP and/or CDC may also be exhibited by antibodies lacking Fc regions. Antibodies may comprise multiple different antigen-binding sites, one directed to ICOS and another directed to a target molecule where engagement of that target molecule induces ADCC, ADCP and/or CDC, e.g., an antibody comprising two scFv regions joined by a linker, where one scFv can engage an effector cell.

An antibody according to the present invention may be one that exhibits ADCC, ADCP and/or CDC. Alternatively, an antibody according to the present invention may lack ADCC, ADCP and/or CDC activity. In either case, an antibody according to the present invention may comprise, or may optionally lack, an Fc region that binds to one or more types of Fc receptor. Use of different antibody formats, and the presence or absence of FcR binding and cellular effector functions, allow the antibody to be tailored for use in particular therapeutic purposes as discussed elsewhere herein.

A suitable antibody format for some therapeutic applications employs a wild-type human IgG1 constant region. A constant region may be an effector-enabled IgG1 constant region, optionally having ADCC and/or CDC and/or ADCP activity. A suitable wild type human IgG1 contant region sequence is SEQ ID NO: 340 (IGHG1*01). Further examples of human IgG1 constant regions are shown in Table S1.

For testing of candidate therapeutic antibodies in mouse models of human disease, an effector positive mouse constant region, such as mouse IgG2a (mIgG2a), may be included instead of an effector positive human constant region.

A constant region may be engineered for enhanced ADCC and/or CDC and/or ADCP.

The potency of Fc-mediated effects may be enhanced by engineering the Fc domain by various established techniques. Such methods increase the affinity for certain Fc-receptors, thus creating potential diverse profiles of activation enhancement. This can achieved by modification of one or several amino acid residues [20]. Human IgG1 constant regions containing specific mutations or altered glycosylation on residue Asn297 (e.g., N297Q, EU index numbering) have been shown to enhance binding to Fc receptors. Example mutations are one or more of the residues selected from 239, 332 and 330 for human IgG1 constant regions (or the equivalent positions in other IgG isotypes). An antibody may thus comprise a human IgG1 constant region having one or more mutations independently selected from N297Q, S239D, I332E and A330L (EU index numbering). A triple mutation (M252Y/S254T/T256E) may

be used to enhance binding to FcRn, and other mutations affecting FcRn binding are discussed in Table 2 of [21], any of which may be employed in the present invention.

Increased affinity for Fc receptors can also be achieved by altering the natural glycosylation profile of the Fc domain by, for example, generating under fucosylated or de-fucosylated variants [22]. Non-fucosylated antibodies harbour a tri-mannosyl core structure of complex-type N-glycans of Fc without fucose residue. These glycoengineered antibodies that lack core fucose residue from the Fc N-glycans may exhibit stronger ADCC than fucosylated equivalents due to enhancement of FcγRIIIa binding capacity. For example, to increase ADCC, residues in the hinge region can be altered to increase binding to Fc-gamma RIII [23]. Thus, an antibody may comprise a human IgG heavy chain constant region that is a variant of a wild-type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human Fcγ receptors selected from the group consisting of FcyRIIB and FcyRIIA with higher affinity than the wild type human IgG heavy chain constant region binds to the human Fcγ receptors. The antibody may comprise a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain constant region, wherein the variant human IgG heavy chain constant region binds to human FcγRIIB with higher affinity than the wild type human IgG heavy chain constant region binds to human FcγRIIB. The variant human IgG heavy chain constant region can be a variant human IgG1, a variant human IgG2, or a variant human IgG4 heavy chain constant region. In one embodiment, the variant human IgG heavy chain constant region comprises one or more amino acid mutations selected from G236D, P238D, S239D, S267E, L328F, and L328E (EU index numbering system). In another embodiment, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S267E and L328F; P238D and L328E; P238D and one or more substitutions selected from the group consisting of E233D, G237D, H268D, P271G, and A330R; P238D, E233D, G237D, H268D, P271G, and A330R; G236D and S267E; S239D and S267E; V262E, S267E, and L328F; and V264E, S267E, and L328F (EU index numbering system).The enhancement of CDC may be achieved by amino acid changes that increase affinity for C1q, the first component of the classic complement activation cascade [24]. Another approach is to create a chimeric Fc domain created from human IgG1 and human IgG3 segments that exploit the higher affinity of IgG3 for C1q [25]. Antibodies of the present invention may comprise mutated amino acids at residues 329, 331 and/or 322 to alter the C1q binding and/or reduced or abolished CDC activity. In another embodiment, the antibodies or antibody fragments disclosed herein may contain Fc regions with modifications at residues 231 and 239, whereby the amino acids are replaced to alter the ability of the antibody to fix complement. In one embodiment, the antibody or fragment has a constant region comprising one or more mutations selected from E345K, E430G, R344D and D356R, in particular a double mutation comprising R344D and D356R (EU index numbering system).

WO2008/137915 described anti-ICOS antibodies with modified Fc regions having enhanced effector function. The antibodies were reported to mediate enhanced ADCC activity as compared to the level of ADCC activity mediated by a parent antibody comprising the VH and VK domains and a wild type Fc region. Antibodies according to the present invention may employ such variant Fc regions having effector function as described therein.

ADCC activity of an antibody may be determined in an assay as described herein. ADCC activity of an anti-ICOS antibody may be determined *in vitro* using an ICOS positive T cell line as described in Example 10 of WO2018/029474. ADCC activity of an anti-PD-L1 antibody may be determined *in vitro* in an ADCC assay using PD-L1 expressing cells.

For certain applications (such as in the context of vaccination) it may be preferred to use antibodies without Fc effector function. Antibodies may be provided without a constant region, or without an Fc region - examples of such antibody formats are described elsewhere herein. Alternatively, an antibody may have a constant region which is effector null. An antibody may have a heavy chain constant region that does not bind Fcγ receptors, for example the constant region may comprise a Leu235Glu mutation (i.e., where the wild type leucine residue is mutated to a glutamic acid residue). Another optional mutation for a heavy chain constant region is Ser228Pro, which increases stability. A heavy chain constant region may be an IgG4 comprising both the Leu235Glu mutation and the Ser228Pro mutation. This "IgG4-PE" heavy chain constant region is effector null.

An alternative effector null human constant region is a disabled IgG1. A disabled IgG1 heavy chain constant region may contain alanine at position 235 and/or 237 (EU index numbering), e.g., it may be a IgG1*01 sequence comprising the L235A and/or G237A mutations ("LAGA").

A variant human IgG heavy chain constant region may comprise one or more amino acid mutations that reduce the affinity of the IgG for human FcɣRIIIA, human FcɣRIIA, or human FcγRI. In one embodiment, the FcγRIIB is expressed on a cell selected from the group consisting of macrophages, monocytes, B-cells, dendritic cells, endothelial cells, and activated T-cells. In one embodiment, the variant human IgG heavy chain constant region comprises one or more of the following amino acid mutations G236A, S239D, F243L, T256A, K290A, R292P, S298A, Y300L, V305I, A330L, I332E, E333A, K334A, A339T, and P396L (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S239D; T256A; K290A; S298A; I332E; E333A; K334A; A339T; S239D and I332E; S239D, A330L, and I332E; S298A, E333A, and K334A; G236A, S239D, and I332E; and F243L, R292P, Y300L, V305I, and P396L (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region comprises a S239D, A330L, or I332E amino acid mutations (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region comprises an

S239D and I332E amino acid mutations (EU index numbering system). In one embodiment, the variant human IgG heavy chain constant region is a variant human IgG1 heavy chain constant region comprising the S239D and I332E amino acid mutations (EU index numbering system). In one embodiment, the antibody or fragment comprises an afucosylated Fc region. In another embodiment, the antibody or fragment thereof is defucosylated. In another embodiment, the antibody or fragment is under fucosylated.

An antibody may have a heavy chain constant region that binds one or more types of Fc receptor but does not induce cellular effector functions, i.e., does not mediate ADCC, CDC or ADCP activity. Such a constant region may be unable to bind the particular Fc receptor(s) responsible for triggering ADCC, CDC or ADCP activity.

Generating and modifying antibodies

Methods for identifying and preparing antibodies are well known. Antibodies may be generated using transgenic mice (eg, the Kymouse™, Velocimouse® , Omnimouse® , Xenomouse®, HuMab Mouse® or MeMo Mouse®), rats (e.g., the Omnirat®), camelids, sharks, rabbits, chickens or other non-human animals immunised with ICOS or a fragment thereof or a synthetic peptide comprising an ICOS sequence motif of interest, followed optionally by humanisation of the constant regions and/or variable regions to produce human or humanised antibodies. In an example, display technologies can be used, such as yeast, phage or ribosome display, as will be apparent to the skilled person. Standard affinity maturation, e.g., using a display technology, can be performed in a further step after isolation of an antibody lead from a transgenic animal, phage display library or other library. Representative examples of suitable technologies are described in US20120093818 (Amgen, Inc), which is incorporated by reference herein in its entirety, eg, the methods set out in paragraphs [0309] to [0346].

Immunisation of an ICOS knock out non-human animal with human ICOS antigen facilitates the generation of antibodies that recognise both human and non-human ICOS. As described herein and illustrated in the Examples, an ICOS knock out mouse can be immunised with cells expressing human ICOS to stimulate production of antibodies to human and mouse ICOS in the mouse, which can be recovered and tested for binding to human ICOS and to mouse ICOS. Cross-reactive antibodies can thus be selected, which may be screened for other desirable properties as described herein. Methods of generating antibodies to an antigen (e.g., a human antigen), through immunisation of animals with the antigen where expression of the endogenous antigen (e.g, endogenous mouse antigen) has been knocked-out in the animal, may be performed in animals capable of generating antibodies comprising human variable domains. The genomes of such animals can be engineered to comprise a human or humanised immunoglobulin locus encoding human variable region gene segments, and optionally an endogenous constant region or a human constant region. Recombination of the human variable

region gene segments generates human antibodies, which may have either a non-human or human constant region. Non-human constant regions may subsequently be replaced by human constant regions where the antibody is intended for in vivo use in humans. Such methods and knock-out transgenic animals are described in WO2013/061078.

Generally, a Kymouse™, VELOCIMMUNE® or other mouse or rat (optionally an ICOS knock out mouse or rat, as noted) can be challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimaeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

Initially, high affinity chimaeric antibodies are isolated having a human variable region and a mouse constant region. The antibodies are characterised and selected for desirable characteristics, including affinity, selectivity, agonism, T-cell dependent killing, neutralising potency, epitope, etc. The mouse constant regions are optionally replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4 (for example, SEQ ID NO: 751, 752, 753 in US2011/0065902 (which is incorporated by reference herein in its entirety). While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Thus, in a further aspect, the present invention provides a transgenic non-human mammal having a genome comprising a human or humanised immunoglobulin locus, wherein the mammal does not express ICOS. The mammal may for instance be a knock-out mouse or rat, or other laboratory animal species. Transgenic mice such as the Kymouse™ contain human heavy and light chain immunoglobulin loci inserted at the corresponding endogenous mouse immunoglobulin loci. A transgenic mammal according to the present invention may be one that contains such targeted insertions, or it may contain human heavy and light chain immunoglobulin loci or immunoglobulin genes that are randomly inserted in its genome, inserted at a locus other than the endogenous Ig locus, or provided on an additional chromosome or chromosomal fragment.

Further aspects of the invention are the use of such non-human mammals for producing antibodies to ICOS, and methods of producing antibodies or antibody heavy and/or light chain variable domains in such mammals.

A method of producing an antibody that binds the extracellular domain of human and non-human ICOS may comprise providing a transgenic non-human mammal having a genome comprising a human or humanised immunoglobulin locus, wherein the mammal does not express ICOS, and

(a) immunising the mammal with human ICOS antigen (e.g., with cells expressing human ICOS or with purified recombinant ICOS protein);

(b) isolating antibodies generated by the mammal;

(c) testing the antibodies for ability to bind human ICOS and non-human ICOS; and

(d) selecting one or more antibodies that binds both human and non-human ICOS.

Testing for ability to bind human ICOS and non-human ICOS may be done using surface plasmon resonance, HTRF, FACS or any other method described herein. Optionally, binding affinities for human and mouse ICOS are determined. The affinity, or fold-difference in affinity, of binding to human ICOS and mouse ICOS may be determined, and antibodies displaying species cross-reactivity may thus be selected (affinity thresholds and fold-differences that may be used as selection criteria are exemplified elsewhere herein). Neutralising potency, or fold difference in neutralising potency, of the antibody for inhibiting human and mouse ICOS ligand binding to the human and mouse ICOS receptor respectively may also or alternatively be determined as a way to screen for cross-reactive antibodies, e.g., in an HTRF assay. Again, possible thresholds and fold-differences that may be used as selection criteria are exemplified elsewhere herein.

The method may comprise testing the antibodies for ability to bind non-human ICOS from the same species or from a different species as the immunised mammal. Thus, where the transgenic mammal is a mouse (e.g., a Kymouse™), antibodies may be tested for ability to bind mouse ICOS. Where the transgenic mammal is a rat, antibodies may be tested for ability to bind rat ICOS. However, it may be equally useful to determine cross-reactivity of an isolated antibody for non-human ICOS of another species. Thus, antibodies generated in goats may be tested for binding to rat or mouse ICOS. Optionally, binding to goat ICOS may be determined instead or additionally.

In other embodiments, the transgenic non-human mammal may be immunised with non-human ICOS, optionally ICOS of the same mammalian species (e.g., an ICOS knock-out mouse may be immunised with mouse ICOS) instead of human ICOS. Affinity of isolated antibodies for binding to human ICOS and non-human ICOS is then determined in the same way, and antibodies that bind both human and non-human ICOS are selected.

Nucleic acid encoding an antibody heavy chain variable domain and/or an antibody light chain variable domain of a selected antibody may be isolated. Such nucleic acid may encode the full antibody heavy chain and/or light chain, or the variable domain(s) without associated constant region(s). As noted, encoding nucleotide sequences may be obtained directly from

antibody-producing cells of a mouse, or B cells may be immortalised or fused to generate hybridomas expressing the antibody, and encoding nucleic acid obtained from such cells. Optionally, nucleic acid encoding the variable domain(s) is then conjugated to a nucleotide sequence encoding a human heavy chain constant region and/or human light chain constant region, to provide nucleic acid encoding a human antibody heavy chain and/or human antibody light chain, e.g., encoding an antibody comprising both the heavy and light chain. As described elsewhere herein, this step is particularly useful where the immunised mammal produces chimaeric antibodies with non-human constant regions, which are preferably replaced with human constant regions to generate an antibody that will be less immunogenic when administered to humans as a medicament. Provision of particular human isotype constant regions is also significant for determining the effector function of the antibody, and a number of suitable heavy chain constant regions are discussed herein.

Other alterations to nucleic acid encoding the antibody heavy and/or light chain variable domain may be performed, such as mutation of residues and generation of variants, as described herein.

The isolated (optionally mutated) nucleic acid may be introduced into host cells, e.g., CHO cells as discussed. Host cells are then cultured under conditions for expression of the antibody, or of the antibody heavy and/or light chain variable domain, in any desired antibody format. Some possible antibody formats are described herein, e.g., whole immunoglobulins, antigen-binding fragments, and other designs.

Variable domain amino acid sequence variants of any of the VH and VL domains or CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention, as discussed.

There are many reasons why it may be desirable to create variants, which include optimising the antibody sequence for large-scale manufacturing, facilitating purification, enhancing stability or improving suitability for inclusion in a desired pharmaceutical formulation. Protein engineering work can be performed at one or more target residues in the antibody sequence, e.g., to substituting one amino acid with an alternative amino acid (optionally, generating variants containing all naturally occurring amino acids at this position, with the possible exception of Cys and Met), and monitoring the impact on function and expression to determine the best substitution. It is in some instances undesirable to substitute a residue with Cys or Met, or to introduce these residues into a sequence, as to do so may generate difficulties in manufacturing – for instance through the formation of new intramolecular or intermolecular cysteine-cysteine bonds. Where a lead candidate has been selected and is being optimised for manufacturing and clinical development, it will generally be desirable to change its antigen-binding properties as little as possible, or at least to retain the affinity and potency of the parent

molecule. However, variants may also be generated in order to modulate key antibody characteristics such as affinity, cross-reactivity or neutralising potency.

An antibody may comprise a set of H and/or L CDRs of any of the disclosed antibodies with one or more amino acid mutations within the disclosed set of H and/or L CDRs. The mutation may be an amino acid substitution, deletion or insertion. Thus for example there may be one or more amino acid substitutions within the disclosed set of H and/or L CDRs. For example, there may be up to 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 or 2 mutations e.g. substitutions, within the set of H and/or L CDRs. For example, there may be up to 6, 5, 4, 3 or 2 mutations, e.g. substitutions, in HCDR3 and/or there may be up to 6, 5, 4, 3, or 2 mutations, e.g. substitutions, in LCDR3. An antibody may comprise the set of HCDRs, LCDRs or a set of 6 (H and L) CDRs shown for any STIM antibody herein or may comprise that set of CDRs with one or two conservative substitutions.

One or more amino acid mutations may optionally be made in framework regions of an antibody VH or VL domain disclosed herein. For example, one or more residues that differ from the corresponding human germline segment sequence may be reverted to germline. Human germline gene segment sequences corresponding to VH and VL domains of example anti-ICOS antibodies are indicated in Table E12-1, Table E12-2 and Table E12-3, and alignments of antibody VH and VL domains to corresponding germline sequences are shown in the drawings.

An antibody may comprise a VH domain that has at least 60, 70, 80, 85, 90, 95, 98 or 99 % amino acid sequence identity with a VH domain of any of the antibodies shown in the appended sequence listing, and/or comprising a VL domain that has at least 60, 70, 80, 85, 90, 95, 98 or 99 % amino acid sequence identity with a VL domain of any of those antibodies. Algorithms that can be used to calculate % identity of two amino acid sequences include e.g. BLAST, FASTA, or the Smith-Waterman algorithm, e.g. employing default parameters. Particular variants may include one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue) .

Alterations may be made in one or more framework regions and/or one or more CDRs. Variants are optionally provided by CDR mutagenesis. The alterations normally do not result in loss of function, so an antibody comprising a thus-altered amino acid sequence may retain an ability to bind ICOS. It may retain the same quantitative binding ability as an antibody in which the alteration is not made, e.g. as measured in an assay described herein. The antibody comprising a thus-altered amino acid sequence may have an improved ability to bind ICOS.

Alteration may comprise replacing one or more amino acid residue with a non-naturally occurring or non-standard amino acid, modifying one or more amino acid residue into a non-naturally occurring or non-standard form, or inserting one or more non- naturally occurring or non-standard amino acid into the sequence. Examples of numbers and locations of alterations in sequences of the invention are described elsewhere herein. Naturally occurring amino acids

include the 20 "standard" L-amino acids identified as G, A, V, L, I, M, P, F, W, S, T, N, Q, Y, C, K, R, H, D, E by their standard single-letter codes. Non-standard amino acids include any other residue that may be incorporated into a polypeptide backbone or result from modification of an existing amino acid residue. Non-standard amino acids may be naturally occurring or non-naturally occurring.

The term "variant" as used herein refers to a peptide or nucleic acid that differs from a parent polypeptide or nucleic acid by one or more amino acid or nucleic acid deletions, substitutions or additions, yet retains one or more specific functions or biological activities of the parent molecule. Amino acid substitutions include alterations in which an amino acid is replaced with a different naturally-occurring amino acid residue. Such substitutions may be classified as "conservative", in which case an amino acid residue contained in a polypeptide is replaced with another naturally occurring amino acid of similar character either in relation to polarity, side chain functionality or size. Such conservative substitutions are well known in the art. Substitutions encompassed by the present invention may also be "non-conservative", in which an amino acid residue which is present in a peptide is substituted with an amino acid having different properties, such as naturally-occurring amino acid from a different group (e.g., substituting a charged or hydrophobic amino; acid with alanine), or alternatively, in which a naturally-occurring amino acid is substituted with a non- conventional amino acid. In some embodiments amino acid substitutions are conservative. Also encompassed within the term variant when used with reference to a polynucleotide or polypeptide, refers to a polynucleotide or polypeptide that can vary in primary, secondary, or tertiary structure, as compared to a reference polynucleotide or polypeptide, respectively (e.g., as compared to a wild- type polynucleotide or polypeptide).

In some aspects, one can use "synthetic variants", "recombinant variants", or "chemically modified" polynucleotide variants or polypeptide variants isolated or generated using methods well known in the art. "Modified variants" can include conservative or non-conservative amino acid changes, as described below. Polynucleotide changes can result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence. Some aspects use include insertion variants, deletion variants or substituted variants with substitutions of amino acids, including insertions and substitutions of amino acids and other molecules) that do not normally occur in the peptide sequence that is the basis of the variant, for example but not limited to insertion of ornithine which do not normally occur in human proteins. The term "conservative substitution," when describing a polypeptide, refers to a change in the amino acid composition of the polypeptide that does not substantially alter the polypeptide's activity. For example, a conservative substitution refers to substituting an amino acid residue for a different amino acid residue that has similar chemical properties (e.g., acidic, basic, positively or negatively charged, polar or

nonpolar, etc.). Conservative amino acid substitutions include replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine. Conservative substitution tables providing functionally similar amino acids are well known in the art. For example, the following six groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W). (See also Creighton, Proteins, W. H. Freeman and Company (1984), incorporated by reference in its entirety.) In some embodiments, individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids can also be considered "conservative substitutions" if the change does not reduce the activity of the peptide. Insertions or deletions are typically in the range of about 1 to 5 amino acids. The choice of conservative amino acids may be selected based on the location of the amino acid to be substituted in the peptide, for example if the amino acid is on the exterior of the peptide and expose to solvents, or on the interior and not exposed to solvents.

One can select the amino acid that will substitute an existing amino acid based on the location of the existing amino acid, including its exposure to solvents (i.e., if the amino acid is exposed to solvents or is present on the outer surface of the peptide or polypeptide as compared to internally localized amino acids not exposed to solvents). Selection of such conservative amino acid substitutions are well known in the art, for example as disclosed in Dordo et al, J. Mol Biol, 1999, 217, 721-739 and Taylor et al, J. Theor. Biol. 119(1986);205-218 and S. French and B. Robson, J. Mol. Evol. 19(1983)171 . Accordingly, one can select conservative amino acid substitutions suitable for amino acids on the exterior of a protein or peptide (i.e. amino acids exposed to a solvent), for example, but not limited to, the following substitutions can be used: substitution of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P.

In alternative embodiments, one can also select conservative amino acid substitutions encompassed suitable for amino acids on the interior of a protein or peptide, for example one can use suitable conservative substitutions for amino acids is on the interior of a protein or peptide (i.e. the amino acids are not exposed to a solvent), for example but not limited to, one can use the following conservative substitutions: where Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V. In some embodiments, non-conservative amino acid substitutions are also encompassed within the term of variants.

The invention includes methods of producing antibodies containing VH and/or VL domain variants of the antibody VH and/or VL domains shown in the appended sequence listing. Such antibodies may be produced by a method comprising

(i) providing, by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a parent antibody VH domain, an antibody VH domain that is an amino acid sequence variant of the parent antibody VH domain,

wherein the parent antibody VH domain is the VH domain of any of antibodies STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 or a VH domain comprising the heavy chain complementarity determining regions of any of those antibodies,

(ii) optionally combining the VH domain thus provided with a VL domain, to provide a VH/VL combination, and

(iii) testing the VH domain or VH/VL domain combination thus provided to identify an antibody with one or more desired characteristics.

Desired characteristics include binding to human ICOS, binding to mouse ICOS, and binding to other non-human ICOS such as cynomolgus ICOS. Antibodies with comparable or higher affinity for human and/or mouse ICOS may be identified. Other desired characteristics include increasing effector T cell function indirectly, via depletion of immunosuppressive TRegs, or directly, via ICOS signalling activation on T effector cells. Identifying an antibody with a desired characteristic may comprise identifying an antibody with a functional attribute described herein, such as its affinity, cross-reactivity, specificity, ICOS receptor agonism, neutralising potency and/or promotion of T cell dependent killing, any of which may be determined in assays as described herein.

When VL domains are included in the method, the VL domain may be a VL domain of any of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or may be a variant provided by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a parent VL domain, wherein the parent VL domain is the VL domain of any of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 or a VL domain comprising the light chain complementarity determining regions of any of those antibodies.

Methods of generating variant antibodies may optionally comprise producing copies of the antibody or VH/VL domain combination. Methods may further comprise expressing the resultant antibody. It is possible to produce nucleotide sequences corresponding to a desired antibody VH and/or VL domain, optionally in one or more expression vectors. Suitable methods of expression, including recombinant expression in host cells, are set out in detail herein.

Encoding nucleic acids and methods of expression

Isolated nucleic acid may be provided, encoding antibodies according to the present invention. Nucleic acid may be DNA and/or RNA. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode an antibody.

The present invention provides constructs in the form of plasmids, vectors, transcription or expression cassettes which comprise at least one polynucleotide as above. Exemplary nucleotide sequences are included in the sequence listing. 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.

The present invention also provides a recombinant host cell that comprises one or more nucleic acids encoding the antibody. Methods of producing the encoded antibody may comprise expression from the nucleic acid, e.g., by culturing recombinant host cells containing the nucleic acid. The antibody may thus be obtained, and may be isolated and/or purified using any suitable technique, then used as appropriate. A method of production may comprise formulating the product into a composition including at least one additional component, such as a pharmaceutically acceptable excipient.

Systems for cloning and expression of a polypeptide in a variety of different host cells are well known. Suitable host cells include bacteria, mammalian cells, plant cells, filamentous fungi, yeast and baculovirus systems and transgenic plants and animals.

The expression of antibodies and antibody fragments in prokaryotic cells is well established in the art. A common bacterial host is E. coli. Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production. Mammalian cell lines available in the art for expression of a heterologous polypeptide include Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney cells, NSO mouse melanoma cells, YB2/0 rat myeloma cells, human embryonic kidney cells, human embryonic retina cells and many others.

Vectors may contain appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Nucleic acid encoding an antibody can be introduced into a host cell. Nucleic acid can be introduced to eukaryotic cells by various methods, including calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, e.g. vaccinia or, for insect cells, baculovirus. Introducing nucleic acid in the host cell, in particular a eukaryotic cell may use a viral or a plasmid based system. The plasmid system may be maintained episomally or may be incorporated into the host cell or into an artificial chromosome. Incorporation may be either by random or targeted integration of one or more copies at single or multiple loci. For bacterial

cells, suitable techniques include calcium chloride transformation, electroporation and transfection using bacteriophage. The introduction may be followed by expressing the nucleic acid, e.g., by culturing host cells under conditions for expression of the gene, then optionally isolating or purifying the antibody.

Nucleic acid of the invention may be integrated into the genome (e.g. chromosome) of the host cell. Integration may be promoted by inclusion of sequences that promote recombination with the genome, in accordance with standard techniques.

The present invention also provides a method that comprises using nucleic acid described herein in an expression system in order to express an antibody.

Therapeutic Use

An antibody described herein may be used in a method of treatment of the human or animal body by therapy, in particular in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression. The antibodies may find use in increasing effector T cell response, which is of benefit for a range of diseases or conditions, including treating cancers or solid tumours and in the context of vaccination. Increased Teff response may be achieved using an antibody that modulates the balance or ratio between Teffs and Tregs in favour of Teff activity.

Anti-ICOS antibodies may be used for depleting regulatory T cells and/or increasing effector T cell response in a patient, and may be administered to a patient to treat a disease or condition amenable to therapy by depleting regulatory T cells and/or increasing effector T cell response.

Generally speaking, the present invention relates to treatment of cancer that are PD-L1 negative or exhibit a low PD-L1 expression. In particular, the present invention relates to the treatment of cancer in patients having a tumour that is PD-L1 negative or exhibits a low PD-L1 expression. The methods comprise administration of a modulator of ICOS to the patient. The tumour cells and/or the tumour-associated immune cells may be PD-L1 negative or may exhibit low PD-L1 expression.

In some embodiments, the patient has or has had a tumour sample tested for PD-L1 expression. This testing may occur at screening, that is the patient is screened fro PD-L1 expression prior to treatment with the ICOS-modulator. In some embodiments, the invention relates to a method of selecting a patient for treatment for cancer, wherein the patient is selected for treatment with an anti-ICOS antibody and optionally an anti-PD-L1 antibody, irrespective of the PD-L1 expression status in a tumour sample from the patient, optionally wherein a sample of a tumour from the patient is determined to be PD-L1 negative or low expressing, or wherein PD-L1 expression status of a tumour sample from the patient is not determined prior to selecting the patient for treatment. Given the present invention provides

methods of treating even no or low-expressing PD-L1 tumours, screening for PD-L1 expression might not be necessary. The method may optionally further comprising administering to the patient an ICOS modulator (for example an anti-ICOS antibody such as an agonistic anti-ICOS antibody) and optionally a PD-L1 inhibitor (such as an anti-PD-L1 or anti-PD-1 antibody).

In some embodiments, the cancer may be associated with infectious agents. The cancer may be a virally-induced cancer. In some embodiments, the virus associated with the virally-induced cancer may be selected from HBV, HCV, HPV (such as cervical cancer, oropharyngeal cancer), and EBV (such as Burkitts lymphomas, gastric cancer, Hodgkin's lymphoma, other EBV positive B cell lymphomas, nasopharyngeal carcinoma and post-transplant lymphoproliferative disease). In some embodiments, the cancer may be selected from the group consisting of head and neck squamous cell carcinoma, cervical cancer, anogenital cancer and oropharyngeal cancer.

In some embodiments, the patient has, or has had, a tumour sample tested for HPV. In some embodiments the tumour is HPV positive. In some embodiments, the tumour is HPV negative. This testing may occur at screening, that is the patient is screened for HPV prior to treatment with the ICOS-modulator, or the HPV status of the tumour may be determined from historical patient data. In some embodiments the methods further comprise a step of determining the HPV status of the tumour. A "HPV positive" tumor is deemed to be associated with or derived from HPV infection. A "HPV negative" tumor is deemed not to be associated with or derived from HPV infection. In some embodiments the tumour cells are PD-L1 negative or exhibit low PD-L1 expression and the tumour is HPV (Human papillomavirus) positive.

In some embodiments, the patient has undergone a test for an infection, for example HPV, HBV, HCV, or EBV infection. In some embodiments the patient has undergone a test for HPV infection. In some embodiments the patient has an HPV infection or has had an HPV infection. Determining if a patient has, or has had, an HPV infection may be using tests known in the art, for example, testing of cells taken from a sample from a patient or DNA analysis of a sample taken from the patient. In some embodiments, the methods further comprise a step of determining the HPV status of the patient.

In some embodiments, the present invention relates to treatment of cancer in a patient who has previously received treatment for the cancer, wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor and the patient did not respond to the previous treatment or ceased responding to the previous treatment, comprising administering to the patient an modulator inhibitor of ICOS. In other words, the cancer may be or may be characterised as refractory to PD-L1 inhibitor treatment. In some embodiments, the cancer may be or may be characterised as refractor to PD-L1 immunotherapy (for example anti-PD-L1 antibody or anti-PD-1 antibody treatment). In some embodiments, the patient may have previously received PD-L1 inhibitor treatment as the sole immunotherapy. Generally the cancer

will be or will have been characterised as a PD-L1 negative cancer or a cancer that exhibits low PD-L1 expression. The present invention therefore includes the use of ICOS modulators as second- or further-line treatment.

In some embodiments, the invention relates to treatment of patients having cancer who have previously been administered a kinase inhibitor (in addition or instead of a PD-L1 inhibitor). In some embodiments the patients may have received surgical treatment for the cancer (for example complete or partial tumour resection) and/or radiotherapy and/or chemotherapy. The chemotherapy may be docetaxel, fluorouracil, cisplatin, paclitaxel and/or nab-paclitaxel. The cancer may be or may have been characterised as refractory to one or all of the previous treatments, or may have stopped responding to the previous treatment(s). In some embodiments, the cancer is or has been characterised as refractory to PD-L1 inhibitor monotherapy treatment. In some embodiments, the cancer is or has been characterised as refractory to treatment with a PD-L1 inhibitor as the sole immunotherapy agent. In some embodiments, the cancer is or has been characterised as refractory to treatment with nivolumab.

In some embodiments, the methods comprise a step of determing the level of PD-L1 expression. This may be done on a tumour sample from the patient. In some embodiments, the methods comprise obtaining a tumour sample from the patient. In some embodiments, the methods may be conducted on a tumour sample previously obtained from the patient. Tumour samples may be any suitable samples for example a tumour tissue sample such as a tumour biopsy. The tumour sample may be a sample of tumour cells.

If a determination is made that the cancer is PD-L1 negative or exhibits low PD-L1 expression, the ICOS modulator (such as an agonistic anti-ICOS antibody) may be administered, or the patient may be recommended for such a treatment, or a report may be generated recommending the patient for such treatment (the present invention therefore extending to the provision of such reports).

A determination of PD-L1 expression status (i.e. whether the cancer or tumour is PD-L1 negative or exhibits low PD-L1 expression) may be determined by any suitable means. In some embodiments, the detemination of PD-L1 expression status may be conducted on a tumour sample (for example a tumour biopsy). In some embodiments, the PD-L1 expression status may be determined by immunohistochemistry (IHC). The sample may be prepared for analysis using IHC, for example slicing and fixing.

The sample may be analysed to determined the number of cells in the tumour sample (for example the number of tumour cells and/or tumour-associted immune cells) that express PD-L1. In some embodiments, the method determines the ratio (e.g. percentage) of tumour cells in the tumour sample that express PD-L1 to tumours cells in the tumour sample that do not express PD-L1. In some embodients, the method the method determines the ratio (e.g.

percentage) of tumour cells in the tumour sample and tumour-assocaited immunce cells in the tumour sample that express PD-L1 to total number of tumour and tumour-assocaited immune cells in the sample.

Generally speaking, the number of tumour and/or tumour-associated immune cells I nthe tumour sample that express PD-L1 will be considered representative of the tumour as a whole.

Generally, for a PD-L1 negative tumour (i.e. a tumour that does not express PD-L1), 0% of the cells (i.e. tumour cells and/or tumour-asscociated immune cells) will express PD-L1.

Different cut-off points may be employed to determine whether a cancer or tumour is a "low" PD-L1 expressing tumour. In some embodiments, the cancer or tumour may be considered a low PD-L1 expressing tumour when about 25% or less of the tumour cells (in the tumour tissue sample or sampled tumour cells) express PD-L1. In some embodiments, a cut-off of less than about 20%, less than about 15%, less than about 10%, less than about 5%, less that about 4%, less than about 3%, less than about 2% or less than about 1% of the tumour cells (in the tumour tissue sample or sampled tumour cells) express PD-L1. In some embodiments, the cancer or tumour may be considered a low PD-L1 expressing tumour when about 25% or less of the tumour-associated immune cells (in the tumour tissue sample or sampled tumour cells) express PD-L1. In some embodiments, a cut-off of less than about 20%, less than about 15%, less than about 10%, less than about 5%, less that about 4%, less than about 3%, less than about 2% or less than about 1% of the tumour-associated immune cells (in the tumour tissue sample or sampled tumour cells) express PD-L1. In some embodiments, the cancer or tumour may be considered a low PD-L1 expressing tumour when about 25% or less of the tumour cells and tumour-associated immune cells (in the tumour tissue sample or sampled tumour cells) express PD-L1. In some embodiments, a cut-off of less than about 20%, less than about 15%, less than about 10%, less than about 5%, less that about 4%, less than about 3%, less than about 2% or less than about 1% of the tumour cells and tumour-associated immune cells (in the tumour tissue sample or sampled tumour cells) express PD-L1. Generally, any non-tumour associated immune cells that may be present in the tumour sample or sample of tumour cells may be excluded (for example neutrophils).

The PD-L1 expression may be calculated or expressed as a percentage. In some embodiments, the percentage of PD-L1 expression (i.e. the percentage of analysed cells that express PD-L1) may be determined according to the following formula: (number of PD-L1 positive tumour cells in the tumour tissue sample or sample of tumour cells / total number of tumour cells in the tumour tissue sample or sample of tumour cells) x 100. In some embodiments, the percentage of PD-L1 expression (i.e. the percentage of analysed cells that express PD-L1) may be determined according to the following formula: (number of PD-L1 positive tumour cells and number of PD-L1 positive tumour-associated immune cells in the tumour tissue sample or sample of tumour cells / total number of tumour cells and tumour-

associated immune in the tumour tissue sample or sample of tumour cells) x 100. Non-tumour associated immune cells (e.g. neutrophils) are generally excluded from the calculation.

The cancer or tumour may be a CD8+ cancer or tumour. In some embodiments, at least 50% of the T-cells in the tumour may be CD8+. CD8 expression status of a cancer or tumour (that is the CD8 expression status of the T cells in the tumour) may be determined by any suitable means, for example by IHC, such as on a tumour sample or sample or tumour cells. In some embodiments, in particular although not limited to embodiments in which expression status is determined using IHC performed on a slice of tumour, the tumour sample or sample of tumour cells may comprise at least 190 cells CD8+ T-cells per mm^2.

The cancer or tumour may be an ICOS+ cancer or tumour, i.e. a cancer or tumour comprising ICOS+ immune cells, e.g. T-cells (more specifically, ICOS+ Treg cells in the tumour microenvironment). In some embodiments, at least 50% of the T-cells (i.e. Tregs) in the tumour may be ICOS+. ICOS expression status of a cancer or tumour (that is the ICOS expression status of the T cells in the tumour) may be determined by any suitable means, for example by IHC, such as on a tumour sample or sample or tumour cells. In some embodiments, the patient may have increased levels of ICOS+ immune cells (such as ICOS+ regulatory T cells in the TME) following treatment with another therapeutic agent. In some embodiments, the methods comprise administering a therapeutic agent to the patient, determining that the patient has an increased level of ICOS-positive+ immune cells (such as ICOS+ regulatory T cells) following the treatment with said agent, and administering an modulator of ICOS (for example an anti-ICOS antibody such as an agonistic anti-ICOS antibody) to the patient to reduce the level of ICOS+ regulatory T cells. In some embodiments, wherein the therapeutic agent is IL-2 or an immunomodulatory antibody (e.g., anti-PDL-1, anti-PD-1 or anti-CTLA-4).

Tumour associated immune cells may also be referred to herein as tumour-infiltrating lymphocytes (TILs) or simply immune cells in the tumour or in the tumour microenvironment (TME).

An antibody disclosed herein, or a composition comprising such an antibody molecule or its encoding nucleic acid, may be used or provided for use in any such method. Use of the antibody, or of a composition comprising it or its encoding nucleic acid, for the manufacture of a medicament for use in any such method is also envisaged. The method typically comprises administering the antibody or composition to a mammal. Suitable formulations and methods of administration are described elsewhere herein.

The cancer may be a solid tumour, e.g., renal cell cancer (optionally renal cell carcinoma, e.g., clear cell renal cell carcinoma), head and neck cancer, melanoma (optionally malignant melanoma), non-small cell lung cancer (e.g., adenocarcinoma), bladder cancer, ovarian cancer, cervical cancer, gastric cancer, liver cancer, pancreatic cancer, breast cancer, testicular germ cell carcinoma, or the metastases of a solid tumour such as those listed, or it

may be a liquid haematological tumour e.g., lymphoma (such as Hodgkin's lymphoma or Non-Hodgkin's lymphoma, e.g., diffuse large B-cell lymphoma, DLBCL) or leukaemia (e.g., acute myeloid leukaemia). An anti-ICOS antibody may enhance tumour clearance in melanoma, head and neck cancer and non-small cell lung cancer and other cancers with a moderate to high mutational load [26]. By enhancing patients' immune response to their neoplastic lesions, immunotherapy using an anti-ICOS antibody offers the prospect of durable cures or long-term remissions, potentially even in the context of late stage disease.

Cancers are a diverse group of diseases, but anti-ICOS antibodies offer the possibility of treating a range of different cancers by exploiting the patient's own immune system, which has the potential to kill any cancer cell through recognition of mutant or overexpressed epitopes that distinguish cancer cells from normal tissue. By modulating the Teff/Treg balance, anti-ICOS antibodies can enable and/or promote immune recognition and killing of cancer cells. While anti-ICOS antibodies are therefore useful therapeutic agents for a wide variety of cancers, there are particular categories of cancers for which anti-ICOS therapy is especially suited and/or where anti-ICOS therapy can be effective when other therapeutic agents are not.

One such group is cancer that is positive for expression of ICOS ligand. Cancer cells may acquire expression of ICOS ligand, as has been described for melanoma [27]. Expression of ICOS ligand may provide the cells with a selective advantage as the surface-expressed ligand binds ICOS on Tregs, promoting the expansion and activation of the Tregs and thereby suppressing the immune response against the cancer. Cancer cells expressing ICOS ligand may depend for their survival on this suppression of the immune system by Tregs, and would thus be vulnerable to treatment with anti-ICOS antibodies that target the Tregs. This applies also to cancers derived from cells that naturally express ICOS ligand. Continued expression of ICOS ligand by these cells again provides a survival advantage through immune suppression. A cancer expressing ICOS ligand may be derived from antigen-presenting cells such as B cells, dendritic cells and monocytes and may be a liquid haematological tumour such as those mentioned herein. Interestingly it has been shown that these types of cancer are also high in ICOS and FOXP3 expression (TCGA data) – see Example 25 of WO2018/029474. Example 20 of WO2018/029474demonstrates efficacy of exemplary anti-ICOS antibodies in treating tumours derived from cancerous B cells (A20 syngeneic cells) that express ICOS ligand.

Accordingly, anti-ICOS antibodies can be used in methods of treating cancers that are positive for expression of ICOS ligand. Further, a cancer to be treated with anti-ICOS antibody according to the present invention may be one that is positive for expression of ICOS and/or FOXP3, and optionally also expresses ICOS ligand.

Patients may undergo testing to determine whether their cancer is positive for expression of the protein of interest (e.g., ICOS ligand, ICOS, FOXP3 and/or CD8) or is positive, negative, or low expression for PD-L1, for example by taking a test sample (e.g.,

tumour biopsy) from the patient and determining expression of the protein of interest. Patients whose cancer has been characterised as negative for PD-L1, or has been characterised as having a low PD-L1 expression, are selected for treatment. Optionally, patients whose cancer has been also been characterised as positive for expression of one, two or all such proteins of interest (.g., ICOS ligand, ICOS, FOXP3 and/or CD8) are selected for treatment with anti-ICOS antibody. As discussed elsewhere herein, anti-ICOS antibody may be used as a monotherapy or in combination with one or more other therapeutic agents.

Anti-ICOS antibodies also offer hope to patients whose cancers are refractory to treatment with antibodies or other drugs directed to immune checkpoint molecules such as CTLA-4, PD-1, PD-L1, CD137, GITR or CD73, but in particular to cancers that are refractory to PD-L1 inhibitors. These immunotherapies are effective against some cancers but in some cases a cancer may not respond, or it may become unresponsive to continued treatment with the antibody. In common with antibodies to immune checkpoint inhibitors, anti-ICOS antibodies modulate the patient's immune system – nevertheless an anti-ICOS antibody may succeed where such other antibodies fail. It is shown herein that animals carrying A20 B cell lymphomas could be treated with anti-ICOS antibodies to reduce growth of the tumour, shrink the tumour and indeed clear the tumour from the body, whereas treatment with an anti-PD-L1 antibody was no better than control. The A20 cell line has also been reported to be resistant to anti-CTLA-4 [28].

Accordingly, anti-ICOS antibodies can be used in methods of treating cancers that are refractory to treatment with one or more immunotherapies, such as (any or all of) an anti-CTLA-4 antibody, anti-PD1 antibody, anti-PD-L1 antibody, anti-CD137 antibody, anti-GITR antibody, or anti-CD73 antibody, although in particular refractory to PD-L1 inhibitors, sich as anti-PD1 or anti-PD-L1 antibodies. A cancer may be characterised as being refractory to treatment with an antibody or other drug if treatment with that antibody or drug does not significantly reduce growth of the cancer, e.g., if a tumour continues to grow or does not reduce in size or if after a response period the tumour re-initiates its growth. Non-response to a therapeutic agent may be determined ex vivo by testing a sample (e.g., tumour biopsy sample) for cancer cell killing or growth inhibition, and/or in the clinical setting by observing (e.g., using an imaging technology, including MRI) that a patient treated with the therapy is not responding to treatment. Patients whose cancer has been characterised as refractory to treatment with such an immunotherapy are selected for treatment with anti-ICOS antibody.

Samples obtained from patients may thus be tested to determine surface expression of a protein of interest, for example ICOS ligand, ICOS, FOXP3 and/or a target receptor to which another therapeutic agent (e.g., anti-receptor antibody) is directed. Surface expression of ICOS ligand, ICOS, FOXP3 and/or lack or loss of surface expression of the target receptor is an indication that the cancer is susceptible to anti-ICOS antibody therapy. Anti-ICOS antibodies

can be provided for administration to a patient whose cancer is characterised by surface expression of ICOS ligand, ICOS, FOXP3 and/or lack or loss of surface expression of a target receptor, optionally where the patient has been previously treated with anti-PD1, anti-PD-L1 or with an antibody to the target receptor and has not responded or has stopped responding to treatment with that antibody, as measured for example by continued or renewed cancer cell growth, e.g., increase in tumour size.

Any suitable method may be employed to determine whether cancer cells test positive for surface expression of a protein such as ICOS ligand, PD-L1 or other target receptors mentioned herein. A typical method is immunohistochemistry, where a sample of the cells (e.g., a tumour biopsy sample) is contacted with an antibody for the protein of interest, and binding of antibody is detected using a labelled reagent – typically a second antibody that recognises the Fc region of the first antibody and carries a detectable label such as a fluorescent marker. A sample may be declared to test positive for ICOS or PD-L1 where at least a certain percentage of cells are labelled, as visualised by cell staining or other detection of the label. The antibody will generally be used in excess. Reagent antibodies to the molecules of interest are available or may be generated by straightforward methods. To test for ICOS ligand, the antibody MAB1651 is currently available from R&D systems as a mouse IgG that recognises human ICOS ligand. To test for PD-L1, the antibody SP263, currently available from Roche as a rabit monoclonal primary antibody that recognises human PD-L1, may be used.Detection of mRNA levels of the ICOS ligand or PD-L1 or target receptor of interest is an alternative technique [27].

A further indication that a tumour will respond to treatment with anti-ICOS antibody is the presence of Tregs in the tumour microenvironment. Activated Tregs are characterised by ICOS-high and Foxp3-high surface expression. The presence of Tregs in a tumour, especially in elevated numbers, provides a further basis on which a patient may be selected for treatment with anti-ICOS antibody. Tregs may be detected in a tumour biopsy sample ex vivo, for example by immunohistochemistry (assaying for co-expression of both Foxp3 and ICOS, using antibodies to the target protein followed by detection of labels, as described above) or by single cell dispersion of the sample for use in FACS with labelled antibodies to ICOS and Foxp3. FACS methods are exemplified in Example 17 and Example 18 of WO2018/029474.In some embodiments, treatment with the ICOS modulator (and optionally the PD-L1 inhibitor) may cause a reduction in the size of tumour (compared to the size of the tumour at the onsent of treatment). In some embodiments, treatment with the ICOS modulator (and optionally the PD-L1 inhibitor) may inhibit tumour growth. In some embodiments, treatment with the ICOS modulator (and optionally the PD-L1 inhibitor) may result in stable disease. Stable disease may be regarded as the tumour does not grow in size by more than 20% since the onset of treatment and does not shrink in size by more than 30% since the onsent of treatment. In some

embodiments, treatment with the ICOS modulator (and optionally the PD-L1 inhibitor) may extend the survival of the patient and/or delay disease progression.

The ICOS modulators such as anti-ICOS antibodies may be used for treating cancers associated with infectious agents, such as virally-induced cancers e.g. cancers that are caused by infection with a virus. In this category are head and neck squamous cell carcinoma, cervical cancer, Merkel cell carcinoma and many others. Viruses associated with cancer include HBV, HCV, HPV (cervical cancer, oropharyngeal cancer), and EBV (Burkitts lymphomas, gastric cancer, Hodgkin's lymphoma, other EBV positive B cell lymphomas, nasopharyngeal carcinoma and post transplant lymphoproliferative disease). The International Agency for Research on Cancer (Monograph 100B) identified the following major cancer sites associated with infectious agents:

- Stomach/Gastric: Heliobacter pylori
- Liver: Hepatitis B virus, hepatitis C virus (HCV), Opisthorchis viverrini, Clonorchis sinensis
- Cervix uteri: Human papillomavirus (HPV) with or without HIV
- Anogenital (penile, vulva, vagina, anus): HPV with or without HIV
- Nasopharynx: Epstein-Barr virus (EBV)
- Oropharynx: HPV with or without tobacco or alcohol consumption
- Kaposi's sarcoma: Human herpes virus type 8 with or without HIV
- Non-Hodgkin lymphoma: H. pylori, EBV with or without HIV, HCV, human T-cell lymphotropic virus type 1
- Hodgkin's lymphoma: EBV with or without HIV
- Bladder: Schistosoma haematobium.

Antibodies according to the present invention may be used for treating cancer associated with or induced by any of these infectious agents, such as the cancers specified above.

In some embodiments, the cancer is liver cancer, renal cell cancer, head and neck cancer, melanoma, non small cell lung cancer, diffuse large B-cell lymphoma, breast cancer, penile cancer, pancreatic cancer or oesophageal cancer. In some embodiments, the liver cancer is hepatocellular carcinoma. In some embodiments the head and neck cancer is metastatic squamous cell carcinoma. In some embodiments, the breast cancer is triple negative breast cancer. The present invention may be particular relevant to solid cancers.

Stimulation of effector T cell response can also contribute to immunity against infectious disease and/or to recovery from infectious disease in a patient. Thus, an anti-ICOS antibody may be used for treating infectious disease by administering the antibody to a patient.

Infectious diseases include those caused by pathogens, e.g., bacterial, fungal, viral or protozoal pathogens, and treatment may be to promote immune response in a patient against

the pathogen infection. An example of a bacterial pathogen is tuberculosis. Examples of viral pathogens are hepatitis B and HIV. Examples of protozoal pathogens are Plasmodium species, which cause malaria, such as P. falciparum.

The antibody may be used for treating infections, e.g., infection by any pathogen mentioned herein. Infection may be persistent or chronic infection. Infection may be localised or systemic. Extended contact between a pathogen and the immune system may lead to exhaustion of the immune system or development of tolerance (manifested for example through increased levels of Tregs, and tipping of the Treg:Teff balance in favour of Tregs) and/or to immune evasion by the pathogen, through evolution and modification of displayed pathogen antigens. These features reflect similar processes that are believed to occur in cancer. Anti-ICOS antibodies present a therapeutic approach to treating infection by a pathogen, e.g., chronic infection, through modulation of the Treg:Teff ratio in favour of Teff and/or other effects described herein.

Treatment may be of patients who have been diagnosed as having an infectious disease or an infection. Alternatively, treatment may be preventative, and administered to a patient to guard against contracting a disease, e.g., as a vaccine, as described elsewhere herein.

The present invention also provides an ICOS modulator for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression. The present invention also provides an ICOS modulator for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor. The present invention also provides use of an ICOS inhibitor modulator in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression. The present invention also provides use of an ICOS inhibitor in the manufacture of a medicament for the treatment of cancer in a patient, wherein the cancer is refractory to PD-L1 inhibitor treatment or has been characterised as being refractory to PD-L1 inhibitor treatment. The present invention also provides use of an ICOS inhibitor modulator in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor. In some embodiments, the ICOS modulator is for use in combination with a PD-L1 inhibitor. In some embodiments, the ICOS modulator is an agonistic anti-ICOS antibody. In some embodiments, the ICOS modulator is a bispecific antibody that is an anti-ICOS agonist and an anti-PD-L1 antagonist or a bispecific antibody that is an anti-ICOS agonist and an anti-PD-1 antagonist. Generally, the cancer (such as a solid cancer) will be a PD-L1 negative cancer or a cancer with low-PD-L1 expression.

Combination therapy

It may be advantageous to combine an anti-ICOS antibody with such an immunomodulator to enhance its therapeutic effects. In particular, the present invention relates in some embodiments to the combination of an ICOS modulator (such as an anti-ICOS antibody, for example an agonistic anti-ICOS antibody) and a PD-L1 inhibitor, i.e a PD-1 or PD-L1 binder that inhibits the bindig of PD-L1 to PD-1 (for example an anti-PD-L1 or anti-PD-1 antibody). In combination therapites, the modulator of ICOS and inhibitor of PD-L1 may be administered simultaneously, separately or sequentially

A patient who has been treated with an immunomodulatory antibody (e.g., anti-PDL-1, anti-PD-1, anti-CTLA-4) may particularly benefit from treatment with an anti-ICOS antibody. One reason for this is that an immunomodulatory antibody may increase the number of ICOS-positive Tregs (e.g., intratumoural Tregs) in the patient. This effect is also observed with certain other therapeutic agents, such as recombinant IL-2. Anti-ICOS antibody may reduce and/or reverse a surge or rise in ICOS+ Tregs (e.g., intratumoural Tregs) resulting from treatment of the patient with another therapeutic agent. A patient selected for treatment with an anti-ICOS antibody may thus be one who has already received treatment with a first therapeutic agent, the first therapeutic agent being an antibody (e.g., immunomodulator antibody) or other agent (e.g., IL-2) that increases the number of ICOS+ Tregs in the patient.

Immunomodulators with which an anti-ICOS antibody may be combined include antibodies to any of: PDL1 (e.g., avelumab), PD-1 (e.g., pembrolizumab or nivolumab) or CTLA-4 (e.g., ipilimumab or tremelimumab). An anti-ICOS antibody may be combined with pidilizumab. In other embodiments, an anti-ICOS antibody is not administered in combination with anti-CTLA-4 antibody, and/or optionally is administered in combination with a therapeutic antibody that is not an anti-CTLA-4 antibody.

For example, an anti-ICOS antibody may be used in combination therapy with an anti-PDL1 antibody. Preferably, the anti-ICOS antibody is one that mediates ADCC, ADCP and/or CDC. Preferably, the anti-PDL1 antibody is one that mediates ADCC, ADCP and/or CDC. An example of such combination therapy is administration of an anti-ICOS antibody with an anti-PDL1 antibody wherein both antibodies have effector positive constant regions. Thus, the anti-ICOS antibody and the anti-PDL1 antibody may both be able to mediate ADCC, CDC and/or ADCP. Fc effector function and selection of constant regions is described in detail elsewhere herein, but as one example an anti-ICOS human IgG1 may be combined with an anti-PD-L1 human IgG1. The anti-ICOS antibody and/or the anti-PD-L1 antibody may comprise a wild type human IgG1 constant region. Alternatively, the effector positive constant region of an antibody may be one that is engineered for enhanced effector function, e.g., enhanced CDC, ADCC and/or ADCP. Example antibody constant regions, including wild type human IgG1 sequences and

mutations that alter effector function, are discussed in detail elsewhere herein.

Anti-PDL1 antibodies with which an anti-ICOS antibody may be combined include:

- Anti-PDL1 antibody that inhibits binding of PD-1 to PDL1 and/or inhibits PDL1, optionally as effector positive human IgG1;
- Anti-PD-1 antibody that inhibits binding of PD-1 to PDL1 and/or PDL2;
- Avelumab, a human IgG1 antibody which inhibits PD-1 binding to PDL-1. See WO2013/079174;
- Durvalumab (or "MEDI4736"), a variant human IgG1 antibody having mutations L234A, L235A and 331. See WO2011/066389;
- Atezolizumab, a variant human IgG1 antibody having mutations N297A, D356E and L358M. See US2010/0203056;
- BMS-936559, a human IgG4 antibody comprising mutation S228P. See WO2007/005874.

Numerous further examples of anti-PD-L1 antibodies are disclosed herein and others are known in the art. Characterisation data for many of the anti-PD-L1 antibodies mentioned here has been published in US9,567,399 and US9,617,338, both incorporated by reference herein. Example anti-PD-L1 antibodies have VH and/or VL domains comprising the HCDRs and/or LCDRs of any of 1D05, 84G09, 1D05 HC mutant 1, 1D05 HC mutant 2, 1D05 HC mutant 3, 1D05 HC mutant 4, 1D05 LC mutant 1, 1D05 LC mutant 2, 1D05 LC mutant 3, 411B08, 411C04, 411D07, 385F01, 386H03, 389A03, 413D08, 413G05, 413F09, 414B06 or 416E01 as set out in US9,567,399 or US9,617,338. The antibody may comprise the VH and VL domain of any of these antibodies, and may optionally comprise a heavy and/or light chain having the heavy and/or light chain amino acid sequence of any of these antibodies. VH and VL domains of these anti-PD-L1 antibodies are further described elsewhere herein.

Further example anti-PD-L1 antibodies have VH and/or VL domains comprising the HCDRs and/or LCDRs of KN-035, CA-170, FAZ-053, M7824, ABBV-368, LY-3300054, GNS-1480, YW243.55.S70, REGN3504, or of an anti-PD-L1 antibody disclosed in any of WO2017/034916, WO2017/020291, WO2017/020858, WO2017/020801, WO2016/111645, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630, WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 and WO2007/005874. The antibody may comprise the VH and VL domain of any of these antibodies, and may optionally comprise a heavy and/or light chain having the heavy and/or light chain amino acid sequence of any of these antibodies.The anti-ICOS antibody which is used in combination therapy with anti-PD-L1 may be an antibody of the present invention as disclosed herein.

Alternatively, the anti-ICOS antibody may comprise the CDRs of, or a VH and/or VL domain of, an anti-ICOS antibody disclosed in any of the following publications:
WO2016154177, US2016304610 - for example any of antibodies 7F12, 37A10, 35A9, 36E10, 16G10, 37A10S713, 37A10S714, 37A10S715, 37A10S716, 37A10S717, 37A10S718, 16G10S71, 16G10S72, 16G10S73, 16G10S83, 35A9S79, 35A9S710, or 35A9S89;
WO16120789, US2016215059 - for example the antibody known as 422.2 and/or H2L5;
WO14033327, EP2892928, US2015239978 - for example the antibody known as 314-8 and/or produced from hybridoma CNCM I-4180;
WO12131004, EP2691419, US9376493, US20160264666 – for example the antibody Icos145-1 and/or antibody produced by hybridoma CNCM I-4179;
WO10056804 – for example the antibody JMAb 136 or "136";
WO9915553, EP1017723B1, US7259247, US7132099, US7125551, US7306800, US7722872, WO05103086, EP1740617, US8318905, US8916155 - for example the antibody MIC-944 or 9F3;
WO983821, US7932358B2, US2002156242, EP0984023, EP1502920, US7030225, US7045615, US7279560, US7226909, US7196175, US7932358, US8389690, WO02070010, EP1286668, EP1374901, US7438905, US7438905, WO0187981, EP1158004, US6803039, US7166283, US7988965, WO0115732, EP1125585, US7465445, US7998478 – for example any JMAb antibody, e.g., any of JMAb-124, JMAb-126, JMAb-127, JMAb-128, JMAb-135, JMAb-136, JMAb-137, JMAb-138, JMAb-139, JMAb-140, JMAb-141, e.g., JMAb136;
WO2014/089113 – for example antibody 17G9;
WO12174338;
US2016145344;
WO11020024, EP2464661, US2016002336, US2016024211, US8840889;
US8497244.

The anti-ICOS antibody optionally comprises the CDRs of 37A10S713 as disclosed in WO2016154177. It may comprise the VH and VL domains of 37A10S713, and may optionally have the antibody heavy and light chains of 37A10S713.

Combination of an anti-ICOS antibody with an immunomodulator may provide an increased therapeutic effect compared with monotherapy, and may allow therapeutic benefit to be achieved with a lower dose of the immunomodulator(s). Thus, for example, an antibody (e.g., anti-PD-L1 antibody, optionally ipilimumab) that is used in combination with anti-ICOS antibody may be dosed at 3 mg/kg rather than a more usual dose of 10 mg/kg. The administration regimen of the anti-PD-L1 or other antibody may involve intravenous administration over a 90 minute period every 3 weeks for a total of 4 doses.

An anti-ICOS antibody may be used to increase the sensitivity of a tumour to treatment with an anti-PD-L1 antibody, which may be recognised as a reduction in the dose at which the anti-

PD-L1 antibody exerts a therapeutic benefit. Thus, anti-ICOS antibody may be administered to a patient to reduce the dose of anti-PD-L1 antibody effective to treat cancer or a tumour in the patient. Administration of anti-ICOS antibody may reduce the recommended or required dosage of anti-PD-L1 antibody administration to that patient to, for example, 75 %, 50 %, 25 %, 20 %, 10 % or less, compared with the dosage when anti-PD-L1 antibody is administered without anti-ICOS. The patient may be treated by administration of anti-ICOS antibody and anti-PD-L1 antibody in a combination therapy as described herein.

The benefit of combining anti-PD-L1 with anti-ICOS may extend to a reduction in dosage of each agent when compared with its use as a monotherapy. Anti-PD-L1 antibody may be used to reduce the dose at which anti-ICOS antibody exerts a therapeutic benefit, and thus may be administered to a patient to reduce the dose of anti-ICOS antibody effective to treat cancer or a tumour in the patient. Thus, an anti-PD-L1 antibody may reduce the recommended or required dosage of anti-ICOS antibody administration to that patient to, for example, 75 %, 50 %, 25 %, 20 %, 10 % or less, compared with the dosage when anti-ICOS antibody is administered without anti-PD-L1. The patient may be treated by administration of anti-ICOS antibody and anti-PD-L1 antibody in a combination therapy as described herein.

As discussed in Example 22 of WO2018/029474, treatment with anti-PD-L1 antibody, especially antibody with effector positive Fc, appears not to increase the expression of ICOS on Teff cells. This is advantageous when administering such antibodies in combination with effector positive anti-ICOS antibodies, where an increase in ICOS expression on Teffs would undesirably render these cells more sensitive to depletion by the anti-ICOS antibody. In a combination with anti-PD-L1, anti-ICOS therapy may thus exploit a differential expression of ICOS on Teffs compared with Tregs, preferentially targeting the ICOS-high Tregs for depletion. This in turn relieves the suppression of TEffs and has a net effect of promoting the effector T cell response in a patient. The effect of targeting immune checkpoint molecules on expression of ICOS on T cells has also been studied previously – see Figure S6C in ref. [29] (supplementary materials), where treatment with CTLA-4 antibody and/or anti-PD-1 antibody was reported to increase the percentage of CD4+ Tregs expressing ICOS. The effect of a therapeutic agent on ICOS expression in Tregs and Teffs may be a factor in selection of appropriate agents for use in combination with anti-ICOS antibodies, noting that effect of the anti-ICOS antibody may be enhanced under conditions where there is high differential expression of ICOS on Tregs versus Teffs.

As described herein, a single dose of anti-ICOS antibody may be sufficient to provide therapeutic effect, especially in combination with other therapeutic agents such as anti-PD-L1 antibody. In tumour therapy, the underlying rationale for this single dose benefit may be that the anti-ICOS antibody mediates its effect, at least in part, by resetting or altering the microenvironment of the tumour sufficiently to render the tumour more sensitive to immune

attack and/or to the effects of other immunomodulators such as those mentioned. Tumour microenviroment resetting is triggered through for example depletion of ICOS positive tumour infiltrating T-regs. So, for example, a patient may be treated with a single dose of an anti-ICOS antibody followed by one or multiple doses of anti-PD-L1 antibody. Over a period of treatment, for example six months or a year, the anti-ICOS antibody may be administered in a single dose while other agents, e.g., anti-PD-L1 antibody, are optionally administered multiple times over that treatment period, preferably with at least one such dose being administered subsequent to treatment with the anti-ICOS antibody.

Further examples of combination therapy include combination of anti-ICOS antibody with:

- an antagonist of an adenosine A2A receptor ("A2AR inhibitor");
- a CD137 agonist (e.g., agonist antibody);
- an antagonist of the enzyme indoleamine-2,3 dioxygenase, which catalyses the breakdown of tryptophan ("IDO inhibitor"). IDO is an immune checkpoint, activated in dendritic cells and macrophages, which contributes to immune suppression/tolerance.

Anti-ICOS antibodies may be used in combination therapy with IL-2 (e.g., recombinant IL-2 such as aldesleukin). The IL-2 may be administered at high dose (HD). Typical HD IL-2 therapy involves bolus infusion of over 500,000 IU/kg, e.g., bolus infusions of 600,000 or 720,000 IU/kg, per cycle of therapy, where 10-15 such bolus infusions are given at intervals of between 5-10 hours, e.g., up to 15 bolus infusions every 8 hours, and repeating the therapy cycle approximately every 14 to 21 days for up to 6 to 8 cycles. HD IL-2 therapy has been successful in treating tumours, especially melanoma (e.g., metastatic melanoma) and renal cell carcinoma, but its use is limited to the high toxicity of IL-2 which can cause severe adverse effects.

Treatment with high dose IL-2 has been shown to increase the population of ICOS-positive Tregs in cancer patients [30]. This increase in ICOS+ TRegs following the first cycle of HD IL-2 therapy was reported to correlate with worse clinical outcome - the higher the number of ICOS+ Tregs, the worse the prognosis. An IL-2 variant F42K has been proposed as an alternative therapy to avoid this undesirable increase in ICOS+ Treg cells [31]. However, another approach would be to exploit the increase in ICOS+ T regs by using an antibody in accordance with the present invention as a second-line therapeutic agent.

It may be beneficial to combine IL-2 therapy with anti-ICOS antibodies, capitalising on the ability of anti-ICOS antibodies to target TRegs that highly express ICOS, inhibiting these cells and improving the prognosis for patients undergoing IL-2 therapy. Concomitant administration of IL-2 and anti-ICOS antibody may increase the response rate while avoiding or reducing adverse events in the treated patient population. The combination may permit IL-2 to be used at lower dose compared with IL-2 monotherapy, reducing the risk or level of adverse events arising from the IL-2 therapy, while retaining or enhancing clinical benefit (e.g., reduction of tumour growth, clearance of solid tumour and/or reduction of metastasis). In this way, addition of anti-ICOS can

improve treatment of patients who are receiving IL-2, whether high-dose (HD) or low-dose (LD) IL-2.

Accordingly, one aspect of the invention provides a method of treating a patient by administering an anti-ICOS antibody to the patient, wherein the patient is also treated with IL-2, e.g., HD IL-2. Another aspect of the invention is an anti-ICOS antibody for use in treating a patient, wherein the patient is also treated with IL-2, e.g., HD IL-2. The anti-ICOS antibody may be used as a second-line therapy. Thus, the patient may be one who has been treated with IL-2, e.g., having received at least one cycle of HD IL-2 therapy, and who has an increased level of ICOS+ Tregs. Assays may be performed on samples of cancer cells, e.g., tumour biopsy samples, using immunohistochemistry or FACS as described elsewhere herein to detect cells positive for ICOS, Foxp3, ICOSL and optionally one or more further markers of interest. Methods may comprise determining that the patient has an increased level of ICOS+ Tregs (e.g., in peripheral blood, or in a tumour biopsy) following IL-2 treatment, where an increased level is indicative that the patient would benefit from treatment with the anti-ICOS antibody. The increase in Tregs may be relative to control (untreated) individuals or to the patient prior to IL-2 therapy. Such patients with elevated Tregs represent a group who may not benefit from continued IL-2 treatment alone, but for whom a combination of anti-ICOS antibody and IL-2 therapy, or treatment with anti-ICOS antibody alone, offers therapeutic benefit. Thus, following a positive determination that the patient has an increased level of ICOS+ Tregs, anti-ICOS antibody and/or further IL-2 therapy may be administered. Treatment with the anti-ICOS antibody may selectively target and deplete the ICOS+ Tregs relative to other T cell populations in such patients. This provides a therapeutic effect by relieving the immunosuppression mediated by these cells and thereby enhancing activity of Teffs against the target cells, e.g., tumour cells or infected cells.

Combination therapy with anti-ICOS antibodies and IL-2 may be used for any therapeutic indication described herein, and particularly for treating a tumour, e.g., melanoma such as metastatic melanoma, or renal cell carcinoma. Thus, in one example, the patient treated with an anti-ICOS antibody is one who presents with metastatic melanoma and has been treated with IL-2, e.g., HD IL-2 therapy or LD IL-2 therapy.

In general, where an anti-ICOS antibody is administered to a patient who has received treatment with a first therapeutic agent (e.g., immunomodulator antibody) or other agent (e.g., IL-2), the anti-ICOS antibody may be administered after a minimum period of, for example, 24 hours, 48 hours, 72 hours, 1 week or 2 weeks following administration of the first therapeutic agent. The anti-ICOS antibody may be administered within 2, 3, 4 or 5 weeks after administration of the first therapeutic agent. This does not exclude additional administrations of either agent at any time, although it may be desirable to minimise the number of treatments administered, for ease of compliance for patients and to reduce costs. Rather, the relative

timing of the administrations will be selected to optimise their combined effect, the first therapeutic agent creating an immunological environment (e.g., elevated ICOS+ Tregs, or antigen release as discussed below) in which the effect of the anti-ICOS antibody is especially advantageous. Thus, sequential administration of the first therapeutic agent and then the anti-ICOS antibody may allow time for the first agent to act, creating *in vivo* conditions in which the anti-ICOS antibody can exhibit its enhanced effect. Various administration regimens, including simultaneous or sequential combination treatments, are described herein and can be utilised as appropriate. Where the first therapeutic agent is one that increases the number of ICOS+ Tregs in the patient, the treatment regimen for the patient may comprise determining that the patient has an increased number of ICOS+ Tregs, and then administering the anti-ICOS antibody.

As noted, use of anti-ICOS antibodies in combination therapy may provide advantages of reducing the effective dose of the therapeutic agents and/or countering adverse effects of therapeutic agents that increase ICOS+ Tregs in patients. Yet further therapeutic benefits may be achieved through selecting a first therapeutic agent that causes release of antigens from target cells through “immunological cell death”, and administering the first therapeutic agent in combination with an anti-ICOS antibody. As noted, administration of the anti-ICOS antibody may sequentially follow administration of the first therapeutic agent, administration of the two agents being separated by a certain time window as discussed above.

Immunological cell death is a recognised mode of cell death, contrasting with apoptosis. It is characterised by release of ATP and HMGB1 from the cell and exposure of calreticulin on the plasma membrane [32, 33].

Immunological cell death in a target tissue or in target cells promotes engulfment of the cell by an antigen-presenting cell, resulting in display of antigens from the target cell, which in turn induces antigen-specific Teff cells. Anti-ICOS antibody may increase the magnitude and/or duration of the Teff response by acting as an agonist of ICOS on the Teff cells. In addition, where the anti-ICOS antibody is Fc effector function enabled (e.g., a human IgG1 antibody), the anti-ICOS antibody may cause depletion of antigen-specific Tregs. Thus, through a combination of either or both of these effects, the balance between Teff and Treg cells is modulated in favour of enhancing Teff activity. Combination of an anti-ICOS antibody with a treatment that induces immunological cell death in a target tissue or cell type, such as in a tumour or in cancer cells, thereby promotes an immune response in the patient against the target tissue or cells, representing a form of vaccination in which the vaccine antigen is generated *in vivo*.

Accordingly, one aspect of the invention is a method of treating cancer in a patient by *in vivo* vaccination of the patient against their cancer cells. Another aspect of the invention is an anti-ICOS antibody for use in such a method. Anti-ICOS antibodies may be used in a method comprising:

treating the patient with a therapy that causes immunological cell death of the cancer cells, resulting in presentation of antigen to antigen-specific effector T cells, and

administering an anti-ICOS antibody to the patient, wherein the anti-ICOS antibody enhances the antigen-specific effector T cell response against the cancer cells.

Treatments that induce immunological cell death include radiation (e.g., ionising irradiation of cells using UVC light or γ rays), chemotherapeutic agents (e.g., oxaliplatin, anthracyclines such as doxorubicin, idarubicin or mitoxantrone, BK channel agonists such as phloretin or pimaric acid, bortezomib, cardiac glycosides, cyclophosphamide, GADD34/PP1 inhibitors with mitomycin, PDT with hypericin, polyinosinic-polycytidylic acid, 5-fluorouracil, gemcitabine, gefitnib, erlotinib, or thapsigargin with cisplatin) and antibodies to tumour-associated antigens. The tumour-associated antigen can be any antigen that is over-expressed by tumour cells relative to non-tumour cells of the same tissue, e.g., HER2, CD20, EGFR. Suitable antibodies include herceptin (anti-HER2), rituximab (anti-CD20), or cetuximab (anti-EGFR).

Thus, it is advantagous to combine an anti-ICOS antibody with one or more such treatments. Optionally, the anti-ICOS antibody is adminstered to a patient who has already received such treatment. The anti-ICOS antibody may be administered after a period of, for example, 24 hours, 48 hours, 72 hours, 1 week or 2 weeks following the treatment that induces immunological cell death, e.g., between 24 to 72 hours after the treatment. The anti-ICOS antibody may be administered within 2, 3, 4 or 5 weeks after the treatment. Other regimens for combination therapy are discussed elsewhere herein.

While “in vivo vaccination” has been described above, it is also possible to treat tumour cells to induce immunological cell death ex vivo, after which the cells may be reintroduced to the patient. Rather than administering the agent or treatment that induces immunological cell death directly to the patient, the treated tumour cells are administered to the patient. Treatment of the patient may be in accordance with administration regimens described above.

As already noted, a single dose of an anti-ICOS antibody may be sufficient to provide therapeutic benefit. Thus, in the methods of treatment described herein, the anti-ICOS antibody is optionally administered as a single dose. A single dose of anti-ICOS antibody may deplete Tregs in a patient, with consequent beneficial effects in diseases such as cancer. It has previously been reported that transient ablation of Tregs has anti-tumour effects, including reducing tumour progression, treating established tumours and metastases and extending survival, and that it can enhance the therapeutic effect of tumour irradiation [34]. Administration of a single dose of anti-ICOS may provide such Treg depletion, and may be used to enhance the effects of other therapeutic approaches used in combination, such as radiotherapy.

The present invention also provides a combination of an ICOS modulator and a PD-L1 inhibitor for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression. The present invention also provides a

combination of an ICOS modulator and a PD-L1 inhibitor for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor. The present invention also provides a modulator of ICOS and an inhibitor of PD-L1 for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative cancer or a cancer with low PD-L1 expression. The present invention also provides a modulator of ICOS and an inhibitor of PD-L1 for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor. The present invention also provides use of a combination of an ICOS modulator and a PD-L1 inhibitor in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression. The present invention also provides use of a combination of an ICOS modulator and a PD-L1 inhibitor in the manufacture of a medicament for the treatment of cancer in a patient and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the patient has previously received treatment for the cancer, wherein the previous treatment for the cancer was a PD-L1 inhibitor. The present invention also provides use of a modulator of ICOS and an inhibitor of PD-L1 in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative cancer or a cancer with low PD-L1 expression. The present invention also provides use of a modulator of ICOS and an inhibitor of PD-L1 in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer, wherein the previous treatment for the cancer was a PD-L1 inhibitor. In some embodiments, the ICOS modulator is for use in combination with a PD-L1 inhibitor. In some embodiments, the ICOS modulator is an agonistic anti-ICOS antibody. In some embodiments, the ICOS modulator is a bispecific antibody that is an anti-ICOS agonist and an anti-PD-L1 antagonist or a bispecific antibody that is an anti-ICOS agonist and an anti-PD-1 antagonist. Generally, the cancer (such as a solid cancer) will be a PD-L1 negative cancer or a cancer with low-PD-L1 expression.

Antibodies to PD-L1

An antibody to PD-L1 for use in combination with an anti-ICOS antibody, whether as a separate therapeutic agent or in a multispecific antibody as described herein, may comprise the antigen-binding site of any anti-PD-L1 antibody. Numerous examples of anti-PD-L1 antibodies are disclosed herein and others are known in the art. Characterisation data for many of the anti-

PD-L1 antibodies mentioned here has been published in US9,567,399 and US9,617,338, both incorporated by reference herein.

1D05 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No: 526, Seq ID No :528, Seq ID No: 530, Seq ID No: 532 or Seq ID No: 534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36). A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

84G09 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:13, comprising the CDRH1 amino acid sequence of Seq ID No:7 (IMGT) or Seq ID No:10 (Kabat), the CDRH2 amino acid sequence of Seq ID No:8 (IMGT) or Seq ID No:11 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:9 (IMGT) or Seq ID No:12 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:14. 84G09 has a light chain variable region (V_L) amino acid sequence of Seq ID No:23 , comprising the CDRL1 amino acid sequence of Seq ID No:17 (IMGT) or Seq ID No:20 (Kabat), the CDRL2 amino acid sequence of Seq ID No:18 (IMGT) or Seq ID No:21 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:19 (IMGT) or Seq ID No:22 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:24. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:15 (heavy chain nucleic

acid sequence Seq ID No:16). A full length light chain amino acid sequence is Seq ID No:25 (light chain nucleic acid sequence Seq ID No:26).

1D05 HC mutant 1 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:47, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 1 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 HC mutant 2 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:48, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 2 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 HC mutant 3 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:49, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31

(Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 3 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 HC mutant 4 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:342, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). 1D05 HC mutant 4 has a light chain variable region (V_L) amino acid sequence of Seq ID No:43, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

1D05 LC mutant 1 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 LC mutant 1has a light chain variable region (V_L) amino acid sequence of Seq ID No:50, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The CDRL2

sequence of 1D05 LC Mutant 1 is as defined by the Kabat or IMGT systems from the V_L sequence of Seq ID No:50. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205 or Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36).

1D05 LC mutant 2 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 LC mutant 2 has a light chain variable region (V_L) amino acid sequence of Seq ID No:51, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), the CDRL2 amino acid sequence of Seq ID No:38 (IMGT) or Seq ID No:41 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36).

1D05 LC mutant 3 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:33, comprising the CDRH1 amino acid sequence of Seq ID No:27 (IMGT) or Seq ID No:30 (Kabat), the CDRH2 amino acid sequence of Seq ID No:28 (IMGT) or Seq ID No:31 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:29 (IMGT) or Seq ID No:32 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:34. 1D05 LC mutant 3 has a light chain variable region (V_L) amino acid sequence of Seq ID No:298, comprising the CDRL1 amino acid sequence of Seq ID No:37 (IMGT) or Seq ID No:40 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:39 (IMGT) or Seq ID No:42 (Kabat). The CDRL2 sequence of 1D05 LC Mutant 3 is as defined by the Kabat or IMGT systems from the V_L sequence of Seq ID No:298. The light chain nucleic acid sequence of the V_L domain is Seq ID No:44. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID

No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205 or Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:35 (heavy chain nucleic acid sequence Seq ID No:36). A full length light chain amino acid sequence is Seq ID No:45 (light chain nucleic acid sequence Seq ID No:46).

411B08 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:58, comprising the CDRH1 amino acid sequence of Seq ID No:52 (IMGT) or Seq ID No:55 (Kabat), the CDRH2 amino acid sequence of Seq ID No:53 (IMGT) or Seq ID No:56 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:54 (IMGT) or Seq ID No:57 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:59. 411B08 has a light chain variable region (V_L) amino acid sequence of Seq ID No:68, comprising the CDRL1 amino acid sequence of Seq ID No:62 (IMGT) or Seq ID No:65 (Kabat), the CDRL2 amino acid sequence of Seq ID No:63 (IMGT) or Seq ID No:66 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:64 (IMGT) or Seq ID No:67 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:69. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:60 (heavy chain nucleic acid sequence Seq ID No:61). A full length light chain amino acid sequence is Seq ID No:70 (light chain nucleic acid sequence Seq ID No:71).

411C04 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:78, comprising the CDRH1 amino acid sequence of Seq ID No:72 (IMGT) or Seq ID No:75 (Kabat), the CDRH2 amino acid sequence of Seq ID No:73 (IMGT) or Seq ID No:76 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:74 (IMGT) or Seq ID No:77 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:79. 411C04 has a light chain variable region (V_L) amino acid sequence of Seq ID No:88, comprising the CDRL1 amino acid sequence of Seq ID No:82 (IMGT) or Seq ID No:85 (Kabat), the CDRL2 amino acid sequence of Seq ID No:83 (IMGT) or Seq ID No:86 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:84 (IMGT) or Seq ID No:87 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:89. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID

No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:80 (heavy chain nucleic acid sequence Seq ID No:81). A full length light chain amino acid sequence is Seq ID No:90 (light chain nucleic acid sequence Seq ID No:91).

411D07 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:98, comprising the CDRH1 amino acid sequence of Seq ID No:92 (IMGT) or Seq ID No:95 (Kabat), the CDRH2 amino acid sequence of Seq ID No:93 (IMGT) or Seq ID No:96 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:94 (IMGT) or Seq ID No:97 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:99. 411D07 has a light chain variable region (V_L) amino acid sequence of Seq ID No:108, comprising the CDRL1 amino acid sequence of Seq ID No:102 (IMGT) or Seq ID No:105 (Kabat), the CDRL2 amino acid sequence of Seq ID No:103 (IMGT) or Seq ID No:106 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:104 (IMGT) or Seq ID No:107 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:109. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:100 (heavy chain nucleic acid sequence Seq ID No:101). A full length light chain amino acid sequence is Seq ID No: 110 (light chain nucleic acid sequence Seq ID No:111).

385F01 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:118, comprising the CDRH1 amino acid sequence of Seq ID No:112 (IMGT) or Seq ID No:115 (Kabat), the CDRH2 amino acid sequence of Seq ID No:113 (IMGT) or Seq ID No:116 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:114 (IMGT) or Seq ID No:117 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:119. 385F01 has a light chain variable region (V_L) amino acid sequence of Seq ID No:128, comprising the CDRL1 amino acid sequence of Seq ID No:122 (IMGT) or Seq ID No:125 (Kabat), the CDRL2 amino acid sequence of Seq ID No:123 (IMGT) or Seq ID No:126 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:124 (IMGT) or Seq ID No:127 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:129. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID

No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:120 (heavy chain nucleic acid sequence Seq ID No:121). A full length light chain amino acid sequence is Seq ID No:130 (light chain nucleic acid sequence Seq ID No:131).

386H03 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:158, comprising the CDRH1 amino acid sequence of Seq ID No:152 (IMGT) or Seq ID No:155 (Kabat), the CDRH2 amino acid sequence of Seq ID No:153 (IMGT) or Seq ID No:156 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:154 (IMGT) or Seq ID No:157 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:159. 386H03 has a light chain variable region (V_L) amino acid sequence of Seq ID No:168, comprising the CDRL1 amino acid sequence of Seq ID No:162 (IMGT) or Seq ID No:165 (Kabat), the CDRL2 amino acid sequence of Seq ID No:163 (IMGT) or Seq ID No:166 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:164 (IMGT) or Seq ID No:167 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:169. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:160 (heavy chain nucleic acid sequence Seq ID No:161). A full length light chain amino acid sequence is Seq ID No:170 (light chain nucleic acid sequence Seq ID No:171).

389A03 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:178, comprising the CDRH1 amino acid sequence of Seq ID No:172 (IMGT) or Seq ID No:175 (Kabat), the CDRH2 amino acid sequence of Seq ID No:173 (IMGT) or Seq ID No:176 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:174 (IMGT) or Seq ID No:177 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:179. 389A03 has a light chain variable region (V_L) amino acid sequence of Seq ID No:188, comprising the CDRL1 amino acid sequence of Seq ID No:182 (IMGT) or Seq ID No:185 (Kabat), the CDRL2 amino acid sequence of Seq ID No:183 (IMGT) or Seq ID No:186 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:184 (IMGT) or Seq ID No:187 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:189. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences

described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:180 (heavy chain nucleic acid sequence Seq ID No:181). A full length light chain amino acid sequence is Seq ID No:190 (light chain nucleic acid sequence Seq ID No:191).

413D08 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:138, comprising the CDRH1 amino acid sequence of Seq ID No:132 (IMGT) or Seq ID No:135 (Kabat), the CDRH2 amino acid sequence of Seq ID No:133 (IMGT) or Seq ID No:136 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:134 (IMGT) or Seq ID No:137 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:139. 413D08 has a light chain variable region (V_L) amino acid sequence of Seq ID No:148, comprising the CDRL1 amino acid sequence of Seq ID No:142 (IMGT) or Seq ID No:145 (Kabat), the CDRL2 amino acid sequence of Seq ID No:143 (IMGT) or Seq ID No:146 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:144 (IMGT) or Seq ID No:147 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:149. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No: 140 (heavy chain nucleic acid sequence Seq ID No:141). A full length light chain amino acid sequence is Seq ID No:150 (light chain nucleic acid sequence Seq ID No:151).

413G05 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:244, comprising the CDRH1 amino acid sequence of Seq ID No:238 (IMGT) or Seq ID No:241 (Kabat), the CDRH2 amino acid sequence of Seq ID No:239 (IMGT) or Seq ID No:242 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:240 (IMGT) or Seq ID No:243 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:245. 413G05 has a light chain variable region (V_L) amino acid sequence of Seq ID No:254, comprising the CDRL1 amino acid sequence of Seq ID No:248 (IMGT) or Seq ID No:251 (Kabat), the CDRL2 amino acid sequence of Seq ID No:249 (IMGT) or Seq ID No:252 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:250 (IMGT) or Seq ID No:253 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:255. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229,

231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:246 (heavy chain nucleic acid sequence Seq ID No:247). A full length light chain amino acid sequence is Seq ID No:256 (light chain nucleic acid sequence Seq ID No:257).

413F09 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:264, comprising the CDRH1 amino acid sequence of Seq ID No:258 (IMGT) or Seq ID No:261 (Kabat), the CDRH2 amino acid sequence of Seq ID No:259 (IMGT) or Seq ID No:262 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:260 (IMGT) or Seq ID No:263 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:265. 413F09 has a light chain variable region (V_L) amino acid sequence of Seq ID No:274, comprising the CDRL1 amino acid sequence of Seq ID No:268 (IMGT) or Seq ID No:271 (Kabat), the CDRL2 amino acid sequence of Seq ID No:269 (IMGT) or Seq ID No:272 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:270 (IMGT) or Seq ID No:273 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:275. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:266 (heavy chain nucleic acid sequence Seq ID No:267). A full length light chain amino acid sequence is Seq ID No:276 (light chain nucleic acid sequence Seq ID No:277).

414B06 has a heavy chain variable (V_H) region amino acid sequence of Seq ID No:284, comprising the CDRH1 amino acid sequence of Seq ID No:278 (IMGT) or Seq ID No:281 (Kabat), the CDRH2 amino acid sequence of Seq ID No:279 (IMGT) or Seq ID No:282 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:280 (IMGT) or Seq ID No:283 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:285. 414B06 has a light chain variable region (V_L) amino acid sequence of Seq ID No:294, comprising the CDRL1 amino acid sequence of Seq ID No:288 (IMGT) or Seq ID No:291(Kabat), the CDRL2 amino acid sequence of Seq ID No:289 (IMGT) or Seq ID No:292 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:290 (IMGT) or Seq ID No:293 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:295. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID

No:286 (heavy chain nucleic acid sequence Seq ID No:287). A full length light chain amino acid sequence is Seq ID No:296 (light chain nucleic acid sequence Seq ID No:297).

416E01 has a heavy chain variable region (V_H) amino acid sequence of Seq ID No:349, comprising the CDRH1 amino acid sequence of Seq ID No:343 (IMGT) or Seq ID No:346 (Kabat), the CDRH2 amino acid sequence of Seq ID No:344 (IMGT) or Seq ID No:347 (Kabat), and the CDRH3 amino acid sequence of Seq ID No:345 (IMGT) or Seq ID No:348 (Kabat). The heavy chain nucleic acid sequence of the V_H domain is Seq ID No:350. 416E01 has a light chain variable region (V_L) amino acid sequence of Seq ID No:359, comprising the CDRL1 amino acid sequence of Seq ID No:353 (IMGT) or Seq ID No:356 (Kabat), the CDRL2 amino acid sequence of Seq ID No:354 (IMGT) or Seq ID No:357 (Kabat), and the CDRL3 amino acid sequence of Seq ID No:355 (IMGT) or Seq ID No:358 (Kabat). The light chain nucleic acid sequence of the V_L domain is Seq ID No:360. The V_H domain may be combined with any of the heavy chain constant region sequences described herein, e.g. Seq ID No:193, Seq ID No:195, Seq ID No:197, Seq ID No:199, Seq ID No:201, Seq ID No:203, Seq ID No:205, Seq ID No:340, Seq ID No:524, Seq ID No:526, Seq ID No:528, Seq ID No:530, Seq ID No:532 or Seq ID No:534. The V_L domain may be combined with any of the light chain constant region sequences described herein, e.g. Seq ID Nos:207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 536 and 538. A full length heavy chain amino acid sequence is Seq ID No:351 (heavy chain nucleic acid sequence Seq ID No:352). A full length light chain amino acid sequence is Seq ID No:361 (light chain nucleic acid sequence Seq ID No:362).

In some embodiments, the anti-PD-L1 antibody is an anti-PD-L1 antibody selected from the group consisting of atezoliumab (Roche), avelumab (Merck), durvalumab/Medi4736 (Medimmune), KN035, CK-301, AUNP12, CA-170, BMS-936559/MDX-1105 (BMS), FAZ-053 M7824, ABBV-368, LY-3300054, GNS-1480, YW243.55.S70, REGN3504 and any of the PD-L1 antibodies disclosed in WO2017/220990 , WO2017/034916, WO2017/020291, WO2017/020858, WO2017/020801, WO2016/111645, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630, WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 or WO2007/005874.

Antibodies to PD-1

In some embodiments, the invention uses anti-PD-1 antibodies, for example an anti-PD-1 antibody selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, JTX-401, spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS 001), dostarlimab (TSR-042, WBP-285), INCMGA00012

(MGA012), AMP-224 and AMP-514, MEDI-0680/AMP514, PDR001, Lambrolizumab, BMS-936558, REGN2810, BGB-A317, BGB-108, PDR-001, SHR-1210, JS-001, JNJ-63723283, AGEN-2034, PF-06801591, genolimzumab, MGA-012 (INCMGA00012), IBI-308, BCD-100, TSR-042 ANA011, AUNP-12, KD033, MCLA-134, mDX400, muDX400, STI-A1110, AB011, 244C8, 388D4, XCE853, or pidilizumab/CT-011, or from any one of the anti-PD-1 antibodies described in WO2015/112800 & US2015/0203579 (including the antibodies in Tables 1 to 3), US9,394,365, US5,897,862 and US7,488,802, WO2017/087599 (including antibody SSI-361 and SHB-617), WO2017/079112, WO2017/071625 (including deposit C2015132, hybridoma LT004, and antibodies 6F5/6 F5 (Re), 6F5H1 L1 and 6F5 H2L2), WO2017/058859 (including PD1AB-1 to PD1AB-6), WO2017/058115 (including 67D9, c67D9, and hu67D9), WO2017/055547 (including 12819.15384, 12748.15381, 12748.16124, 12865.15377, 12892.15378, 12796.15376, 12777.15382, 12760.15375 and 13112.15380), WO2017/040790 (including AGEN2033w, AGEN2034w, AGEN2046w, AGEN2047w, AGEN2001w and AGEN2002w), WO2017/025051 & WO2017/024515 (including 1.7.3 hAb, 1.49.9 hAb, 1.103.11 hAb, 1.103.11-v2 hAb, 1.139.15 hAb and 1.153.7 hAb), WO2017/025016 & WO2017/024465 (including antibody A to antibody I), WO2017/020858 & WO2017/020291 (including 1.4.1, 1.14.4, 1.20.15 and 1.46.11), WO2017/019896 & WO2015/112900 & US2015/0210769 (including BAP049-hum01 to BAP049-hum16 and BAP049-Clone-A to BAP049-Clone-E), WO2017/019846 (including PD-1 mAb 1 to PD-1 mAb 15), WO2017/016497 (including MHC723, MHC724, MHC725, MHC728, MHC729, m136-M13, m136-M19, m245-M3, m245-M5 and m136-M14), WO2016/201051 (including antibody EH12.2H7, antibody hPD-1 mAb2, antibody hPD-1 mAb7, antibody hPD-1 mAb9, antibody hPD-1 mAb15, or an anti-PD-1 antibody selected from Table 1), WO2016/197497 (including DFPD1-1 to DFPD1-13), WO2016/197367 (including 2.74.15 and 2.74.15.hAb4 to 2.74.15.hAb8), WO2016/196173 (including the antibodies in Table 5, and Figures 1-5), WO2016/127179 (including R3A1, R3A2, R4B3, and R3D6), WO2016/077397 (including the antibodies described in Table 1 of Example 9), WO2016/106159 (including the murine antibodies in Table 3 of Example 2 and the humanised antibodies in Tables 7, 8 and 9 of Example 3), WO2016/092419 (including C1, C2, C3, EH12.1, mAb7-G4, mAb15-G4, mAb-AAA, mAb15-AAA), WO2016/068801 (including clone A3 and its variants and the other antibodies described in Figures 1 to 4), WO2016/014688 (including 10D1, 4C10, 7D3, 13F1, 15H5, 14A6, 22A5, 6E1, 5A8, 7A4, and 7A4D and the humanised antibodies of Examples 9/10), WO2016/015685 (including 10F8, BA08-1, BA-08-2 and 15H6), WO2015/091911 & WO2015/091910 (including the anti-canine PD-1 antibodies in Examples 2, 3 and 4) , WO2015/091914 (including the anti-canine PD-1 antibodies in Table 3), WO2015/085847 (including mAb005, H005-1 to H005-4), WO2015/058573 (including cAB7), WO2015/036394 (including LOPD180), WO2015/035606 (including the antibodies in Table 1 of Example 2, in Tables 14, 15 and 16 of Example 7 and in tables 20, 21 and 22 of Example 11),

WO2014/194302 (including GA2, RG1B3, RG1H10, RG2A7, RG2H10, SH-A4, RG4A6, GA1, GB1, GB6, GH1, A2, C7, H7, SH-A4, SH-A9, RG1H11, and RG6B), WO2014/179664 (including 9A2, 10B11, 6E9, APE1922, APE1923, APE1924, APE1950, APE1963 and APE2058), WO2014/206107 (including clone 1, 10, 11, 55, 64, 38, 39, 41 and 48), WO2012/135408 (including h409A11, h409A16, and h409A17), WO2012/145493 (including antibodies 1E3, 1E8, 1H3 and h1H3 Var 1 to h1H3 Var 14), WO2011/110621 (including antibody 949 and the modified versions disclosed in Figures 1 to 11), WO2011/110604 (including antibody 948 and the modified versions disclosed in Figures 3 to 11), WO2010/089411 (including CNCM deposit number 1-4122, 1-4080 or 1-4081), WO2010/036959 (including the antibodies in Table 1 of Example 1), WO2010/029435 & WO2010/029434 (including clones 2, 10 and 19), WO2008/156712 (including hPD-1.08A, hPD-1.09A, h409A11, h409A16 and h409A17 and the antibodies described in Example 2, Table H, Example 4 and table IV), WO2006/121168 (including clones 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, and 2D3), WO2004/004771 and WO2004/056875 (including PD1-17, PD1-28, PD1-33, PD1-35, PD1-F2 and the Abs described in Table 1).

Antibody-drug conjugates

Anti-ICOS antibodies can be used as carriers of cytotoxic agents, to target Tregs. As reported in Example 18 of WO2018/029474, Tregs located in the tumour microenvironment (TME) strongly express ICOS. ICOS is more strongly expressed on intratumoural Tregs than on intratumoural Teffs or peripheral Tregs. Thus, anti-ICOS antibodies labelled with a toxic drug or pro-drug may preferentially target Tregs in the TME to deliver the toxic payload, selectively inhibiting those cells. Such targeting of cytotoxic agents provides an additional route to removing the immune suppressive effect of Tregs, thereby altering the Treg:Teff balance in favour of Teff activity and may be used as an alternative to, or in combination with, any one or more of the other therapeutic approaches discussed herein (e.g., Fc effector-mediated inhibition of Tregs, agonism of effector T cells).

Accordingly, the invention provides an anti-ICOS antibody that is conjugated to a cytotoxic drug or pro-drug. In the case of a pro-drug, the pro-drug is activatable in the TME or other target site of therapeutic activity to generate the cytotoxic agent. Activation may be in response to a trigger such as photoactivation, e.g., using near-infrared light to activate a photoabsorber conjugate [35]. Spatially-selective activation of a pro-drug further enhances the cytotoxic effect of the antibody-drug conjugate, combining with the high ICOS expression on intratumoural Tregs to provide a cytotoxic effect that is highly selective for these cells.

For use in an antibody-drug conjugate, the cytotoxic drug or pro-drug is preferably non-immunogenic and non-toxic (dormant or inactive) during circulation of the antibody-drug conjugate in the blood. Preferably the cytotoxic drug (or the pro-drug, when activated) is potent -

e.g., two to four molecules of the drug may be sufficient to kill the target cell. A photoactivatable pro-drug is silicapthalocyanine dye (IRDye 700 DX), which induces lethal damage to the cell membrane after near-infrared light exposure. Cytotoxic drugs include anti-mitotic agents such as monomethyl auristatin E and microtubule inhibitors such as maytansine derivatives, e.g., mertansine, DM1, emtansine.

Conjugation of the drug (or pro-drug) to the antibody will usually be via a linker. The linker may be a cleavable linker, e.g., disulphide, hydrazone or peptide link. Cathepsin-cleavable linkers may be used, so that the drug is released by cathepsin in tumour cells. Alternatively, non-cleavable linkers can be used, e.g., thioether linkage. Additional attachment groups and/or spacers may also be included.

The antibody in the antibody-drug conjugate may be an antibody fragment, such as Fab'2 or other antigen-binding fragment as described herein, as the small size of such fragments may assist penetration to the tissue site (e.g., solid tumour).

An anti-ICOS antibody according to the present invention may be provided as an immunocytokine. Anti-ICOS antibodies may also be administered with immunocytokines in combination therapy. A number of examples of antibodies are described herein for use in combination therapy with anti-ICOS, and any of these (e.g., an anti-PD-L1 antibody) may be provided as immunocytokines for use in the present invention. An immunocytokine comprises an antibody molecule conjugated to a cytokine, such as IL-2. Anti-ICOS:IL-2 conjugates and anti-PD-L1:IL-2 conjugates are thus further aspects of the present invention.

An IL-2 cytokine may have activity at the high ($\alpha\beta\gamma$) affinity IL-2 receptor and/or the intermediate affinity ($\alpha\beta$) IL-2 receptor. IL-2 as used in an immunocytokine may be human wild type IL-2 or a variant IL-2 cytokine having one or more amino acid deletions, substitutions or additions, e.g., IL-2 having a 1 to 10 amino acid deletion at the N-terminus. Other IL-2 variants include mutations R38A or R38Q.

An example anti-PD-L1 immunocytokine comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the heavy chain comprises in N- to C-terminal direction:

a) A V_H domain comprising CDRH1, CDRH2 and CDRH3; and
b) A heavy chain constant region;

and wherein the light chain comprises in N- to C-terminal direction:

c) A V_L domain comprising CDRL1, CDRL2 and CDRL3;
d) A light chain constant region, (C_L);
e) Optionally, a linker, (L); and
f) An IL-2 cytokine;

wherein the V_H domain and V_L domain are comprised by an antigen-binding site that specifically binds to human PD-L1; and

wherein the immunocytokine comprises a V_H domain which comprises a CDRH3 comprising the motif X_1GSGX_2YGX_3X_4FD (SEQ ID NO: 609), wherein X_1, X_2 and X_3 are independently any amino acid, and X_4 is either present or absent, and if present, may be any amino acid.

The VH and VL domain may be the VH and VL domain of any anti-PD-L1 antibody mentioned herein, e.g., the 1D05 VH and VL domains.

The IL-2 may be human wild type or variant IL-2.

Vaccination

Anti-ICOS antibodies may be provided in vaccine compositions or co-administered with vaccines preparations. ICOS is involved in T follicular helper cell formation and the germinal centre reaction [36]. Agonist ICOS antibodies thus have potential clinical utility as molecular adjuvants to enhance vaccine efficacy. The antibodies may be used to increase protective efficacy of numerous vaccines, such as those against hepatitis B, malaria, HIV.

In the context of vaccination, the anti-ICOS antibody will generally be one that lacks Fc effector function, and thus does not mediate ADCC, CDC or ADCP. The antibody may be provided in a format lacking an Fc region, or having an effector null constant region. Optionally, an anti-ICOS antibody may have a heavy chain constant region that binds one or more types of Fc receptor but does not induce ADCC, CDC or ADCP activity, or that exhibits lower ADCC, CDC and ADCP activity compared with wild type human IgG1. Such a constant region may be unable to bind, or may bind with lower affinity, the particular Fc receptor(s) responsible for triggering ADCC, CDC or ADCP activity. Alternatively, where cellular effector functions are acceptable or desirable in the context of the vaccination, the anti-ICOS antibody may comprise a heavy chain constant region that is Fc effector function positive. Any of IgG1, IgG4 and IgG4.PE formats may for instance be used for anti-ICOS antibodies in vaccination regimens, and other examples of suitable isotypes and antibody constant regions are set out in more detail elsewhere herein.

Formulations and Administration

Antibodies may be monoclonal or polyclonal, but are preferably provided as monoclonal antibodies for therapeutic use. They may be provided as part of a mixture of other antibodies, optionally including antibodies of different binding specificity.

Antibodies according to the invention, and encoding nucleic acid, will usually be provided in isolated form. Thus, the antibodies, VH and/or VL domains, and nucleic acids may be provided purified from their natural environment or their production environment. Isolated antibodies and isolated nucleic acid will be free or substantially free of material with which they are naturally associated, such as other polypeptides or nucleic acids with which they are found

in vivo, or the environment in which they are prepared (e.g., cell culture) when such preparation is by recombinant DNA technology in vitro. Optionally an isolated antibody or nucleic acid (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature.

Antibodies or nucleic acids may be formulated with diluents or adjuvants and still for practical purposes be isolated - for example they may be mixed with carriers if used to coat microtitre plates for use in immunoassays, and may be mixed with pharmaceutically acceptable carriers or diluents when used in therapy. As described elsewhere herein, other active ingredients may also be included in therapeutic preparations. Antibodies may be glycosylated, either naturally in vivo or by systems of heterologous eukaryotic cells such as CHO cells, or they may be (for example if produced by expression in a prokaryotic cell) unglycosylated. The invention encompasses antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase ADCC function [37]. In other applications, modification of galactosylation can be made in order to modify CDC.

Typically, an isolated product constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. An antibody may be substantially free from proteins or polypeptides or other contaminants that are found in its natural or production environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

An antibody may have been identified, separated and/or recovered from a component of its production environment (eg, naturally or recombinantly). The isolated antibody may be free of association with all other components from its production environment, eg, so that the antibody has been isolated to an FDA-approvable or approved standard. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In some embodiments, the antibody will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or silver stain. Isolated antibody includes the antibody in situ within recombinant cells since

at least one component of the antibody's natural environment will not be present. Ordinarily, however, an isolated antibody or its encoding nucleic acid will be prepared by at least one purification step.

The invention provides therapeutic compositions comprising the antibodies described herein. Therapeutic compositions comprising nucleic acid encoding such antibodies are also provided. Encoding nucleic acids are described in more detail elsewhere herein and include DNA and RNA, e.g., mRNA. In therapeutic methods described herein, use of nucleic acid encoding the antibody, and/or of cells containing such nucleic acid, may be used as alternatives (or in addition) to compositions comprising the antibody itself. Cells containing nucleic acid encoding the antibody, optionally wherein the nucleic acid is stably integrated into the genome, thus represent medicaments for therapeutic use in a patient. Nucleic acid encoding the anti-ICOS antibody may be introduced into human B lymphocytes, optionally B lymphocytes derived from the intended patient and modified ex vivo. Optionally, memory B cells are used. Administration of cells containing the encoding nucleic acid to the patient provides a reservoir of cells capable of expressing the anti-ICOS antibody, which may provide therapeutic benefit over a longer term compared with administration of isolated nucleic acid or isolated antibody.

Compositions may contain suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTINT™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311. Compositions may comprise the antibody or nucleic acid in combination with medical injection buffer and/or with adjuvant.

Antibodies, or their encoding nucleic acids, may be formulated for the desired route of administration to a patient, e.g., in liquid (optionally aqueous solution) for injection. Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. Formulating antibodies for subcutaneous administration typically requires concentrating them into a smaller volume compared with intravenous preparations. The high potency of antibodies according to the present invention may lend them to use at sufficiently low doses to make subcutaneous formulation practical, representing an advantage compared with less potent anti-ICOS antibodies.

The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533 ; Treat et al. (1989) in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez Berestein and Fidler (eds.), Liss, New York, pp. 353-365 ; Lopez-Berestein, ibid., pp. 317-327 ; see generally ibid.).

In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton (1987) CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974). In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138, 1984).

The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule. A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. It is envisaged that treatment will not be restricted to use in the clinic. Therefore, subcutaneous injection using a needle-free device is also advantageous. With respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen

delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded. Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPENT™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIKT™ (Sanofi-Aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (Sanofi-Aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly).

Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, the aforesaid antibody may be contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

The antibody, nucleic acid, or composition comprising it, may be contained in a medical container such as a phial, syringe, IV container or an injection device. In an example, the antibody, nucleic acid or composition is in vitro, and may be in a sterile container. In an example, a kit is provided comprising the antibody, packaging and instructions for use in a therapeutic method as described herein.

One aspect of the invention is a composition comprising an antibody or nucleic acid of the invention and one or more pharmaceutically acceptable excipients, examples of which are listed above. "Pharmaceutically acceptable" refers to approved or approvable by a regulatory agency of the USA Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, including humans. A pharmaceutically acceptable carrier, excipient, or adjuvant can be administered to a patient, together with an agent, e.g., any antibody or antibody chain described herein, and does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the agent.

In some embodiments, an anti-ICOS antibody will be the sole active ingredient in a composition according to the present invention. Thus, a composition may consist of the antibody or it may consist of the antibody with one or more pharmaceutically acceptable excipients. However, compositions according to the present invention optionally include one or more additional active ingredients. Detailed description of agents with which the anti-ICOS antibodies may be combined is provided elsewhere herein. Optionally, compositions contain multiple antibodies (or encoding nucleic acids) in a combined preparation, e.g., a single formulation comprising the anti-ICOS antibody and one or more other antibodies. Other therapeutic agents that it may be desirable to administer with antibodies or nucleic acids according to the present invention include analgaesic agents. Any such agent or combination of agents may be administered in combination with, or provided in compositions with antibodies or nucleic acids according to the present invention, whether as a combined or separate preparation. The antibody or nucleic acid according to the present invention may be administered separately and sequentially, or concurrently and optionally as a combined preparation, with another therapeutic agent or agents such as those mentioned.

Anti-ICOS antibodies for use in a particular therapeutic indication may be combined with the accepted standard of care. Thus, for anti-cancer treatment, the antibody therapy may be employed in a treatment regimen that also includes chemotherapy, surgery and/or radiation therapy for example. Radiotherapy may be single dose or in fractionated doses, either delivered to affected tissues directly or to the whole body.

Multiple compositions can be administered separately or simultaneously. Separate administration refers to the two compositions being administered at different times, e.g. at least 10, 20, 30, or 10-60 minutes apart, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 hours apart. One can also administer compositions at 24 hours apart, or even longer apart. Alternatively, two or more compositions can be administered simultaneously, e.g. less than 10 or less than 5 minutes apart. Compositions administered simultaneously can, in some aspects, be administered as a mixture, with or without similar or different time release mechanism for each of the components.

Antibodies, and their encoding nucleic acids, can be used as therapeutic agents. Patients herein are generally mammals, typically humans. An antibody or nucleic acid may be administered to a mammal, e.g., by any route of administration mentioned herein.

Administration is normally in a "therapeutically effective amount", this being an amount that produces the desired effect for which it is administered, sufficient to show benefit to a patient. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding). Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors and may depend on the severity of the symptoms and/or progression of a

disease being treated. A therapeutically effective amount or suitable dose of antibody or nucleic acid can be determined by comparing its in vitro activity and in vivo activity in an animal model. Methods for extrapolation of effective dosages in mice and other test animals to humans are known.

As indicated by the *in vivo* studies described in the Examples of WO2018/029474, anti-ICOS antibody may be effective at a range of doses. Pharmacodynamic studies are reported in Example 24 of WO2018/029474.

Anti-ICOS antibodies may be administered in an amount in one of the following ranges per dose:

about 10 µg/kg body weight to about 100 mg/kg body weight,

about 50 µg/kg body weight to about 5 mg/kg body weight,

about 100 µg/kg body weight to about 10 mg/kg body weight,

about 100 µg/kg body weight to about 20 mg/kg body weight,

about 0.5 mg/kg body weight to about 20 mg/kg body weight, or

about 5 mg/kg body weight or lower, for example less than 4, less than 3, less than 2, or less than 1 mg/kg of the antibody.

An optimal therapeutic dose may be between 0.1 and 0.5 mg/kg in a human, for example about 0.1 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.35 mg/kg, 0.4 mg/kg, 0.45 mg/kg or 0.5 mg/kg. For fixed dosing in adult humans, a suitable dose may be between 8 and 50 mg, or between 8 and 25 mg, e.g., 15 mg or 20 mg.

In methods of treatment described herein, one or more doses may be administered. In some cases, a single dose may be effective to achieve a long-term benefit. Thus, the method may comprise administering a single dose of the antibody, its encoding nucleic acid, or the composition. Alternatively, multiple doses may be administered, usually sequentially and separated by a period of days, weeks or months. Anti-ICOS antibody may be repeatedly administered to a patient at intervals of 4 to 6 weeks, e.g., every 4 weeks, every 5 weeks, or every 6 weeks. Optionally, the anti-ICOS antibody may be administered to a patient once a month, or less frequently, e.g., every two months or every three months. Accordingly, a method of treating a patient may comprise administering a single dose of the anti-ICOS antibody to the patient, and not repeating the administration for at least one month, at least two months, at least three months, and optionally not repeating the administration for at least 12 months..

As discussed in Example 11c of WO2018/029474, comparable therapeutic effects may be obtained using either one or multiple doses of anti-ICOS antibody, which may be a result of a single dose of antibody being effective to reset the tumour microenvironment. Physicians can tailor the administration regimen of the anti-ICOS antibody to the disease and the patient undergoing therapy, taking into account the disease status and any other therapeutic agents or therapeutic measures (e.g., surgery, radiotherapy etc) with which the anti-ICOS antibody is

being combined. In some embodiments, an effective dose of an anti-ICOS antibody is administered more frequently than once a month, such as, for example, once every three weeks, once every two weeks, or once every week. Treatment with anti-ICOS antibody may include multiple doses administered over a period of at least a month, at least six months, or at least a year.

As used herein, the terms "treat," "treatment," "treating," or "amelioration" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with a disease or disorder. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilised (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment). For treatment to be effective a complete cure is not contemplated. The method can in certain aspects include cure as well. In the context of the invention, treatment may be preventative treatment.

T cell therapy

WO2011/097477 described use of anti-ICOS antibodies for generating and expanding T cells, by contacting a population of T cells with a first agent that provides a primary activation signal (e.g., an anti-CD3 antibody) and a second agent that activates ICOS (e.g., an anti-ICOS antibody), optionally in the presence of a Th17 polarising agent such as IL-1β, IL-6, neutralising anti-IFNγ and/or anti-IL-4. Anti-ICOS antibodies described herein may be used in such methods to provide T cell populations. Populations of cultured expanded T cells having therapeutic activity (e.g., anti-tumour activity) may be generated. As described in WO2011/097477, such T cells may be used therapeutically in methods of treating patients by immunotherapy.

Morphological assay for anti-ICOS antibodies as therapeutic candidates

It was observed that when candidate therapeutic anti-ICOS antibodies were coupled to a solid surface and brought into contact with ICOS-expressing T cells, they were able to induce morphological change in the cells. On addition of ICOS+ T cells to wells that were internally

coated with anti-ICOS antibodies, cells were seen to change from their initial rounded shape, adopting a spindle-shape, spreading and adhering to the antibody-coated surface. This morphological change was not observed with control antibody. Moreover, the effect was found to be dose-dependent, with faster and/or more pronounced shape change occurring as the concentration of antibody on the surface increased. The shape change provides a surrogate indicator of T cell binding to ICOS, and/or of agonism by anti-ICOS antibody. The assay may be used to identify an antibody that promotes multimerisation of ICOS on the T cell surface. Such antibodies represent therapeutic candidate agonist antibodies. Conveniently, the visual indicator provided by this assay is a simple method of screening antibodies or cells, particularly in large numbers. The assay may be automated to run in a high-throughput system.

Accordingly, one aspect of the invention is an assay for selecting an antibody that binds ICOS, optionally for selecting an ICOS agonist antibody, the assay comprising:

providing an array of antibodies immobilised (attached or adhered) to a substrate in a test well;

adding ICOS-expressing cells (e.g., activated primary T cells, or MJ cells) to the test well;

observing morphology of the cells;

detecting shape change in the cells from rounded to flattened against the substrate within the well; wherein the shape change indicates that the antibody is an antibody that binds ICOS, optionally an ICOS agonist antibody, and

selecting the antibody from the test well.

The assay may be run with multiple test wells, each containing a different antibody for testing, optionally in parallel, e.g., in a 96 well plate format. The substrate is preferably an inner surface of the well. Thus, a two-dimensional surface is provided against which flattening of the cells may be observed. For example, the bottom and/or wall of a well may be coated with antibody. Tethering of antibody to the substrate may be via a constant region of the antibody.

A negative control may be included, such an an antibody known not to bind ICOS, preferably an antibody that does not bind an antigen on the surface of the ICOS-expressing cells to be used. The assay may comprise quantifying the degree of morphological change and, where multiple antibodies are tested, selecting an antibody that induces greater morphological change than one or more other test antibodies.

Selection of antibody may comprise expressing nucleic acid encoding the antibody present in the test well of interest, or expressing an antibody comprising the CDRs or antigen binding domain of that antibody. The antibody may optionally be reformatted, for example to provide an antibody comprising the antigen binding domain of the selected antibody, e.g., an antibody fragment, or an antibody comprising a different constant region. A selected antibody is preferably provided with a human IgG1 constant region or other constant region as described

herein. A selected antibody may further be formulated in a composition comprising one or more additional ingredients – suitable pharmaceutical formations are discussed elsewhere herein.

Various further aspects and embodiments of the present invention will be apparent to those skilled in the art in view of the present disclosure. All documents mentioned in this specification, including published US counterparts of any patents or patent applications referred to, are incorporated herein by reference in their entirety.

Experimental Examples

Example 1 – Study background and design

KY1044 (aka STIM003), is a fully human IgG1 anti ICOS (inducible T-cell co-stimulator) antibody designed to stimulate Teffs and to deplete ICOS high Tregs in the tumor microenvironment. ICOS is an important co-stimulatory receptor on effector T cells (Teffs) that also promotes tumor growth due to its high expression on regulatory T cells (Tregs). KY1044 is a fully human IgG1 that targets ICOS, acting via a dual mode of action (MoA) by depleting $ICOS_{high}$ Tregs and stimulating $ICOS_{Low}$ Teffs (Sainson RCA, Thotakura AK, Kosmac M, et al. An Antibody Targeting ICOS Increases Intratumoral Cytotoxic to Regulatory T-cell Ratio and Induces Tumor Regression. Cancer Immunology Research. 2020;8(12):1568–1582) - see Figure 1. KY1044-CT01 (ClinicalTrials.gov Identifier: NCT03829501) is a first-in-human study evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor activity of KY1044 as single agent and in combination with atezolizumab in patients with advanced/metastatic malignancies. Using longitudinal blood samples and tumor biopsies, we aim to correlate KY1044 target engagement levels with pharmacodynamic (PD) properties (e.g., dual MoA) in the tumor microenvironment (TME) and the circulation. The study consists of a Phase 1 dose escalation and enrichment cohorts and a Phase 2 part.

Study Objectives:

Primary:

- To characterize the safety and tolerability of KY1044 as single agent and in combination with atezolizumab and to identify recommended doses for future studies.

Secondary:

- To evaluate the preliminary anti tumor activity of KY1044 as single agent and in combination with atezolizumab.
- To characterize the PK profile of KY1044 as single agent and in combination with atezolizumab.

Exploratory:

- To assess the pharmacodynamic effect of KY1044 as single agent and in combination with atezolizumab in tumor tissue and peripheral blood.

Methods

Key Inclusion Criteria:

- Histologically documented advanced/metastatic malignancies who have measurable disease by RECIST 1.1 (non-measurable disease is allowed only in Phase 1)
- Prior therapy with anti PD-(L)1 inhibitors is allowed provided any toxicity attributed to prior anti PD (L)1 directed therapy did not lead to discontinuation of therapy.
- Eastern Cooperative Oncology Group performance status 0 or 1
- Must have a site of disease amendable to biopsy, and be candidate for tumor biopsy, according to the treating institution's guidelines.

Key Exclusion Criteria:

- Symptomatic CNS metastases, or CNS metastases that require local CNS directed therapy.
- Severe hypersensitivity reactions to other monoclonal antibodies or excipients.
- Out-of-range laboratory values as defined in protocol for renal and hepatic function or hematology parameters.
- Clinically significant heart disease and/or QT prolongation.
- Active autoimmune disease or a documented history of autoimmune disease.
- Systemic steroid therapy or any immunosuppressive therapy (≥10 mg/day prednisone or equivalent).
- Presence of CTCAE v5 ≥Grade 2 toxicity due to prior anti-cancer therapy

Figure 2 outlines the study design.

Results

PD-L1 expression in the tumour microenvironment (TMW) was assessed on tumour and immune cells using the anti-PD-L1 antibody SP263 (see Figure 3). Figure 4 shows PD-L1 immune cell expression and CD8+ T cells in the TME (baseline).

The effect of treatment on 3 patients (patients A, B and C) having PD-L1 negative tumours or PD-L1 low expression tumours was assessed. The results for Patient A are shown in Figures 5 and 6. The results for Patient B are shown in Figures 7 and 8. Despite having low PD-L1 expression, both patients arrived at a stable disease state (tumours neither growing nor shrinking) post treatment:

Patient	COHORT	PATIENT STATUS	CANCER TYPE	NAÏVE/ PRE-TREATED	EOT	TTD	STATUS	BOR
B	3M	Off treatment	HCC	Pre-treated	Discontinued	27.3	Ended	SD
A	3M	Enrolled	HCC	Naive		55.1	Ongoing	SD

(SD = stable disease); (BOR = best overall response); (TTD = time to treatment discontinuation); (EOT = end of test)

The results for Patient C are shown in Figure 9. This patient responded well with a significant decrease in lesion size from baseline at C3D8 (3rd cycle, day 8) and C10D1 (10th cycle, day 1).

HPV status

Where the HPV status of the tumor was available, as part of the medical/tumor history of the patients enrolled, it was recorded.

A “HPV positive” tumor is deemed to be associated with or derived from HPV infection. A “HPV negative” tumor is deemed not to be associated with or derived from HPV infection.

Tests for the HPV status of a tumor are known in the art. Tests may include viral DNA detection, by polymerase chain reaction or in situ hybridization, or HPV RNA detection by reverse-transcription polymerase chain reaction or in situ hybridization. Tests for HPV status can be conducted on tissue biopsies, Fine-Needle Aspiration biopsy specimens, blood samples, or saliva samples, depending on the patient and the type of tumor.

The effect of treatment on 5 patients (patients D-H) was assessed. The results are shown below. Despite having low PD-L1 expression on tumor cells as well as on immune infiltrate, the patients reached partial response (PR). Moreover, the three patients (Patients E, G, and H) have been documented having a HPV positive tumor.

Without being bound by theory, the favourable outcome might be attributed to properties of HPV-positive tumor cells, such as, a decreased proliferation rate, or the patients having an improved immune response due to existing immune response directed towards the virus.

Patient	BOR (best	HPV Status	PD-L1+ on tumor cell in TME (%) (as determined by IHC)	PD-L1+ on immune infiltrate cell in TME (%)(as determined by IHC)

	overall response)			
D	PR	POSITIVE	100	5
E	PR	POSITIVE	3	2
F	PR	NEGATIVE	0	3
G*	PR	POSITIVE	1	5
H	PR	POSITIVE	2	2

* Unconfirmed

(PR = partial response)

Conclusions

The study concluded as follows:

- Partial and transient receptor occupancy observed up to Dose Level 2 (2.4 mg) and complete and prolonged receptor occupancy at Dose Level 3 (8 mg) and above.
- No significant depletion of ICOS+ T cells in the periphery.
- KY1044 reduces ICOS+ Tregs and improves the ratio of CD8 to ICOS+ Tregs in the tumor microenvironment (Dose dependent, plateaued from dose level 3 [8 mg])
- Sign of anti-tumor activity (PR/CR) observed in both PD-L1 low and PD-L1 high tumors.

Example 2: Antibody sequence analysis

Framework regions of antibodies STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 and STIM009 were compared with human germline gene segments to identify the closest match. See Table E12-1 and Table E12-2.

Heavy chain	V	D	J
STIM001	IGHV1-18*01	IGHD6-19*01	IGHJ6*02
STIM002	IGHV1-18*01	IGHD3-10*01	IGHJ6*02
STIM002-B	IGHV1-18*01	IGHD3-10*01	IGHJ6*02
STIM003	IGHV3-20*d01	IGHD3-10*01	IGHJ4*02
STIM004	IGHV3-20*d01	IGHD3-10*01	IGHJ4*02
STIM005	IGHV1-18*01	IGHD3-9*01	IGHJ3*02
STIM006	IGHV3-11*01	IGHD3-10*01	IGHJ6*02
STIM007	IGHV2-5*10	IGHD3-10*01	IGHJ6*02
STIM008	IGHV2-5*10	IGHD3-10*01	IGHJ6*02
STIM009	IGHV3-11*01	IGHD3-9*01	IGHJ6*02

Table E12-1. Heavy chain germline gene segments of anti-ICOS Abs

Light chain	V	J
STIM001	IGKV2-28*01	IGKJ4*01
STIM002	IGKV2-28*01	IGKJ2*04
STIM002-B	IGKV2-28*01	IGKJ2*04
STIM003	IGKV3-20*01	IGKJ3*01
STIM004	IGKV3-20*01	IGKJ3*01
STIM005	IGKV1D-39*01	IGKJ1*01
STIM006	IGKV2-28*01	IGKJ2*04
STIM007	IGKV3-11*01	IGKJ4*01
STIM008	IGKV3-11*01	IGKJ4*01
STIM009	IGKV2-28*01	IGKJ1*01

Table E12-2. Kappa light chain germline gene segments of anti-ICOS Abs

Additional antibody sequences were obtained by next generation sequencing of PCR-amplified antibody DNA from further ICOS-specific cells that were sorted from the immunised mice as described in Example 3 of WO2018/029474. This identified a number of antibodies that could be grouped into clusters with STIM001, STIM002 or STIM003 based their heavy and light chain v and j gene segments and CDR3 length. CL-61091 clustered with STIM001; CL-64536, CL-64837, CL-64841 and CL-64912 clustered with STIM002; and CL-71642 and CL-74570 clustered with STIM003. Sequence alignments of the antibody VH and VL domains are shown in Figures 10 to 12.

ANTIBODIES	VH_V_GENE	VH_J_GENE	VH_CDR3_NT_LENGTH	VL_V_GENE	VL_J_GENE	VL_CDR3_NT_LENGTH
STIM001, CL-61091	1-18	6	42	2-28	4	27
STIM002, CL-64536, CL-64837, CL-64841, CL-64912	1-18	6	51	2-28	2	27
STIM003, CL-71642, CL-74570	3-20	4	51	3-20	3	27
STIM004	3-20	4	51	3-20	3	24
STIM005	1-18	3	51	1D-39	1	24
STIM006	3-11	6	63	2-28	2	30
STIM007,STIM008	2-5	6	48	3-11	4	27
STIM009	3-11	6	60	2-28	1	27

Table E12-3. Antibodies clustered by sequence.

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37 Crotty S. T follicular helper cell differentiation, function, and roles in disease. Immunity. 2014 Oct 16;41(4):529-42.

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Sequences

Antibody STIM001

VH domain nucleotide sequence: SEQ ID NO: 367

CAGGTTCAGGTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGG
TTACACCTTTTCCACCTTTGGTATCACCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAATGGATGGGATGGATCA
GCGCTTACAATGGTGACACAAACTATGCACAGAATCTCCAGGGCAGAGTCATCATGACCACAGACACATCCACGAGC
ACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTTTATTACTGTGCGAGGAGCAGTGGCCACTA
CTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 366

QVQVVQSGAEVKKPGASVKVSCKASGYTFSTFGITWVRQAPGQGLEWMGWISAYNGDTNYAQNLQGRVIMTTDTSTS
TAYMELRSLRSDDTAVYYCARSSGHYYYYGMDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GYTFSTFG SEQ ID NO: 363

VH CDR2 amino acid sequence: ISAYNGDT SEQ ID NO: 364

VH CDR3 amino acid sequence: ARSSGHYYYYGMDV SEQ ID NO: 365

VL domain nucleotide sequence: SEQ ID NO: 374

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTGCATAGTAATGAATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCC
TGATCTTTTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACA
CTGAAAATCACCAGAGTGGAGGCTGAGGATGTTGGAATTTATTACTGCATGCAATCTCTACAAACTCCGCTCACTTT
CGGCGGAGGGACCAAGGTGGAGATCAAA

VL domain amino acid sequence: SEQ ID NO: 373

DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNEYNYLDWYLQKPGQSPQLLIFLGSNRASGVPDRFSGSGSGTDFT
LKITRVEAEDVGIYYCMQSLQTPLTFGGGTKVEIK

VL CDR1 amino acid sequence: QSLLHSNEYNY SEQ ID NO: 370

VL CDR2 amino acid sequence: LGS SEQ ID NO: 371

VL CDR3 amino acid sequence: MQSLQTPLT SEQ ID NO: 372

Antibody STIM002

VH domain nucleotide sequence: SEQ ID NO: 381

CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGG
TTACACCTTTACCAGCTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTAGAGTGGATGGGATGGATCA
GCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGC

ACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGATCTACGTATTTCTA
TGGTTCGGGGACCCTCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 380
QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTS
TAYMELRSLRSDDTAVYYCARSTYFYGSGTLYGMDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GYTFTSYG SEQ ID NO: 377

VH CDR2 amino acid sequence: ISAYNGNT SEQ ID NO: 378

VH CDR3 amino acid sequence: ARSTYFYGSGTLYGMDV SEQ ID NO: 379

VL domain nucleotide sequence: 388
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTGCATAGTGATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCC
TGATCTATTTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACA
CTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTT
TGGCCAGGGGACCAAGCTGGAGATCAAA

Corrected STIM002 VL domain nucleotide sequence: SEQ ID NO: 519
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTGCATAGTGATGGATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCC
TGATCTATTTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACA
CTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGCTCAGTTT
TGGCCAGGGGACCAAGCTGGAGATCAAA

VL domain amino acid sequence: SEQ ID NO: 387
DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPGQSPQLLIYLGSTRASGFPDRFSGSGSGTDFT
LKISRVEAEDVGVYYCMQALQTPLSFGQGTKLEIK

VL CDR1 amino acid sequence: QSLLHSDGYNY SEQ ID NO: 384

VL CDR2 amino acid sequence: LGS SEQ ID NO: 385

VL CDR3 amino acid sequence: MQALQTPLS SEQ ID NO: 386

Antibody STIM002-B

VH domain nucleotide sequence: SEQ ID NO: 395
CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGG
TTACACCTTTACCAGCTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTAGAGTGGATGGGATGGATCA
GCGCTTACAATGGTAACACAAACTATGCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAGC

ACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGATCTACGTATTTCTA
TGGTTCGGGGACCCTCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 394
QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTS
TAYMELRSLRSDDTAVYYCARSTYFYGSGTLYGMDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GYTFTSYG SEQ ID NO: 391

VH CDR2 amino acid sequence: ISAYNGNT SEQ ID NO: 392

VH CDR3 amino acid sequence: ARSTYFYGSGTLYGMDV SEQ ID NO: 393

VL domain nucleotide sequence: SEQ ID NO: 402
GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTGCATAGTGATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCC
TGATCTATTTGGGTTCTACTCGGGCCTCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACA
CTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTT
TGGCCAGGGGACCAAGCTGGAGATCAAA

VL domain amino acid sequence: SEQ ID NO: 401
DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNCLDWYLQKPGQSPQLLIYLGSTRASGFPDRFSGSGSGTDFT
LKISRVEAEDVGVYYCMQALQTPCSFGQGTKLEIK

VL CDR1 amino acid sequence: QSLLHSDGYNC SEQ ID NO: 398

VL CDR2 amino acid sequence: LGS SEQ ID NO: 399

VL CDR3 amino acid sequence: MQALQTPCS SEQ ID NO: 400

Antibody STIM003

VH domain nucleotide sequence: SEQ ID NO: 409
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG
AGTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAAGGGGCTGGARTGGGTCTCTGGTATTA
ATTGGAATGGTGGCGACACAGATTATTCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC
TCCCTGTATCTACAAATGAATAGTCTGAGAGCCGAGGACACGGCCTTGTATTACTGTGCGAGGGATTTCTATGGTTC
GGGGAGTTATTATCACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCACCGTCTCCTCA

Corrected STIM003 VH domain nucleotide sequence: SEQ ID NO: 521
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGG
AGTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAAGGGGCTGGAGTGGGTCTCTGGTATTA
ATTGGAATGGTGGCGACACAGATTATTCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC

TCCCTGTATCTACAAATGAATAGTCTGAGAGCCGAGGACACGGCCTTGTATTACTGTGCGAGGGATTTCTATGGTTC
GGGGAGTTATTATCACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 408
EVQLVESGGGVVRPGGSLRLSCVASGVTFDDYGMSWVRQAPGKGLEWVSGINWNGGDTDYSDSVKGRFTISRDNAKN
SLYLQMNSLRAEDTALYYCARDFYGSGSYYHVPFDYWGQGILVTVSS

VH CDR1 amino acid sequence: GVTFDDYG SEQ ID NO: 405

VH CDR2 amino acid sequence: INWNGGDT SEQ ID NO: 406

VH CDR3 amino acid sequence: ARDFYGSGSYYHVPFDY SEQ ID NO: 407

VL domain nucleotide sequence: SEQ ID NO: 416
GAAATTGTGTTGACGCAGTCTCCAGGGACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAG
TCAGAGTGTTAGCAGAAGCTACTTAGCCTGGTACCAGCAGAAACGTGGCCAGGCTCCCAGGCTCCTCATCTATGGTG
CATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCGATGGGTCTGGGACAGACTTCACTCTCTCCATCAGC
AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCACCAGTATGATATGTCACCATTCACTTTCGGCCCTGGGAC
CAAAGTGGATATCAAA

VL domain amino acid sequence: SEQ ID NO: 415
EIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPRLLIYGASSRATGIPDRFSGDGSGTDFTLSIS
RLEPEDFAVYYCHQYDMSPFTFGPGTKVDIK

VL CDR1 amino acid sequence: QSVSRSY SEQ ID NO: 412

VL CDR2 amino acid sequence: GAS SEQ ID NO: 413

VL CDR3 amino acid sequence: HQYDMSPFT SEQ ID NO: 414

Antibody STIM004

VH domain nucleotide sequence:
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG
ACTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAAGTTCCAGGGAAGGGGCTGGAGTGGGTCTCTGGTATTA
ATTGGAATGGTGATAACACAGATTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAC
TCCCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCCTTGTATTACTGTGCGAGGGATTACTATGGTTC
GGGGAGTTATTATAACGTTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA SEQ ID NO:
423

VH domain amino acid sequence:
EVQLVESGGGVVRPGGSLRLSCAASGLTFDDYGMSWVRQVPGKGLEWVSGINWNGDNTDYADSVKGRFTISRDNAKN
SLYLQMNSLRAEDTALYYCARDYYGSGSYYNVPFDYWGQGTLVTVSS SEQ ID NO: 422

VH CDR1 amino acid sequence: GLTFDDYG SEQ ID NO: 419

VH CDR2 amino acid sequence: INWNGDNT SEQ ID NO: 420

VH CDR3 amino acid sequence: ARDYYGSGSYYNVPFDY SEQ ID NO: 421

VL domain nucleotide sequence: SEQ ID NO: 431
GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAG
TCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATATATGGTG
CATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGA
AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGTTCACCATTCACTTCGGCCCTGGGACC
AAAGTGGATATCAAA

VL domain amino acid sequence as encoded by the above VL domain nucleotide sequence.

Corrected VL domain nucleotide sequence: SEQ ID NO: 430
GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAG
TCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATATATGGTG
CATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGA
AGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGTTCACCATTCTTCGGCCCTGGGACCAA
AGTGGATATCAAA

Corrected VL domain amino acid sequence: SEQ ID NO: 432
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTIR
RLEPEDFAVYYCQQYGSSPFFGPGTKVDIK

VL CDR1 amino acid sequence: QSVSSSY SEQ ID NO: 426

VL CDR2 amino acid sequence: GAS SEQ ID NO: 427

VL CDR3 amino acid sequence: QQYGSSPF SEQ ID NO: 428

Antibody STIM005

VH domain nucleotide sequence: SEQ ID NO: 439
CAGGTTCAGTTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGG
TTACACCTTTAATAGTTATGGTATCATCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCA
GCGTTCACAATGGTAACACAAACTGTGCACAGAAGCTCCAGGGTAGAGTCACCATGACCACAGACACATCCACGAGC
ACAGCCTACATGGAGCTGAGGAGCCTGAGAACTGACGACACGGCCGTGTATTACTGTGCGAGAGCGGGTTACGATAT
TTTGACTGATTTTTCCGATGCTTTTGATATCTGGGGCCACGGGACAATGGTCACCGTCTCTTCA

VH domain amino acid sequence: SEQ ID NO: 438

QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGIIWVRQAPGQGLEWMGWISVHNGNTNCAQKLQGRVTMTTDTSTS
TAYMELRSLRTDDTAVYYCARAGYDILTDFSDAFDIWGHGTMVTVSS

VH CDR1 amino acid sequence: GYTFNSYG SEQ ID NO: 435

VH CDR2 amino acid sequence: ISVHNGNT SEQ ID NO: 436

VH CDR3 amino acid sequence: ARAGYDILTDFSDAFDI SEQ ID NO: 437

VL domain nucleotide sequence: SEQ ID NO: 446
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAG
TCAGAACATTAATAACTTTTTAAATTGGTATCAGCAGAAAGAAGGGAAAGGCCCTAAGCTCCTGATCTATGCAGCAT
CCAGTTTGCAAAGAGGGATACCATCAACGTTCAGTGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAGT
CTGCAACCTGAAGATTTTGCAACTTACATCTGTCAACAGAGCTACGGTATCCCGTGGGTCGGCCAAGGGACCAAGGT
GGAAATCAAA

VL domain amino acid sequence: SEQ ID NO: 445
DIQMTQSPSSLSASVGDRVTITCRASQNINNFLNWYQQKEGKGPKLLIYAASSLQRGIPSTFSGSGSGTDFTLTISS
LQPEDFATYICQQSYGIPWVGQGTKVEIK

VL CDR1 amino acid sequence: QNINNF SEQ ID NO: 442

VL CDR2 amino acid sequence: AAS SEQ ID NO: 443

VL CDR3 amino acid sequence: QQSYGIPW SEQ ID NO: 444

Antibody STIM006

VH domain nucleotide sequence: SEQ ID NO: 453
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG
ATTCACCTTCAGTGACTACTTCATGAGCTGGATCCGCCAGGCGCCAGGGAAGGGGCTGGAGTGGATTTCATACATTA
GTTCTAGTGGTAGTACCATATACTACGCAGACTCTGTGAGGGGCCGATTCACCATCTCCAGGGACAACGCCAAGTAC
TCACTGTATCTGCAAATGAACAGCCTGAGATCCGAGGACACGGCCGTGTATTACTGTGCGAGAGATCACTACGATGG
TTCGGGGATTTATCCCCTCTACTACTATTACGGTTTGGACGTCTGGGGCCAGGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 454
QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYFMSWIRQAPGKGLEWISYISSSGSTIYYADSVRGRFTISRDNAKY
SLYLQMNSLRSEDTAVYYCARDHYDGSGIYPLYYYYGLDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GFTFSDYF SEQ ID NO: 449

VH CDR2 amino acid sequence: ISSSGSTI SEQ ID NO: 450

VH CDR3 amino acid sequence: ARDHYDGSGIYPLYYYYGLDV SEQ ID NO: 451

VL domain nucleotide sequence: SEQ ID NO: 460
ATTGTGATGACTCAGTCTCCACTCTCCCTACCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCA
GAGCCTCCTGCATAGTAATGGATACAACTATTTGGATTATTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGA
TCTATTTGGGTTCTTATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACACTG
AAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCTCGCAGTTTTGG
CCAGGGGACCACGCTGGAGATCAAA

VL domain amino acid sequence: SEQ ID NO: 459
IVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDYYLQKPGQSPQLLIYLGSYRASGVPDRFSGSGSGTDFTL
KISRVEAEDVGVYYCMQALQTPRSFGQGTTLEIK

VL CDR1 amino acid sequence: QSLLHSNGYNY SEQ ID NO: 456

VL CDR2 amino acid sequence: LGS SEQ ID NO: 457

VL CDR3 amino acid sequence: MQALQTPRS SEQ ID NO: 458

Antibody STIM007

VH domain nucleotide sequence: SEQ ID NO: 467
CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACACAGACCCTCACGCTGACCTGCACCTTCTCTGG
GTTCTCACTCAGCACTACTGGAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGCTTGCAG
TCATTTATTGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCAGACTCACCATCACCAAGGACACCTCCAAA
AACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGCCACATATTTCTGTACACACGGATATGGTTC
GGCGAGTTATTACCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 466
QITLKESGPTLVKPTQTLTLTCTFSGFSLSTTGVGVGWIRQPPGKALEWLAVIYWDDDKRYSPSLKSRLTITKDTSK
NQVVLTMTNMDPVDTATYFCTHGYGSASYYHYGMDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GFSLSTTGVG SEQ ID NO: 463

VH CDR2 amino acid sequence: IYWDDDK SEQ ID NO: 464

VH CDR3 amino acid sequence: THGYGSASYYHYGMDV SEQ ID NO: 465

VL domain nucleotide sequence: SEQ ID NO: 474
GAAATTGTATTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAG
TCAGAGTGTTACCAACTACTTAGCCTGGCACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCAT
CCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGC
CTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCACCGTAGCAACTGGCCTCTCACTTTCGGCGGAGGGACCAA
GGTGGAGATCAAAC

VL domain amino acid sequence: SEQ ID NO: 473
EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS
LEPEDFAVYYCQHRSNWPLTFGGGTKVEIK

VL CDR1 amino acid sequence: QSVTNY SEQ ID NO: 470

VL CDR2 amino acid sequence: DAS SEQ ID NO: 471

VL CDR3 amino acid sequence: QHRSNWPLT SEQ ID NO: 472

Antibody STIM008

VH domain nucleotide sequence: SEQ ID NO: 481
CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACACAGACCCTCACGCTGACCTGCACCTTCTCTGG
GTTCTCACTCAGCACTAGTGGAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTGGAGTGGCTTGCAG
TCATTTATTGGGATGATGATAAGCGCTACAGCCCATCTCTGAAGAGCAGGCTCACCATCACCAAGGACACCTCCAAA
AACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACAGCCACATATTTCTGTACACACGGATATGGTTC
GGCGAGTTATTACCACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 480
QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKALEWLAVIYWDDDKRYSPSLKSRLTITKDTSK
NQVVLTMTNMDPVDTATYFCTHGYGSASYYHYGMDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GFSLSTSGVG SEQ ID NO: 477

VH CDR2 amino acid sequence: IYWDDDK SEQ ID NO: 478

VH CDR3 amino acid sequence: THGYGSASYYHYGMDV SEQ ID NO: 479

VL domain nucleotide sequence: SEQ ID NO: 488
GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAG
TCAGAGTGTTACCAACTACTTAGCCTGGCACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGATGCAT
CCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGC
CTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCTCTCACTTTCGGCGGAGGGACCAA
GGTGGAGATCAAA

VL domain amino acid sequence: SEQ ID NO: 489
EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISS
LEPEDFAVYYCQQRSNWPLTFGGGTKVEIK

VL CDR1 amino acid sequence: QSVTNY SEQ ID NO: 484

VL CDR2 amino acid sequence: DAS SEQ ID NO: 485

VL CDR3 amino acid sequence: QQRSNWPLT SEQ ID NO: 486

Antibody STIM009

VH domain nucleotide sequence: SEQ ID NO: 495

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG
ATTCACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTA
GTAGTAGTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAAC
TCACTGTATCTGCAAATTAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGAGATTTTTACGATAT
TTTGACTGATAGTCCGTACTTCTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

VH domain amino acid sequence: SEQ ID NO: 494

QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKN
SLYLQINSLRAEDTAVYYCARDFYDILTDSPYFYYGVDVWGQGTTVTVSS

VH CDR1 amino acid sequence: GFTFSDYY SEQ ID NO: 491

VH CDR2 amino acid sequence: ISSSGSTI SEQ ID NO: 492

VH CDR3 amino acid sequence: ARDFYDILTDSPYFYYGVDV SEQ ID NO: 493

VL domain nucleotide sequence: SEQ ID NO: 502

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAG
TCAGAGCCTCCTGCATAGTAATGGATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCC
TGATCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACA
CTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCTCGGACGTT
CGGCCAAGGGACCAAGGTGGAAATCAAA

VL domain amino acid sequence: SEQ ID NO: 501

DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFT
LKISRVEAEDVGVYYCMQALQTPRTFGQGTKVEIK

VL CDR1 amino acid sequence: QSLLHSNGYNY SEQ ID NO: 498

VL CDR2 amino acid sequence: LGS SEQ ID NO: 499

VL CDR3 amino acid sequence: MQALQTPRT SEQ ID NO: 500

Table S1. SEQ ID NOS: 1-342

SEQ ID NO:	Name	Description	Sequence
1	Human PD-L1	NCBI number: NP_054862.1 (ECD highlighted in **BOLD**, cytoplasmic domain underlined)	MRIFAVFIFMTYWHLLNA**FTVTVPKDLYVVEYGSNMTIECKFPVEKQL DLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGN AALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVV DPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFN VTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERT**H LVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLE ET
2	Cyno PD-L1	NCBI number: XP_014973154.1 (ECD highlighted in **BOLD**)	MGWSCIILFLVATATGVHSM**FTVTVPKDLYVVEYGSNMTIECKFPVEK QLDLTSLIVYWEMEDKNIIQFVHGEEDLKVQHSNYRQRAQLLKDQLSL GNAALRITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRIL VVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKL LNVTSTLRINTTANEIFYCIFRRLDPEENHTAELVIPELPLALPPNER T**
3	Human PD-L1 His	Human PD-L1 ECD with C-terminal His tag	MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQL DLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGN AALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVV DPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFN VTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERT**H HHHHH**
4	Human PD-L1 Fc	Human PD-L1 ECD with C-term Fc fusion (in bold)	MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQL DLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGN AALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVV DPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFN VTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERT**I EGREPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**
5	Cyno PD-L1 FLAG	Cynomolgus PD-L1 ECD with N-term FLAG tag	MGWSCIILFLVATATGVHSMFTVTVPKDLYVVEYGSNMTIECKFPVEK QLDLTSLIVYWEMEDKNIIQFVHGEEDLKVQHSNYRQRAQLLKDQLSL GNAALRITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRIL VVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKL LNVTSTLRINTTANEIFYCIFRRLDPEENHTAELVIPELPLALPPNER T**DYKDDDDK**

SEQ ID NO:	Name	Description	Sequence
6	Human PD-1 Fc	Human PD-1 full length sequence derived from cDNA as human Fc fusion	MGWSCIILFLVATATGVHSLDSPDRPWNPPTFSPALLVVTEGDNATFT CSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLP NGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRA EVPTAHPSPSPRPAGQ**KLENLYFQGIEGRMDEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSP**
7	84G09 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 84G09 using IMGT	GFTFDDYA
8	84G09 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 84G09 using IMGT	ISWKSNII
9	84G09 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 84G09 using IMGT	ARDITGSGSYGWFDP
10	84G09 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 84G09 using Kabat	DYAMH
11	84G09 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 84G09 using Kabat	GISWKSNIIGYADSVKG
12	84G09 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 84G09 using Kabat	DITGSGSYGWFDP
13	84G09 - Heavy chain variable region	Amino acid sequence of V_H of 84G09(mutations from germline are shown in bold letters)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ**T**PGKGLEWV SGISW**K**S**NI**IGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYC ARDITGSGSYGWFDPWGQGTLVTVSS

SEQ ID NO:	Name	Description	Sequence
14	84G09 - Heavy chain variable region	Nucleic acid sequence of V_H of 84G09	CAaGAAAAAGCTTGCCGCCACCATGGAGTTTGGGCTGAGCTGGATTTT CCTTTTGGCTATTTTAAAAGGTGTCCAGTGTGAAGTACAATTGGTGGA GTCCGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTG TGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCG ACAAACTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATAAGTTGGAA GAGTAATATCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCAT CTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAGTCT GAGAGCTGAGGACACGGCCTTGTATTATTGTGCAAGAGATATAACGGG TTCGGGGAGTTATGGCTGGTTCGACCCCTGGGGCCAGGGAACCCTGGT CACCGTCTCCTCAGCCAAAACGACACCCCCATCTGTCTATCCACTGGC CCCTGAATCTGCTAAAACTCAGCCTCCG
15	84G09 - full heavy chain sequence	Amino acid sequence of 84G09 heavy chain (mutations from germline are shown in bold letters)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWV SGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYC ARDITGSGSYGWFDPWGQGTLVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK

SEQ ID NO:	Name	Description	Sequence
16	84G09 - full heavy chain sequence	Nucleic acid sequence of 84G09 heavy chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCAGA TCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCGACGACTAC GCTATGCACTGGGTGCGACAGACCCCTGGCAAGGGCCTGGAATGGGTG TCCGGCATCTCCTGGAAGTCCAACATCATCGGCTACGCCGACTCCGTG AAGGGCCGGTTCACCATCTCCCGGGACAACGCCAAGAACTCCCTGTAC CTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCCTGTACTACTGC GCCAGAGACATCACCGGCTCCGGCTCCTACGGATGGTTCGATCCTTGG GGCCAGGGCACCCTCGTGACCGTGTCCTCTGCCAGCACCAAGGGCCCC TCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACA GCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACC GTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCT GCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACC GTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAAC CACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCC TGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTG GGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTG ATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCC CACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAA GTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACC TACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAAC GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCC ATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAG GTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTG TCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTG GAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCC CCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACA GTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTG ATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTG AGCCCCGGCAAG
17	84G09 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 84G09 using IMGT	QSISSY
18	84G09 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 84G09 using IMGT	VAS
19	84G09 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 84G09 using IMGT	QQSYSNPIT
20	84G09 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 84G09 using Kabat	RASQSISSYLN

SEQ ID NO:	Name	Description	Sequence
21	84G09 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 84G09 using Kabat	VASSLQS
22	84G09 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 84G09 using Kabat	QQSYSNPIT
23	84G09 - Light chain variable region	Amino acid sequence of V_L of 84G09	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLI YVASSLQSGVPSSFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSNPI TFGQGTRLEIK
24	84G09 - Light chain variable region	Nucleic acid sequence of V_L of 84G09	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTAT TTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCCCCTGATC TATGTTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGTTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTAATCCGATC ACCTTCGGCCAAGGGACACGACTGGAGATCAAA
25	84G09 - full light chain sequence	Amino acid sequence of 84G09 light chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLI YVASSLQSGVPSSFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSNPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
26	84G09 - full light chain sequence	Nucleic acid sequence of 84G09 light chain	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTAT TTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCCCCTGATC TATGTTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGTTTCAGTGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCT GAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTAATCCGATC ACCTTCGGCCAAGGGACACGACTGGAGATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
27	1D05 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 1D05 using IMGT	GFTFDDYA
28	1D05 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 1D05 using IMGT	ISWIRTGI

SEQ ID NO:	Name	Description	Sequence
29	1D05 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 1D05 using IMGT	AKDMKGSGTYGGWFDT
30	1D05 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 1D05 using Kabat	DYAMH
31	1D05 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 1D05 using Kabat	GISWIRTGIGYADSVKG
32	1D05 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 1D05 using Kabat	DMKGSGTYGGWFDT
33	1D05 - Heavy chain variable region	Amino acid sequence of V_H of 1D05 (mutations from germline are shown in bold letters)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ**V**PGKGLEWV SGISW**IRTG**IGYADSVKGRFTI**F**RDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSS
34	1D05 - Heavy chain variable region	Nucleic acid sequence of V_H of 1D05	AAGCTTGCCGCCACCATGGAGTTTGGGCTGAGCTGGATTTTCCTTTTG GCTATTTTAAAAGGTGTCCAGTGTGAAGTGCAGCTGGTGGAGTCTGGG GGAGGCTTGGTGCAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCC TCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGTT CCAGGGAAGGGCCTGGAATGGGTCTCAGGCATTAGTTGGATTCGTACT GGCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATTTTCAGA GACAACGCCAAGAATTCCCTGTATCTGCAAATGAACAGTCTGAGAGCT GAGGACACGGCCTTGTATTACTGTGCAAAAGATATGAAGGGTTCGGGG ACTTATGGGGGGTGGTTCGACACCTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAGCCAAAACAACAGCCCCATCGGTCTATCCACTGGCCCCT GC
35	1D05 - full heavy chain sequence	Amino acid sequence of 1D05 heavy chain	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWV SGISWIRTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK

SEQ ID NO:	Name	Description	Sequence
36	1D05 - full heavy chain sequence	Nucleic acid sequence of 1D05 heavy chain	GAAGTGCAGCTGGTGGAATCTGGCGGCGGACTGGTGCAGCCTGGCAGA TCCCTGAGACTGTCTTGTGCCGCCTCCGGCTTCACCTTCGACGACTAC GCTATGCACTGGGTGCGACAGGTGCCAGGCAAGGGCCTGGAATGGGTG TCCGGCATCTCTTGGATCCGGACCGGCATCGGCTACGCCGACTCTGTG AAGGGCCGGTTCACCATCTTCCGGGACAACGCCAAGAACTCCCTGTAC CTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCCTGTACTACTGC GCCAAGGACATGAAGGGCTCCGGCACCTACGGCGGATGGTTCGATACT TGGGGCCAGGGCACCCTCGTGACCGTGTCCTCTGCCAGCACCAAGGGC CCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGA ACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTG ACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTC CCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTG ACCGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTG AACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAG TCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTG CTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACC CTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTG GAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC ACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTG AACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCC CCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCC CAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAG GTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCC GTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACC CCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTG ACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCC GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCC CTGAGCCCCGGCAAG
37	1D05 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 1D05 using IMGT	QSISSY
38	1D05 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 1D05 using IMGT	VAS
39	1D05 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 1D05 using IMGT	QQSYSTPIT
40	1D05 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 1D05 using Kabat	RASQSISSYLN

SEQ ID NO:	Name	Description	Sequence
41	1D05 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 1D05 using Kabat	VASSLQS
42	1D05 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 1D05 using Kabat	QQSYSTPIT
43	1D05 - Light chain variable region	Amino acid sequence of V_L of 1D05(mutations from germline are shown in bold letters)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YVASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIK
44	1D05 - Light chain variable region	Nucleic acid sequence of V_L of 1D05	AAAGCTTGCCGCCACCATGAGGCTCCCTGCTCAGCTTCTGGGGCTCCT GCTACTCTGGCTCCGAGGTGCCAGATGTGACATCCAGATGACCCAGTC TCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTG CCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAA ACCAGGGAAAGCCCCTAAACTCCTGATCTATGTTGCATCCAGTTTGCA AAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTT CACTCTCACTATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTA CTGTCAACAGAGTTACAGTACCCCGATCACCTTCGGCCAAGGGACACG TCTGGAGATCAAACGTACGGATGCTGCACCAACT
45	1D05 - full light chain sequence	Amino acid sequence of 1D05 light chain	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YVASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
46	1D05 - full light chain sequence	Nucleic acid sequence of 1D05 light chain	GACATCCAGATGACCCAGTCCCCCTCCAGCCTGTCTGCTTCCGTGGGC GACAGAGTGACCATCACCTGTCGGGCCTCCCAGTCCATCTCCTCCTAC CTGAACTGGTATCAGCAGAAGCCCGGCAAGGCCCCCAAGCTGCTGATC TACGTGGCCAGCTCTCTGCAGTCCGGCGTGCCCTCTAGATTCTCCGGC TCTGGCTCTGGCACCGACTTTACCCTGACCATCAGCTCCCTGCAGCCC GAGGACTTCGCCACCTACTACTGCCAGCAGTCCTACTCCACCCCTATC ACCTTCGGCCAGGGCACCCGGCTGGAAATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT

SEQ ID NO:	Name	Description	Sequence
47	Mutated 1D05 - HC mutant 1	Amino acid sequence of 1D05 heavy chain with V to A back-mutation in framework region to germline highlighted with IgG1 disabled (LAGA) constant region	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ**A**PGKGLEWV SGISWIRTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE**LAGA** PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK
48	Mutated 1D05 - HC mutant 2	Amino acid sequence of 1D05 heavy chain with F to S back-mutation in framework region to germline highlighted with IgG1 disabled (LAGA) constant region	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWV SGISWIRTGIGYADSVKGRFTI**S**RDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE**LAGA** PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK
49	Mutated 1D05 - HC mutant 3	Amino acid sequence of 1D05 heavy chain with ELLG to -PVA back-mutation in constant region to germline highlighted	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWV SGISWIRTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAP**-PVA**GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSC SVMHEALHNHYTQKSLSLSLGK
50	Mutated 1D05 - LC mutant 1	Amino acid sequence of 1D05 kappa light chain with V to A back-mutation in CDRL2 to germline highlighted	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI Y**A**ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
51	Mutated 1D05 - LC mutant 2	Amino acid sequence of 1D05 kappa light chain with L to F back-mutation in framework to germline highlighted	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKL**F**I YVASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
52	411B08 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 411B08 using IMGT	GFTFSSYW
53	411B08 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 411B08 using IMGT	IKEDGSEK
54	411B08 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 411B08 using IMGT	ARNRLYSDFLDN
55	411B08 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 411B08 using Kabat	SYWMS
56	411B08 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 411B08 using Kabat	NIKEDGSEKYYVDSVKG
57	411B08 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 411B08 using Kabat	NRLYSDFLDN
58	411B08 - Heavy chain variable region	Amino acid sequence of V_H of 411B08	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYC ARNRLYSDFLDNWGQGTLVTVSS
59	411B08 - Heavy chain variable region	Nucleic acid sequence of V_H of 411B08	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTAT TGGATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTG GCCAACATCAAAGAAGATGGAAGTGAGAAATACTATGTCGACTCTGTG AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGTCTGTGTATTACTGT GCGAGAAATCGACTCTACAGTGACTTCCTTGACAACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCAG
60	411B08 - full heavy chain sequence	Amino acid sequence of 411B08 heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYC ARNRLYSDFLDNWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
61	411B08 - full heavy chain sequence	Nucleic acid sequence of 411B08 heavy chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTAT TGGATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTG GCCAACATCAAAGAAGATGGAAGTGAGAAATACTATGTCGACTCTGTG AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGTCTGTGTATTACTGT GCGAGAAATCGACTCTACAGTGACTTCCTTGACAACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTC CCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTG GGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGG AACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTG CAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCC AGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCC TCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAG ACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCT TCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCC CGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGAC CCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAAC GCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAG TACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAG ACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACA CTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACC TGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAG TCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAG TCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAG GCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGC AAG
62	411B08 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 411B08 using IMGT	QGVSSW
63	411B08 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 411B08 using IMGT	GAS
64	411B08 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 411B08 using IMGT	QQANSIPFT
65	411B08 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 411B08 using Kabat	RASQGVSSWLA

SEQ ID NO:	Name	Description	Sequence
66	411B08 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 411B08 using Kabat	GASSLQS
67	411B08 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 411B08 using Kabat	QQANSIPFT
68	411B08 - Light chain variable region	Amino acid sequence of V_L of 411B08	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLI YGASSLQSGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPF TFGPGTKVDIK
69	411B08 - Light chain variable region	Nucleic acid sequence of V_L of 411B08	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGG TTAGCCTGGTATCAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGATTCAGCGGC AGTGGATCTGGGACAGAGTTCATTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTATCCCATTC ACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC
70	411B08 - full light chain sequence	Amino acid sequence of 411B08 light chain	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLI YGASSLQSGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPF TFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
71	411B08 - full light chain sequence	Nucleic acid sequence of 411B08 light chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGG TTAGCCTGGTATCAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGATTCAGCGGC AGTGGATCTGGGACAGAGTTCATTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTATCCCATTC ACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
72	411C04 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 411C04 using IMGT	GFTFSSYW

SEQ ID NO:	Name	Description	Sequence
73	411C04 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 411C04 using IMGT	IKEDGSEK
74	411C04 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 411C04 using IMGT	ARVRLYSDFLDY
75	411C04 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 411C04 using Kabat	SYWMS
76	411C04 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 411C04 using Kabat	NIKEDGSEKYYVDSLKG
77	411C04 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 411C04 using Kabat	VRLYSDFLDY
78	411C04 - Heavy chain variable region	Amino acid sequence of V_H of 411C04	EVQLVDSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKEDGSEKYYVDSLKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYC ARVRLYSDFLDYWGQGTLVTVSS
79	411C04 - Heavy chain variable region	Nucleic acid sequence of V_H of 411C04	GAGGTGCAGCTGGTGGACTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTAT TGGATGAGTTGGGTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTG GCCAACATAAAAGAAGATGGAAGTGAGAAATACTATGTAGACTCTTTG AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGTCTGTGTATTACTGT GCGAGAGTTCGACTCTACAGTGACTTCCTTGACTACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCAG
80	411C04 - full heavy chain sequence	Amino acid sequence of 411C04 heavy chain	EVQLVDSGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKEDGSEKYYVDSLKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYC ARVRLYSDFLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
81	411C04 - full heavy chain sequence	Nucleic acid sequence of 411C04 heavy chain	GAGGTGCAGCTGGTGGACTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTAT TGGATGAGTTGGGTCCGCCAGGCTCCAGGAAAGGGGCTGGAGTGGGTG GCCAACATAAAAGAAGATGGAAGTGAGAAATACTATGTAGACTCTTTG AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGTCTGTGTATTACTGT GCGAGAGTTCGACTCTACAGTGACTTCCTTGACTACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTC CCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTG GGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGG AACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTG CAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCC AGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCC TCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAG ACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCT TCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCC CGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGAC CCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAAC GCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAG TACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAG ACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACA CTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACC TGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAG TCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAG TCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAG GCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGC AAG
82	411C04 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 411C04 using IMGT	QGVSSW
83	411C04 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 411C04 using IMGT	GAS
84	411C04 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 411C04 using IMGT	QQANSIPFT
85	411C04 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 411C04 using Kabat	RASQGVSSWLA

SEQ ID NO:	Name	Description	Sequence
86	411C04 – CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 411C04 using Kabat	GASSLQS
87	411C04 – CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 411C04 using Kabat	QQANSIPFT
88	411C04 – Light chain variable region	Amino acid sequence of V_L of 411C04	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLI YGASSLQSGVPSRFSGSGSGTEFILSISSLQPEDFATYYCQQANSIPF TFGPGTKVDIK
89	411C04 – Light chain variable region	Nucleic acid sequence of V_L of 411C04	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGTTGG TTAGCCTGGTATCAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTGCCTCCAGTTTGCAAAGTGGGGTCCCATCAAGATTCAGCGGC AGTGGATCTGGGACAGAGTTCATTCTCAGCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTATCCCATTC ACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC
90	411C04 – full light chain sequence	Amino acid sequence of 411C04 light chain	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLI YGASSLQSGVPSRFSGSGSGTEFILSISSLQPEDFATYYCQQANSIPF TFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
91	411C04 – full light chain sequence	Nucleic acid sequence of 411C04 light chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGTTGG TTAGCCTGGTATCAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTGCCTCCAGTTTGCAAAGTGGGGTCCCATCAAGATTCAGCGGC AGTGGATCTGGGACAGAGTTCATTCTCAGCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTATCCCATTC ACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
92	411D07 – CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 411D07 using IMGT	GGSIISSDW

SEQ ID NO:	Name	Description	Sequence
93	411D07 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 411D07 using IMGT	IFHSGRT
94	411D07 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 411D07 using IMGT	ARDGSGSY
95	411D07 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 411D07 using Kabat	SSDWWN
96	411D07 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 411D07 using Kabat	EIFHSGRTNYNPSLKS
97	411D07 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 411D07 using Kabat	DGSGSY
98	411D07 - Heavy chain variable region	Amino acid sequence of V_H of 411D07	QVQLQESGPGLVKPSGTLSLTCIVSGGSIISSDWWNWVRQPPGKGLEW IGEIFHSGRTNYNPSLKSRVTISIDKSKNQFSLRLSSVTAADTAVYYC ARDGSGSYWGQGTLVTVSS
99	411D07 - Heavy chain variable region	Nucleic acid sequence of V_H of 411D07	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGG ACCCTGTCCCTCACCTGCATTGTCTCTGGTGGCTCCATCATCAGTAGT GACTGGTGGAATTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGG ATTGGAGAAATCTTTCATAGTGGGAGGACCAACTACAACCCGTCCCTC AAGAGTCGAGTCACCATATCAATAGACAAGTCCAAGAATCAGTTCTCC CTGAGGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGT GCGAGAGATGGTTCGGGGAGTTACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAG
100	411D07 - full heavy chain sequence	Amino acid sequence of 411D07 heavy chain	QVQLQESGPGLVKPSGTLSLTCIVSGGSIISSDWWNWVRQPPGKGLEW IGEIFHSGRTNYNPSLKSRVTISIDKSKNQFSLRLSSVTAADTAVYYC ARDGSGSYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
101	411D07 - full heavy chain sequence	Nucleic acid sequence of 411D07 heavy chain	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGG ACCCTGTCCCTCACCTGCATTGTCTCTGGTGGCTCCATCATCAGTAGT GACTGGTGGAATTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGG ATTGGAGAAATCTTTCATAGTGGGAGGACCAACTACAACCCGTCCCTC AAGAGTCGAGTCACCATATCAATAGACAAGTCCAAGAATCAGTTCTCC CTGAGGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGT GCGAGAGATGGTTCGGGGAGTTACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCT TCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTG AAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCT CTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGC CTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGC ACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAG GTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGT CCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTG TTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAA GTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAG TTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAG CCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAG GTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAG GCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGC AGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAA GGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAG CCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGC TCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAG CAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
102	411D07 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 411D07 using IMGT	QSVLYSSNNKNY
103	411D07 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 411D07 using IMGT	WAS
104	411D07 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 411D07 using IMGT	QQYYSNRS
105	411D07 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 411D07 using Kabat	KSSQSVLYSSNNKNYLA
106	411D07 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 411D07 using Kabat	WASTRES

SEQ ID NO:	Name	Description	Sequence
107	411D07 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 411D07 using Kabat	QQYYSNRS
108	411D07 - Light chain variable region	Amino acid sequence of V_L of 411D07	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKSGQ PPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQTEDVAVYYCQQ YYSNRSFGQGTKLEIK
109	411D07 - Light chain variable region	Nucleic acid sequence of V_L of 411D07	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC GAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGC TCCAACAATAAGAATTACTTAGCTTGGTACCAGCAGAAATCAGGACAG CCTCCTAAGTTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTC CCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGCAGACTGAAGATGTGGCAGTTTATTACTGTCAGCAA TATTATAGTAATCGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAA C
110	411D07 - full light chain sequence	Amino acid sequence of 411D07 light chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKSGQ PPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQTEDVAVYYCQQ YYSNRSFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
111	411D07 - full light chain sequence	Nucleic acid sequence of 411D07 light chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC GAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGC TCCAACAATAAGAATTACTTAGCTTGGTACCAGCAGAAATCAGGACAG CCTCCTAAGTTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTC CCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGCAGACTGAAGATGTGGCAGTTTATTACTGTCAGCAA TATTATAGTAATCGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAA CGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAG CAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTC TACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG TCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGC ACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCTAGC CCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
112	385F01 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 385F01 using IMGT	GFTFSSYW
113	385F01 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 385F01 using IMGT	IKEDGSEK

SEQ ID NO:	Name	Description	Sequence
114	385F01 – CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 385F01 using IMGT	ARNRLYSDFLDN
115	385F01 – CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 385F01 using Kabat	SYWMS
116	385F01 – CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 385F01 using Kabat	NIKEDGSEKYYVDSVKG
117	385F01 – CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 385F01 using Kabat	NRLYSDFLDN
118	385F01 – Heavy chain variable region	Amino acid sequence of V_H of 385F01	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYC ARNRLYSDFLDNWGQGTLVTVSS
119	385F01 – Heavy chain variable region	Nucleic acid sequence of V_H of 385F01	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTAT TGGATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTG GCCAACATCAAAGAAGATGGAAGTGAGAAATACTATGTCGACTCTGTG AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGTCTGTGTATTACTGT GCGAGAAATCGACTCTACAGTGACTTCCTTGACAACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCAG
120	385F01 – full heavy chain sequence	Amino acid sequence of 385F01 heavy chain	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWV ANIKEDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTSVYYC ARNRLYSDFLDNWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
121	385F01 - full heavy chain sequence	Nucleic acid sequence of 385F01 heavy chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGTAGCTAT TGGATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTG GCCAACATCAAAGAAGATGGAAGTGAGAAATACTATGTCGACTCTGTG AAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGTCTGTGTATTACTGT GCGAGAAATCGACTCTACAGTGACTTCCTTGACAACTGGGGCCAGGGA ACCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTC CCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTG GGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGG AACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTG CAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCC AGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCC TCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAG ACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCT TCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCC CGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGAC CCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAAC GCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAG TACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAG ACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACA CTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACC TGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAG TCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAG TCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAG GCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGC AAG
122	385F01 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 385F01 using IMGT	QGVSSW
123	385F01 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 385F01 using IMGT	GAS
124	385F01 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 385F01 using IMGT	QQANSIPFT
125	385F01 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 385F01 using Kabat	RASQGVSSWLA

SEQ ID NO:	Name	Description	Sequence
126	385F01 – CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 385F01 using Kabat	GASSLQS
127	385F01 – CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 385F01 using Kabat	QQANSIPFT
128	385F01 – Light chain variable region	Amino acid sequence of V_L of 385F01	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQSGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPFTFGPGTKVDIK
129	385F01 – Light chain variable region	Nucleic acid sequence of V_L of 385F01	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGGTTAGCCTGGTATCAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTTCATTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC
130	385F01 – full light chain sequence	Amino acid sequence of 385F01 light chain	DIQMTQSPSSVSASVGDRVTITCRASQGVSSWLAWYQQKSGKAPKLLIYGASSLQSGVPSRFSGSGSGTEFILTISSLQPEDFATYYCQQANSIPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
131	385F01 – full light chain sequence	Nucleic acid sequence of 385F01 light chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTCGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTGTTAGCAGCTGGTTAGCCTGGTATCAGCAGAAATCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAGAGTTCATTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTATCCCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
132	413D08 – CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 413D08 using IMGT	GFTFRIYG

SEQ ID NO:	Name	Description	Sequence
133	413D08 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 413D08 using IMGT	IWYDGSNK
134	413D08 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 413D08 using IMGT	ARDMDYFGMDV
135	413D08 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 413D08 using Kabat	IYGMH
136	413D08 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 413D08 using Kabat	VIWYDGSNKYYADSVKG
137	413D08 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 413D08 using Kabat	DMDYFGMDV
138	413D08 - Heavy chain variable region	Amino acid sequence of V_H of 413D08	QVQLVESGGGVVQPGRSLRLSCAASGFTFRIYGMHWVRQAPGKGLEWV AVIWYDGSNKYYADSVKGRFTISRDNSDNTLYLQMNSLRAEDTAVYYC ARDMDYFGMDVWGQGTTVTVSS
139	413D08 - Heavy chain variable region	Nucleic acid sequence of V_H of 413D08	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGG TCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCCGTATTTAT GGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTG GCAGTTATATGGTATGATGGAAGTAATAAATACTATGCTGACTCCGTG AAGGGCCGATTCACCATCTCCAGAGACAATTCCGACAACACGCTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGT GCGAGAGATATGGACTACTTCGGTATGGACGTCTGGGGCCAAGGGACC ACGGTCACCGTCTCCTCAG
140	413D08 - full heavy chain sequence	Amino acid sequence of 413D08 heavy chain	QVQLVESGGGVVQPGRSLRLSCAASGFTFRIYGMHWVRQAPGKGLEWV AVIWYDGSNKYYADSVKGRFTISRDNSDNTLYLQMNSLRAEDTAVYYC ARDMDYFGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
141	413D08 - full heavy chain sequence	Nucleic acid sequence of 413D08 heavy chain	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGG TCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCCGTATTTAT GGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTG GCAGTTATATGGTATGATGGAAGTAATAAATACTATGCTGACTCCGTG AAGGGCCGATTCACCATCTCCAGAGACAATTCCGACAACACGCTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGT GCGAGAGATATGGACTACTTCGGTATGGACGTCTGGGGCCAAGGGACC ACGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCT CTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGC TGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAAC TCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAG TCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGC TCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCC AACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACC CACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCC GTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGG ACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCT GAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCC AAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTG TCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTAC AAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACC ATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTG CCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGT CTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCC AACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGAC TCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCC CGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
142	413D08 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 413D08 using IMGT	QGIRND
143	413D08 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 413D08 using IMGT	AAS
144	413D08 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 413D08 using IMGT	LQHNSYPRT
145	413D08 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 413D08 using Kabat	RASQGIRNDLG
146	413D08 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 413D08 using Kabat	AASSLQS

SEQ ID NO:	Name	Description	Sequence
147	413D08 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 413D08 using Kabat	LQHNSYPRT
148	413D08 - Light chain variable region	Amino acid sequence of V_L of 413D08	DLQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLI YAASSLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPR TFGQGTKVEIK
149	413D08 - Light chain variable region	Nucleic acid sequence of V_L of 413D08	GACCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGAT TTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCTCGG ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAAC
150	413D08 - full light chain sequence	Amino acid sequence of 413D08 light chain	DLQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLI YAASSLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPR TFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
151	413D08 - full light chain sequence	Nucleic acid sequence of 413D08 light chain	GACCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGAT TTAGGCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTATTACTGTCTACAGCATAATAGTTACCCTCGG ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
152	386H03 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 386H03 using IMGT	GGSISSSDW
153	386H03 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 386H03 using IMGT	IFHSGNT

SEQ ID NO:	Name	Description	Sequence
154	386H03 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 386H03 using IMGT	VRDGSGSY
155	386H03 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 386H03 using Kabat	SSDWWS
156	386H03 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 386H03 using Kabat	EIFHSGNTNYNPSLKS
157	386H03 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 386H03 using Kabat	DGSGSY
158	386H03 - Heavy chain variable region	Amino acid sequence of V_H of 386H03	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSDWWSWVRQPPGKGLEW IGEIFHSGNTNYNPSLKSRVTISVDKSKNQISLRLNSVTAADTAVYYC VRDGSGSYWGQGTLVTVSS
159	386H03 - Heavy chain variable region	Nucleic acid sequence of V_H of 386H03	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGG ACCCTGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTAGT GACTGGTGGAGTTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGG ATTGGGGAAATCTTTCATAGTGGGAACACCAACTACAACCCGTCCCTC AAGAGTCGAGTCACCATATCAGTAGACAAGTCCAAGAACCAGATCTCC CTGAGGCTGAACTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGT GTGAGAGATGGTTCGGGGAGTTACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAG
160	386H03 - full heavy chain sequence	Amino acid sequence of 386H03 heavy chain	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSDWWSWVRQPPGKGLEW IGEIFHSGNTNYNPSLKSRVTISVDKSKNQISLRLNSVTAADTAVYYC VRDGSGSYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
161	386H03 - full heavy chain sequence	Nucleic acid sequence of 386H03 heavy chain	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGG ACCCTGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTAGT GACTGGTGGAGTTGGGTCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGG ATTGGGGAAATCTTTCATAGTGGGAACACCAACTACAACCCGTCCCTC AAGAGTCGAGTCACCATATCAGTAGACAAGTCCAAGAACCAGATCTCC CTGAGGCTGAACTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGT GTGAGAGATGGTTCGGGGAGTTACTGGGGCCAGGGAACCCTGGTCACC GTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCT TCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTG AAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCT CTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGC CTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGC ACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAG GTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGT CCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTG TTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAA GTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAG TTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAG CCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAG GTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAG GCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGC AGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAA GGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAG CCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGC TCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAG CAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAG
162	386H03 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 386H03 using IMGT	QSVLYSSNNKNY
163	386H03 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 386H03 using IMGT	WAS
164	386H03 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 386H03 using IMGT	QQYYSTRS
165	386H03 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 386H03 using Kabat	KSSQSVLYSSNNKNYLA
166	386H03 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 386H03 using Kabat	WASTRES

SEQ ID NO:	Name	Description	Sequence
167	386H03 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 386H03 using Kabat	QQYYSTRS
168	386H03 - Light chain variable region	Amino acid sequence of V_L of 386H03	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQ PPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQ YYSTRSFGQGTKLEIK
169	386H03 - Light chain variable region	Nucleic acid sequence of V_L of 386H03	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC GAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGC TCCAACAATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGACAG CCTCCTAAACTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTC CCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAA TATTATAGTACTCGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAA C
170	386H03 - full light chain sequence	Amino acid sequence of 386H03 light chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQ PPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQ YYSTRSFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
171	386H03 - full light chain sequence	Nucleic acid sequence of 386H03 light chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC GAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGC TCCAACAATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGACAG CCTCCTAAACTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTC CCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACC ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAA TATTATAGTACTCGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAA CGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAG CAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTC TACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAG TCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGC ACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAG AAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCTAGC CCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
172	389A03 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 389A03 using IMGT	GGSISSSSYY
173	389A03 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 389A03 using IMGT	IYSTGYT

SEQ ID NO:	Name	Description	Sequence
174	389A03 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 389A03 using IMGT	AISTAAGPEYFHR
175	389A03 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 389A03 using Kabat	SSSYYCG
176	389A03 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 389A03 using Kabat	SIYSTGYTYYNPSLKS
177	389A03 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 389A03 using Kabat	STAAGPEYFHR
178	389A03 - Heavy chain variable region	Amino acid sequence of V_H of 389A03	QLQESGPGLVKPSETLSLTCTVSGGSISSSSYYCGWIRQPPGKGLDWI GSIYSTGYTYYNPSLKSRVTISIDTSKNQFSCLILTSVTAADTAVYYC AISTAAGPEYFHRWGQGTLVTVSS
179	389A03 - Heavy chain variable region	Nucleic acid sequence of V_H of 389A03	CAGCTGCAGGAGTCGGGCCCAGGCCTGGTGAAGCCTTCGGAGACCCTG TCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTAGTTAT TACTGCGGCTGGATCCGCCAGCCCCCTGGGAAGGGGCTGGACTGGATT GGGAGTATCTATTCTACTGGGTACACCTACTACAACCCGTCCCTCAAG AGTCGAGTCACCATTTCCATAGACACGTCCAAGAACCAGTTCTCATGC CTGATACTGACCTCTGTGACCGCCGCAGACACGGCTGTGTATTACTGT GCGATAAGTACAGCAGCTGGCCCTGAATACTTCCATCGCTGGGGCCAG GGCACCCTGGTCACCGTCTCCTCAG
180	389A03 - full heavy chain sequence	Amino acid sequence of 389A03 heavy chain	QLQESGPGLVKPSETLSLTCTVSGGSISSSSYYCGWIRQPPGKGLDWI GSIYSTGYTYYNPSLKSRVTISIDTSKNQFSCLILTSVTAADTAVYYC AISTAAGPEYFHRWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
181	389A03 - full heavy chain sequence	Nucleic acid sequence of 389A03 heavy chain	CAGCTGCAGGAGTCGGGCCCAGGCCTGGTGAAGCCTTCGGAGACCCTG TCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTAGTAGTTAT TACTGCGGCTGGATCCGCCAGCCCCCTGGGAAGGGGCTGGACTGGATT GGGAGTATCTATTCTACTGGGTACACCTACTACAACCCGTCCCTCAAG AGTCGAGTCACCATTTCCATAGACACGTCCAAGAACCAGTTCTCATGC CTGATACTGACCTCTGTGACCGCCGCAGACACGGCTGTGTATTACTGT GCGATAAGTACAGCAGCTGGCCCTGAATACTTCCATCGCTGGGGCCAG GGCACCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTG TTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCT CTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCC TGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTG CTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCT TCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAG CCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGAC AAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGA CCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATC TCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAG GACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCAC AACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGG GTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAA GAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAA AAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTAC ACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTG ACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGG GAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTG CTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGAC AAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCAC GAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCC GGCAAG
182	389A03 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 389A03 using IMGT	QSVLYSSNSKNF
183	389A03 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 389A03 using IMGT	WAS
184	389A03 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 389A03 using IMGT	QQYYSTPRT
185	389A03 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 389A03 using Kabat	KSSQSVLYSSNSKNFLA

SEQ ID NO:	Name	Description	Sequence
186	389A03 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 389A03 using Kabat	WASTRGS
187	389A03 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 389A03 using Kabat	QQYYSTPRT
188	389A03 - Light chain variable region	Amino acid sequence of V_L of 389A03	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNSKNFLAWYQQKPGQ PPKLFIYWASTRGSGVPDRISGSGSGTDFNLTISSLQAEDVAVYYCQQ YYSTPRTFGQGTKVEIK
189	389A03 - Light chain variable region	Nucleic acid sequence of V_L of 389A03	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC GAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGC TCCAACAGTAAGAACTTCTTAGCTTGGTACCAGCAGAAACCGGGACAG CCTCCTAAGCTGTTCATTTACTGGGCATCTACCCGGGGATCCGGGGTC CCTGACCGAATCAGTGGCAGCGGGTCTGGGACAGATTTCAATCTCACC ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAACAA TATTATAGTACTCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAGATC AAAC
190	389A03 - full light chain sequence	Amino acid sequence of 389A03 light chain	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNSKNFLAWYQQKPGQ PPKLFIYWASTRGSGVPDRISGSGSGTDFNLTISSLQAEDVAVYYCQQ YYSTPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
191	389A03 - full light chain sequence	Nucleic acid sequence of 389A03 light chain	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGC GAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGC TCCAACAGTAAGAACTTCTTAGCTTGGTACCAGCAGAAACCGGGACAG CCTCCTAAGCTGTTCATTTACTGGGCATCTACCCGGGGATCCGGGGTC CCTGACCGAATCAGTGGCAGCGGGTCTGGGACAGATTTCAATCTCACC ATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAACAA TATTATAGTACTCCTCGGACGTTCGGCCAAGGGACCAAGGTGGAGATC AAACGTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGAC GAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAAC TTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTG CAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGAC AGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTAC GAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCT AGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT

SEQ ID NO:	Name	Description		Sequence
192	Human IgG4 heavy chain constant region #1	IGHG*01 & IGHG4*04	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttcccccctggcgccctgctccagg agcacctccgagagcacagccgccctgggctgcctggtcaaggactac ttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcctcaggactctactcc ctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacc tacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaag agagttgagtccaaatatggtcccccatgcccatcatgcccagcacct gagttcctgggggggaccatcagtcttcctgttcccccaaaacccaag gacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtg gacgtgagccaggaagaccccgaggtccagttcaactggtacgtggat ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttc aacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggac tggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctc ccgtcctccatcgagaaaaccatctccaaagccaaagggcagccccga gagccacaggtgtacaccctgcccccatcccaggaggagatgaccaag aaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcgac atcgccgtggagtgggagagcaatgggcagccggagaacaactacaag accacgcctcccgtgctggactccgacggctccttcttcctctacagc aggctaaccgtggacaagagcaggtggcaggaggggaatgtcttctca tgctccgtgatgcatgaggctctgcacaaccactacacacagaagagc ctctccctgtctctgggtaaa
193			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
194	Human IgG4 heavy chain constant region #2	IGHG*02	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttcccccctggcgccctgctccagg agcacctccgagagcacagccgccctgggctgcctggtcaaggactac ttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcctcaggactctactcc ctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacc tacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaag agagttgagtccaaatatggtcccccgtgcccatcatgcccagcacct gagttcctgggggggaccatcagtcttcctgttcccccaaaacccaag gacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtg gacgtgagccaggaagaccccgaggtccagttcaactggtacgtggat ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttc aacagcacgtaccgtgtggtcagcgtcctcaccgtcgtgcaccaggac tggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctc ccgtcctccatcgagaaaaccatctccaaagccaaagggcagccccga gagccacaggtgtacaccctgcccccatcccaggaggagatgaccaag aaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcgac atcgccgtggagtgggagagcaatgggcagccggagaacaactacaag accacgcctcccgtgctggactccgacggctccttcttcctctacagc aggctaaccgtggacaagagcaggtggcaggaggggaatgtcttctca tgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagc ctctccctgtctctgggtaaa
195			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVVHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:	Name	Description		Sequence
196	Human IgG4 heavy chain constant region #3	IGHG*03	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttcccccctggcgccctgctccagg agcacctccgagagcacagccgccctgggctgcctggtcaaggactac ttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcctcaggactctactcc ctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacc tacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaag agagttgagtccaaatatggtcccccatgcccatcatgcccagcacct gagttcctgggggggaccatcagtcttcctgttcccccaaaacccaag gacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtg gacgtgagccaggaagaccccgaggtccagttcaactggtacgtggat ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttc aacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggac tggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctc ccgtcctccatcgagaaaaccatctccaaagccaaagggcagccccga gagccacaggtgtacaccctgcccccatcccaggaggagatgaccaag aaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcgac atcgccgtggagtgggagagcaatgggcagccggagaacaactacaag accacgcctcccgtgctggactccgacggctccttcttcctctacagc aagctcaccgtggacaagagcaggtggcaggaggggaacgtcttctca tgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagc ctctccctgtctctgggtaaa
197			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
198	IgG4 heavy chain constant region - IgG4-PE	- IgG4-PE	Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version A	gcctccaccaagggcccatccgtcttcccccctggcgccctgctccagg agcacctccgagagcacggccgccctgggctgcctggtcaaggactac ttccccgaaccagtgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcctcaggactctactcc ctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacc tacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaag agagttgagtccaaatatggtcccccatgcccaccatgcccagcgcct gaatttgagggggggaccatcagtcttcctgttcccccaaaacccaag gacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtg gacgtgagccaggaagaccccgaggtccagttcaactggtacgtggat ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttc aacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggac tggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctc ccgtcatcgatcgagaaaaccatctccaaagccaaagggcagccccga gagccacaggtgtacaccctgcccccatcccaggaggagatgaccaag aaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcgac atcgccgtggagtgggagagcaatgggcagccggagaacaactacaag accacgcctcccgtgctggactccgacggatccttcttcctctacagc aggctaaccgtggacaagagcaggtggcaggaggggaatgtcttctca tgctccgtgatgcatgaggctctgcacaaccactacacacagaagagc ctctccctgtctctgggtaaa

SEQ ID NO:	Name	Description		Sequence
199	IgG4 heavy chain constant region - IgG4-PE		Heavy Chain Constant Region Amino Acid Sequence - Encoded by Synthetic Version A, B & C(Two residues that differ from the wild-type sequence are identified in bold)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCP**P**CPAPEF**E**GGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
200	IgG4 heavy chain constant region- IgG4-PE		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version B	Gcctccaccaagggacctagcgtgttccctctcgccccctgttccagg tccacaagcgagtccaccgctgccctcggctgtctggtgaaagactac tttcccgagcccgtgaccgtctcctggaatagcggagccctgacctcc ggcgtgcacacatttcccgccgtgctgcagagcagcggactgtatagc ctgagcagcgtggtgaccgtgcccagctccagcctcggcaccaaaacc tacacctgcaacgtggaccacaagccctccaacaccaaggtggacaag cgggtggagagcaagtacggccccccttgccctccttgtcctgccccct gagttcgagggaggaccctccgtgttcctgtttcccccaaacccaag gacaccctgatgatctcccggacacccgaggtgacctgtgtggtcgtg gacgtcagccaggaggaccccgaggtgcagttcaactggtatgtggac ggcgtggaggtgcacaatgccaaaaccaagcccagggaggagcagttc aattccacctacagggtggtgagcgtgctgaccgtcctgcatcaggat tggctgaacggcaaggagtacaagtgcaaggtgtccaacaagggactg cccagctccatcgagaagaccatcagcaaggctaagggccagccgagg gagccccaggtgtataccctgcctcctagccaggaagagatgaccaag aaccaagtgtccctgacctgcctggtgaagggattctacccctccgac atcgccgtggagtgggagagcaatggccagcccgagaacaactacaaa acaacccctcccgtgctcgatagcgacggcagcttctttctctacagc cggctgacagtggacaagagcaggtggcaggagggcaacgtgttctcc tgttccgtgatgcacgaggccctgcacaatcactacacccagaagagc ctctccctgtccctgggcaag
201	IgG4 heavy chain constant region- IgG4-PE		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version C	gccagcaccaagggcccttccgtgttcccccctggcccccttgcagcagg agcacctccgaatccacagctgccctgggctgtctggtgaaggactac tttcccgagcccgtgaccgtgagctggaacagcggcgctctgacatcc ggcgtccacacctttcctgccgtcctgcagtcctccggcctctactcc ctgtcctccgtggtgaccgtgcctagctcctccctcggcaccaagacc tacacctgtaacgtggaccacaaaccctccaacaccaaggtggacaaa cgggtcgagagcaagtacggccctccctgccctccttgtcctgccccc gagttcgaaggcggacccagcgtgttcctgttccctcctaagcccaag gacaccctcatgatcagccggacacccgaggtgacctgcgtggtggtg gatgtgagccaggaggaccctgaggtccagttcaactggtatgtggat ggcgtggaggtgcacaacgccaagacaaagccccgggaagagcagttc aactccacctacagggtggtcagcgtgctgaccgtgctgcatcaggac tggctgaacggcaaggagtacaagtgcaaggtcagcaataagggactg cccagcagcatcgagaagaccatctccaaggctaaaggccagccccgg gaacctcaggtgtacaccctgcctcccagccaggaggagatgaccaag aaccaggtgagcctgacctgcctggtgaagggattctacccttccgac atcgccgtggagtgggagtccaacggccagcccgagaacaattataag accacccctcccgtcctcgacagcgacggatccttctttctgtactcc aggctgaccgtggataagtccaggtggcaggaaggcaacgtgttcagc tgctccgtgatgcacgaggccctgcacaatcactacacccagaagtcc ctgagcctgtccctgggaaag

SEQ ID NO:	Name	Description		Sequence
202	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version D	gcctccaccaagggcccatccgtcttcccccctggcgccctgctccagg agcacctccgagagcacggccgccctgggctgcctggtcaaggactac ttccccgaaccagtgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcctcaggactctactcc ctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacc tacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaag agagttgagtccaaatatggtcccccatgcccaccatgcccagcgcct ccagttgcgggggacatcagtcttcctgttcccccaaaacccaag gacactctcatgatctcccggaccctgaggtcacgtgcgtggtggtg gacgtgagccaggaagaccccgaggtccagttcaactggtacgtggat ggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttc aacagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggac tggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctc ccgtcatcgatcgagaaaaccatctccaaagccaaagggcagccccga gagccacaggtgtacaccctgcccccatcccaggaggagatgaccaag aaccaggtcagcctgacctgcctggtcaaaggcttctaccccagcgac atcgccgtggagtgggagagcaatgggcagccggagaacaactacaag accacgcctcccgtgctggactccgacggatccttcttcctctacagc aggctaaccgtggacaagagcaggtggcaggaggggaatgtcttctca tgctccgtgatgcatgaggctctgcacaaccactacacacagaagagc ctctccctgtctctgggtaaa
203			Heavy Chain Constant Region Amino Acid Sequence - encoded by Synthetic Version D	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
204	Disabled Human IgG1 heavy chain constant region	Disabled IGHG1	Heavy Chain Constant Region Nucleotide Sequence	gcctccaccaagggcccatcggtcttcccccctggcaccctcctccaag agcacctctgggggcacagcggccctgggctgcctggtcaaggactac ttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagc ggcgtgcacaccttcccggctgtcctacagtcctcaggactctactcc ctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacc tacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaag aaagtggagcccaaatcttgtgacaaaactcacacatgcccaccgtgc ccagcacctgaactcgcgggggcaccgtcagtcttcctcttccccca aaacccaaggacaccctcatgatctcccggacccctgaggtcacatgc gtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactgg tacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggag gagcagtacaacagcacgtaccgtgtggtcagcgtcctcaccgtcctg caccaggactggctgaatggcaaggagtacaagtgcaaggtctccaac aaagccctcccagccccatcgagaaaaccatctccaaagccaaaggg cagccccgagaaccacaggtgtacaccctgcccccatcccgggatgag ctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctat cccagcgacatcgccgtggagtgggagagcaatgggcagccggagaac aactacaagaccacgcctcccgtgctggactccgacggctccttcttc ctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaac gtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacg cagaagagcctctccctgtctccgggtaaa
205			Heavy Chain Constant Region Amino Acid Sequence (Two residues that differ from the wild-type sequence are identified in bold)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEL**A**G**A**PSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description		Sequence
206	Human Cκ constant region	IGKC*01	Cκ Light Chain Constant Region Nucleotide Sequence	cgtacggtggccgctccctccgtgttcatcttcccaccttccgacgag cagctgaagtccggcaccgcttctgtcgtgtgcctgctgaacaacttc tacccccgcgaggccaaggtgcagtggaaggtggacaacgccctgcag tccggcaactcccaggaatccgtgaccgagcaggactccaaggacagc acctactccctgtcctccaccctgaccctgtccaaggccgactacgag aagcacaaggtgtacgcctgcgaagtgacccaccagggcctgtctagc cccgtgaccaagtctttcaaccggggcgagtgt
207			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC
208	Human Cκ constant region	IGKC*02	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgag cagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttc tatcccagagaggccaaagtacagtggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagc acctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgccggcgaagtcacccatcagggcctgagctcg cccgtcacaaagagcttcaacaggggagagtgt
209			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQESKDSTYSLSSTLTLSKADYEKHKVYAGEVTHQGLSS PVTKSFNRGEC
210	Human Cκ constant region	IGKC*03	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgag cagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttc tatcccagagaggccaaagtacagcggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggagagcaaggacagc acctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcg cccgtcacaaagagcttcaacaggggagagtgt
211			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQRKVDNALQ SGNSQESVTEQESKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC
212	Human Cκ constant region	IGKC*04	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgag cagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttc tatcccagagaggccaaagtacagtggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagc acctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaactctacgcctgcgaagtcacccatcagggcctgagctcg cccgtcacaaagagcttcaacaggggagagtgt
213			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYACEVTHQGLSS PVTKSFNRGEC
214	Human Cκ constant region	IGKC*05	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgag cagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttc tatcccagagaggccaaagtacagtggaaggtggataacgccctccaa tcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagc acctacagcctcagcaacaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcg cccgtcacaaagagcttcaacaggggagagtgc
215			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSNTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

SEQ ID NO:	Name	Description		Sequence
216	Human Cλ constant region	IGCλ1*01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggccaaccccacggtcactctgttcccgccctcctctgaggag ctccaagccaacaaggccacactagtgtgtctgatcagtgacttctac ccgggagctgtgacagtggcttggaaggcagatggcagccccgtcaag gcgggagtggagacgaccaaaccctccaaacagagcaacaacaagtac gcggccagcagctacctgagcctgacgcccgagcagtggaagtcccac agaagctacagctgccaggtcacgcatgaagggagcaccgtggagaag acagtggcccctacagaatgttca
217			Cλ Light Chain Constant Region Amino Acid Sequence	PKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVK AGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEK TVAPTECS
218	Human Cλ constant region	IGCλ1*02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctct gaggagctccaagccaacaaggccacactagtgtgtctgatcagtgac ttctacccgggagctgtgacagtggcctggaaggcagatggcagcccc gtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaac aagtacgcggccagcagctacctgagcctgacgcccgagcagtggaag tcccacagaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctacagaatgttca
219			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSP VKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS
220	Human Cλ constant region	IGCλ2*01	Cλ Light Chain Constant Region Nucleotide Sequence - Version A	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctct gaggagctccaagccaacaaggccacactagtgtgtctgatcagtgac ttctacccgggagctgtgacagtggcctggaaggcagatggcagcccc gtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaac aagtacgcggccagcagctacctgagcctgacgcccgagcagtggaag tcccacagaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctacagaatgttca
221			Cλ Light Chain Constant Region Nucleotide Sequence - Version B	ggccagcctaaggccgctccttctgtgaccctgttcccccatcctcc gaggaactgcaggctaacaaggccacccctcgtgtgcctgatcagcgac ttctaccctggcgccgtgaccgtggcctggaaggctgatagctctcct gtgaaggccggcgtggaaaccaccacccctccaagcagtccaacaac aaatacgccgcctcctcctacctgtccctgacccctgagcagtggaag tcccaccggtcctacagctgccaagtgacccacgagggctccaccgtg gaaaagaccgtggctcctaccgagtgctcc
222			Cλ Light Chain Constant Region Nucleotide Sequence - Version C	ggccagcctaaagctgcccccagcgtcaccctgtttcctccctccagc gaggagctccaggccaacaaggccacccctcgtgtgcctgatctccgac ttctatcccggcgctgtgaccgtggcttggaaagccgactccagccct gtcaaagccggcgtggagaccaccacaccctccaagcagtccaacaac aagtacgccgcctccagctatctctccctgacccctgagcagtggaag tcccaccggtcctactcctgtcaggtgacccacgagggctccaccgtg gaaaagaccgtcgcccccaccgagtgctcc
223			Cλ Light Chain Constant Region Amino Acid Sequence - Encoded by Version A, B & C	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSP VKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS
224	Human Cλ constant region	IGCλ2*02 & IGLC2*03	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctct gaggagcttcaagccaacaaggccacactggtgtgtctcataagtgac ttctacccgggagccgtgacagtggcctggaaggcagatagcagcccc gtcaaggcgggagtggagaccacacaccctccaaacaaagcaacaac aagtacgcggccagcagctatctgagcctgacgcctgagcagtggaag tcccacagaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctacagaatgttca

SEQ ID NO:	Name	Description		Sequence
225			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS
226	Human Cλ constant region	IGCλ3* 01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggctgccccctcggtcactctgttcccaccctcctctgaggag cttcaagccaacaaggccacactggtgtgtctcataagtgacttctac ccgggagccgtgacagttgcctggaaggcagatagcagccccgtcaag gcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtac gcggccagctacctgagcctgacgcctgagcagtggaagtcccac aaaagctacagctgccaggtcacgcatgaagggagcaccgtggagaag acagttgcccctacggaatgttca
227			Cλ Light Chain Constant Region Amino Acid Sequence	PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVK AGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEK TVAPTECS
228	Human Cλ constant region	IGCλ3* 02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctct gaggagcttcaagccaacaaggccacactggtgtgtctcataagtgac ttctacccggggccagtgacagttgcctggaaggcagatagcagcccc gtcaaggcgggggtggagaccaccacaccctccaaacaaagcaacaac aagtacgcggccagcagctacctgagcctgacgcctgagcagtggaag tcccacaaaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctacggaatgttca
229			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGPVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTV EKTVAPTECS
230	Human Cλ constant region	IGCλ3* 03	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctct gaggagcttcaagccaacaaggccacactggtgtgtctcataagtgac ttctacccgggagccgtgacagtggcctggaaggcagatagcagcccc gtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaac aagtacgcggccagcagctacctgagcctgacgcctgagcagtggaag tcccacaaaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctacagaatgttca
231			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTV EKTVAPTECS
232	Human Cλ constant region	IGCλ3* 04	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctct gaggagcttcaagccaacaaggccacactggtgtgtctcataagtgac ttctacccgggagccgtgacagtggcctggaaggcagatagcagcccc gtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaac aagtacgcggccagcagctacctgagcctgacgcctgagcagtggaag tcccacagaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctacagaatgttca
233			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTECS
234	Human Cλ constant region	IGCλ6* 01	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccgccctcctct gaggagcttcaagccaacaaggccacactggtgtgcctgatcagtgac ttctacccgggagctgtgaaagtggcctggaaggcagatggcagcccc gtcaacacgggagtggagaccaccacaccctccaaacagagcaacaac aagtacgcggccagcagctacctgagcctgacgcctgagcagtggaag tcccacagaagctacagctgccaggtcacgcatgaagggagcaccgtg gagaagacagtggcccctgcagaatgttca

SEQ ID NO:	Name	Description		Sequence
235			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSP VNTGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPAECS
236	Human Cλ constant region	IGLC7* 01 & IGCλ7* 02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccaccctcctct gaggagcttcaagccaacaaggccacactggtgtgtctcgtaagtgac ttctacccgggagccgtgacagtggcctggaaggcagatggcagcccc gtcaaggtgggagtggagaccaccaaaccctccaaacaaagcaacaac aagtatgcggccagcagctacctgagcctgacgcccgagcagtggaag tcccacagaagctacagctgccgggtcacgcatgaagggagcaccgtg gagaagacagtggcccctgcagaatgctct
237			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFYPGAVTVAWKADGSP VKVGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTV EKTVAPAECS
238	413G05 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 413G05 using IMGT		GFTFSDYY
239	413G05 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 413G05 using IMGT		ISTSGSTI
240	413G05 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 413G05 using IMGT		ARGITGTNFYHYGLGV
241	413G05 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 413G05 using Kabat		DYYMS
242	413G05 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 413G05 using Kabat		YISTSGSTIYYADSVKG
243	413G05 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 413G05 using Kabat		GITGTNFYHYGLGV
244	413G05 - Heavy chain variable region	Amino acid sequence of V_H of 413G05		QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQVPGKGLEWV SYISTSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDAAVYHC ARGITGTNFYHYGLGVWGQGTTVTVSS
245	413G05 - Heavy chain variable region	Nucleic acid sequence of V_H of 413G05		CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTAC TACATGAGCTGGATCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGGTT TCATACATTAGTACTAGTGGTAGTACCATATACTACGCAGACTCTGTG AAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACTGTAT CTACAAATGAACAGCCTGAGAGCCGAGGACGCGGCCGTGTATCACTGT GCGAGAGGTATAACTGGAACTAACTTCTACCACTACGGTTTGGGCGTC TGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG
246	413G05 - full heavy chain sequence	Amino acid sequence of 413G05 heavy chain		QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQVPGKGLEWV SYISTSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDAAVYHC ARGITGTNFYHYGLGVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
247	413G05 - full heavy chain sequence	Nucleic acid sequence of 413G05 heavy chain	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTAC TACATGAGCTGGATCCGCCAGGTTCCAGGGAAGGGGCTGGAGTGGGTT TCATACATTAGTACTAGTGGTAGTACCATATACTACGCAGACTCTGTG AAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACTGTAT CTACAAATGAACAGCCTGAGAGCCGAGGACGCGGCCGTGTATCACTGT GCGAGAGGTATAACTGGAACTAACTTCTACCACTACGGTTTGGGCGTC TGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCAGCACCAAGGGC CCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGA ACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTG ACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTC CCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTG ACCGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTG AACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAG TCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTG CTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACC CTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTG GAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC ACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTG AACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCC CCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCC CAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAG GTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCC GTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACC CCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTG ACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCC GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCC CTGAGCCCCGGCAAG
248	413G05 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 413G05 using IMGT	QGINSW
249	413G05 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 413G05 using IMGT	AAS
250	413G05 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 413G05 using IMGT	QQVNSFPLT
251	413G05 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 413G05 using Kabat	RASQGINSWLA
252	413G05 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 413G05 using Kabat	AASTLQS
253	413G05 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 413G05 using Kabat	QQVNSFPLT
254	413G05 - Light chain variable region	Amino acid sequence of V_L of 413G05	DIQMTQSPSSVSASVGDRVTITCRASQGINSWLAWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGADFTLTISSLQPEDFATYYCQQVNSFPL TFGGGTKVEIK
255	413G05 - Light chain variable region	Nucleic acid sequence of V_L of 413G05	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAACAGCTGG TTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGGTCTGGGGCAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGTTAACAGTTTCCCGCTC ACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC

SEQ ID NO:	Name	Description	Sequence
256	413G05 - full light chain sequence	Amino acid sequence of 413G05 light chain	DIQMTQSPSSVSASVGDRVTITCRASQGINSWLAWYQQKPGKAPKLLI YAASTLQSGVPSRFSGSGSGADFTLTISSLQPEDFATYYCQQVNSFPL TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
257	413G05 - full light chain sequence	Nucleic acid sequence of 413G05 light chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAACAGCTGG TTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGGTCTGGGGCAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGTTAACAGTTTCCCGCTC ACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
258	413F09 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 413F09 using IMGT	GFTFSYYA
259	413F09 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 413F09 using IMGT	ISGGGGNT
260	413F09 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 413F09 using IMGT	AKDRMKQLVRAYYFDY
261	413F09 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 413F09 using Kabat	YYAMS
262	413F09 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 413F09 using Kabat	TISGGGGNTHYADSVKG
263	413F09 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 413F09 using Kabat	DRMKQLVRAYYFDY
264	413F09 - Heavy chain variable region	Amino acid sequence of V_H of 413F09	EVPLVESGGGLVQPGGSLRLSCAASGFTFSYYAMSWVRQAPGKGLDWV STISGGGGNTHYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAVYYC AKDRMKQLVRAYYFDYWGQGTLVTVSS
265	413F09 - Heavy chain variable region	Nucleic acid sequence of V_H of 413F09	GAGGTGCCGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGCTACTAT GCCATGAGCTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGACTGGGTC TCAACTATTAGTGGTGGTGGTGGTAACACACACTACGCAGACTCCGTG AAGGGCCGATTCACTATATCCAGAGACAATTCCAAGAACACGCTGTAT CTGCACATGAACAGCCTGAGAGCCGAAGACACGGCCGTCTATTACTGT GCGAAGGATCGGATGAAACAGCTCGTCCGGGCCTACTACTTTGACTAC TGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG
266	413F09 - full heavy chain sequence	Amino acid sequence of 413F09 heavy chain	EVPLVESGGGLVQPGGSLRLSCAASGFTFSYYAMSWVRQAPGKGLDWV STISGGGGNTHYADSVKGRFTISRDNSKNTLYLHMNSLRAEDTAVYYC AKDRMKQLVRAYYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
267	413F09 - full heavy chain sequence	Nucleic acid sequence of 413F09 heavy chain	GAGGTGCCGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACGTTTAGCTACTAT GCCATGAGCTGGGTCCGTCAGGCTCCAGGGAAGGGGCTGGACTGGGTC TCAACTATTAGTGGTGGTGGTGGTAACACACACTACGCAGACTCCGTG AAGGGCCGATTCACTATATCCAGAGACAATTCCAAGAACACGCTGTAT CTGCACATGAACAGCCTGAGAGCCGAAGACACGGCCGTCTATTACTGT GCGAAGGATCGGATGAAACAGCTCGTCCGGGCCTACTACTTTGACTAC TGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGC CCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGA ACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTG ACCGTGTCCTGGAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTC CCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTG ACCGTGCCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTG AACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAG TCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTG CTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACC CTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTG GAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCC ACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTG AACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCC CCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCC CAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAG GTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCC GTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACC CCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTG ACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCC GTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCC CTGAGCCCCGGCAAG
268	413F09 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 413F09 using IMGT	QDISTY
269	413F09 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 413F09 using IMGT	GTS
270	413F09 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 413F09 using IMGT	QQLHTDPIT
271	413F09 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 413F09 using Kabat	WASQDISTYLG
272	413F09 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 413F09 using Kabat	GTSSLQS
273	413F09 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 413F09 using Kabat	QQLHTDPIT
274	413F09 - Light chain variable region	Amino acid sequence of V_L of 413F09	DIQLTQSPSFLSASVGDRVTITCWASQDISTYLGWYQQKPGKAPKLLI YGTSSLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLHTDPI TFGQGTRLEIK
275	413F09 - Light chain variable region	Nucleic acid sequence of V_L of 413F09	GACATCCAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCTGGGCCAGTCAGGACATTAGCACTTAT TTAGGCTGGTATCAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTACATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTATTACTGTCAACAGCTTCATACTGACCCGATC ACCTTCGGCCAAGGGACACGACTGGAGATCAAAC

SEQ ID NO:	Name	Description	Sequence
276	413F09 - full light chain sequence	Amino acid sequence of 413F09 light chain	DIQLTQSPSFLSASVGDRVTITCWASQDISTYLGWYQQKPGKAPKLLI YGTSSLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLHTDPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
277	413F09 - full light chain sequence	Nucleic acid sequence of 413F09 light chain	GACATCCAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGCTGGGCCAGTCAGGACATTAGCACTTAT TTAGGCTGGTATCAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGGTACATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTATTACTGTCAACAGCTTCATACTGACCCGATC ACCTTCGGCCAAGGGACACGACTGGAGATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
278	414B06 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 414B06 using IMGT	GFTFSSYW
279	414B06 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 414B06 using IMGT	IKQDGSEK
280	414B06 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 414B06 using IMGT	ARVRQWSDYSDY
281	414B06 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 414B06 using Kabat	SYWMN
282	414B06 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 414B06 using Kabat	NIKQDGSEKYYVDSVKG
283	414B06 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 414B06 using Kabat	VRQWSDYSDY
284	414B06 - Heavy chain variable region	Amino acid sequence of V_H of 414B06	EVHLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLEWV ANIKQDGSEKYYVDSVKGRFTVSRDNAKNSLYLQMNSLRAEDTAVYYC ARVRQWSDYSDYWGQGTPVTVSS
285	414B06 - Heavy chain variable region	Nucleic acid sequence of V_H of 414B06	GAGGTGCACCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTAT TGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTG GCCAACATAAAGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTG AAGGGCCGCTTCACCGTCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGT GCGAGAGTTCGACAATGGTCCGACTACTCTGACTACTGGGGCCAGGGA ACCCCGGTCACCGTCTCCTCAG
286	414B06 - full heavy chain sequence	Amino acid sequence of 414B06 heavy chain	EVHLVESGGGLVQPGGSLRLSCAASGFTFSSYWMNWVRQAPGKGLEWV ANIKQDGSEKYYVDSVKGRFTVSRDNAKNSLYLQMNSLRAEDTAVYYC ARVRQWSDYSDYWGQGTPVTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
287	414B06 - full heavy chain sequence	Nucleic acid sequence of 414B06 heavy chain	GAGGTGCACCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGG TCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAGCTAT TGGATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTG GCCAACATAAAGCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTG AAGGGCCGCTTCACCGTCTCCAGAGACAACGCCAAGAACTCACTGTAT CTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGT GCGAGAGTTCGACAATGGTCCGACTACTCTGACTACTGGGGCCAGGGA ACCCCGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTC CCTCTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTG GGCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGG AACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTG CAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCC AGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCC TCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAG ACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCT TCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCC CGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGAC CCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAAC GCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTG GTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAG TACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAG ACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACACA CTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACC TGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAG TCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTG GACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACAGTGGACAAG TCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAG GCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGC AAG
288	414B06 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 414B06 using IMGT	QGISSW
289	414B06 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 414B06 using IMGT	AAS
290	414B06 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 414B06 using IMGT	QQANSFPFT
291	414B06 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 414B06 using Kabat	RASQGISSWLA
292	414B06 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 414B06 using Kabat	AASSLQS
293	414B06 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 414B06 using Kabat	QQANSFPFT
294	414B06 - Light chain variable region	Amino acid sequence of V_L of 414B06	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPF TFGPGTKVDIK
295	414B06 - Light chain variable region	Nucleic acid sequence of V_L of 414B06	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCTGG TTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTTTCCCATTC ACTTTCGGCCCTGGGACCAAAGTGGATATCAAAC

SEQ ID NO:	Name	Description	Sequence
296	414B06 - full light chain sequence	Amino acid sequence of 414B06 light chain	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPF TFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
297	414B06 - full light chain sequence	Nucleic acid sequence of 414B06 light chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGA GACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCTGG TTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATC TATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGC AGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCT GAAGATTTTGCAACTTACTATTGTCAACAGGCTAACAGTTTCCCATTC ACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTACGGTGGCCGCT CCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGC ACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCC AAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAG GAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCC TCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCT TTCAACCGGGGCGAGTGT
298	Mutated 1D05 - LC mutant 3	Amino acid sequence of 1D05 kappa light chain with V to Y mutation in CDRL2 highlighted	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI Y**Y**ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
299	1D05 - heavy chain disabled IgG1 Fc	Amino acid sequence of IgG1 disabled variant of 1D05	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWV SGISWIRTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**L AGA**PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK
300	1D05 - light chain IL-2 fusion	1D05 Light chain sequence fused to wild-type human IL-2 sequence (IL-2 amino acid sequence is underlined and region to be varied is shown in bold)	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLI YVASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPI TFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC**APTSSSTKKTQLQLEHLLLD**LQMILN GINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQ SKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWI TFCQSIISTLT
301	Human IL-2	Uniprot number: P60568 Full length amino acid sequence of human IL-2 (minus signal sequence)	**APTSSSTKKTQLQLEHLLLD**LQMILNGINNYKNPKLTRMLTFKFYMPK KATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLEL KGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
302	Control 1D05 immunocytokine HC C-terminal fusion	Heavy chain 1D05 IgG1 variant fused at the N-terminus to wild-type human IL2 sequence (control)	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQVPGKGLEWV SGISWIRTGIGYADSVKGRFTIFRDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**L AGA**PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGKAPTSSSTKKTQLQLEHLLLDLQMILNG INNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQS KNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWIT FCQSIISTLT

SEQ ID NO:	Name	Description	Sequence
303	IL-2 D5-9	IL-2 IC45 (Del 5-9) N terminal IL-2 sequence	**APTSTQLQLELLLD**
304	IL-2 D1-9	IL-2 IC46 (Del 1-9) N terminal IL-2 sequence	**TQLQLEHLLLD**
305	IL-2 D5-7	IL-2 IC64 (Del 5-7) N terminal IL-2 sequence	**APTSKKTQLQLEHLLLD**
306	IL-2 D1	IL-2 D1 N terminal IL-2 sequence	**PTSSSTKKTQLQLEHLLLD**
307	IL-2 D1-2	IL-2 D1-2 N terminal IL-2 sequence	**TSSSTKKTQLQLEHLLLD**
308	IL-2 D1-3	IL-2 D1-3 N terminal IL-2 sequence	**SSSTKKTQLQLEHLLLD**
309	IL-2 D1-4	IL-2 D1-4 N terminal IL-2 sequence	**SSTKKTQLQLEHLLLD**
310	IL-2 D1-5	IL-2 D1-5 N terminal IL-2 sequence	**STKKTQLQLEHLLLD**
311	IL-2 D1-6	IL-2 D1-6 N terminal IL-2 sequence	**TKKTQLQLEHLLLD**
312	IL-2 D1-7	IL-2 D1-7 N terminal IL-2 sequence	**KKTQLQLEHLLLD**
313	IL-2 D1-8	IL-2 D1-8 N terminal IL-2 sequence	**KTQLQLEHLLLD**
314	IL-2 D9	IL-2 D9 N terminal IL-2 sequence	**APTSSSTKTQLQLEHLLLD**
315	IL-2 D9-8	IL-2 D9-8 N terminal IL-2 sequence	**APTSSSTTQLQLEHLLLD**
316	IL-2 D9-7	IL-2 D9-7 N terminal IL-2 sequence	**APTSSSTQLQLEHLLLD**
317	IL-2 D9-6	IL-2 D9-6 N terminal IL-2 sequence	**APTSSTQLQLEHLLLD**
318	IL-2 D9-4	IL-2 D9-4 N terminal IL-2 sequence	**APTTQLQLEHLLLD**
319	IL-2 D9-3	IL-2 D9-3 N terminal IL-2 sequence	**APTQLQLEHLLLD**
320	IL-2 D9-2	IL-2 D9-2 N terminal IL-2 sequence	**ATQLQLEHLLLD**
321	IL-2 D2-6	IL-2 D2-6 N terminal IL-2 sequence	**ATKKTQLQLEHLLLD**
322	IL-2 D3-7	IL-2 D3-7 N terminal IL-2 sequence	**APKKTQLQLEHLLLD**
323	IL-2 D4-8	IL-2 D4-8 N terminal IL-2 sequence	**APTKTQLQLEHLLLD**

SEQ ID NO:	Name	Description	Sequence
324	C-terminal amino acid sequence of hIL-2	Amino acids 21 to 133 of hIL-2	LQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEE VLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVE FLNRWITFCQSIISTLT
325	Mouse PD-L1	Uniprot number: Q9EP73 (ECD highlighted in **BOLD**, and cytoplasmic domain underlined)	MRIFAGIIFTACCHLLRA**FTITAPKDLYVVEYGSNVTMECRFPVEREL DLLALVVYWEKEDEQVIQFVAGEEDLKPQHSNFRGRASLPKDQLLKGN AALQITDVKLQDAGVYCCIISYGGADYKRITLKVNAPYRKINQRISVD PATSEHELICQAEGYPEAEVIWTNSDHQPVSGKRSVTTSRTEGMLLNV TSSLRVNATANDVFYCTFWRSQPGQNHTAELIIPELPATHPPQNRT**HW VLLGSILLFLIVVSTVLLFLRKQVRMLDVEKCGVEDTSSKNRNDTQFE ET
326	Mouse PD-L1 ECD His	Mouse PD-L1 extracellular domain with his tag	FTITAPKDLYVVEYGSNVTMECRFPVERELDLLALVVYWEKEDEQVIQ FVAGEEDLKPQHSNFRGRASLPKDQLLKGNAALQITDVKLQDAGVYCC IISYGGADYKRITLKVNAPYRKINQRISVDPATSEHELICQAEGYPEA EVIWTNSDHQPVSGKRSVTTSRTEGMLLNVTSSLRVNATANDVFYCTF WRSQPGQNHTAELIIPELPATHPPQNRT**HHHHHH**
327	Human IL-2Rα chain	Human IL-2 receptor alpha chain	ELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSGSLYMLCTG NSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVD QASLPGHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAE SVCKMTHGKTRWTQPQLICTGEMETSQFPGEEKPQASPEGRPESETSC LVTTTDFQIQTEMAATMETSIFTTEYQVAVAGCVFLLISVLLLSGLTW QRRQRKSRRTI
328	Human IL-2Rβ chain	Human IL-2 receptor beta chain	AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDRRRWNQTC ELLPVSQASWACNLILGAPDSQKLTTVDIVTLRVLCREGVRWRVMAIQ DFKPFENLRLMAPISLQVVHVETHRCNISWEISQASHYFERHLEFEAR TLSPGHTWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPLQGEFT TWSPWSQPLAFRTKPAALGKDTIPWLGHLLVGLSGAFGFIILVYLLIN CRNTGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPFPSSSFS PGGLAPEISPLEVLERDKVTQLLLQQDKVPEPASLSSNHSLTSCFTNQ GYFFFHLPDALEIEACQVYFTYDPYSEEDPDEGVAGAPTGSSPQPLQP LSGEDDAYCTFPSRDDLLLFSPSLLGGPSPPSTAPGGSGAGEERMPPS LQERVPRDWDPQPLGPPTPGVPDLVDFQPPPELVLREAGEEVPDAGPR EGVSFPWSRPPGQGEFRALNARLPLNTDAYLSLQELQGQDPTHLV
329	Human IL-2Rγ chain	Human IL-2 receptor common gamma chain	LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYM NCTWNSSSEPQPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQ KKEIHLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHKLS ESQLELNWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVD GQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNTSKENPFLFALEA VVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAW SGVSKGLAESLQPDYSERLCLVSEIPPKGGALGEGPGASPCNQHSPYW APPCYTLKPET
330	IL-7	Human IL-7 amino acid sequence	DCDIEGKDGKQYESVLMVSIDQLLDSMKEIGSNCLNNEFNFFKRHICD ANKEGMFLFRAARKLRQFLKMNSTGDFDLHLLKVSEGTTILLNCTGQV KGRKPAALGEAQPTKSLEENKSLKEQKKLNDLCFLKRLLQEIKTCWNK ILMGTKEH
331	IL-15	Human IL-15 amino acid sequence	GIHVFILGCFSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTES DVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSN GNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS
332	IL-21	Human IL-21 amino acid sequence	QGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFS CFQKAQLKSANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSC DSYEKKPPKEFLERFKSLLQKMIHQHLSSRTHGSEDS
333	GM-CSF	Human GM-CSF amino acid sequence	APARSPSPSTQPWEHVNAIQEARRLLNLSRDTAAEMNETVEVISEMFD LQEPTCLQTRLELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETSC ATQIITFESFKENLKDFLLVIPFDCWEPVQE
334	IFNα	Human IFN-α amino acid sequence	CDLPQNHGLLSRNTLVLLHQMRRISPFLCLKDRRDFRFPQEMVKGSQL QKAHVMSVLHEMLQQIFSLFHTERSSAAWNMTLLDQLHTELHQQLQHL ETCLLQVVGEGESAGAISSPALTLRRYFQGIRVYLKEKKYSDCAWEVV RMEIMKSLFLSTNMQERLRSKDRDLGS
335	TNFα	Extracellular portion of human TNF-α amino acid sequence	GPQREEFPRDLSLISPLAQAVRSSSRTPSDKPVAHVVANPQAEGQLQW LNRRANALLANGVELRDNQLVVPSEGLYLIYSQVLFKGQGCPSTHVLL THTISRIAVSYQTKVNLLSAIKSPCQRETPEGAEAKPWYEPIYLGGVF QLEKGDRLSAEINRPDYLDFAESGQVYFGIIAL

SEQ ID NO:	Name	Description		Sequence
336	IL-12α	Alpha chain of human IL-12 amino acid sequence		RNLPVATPDPGMFPCLHHSQNLLRAVSNMLQKARQTLEFYPCTSEEID HEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRKTSF MMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDEL MQALNFNSETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMS YLNAS
337	IL-12β	Beta chain of human IL-12 amino acid sequence		IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLG SGKTLTIQVKEFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILK DQKEPKNKTFLRCEAKNYSGRFTCWWLTTISTDLTFSVKSSRGSSDPQ GVTCGAATLSAERVRGDNKEYEYSVECQEDSACPAAEESLPIEVMVDA VHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEYPDTW STPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRA QDRYYSSSWSEWASVPCS
338	CXCL9	Human CXCL-9 amino acid sequence		TPVVRKGRCSCISTNQGTIHLQSLKDLKQFAPSPSCEKIEIIATLKNG VQTCLNPDSADVKELIKKWEKQVSQKKKQKNGKKHQKKKVLKVRKSQR SRQKKTT
339	CXCL10	Human CXCL-10 amino acid sequence		VPLSRTVRCTCISISNQPVNPRSLEKLEIIPASQFCPRVEIIATMKKK GEKRCLNPESKAIKNLLKAVSKERSKRSP
340	Human WT IgG1 constant region	IGHG1* 01 & IGHG1* 02 & IGHG1* 05 (IgG1)	WT human IgG1 amino acid sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
341			WT human IgG1 nucleic acid sequence	GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAG TCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTAC TTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAGC GGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCCTGTACTCC CTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCCAGACC TACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAG AAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGT CCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCA AAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGC GTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGG TACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAG GAACAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTG CACCAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAAC AAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGC CAGCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAG CTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTAC CCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAAC AACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTC CTGTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAAC GTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACC CAGAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
342	Mutated 1D05 - HC mutant 2	Amino acid sequence of 1D05 heavy chain with V to A and F to S back-mutation in framework region to germline highlighted with IgG1 disabled (LAGA) constant region		EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQ**A**PGKGLEWV SGISWIRTGIGYADSVKGRFTI**S**RDNAKNSLYLQMNSLRAEDTALYYC AKDMKGSGTYGGWFDTWGQGTLVTVSSASTKGPSVFPLAPCSRSTSES TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPE**LAGA** PSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVH NAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH EALHNHYTQKSLSLSLGK

Table S2. SEQ ID NOS: 343-538

SEQ ID NO:	Name	Description	Sequence
343	416E01 - CDRH1 (IMGT)	Amino acid sequence of CDRH1 of 416E01 using IMGT	GFTFSNYA
344	416E01 - CDRH2 (IMGT)	Amino acid sequence of CDRH2 of 416E01 using IMGT	ISFSGGTT
345	416E01 - CDRH3 (IMGT)	Amino acid sequence of CDRH3 of 416E01 using IMGT	AKDEAPAGATFFDS
346	416E01 - CDRH1 (Kabat)	Amino acid sequence of CDRH1 of 416E01 using Kabat	NYAMS
347	416E01 - CDRH2 (Kabat)	Amino acid sequence of CDRH2 of 416E01 using Kabat	AISFSGGTTYYADSVKG
348	416E01 - CDRH3 (Kabat)	Amino acid sequence of CDRH3 of 416E01 using Kabat	DEAPAGATFFDS
349	416E01 - Heavy chain variable region	Amino acid sequence of V_H of 416E01 (mutations from germline are shown in bold letters)	EVQL**A**ESGGGLVQPGGSLRLSCAASGFTFS**N**YAMSWVRQ**T**PGKGLE WVSAIS**F**SGG**T**TYYADSVKGRFTISRDNSKNTLYL**H**MNSLRA**D**DTA VYYCAK**DEA**PA**GATF**FD**S**WGQGTLVTVSS
350	416E01 - Heavy chain variable region	Nucleic acid sequence of V_H of 416E01	GAAGTGCAACTGGCGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAA CTATGCCATGAGTTGGGTCCGCCAGACTCCAGGAAAGGGGCTGGAG TGGGTCTCAGCTATTAGTTTTAGTGGTGGTACTACATACTACGCTG ACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAA CACGCTGTATTTGCACATGAACAGCCTGAGAGCCGATGACACGGCC GTATATTACTGTGCGAAAGATGAGGCACCAGCTGGCGCAACCTTCT TTGACTCCTGGGGCCAGGGAACGCTGGTCACCGTCTCCTCAG
351	416E01 - full heavy chain sequence	Amino acid sequence of 416E01 heavy chain	EVQLAESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQTPGKGLE WVSAISFSGGTTYYADSVKGRFTISRDNSKNTLYLHMNSLRADDTA VYYCAKDEAPAGATFFDSWGQGTLVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVD KSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO:	Name	Description	Sequence
352	416E01 - full heavy chain sequence	Nucleic acid sequence of 416E01 heavy chain	GAAGTGCAACTGGCGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAA CTATGCCATGAGTTGGGTCCGCCAGACTCCAGGAAAGGGGCTGGAG TGGGTCTCAGCTATTAGTTTTAGTGGTGGTACTACATACTACGCTG ACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAA CACGCTGTATTTGCACATGAACAGCCTGAGAGCCGATGACACGGCC GTATATTACTGTGCGAAAGATGAGGCACCAGCTGGCGCAACCTTCT TTGACTCCTGGGGCCAGGGAACGCTGGTCACCGTCTCCTCAGCCAG CACCAAGGGCCCTTCCGTGTTCCCCCTGGCCCCTTGCAGCAGGAGC ACCTCCGAATCCACAGCTGCCCTGGGCTGTCTGGTGAAGGACTACT TTCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCTCTGACATC CGGCGTCCACACCTTTCCTGCCGTCCTGCAGTCCTCCGGCCTCTAC TCCCTGTCCTCCGTGGTGACCGTGCCTAGCTCCTCCCTCGGCACCA AGACCTACACCTGTAACGTGGACCACAAACCCTCCAACACCAAGGT GGACAAACGGGTCGAGAGCAAGTACGGCCCTCCCTGCCCTCCTTGT CCTGCCCCCGAGTTCGAAGGCGGACCCAGCGTGTTCCTGTTCCCTC CTAAGCCCAAGGACACCCTCATGATCAGCCGGACACCCGAGGTGAC CTGCGTGGTGGTGGATGTGAGCCAGGAGGACCCTGAGGTCCAGTTC AACTGGTATGTGGATGGCGTGGAGGTGCACAACGCCAAGACAAAGC CCCGGGAAGAGCAGTTCAACTCCACCTACAGGGTGGTCAGCGTGCT GACCGTGCTGCATCAGGACTGGCTGAACGGCAAGGAGTACAAGTGC AAGGTCAGCAATAAGGGACTGCCCAGCAGCATCGAGAAGACCATCT CCAAGGCTAAAGGCCAGCCCCGGGAACCTCAGGTGTACACCCTGCC TCCCAGCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGC CTGGTGAAGGGATTCTACCCTTCCGACATCGCCGTGGAGTGGGAGT CCAACGGCCAGCCCGAGAACAATTATAAGACCACCCCTCCCGTCCT CGACAGCGACGGATCCTTCTTTCTGTACTCCAGGCTGACCGTGGAT AAGTCCAGGTGGCAGGAAGGCAACGTGTTCAGCTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGAGCCTGTC CCTGGGAAAG
353	416E01 - CDRL1 (IMGT)	Amino acid sequence of CDRL1 of 416E01 using IMGT	QGIRRW
354	416E01 - CDRL2 (IMGT)	Amino acid sequence of CDRL2 of 416E01 using IMGT	GAS
355	416E01 - CDRL3 (IMGT)	Amino acid sequence of CDRL3 of 416E01 using IMGT	QQANSFPIT
356	416E01 - CDRL1 (Kabat)	Amino acid sequence of CDRL1 of 416E01 using Kabat	RASQGIRRWLA
357	416E01 - CDRL2 (Kabat)	Amino acid sequence of CDRL2 of 416E01 using Kabat	GASSLQS
358	416E01 - CDRL3 (Kabat)	Amino acid sequence of CDRL3 of 416E01 using Kabat	QQANSFPIT
359	416E01 - Light chain variable region	Amino acid sequence of V_L of 416E01(mutations from germline are shown in bold letters)	DIQMTQSPSSVSASVGDRVTITCRASQGI**RR**WLAWYQQKPGKAPKL LI**SG**ASSLQSGVPSRFSGSGSGTDFTL**I**I**T**SLQPEDFATYYCQQAN SFPITFGQGTRLEIK
360	416E01 - Light chain variable region	Nucleic acid sequence of V_L of 416E01	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAG GAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGGAG GTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTC CTGATCTCTGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCATCATTACCAG TCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGCTAAC AGTTTCCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAAC

SEQ ID NO:	Name	Description	Sequence
361	416E01 - full light chain sequence	Amino acid sequence of 416E01 light chain	DIQMTQSPSSVSASVGDRVTITCRASQGIRRWLAWYQQKPGKAPKL LISGASSLQSGVPSRFSGSGSGTDFTLIITSLQPEDFATYYCQQAN SFPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC
362	416E01 - full light chain sequence	Nucleic acid sequence of 416E01 light chain	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAG GAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGGAG GTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTC CTGATCTCTGGTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGT TCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCATCATTACCAG TCTGCAGCCTGAAGATTTTGCAACTTACTATTGTCAACAGGCTAAC AGTTTCCCGATCACCTTCGGCCAAGGGACACGACTGGAGATCAAAC GTACGGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGA GCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAAC TTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCC TGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAA GGACAGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCC GACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGG GCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGT
363	STIM001 - CDRH1	Amino acid sequence of CDRH1 of STIM001 using IMGT	GYTFSTFG
364	STIM001 - CDRH2	Amino acid sequence of CDRH2 of STIM001 using IMGT	ISAYNGDT
365	STIM001 - CDRH3	Amino acid sequence of CDRH3 of STIM001 using IMGT	ARSSGHYYYYGMDV
366	STIM001 - Heavy chain variable region	Amino acid sequence of V_H of STIM001	QVQVVQSGAEVKKPGASVKVSCKASGYTFSTFGITWVRQAPGQGLE WMGWISAYNGDTNYAQNLQGRVIMTTDTSTSTAYMELRSLRSDDTA VYYCARSSGHYYYYGMDVWGQGTTVTVSS
367	STIM001 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM001	CAGGTTCAGGTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTTCCAC CTTTGGTATCACCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAA TGGATGGGATGGATCAGCGCTTACAATGGTGACACAAACTATGCAC AGAATCTCCAGGGCAGAGTCATCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCC GTTTATTACTGTGCGAGGAGCAGTGGCCACTACTACTACTACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
368	STIM001 - full heavy chain sequence	Amino acid sequence of STIM001 heavy chain	QVQVVQSGAEVKKPGASVKVSCKASGYTFSTFGITWVRQAPGQGLE WMGWISAYNGDTNYAQNLQGRVIMTTDTSTSTAYMELRSLRSDDTA VYYCARSSGHYYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTC PPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
369	STIM001 - full heavy chain sequence	Nucleic acid sequence of STIM001 heavy chain	CAGGTTCAGGTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTTCCAC CTTTGGTATCACCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAA TGGATGGGATGGATCAGCGCTTACAATGGTGACACAAACTATGCAC AGAATCTCCAGGGCAGAGTCATCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCC GTTTATTACTGTGCGAGGAGCAGTGGCCACTACTACTACTACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCAG CACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCC ACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTACT TCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTGACCAG CGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCCTGTAC TCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGGCACCC AGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACCAAGGT GGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACACCTGT CCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCC TGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCC CGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAA GTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCA AGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGGGTGGT GTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAG TACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCATCGAAA AGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTA CACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCC CTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGG AATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCC CCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTG ACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCT CCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCT GTCCCTGAGCCCCGGCAAGTGATGA
370	STIM001 - CDRL1	Amino acid sequence of CDRL1 of STIM001 using IMGT	QSLLHSNEYNY
371	STIM001 - CDRL2	Amino acid sequence of CDRL2 of STIM001 using IMGT	LGS
372	STIM001 - CDRL3	Amino acid sequence of CDRL3 of STIM001 using IMGT	MQSLQTPLT
373	STIM001 - Light chain variable region	Amino acid sequence of V_L of STIM001	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNEYNYLDWYLQKPG QSPQLLIFLGSNRASGVPDRFSGSGSGTDFTLKITRVEAEDVGIYY CMQSLQTPLTFGGGTKVEIK
374	STIM001 - Light chain variable region	Nucleic acid sequence of V_L of STIM001	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTAATGAATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTTTTTGGGTTCTAATCGGGCCTCCG GGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCACCAGAGTGGAGGCTGAGGATGTTGGAATTTATTAC TGCATGCAATCTCTACAAACTCCGCTCACTTTCGGCGGAGGGACCA AGGTGGAGATCAAA
375	STIM001 - full light chain sequence	Amino acid sequence of STIM001 light chain	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNEYNYLDWYLQKPG QSPQLLIFLGSNRASGVPDRFSGSGSGTDFTLKITRVEAEDVGIYY CMQSLQTPLTFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
376	STIM001 - full light chain sequence	Nucleic acid sequence of STIM001 light chain	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTAATGAATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTTTTTGGGTTCTAATCGGGCCTCCG GGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCACCAGAGTGGAGGCTGAGGATGTTGGAATTTATTAC TGCATGCAATCTCTACAAACTCCGCTCACTTTCGGCGGAGGGACCA AGGTGGAGATCAAAcgtacggtggccgctccctccgtgttcatctt cccaccttccgacgagcagctgaagtccggcaccgcttctgtcgtg tgcctgctgaacaacttctacccccgcgaggccaaggtgcagtgga aggtggacaacgccctgcagtccggcaactcccaggaatccgtgac cgagcaggactccaaggacagcacctactccctgtcctccaccctg accctgtccaaggccgactacgagaagcacaaggtgtacgcctgcg aagtgacccaccagggcctgtctagccccgtgaccaagtctttcaa ccggggcgagtgt
377	STIM002 - CDRH1	Amino acid sequence of CDRH1 of STIM002 using IMGT	GYTFTSYG
378	STIM002 - CDRH2	Amino acid sequence of CDRH2 of STIM002 using IMGT	ISAYNGNT
379	STIM002 - CDRH3	Amino acid sequence of CDRH3 of STIM002 using IMGT	ARSTYFYGSGTLYGMDV
380	STIM002 - Heavy chain variable region	Amino acid sequence of V_H of STIM002	QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTA VYYCARSTYFYGSGTLYGMDVWGQGTTVTVSS
381	STIM002 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM002	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAG CTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTAGAG TGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTATGCAC AGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGACACGGCC GTGTATTACTGTGCGAGATCTACGTATTTCTATGGTTCGGGGACCC TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA
382	STIM002 - full heavy chain sequence	Amino acid sequence of STIM002 heavy chain	QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTA VYYCARSTYFYGSGTLYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
383	STIM002 - full heavy chain sequence	Nucleic acid sequence of STIM002 heavy chain	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAG CTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTAGAG TGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTATGCAC AGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGACACGGCC GTGTATTACTGTGCGAGATCTACGTATTTCTATGGTTCGGGGACCC TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCA AGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGA CTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTG ACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCC TGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGG CACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACC AAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACA CCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGT GTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGG ACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACC CTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAA CGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGG GTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCAT CGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAG GTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGG TGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGC CGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACC ACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCA AGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAG TCCCTGTCCCTGAGCCCCGGCAAGTGATGA
384	STIM002 - CDRL1	Amino acid sequence of CDRL1 of STIM002 using IMGT	QSLLHSDGYNY
385	STIM002 - CDRL2	Amino acid sequence of CDRL2 of STIM002 using IMGT	LGS
386	STIM002 - CDRL3	Amino acid sequence of CDRL3 of STIM002 using IMGT	MQALQTPLS
387	STIM002 - Light chain variable region	Amino acid sequence of V_L of STIM002	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPG QSPQLLIYLGSTRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPLSFGQGTKLEIK
388	STIM002 - Light chain variable region	Nucleic acid sequence of V_L of STIM002	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTGATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCCTCCG GGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAGGGGACCA AGCTGGAGATCAAA
389	STIM002 - full light chain sequence	Amino acid sequence of STIM002 light chain	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNYLDWYLQKPG QSPQLLIYLGSTRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPLSFGQGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
390	STIM002 - full light chain sequence	Nucleic acid sequence of STIM002 light chain	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTGATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCCTCCG GGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAGGGGACCA AGCTGGAGATCAAAcgtacggtggccgctccctccgtgttcatctt cccaccttccgacgagcagctgaagtccggcaccgcttctgtcgtg tgcctgctgaacaacttctacccccgcgaggccaaggtgcagtgga aggtggacaacgccctgcagtccggcaactcccaggaatccgtgac cgagcaggactccaaggacagcacctactccctgtcctccaccctg accctgtccaaggccgactacgagaagcacaaggtgtacgcctgcg aagtgacccaccagggcctgtctagccccgtgaccaagtctttcaa ccggggcgagtgt
391	STIM002-B - CDRH1	Amino acid sequence of CDRH1 of STIM002-B using IMGT	GYTFTSYG
392	STIM002-B - CDRH2	Amino acid sequence of CDRH2 of STIM002-B using IMGT	ISAYNGNT
393	STIM002-B - CDRH3	Amino acid sequence of CDRH3 of STIM002-B using IMGT	ARSTYFYGSGTLYGMDV
394	STIM002-B - Heavy chain variable region	Amino acid sequence of V_H of STIM002-B	QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTA VYYCARSTYFYGSGTLYGMDVWGQGTTVTVSS
395	STIM002-B - Heavy chain variable region	Nucleic acid sequence of V_H of STIM002-B	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAG CTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTAGAG TGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTATGCAC AGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGACACGGCC GTGTATTACTGTGCGAGATCTACGTATTTCTATGGTTCGGGGACCC TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA
396	STIM002-B - full heavy chain sequence	Amino acid sequence of STIM002-B heavy chain	QVQLVQSGGEVKKPGASVKVSCKASGYTFTSYGFSWVRQAPGQGLE WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTA VYYCARSTYFYGSGTLYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
397	STIM002-B - full heavy chain sequence	Nucleic acid sequence of STIM002-B heavy chain	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAG CTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTAGAG TGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTATGCAC AGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGACACGGCC GTGTATTACTGTGCGAGATCTACGTATTTCTATGGTTCGGGGACCC TCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCC AGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGA AGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGC TCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCC GGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTC TGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAA CACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACC CACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTT CCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTC CCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAG GACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGC ACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAAC GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCC CCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACC CCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATA TCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAA GACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTAC AGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGT TCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCA GAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
398	STIM002-B - CDRL1	Amino acid sequence of CDRL1 of STIM002-B using IMGT	QSLLHSDGYNC
399	STIM002-B - CDRL2	Amino acid sequence of CDRL2 of STIM002-B using IMGT	LGS
400	STIM002-B - CDRL3	Amino acid sequence of CDRL3 of STIM002-B using IMGT	MQALQTPCS
401	STIM002-B - Light chain variable region	Amino acid sequence of V_L of STIM002-B	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNCLDWYLQKPG QSPQLLIYLGSTRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPCSFGQGTKLEIK
402	STIM002-B - Light chain variable region	Nucleic acid sequence of V_L of STIM002-B	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTGATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCCTCCG GGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAGGGGACCA AGCTGGAGATCAAA
403	STIM002-B - full light chain sequence	Amino acid sequence of STIM002-B light chain	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSDGYNCLDWYLQKPG QSPQLLIYLGSTRASGFPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPCSFGQGTKLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
404	STIM002-B - full light chain sequence	Nucleic acid sequence of STIM002-B light chain	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTGATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCCTCCG GGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAGGGGACCA AGCTGGAGATCAAAcgtacggtggccgctccctccgtgttcatctt cccaccttccgacgagcagctgaagtccggcaccgcttctgtcgtg tgcctgctgaacaacttctacccccgcgaggccaaggtgcagtgga aggtggacaacgccctgcagtccggcaactcccaggaatccgtgac cgagcaggactccaaggacagcacctactccctgtcctccaccctg accctgtccaaggccgactacgagaagcacaaggtgtacgcctgcg aagtgacccaccagggcctgtctagccccgtgaccaagtctttcaa ccggggcgagtgt
405	STIM003 - CDRH1	Amino acid sequence of CDRH1 of STIM003 using IMGT	GVTFDDYG
406	STIM003 - CDRH2	Amino acid sequence of CDRH2 of STIM003 using IMGT	INWNGGDT
407	STIM003 - CDRH3	Amino acid sequence of CDRH3 of STIM003 using IMGT	ARDFYGSGSYYHVPFDY
408	STIM003 - Heavy chain variable region	Amino acid sequence of V_H of STIM003	EVQLVESGGGVVRPGGSLRLSCVASGVTFDDYGMSWVRQAPGKGLE WVSGINWNGGDTDYSDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA LYYCARDFYGSGSYYHVPFDYWGQGILVTVSS
409	STIM003 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM003	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGG GGTCCCTGAGACTCTCCTGTGTAGCCTCTGGAGTCACCTTTGATGA TTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAAGGGGCTGGAR TGGGTCTCTGGTATTAATTGGAATGGTGGCGACACAGATTATTCAG ACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCCCTGTATCTACAAATGAATAGTCTGAGAGCCGAGGACACGGCC TTGTATTACTGTGCGAGGGATTTCTATGGTTCGGGGAGTTATTATC ACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCACCGTCTC CTCA
410	STIM003 - full heavy chain sequence	Amino acid sequence of STIM003 heavy chain	EVQLVESGGGVVRPGGSLRLSCVASGVTFDDYGMSWVRQAPGKGLE WVSGINWNGGDTDYSDSVKGRFTISRDNAKNSLYLQMNSLRAEDTA LYYCARDFYGSGSYYHVPFDYWGQGILVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
411	STIM003 - full heavy chain sequence	Nucleic acid sequence of STIM003 heavy chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGG GGTCCCTGAGACTCTCCTGTGTAGCCTCTGGAGTCACCTTTGATGA TTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAAGGGGCTGGAR TGGGTCTCTGGTATTAATTGGAATGGTGGCGACACAGATTATTCAG ACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCCCTGTATCTACAAATGAATAGTCTGAGAGCCGAGGACACGGCC TTGTATTACTGTGCGAGGGATTTCTATGGTTCGGGGAGTTATTATC ACGTTCCTTTTGACTACTGGGGCCAGGGAATCCTGGTCACCGTCTC CTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCC AGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGA AGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGC TCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCC GGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTC TGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAA CACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACC CACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTT CCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTC CCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAG GACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGC ACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAAC GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCC CCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACC CCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATA TCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAA GACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTAC AGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGT TCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCA GAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
412	STIM003 - CDRL1	Amino acid sequence of CDRL1 of STIM003 using IMGT	QSVSRSY
413	STIM003 - CDRL2	Amino acid sequence of CDRL2 of STIM003 using IMGT	GAS
414	STIM003 - CDRL3	Amino acid sequence of CDRL3 of STIM003 using IMGT	HQYDMSPFT
415	STIM003 - Light chain variable region	Amino acid sequence of V_L of STIM003	EIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPR LLIYGASSRATGIPDRFSGDGSGTDFTLSISRLEPEDFAVYYCHQY DMSPFTFGPGTKVDIK
416	STIM003 - Light chain variable region	Nucleic acid sequence of V_L of STIM003	GAAATTGTGTTGACGCAGTCTCCAGGGACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAG AAGCTACTTAGCCTGGTACCAGCAGAAACGTGGCCAGGCTCCCAGG CTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCGATGGGTCTGGGACAGACTTCACTCTCTCCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCACCAGTAT GATATGTCACCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCA AA
417	STIM003 - full light chain sequence	Amino acid sequence of STIM003 light chain	EIVLTQSPGTLSLSPGERATLSCRASQSVSRSYLAWYQQKRGQAPR LLIYGASSRATGIPDRFSGDGSGTDFTLSISRLEPEDFAVYYCHQY DMSPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
418	STIM003 - full light chain sequence	Nucleic acid sequence of STIM003 light chain	GAAATTGTGTTGACGCAGTCTCCAGGGACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAG AAGCTACTTAGCCTGGTACCAGCAGAAACGTGGCCAGGCTCCCAGG CTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCGATGGGTCTGGGACAGACTTCACTCTCTCCATCAG CAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCACCAGTAT GATATGTCACCATTCACTTTCGGCCCTGGGACCAAAGTGGATATCA AAcgtacggtggccgctccctccgtgttcatcttcccaccttccga cgagcagctgaagtccggcaccgcttctgtcgtgtgcctgctgaac aacttctacccccgcgaggccaaggtgcagtggaaggtggacaacg ccctgcagtccggcaactcccaggaatccgtgaccgagcaggactc caaggacagcacctactccctgtcctccaccctgaccctgtccaag gccgactacgagaagcacaaggtgtacgcctgcgaagtgacccacc agggcctgtctagccccgtgaccaagtctttcaaccggggcgagtg t
419	STIM004 - CDRH1	Amino acid sequence of CDRH1 of STIM004 using IMGT	GLTFDDYG
420	STIM004 - CDRH2	Amino acid sequence of CDRH2 of STIM004 using IMGT	INWNGDNT
421	STIM004 - CDRH3	Amino acid sequence of CDRH3 of STIM004 using IMGT	ARDYYGSGSYYNVPFDY
422	STIM004 - Heavy chain variable region	Amino acid sequence of V_H of STIM004	EVQLVESGGGVVRPGGSLRLSCAASGLTFDDYGMSWVRQVPGKGLE WVSGINWNGDNTDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTA LYYCARDYYGSGSYYNVPFDYWGQGTLVTVSS
423	STIM004 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM004	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGACTCACCTTTGATGA TTATGGCATGAGCTGGGTCCGCCAAGTTCCAGGGAAGGGGCTGGAG TGGGTCTCTGGTATTAATTGGAATGGTGATAACACAGATTATGCAG ACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCCCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCC TTGTATTACTGTGCGAGGGATTACTATGGTTCGGGGAGTTATTATA ACGTTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTC CTCA
424	STIM004 - full heavy chain sequence	Amino acid sequence of STIM004 heavy chain	EVQLVESGGGVVRPGGSLRLSCAASGLTFDDYGMSWVRQVPGKGLE WVSGINWNGDNTDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTA LYYCARDYYGSGSYYNVPFDYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
425	STIM004 - full heavy chain sequence	Nucleic acid sequence of STIM004 heavy chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGGG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGACTCACCTTTGATGA TTATGGCATGAGCTGGGTCCGCCAAGTTCCAGGGAAGGGGCTGGAG TGGGTCTCTGGTATTAATTGGAATGGTGATAACACAGATTATGCAG ACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAA CTCCCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCC TTGTATTACTGTGCGAGGGATTACTATGGTTCGGGGAGTTATTATA ACGTTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTC CTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCC AGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGA AGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGC TCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCC GGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTC TGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAA CACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACC CACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTT CCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTC CCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAG GACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGC ACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAAC GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCC CCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACC CCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATA TCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAA GACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTAC AGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGT TCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCA GAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
426	STIM004 - CDRL1	Amino acid sequence of CDRL1 of STIM004 using IMGT	QSVSSSY
427	STIM004 - CDRL2	Amino acid sequence of CDRL2 of STIM004 using IMGT	GAS
428	STIM004 - CDRL3	Amino acid sequence of CDRL3 of STIM004 using IMGT	QQYGSSPF
429	STIM004 - Corrected light chain variable region	Amino acid sequence of corrected V_L of STIM004	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQY GSSPFFGPGTKVDIK
430	STIM004 - Corrected light chain variable region	Nucleic acid sequence of corrected V_L of STIM004	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATATATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAG AAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTAGTTCACCATTCTTCGGCCCTGGGACCAAAGTGGATATCAAA
431	STIM004 - Light chain variable region	Nucleic acid sequence of V_L of STIM004	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATATATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAG AAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTAGTTCACCATTCACTTCGGCCCTGGGACCAAAGTGGATATCAA A

SEQ ID NO:	Name	Description	Sequence
432	STIM004 - full corrected light chain sequence	Amino acid sequence of STIM004 light chain	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPR LLIYGASSRATGIPDRFSGSGSGTDFTLTIRRLEPEDFAVYYCQQY GSSPFFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC
433	STIM004 - full corrected light chain sequence	Nucleic acid sequence of corrected STIM004 light chain	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATATATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAG AAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTAGTTCACCATTCTTCGGCCCTGGGACCAAAGTGGATATCAAAc gtacggtggccgctccctccgtgttcatcttcccaccttccgacga gcagctgaagtccggcaccgcttctgtcgtgtgcctgctgaacaac ttctacccccgcgaggccaaggtgcagtggaaggtggacaacgccc tgcagtccggcaactcccaggaatccgtgaccgagcaggactccaa ggacagcacctactccctgtcctccaccctgaccctgtccaaggcc gactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagg gcctgtctagccccgtgaccaagtctttcaaccggggcgagtgt
434	STIM004 - full light chain sequence	Nucleic acid sequence of STIM004 light chain	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAG CAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATATATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACA GGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAG AAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTAGTTCACCATTCACTTCGGCCCTGGGACCAAAGTGGATATCAA Acgtacggtggccgctccctccgtgttcatcttcccaccttccgac gagcagctgaagtccggcaccgcttctgtcgtgtgcctgctgaaca acttctacccccgcgaggccaaggtgcagtggaaggtggacaacgc cctgcagtccggcaactcccaggaatccgtgaccgagcaggactcc aaggacagcacctactccctgtcctccaccctgaccctgtccaagg ccgactacgagaagcacaaggtgtacgcctgcgaagtgacccacca gggcctgtctagccccgtgaccaagtctttcaaccggggcgagtgt
435	STIM005 - CDRH1	Amino acid sequence of CDRH1 of STIM005 using IMGT	GYTFNSYG
436	STIM005 - CDRH2	Amino acid sequence of CDRH2 of STIM005 using IMGT	ISVHNGNT
437	STIM005 - CDRH3	Amino acid sequence of CDRH3 of STIM005 using IMGT	ARAGYDILTDFSDAFDI
438	STIM005 - Heavy chain variable region	Amino acid sequence of V_H of STIM005	QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGIIWVRQAPGQGLE WMGWISVHNGNTNCAQKLQGRVTMTTDTSTSTAYMELRSLRTDDTA VYYCARAGYDILTDFSDAFDIWGHGTMVTVSS
439	STIM005 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM005	CAGGTTCAGTTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTAATAG TTATGGTATCATCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAG TGGATGGGATGGATCAGCGTTCACAATGGTAACACAAACTGTGCAC AGAAGCTCCAGGGTAGAGTCACCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCCTGAGAACTGACGACACGGCC GTGTATTACTGTGCGAGAGCGGGTTACGATATTTTGACTGATTTTT CCGATGCTTTTGATATCTGGGGCCACGGGACAATGGTCACCGTCTC TTCA

SEQ ID NO:	Name	Description	Sequence
440	STIM005 - full heavy chain sequence	Amino acid sequence of STIM005 heavy chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGIIWVRQAPGQGLE WMGWISVHNGNTNCAQKLQGRVTMTTDTSTSTAYMELRSLRTDDTA VYYCARAGYDILTDFSDAFDIWGHGTMVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
441	STIM005 - full heavy chain sequence	Nucleic acid sequence of STIM005 heavy chain	CAGGTTCAGTTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGG CCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTAATAG TTATGGTATCATCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAG TGGATGGGATGGATCAGCGTTCACAATGGTAACACAAACTGTGCAC AGAAGCTCCAGGGTAGAGTCACCATGACCACAGACACATCCACGAG CACAGCCTACATGGAGCTGAGGAGCCTGAGAACTGACGACACGGCC GTGTATTACTGTGCGAGAGCGGGTTACGATATTTTGACTGATTTTT CCGATGCTTTTGATATCTGGGGCCACGGGACAATGGTCACCGTCTC TTCA GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCA AGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGA CTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTG ACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCC TGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGG CACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACC AAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACA CCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGT GTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGG ACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACC CTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAA CGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGG GTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCAT CGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAG GTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGG TGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGC CGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACC ACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCA AGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAG TCCCTGTCCCTGAGCCCCGGCAAGTGATGA
442	STIM005 - CDRL1	Amino acid sequence of CDRL1 of STIM005 using IMGT	QNINNF
443	STIM005 - CDRL2	Amino acid sequence of CDRL2 of STIM005 using IMGT	AAS
444	STIM005 - CDRL3	Amino acid sequence of CDRL3 of STIM005 using IMGT	QQSYGIPW
445	STIM005 - Light chain variable region	Amino acid sequence of V_L of STIM005	DIQMTQSPSSLSASVGDRVTITCRASQNINNFLNWYQQKEGKGPKL LIYAASSLQRGIPSTFSGSGSGTDFTLTISSLQPEDFATYICQQSY GIPWVGQGTKVEIK
446	STIM005 - Light chain variable region	Nucleic acid sequence of V_L of STIM005	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAG GAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAACATTAATAA CTTTTTAAATTGGTATCAGCAGAAAGAAGGGAAAGGCCCTAAGCTC CTGATCTATGCAGCATCCAGTTTGCAAAGAGGGATACCATCAACGT TCAGTGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAG TCTGCAACCTGAAGATTTTGCAACTTACATCTGTCAACAGAGCTAC GGTATCCCGTGGGTCGGCCAAGGGACCAAGGTGGAAATCAAA

SEQ ID NO:	Name	Description	Sequence
447	STIM005 - full light chain sequence	Amino acid sequence of STIM005 light chain	DIQMTQSPSSLSASVGDRVTITCRASQNINNFLNWYQQKEGKGPKL LIYAASSLQRGIPSTFSGSGSGTDFTLTISSLQPEDFATYICQQSY GIPWVGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC
448	STIM005 - full light chain sequence	Nucleic acid sequence of STIM005 light chain	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAG GAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAACATTAATAA CTTTTTAAATTGGTATCAGCAGAAAGAAGGGAAAGGCCCTAAGCTC CTGATCTATGCAGCATCCAGTTTGCAAAGAGGGATACCATCAACGT TCAGTGGCAGTGGATCTGGGACAGACTTCACTCTCACCATCAGCAG TCTGCAACCTGAAGATTTTGCAACTTACATCTGTCAACAGAGCTAC GGTATCCCGTGGGTCGGCCAAGGGACCAAGGTGGAAATCAAAcgta cggtggccgctccctccgtgttcatcttcccaccttccgacgagca gctgaagtccggcaccgcttctgtcgtgtgcctgctgaacaacttc tacccccgcgaggccaaggtgcagtggaaggtggacaacgccctgc agtccggcaactcccaggaatccgtgaccgagcaggactccaagga cagcacctactccctgtcctccaccctgaccctgtccaaggccgac tacgagaagcacaaggtgtacgcctgcgaagtgacccaccagggcc tgtctagccccgtgaccaagtctttcaaccggggcgagtgt
449	STIM006 - CDRH1	Amino acid sequence of CDRH1 of STIM006 using IMGT	GFTFSDYF
450	STIM006 - CDRH2	Amino acid sequence of CDRH2 of STIM006 using IMGT	ISSSGSTI
451	STIM006 - CDRH3	Amino acid sequence of CDRH3 of STIM006 using IMGT	ARDHYDGSGIYPLYYYYGLDV
452	STIM006 - Heavy chain variable region	Amino acid sequence of V_H of STIM006	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYFMSWIRQAPGKGLE WISYISSSGSTIYYADSVRGRFTISRDNAKYSLYLQMNSLRSEDTA VYYCARDHYDGSGIYPLYYYYGLDVWGQGTTVTVSS
453	STIM006 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM006	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGA CTACTTCATGAGCTGGATCCGCCAGGCGCCAGGGAAGGGGCTGGAG TGGATTTCATACATTAGTTCTAGTGGTAGTACCATATACTACGCAG ACTCTGTGAGGGGCCGATTCACCATCTCCAGGGACAACGCCAAGTA CTCACTGTATCTGCAAATGAACAGCCTGAGATCCGAGGACACGGCC GTGTATTACTGTGCGAGAGATCACTACGATGGTTCGGGGATTTATC CCCTCTACTACTATTACGGTTTGGACGTCTGGGGCCAGGGGACCAC GGTCACCGTCTCCTCA
454	STIM006 - full heavy chain sequence	Amino acid sequence of STIM006 heavy chain	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYFMSWIRQAPGKGLE WISYISSSGSTIYYADSVRGRFTISRDNAKYSLYLQMNSLRSEDTA VYYCARDHYDGSGIYPLYYYYGLDVWGQGTTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
455	STIM006 - full heavy chain sequence	Nucleic acid sequence of STIM006 heavy chain	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGA CTACTTCATGAGCTGGATCCGCCAGGCGCCAGGGAAGGGGCTGGAG TGGATTTCATACATTAGTTCTAGTGGTAGTACCATATACTACGCAG ACTCTGTGAGGGGCCGATTCACCATCTCCAGGGACAACGCCAAGTA CTCACTGTATCTGCAAATGAACAGCCTGAGATCCGAGGACACGGCC GTGTATTACTGTGCGAGAGATCACTACGATGGTTCGGGGATTTATC CCCTCTACTACTATTACGGTTTGGACGTCTGGGGCCAGGGGACCAC GGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCT CTGGCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGG GCTGCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTG GAACTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTG CTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGC CTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCA CAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCC TGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGC TGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACAC CCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGAT GTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACG GCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTA CAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAG GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGG CCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCA GCCCCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAG CTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCT ACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGA GAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCA TTCTTCCTGTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGC AGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
456	STIM006 - CDRL1	Amino acid sequence of CDRL1 of STIM006 using IMGT	QSLLHSNGYNY
457	STIM006 - CDRL2	Amino acid sequence of CDRL2 of STIM006 using IMGT	LGS
458	STIM006 - CDRL3	Amino acid sequence of CDRL3 of STIM006 using IMGT	MQALQTPRS
459	STIM006 - Light chain variable region	Amino acid sequence of V_L of STIM006	IVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDYYLQKPGQ SPQLLIYLGSYRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQALQTPRSFGQGTTLEIK
460	STIM006 - Light chain variable region	Nucleic acid sequence of V_L of STIM006	ATTGTGATGACTCAGTCTCCACTCTCCCTACCCGTCACCCCTGGAG AGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAG TAATGGATACAACTATTTGGATTATTACCTGCAGAAGCCAGGGCAG TCTCCACAGCTCCTGATCTATTTGGGTTCTTATCGGGCCTCCGGGG TCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACACT GAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGC ATGCAAGCTCTACAAACTCCTCGCAGTTTTGGCCAGGGGACCACGC TGGAGATCAAA
461	STIM006 - full light chain sequence	Amino acid sequence of STIM006 light chain	IVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDYYLQKPGQ SPQLLIYLGSYRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQALQTPRSFGQGTTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
462	STIM006 - full light chain sequence	Nucleic acid sequence of STIM006 light chain	ATTGTGATGACTCAGTCTCCACTCTCCCTACCCGTCACCCCTGGAG AGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAG TAATGGATACAACTATTTGGATTATTACCTGCAGAAGCCAGGGCAG TCTCCACAGCTCCTGATCTATTTGGGTTCTTATCGGGCCTCCGGGG TCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACACT GAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGC ATGCAAGCTCTACAAACTCCTCGCAGTTTTGGCCAGGGGACCACGC TGGAGATCAAAcgtacggtggccgctccctccgtgttcatcttccc accttccgacgagcagctgaagtccggcaccgcttctgtcgtgtgc ctgctgaacaacttctacccccgcgaggccaaggtgcagtggaagg tggacaacgccctgcagtccggcaactcccaggaatccgtgaccga gcaggactccaaggacagcacctactccctgtcctccaccctgacc ctgtccaaggccgactacgagaagcacaaggtgtacgcctgcgaag tgacccaccagggcctgtctagccccgtgaccaagtctttcaaccg gggcgagtgt
463	STIM007 - CDRH1	Amino acid sequence of CDRH1 of STIM007 using IMGT	GFSLSTTGVG
464	STIM007 - CDRH2	Amino acid sequence of CDRH2 of STIM007 using IMGT	IYWDDDK
465	STIM007 - CDRH3	Amino acid sequence of CDRH3 of STIM007 using IMGT	THGYGSASYYHYGMDV
466	STIM007 - Heavy chain variable region	Amino acid sequence of V_H of STIM007	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTTGVGVGWIRQPPGKA LEWLAVIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDT ATYFCTHGYGSASYYHYGMDVWGQGTTVTVSS
467	STIM007 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM007	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACAC AGACCCTCACGCTGACCTGCACCTTCTCTCTGGGTTCTCACTCAGCAC TACTGGAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCC CTGGAGTGGCTTGCAGTCATTTATTGGGATGATGATAAGCGCTACA GCCCATCTCTGAAGAGCAGACTCACCATCACCAAGGACACCTCCAA AAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACA GCCACATATTTCTGTACACACGGATATGGTTCGGCGAGTTATTACC ACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA
468	STIM007 - full heavy chain sequence	Amino acid sequence of STIM007 heavy chain	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTTGVGVGWIRQPPGKA LEWLAVIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDT ATYFCTHGYGSASYYHYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
469	STIM007 - full heavy chain sequence	Nucleic acid sequence of STIM007 heavy chain	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACAC AGACCCTCACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCAC TACTGGAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCC CTGGAGTGGCTTGCAGTCATTTATTGGGATGATGATAAGCGCTACA GCCCATCTCTGAAGAGCAGACTCACCATCACCAAGGACACCTCCAA AAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACA GCCACATATTTCTGTACACACGGATATGGTTCGGCGAGTTATTACC ACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA GCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCCAGCA AGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGA CTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCTCTG ACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCCGGCC TGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTCTGGG CACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAACACC AAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACCCACA CCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGT GTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGG ACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACC CTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAA CGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTACCGG GTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCA AAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCCAT CGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAG GTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGG TGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGC CGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACC ACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCA AGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTC CTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAG TCCCTGTCCCTGAGCCCCGGCAAGTGATGA
470	STIM007-CDRL1	Amino acid sequence of CDRL1 of STIM007 using IMGT	QSVTNY
471	STIM007-CDRL2	Amino acid sequence of CDRL2 of STIM007 using IMGT	DAS
472	STIM007-CDRL3	Amino acid sequence of CDRL3 of STIM007 using IMGT	QHRSNWPLT
473	STIM007 - Light chain variable region	Amino acid sequence of V_L of STIM007	EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRS NWPLTFGGGTKVEIK
474	STIM007 - Light chain variable region	Nucleic acid sequence of V_L of STIM007	GAAATTGTATTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAA CTACTTAGCCTGGCACCAACAGAAACCTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGT TCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAG CCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCACCGTAGC AACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC
475	STIM007 - full light chain sequence	Amino acid sequence of STIM007 light chain	EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHRS NWPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
476	STIM007 - full light chain sequence	Nucleic acid sequence of STIM007 light chain	GAAATTGTATTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAA CTACTTAGCCTGGCACCAACAGAAACCTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGT TCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAG CCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCACCGTAGC AACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAC cgtacggtggccgctccctccgtgttcatcttcccaccttccgacg agcagctgaagtccggcaccgcttctgtcgtgtgcctgctgaacaa cttctacccccgcgaggccaaggtgcagtggaaggtggacaacgcc ctgcagtccggcaactcccaggaatccgtgaccgagcaggactcca aggacagcacctactccctgtcctccaccctgaccctgtccaaggc cgactacgagaagcacaaggtgtacgcctgcgaagtgacccaccag ggcctgtctagccccgtgaccaagtctttcaaccggggcgagtgt
477	STIM008-CDRH1	Amino acid sequence of CDRH1 of STIM008 using IMGT	GFSLSTSGVG
478	STIM008-CDRH2	Amino acid sequence of CDRH2 of STIM008 using IMGT	IYWDDDK
479	STIM008-CDRH3	Amino acid sequence of CDRH3 of STIM008 using IMGT	THGYGSASYYHYGMDV
480	STIM008 - Heavy chain variable region	Amino acid sequence of V_H of STIM008	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKA LEWLAVIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDT ATYFCTHGYGSASYYHYGMDVWGQGTTVTVSS
481	STIM008 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM008	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACAC AGACCCTCACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCAC TAGTGGAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCC CTGGAGTGGCTTGCAGTCATTTATTGGGATGATGATAAGCGCTACA GCCCATCTCTGAAGAGCAGGCTCACCATCACCAAGGACACCTCCAA AAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACA GCCACATATTTCTGTACACACGGATATGGTTCGGCGAGTTATTACC ACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA
482	STIM008 - full heavy chain sequence	Amino acid sequence of STIM008 heavy chain	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKA LEWLAVIYWDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDT ATYFCTHGYGSASYYHYGMDVWGQGTTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
483	STIM008 - full heavy chain sequence	Nucleic acid sequence of STIM008 heavy chain	CAGATCACCTTGAAGGAGTCTGGTCCTACGCTGGTGAAACCCACAC AGACCCTCACGCTGACCTGCACCTTCTCTGGGTTCTCACTCAGCAC TAGTGGAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCC CTGGAGTGGCTTGCAGTCATTTATTGGGATGATGATAAGCGCTACA GCCCATCTCTGAAGAGCAGGCTCACCATCACCAAGGACACCTCCAA AAACCAGGTGGTCCTTACAATGACCAACATGGACCCTGTGGACACA GCCACATATTTCTGTACACACGGATATGGTTCGGCGAGTTATTACC ACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTGGCCCCTTCC AGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCTGCCTCGTGA AGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGC TCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAGTCCTCC GGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTTCCAGCTCTC TGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCTCCAA CACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGCGACAAGACC CACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTT CCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTC CCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAG GACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGC ACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAACTCCACCTA CCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAAC GGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCC CCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACC CCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATA TCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAA GACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTAC AGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGT TCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCA GAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
484	STIM008-CDRL1	Amino acid sequence of CDRL1 of STIM008 using IMGT	QSVTNY
485	STIM008-CDRL2	Amino acid sequence of CDRL2 of STIM008 using IMGT	DAS
486	STIM008-CDRL3	Amino acid sequence of CDRL3 of STIM008 using IMGT	QQRSNWPLT
487	STIM008 - Light chain variable region	Amino acid sequence of V_L of STIM008	EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRS NWPLTFGGGTKVEIK
488	STIM008 - Light chain variable region	Nucleic acid sequence of V_L of STIM008	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAA CTACTTAGCCTGGCACCAACAGAAACCTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGT TCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAG CCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGC AACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA
489	STIM008 - full light chain sequence	Amino acid sequence of STIM008 light chain	EIVLTQSPATLSLSPGERATLSCRASQSVTNYLAWHQQKPGQAPRL LIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRS NWPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
490	STIM008 - full light chain sequence	Nucleic acid sequence of STIM008 light chain	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAG GGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAA CTACTTAGCCTGGCACCAACAGAAACCTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGT TCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAG CCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGC AACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAAc gtacggtggccgctccctccgtgttcatcttcccaccttccgacga gcagctgaagtccggcaccgcttctgtcgtgtgcctgctgaacaac ttctacccccgcgaggccaaggtgcagtggaaggtggacaacgccc tgcagtccggcaactcccaggaatccgtgaccgagcaggactccaa ggacagcacctactccctgtcctccaccctgaccctgtccaaggcc gactacgagaagcacaaggtgtacgcctgcgaagtgacccaccagg gcctgtctagccccgtgaccaagtctttcaaccggggcgagtgt
491	STIM009-CDRH1	Amino acid sequence of CDRH1 of STIM009 using IMGT	GFTFSDYY
492	STIM009-CDRH2	Amino acid sequence of CDRH2 of STIM009 using IMGT	ISSSGSTI
493	STIM009-CDRH3	Amino acid sequence of CDRH3 of STIM009 using IMGT	ARDFYDILTDSPYFYYGVDV
494	STIM009 - Heavy chain variable region	Amino acid sequence of V_H of STIM009	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLE WVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQINSLRAEDTA VYYCARDFYDILTDSPYFYYGVDVWGQGTTVTVSS
495	STIM009 - Heavy chain variable region	Nucleic acid sequence of V_H of STIM009	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGA CTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAG ACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAA CTCACTGTATCTGCAAATTAACAGCCTGAGAGCCGAGGACACGGCC GTGTATTACTGTGCGAGAGATTTTTACGATATTTTGACTGATAGTC CGTACTTCTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGT CACCGTCTCCTCA
496	STIM009 - full heavy chain sequence	Amino acid sequence of STIM009 heavy chain	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLE WVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQINSLRAEDTA VYYCARDFYDILTDSPYFYYGVDVWGQGTTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	Name	Description	Sequence
497	STIM009 - full heavy chain sequence	Nucleic acid sequence of STIM009 heavy chain	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAG GGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGA CTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTTTCATACATTAGTAGTAGTGGTAGTACCATATACTACGCAG ACTCTGTGAAGGGCCGATTCACCATCTCCAGGGACAACGCCAAGAA CTCACTGTATCTGCAAATTAACAGCCTGAGAGCCGAGGACACGGCC GTGTATTACTGTGCGAGAGATTTTTACGATATTTTGACTGATAGTC CGTACTTCTACTACGGTGTGGACGTCTGGGGCCAAGGGACCACGGT CACCGTCTCCTCAGCCAGCACCAAGGGCCCCTCTGTGTTCCCTCTG GCCCCTTCCAGCAAGTCCACCTCTGGCGGAACAGCCGCTCTGGGCT GCCTCGTGAAGGACTACTTCCCCGAGCCTGTGACCGTGTCCTGGAA CTCTGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTG CAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTGCCTT CCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAA GCCCTCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCCTGC GACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGG GCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCT GATGATCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTGGACGGCG TGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAA CTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAT TGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCC TGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCC CCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTG ACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACC CCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAA CAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTC TTCCTGTACAGCAAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGG GCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCA CTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAGTGATGA
498	STIM009-CDRL1	Amino acid sequence of CDRL1 of STIM009 using IMGT	QSLLHSNGYNY
499	STIM009-CDRL2	Amino acid sequence of CDRL2 of STIM009 using IMGT	LGS
500	STIM009-CDRL3	Amino acid sequence of CDRL3 of STIM009 using IMGT	MQALQTPRT
501	STIM009 - Light chain variable region	Amino acid sequence of V_L of STIM009	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPRTFGQGTKVEIK
502	STIM009 - Light chain variable region	Nucleic acid sequence of V_L of STIM009	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTAATGGATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCG GGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAAACTCCTCGGACGTTCGGCCAAGGGACCA AGGTGGAAATCAAA
503	STIM009 - full light chain sequence	Amino acid sequence of STIM009 light chain	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	Name	Description	Sequence
504	STIM009 - full light chain sequence	Nucleic acid sequence of STIM009 light chain	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTG GAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCA TAGTAATGGATACAACTATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCG GGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGATTTTAC ACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAAACTCCTCGGACGTTCGGCCAAGGGACCA AGGTGGAAATCAAAcgtacggtggccgctccctccgtgttcatctt cccaccttccgacgagcagctgaagtccggcaccgcttctgtcgtg tgcctgctgaacaacttctacccccgcgaggccaaggtgcagtgga aggtggacaacgccctgcagtccggcaactcccaggaatccgtgac cgagcaggactccaaggacagcacctactccctgtcctccaccctg accctgtccaaggccgactacgagaagcacaaggtgtacgcctgcg aagtgacccaccagggcctgtctagccccgtgaccaagtctttcaa ccggggcgagtgt
505	Human PD-L1 Flag His (KYPROT286)	Amino acid sequence of KYPROT286 with **FLAG tag** in bold and underlined and **histidine tag** in bold	FTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNI IQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAG VYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHELTCQ AEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTT TNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTIEGR**DYKDD DDKHHHHHH**
506	Mature human ICOS	Mature amino acid sequence of human ICOS	EINGSANYEMFIFHNGGVQILCKYPDIVQQFKMQLLKGGQILCDLT KTKGSGNTVSIKSLKFCHSQLSNNSVSFFLYNLDHSHANYYFCNLS IFDPPPFKVTLTGGYLHIYESQLCCQLKFWLPIGCAAFVVVCILGC ILICWLTKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL
507	Human ICOS extracellular domain	Amino acid sequence of human ICOS extracellular domain	EINGSANYEMFIFHNGGVQILCKYPDIVQQFKMQLLKGGQILCDLT KTKGSGNTVSIKSLKFCHSQLSNNSVSFFLYNLDHSHANYYFCNLS IFDPPPFKVTLTGGYLHIYESQLCCQLKF
508	Human ICOS with signal peptide	Amino acid sequence of human ICOS (signal peptide is underlined)	MKSGLWYFFLFCLRIKVLTGEINGSANYEMFIFHNGGVQILCKYPD IVQQFKMQLLKGGQILCDLTKTKGSGNTVSIKSLKFCHSQLSNNSV SFFLYNLDHSHANYYFCNLSIFDPPPFKVTLTGGYLHIYESQLCCQ LKFWLPIGCAAFVVVCILGCILICWLTKKKYSSSVHDPNGEYMFMR AVNTAKKSRLTDVTL
509	Isoform of human ICOS (Q9Y6W8-2)	Amino acid sequence of a human ICOS isoform	The sequence of this isoform differs from the canonical sequence in its cytoplasmic domain as follows: 168-199: KYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTLM
510	Mature mouse ICOS	Mature amino acid sequence of mouse ICOS	EINGSADHRMFSFHNGGVQISCKYPETVQQLKMRLFREREVLCELT KTKGSGNAVSIKNPMLCLYHLSNNSVSFFLNNPDSSQGSYYFCSLS IFDPPPFQERNLSGGYLHIYESQLCCQLKIVVQVTE
511	Mouse ICOS extracellular domain	Amino acid sequence of the extracellular domain of mouse ICOS	EINGSADHRMFSFHNGGVQISCKYPETVQQLKMRLFREREVLCELT KTKGSGNAVSIKNPMLCLYHLSNNSVSFFLNNPDSSQGSYYFCSLS IFDPPPFQERNLSGGYLHIYESQLCCQLK
512	Mouse ICOS with signal peptide	Amino acid sequence of mouse ICOS (signal peptide is underlined)	MGWSCIILFLVATATGVHSEINGSADHRMFSFHNGGVQISCKYPET VQQLKMRLFREREVLCELTKTKGSGNAVSIKNPMLCLYHLSNNSVS FFLNNPDSSQGSYYFCSLSIFDPPPFQERNLSGGYLHIYESQLCCQ LKIVVQVTE
513	Cynomolgus ICOS with signal peptide	Amino acid sequence of cynomolgus ICOS (signal peptide is underlined)	MKSGLWYFFL FCLHMKVLTG EINGSANYEM FIFHNGGVQI LCKYPDIVQQ FKMQLLKGGQILCDLTKTKGSGNKVSIKSLKFCHSQLSNNSVSFFL YNLD RSHANYYFCNLSIFDPPPFKVTLTGGYLHIYESQLCCQLKFWLPIG CATF VVVCIFGCILICWLTKKKYSSTVHDPNGEYMFMRAVNTAKKSRLTG TTP

SEQ ID NO:	Name	Description	Sequence
514	Cynomolgus ICOS extracellular domain	Amino acid sequence of cynomolgus ICOS extracellular domain	EINGSANYEMFIFHNGGVQILCKYPDIVQQFKMQLLKGGQILCDLT KTKG SGNKVSIKSLKFCHSQLSNNSVSFFLYNLDRSHANYYFCNLSIFDP PPFK VTLTGGYLHIYESQLCCQLK
515	Human ICOS ligand	Amino acid sequence of human ICOS ligand comprising extracellular domain	DTQEKEVRAMVGSDVELSCACPEGSRFDLNDVYVYWQTSESKTVVT YHIPQNSSLENVDSRYRNRALMSPAGMLRGDFSLRLFNVTPQDEQK FHCLVLSQSLGFQEVLSVEVTLHVAANFSVPVVSAPHSPSQDELTF TCTSINGYPRPNVYWINKTDNSLLDQALQNDTVFLNMRGLYDVVSV LRIARTPSVNIGCCIENVLLQQNLTVGSQTGNDIGERDKITENPVS TGEKNAATWS
516	Human ICOS ligand	Amino acid sequence of human ICOS ligand including signal peptide	MRLGSPGLLFLLFSSLRADTQEKEVRAMVGSDVELSCACPEGSRFD LNDVYVYWQTSESKTVVTYHIPQNSSLENVDSRYRNRALMSPAGML RGDFSLRLFNVTPQDEQKFHCLVLSQSLGFQEVLSVEVTLHVAANF SVPVVSAPHSPSQDELTFTCTSINGYPRPNVYWINKTDNSLLDQAL QNDTVFLNMRGLYDVVSVLRIARTPSVNIGCCIENVLLQQNLTVGS QTGNDIGERDKITENPVSTGEKNAATWSILAVLCLLVVVAVAIGWV CRDRCLQHSYAGAWAVSPETELTGHV

SEQ ID NO: 610 ICOSL-Fc

DTQEKEVRAMVGSDVELSCACPEGSRFDLNDVYVYWQTSESKTVVTYHIPQNSSLENVDSRYRNRALMSPAGMLRGDFSLRLFNVT PQDEQKFHCLVLSQSLGFQEVLSVEVTLHVAANFSVPVVSAPHSPSQDELTFTCTSINGYPRPNVYWINKTDNSLLDQALQNDTVF LNMRGLYDVVSVLRIARTPSVNIGCCIENVLLQQNLTVGSQTGNDIGERDKITENPVSTGEKNAATWS**DIEGRMD**PKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Linker is underlined and in bold. Sequence preceding linker is human ICOSL (B7-H2). Sequence following linker is human IgG1 Fc.

517	C-terminal amino acid sequence of hIL-2	Amino acids 21 to 133 of hIL-2 with R38W mutation (**bold** & underlined)	LQMILNGINNYKNPKLT**A**MLTFKFYMPKKATELKHLQCL EEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKG SETTFMCEYADETATIVEFLNRWITFCQSIISTLT
518	C-terminal amino acid sequence of hIL-2	Amino acids 21 to 133 of hIL-2 with R38Q mutation (**bold** & underlined)	LQMILNGINNYKNPKLT**Q**MLTFKFYMPKKATELKHLQCL EEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKG SETTFMCEYADETATIVEFLNRWITFCQSIISTLT
519	STIM002 – Corrected Light chain variable region	Nucleic acid sequence of corrected V_L of STIM002	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTC ACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGT CAGAGCCTCCTGCATAGTGATGGATACAACTATTTGGAT TGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTG ATCTATTTGGGTTCTACTCGGGCCTCCGGGTTCCCTGAC AGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACACTG AAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTAT TACTGCATGCAAGCTCTACAAACTCCGCTCAGTTTTGGC CAGGGGACCAAGCTGGAGATCAAA

520	STIM002 – Corrected full light chain sequence	Nucleic acid sequence of corrected STIM002 light chain	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTC ACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGT CAGAGCCTCCTGCATAGTGATGGATACAACTATTTGGAT TGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTG ATCTATTTGGGTTCTACTCGGGCCTCCGGGTTCCCTGAC AGGTTCAGTGGCAGTGGATCAGGCACAGATTTTACACTG AAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTAT TACTGCATGCAAGCTCTACAAACTCCGCTCAGTTTTGGC CAGGGGACCAAGCTGGAGATCAAAcgtacggtggccgct ccctccgtgttcatcttcccaccttccgacgagcagctg aagtccggcaccgcttctgtcgtgtgcctgctgaacaac ttctaccccgcgaggccaaggtgcagtggaaggtggac aacgccctgcagtccggcaactcccaggaatccgtgacc gagcaggactccaaggacagcacctactccctgtcctcc accctgaccctgtccaaggccgactacgagaagcacaag gtgtacgcctgcgaagtgacccaccagggcctgtctagc cccgtgaccaagtctttcaaccggggcgagtgt
521	STIM003 – Corrected heavy chain variable region	Nucleic acid sequence of corrected V_H of STIM003	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGG CCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA GTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAA GCTCCAGGGAAGGGGCTGGAGTGGGTCTCTGGTATTAAT TGGAATGGTGGCGACACAGATTATTCAGACTCTGTGAAG GGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCC CTGTATCTACAAATGAATAGTCTGAGAGCCGAGGACACG GCCTTGTATTACTGTGCGAGGGATTTCTATGGTTCGGGG AGTTATTATCACGTTCCTTTTGACTACTGGGGCCAGGGA ATCCTGGTCACCGTCTCCTCA
522	STIM003 – Corrected full heavy chain sequence	Nucleic acid sequence of corrected STIM003 heavy chain	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGG CCTGGGGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGA GTCACCTTTGATGATTATGGCATGAGCTGGGTCCGCCAA GCTCCAGGGAAGGGGCTGGAGTGGGTCTCTGGTATTAAT TGGAATGGTGGCGACACAGATTATTCAGACTCTGTGAAG GGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCC CTGTATCTACAAATGAATAGTCTGAGAGCCGAGGACACG GCCTTGTATTACTGTGCGAGGGATTTCTATGGTTCGGGG AGTTATTATCACGTTCCTTTTGACTACTGGGGCCAGGGA ATCCTGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCC TCTGTGTTCCCTCTGGCCCCTTCCAGCAAGTCCACCTCT GGCGGAACAGCCGCTCTGGGCTGCCTCGTGAAGGACTAC TTCCCCGAGCCTGTGACCGTGTCCTGGAACTCTGGCGCT CTGACCAGCGGAGTGCACACCTTCCCTGCTGTGCTGCAG TCCTCCGGCCTGTACTCCCTGTCCTCCGTCGTGACCGTG CCTTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAAC GTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAG GTGGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCC CCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTG TTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATC TCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTG TCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTACGTG GACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGA GAGGAACAGTACAACTCCACCTACCGGGTGGTGTCCGTG CTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAAGAG TACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCCCCC ATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGG GAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAG CTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAA GGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCC AACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCT GTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAG CTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTG TTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCAC TACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAGTGA TGA

523	Human IgG1 constant region	IGHG 1*03	Human Heavy Chain Constant Region (IGHG1*03) Nucleotide Sequence	gcctccaccaagggcccatcggtcttcccctggcaccc tcctccaagagcacctctgggggcacagcggccctgggc tgcctggtcaaggactacttccccgaaccggtgacggtg tcgtggaactcaggcgccctgaccagcggcgtgcacacc ttcccggctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcagcttgggcacc cagacctacatctgcaacgtgaatcacaagcccagcaac accaaggtggacaagagagttgagcccaaatcttgtgac aaaactcacacatgcccaccgtgcccagcacctgaactc ctgggggggaccgtcagtcttcctcttcccccaaaaccc aaggacaccctcatgatctcccggaccctgaggtcaca tgcgtggtggtggacgtgagccacgaagaccctgaggtc aagttcaactggtacgtggacggcgtggaggtgcataat gccaagacaaagccgcgggaggagcagtacaacagcacg taccgtgtggtcagcgtcctcaccgtcctgcaccaggac tggctgaatggcaaggagtacaagtgcaaggtctccaac aaagccctcccagccccatcgagaaaaccatctccaaa gccaaagggcagccccgagaaccacaggtgtacaccctg cccccatcccgggaggagatgaccaagaaccaggtcagc ctgacctgcctggtcaaaggcttctatcccagcgacatc gccgtggagtgggagagcaatgggcagccggagaacaac tacaagaccacgcctcccgtgctggactccgacggctcc ttcttcctctatagcaagctcaccgtggacaagagcagg tggcagcaggggaacgtcttctcatgctccgtgatgcat gaggctctgcacaaccactacacgcagaagagcctctcc ctgtccccgggtaaa
524			Human Heavy Chain Constant Region (IGHG1*03) Protein Sequence	A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
525	Human IgG1 constant region	IGHG 1*04	Human Heavy Chain Constant Region (IGHG1*04) Nucleotide Sequence	gcctccaccaagggcccatcggtcttcccctggcaccc tcctccaagagcacctctgggggcacagcggccctgggc tgcctggtcaaggactacttccccgaaccggtgacggtg tcgtggaactcaggcgccctgaccagcggcgtgcacacc ttcccggctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcagcttgggcacc cagacctacatctgcaacgtgaatcacaagcccagcaac accaaggtggacaagaaagttgagcccaaatcttgtgac aaaactcacacatgcccaccgtgcccagcacctgaactc ctgggggggaccgtcagtcttcctcttcccccaaaaccc aaggacaccctcatgatctcccggaccctgaggtcaca tgcgtggtggtggacgtgagccacgaagaccctgaggtc aagttcaactggtacgtggacggcgtggaggtgcataat gccaagacaaagccgcgggaggagcagtacaacagcacg taccgtgtggtcagcgtcctcaccgtcctgcaccaggac tggctgaatggcaaggagtacaagtgcaaggtctccaac aaagccctcccagccccatcgagaaaaccatctccaaa gccaaagggcagccccgagaaccacaggtgtacaccctg cccccatcccgggatgagctgaccaagaaccaggtcagc ctgacctgcctggtcaaaggcttctatcccagcgacatc gccgtggagtgggagagcaatgggcagccggagaacaac tacaagaccacgcctcccgtgctggactccgacggctcc ttcttcctctacagcaagctcaccgtggacaagagcagg tggcagcaggggaacatcttctcatgctccgtgatgcat gaggctctgcacaaccactacacgcagaagagcctctcc ctgtctccgggtaaa

526			Human Heavy Chain Constant Region (IGHG1*04) Protein Sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMH EALHNHYTQKSLSLSPGK
527	Human IgG2 constant region	IGHG 2*01 & IGHG 2*03 & IGHG 2*05	Human Heavy Chain Constant Region (IGHG2*01) Nucleotide Sequence	gcctccaccaagggcccatcggtcttcccccctggcgccc tgctccaggagcacctccgagagcacagccgccctgggc tgcctggtcaaggactacttccccgaaccggtgacggtg tcgtggaactcaggcgctctgaccagcggcgtgcacacc ttcccagctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcaacttcggcacc cagacctacacctgcaacgtagatcacaagcccagcaac accaaggtggacaagacagttgagcgcaaatgttgtgtc gagtgcccaccgtgcccagcaccacctgtggcaggaccg tcagtcttcctcttcccccaaaacccaaggacaccctc atgatctcccggaccctgaggtcacgtgcgtggtggtg gacgtgagccacgaagaccccgaggtccagttcaactgg tacgtggacggcgtggaggtgcataatgccaagacaaag ccacgggaggagcagttcaacagcacgttccgtgtggtc agcgtcctcaccgttgtgcaccaggactggctgaacggc aaggagtacaagtgcaaggtctccaacaaaggcctccca gccccatcgagaaaaccatctccaaaaccaaagggcag ccccgagaaccacaggtgtacaccctgcccccatcccgg gaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctaccccagcgacatcgccgtggagtgg gagagcaatgggcagccggagaacaactacaagaccaca cctcccatgctggactccgacggctccttcttcctctac agcaagctcaccgtggacaagagcaggtggcagcagggg aacgtcttctcatgctccgtgatgcatgaggctctgcac aaccactacacgcagaagagcctctccctgtctccgggt aaa
528			Human Heavy Chain Constant Region (IGHG2*01) Protein Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK
529	Human IgG2 constant region	IGHG 2*02	Human Heavy Chain Constant Region (IGHG2*02) Nucleotide Sequence	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCC TGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGC TGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACC TTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGACCTCCAGCAACTTCGGCACC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC ACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCG TCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTC ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTG GACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGG TACGTGGACGGCATGGAGGTGCATAATGCCAAGACAAAG CCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTC AGCGTCCTCACCGTCGTGCACCAGGACTGGCTGAACGGC AAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCA GCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAG CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG GAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACA CCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT AAA

530			Human Heavy Chain Constant Region (IGHG2*02) Protein Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVTSSNFGT QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGMEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK
531	Human IgG2 constant region	IGHG 2*04	Human Heavy Chain Constant Region (IGHG2*04) Nucleotide Sequence	gcctccaccaagggcccatcggtcttcccccctggcgccc tgctccaggagcacctccgagagcacagcggccctgggc tgcctggtcaaggactacttccccgaaccggtgacggtg tcgtggaactcaggcgctctgaccagcggcgtgcacacc ttcccagctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcagcttgggcacc cagacctacacctgcaacgtagatcacaagcccagcaac accaaggtggacaagacagttgagcgcaaatgttgtgtc gagtgcccaccgtgcccagcaccacctgtggcaggaccg tcagtcttcctcttcccccaaaacccaaggacaccctc atgatctcccggaccctgaggtcacgtgcgtggtggtg gacgtgagccacgaagaccccgaggtccagttcaactgg tacgtggacggcgtggaggtgcataatgccaagacaaag ccacgggaggagcagttcaacagcacgttccgtgtggtc agcgtcctcaccgttgtgcaccaggactggctgaacggc aaggagtacaagtgcaaggtctccaacaaaggcctccca gcccccatcgagaaaaccatctccaaaaccaaagggcag ccccgagaaccacaggtgtacaccctgcccccatcccgg gaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctaccccagcgacatcgccgtggagtgg gagagcaatgggcagccggagaacaactacaagaccaca cctcccatgctggactccgacggctccttcttcctctac agcaagctcaccgtggacaagagcaggtggcagcagggg aacgtcttctcatgctccgtgatgcatgaggctctgcac aaccactacacgcagaagagcctctccctgtctccgggt aaa
532			Human Heavy Chain Constant Region (IGHG2*04) Protein Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK
533	Human IgG2 constant region	IGHG 2*06	Human Heavy Chain Constant Region (IGHG2*06) Nucleotide Sequence	GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCC TGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGC TGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACC TTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC ACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCG TCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTC ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTG GACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAG CCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTC AGCGTCCTCACCGTCGTGCACCAGGACTGGCTGAACGGC AAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCA GCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAG CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG GAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTACCCCAGCGACATCTCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACA CCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC AACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT AAA

534			Human Heavy Chain Constant Region (IGHG2*06) Protein Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDISVEWESNGQPENNYKTT PPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK
535	Human Cλ constant region	IGLC 7*03	Cλ Light Chain Constant Region (IGLC7*03) Nucleotide Sequence	GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCA CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTG GTGTGTCTCGTAAGTGACTTCAACCCGGGAGCCGTGACA GTGGCCTGGAAGGCAGATGGCAGCCCCGTCAAGGTGGGA GTGGAGACCACCAAACCCTCCAAACAAAGCAACAACAAG TATGCGGCCAGCAGCTACCTGAGCCTGACGCCCGAGCAG TGGAAGTCCCACAGAAGCTACAGCTGCCGGGTCACGCAT GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTGCAGAA TGCTCT
536			Cλ Light Chain Constant Region (IGLC7*03) Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFNPGAVT VAWKADGSPVKVGVETTKPSKQSNNKYAASSYLSLTPEQ WKSHRSYSCRVTHEGSTVEKTVAPAECS
537	Human WT IgG1 constant region	IGHG 1*01 & IGHG 1*05 (IgG 1)	WT human IgG1 nucleotide sequence #2	gcctccaccaagggcccatcggtcttcccccctggcaccc tcctccaagagcacctctgggggcacagcggccctgggc tgcctggtcaaggactacttccccgaaccggtgacggtg tcgtggaactcaggcgccctgaccagcggcgtgcacacc ttcccggctgtcctacagtcctcaggactctactccctc agcagcgtggtgaccgtgccctccagcagcttgggcacc cagacctacatctgcaacgtgaatcacaagcccagcaac accaaggtggacaagaaagttgagcccaaatcttgtgac aaaactcacacatgcccaccgtgcccagcacctgaactc ctgggggggaccgtcagtcttcctcttcccccaaaaccc aaggacaccctcatgatctcccggacccctgaggtcaca tgcgtggtggtggacgtgagccacgaagaccctgaggtc aagttcaactggtacgtggacggcgtggaggtgcataat gccaagacaaagccgcgggaggagcagtacaacagcacg taccgggtggtcagcgtcctcaccgtcctgcaccaggac tggctgaatggcaaggagtacaagtgcaaggtctccaac aaagccctcccagccccatcgagaaaaccatctccaaa gccaaagggcagccccgagaaccacaggtgtacaccctg cccccatcccgggatgagctgaccaagaaccaggtcagc ctgacctgcctggtcaaaggcttctatcccagcgacatc gccgtggagtgggagagcaatgggcagccggagaacaac tacaagaccacgcctcccgtgctggactccgacggctcc ttcttcctctacagcaagctcaccgtggacaagagcagg tggcagcaggggaacgtcttctcatgctccgtgatgcat gaggctctgcacaaccactacacgcagaagagcctctcc ctgtctccgggtaaa
538	Human Cλ constant region	IGLC 2*01	Cλ Light Chain Constant Region Amino Acid Sequence #2 - Encoded by nucleotide sequence version A & B	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVT VAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQ WKSHRSYSCQVTHEGSTVEKTVAPTECS

Table S3. SEQ ID NOS: 539-562

		Sequence
hIgG1 FIT-Ig bispecific 1a		
Antibody A	anti-ICOS STIM003	
Antibody B	anti-PD-L1 84G09	
FIT-Ig Construct #1	SEQ ID NO: 539	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG ECEVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFI RSGSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHN TFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT-Ig Construct #2	SEQ ID NO: 540	EVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGLEWVASISY EGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCARQREANWED WGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKV
FIT-Ig Construct #3	SEQ ID NO: 541	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

hIgG1 FIT-Ig bispecific 1b		
Antibody A	anti-PD-L1 84G09	
Antibody B	anti-ICOS STIM003	
FIT-Ig Construct #1	SEQ ID NO: 542	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGECEVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGL EWVASISYEGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCAR QREANWEDWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
FIT-Ig Construct #2	SEQ ID NO: 543	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRS GSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTF DSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKV
FIT-Ig Construct #3	SEQ ID NO: 544	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

hIgG1 FIT-Ig bispecific 2a		
Antibody A	anti-ICOS STIM001	
Antibody B	anti-PD-L1 1D05	
FIT-Ig Construct #1	SEQ ID NO: 545	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTDAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGV LNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRN ECEVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFI RSGSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHN TFDSWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVT LTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASST KVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTC VVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGK
FIT-Ig Construct #2	SEQ ID NO: 546	EVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGLEWVASISY EGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCARQREANWED WGQGVMVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWN SGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDK KI
FIT-Ig Construct #3	SEQ ID NO: 547	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTDAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGS ERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIV KSFNRNEC

hIgG1 FIT-Ig bispecific 2b		
Antibody A	anti-PD-L1 1D05	
Antibody B	anti-ICOS STIM001	
FIT-Ig Construct #1	SEQ ID NO: 548	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTDAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGS ERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIV KSFNRNECEVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGL EWVASISYEGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCAR QREANWEDWGQGVMVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFP EPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHP ASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSP IVTCVVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQH QDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQV TLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKN WVERNSYSCSVVHEGLHNHHTTKSFSRTPGK
FIT-Ig Construct #2	SEQ ID NO: 549	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRS GSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTF DSWGQGTLVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKV DKKI
FIT-Ig Construct #3	SEQ ID NO: 550	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTDAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGV LNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVKSFNRN EC

hIgG1 FIT-Ig bispecific 3a		
Antibody A	anti-ICOS STIM003	
Antibody B	anti-PD-L1 1D05	
FIT-Ig Construct #1	SEQ ID NO: 551	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG ECEVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFI RSGSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHN TFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKE FKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYS CSVVHEGLHNHHTTKSFSRTPGK
FIT-Ig Construct #2	SEQ ID NO: 552	EVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGLEWVASISY EGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCARQREANWED WGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKV
FIT-Ig Construct #3	SEQ ID NO: 553	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

hIgG1 FIT-Ig bispecific 3b		
Antibody A	anti-PD-L1 1D05	
Antibody B	anti-ICOS STIM003	
FIT-Ig Construct #1	SEQ ID NO: 554	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGECEVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGL EWVASISYEGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCAR QREANWEDWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPNLLGGPSVFIFPPKIKDVLMISLSPIVTC VVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGK
FIT-Ig Construct #2	SEQ ID NO: 555	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRS GSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTF DSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKV
FIT-Ig Construct #3	SEQ ID NO: 556	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

hIgG1 FIT-Ig bispecific 4a		
Antibody A	anti-ICOS STIM001	
Antibody B	anti-PD-L1 84G09	
FIT-Ig Construct #1	SEQ ID NO: 557	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG ECEVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFI RSGSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHN TFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVD VSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKE FKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYS CSVVHEGLHNHHTTKSFSRTPGK
FIT-Ig Construct #2	SEQ ID NO: 558	EVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGLEWVASISY EGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCARQREANWED WGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKV
FIT-Ig Construct #3	SEQ ID NO: 559	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

hIgG1 FIT-Ig bispecific 4b		
Antibody A	anti-PD-L1 84G09	
Antibody B	anti-ICOS STIM001	
FIT-Ig Construct #1	SEQ ID NO: 560	DIVMTQSPSSLAVSPGEKVTMTCKSSQSLYYSGVKENLLAWYQQKPGQSPKLL IYYASIRFTGVPDRFTGSGSGTDYTLTITSVQAEDMGQYFCQQGINNPLTFGD GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGECEVQLVESGGGLVQPGRSLKLSCAASGFTFSDFYMAWVRQAPKKGL EWVASISYEGSSTYYGDSVMGRFTISRDNAKSTLYLQMNSLRSEDTATYYCAR QREANWEDWGQGVMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPNLLGGPSVFIFPPKIKDVLMISLSPIVTC VVVDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWM SGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTC MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVER NSYSCSVVHEGLHNHHTTKSFSRTPGK
FIT-Ig Construct #2	SEQ ID NO: 561	EVQLVESGGGLTQPGKSLKLSCEASGFTFSSFTMHWVRQSPGKGLEWVAFIRS GSGIVFYADAVRGRFTISRDNAKNLLFLQMNDLKSEDTAMYYCARRPLGHNTF DSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKV
FIT-Ig Construct #3	SEQ ID NO: 562	DIQMTQSPASLSASLGETVTIQCRASEDIYSGLAWFQQKPGKSPQLLIYGASS LQDGVPSRFSGSGSGTQYSLKISSMQTEDEGVYFCQQGLKYPPTFGSGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

Table S4: Sequences of antibody heavy chain variable regions obtained from additional clones

CDRs are defined according to IMGT.

CLONE_ID	VH_NUCLEOTIDE_SEQUENCE	VH_AMINO_ACID_SEQ	HCDR1	HCDR2	HCDR3
CL-61091	CAGGTTCAACTGATGCAGTCTGGAACTGAGGTGAAGAAGCCTGGG GCCTCAGTGAAGGTCTCCTGCAAGACTTCTGGTTACACCTTTACC ACCTATGGTATCACTTGGGTGCGACAGGCCCCTGGACAAGGGCTT GAGTGGATGGGATGGATCAGCGCTTACAGTGGTGACACAGACTAT GCACAGAAGTTCCAGGGCAGAGTCACCGTGACAACAGACACATCC ACGAACACAGCCTACATGGAGTTGAGGAGCCTGAAATCTGACGAC ACGGCCGTGTATTATTGTGCGAGAAGTAGTGGCTGGCCCCACCAC TACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCC TCAG SEQ ID NO: 563	QVQLMQSGTEVKKPGASV KVSCKTSGYTFTTYGITW VRQAPGQGLEWMGWISAY SGDTDYAQKFQGRVTVTT DTSTNTAYMELRSLKSDD TAVYYCARSSGWPHHYGM DVWGQGTTVTVSS SEQ ID NO: 564	GYTFTTYG SEQ ID NO: 565	ISAYSGDT SEQ ID NO: 566	ARSSGWPHHYGMDV SEQ ID NO: 567
CL-64536	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAAAAGCCTGGG GCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACC AGCTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTA GAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT GCACAGAAGCTCCAGGGCAGAGTCTCCATGACCACAGACACATCC ACGAGCACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGAC ACGGCCGTGTATTTCTGTGCGCGATCTACGTCTTACTATGGTTCG GGGACCCTATACGGTATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCCTCAG SEQ ID NO: 568	QVQLVQSGGEVKKPGASV KVSCKASGYTFTSYGFSW VRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVSMTT DTSTSTAYMELRSLRSDD TAVYFCARSTSYYGSGTL YGMDVWGQGTTVTVSS SEQ ID NO: 569	GYTFTSYG SEQ ID NO: 377	ISAYNGNT SEQ ID NO: 378	ARSTSYYGSGTLYGMDV SEQ ID NO: 570
CL-64837	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAGAAGCCTGGG GCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACC AGCTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTA GAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT GCACAGAAGCTCCAGGGCAGAGTCTCCATGACCACAGACACATCC ACGAGCACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGAC ACGGCCGTGTATTACTGTGCGCGATCTACGTCTTACTATGGTTCG GGGACCCTCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCCTCAG SEQ ID NO: 571	QVQLVQSGGEVKKPGASV KVSCKASGYTFTSYGFSW VRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVSMTT DTSTSTAYMELRSLRSDD TAVYYCARSTSYYGSGTL YGMDVWGQGTTVTVSS SEQ ID NO: 572	GYTFTSYG SEQ ID NO: 377	ISAYNGNT SEQ ID NO: 378	ARSTSYYGSGTLYGMDV SEQ ID NO: 570

CLONE_ID	VH_NUCLEOTIDE_SEQUENCE	VH_AMINO_ACID_SEQ	HCDR1	HCDR2	HCDR3
CL-64841	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAAAAGCCTGGG GCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACC AGCTATGGTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGACTA GAGTGGATGGGATGGATCAGCGCTTACAATGGTAACACAAACTAT GCACAGAAGCTCCAGGGCAGAGTCTCCATGACCACAGACACATCC ACGAGCACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGAC ACGGCCGTGTATTTCTGTGCGCGATCTACGTCTTACTATGGTTCG GGGACCCTATACGGTATGGACGTCTGGGGCCAAGGGACCACGGTC ACCGTCTCCTCAG SEQ ID NO: 573	QVQLVQSGGEVKKPGASV KVSCKASGYTFTSYGFSW VRQAPGQGLEWMGWISAY NGNTNYAQKLQGRVSMTT DTSTSTAYMELRSLRSDD TAVYFCARSTSYYGSGTL YGMDVWGQGTTVTVSS SEQ ID NO: 574	GYTFTSYG SEQ ID NO: 377	ISAYNGNT SEQ ID NO: 378	ARSTSYYGSGTLYGMDV SEQ ID NO: 570
CL-64912	CAGGTTCAACTGGTGCAGTCTGGAGGTGAGGTGAAAAAGCCTCGG GCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACC AGCTATGTGTTCAGCTGGGTGCGACATGCCGCTGGACAAGGACTA GAGTGGATGGGATGGATCAGCGGTTACAATGGTAACACAAACTAT GCACAGAAGCTCCAGTGCGGAGTCTCGATGACCGCAGACACATCC ACGAGCACAGCCTACATGGAGCTGAGGAGCTTGAGATCTGACGAC ACGGCCGTGTATTTCTGTGCGCGATCTACGTCTTACTATGGTGCG GGGACCCTATACGGTATTTCTGTGGGCCAAGGGACCACGGTC ACCGTCTCCTCAG SEQ ID NO: 575	QVQLVQSGGEVKKPRASV KVSCKASGYTFTSYVFSW VRHAAGQGLEWMGWISGY NGNTNYAQKLQCGVSMTA DTSTSTAYMELRSLRSDD TAVYFCARSTSYYGAGTL YGMDVWGQGTTVTVSS SEQ ID NO: 576	GYTFTSYV SEQ ID NO: 577	ISGYNGNT SEQ ID NO: 578	ARSTSYYGAGTLYGMDV SEQ ID NO: 579
CL-71642	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCTGGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGAT GATTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAAGGGGCTG GAGTGGGTCTCTGGTATTAATTGGAATGGTGGTAGCACAGGTTAT GCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGAC ACGGCCTTGTATTACTGTGCGGCCGATTACTATGGTTCGGGGAGT TATTATAACGTCCCCTTTGACTACTGGGGCCAGGGAACCCTGGTC ACCGTCTCCTCAG SEQ ID NO: 580	EVQLVESGGGVVRPGGSL RLSCAASGFTFDDYGMSW VRQAPGKGLEWVSGINWN GGSTGYADSVKGRFTISR DNAKNSLYLQMNSLRAED TALYYCAADYYGSGSYYN VPFDYWGQGTLVTVSS SEQ ID NO: 581	GFTFDDYG SEQ ID NO: 582	INWNGGST SEQ ID NO: 583	AADYYGSGSYYNVPFDY SEQ ID NO: 584

CLONE_ID	VH_NUCLEOTIDE_SEQUENCE	VH_AMINO_ACID_SEQ	HCDR1	HCDR2	HCDR3
CL-74570	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGATACGGCCTGGG GGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGAT GATTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAAGGGGCTG GAGTGGGTCTCTGGTATTAATTGGATTGGTGATAACACAGATTAT GCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC AAGAACTCCCTATATCTGCAAATGAACAGTCTGAGAGCCGAGGAC ACGGCCTTGTATTACTGTGCGAGAGATTACTTTGGTTCGGGGAGT TATTATAACGTTCCCTTTGACTACTGGGGCCAGGGAACCCTGGTC ACCGTCTCCTCAG SEQ ID NO: 585	EVQLVESGGGVIRPGGSL RLSCAASGFTFDDYGMSW VRQAPGKGLEWVSGINWI GDNTDYADSVKGRFTISR DNAKNSLYLQMNSLRAED TALYYCARDYFGSGSYYN VPFDYWGQGTLVTVSS SEQ ID NO: 586	GFTFDDYG SEQ ID NO: 582	INWIGDNT SEQ ID NO: 587	ARDYFGSGSYYNVPFDY SEQ ID NO: 588

Table S5: Sequences of antibody light chain variable regions obtained from additional clones

N terminal E and 5' nucleotide additions in CL-71642 are shown in bold. These were not recovered in sequencing but were determined to be present in the sequence by comparison against the related clones as shown in Figure 11. CDRs are defined according to IMGT.

CLONE_ID	VL_NUCLEOTIDE_SEQUENCE	VL_AMINO_ACID_SEQ	LCDR1	LCDR2	LCDR3
CL-61091	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCT GGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTG CATAGTAATGGATTCAACTATTTCGATTGGTACCTGCAGAAGCCA GGACAGTCTCCACAGCTCCTGATCTTTTTGGTTTCTAATCGGGCC TCCGGGGTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGAT TTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGATT TATTACTGCATGCAAGCTCTACAAACTCCGCTCACTTTCGGCGGA GGGACCAAGGTGGAGATCAAAC SEQ ID NO: 589	DIVMTQSPLSLPVTPGEPA SISCRSSQSLLHSNGFNYF DWYLQKPGQSPQLLIFLVS NRASGVPDRFSGSGSGTDF TLKISRVEAEDVGIYYCMQ ALQTPLTFGGGTKVEIK SEQ ID NO: 590	QSLLHSNGFNY SEQ ID NO: 591	LVS SEQ ID NO: 592	MQALQTPLT SEQ ID NO: 593

CLONE_ID	VL_NUCLEOTIDE_SEQUENCE	VL_AMINO_ACID_SEQ	LCDR1	LCDR2	LCDR3
CL-64536	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCT GGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTG CATAGTAATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCA GGGCAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCC TCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGAT TTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTT TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAG GGGACCAAGCTGGAGATCAAAC SEQ ID NO: 594	DIVMTQSPLSLPVTPGEPA SISCRSSQSLLHSNGYNCL DWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDF TLKISRVEAEDVGVYYCMQ ALQTPCSFGQGTKLEIK SEQ ID NO: 595	QSLLHSNGYNC SEQ ID NO: 596	LGS SEQ ID NO: 371	MQALQTPCS SEQ ID NO: 400
CL-64837	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCT GGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTG CATAGTAATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCA GGGCAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCC TCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGAT TTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTT TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAG GGGACCAAGCTGGAGATCAAAC SEQ ID NO: 597	DIVMTQSPLSLPVTPGEPA SISCRSSQSLLHSNGYNCL DWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDF TLKISRVEAEDVGVYYCMQ ALQTPCSFGQGTKLEIK SEQ ID NO: 598	QSLLHSNGYNC SEQ ID NO: 596	LGS SEQ ID NO: 371	MQALQTPCS SEQ ID NO: 400
CL-64841	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCT GGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTG CATAGTAATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCA GGGCAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCC TCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGAT TCTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTT TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAG GGGACCAAGCTGGAGATCAAAC SEQ ID NO: 599	DIVMTQSPLSLPVTPGEPA SISCRSSQSLLHSNGYNCL DWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDS TLKISRVEAEDVGVYYCMQ ALQTPCSFGQGTKLEIK SEQ ID NO: 600	QSLLHSNGYNC SEQ ID NO: 596	LGS SEQ ID NO: 371	MQALQTPCS SEQ ID NO: 400
CL-64912	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCT GGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTG CATAGTAATGGATACAACTGTTTGGATTGGTACCTGCAGAAGCCA GGGCAGTCTCCACAGCTCCTGATCTATTTGGGTTCTACTCGGGCC TCCGGGTTCCCTGACAGGTTCAGTGGCAGTGGATCAGGCACAGAT TTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTT TATTACTGCATGCAAGCTCTACAAACTCCGTGCAGTTTTGGCCAG GGGACCAAGCTGGAGATCAAAC SEQ ID NO: 601	DIVMTQSPLSLPVTPGEPA SISCRSSQSLLHSNGYNCL DWYLQKPGQSPQLLIYLGS TRASGFPDRFSGSGSGTDF TLKISRVEAEDVGVYYCMQ ALQTPCSFGQGTKLEIK SEQ ID NO: 602	QSLLHSNGYNC SEQ ID NO: 596	LGS SEQ ID NO: 371	MQALQTPCS SEQ ID NO: 400

CLONE_ID	VL_NUCLEOTIDE_SEQUENCE	VL_AMINO_ACID_SEQ	LCDR1	LCDR2	LCDR3
CL-71642	**GA**AATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAG CAGTATGGTAGCTCACCTTTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAAC SEQ ID NO: 603	**E**IVLTQSPGTLSLSPGERA TLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYCQQYGSS PFTFGPGTKVDIK SEQ ID NO: 604	QSVSSSY SEQ ID NO: 426	GAS SEQ ID NO: 413	QQYGSSPFT SEQ ID NO: 605
CL-74570	GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGC AGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTGGCATCCCA GACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC ATCAGCAGACTGGAACCTGAAGATTTTGCAGTATATTACTGTCAC CAGTATGGTAATTCACCATTCACTTTCGGCCCTGGGACCAAAGTG GATATCAAAC SEQ ID NO: 606	EIVLTQSPGTLSLSPGERA TLSCRASQSVSSSYLAWYQ QKPGQAPRLLIYGASSRAT GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYCHQYGNS PFTFGPGTKVDIK SEQ ID NO: 607	QSVSSSY SEQ ID NO: 426	GAS SEQ ID NO: 413	HQYGNSPFT SEQ ID NO: 608

CLAUSES

1. A method of treating cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression, comprising administering to the patient a modulator of ICOS.

2. The method of clause 1, comprising administering to the patient a modulator of ICOS and an inhibitor of PD-L1.

3. A method of treating cancer in a patient who has previously received treatment for the cancer, wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor and the patient did not respond to the previous treatment or ceased responding to the previous treatment, and wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression, comprising administering to the patient a modulator of ICOS.

4. The method of clause 3, comprising administering to the patient a modulator of ICOS and an inhibitor of PD-L1.

5. The method of any preceding clause, comprising determining the level of PD-L1 expression in a tumour sample from the patient, and if the tumour is PD-L1 negative or a PD-L1 low expression tumour, then administering to the patient an ICOS modulator.

6. The method of clause 5, comprising administering to the patient a modulator of ICOS and an inhibitor of PD-L1.

7. The method of any one of clauses 2, 4, and 6, wherein the modulator of ICOS and an inhibitor of PD-L1 are administered simultaneously, separately or sequentially.

8. The method of any preceding clause, wherein the ICOS modulator is an ICOS agonist.

9. The method of any preceding clause, wherein the ICOS agonist is an agonistic anti-ICOS antibody.

10. The method of clause 9, wherein the anti-ICOS antibody is a bispecific antibody that specifically binds ICOS and PD-L1 or specifically binds ICOS and PD-1.

11. The method of clause 9, wherein the bispecific antibody is an ICOS agonist and a PD-L1 antagonist, or an ICOS agonist and a PD-1 antagonist.

12. The method of any preceding clause, wherein the PD-L1 inhibitor is an anti-PD-L1 binding molecule.

13. The method of any preceding clause, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody or an anti-PD-1 antibody.

14. The method of any preceding clause, wherein the PD-L1 inhibitor inhibits the binding of PD-L1 to PD-1.

15. The method of any preceding clause, wherein the PD-L1 inhibitor is an antagonistic anti-PD-L1 antibody or an antagonistic anti-PD-1 antibody.

16. The method of any preceding clause, wherein the tumour cells are PD-L1 negative or exhibit low PD-L1 expression.

17. The method of any preceding clause, wherein the tumour comprises immune cells, and the immune cells are PD-L1 negative or exhibit low PD-L1 expression.

18. The method of clause 17, wherein the tumour cells are PD-L1 negative or exhibit low PD-L1 expression and the immune cells are PD-L1 negative or exhibit low PD-L1 expression.

19. The method of any preceding clause, wherein the cancer is associated with infectious agents.

20. The method of clause 19, wherein the cancer is a virally-induced cancer.

21. The method of clause 20, wherein the virus associated with the virally-induced cancer is selected from HPV (cervical cancer, oropharyngeal cancer), HBV, HCV, and EBV (Burkitts lymphomas, gastric cancer, Hodgkin's lymphoma, other EBV positive B cell lymphomas, nasopharyngeal carcinoma and post-transplant lymphoproliferative disease).

22. The method of clause 21, wherein the cancer is selected from the group consisting of head and neck squamous cell carcinoma, cervical cancer, anogenital cancer and oropharyngeal cancer.

23. The method of any preceding clause, wherein the tumour is HPV (Human papillomavirus) positive.

24. The method of any preceding clause, wherein the patient has undergone a test for an infection, optionally wherein the infection is selected from HPV, HBV, HCV, or EBV infection.

25. The method of clause 24, wherein the patient has undergone a test for HPV infection.

26. The method of any preceding clause, wherein the patient has an HPV infection or has had an HPV infection.

27. The method of any preceding clause, comprising the step of determining the HPV status of the patient and/or determining the HPV status of the tumour.

28. The method of any preceding clause, wherein the tumour cells are PD-L1 negative or exhibit low PD-L1 expression and the tumour is HPV (Human papillomavirus) positive.

29. The method of any preceding clause, wherein the patient has previously been administered a kinase inhibitor.

30. The method of any preceding clause, wherein the patient has previously received surgical treatment for the cancer (for example complete or partial tumour resection) and/or radiotherapy and/or chemotherapy.

31. The method of clause 30, wherein the chemotherapy comprises docetaxel, fluorouracil, cisplatin, paclitaxel and/or nab-paclitaxel.

32. The method of any preceding clause, wherein the cancer is or has been characterised as refractory to PD-L1 inhibitor treatment (for example refractory to anti-PD-L1 antibody or anti-PD-1 antibody monotherapy).

33. The method of clause 32, wherein the cancer is or has been characterised as refractory to PD-L1 inhibitor monotherapy treatment.

34. The method of clause 32, wherein the cancer is or has been characterised as refractory to treatment with a PD-L1 inhibitor as the sole immunotherapy agent.

35. The method of any one of clauses 32 to 34, wherein the cancer is or has been characterised as refractory to treatment with nivolumab.

36. The method of any preceding clause, wherein the patient has previously received treatment for the cancer.

37. The method of clause 36 wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor (for example an anti-PD-L1 antibody or an anti-PD-1 antibody).

38. The method of clause 36, wherein the previous treatment for the cancer was PD-L1 inhibitor monotherapy.

39. The method of clause 36, wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor as the sole immunotherapeutic agent.

40. The method of any preceding clause, wherein the PD-L1 expression status is determined by immunohistochemistry (IHC).

41. The method of clause 40, wherein the IHC is performed on a tumour sample.

42. The method of clause 41, wherein the tumour sample is tumour tissue sample or a sample of tumour cells.

43. The method of any preceding clause, wherein the tumour is a low PD-L1 expressing tumour when 25% or less of the tumour cells express PD-L1.

44. The method of any preceding clause, wherein the tumour is a low PD-L1 expressing tumour when less than 20%, less than 15%, less than 10%, less than 5%, less that about 4%, less than about 3%, less than about 2% or less than about 1% of tumour cells express PD-L1.

45. The method of any preceding clause, wherein 0% of tumour cells express PD-L1.

46. The method of any preceding clause, wherein the tumour is a low PD-L1 expressing tumour when 25% or less of the tumour cells and tumour-associated immune cells express PD-L1.

47. The method of any preceding clause, wherein the tumour is a low PD-L1 expressing tumour when less than 20%, less than 15%, less than 10%, less than 5%, less than about 5%, less that about 4%, less than about 3%, less than about 2% or less than about 1% of tumour cells and tumour-associated immune cells express PD-L1.

48. The method of any preceding clause, wherein 0% of tumor cells and tumour-associated immune cells express PD-L1.

49. The method of any one of clauses 43 to 48, wherein the percentage of PD-L1 expression is determined according to the following formula: (number of PD-L1 positive tumour cells in the tumour tissue sample or sample of tumour cells / total number of tumour cells in the tumour tissue sample or sample of tumour cells) x 100.

50. The method of any one of clauses 43 to 48, wherein the percentage of PD-L1 expression is determined according to the following formula: (number of PD-L1 positive tumour cells and number of PD-L1 positive tumour-associated immune cells in the tumour tissue sample or sample of tumour cells / total number of tumour cells and tumour-associated immune in the tumour tissue sample or sample of tumour cells) x 100.

51. The method of any preceding clause, wherein the tumour is a CD8+ tumour.

52. The method of clause 51, wherein the CD8 expression status is determined by immunohistochemistry (IHC).

53. The method of clause 51 or clause 52, wherein the at least 50% of the T-cells in the tumour are CD8+.

54. The method of clause 51 or clause 52 or clause 53, wherein the tumour tissue sample or sample of tumour cells comprises at least 190 cells CD8+ T-cells per mm^2.

55. The method of any preceding clause, wherein the tumour is a ICOS+ tumour.

56. The method of clause 55, wherein the ICOS expression status is determined by immunohistochemistry (IHC).

57. The method of clause 55 or clause 56, wherein the at least 50% of the immune cells in the tumour are ICOS+.

58. The method of any preceding clause, wherein the patient has an increased level of $ICOS^+$ immune cells (such as $ICOS^+$ regulatory T cells) following treatment with another therapeutic agent.

59. The method of clause 58, wherein the method comprises administering a therapeutic agent to the patient, determining that the patient has an increased level of $ICOS^+$ immune cells (such as $ICOS^+$ regulatory T cells) following the treatment with said agent, and administering a modulator of ICOS (for example an anti-ICOS antibody such as an agonistic anti-ICOS antibody) to the patient to reduce the level of $ICOS^+$ regulatory T cells.

60. The method of clause 58 or clause 59, wherein the therapeutic agent is IL-2 or an immunomodulatory antibody (e.g., anti-PDL-1, anti-PD-1 or anti-CTLA-4).

61. The method of any preceding clause, comprising administering a single dose of the ICOS modulator.

62. The method of any preceding clause, comprising administering a single dose of the ICOS modulator followed by multiple doses of the PD-L1 inhibitor.

63. The method of any preceding clause, wherein the ICOS modulator and the PD-L1 inhibitor are provided in separate compositions for administration.

64. The method of any preceding clause, wherein the ICOS modulator depletes ICOS+ immune cells, e.g. ICOS+ Treg cells.

65. The method of any preceding clause, wherein treatment results in reducing the size of the tumour.

66. The method of any preceding clause, wherein treatment inhibits tumour growth.

67. The method of any preceding clause, wherein treatment results in stable disease.

68. The method of any preceding clause, wherein treatment extends the survival of the patient and/or delays disease progression.

69. The method of any preceding clause, wherein the treatment depletes ICOS+ immune cells (such as $ICOS^+$ regulatory T cells) in the tumour microenvironment.

70. The method of any preceding clause, where treatment increases the CD8+ to ICOS+ immune cell ratio (for example the CD8+ to ICOS+ regulatory T cell ration) in the tumour microenvironment.

71. The method of any preceding clause, wherein the ICOS modulator is an anti-ICOS antibody.

72. The method of clause 71, wherein the anti-ICOS antibody is any of the following antibodies, may comprise the VH and VL domains of any of the following antibodies or may comprise the HCDRs and/or LCDRs of any of the following antibodies:
    a. KY1044;
    b. anti-ICOS antibodies described in PCT/GB2017/052352 WO2018/029474 or US9957323, the contents of which are incorporated herein by reference (e.g., STIM001, STIM002, STIM002B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009);
    c. anti-ICOS antibodies described in PCT/GB2018/053701 WO2019/122884 the contents of which are incorporated herein by reference (e.g., STIM017, STIM020, STIM021, STIM022, STIM023, STIM039, STIM040, STIM041, STIM042, STIM043, STIM044, STIM050, STIM051, STIM052, STIM053, STIM054, STIM055, STIM056, STIM057, STIM058, STIM059, STIM060, STIM061, STIM062, STIM063, STIM064, STIM065 or STIM066);
    d. anti-ICOS/PD-L1 mAb2 bispecific antibodies described in PCT/GB2018/053698 WO2019/122882;
    e. vopratelimab;
    f. anti-ICOS antibodies described in WO2016/154177 or US2016/0304610 (e.g., 37A10S713, 7F12, 37A10, 35A9, 36E10, 16G10, 37A10S714, 37A10S715, 37A10S716, 37A10S717, 37A10S718, 16G10S71, 16G10S72, 16G10S73, 16G10S83, 35A9S79, 35A9S710 or 35A9S89);
    g. anti-ICOS antibodies described in WO2016/120789 or US2016/0215059 (e.g., 422.2 H2L5);

h. antibody C398.4 or a humanised antibody thereof as described in WO2018/187613 or US2018/0289790, e.g., ICOS.33 IgG1f S267E, ICOS.4, ICOS34 G1f, ICOS35 G1f, 17C4, 9D5, 3E8, 1D7a, 1D7b or 2644 (for sequences see WO2018187613 Table 35), e.g., the antibody BMS-986226 in NCT03251924;
i. antibody JMAb 136, "136", or any other antibody described in WO2010/056804;
j. antibody 314-8, the antibody produced from hybridoma CNCM I-4180, or any other anti-ICOS antibody described in WO2012/131004, WO2014/033327 or US2015/0239978;
k. antibody Icos145-1, the antibody produced by hybridoma CNCM I-4179, or any other antibody described in WO2012/131004, US9,376,493 or US2016/0264666;
l. antibody MIC-944 (from hybridoma DSMZ 2645), 9F3 (DSMZ 2646) or any other anti-ICOS antibody described in WO99/15553, US7,259,247, US7,132,099, US7,125,551, US7,306,800, US7,722,872, WO05/103086, US8,318.905 or US8,916,155;
m. anti-ICOS antibodies described in WO98/3821, US7,932,358B2, US2002/156242, US7,030,225, US7,045,615, US7,279,560, US7,226,909, US7,196,175, US7,932,358, US8,389,690, WO02/070010, US7,438,905, US7,438,905, WO01/87981, US6,803,039, US7,166,283, US7,988,965, WO01/15732, US7,465,445 or US7,998,478 (e.g., JMAb-124, JMAb-126, JMAb-127, JMAb-128, JMAb-135, JMAb-136, JMAb-137, JMAb-138, JMAb-139, JMAb-140 or JMAb-141, e.g., JMAb136);
n. anti-ICOS antibodies described in WO2014/08911;
o. anti-ICOS antibodies described in WO2012/174338;
p. anti-ICOS antibodies described in US2016/0145344;
q. anti-ICOS antibodies described in WO2011/020024, US2016/002336, US2016/024211 or US8,840,889;
r. anti-ICOS antibodies described in US8,497,244; or
s. antibody clone ISA-3 (eBioscience), clone SP98 (Novus Biologicals), clone 1 G1, clone 3G4 (Abnova Corporation), clone 669222 (R&D Systems), clone TQ09 (Creative Diagnostics), clone 2C7 (Deng et al. Hybridoma Hybridomics 2004), clone ISA-3 (eBioscience) or clone 17G9 (McAdam et al. J Immunol 2000).

73. The method of clause 71, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and/or mouse ICOS, wherein the antibody comprises a VH domain comprising an amino acid sequence having at least 95 % sequence identity to the STIM003 VH domain SEQ ID NO: 408 and a VL domain comprising an amino acid

sequence having at least 95 % sequence identity to the STIM003 VL domain SEQ ID NO: 415.

74. The method of clause 73, wherein the VH domain comprises a set of heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3, wherein
    a. HCDR1 is the STIM003 HCDR1 having amino acid sequence SEQ ID NO: 405,
    b. HCDR2 is the STIM003 HCDR2 having amino acid sequence SEQ ID NO: 406,
    c. HCDR3 is the STIM003 HCDR3 having amino acid sequence SEQ ID NO: 407.

75. The method of clause 73 or clause 74, wherein the VL domain comprises a set of light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3, wherein:
    a. LCDR1 is the STIM003 LCDR1 having amino acid sequence SEQ ID NO: 412,
    b. LCDR2 is the STIM003 LCDR2 having amino acid sequence SEQ ID NO: 413,
    c. LCDR3 is the STIM003 LCDR3 having amino acid sequence SEQ ID NO: 414.

76. The method of clause 73, wherein the VH domain amino acid sequence is SEQ ID NO: 408 and/or wherein the VL domain amino acid sequence is SEQ ID NO: 415.

77. The method of clause 71, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and/or mouse ICOS, comprising

    an antibody VH domain comprising complementarity determining regions (CDRs) HCDR1, HCDR2 and HCDR3, and

    an antibody VL domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein

    HCDR1 is the HCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

    HCDR2 is the HCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

    HCDR3 is the HCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that HCDR3 with 1, 2, 3, 4 or 5 amino acid alterations.

78. The method of clause 77, wherein the antibody heavy chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005,

STIM006, STIM007, STIM008 or STIM009 heavy chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations.

79. The method of clause 78, wherein the antibody VH domain has the heavy chain CDRs of STIM003.

80. The method of clause 71, wherein the anti-ICOS antibody is an antibody binds the extracellular domain of human and/or mouse ICOS, comprising

an antibody VH domain comprising complementarity determining regions HCDR1, HCDR2 and HCDR3, and

an antibody VL domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3,

wherein LCDR1 is the LCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004 STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

LCDR2 is the LCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

LCDR3 is the LCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that LCDR3 with 1, 2, 3, 4 or 5 amino acid alterations.

81. The method of any one of clauses 77 to 80, wherein the antibody light chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 light chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations.

82. The method according to clause 81, wherein the antibody VL domain has the light chain CDRs of STIM003.

83. The method according to any of clauses 77 to 82, wherein the antibody comprises VH and/or VL domain framework regions of human germline gene segment sequences.

84. The method according to any of clauses 77 to 83, wherein the antibody comprises a VH domain which

(i) is derived from recombination of a human heavy chain V gene segment, a human heavy chain D gene segment and a human heavy chain J gene segment, wherein

the V segment is IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10);

the D gene segment is IGHD6-19 (e.g., IGHD6-19*01), IGHD3-10 (e.g., IGHD3-10*01) or IGHD3-9 (e.g., IGHD3-9*01); and/or

the J gene segment is IGHJ6 (e.g., IGHJ6*02), IGHJ4 (e.g., IGHJ4*02) or IGHJ3 (e.g., IGHJ3*02), or

(ii) comprises framework regions FR1, FR2, FR3 and FR4, wherein

FR1 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR2 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR3 aligns with human germline V gene segment IGHV1-18 (e.g., V1-18*01), IGVH3-20 (e.g. V3-20*d01), IGVH3-11 (e.g, V3-11*01) or IGVH2-5 (e.g., V2-5*10), optionally with 1, 2, 3, 4 or 5 amino acid alterations, and/or

FR4 aligns with human germline J gene segment IGJH6 (e.g., JH6*02), IGJH4 (e.g., JH4*02) or IGJH3 (e.g., JH3*02), optionally with 1, 2, 3, 4 or 5 amino acid alterations.

85. The method according to any of clauses 77 to 84, wherein the antibody comprises an antibody VL domain which

(i) is derived from recombination of a human light chain V gene segment and a human light chain J gene segment, wherein

the V segment is IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), and/or

the J gene segment is IGKJ4 (e.g., IGKJ4*01), IGKJ2 (e.g., IGKJ2*04), IGLJ3 (e.g., IGKJ3*01) or IGKJ1 (e.g., IGKJ1*01); or

(ii) comprises framework regions FR1, FR2, FR3 and FR4, wherein

FR1 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR2 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations,

FR3 aligns with human germline V gene segment IGKV2-28 (e.g., IGKV2-28*01), IGKV3-20 (e.g., IGKV3-20*01), IGKV1D-39 (e.g., IGKV1D-39*01) or IGKV3-11 (e.g., IGKV3-11*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations, and/or

FR4 aligns with human germline J gene segment IGKJ4 (e.g., IGKJ4*01), IGKJ2 (e.g., IGKJ2*04), IGKJ3 (e.g., IGKJ3*01) or IGKJ1 (e.g., IGKJ1*01), optionally with 1, 2, 3, 4 or 5 amino acid alterations.

86. The method according to any of clauses 77 to 85, wherein the antibody comprises an antibody VH domain which is the VH domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

87. The method according to any of clauses 77 to 86, wherein the antibody comprises an antibody VL domain which is the VL domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VL domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

88. The method according to clause 87, wherein the antibody comprises:

an antibody VH domain which is selected from the VH domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, and

an antibody VL domain which is the VL domain of said selected antibody, or which has an amino acid sequence at least 90 % identical to the antibody VL domain sequence of said selected antibody.

89. The method according to clause 88, wherein the antibody comprises the STIM003 VH domain and the STIM003 VL domain.

90. The method of any one of clauses 71 or 73 to 89, wherein antibody comprises an antibody constant region.

91. The method according to clause 90, wherein the constant region comprises a human heavy and/or light chain constant region.

92. The method according to clause 90 or clause 91, wherein the constant region is Fc effector positive.

93. The method according to clause 92, wherein the antibody comprises an Fc region that has enhanced ADCC, ADCP and/or CDC function compared with a native human Fc region.

94. The method according to any of clauses 90 to 93, wherein the antibody is an IgG1.

95. The method according to clause 91 or clause 92, wherein the antibody is afucosylated.

96. The method according to any of clauses 71 or 73 to 95 wherein the antibody is conjugated to a cytotoxic drug or pro-drug.

97. The method according to any of clauses 71 or 73 to 96, wherein the antibody is a multispecific antibody.

98. The method according to clause 71, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and mouse ICOS with an affinity (KD) of less than 50 nM as determined by surface plasmon resonance.

99. The method according to clause 98, wherein the antibody binds the extracellular domain of human and mouse ICOS with an affinity (KD) of less than 5 nM as determined by surface plasmon resonance.

100. The method according to clause 98 or clause 99, wherein the KD of binding the extracellular domain of human ICOS is within 10-fold of the KD of binding the extracellular domain of mouse ICOS.

101. The method of clause 71, wherein the anti-ICOS antibody is STIM0003.

102. The method of any preceding clause, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody selected from the group consisting of atezoliumab (Roche), avelumab (Merck), durvalumab/Medi4736 (Medimmune), KN035, CK-301, AUNP12, CA-170, BMS-936559/MDX-1105 (BMS), FAZ-053 M7824, ABBV-368, LY-3300054, GNS-1480,

YW243.55.S70, REGN3504 and any of the PD-L1 antibodies disclosed in WO2017/220990, WO2017/034916, WO2017/020291, WO2017/020858, WO2017/020801, WO2016/111645, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630, WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 or WO2007/005874.

103. The method of any preceding clause, wherein the PD-L1 inhibitor is an anti-PD-1 antibody selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, JTX-401, spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS 001), dostarlimab (TSR-042, WBP-285), INCMGA00012 (MGA012), AMP-224 and AMP-514, MEDI-0680/AMP514, PDR001, Lambrolizumab, BMS-936558, REGN2810, BGB-A317, BGB-108, PDR-001, SHR-1210, JS-001, JNJ-63723283, AGEN-2034, PF-06801591, genolimzumab, MGA-012 (INCMGA00012), IBI-308, BCD-100, TSR-042 ANA011, AUNP-12, KD033, MCLA-134, mDX400, muDX400, STI-A1110, AB011, 244C8, 388D4, XCE853, or pidilizumab/CT-011, or from any one of the anti-PD-1 antibodies described in WO2015/112800 & US2015/0203579 (including the antibodies in Tables 1 to 3), US9,394,365, US5,897,862 and US7,488,802, WO2017/087599 (including antibody SSI-361 and SHB-617), WO2017/079112, WO2017/071625 (including deposit C2015132, hybridoma LT004, and antibodies 6F5/6 F5 (Re), 6F5H1 L1 and 6F5 H2L2), WO2017/058859 (including PD1AB-1 to PD1AB-6), WO2017/058115 (including 67D9, c67D9, and hu67D9), WO2017/055547 (including 12819.15384, 12748.15381, 12748.16124, 12865.15377, 12892.15378, 12796.15376, 12777.15382, 12760.15375 and 13112.15380), WO2017/040790 (including AGEN2033w, AGEN2034w, AGEN2046w, AGEN2047w, AGEN2001w and AGEN2002w), WO2017/025051 & WO2017/024515 (including 1.7.3 hAb, 1.49.9 hAb, 1.103.11 hAb, 1.103.11-v2 hAb, 1.139.15 hAb and 1.153.7 hAb), WO2017/025016 & WO2017/024465 (including antibody A to antibody I), WO2017/020858 & WO2017/020291 (including 1.4.1, 1.14.4, 1.20.15 and 1.46.11), WO2017/019896 & WO2015/112900 & US2015/0210769 (including BAP049-hum01 to BAP049-hum16 and BAP049-Clone-A to BAP049-Clone-E), WO2017/019846 (including PD-1 mAb 1 to PD-1 mAb 15), WO2017/016497 (including MHC723, MHC724, MHC725, MHC728, MHC729, m136-M13, m136-M19, m245-M3, m245-M5 and m136-M14), WO2016/201051 (including antibody EH12.2H7, antibody hPD-1 mAb2, antibody hPD-1 mAb7, antibody hPD-1 mAb9, antibody hPD-1 mAb15, or an anti-PD-1 antibody selected

from Table 1), WO2016/197497 (including DFPD1-1 to DFPD1-13), WO2016/197367 (including 2.74.15 and 2.74.15.hAb4 to 2.74.15.hAb8), WO2016/196173 (including the antibodies in Table 5, and Figures 1-5), WO2016/127179 (including R3A1, R3A2, R4B3, and R3D6), WO2016/077397 (including the antibodies described in Table 1 of Example 9), WO2016/106159 (including the murine antibodies in Table 3 of Example 2 and the humanised antibodies in Tables 7, 8 and 9 of Example 3), WO2016/092419 (including C1, C2, C3, EH12.1, mAb7-G4, mAb15-G4, mAb-AAA, mAb15-AAA), WO2016/068801 (including clone A3 and its variants and the other antibodies described in Figures 1 to 4), WO2016/014688 (including 10D1, 4C10, 7D3, 13F1, 15H5, 14A6, 22A5, 6E1, 5A8, 7A4, and 7A4D and the humanised antibodies of Examples 9/10), WO2016/015685 (including 10F8, BA08-1, BA-08-2 and 15H6), WO2015/091911 & WO2015/091910 (including the anti-canine PD-1 antibodies in Examples 2, 3 and 4) , WO2015/091914 (including the anti-canine PD-1 antibodies in Table 3), WO2015/085847 (including mAb005, H005-1 to H005-4), WO2015/058573 (including cAB7), WO2015/036394 (including LOPD180), WO2015/035606 (including the antibodies in Table 1 of Example 2, in Tables 14, 15 and 16 of Example 7 and in tables 20, 21 and 22 of Example 11), WO2014/194302 (including GA2, RG1B3, RG1H10, RG2A7, RG2H10, SH-A4, RG4A6, GA1, GB1, GB6, GH1, A2, C7, H7, SH-A4, SH-A9, RG1H11, and RG6B), WO2014/179664 (including 9A2, 10B11, 6E9, APE1922, APE1923, APE1924, APE1950, APE1963 and APE2058), WO2014/206107 (including clone 1, 10, 11, 55, 64, 38, 39, 41 and 48), WO2012/135408 (including h409A11, h409A16, and h409A17), WO2012/145493 (including antibodies 1E3, 1E8, 1H3 and h1H3 Var 1 to h1H3 Var 14), WO2011/110621 (including antibody 949 and the modified versions disclosed in Figures 1 to 11), WO2011/110604 (including antibody 948 and the modified versions disclosed in Figures 3 to 11), WO2010/089411 (including CNCM deposit number 1-4122, 1-4080 or 1-4081), WO2010/036959 (including the antibodies in Table 1 of Example 1), WO2010/029435 & WO2010/029434 (including clones 2, 10 and 19), WO2008/156712 (including hPD-1.08A, hPD-1.09A, h409A11, h409A16 and h409A17 and the antibodies described in Example 2, Table H, Example 4 and table IV), WO2006/121168 (including clones 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, and 2D3), WO2004/004771 and WO2004/056875 (including PD1-17, PD1-28, PD1-33, PD1-35, PD1-F2 and the Abs described in Table 1).

104. The method of any preceding clause, wherein the ICOS modulator is an IgG1 anti-ICOS antibody and/or the PD-L1 inhibitor is an IgG1 anti-PD-L1 antibody or an IgG1 anti-PD-1 antibody.

105. The method of clause 104, wherein the IgG1 anti-ICOS antibody and/or the IgG1 anti-PD-L1 antibody or anti-PD-1 antibody comprises a human IgG1 constant region comprising amino acid sequence SEQ ID NO: 340.

106. The method of any preceding clause, wherein the cancer is liver cancer, renal cell cancer, head and neck cancer, melanoma, non small cell lung cancer, diffuse large B-cell lymphoma, breast cancer, penile cancer, pancreatic cancer or oesophageal cancer

107. The method of clause 106, wherein the liver cancer is hepatocellular carcinoma.

108. The method of clause 106, wherein the head and neck cancer is metastatic squamous cell carcinoma.

109. The method of clause 106, wherein the breast cancer is triple negative breast cancer.

110. An ICOS modulator for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

111. An ICOS modulator for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor.

112. The ICOS modulator for use as claimed in clause 110 or clause 111, wherein the ICOS modulator is for use in combination with a PD-L1 inhibitor.

113. The ICOS modulator for use as claimed in any one of clauses 110 to 112, wherein the ICOS modulator is an agonistic anti-ICOS antibody.

114. The ICOS modulator for use as claimed in any one of clauses 110 to 113, wherein the ICOS modulator is a bispecific antibody that is an anti-ICOS agonist and an anti-PD-L1 antagonist or a bispecific antibody that is an anti-ICOS agonist and an anti-PD-1 antagonist.

115. The ICOS modulator for use according to any one clauses 110 to 114, wherein the method is the method of any one of clauses 1 to 109.

116. A combination of an ICOS modulator and a PD-L1 inhibitor for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

117. A combination of an ICOS modulator and a PD-L1 inhibitor for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor

118. The combination of clause 116 or clause 117, wherein the ICOS modulator is an agonistic anti-ICOS antibody.

119. The combination for use according to any one of clauses 116 to 118, wherein the method is the method of any one of clauses 1 to 109.

120. A modulator of ICOS and an inhibitor of PD-L1 for use in the treatment of cancer in a patient, wherein the patient has a PD-L1 negative cancer or a cancer with low PD-L1 expression.

121. A modulator of ICOS and an inhibitor of PD-L1 for use in the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor

122. The modulator of ICOS and inhibitor of PD-L1 for use according to any one of clauses 120 to 121, wherein the modulator of ICOS and inhibitor of PD-L1 is a bispecific antibody that specifically binds to ICOS and PD-L1.

123. The modulator of ICOS and inhibitor of PD-L1 for use according to any one of clauses 120 to 122, wherein the ICOS modulator is an agonistic anti-ICOS antibody.

124. The modulator of ICOS and inhibitor of PD-L1 for use according to any one of clauses 120 to 123, wherein the method is the method of any one of clauses 1 to 109.

125. Use of an ICOS modulator in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

126. Use of an ICOS modulator in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor, and wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

127. The use of clause 125 or clause 126, wherein the ICOS modulator is an agonistic anti-ICOS antibody.

128. The use of any one of clauses 125 to 127, wherein the ICOS modulator is a bispecific antibody that is an anti-ICOS agonist and an anti-PD-L1 antagonist or a bispecific antibody that is an anti-ICOS agonist and an anti-PD-1 antagonist.

129. The use of any one of clauses 125 to 127, wherein the treatment of cancer in a patient is the treatment by a method of any one of clauses 1 to 109.

130. Use of a combination of an ICOS modulator and a PD-L1 inhibitor in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

131. Use of a combination of an ICOS modulator and a PD-L1 inhibitor in the manufacture of a medicament for the treatment of cancer in a patient and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the patient has previously received treatment for the cancer, wherein the previous treatment for the cancer was a PD-L1 inhibitor, and wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

132. Use of a modulator of ICOS and an inhibitor of PD-L1 in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has a PD-L1 negative cancer or a cancer with low PD-L1 expression.

133. Use of a modulator of ICOS and an inhibitor of PD-L1 in the manufacture of a medicament for the treatment of cancer in a patient, wherein the patient has previously received treatment for the cancer, wherein the previous treatment for the cancer was a PD-L1 inhibitor, and wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression.

134. The use of any one of clauses 132 to 133, wherein the tumour is HPV (Human papillomavirus) positive.

135. The use of any one of clauses 132 to 133, wherein the patient has, or has had, HPV (Human papillomavirus).

136. The use of any one of clauses 130 to 135, wherein the modulator of ICOS is an agonistic anti-ICOS antibody.

137. The use of any one of clauses 130 to 136, wherein the treatment of cancer in a patient is the treatment by a method of any one of clauses 1 to 109.

CLAIMS

What is claimed is:

1. A method of treating cancer in a patient, wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression, comprising administering to the patient a modulator of ICOS.

2. A method of treating cancer in a patient who has previously received treatment for the cancer, wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor and the patient did not respond to the previous treatment or ceased responding to the previous treatment, and wherein the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression, comprising administering to the patient a modulator of ICOS.

3. The method of any preceding claim, comprising determining the level of PD-L1 expression in a tumour sample from the patient, and if the tumour is PD-L1 negative or a PD-L1 low expression tumour, then administering to the patient an ICOS modulator.

4. The method of of any preceding claim, comprising administering to the patient a modulator of ICOS and an inhibitor of PD-L1, optionally wherein the modulator of ICOS and an inhibitor of PD-L1 are administered simultaneously, separately or sequentially.

5. The method of any preceding claim, wherein the ICOS modulator is an ICOS agonist, optionally wherein the ICOS agonist is an agonistic anti-ICOS antibody, optionally wherein the anti-ICOS antibody is a bispecific antibody that specifically binds ICOS and PD-L1 or specifically binds ICOS and PD-1, optionally wherein the bispecific antibody is an ICOS agonist and a PD-L1 antagonist, or an ICOS agonist and a PD-1 antagonist.

6. The method of any preceding claim, wherein the PD-L1 inhibitor is an anti-PD-L1 binding molecule, optionally wherein the PD-L1 inhibitor is an anti-PD-L1 antibody or an anti-PD-1 antibody, optionally wherein the PD-L1 inhibitor inhibits the binding of PD-L1 to PD-1, optionally wherein the PD-L1 inhibitor is an antagonistic anti-PD-L1 antibody or an antagonistic anti-PD-1 antibody.

7. The method of any preceding claim, wherein the tumour cells are PD-L1 negative or exhibit low PD-L1 expression.

8. The method of any preceding claim, wherein the tumour comprises immune cells, and the immune cells are PD-L1 negative or exhibit low PD-L1 expression, optionally wherein the tumour cells are PD-L1 negative or exhibit low PD-L1 expression and the immune cells are PD-L1 negative or exhibit low PD-L1 expression.

9. The method of any preceding claim, wherein the cancer is associated with infectious agents, optionally wherein the cancer is a virally-induced cancer, optionally wherein the virus associated with the virally-induced cancer is selected from HPV (cervical cancer, oropharyngeal cancer), HBV, HCV, and EBV (Burkitts lymphomas, gastric cancer, Hodgkin's lymphoma, other EBV positive B cell lymphomas, nasopharyngeal carcinoma and post transplant lymphoproliferative disease).

10. The method of claim 9, wherein the cancer is selected from the group consisting of head and neck squamous cell carcinoma, cervical cancer, anogenital cancer and oropharyngeal cancer.

11. The method of any preceding claim, wherein the tumour is HPV (Human papillomavirus) positive.

12. The method of any preceding claim, wherein the patient has undergone a test for HPV infection and/or wherein the patient has an HPV infection or has had an HPV infection.

13. The method of any preceding claim, comprising the step of determining the HPV status of the patient and/or determining the HPV status of the tumour.

14. The method of any preceding claim, wherein the patient has previously
    a. been administered a kinase inhibitor;
    b. received surgical treatment for the cancer (for example complete or partial tumour resection) and/or radiotherapy and/or chemotherapy, optionally wherein the chemotherapy comprises docetaxel, fluorouracil, cisplatin, paclitaxel and/or nab-paclitaxel; and/or
    c. received treatment for the cancer, optionally wherein the previous treatment for the cancer was administration of a PD-L1 inhibitor (for example an anti-PD-L1 antibody or an anti-PD-1 antibody), optionally wherein the previous treatment for the cancer was PD-L1 inhibitor monotherapy or administration of a PD-L1 inhibitor as the sole immunotherapeutic agent.

15. The method of any preceding claim, wherein the cancer is or has been characterised as refractory to:
    a. PD-L1 inhibitor treatment (for example refractory to anti-PD-L1 antibody or anti-PD-1 antibody monotherapy);
    b. PD-L1 inhibitor monotherapy treatment;
    c. treatment with a PD-L1 inhibitor as the sole immunotherapy agent; and/or
    d. treatment with nivolumab.

16. The method of any preceding claim, wherein the tumour is a CD8+ tumour and/or a ICOS+ tumour.

17. The method of any preceding claim, wherein the patient has an increased level of $ICOS^+$ immune cells (such as $ICOS^+$ regulatory T cells) following treatment with another therapeutic agent, optionally wherein the method comprises administering a therapeutic agent to the patient, determining that the patient has an increased level of $ICOS^+$ immune cells (such as $ICOS^+$ regulatory T cells) following the treatment with said agent, and administering a modulator of ICOS (for example an anti-ICOS antibody such as an agonistic anti-ICOS antibody) to the patient to reduce the level of $ICOS^+$ regulatory T cells, optionally wherein the therapeutic agent is IL-2 or an immunomodulatory antibody (e.g., anti-PDL-1, anti-PD-1 or anti-CTLA-4).

18. The method of any preceding claim, comprising administering a single dose of the ICOS modulator optionally followed by multiple doses of the PD-L1 inhibitor.

19. The method of any preceding claim, wherein treatment
    a. results in reducing the size of the tumour;
    b. inhibits tumour growth;
    c. results in stable disease;
    d. extends the survival of the patient and/or delays disease progression;
    e. depletes ICOS+ immune cells (such as $ICOS^+$ regulatory T cells) in the tumour microenvironment; and/or
    f. increases the CD8+ to ICOS+ immune cell ratio (for example the CD8+ to ICOS+ regulatory T cell ration) in the tumour microenvironment.

20. The method of any preceding claim, wherein the ICOS modulator is an anti-ICOS antibody, optionally wherein the anti-ICOS antibody is any of the following antibodies, may comprise

the VH and VL domains of any of the following antibodies or may comprise the HCDRs and/or LCDRs of any of the following antibodies:

a. KY1044;
b. anti-ICOS antibodies described in PCT/GB2017/052352 WO2018/029474 or US9957323, the contents of which are incorporated herein by reference (e.g., STIM001, STIM002, STIM002B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009);
c. anti-ICOS antibodies described in PCT/GB2018/053701 WO2019/122884 the contents of which are incorporated herein by reference (e.g., STIM017, STIM020, STIM021, STIM022, STIM023, STIM039, STIM040, STIM041, STIM042, STIM043, STIM044, STIM050, STIM051, STIM052, STIM053, STIM054, STIM055, STIM056, STIM057, STIM058, STIM059, STIM060, STIM061, STIM062, STIM063, STIM064, STIM065 or STIM066);
d. anti-ICOS/PD-L1 mAb2 bispecific antibodies described in PCT/GB2018/053698 WO2019/122882;
e. vopratelimab;
f. anti-ICOS antibodies described in WO2016/154177 or US2016/0304610 (e.g., 37A10S713, 7F12, 37A10, 35A9, 36E10, 16G10, 37A10S714, 37A10S715, 37A10S716, 37A10S717, 37A10S718, 16G10S71, 16G10S72, 16G10S73, 16G10S83, 35A9S79, 35A9S710 or 35A9S89);
g. anti-ICOS antibodies described in WO2016/120789 or US2016/0215059 (e.g., 422.2 H2L5);
h. antibody C398.4 or a humanised antibody thereof as described in WO2018/187613 or US2018/0289790, e.g., ICOS.33 IgG1f S267E, ICOS.4, ICOS34 G1f, ICOS35 G1f, 17C4, 9D5, 3E8, 1D7a, 1D7b or 2644 (for sequences see WO2018187613 Table 35), e.g., the antibody BMS-986226 in NCT03251924;
i. antibody JMAb 136, “136”, or any other antibody described in WO2010/056804;
j. antibody 314-8, the antibody produced from hybridoma CNCM I-4180, or any other anti-ICOS antibody described in WO2012/131004, WO2014/033327 or US2015/0239978;
k. antibody Icos145-1, the antibody produced by hybridoma CNCM I-4179, or any other antibody described in WO2012/131004, US9,376,493 or US2016/0264666;
l. antibody MIC-944 (from hybridoma DSMZ 2645), 9F3 (DSMZ 2646) or any other anti-ICOS antibody described in WO99/15553, US7,259,247, US7,132,099, US7,125,551, US7,306,800, US7,722,872, WO05/103086, US8,318.905 or US8,916,155;
m. anti-ICOS antibodies described in WO98/3821, US7,932,358B2, US2002/156242, US7,030,225, US7,045,615, US7,279,560, US7,226,909, US7,196,175,

US7,932,358, US8,389,690, WO02/070010, US7,438,905, US7,438,905, WO01/87981, US6,803,039, US7,166,283, US7,988,965, WO01/15732, US7,465,445 or US7,998,478 (e.g., JMAb-124, JMAb-126, JMAb-127, JMAb-128, JMAb-135, JMAb-136, JMAb-137, JMAb-138, JMAb-139, JMAb-140 or JMAb-141, e.g., JMAb136);

n. anti-ICOS antibodies described in WO2014/08911;
o. anti-ICOS antibodies described in WO2012/174338;
p. anti-ICOS antibodies described in US2016/0145344;
q. anti-ICOS antibodies described in WO2011/020024, US2016/002336, US2016/024211 or US8,840,889;
r. anti-ICOS antibodies described in US8,497,244; or
s. antibody clone ISA-3 (eBioscience), clone SP98 (Novus Biologicals), clone 1 G1, clone 3G4 (Abnova Corporation), clone 669222 (R&D Systems), clone TQ09 (Creative Diagnostics), clone 2C7 (Deng et al. Hybridoma Hybridomics 2004), clone ISA-3 (eBioscience) or clone 17G9 (McAdam et al. J Immunol 2000).

21. The method of claim 20, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and/or mouse ICOS, wherein the antibody comprises a VH domain comprising an amino acid sequence having at least 95 % sequence identity to the STIM003 VH domain SEQ ID NO: 408 and a VL domain comprising an amino acid sequence having at least 95 % sequence identity to the STIM003 VL domain SEQ ID NO: 415.

22. The method of claim 21, wherein the VH domain comprises a set of heavy chain complementarity determining regions (HCDRs) HCDR1, HCDR2 and HCDR3, wherein

a. HCDR1 is the STIM003 HCDR1 having amino acid sequence SEQ ID NO: 405,
b. HCDR2 is the STIM003 HCDR2 having amino acid sequence SEQ ID NO: 406,
c. HCDR3 is the STIM003 HCDR3 having amino acid sequence SEQ ID NO: 407; and/or wherein the VL domain comprises a set of light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3, wherein:
d. LCDR1 is the STIM003 LCDR1 having amino acid sequence SEQ ID NO: 412,
e. LCDR2 is the STIM003 LCDR2 having amino acid sequence SEQ ID NO: 413,
f. LCDR3 is the STIM003 LCDR3 having amino acid sequence SEQ ID NO: 414.

23. The method of claim 21, wherein the VH domain amino acid sequence is SEQ ID NO: 408 and/or wherein the VL domain amino acid sequence is SEQ ID NO: 415.

24. The method of claim 21, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and/or mouse ICOS, comprising

an antibody VH domain comprising complementarity determining regions (CDRs) HCDR1, HCDR2 and HCDR3, and

an antibody VL domain comprising complementarity determining regions LCDR1, LCDR2 and LCDR3, wherein

HCDR1 is the HCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

HCDR2 is the HCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that HCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

HCDR3 is the HCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that HCDR3 with 1, 2, 3, 4 or 5 amino acid alterations; and/or

wherein LCDR1 is the LCDR1 of STIM001, STIM002, STIM002-B, STIM003, STIM004 STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR1 with 1, 2, 3, 4 or 5 amino acid alterations,

LCDR2 is the LCDR2 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprises that LCDR2 with 1, 2, 3, 4 or 5 amino acid alterations, and/or

LCDR3 is the LCDR3 of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprises that LCDR3 with 1, 2, 3, 4 or 5 amino acid alterations.

25. The method of claim 24, wherein the antibody heavy chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 heavy chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations; and/or wherein the antibody light chain CDRs are those of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or comprise the STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009 light chain CDRs with 1, 2, 3, 4 or 5 amino acid alterations.

26. The method of claim 25, wherein the antibody VH domain has the heavy chain CDRs of STIM003 and/or wherein the antibody VL domain has the light chain CDRs of STIM003.

27. The method according to any of claims 24 to 26, wherein the antibody comprises VH and/or VL domain framework regions of human germline gene segment sequences.

28. The method according to any of claims 24 to 27, wherein the antibody comprises an antibody VH domain which is the VH domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VH domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009; and/or wherein the antibody comprises an antibody VL domain which is the VL domain of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009, or which has an amino acid sequence at least 90 % identical to the antibody VL domain sequence of STIM001, STIM002, STIM002-B, STIM003, STIM004, STIM005, STIM006, STIM007, STIM008 or STIM009.

29. The method according to claim 28, wherein the antibody comprises the STIM003 VH domain and the STIM003 VL domain, optionally wherein the anti-ICOS antibody is STIM0003.

30. The method of any one of claims 20 to 29, wherein antibody comprises an antibody constant region, optionally wherein the constant region comprises a human heavy and/or light chain constant region, optionally wherein the constant region is Fc effector positive.

31. The method according to any of claims 20 to 30, wherein the antibody is a multispecific antibody.

32. The method according to claim 20, wherein the anti-ICOS antibody is an antibody that binds the extracellular domain of human and mouse ICOS with an affinity (KD) of less than 50 nM as determined by surface plasmon resonance, or less than 5 nM as determined by surface plasmon resonance.

33. The method of any preceding claim, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody selected from the group consisting of atezoliumab (Roche), avelumab (Merck), durvalumab/Medi4736 (Medimmune), KN035, CK-301, AUNP12, CA-170, BMS-936559/MDX-1105 (BMS), FAZ-053 M7824, ABBV-368, LY-3300054, GNS-1480, YW243.55.S70, REGN3504 and any of the PD-L1 antibodies disclosed in WO2017/220990, WO2017/034916, WO2017/020291, WO2017/020858, WO2017/020801,

WO2016/111645, WO2016/197367, WO2016/061142, WO2016/149201, WO2016/000619, WO2016/160792, WO2016/022630, WO2016/007235, WO2015/179654, WO2015/173267, WO2015/181342, WO2015/109124, WO2015/112805, WO2015/061668, WO2014/159562, WO2014/165082, WO2014/100079, WO2014/055897, WO2013/181634, WO2013/173223, WO2013/079174, WO2012/145493, WO2011/066389, WO2010/077634, WO2010/036959, WO2010/089411 or WO2007/005874.

34. The method of any preceding claim, wherein the PD-L1 inhibitor is an anti-PD-1 antibody selected from the group consisting of pembrolizumab, nivolumab, cemiplimab, JTX-401, spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS 001), dostarlimab (TSR-042, WBP-285), INCMGA00012 (MGA012), AMP-224 and AMP-514, MEDI-0680/AMP514, PDR001, Lambrolizumab, BMS-936558, REGN2810, BGB-A317, BGB-108, PDR-001, SHR-1210, JS-001, JNJ-63723283, AGEN-2034, PF-06801591, genolimzumab, MGA-012 (INCMGA00012), IBI-308, BCD-100, TSR-042 ANA011, AUNP-12, KD033, MCLA-134, mDX400, muDX400, STI-A1110, AB011, 244C8, 388D4, XCE853, or pidilizumab/CT-011, or from any one of the anti-PD-1 antibodies described in WO2015/112800 & US2015/0203579 (including the antibodies in Tables 1 to 3), US9,394,365, US5,897,862 and US7,488,802, WO2017/087599 (including antibody SSI-361 and SHB-617), WO2017/079112, WO2017/071625 (including deposit C2015132, hybridoma LT004, and antibodies 6F5/6 F5 (Re), 6F5H1 L1 and 6F5 H2L2), WO2017/058859 (including PD1AB-1 to PD1AB-6), WO2017/058115 (including 67D9, c67D9, and hu67D9), WO2017/055547 (including 12819.15384, 12748.15381, 12748.16124, 12865.15377, 12892.15378, 12796.15376, 12777.15382, 12760.15375 and 13112.15380), WO2017/040790 (including AGEN2033w, AGEN2034w, AGEN2046w, AGEN2047w, AGEN2001w and AGEN2002w), WO2017/025051 & WO2017/024515 (including 1.7.3 hAb, 1.49.9 hAb, 1.103.11 hAb, 1.103.11-v2 hAb, 1.139.15 hAb and 1.153.7 hAb), WO2017/025016 & WO2017/024465 (including antibody A to antibody I), WO2017/020858 & WO2017/020291 (including 1.4.1, 1.14.4, 1.20.15 and 1.46.11), WO2017/019896 & WO2015/112900 & US2015/0210769 (including BAP049-hum01 to BAP049-hum16 and BAP049-Clone-A to BAP049-Clone-E), WO2017/019846 (including PD-1 mAb 1 to PD-1 mAb 15), WO2017/016497 (including MHC723, MHC724, MHC725, MHC728, MHC729, m136-M13, m136-M19, m245-M3, m245-M5 and m136-M14), WO2016/201051 (including antibody EH12.2H7, antibody hPD-1 mAb2, antibody hPD-1 mAb7, antibody hPD-1 mAb9, antibody hPD-1 mAb15, or an anti-PD-1 antibody selected from Table 1), WO2016/197497 (including DFPD1-1 to DFPD1-13), WO2016/197367 (including 2.74.15 and 2.74.15.hAb4 to 2.74.15.hAb8), WO2016/196173 (including the

antibodies in Table 5, and Figures 1-5), WO2016/127179 (including R3A1, R3A2, R4B3, and R3D6), WO2016/077397 (including the antibodies described in Table 1 of Example 9), WO2016/106159 (including the murine antibodies in Table 3 of Example 2 and the humanised antibodies in Tables 7, 8 and 9 of Example 3), WO2016/092419 (including C1, C2, C3, EH12.1, mAb7-G4, mAb15-G4, mAb-AAA, mAb15-AAA), WO2016/068801 (including clone A3 and its variants and the other antibodies described in Figures 1 to 4), WO2016/014688 (including 10D1, 4C10, 7D3, 13F1, 15H5, 14A6, 22A5, 6E1, 5A8, 7A4, and 7A4D and the humanised antibodies of Examples 9/10), WO2016/015685 (including 10F8, BA08-1, BA-08-2 and 15H6), WO2015/091911 & WO2015/091910 (including the anti-canine PD-1 antibodies in Examples 2, 3 and 4) , WO2015/091914 (including the anti-canine PD-1 antibodies in Table 3), WO2015/085847 (including mAb005, H005-1 to H005-4), WO2015/058573 (including cAB7), WO2015/036394 (including LOPD180), WO2015/035606 (including the antibodies in Table 1 of Example 2, in Tables 14, 15 and 16 of Example 7 and in tables 20, 21 and 22 of Example 11), WO2014/194302 (including GA2, RG1B3, RG1H10, RG2A7, RG2H10, SH-A4, RG4A6, GA1, GB1, GB6, GH1, A2, C7, H7, SH-A4, SH-A9, RG1H11, and RG6B), WO2014/179664 (including 9A2, 10B11, 6E9, APE1922, APE1923, APE1924, APE1950, APE1963 and APE2058), WO2014/206107 (including clone 1, 10, 11, 55, 64, 38, 39, 41 and 48), WO2012/135408 (including h409A11, h409A16, and h409A17), WO2012/145493 (including antibodies 1E3, 1E8, 1H3 and h1H3 Var 1 to h1H3 Var 14), WO2011/110621 (including antibody 949 and the modified versions disclosed in Figures 1 to 11), WO2011/110604 (including antibody 948 and the modified versions disclosed in Figures 3 to 11), WO2010/089411 (including CNCM deposit number 1-4122, 1-4080 or 1-4081), WO2010/036959 (including the antibodies in Table 1 of Example 1), WO2010/029435 & WO2010/029434 (including clones 2, 10 and 19), WO2008/156712 (including hPD-1.08A, hPD-1.09A, h409A11, h409A16 and h409A17 and the antibodies described in Example 2, Table H, Example 4 and table IV), WO2006/121168 (including clones 17D8, 4H1, 5C4, 4A11, 7D3, 5F4, and 2D3), WO2004/004771 and WO2004/056875 (including PD1-17, PD1-28, PD1-33, PD1-35, PD1-F2 and the Abs described in Table 1).

35. The method of any preceding claim, wherein the ICOS modulator is an IgG1 anti-ICOS antibody and/or the PD-L1 inhibitor is an IgG1 anti-PD-L1 antibody or an IgG1 anti-PD-1 antibody, optionally wherein the IgG1 anti-ICOS antibody and/or the IgG1 anti-PD-L1 antibody or anti-PD-1 antibody comprises a human IgG1 constant region comprising amino acid sequence SEQ ID NO: 340.

36. The method of any preceding claim, wherein the cancer is liver cancer (e.g. hepatocellular carcinoma), renal cell cancer, head and neck cancer (e.g. metastatic squamous cell carcinoma), melanoma, non small cell lung cancer, diffuse large B-cell lymphoma, breast cancer (e.g. triple negative breast cancer), penile cancer, pancreatic cancer or oesophageal cancer

37. An ICOS modulator for use in a method of treating cancer in a patient, wherein
    a. the patient has a PD-L1 negative tumour or a tumour with low PD-L1 expression; or
    b. the patient has previously received treatment for the cancer and the patient did not respond to the previous treatment or ceased responding to the previous treatment, wherein the previous treatment for the cancer was a PD-L1 inhibitor.

38. The ICOS modulator for use as claimed in claim 37, wherein the ICOS modulator is for use in combination with a PD-L1 inhibitor, optionally wherein the ICOS modulator is an agonistic anti-ICOS antibody, optionally wherein the ICOS modulator is a bispecific antibody that is an anti-ICOS agonist and an anti-PD-L1 antagonist or a bispecific antibody that is an anti-ICOS agonist and an anti-PD-1 antagonist.

39. The ICOS modulator for use according to any one of claims 37 to 38, wherein the method is the method of any one of claims 1 to 36.