Combination Treatment

This application claims priority from GB2405551.9 filed 19 April 2024, the contents and elements of which are herein incorporated by reference for all purposes.

Technical Field

The present invention relates to combination therapy for treatment and prophylaxis of fibrosis and/or pathological angiogenesis, particularly in the eye.

Background

Fibrosis is an essential process that is a critical part of wound healing. Excessive fibrosis is common in many rare and common disease conditions and is important in disease pathogenesis. Diseases characterized by excessive fibrosis include but are not restricted to: systemic sclerosis, scleroderma, hypertrophic cardiomyopathy, dilated cardiomyopathy (DCM), atrial fibrillation, ventricular fibrillation, myocarditis, liver cirrhosis, kidney diseases, asthma, diseases of the eye, cystic fibrosis, arthritis and idiopathic pulmonary fibrosis.

Angiogenesis is an essential process in normal growth and development, as well as in wound healing. Abnormal angiogenesis is linked to a number of diseases and conditions, including age-related wet macular degeneration (wet AMD). Angiogenesis is also closely linked with inflammation and fibrosis, with many studies demonstrating a relationship between angiogenesis and fibrotic disease progression (see, for example, Matsuda *et al.* Molecular Therapy Nucleic Acids. (2019) 17:819-828; Wan *et al.* Respir Res. (2013) 14(1):56; Liu *et al.* Nature Materials. (2017) 16:1252-1261).

Gp130 is a constituent protein of receptors of a diversity of cytokines including IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 and IL-35, which are often referred to collectively as IL-6 family cytokines. Certain IL-6 family cytokines such as IL-6 and IL-11 are implicated in the pathology of a broad spectrum of diseases/conditions characterised by inflammation and/or fibrosis (see *e.g.* Rose-John, F1000Res. (2020) 9:F1000 Faculty Rev-1013, Tanaka *et al.*, Cold Spring Harb Perspect Biol. (2014) 6(10): a016295, Hirano *et al.* International Immunology (2021) 33(3): 127–148, Putoczki and Ernst, Immunotherapy (2015) 7(4): 441-453, Nguyen *et al.* Growth Factors (2019) 37(1-2):1-11, Cook and Schafer Annu. Rev. Med. (2020) 71:263-276 and Fung *et al.*, Cytokine (2022) 149:155750).

Despite the large impact on human health, therapeutic and diagnostic approaches to fibrosis are still an unmet medical need.

Monoclonal antibodies that bind to gp130 and antagonise gp130-mediated signalling have previously been described, including mAb16673 which is described in WO 2019/126071 A1. Combination therapy using VEGF decoy receptor aflibercept in combination with anti-IL6R antibody (sarilumab) has been described in Zhang *et al.* Cancer Res. (2012) 72:2723-2723.

Summary

In a first aspect, the present disclosure provides an antigen-binding molecule that binds to gp130 for use in a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation wherein the method comprises administering to a subject an antagonist of an angiogenic factor.

Also provided is the use of an antigen-binding molecule that binds to gp130 in the manufacture of a medicament for use in a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation, and/or a disease/condition characterised by inflammation, wherein the method comprises administering an antagonist of an angiogenic factor.

Also provided is a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation, and/or a disease/condition characterised by inflammation comprising administering to a subject a therapeutically- or prophylactically-effective amount of (i) an antigen-binding molecule that binds to gp130 and (ii) an antagonist of an angiogenic factor.

Also provided is a combination comprising an antigen-binding molecule that binds to gp130 and an antagonist of an angiogenic factor.

Also provided is a combination according to the present disclosure, for use in a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation.

Also provided is the use of a combination according to the present disclosure, in the manufacture of a medicament for treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation, and/or a disease/condition characterised by inflammation.

Also provided is a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation, and/or a disease/condition characterised by inflammation, comprising administering to a subject a therapeutically- or prophylactically-effective amount of a combination according to the present disclosure.

In some embodiments in accordance with the various different aspects of the present disclosure, the fibrosis, disease/condition characterised by fibrosis, pathological angiogenesis, disease/condition characterised by angiogenesis, pathological inflammation, and/or disease/condition characterised by inflammation affects tissue of the eye.

In some embodiments, the fibrosis, disease/condition characterised by fibrosis, pathological angiogenesis, disease/condition characterised by angiogenesis, pathological inflammation and/or disease/condition characterised by inflammation is selected from: choroidal neovascularization, retinal fibrosis, epiretinal fibrosis, idiopathic pre-macular fibrosis, retinal detachment, macular degeneration, subretinal fibrosis associated with wet age-related macular degeneration, diabetic retinopathy, glaucoma, geographic atrophy, corneal fibrosis, post-surgical fibrosis, post-surgical fibrosis of the posterior capsule following cataract surgery, post-surgical fibrosis of the bleb following trabeculectomy for glaucoma, conjunctival fibrosis, subconjunctival fibrosis, proliferative retinal vasculopathy, dacryoadenitis, scleritis, episcleritis, keratitis, retinitis, chorioretinitis, blepharitis, conjunctivitis, uveitis, autoimmune uveitis, infectious uveitis, Bechet's disease, cataracts, keratic precipitates, conjunctival ulcers, corneal immune ring opacities, post-surgical inflammation, dry eye disease, retinitis pigmentosa, glaucoma, toxic anterior segment syndrome (TASS), Eales' disease, diabetic retinopathy, retinal dystrophy (*e.g.* retinitis pigmentosa) and Sjögrens syndrome.

In some embodiments, the fibrosis, disease/condition characterised by fibrosis, pathological angiogenesis, disease/condition characterised by angiogenesis, pathological inflammation and/or disease/condition characterised by inflammation is selected from: choroidal neovascularization, retinal fibrosis, epiretinal fibrosis, subretinal fibrosis, dacryoadenitis, uveitis, autoimmune uveitis, infectious uveitis, Bechet's disease, and dry eye disease.

Also provided is a kit of parts, comprising predetermined quantities of: (i) an antigen-binding molecule that binds to gp130, and (ii) an antagonist of an angiogenic factor.

In some embodiments in accordance with the various different aspects of the present disclosure, the antigen-binding molecule that binds to gp130 inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:2

HC-CDR2 having the amino acid sequence of SEQ ID NO:3

HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:10

LC-CDR2 having the amino acid sequence of SEQ ID NO:11

LC-CDR3 having the amino acid sequence of SEQ ID NO:12.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

(a)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:112, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:121; or

(b)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:117, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:126; or

(c)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or

(d)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

(e)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or

(f)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or

(g)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

(h)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or

(i)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or

(j)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

(k)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or

(l)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:1, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:9.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:18

HC-CDR2 having the amino acid sequence of SEQ ID NO:19

HC-CDR3 having the amino acid sequence of SEQ ID NO:20; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:26

LC-CDR2 having the amino acid sequence of SEQ ID NO:27

LC-CDR3 having the amino acid sequence of SEQ ID NO:28.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:17, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:25.

In some embodiments in accordance with the various different aspects of the present disclosure, the antigen-binding molecule that binds to gp130 inhibits signalling mediated by gp130:IL-6Rα and/or gp130:IL-11Rα, and wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMRβ, gp130:LIFRβ, gp130:LIFRβ:CNTFRα, gp130:IL-27Rα and gp130:IL-12Rβ2.

In some embodiments, the antigen-binding molecule that binds to gp130 inhibits signalling mediated by gp130:IL-6Rα and gp130:IL-11Rα.

In some embodiments, the antigen-binding molecule that binds to gp130 does not inhibit signalling mediated by gp130:OSMRβ, and does not inhibit signalling mediated by gp130:LIFRβ, and does not inhibit signalling mediated by gp130:LIFRβ:CNTFRα.

In some embodiments, the antigen-binding molecule that binds to gp130 contacts the region of gp130 shown in SEQ ID NO:517.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

(a)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180

HC-CDR2 having the amino acid sequence of SEQ ID NO:380

HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:417; or

(b)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180

HC-CDR2 having the amino acid sequence of SEQ ID NO:377

HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:412; or

(c)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180

HC-CDR2 having the amino acid sequence of SEQ ID NO:375

HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:415; or

(d)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180

HC-CDR2 having the amino acid sequence of SEQ ID NO:376

HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188

LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:412; or

(e)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:240
HC-CDR2 having the amino acid sequence of SEQ ID NO:241
HC-CDR3 having the amino acid sequence of SEQ ID NO:242; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:243
LC-CDR2 having the amino acid sequence of SEQ ID NO:244
LC-CDR3 having the amino acid sequence of SEQ ID NO:245; or

(f)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:181
HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:190; or

(g)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:196
HC-CDR2 having the amino acid sequence of SEQ ID NO:197
HC-CDR3 having the amino acid sequence of SEQ ID NO:198; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:202
LC-CDR2 having the amino acid sequence of SEQ ID NO:203
LC-CDR3 having the amino acid sequence of SEQ ID NO:204; or

(h)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:196
HC-CDR2 having the amino acid sequence of SEQ ID NO:197
HC-CDR3 having the amino acid sequence of SEQ ID NO:210; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:202
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:190; or

(i)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:215
HC-CDR2 having the amino acid sequence of SEQ ID NO:216

HC-CDR3 having the amino acid sequence of SEQ ID NO:217; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:223

LC-CDR2 having the amino acid sequence of SEQ ID NO:224

LC-CDR3 having the amino acid sequence of SEQ ID NO:225; or

(j)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:230

HC-CDR2 having the amino acid sequence of SEQ ID NO:231

HC-CDR3 having the amino acid sequence of SEQ ID NO:232; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:202

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:236.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:352, 372, 350, 370, 351, 371, 252, 284, 256, 258, 261, 179, 195, 209, 214, 229, 264 or 265; and

a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:402, 405, 253, 288, 266, 269, 273, 276, 278, 187, 201, 212, 222 or 235.

In some embodiments, the antigen-binding molecule that binds to gp130 comprises:

a VH region having an amino acid sequence having at least 70% amino acid sequence identity to an amino acid sequence indicated in column A of Table G, and

a VL region having an amino acid sequence having at least 70% amino acid sequence identity to an amino acid sequence indicated in column B of Table G;

wherein the sequences of columns A and B are selected from the same row of Table G.

In some embodiments in accordance with the various different aspects of the present disclosure, the angiogenic factor is selected from vascular endothelial growth factor (VEGF), a fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). In some embodiments, the angiogenic factor is VEGF.

In some embodiments, the antagonist of an angiogenic factor is selected from: a VEGF decoy receptor, an antigen-binding molecule that binds to VEGF, or an antigen-binding molecule that binds to a VEGF receptor. In some embodiments, the antagonist of an angiogenic factor is aflibercept.

Description

Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

gp130

Human gp130 (also known as IL6ST, CD130) is the protein identified by UniProt P40189. The structure and function of gp130 is described *e.g.* in Silver and Hunter, J Leukoc Biol. (2010) 88(6):1145-1156 and Rose-John, Cold Spring Harb Perspect Biol. (2018) 10(2):a028415, which are hereby incorporated by reference in their entirety.

The canonical isoform of human gp130 (isoform 1) has the amino acid sequence shown in SEQ ID NO:70. Alternative splicing of mRNA encoded by the human *IL6ST* gene yields three main gp130 isoforms: isoform 1 (SEQ ID NO:70), isoform 2 (also known as gp130-RAPS; SEQ ID NO:71) and isoform 3 (SEQ ID NO:72). Isoform 2 differs from isoform 1 in that positions 325 to 329 of SEQ ID NO:70 are different, and positions 330-918 are absent. Positions 423 to 483 of SEQ ID NO:70 are absent from isoform 3.

The canonical isoform of human gp130 comprises an N-terminal signal peptide (SEQ ID NO:73), followed by an extracellular domain (SEQ ID NO:75), a single-pass transmembrane domain (SEQ ID NO:76) and a cytoplasmic domain (SEQ ID NO:77) at the C-terminus. The mature form of human gp130 isoform 1 is shown in SEQ ID NO:74.

The extracellular domain comprises an N-terminal Ig-like C2-type domain (SEQ ID NO:78), followed by five fibronectin type III (FNIII) domains (shown in SEQ ID NOs:79, 80, 82, 83 and 84, respectively). The cytokine-binding module (CBM) of gp130 is formed by the Ig-like C2-type domain, and FNIII domains 1 and 2 (SEQ ID NO:85). FNIII domain 2 comprises the WSXWS motif shown in SEQ ID NO:81. WSXWS motifs are conserved among type I cytokine receptor polypeptides, and the WSXWS motif of gp130 is thought to be important for cytokine binding.

gp130 is a constituent polypeptide of all receptors in the IL-6 receptor family, providing for signal transduction. Two gp130 polypeptides associate with two IL-6Rα polypeptides to form the receptor for IL-6, and similarly two gp130 polypeptides associate with two IL-11Rα polypeptides to form the receptor for IL-11. gp130 associates with OSMRβ to form the type II receptor for OSM, or with LIFRβ to form the type I receptor for OSM, which also serves as a receptor for LIF and CT-1. gp130 also associates with LIFRβ and CNTFRα to form the receptor for CNTF and CLC. gp130 associates with IL-27Rα to form the receptor for IL-27, and associates with IL-12Rβ2 to form the receptor for IL-35.

Following the formation of complexes with its receptor interaction partner(s) and cognate ligand, gp130 is phosphorylated at tyrosine residues in its cytoplasmic domain (particularly Y767, Y814, Y905 and Y915), triggering downstream signalling through the JAK/STAT and MAPK/ERK signal transduction pathways. gp130 can also trigger signalling through PI3K/AKT. Receptor engagement leads to phosphorylation and activation of JAK1 and JAK2, which then phosphorylate STAT1, STAT3 and STAT5. Phosphorylation of gp130 tyrosine residues also results in the recruitment and activation of SHP2, which in turn activates signalling through the Ras-ERK1/ERK2 MAPK and PI3K/AKT signalling pathways.

In this specification 'gp130' refers to gp130 from any species, and includes isoforms, fragments, variants or homologues from any species. In some embodiments gp130 is gp130 from a mammal (*e.g.* a therian, placental, epitherian, preptotheria, archontan, primate (rhesus, cynomolgous, non-human primate or human)). In some embodiments, the gp130 is human gp130, rhesus gp130, mouse gp130, rat gp130 or canine gp130. In some embodiments, the gp130 is human gp130 or mouse gp130.

As used herein, isoforms, fragments, variants or homologues of a given reference protein (*e.g.* gp130) may be characterised as having at least 70% sequence identity, preferably one of ≥80%, ≥85%, ≥90%, ≥91%, ≥92%, ≥93%, ≥94%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% amino acid sequence identity to the amino acid sequence of the reference protein.

A 'fragment' generally refers to a fraction of the reference protein. A 'variant' generally refers to a protein having an amino acid sequence comprising one or more amino acid substitutions, insertions, deletions or other modifications relative to the amino acid sequence of the reference protein, but retaining a considerable degree of sequence identity (*e.g.* at least 60%) to the amino acid sequence of the reference protein. An 'isoform' generally refers to a variant of the reference protein expressed by the same species as the species of the reference protein. A 'homologue' generally refers to a variant of the reference protein produced by a different species as compared to the species of the reference protein. Homologues include orthologues. Homologues of human gp130 include *e.g.* mouse gp130 (UniProt Q00560) and rat gp130 (UniProt P40190).

Isoforms, fragments, variants or homologues of a given reference protein may optionally be characterised as having at least 70%, preferably one of ≥80%, ≥85%, ≥90%, ≥91%, ≥92%, ≥93%, ≥94%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99% or 100% amino acid sequence identity to the amino acid sequence of an immature or mature (*i.e.* after processing to remove signal peptide) form of a specified isoform of the relevant protein from a given species, *e.g.* human.

Isoforms, fragments, variants or homologues of gp130 according to the present disclosure may optionally be characterised as having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of an immature or mature gp130 isoform from a given species, *e.g.* human.

Isoforms, fragments, variants or homologues may optionally be functional isoforms, fragments, variants or homologues, *e.g.* having a functional property/activity of the reference gp130 (*e.g.* human gp130 isoform 1), as determined by analysis by a suitable assay for the functional property/activity. For example, an isoform, fragment, variant or homologue of gp130 may associate with IL-6Rα, IL-11Rα, OSMRβ, LIFRβ and/or CNTFRα.

In some embodiments, the gp130 comprises, or consists of, an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:70, 71 or 72.

In some embodiments, the gp130 comprises, or consists of, an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:70 or 74.

A 'fragment' of a reference protein may be of any length (by number of amino acids), although may optionally be at least 25% of the length of the reference protein (that is, the protein from which the fragment is derived) and may have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of the reference protein.

A fragment of gp130 may have a minimum length of one of 10, 20, 30, 40, 50, 100, 150, 200, 300, 400, 500, 600, 700, 800 or 900 amino acids, and may have a maximum length of one of 20, 30, 40, 50, 100, 150, 200, 300, 400, 500, 600, 700, 800 or 900 amino acids.

In some embodiments, a fragment of gp130 comprises, or consists of, an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:74.

In some embodiments, a fragment of gp130 comprises, or consists of, an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:75.

In some embodiments, a fragment of gp130 comprises, or consists of, an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:85.

In this specification 'gp130-mediated signalling' refers to signalling mediated by gp130 and/or multimeric receptor complexes comprising gp130 (*e.g.* comprising gp130 and another member of the IL-6 receptor family). 'Signalling' refers to signal transduction and other cellular processes governing cellular activity.

gp130-mediated signalling may be mediated by a gp130-containing polypeptide complex (*i.e.* a polypeptide complex comprising one or more gp130 polypeptides). Polypeptide complexes according to the present disclosure may be characterised by non-covalent, protein:protein interaction between constituent polypeptide(s)/peptide(s). In some embodiments, the association comprises electrostatic interaction (*e.g.* ionic bonding, hydrogen bonding) and/or Van der Waals forces.

gp130-mediated signalling may be mediated by heteromultimeric polypeptide complexes comprising one or more gp130 polypeptides, and additionally comprising one or more polypeptides of one or more polypeptides of the IL-6 receptor family (*e.g.* selected from IL-6Rα, IL-11Rα, OSMRβ, LIFRβ, CNTFRα, IL-27Rα and IL-12Rβ2).

In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex forming a receptor for an IL-6 family cytokine. For example, gp130-mediated signalling may be mediated by a polypeptide complex forming a receptor for IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 or IL-35.

In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and another polypeptide of the IL-6 receptor family (*e.g.* selected from IL-6Rα, IL-11Rα, OSMRβ, LIFRβ, CNTFRα, IL-27Rα and IL-12Rβ2). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-6Rα (*i.e.* a gp130:IL-6Rα complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-11Rα (*i.e.* a gp130:IL-11Rα complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and OSMRβ (*i.e.* a gp130:OSMRβ complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and LIFRβ (*i.e.* a gp130:LIFRβ complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130, LIFRβ and CNTFRα (*i.e.* a gp130:LIFRβ:CNTFRα complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-27Rα (*i.e.* a gp130:IL-27Rα complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-12Rβ2 (*i.e.* a gp130:IL-12Rβ2 complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising more than one gp130 polypeptide. In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising two gp130 polypeptides. In some embodiments gp130-mediated signalling may be mediated by a polypeptide complex comprising two gp130 polypeptides and IL-6Rα (*i.e.* a gp130:gp130:IL-6Rα complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising two gp130 polypeptides and IL-11Rα (*i.e.* a gp130:gp130:IL-11Rα complex).

gp130-mediated signalling through the polypeptide complexes described in the preceding paragraph may be triggered by binding of their cognate cytokine(s). That is, in some embodiments, gp130-mediated signalling through a polypeptide complex comprising (i) gp130 and (ii) another polypeptide of the IL-6 receptor family may be triggered by binding of a cytokine to the polypeptide complex formed by protein-protein interaction between (i) and (ii). In some embodiments, gp130-mediated signalling is triggered by binding of IL-6 to a polypeptide complex comprising gp130 and IL-6Rα (*i.e.* a gp130:IL-6Rα complex). In some embodiments, gp130-mediated signalling is triggered by binding of IL-11 to a polypeptide complex comprising gp130 and IL-11Rα (*i.e.* a gp130:IL-11Rα complex). In some embodiments, gp130-mediated signalling is triggered by binding of OSM to a polypeptide complex comprising gp130 and OSMRβ (*i.e.* a gp130:OSMRβ complex). In some embodiments, gp130-mediated signalling is triggered by binding of OSM, LIF or CT-1 to a polypeptide complex comprising gp130 and LIFRβ (*i.e.* a gp130:LIFRβ complex). In some embodiments, gp130-mediated signalling is triggered by binding of CNTF or CLC to a polypeptide complex comprising gp130, LIFRβ and CNTFRα (*i.e.* a gp130:LIFRβ:CNTFRα complex). In some embodiments, gp130-mediated signalling is triggered by binding of IL-27 to a polypeptide complex comprising gp130 and IL-27Rα (*i.e.* a gp130:IL-27Rα complex). In some embodiments, gp130-mediated signalling is triggered by binding of IL-35 to a polypeptide complex comprising gp130 and IL-12Rβ2 (*i.e.* a gp130:IL-12Rβ2 complex).

Antigen-binding molecules

The present disclosure relates to the therapeutic and prophylactic use of antigen-binding molecules capable of binding to gp130. An antigen-binding molecule that is capable of binding to gp130 may also be described as an antigen-binding molecule that binds to gp130.

An 'antigen-binding molecule' refers to a molecule that binds to a given target antigen. Antigen-binding molecules include antibodies (*i.e.* immunoglobulins (Igs)) and antigen-binding fragments thereof. As used herein, 'antibodies' include monoclonal antibodies, polyclonal antibodies, monospecific and multispecific (*e.g.*, bispecific, trispecific, *etc.*) antibodies, and antibody-derived antigen-binding molecules such as scFv, scFab, diabodies, triabodies, scFv-Fc, minibodies, single domain antibodies (*e.g.* VhH), *etc.* Antigen-binding fragments of antibodies include *e.g.* Fv, Fab, $F(ab')_2$ and F(ab') fragments. In some embodiments, an antigen-binding molecule may be an antibody or an antigen-binding fragment thereof.

Antigen-binding molecules according to the present disclosure also include antibody-derived molecules, *e.g.* molecules comprising an antigen-binding region/domain derived from an antibody. Antibody-derived antigen-binding molecules may comprise an antigen-binding region/domain that comprises, or consists of, the antigen-binding region of an antibody (*e.g.* an antigen-binding fragment of an antibody). In some embodiments, the antigen-binding region/domain of an antibody-derived antigen-binding molecule may be or comprise the Fv (*e.g.* provided as an scFv or dsFv) or the Fab region of an antibody, or the whole antibody. For example, antigen-binding molecules according to the present disclosure include antibody-drug conjugates (ADCs) comprising a (cytotoxic) drug moiety (*e.g.* as described hereinbelow). Antigen-binding molecules according to the present disclosure also include multispecific antigen-binding molecules such as immune cell engager molecules comprising a domain for recruiting (effector) immune cells (reviewed *e.g.* in Goebeler and Bargou, Nat. Rev. Clin. Oncol. (2020) 17: 418–434 and Ellerman, Methods (2019) 154:102-117, both of which are hereby incorporated by reference in their entirety), including BiTEs, BiKEs and TriKEs. Antigen-binding molecules according to the present disclosure also include chimeric antigen receptors (CARs), which are recombinant receptors providing both antigen-binding and T cell activating functions (CAR structure, function and engineering is reviewed *e.g.* in Dotti *et al.*, Immunol Rev (2014) 257(1) and Jayaraman *et al.*, EBioMedicine (2020) 58:102931, both of which are hereby incorporated by reference in their entirety).

The antigen-binding molecule of the present disclosure comprises a moiety or moieties capable of binding to a target antigen(s). In some embodiments, the moiety capable of binding to a target antigen comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL) of an antibody capable of specific binding to the target antigen. In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an aptamer capable of binding to the target antigen, *e.g.* a nucleic acid aptamer (reviewed, for example, in Zhou and Rossi Nat Rev Drug Discov. 2017 16(3):181-202). In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an antigen-binding peptide/polypeptide, *e.g.* a peptide aptamer, thioredoxin, monobody, anticalin, Kunitz domain, avimer, knottin, fynomer, atrimer, DARPin, affibody, nanobody (*i.e.* a single-

domain antibody (sdAb)), affilin, armadillo repeat protein (ArmRP), OBody or fibronectin – reviewed *e.g.* in Reverdatto *et al.*, Curr Top Med Chem. 2015; 15(12): 1082–1101, which is hereby incorporated by reference in its entirety (see also *e.g.* Boersma *et al.*, J Biol Chem (2011) 286:41273-85 and Emanuel *et al.*, Mabs (2011) 3:38-48).

As used herein, a 'peptide' refers to a chain of two or more amino acid monomers linked by peptide bonds. A peptide typically has a length in the region of about 2 to 50 amino acids. A 'polypeptide' is a polymer chain of two or more peptides. Polypeptides typically have a length greater than about 50 amino acids.

The antigen-binding molecules of the present disclosure generally comprise an antigen-binding domain comprising a VH and a VL of an antibody capable of specific binding to the target antigen. The antigen-binding domain formed by a VH and a VL may also be referred to herein as an Fv region.

An antigen-binding molecule may be, or may comprise, an antigen-binding polypeptide, or an antigen-binding polypeptide complex. An antigen-binding molecule may comprise more than one polypeptide which together form an antigen-binding domain. The polypeptides may associate covalently or non-covalently. In some embodiments, the polypeptides form part of a larger polypeptide comprising the polypeptides (*e.g.* in the case of scFv comprising VH and VL, or in the case of scFab comprising VH-CH1 and VL-CL).

An antigen-binding molecule may refer to a non-covalent or covalent complex of more than one polypeptide (*e.g.* 2, 3, 4, 6, or 8 polypeptides), *e.g.* an IgG-like antigen-binding molecule comprising two heavy chain polypeptides and two light chain polypeptides.

The antigen-binding molecules of the present disclosure may be designed and prepared using the sequences of monoclonal antibodies (mAbs) capable of binding to a given target antigen (*e.g.* gp130 or an angiogenic factor). Antigen-binding regions of antibodies, such as single chain variable fragment (scFv), Fab and $F(ab')_2$ fragments may also be used/provided. An 'antigen-binding region' is any fragment of an antibody that binds to the target for which the given antibody is specific.

Antibodies generally comprise six complementarity-determining regions CDRs; three in the heavy chain variable (VH) region: HC-CDR1, HC-CDR2 and HC-CDR3, and three in the light chain variable (VL) region: LC-CDR1, LC-CDR2, and LC-CDR3. The six CDRs together define the paratope of the antibody, which is the part of the antibody that binds to the target antigen.

The VH region and VL region comprise framework regions (FRs) either side of each CDR, which provide a scaffold for the CDRs. From N-terminus to C-terminus, VH regions comprise the following structure: N term-[HC-FR1]-[HC-CDR1]-[HC-FR2]-[HC-CDR2]-[HC-FR3]-[HC-CDR3]-[HC-FR4]-C term; and VL regions comprise the following structure: N term-[LC-FR1]-[LC-CDR1]-[LC-FR2]-[LC-CDR2]-[LC-FR3]-[LC-CDR3]-[LC-FR4]-C term.

There are several different conventions for defining antibody CDRs and FRs, such as those described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991), Chothia *et al.*, J. Mol. Biol. 196:901-917 (1987), and VBASE2, as described in Retter *et al.*, Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674. The CDRs and FRs of the VH regions and VL regions of the antibody clones described herein were defined according to the international IMGT (ImMunoGeneTics) information system (LeFranc *et al.*, Nucleic Acids Res. (2015) 43 (Database issue):D413-22), which uses the IMGT V-DOMAIN numbering rules as described in Lefranc *et al.*, Dev. Comp. Immunol. (2003) 27:55-77. In preferred embodiments, the CDRs and FRs of antigen-binding molecules referred to herein are defined according to the IMGT information system.

In some embodiments, the antigen-binding molecule comprises the CDRs of an antigen-binding molecule that binds to gp130. In some embodiments, the antigen-binding molecule comprises the FRs of an antigen-binding molecule that binds to gp130. In some embodiments, the antigen-binding molecule comprises the CDRs and the FRs of an antigen-binding molecule that binds to gp130. That is, in some embodiments, the antigen-binding molecule comprises the VH region and the VL region of an antigen-binding molecule that binds to gp130.

In some embodiments, the antigen-binding molecule comprises the CDRs, FRs and/or the VH and/or VL regions of a gp130-binding antibody described herein, or CDRs, FRs and/or VH and/or VL regions which are derived from those of a gp130-binding antibody described herein. In some embodiments, a gp130-binding antibody is selected from an antibody of Table C herein.

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(1) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:2

HC-CDR2 having the amino acid sequence of SEQ ID NO:3

HC-CDR3 having the amino acid sequence of SEQ ID NO:4,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:18

HC-CDR2 having the amino acid sequence of SEQ ID NO:19

HC-CDR3 having the amino acid sequence of SEQ ID NO:20,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(3) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:113
HC-FR2 having the amino acid sequence of SEQ ID NO:114
HC-FR3 having the amino acid sequence of SEQ ID NO:115
HC-FR4 having the amino acid sequence of SEQ ID NO:116,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(4) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:118
HC-FR2 having the amino acid sequence of SEQ ID NO:119
HC-FR3 having the amino acid sequence of SEQ ID NO:120
HC-FR4 having the amino acid sequence of SEQ ID NO:24,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(5) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:5
HC-FR2 having the amino acid sequence of SEQ ID NO:6
HC-FR3 having the amino acid sequence of SEQ ID NO:7
HC-FR4 having the amino acid sequence of SEQ ID NO:8,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(6) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:95
HC-FR2 having the amino acid sequence of SEQ ID NO:96
HC-FR3 having the amino acid sequence of SEQ ID NO:97
HC-FR4 having the amino acid sequence of SEQ ID NO:24,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(7) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:99
HC-FR2 having the amino acid sequence of SEQ ID NO:100
HC-FR3 having the amino acid sequence of SEQ ID NO:101
HC-FR4 having the amino acid sequence of SEQ ID NO:24,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(8) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:99

HC-FR2 having the amino acid sequence of SEQ ID NO:175

HC-FR3 having the amino acid sequence of SEQ ID NO:101

HC-FR4 having the amino acid sequence of SEQ ID NO:24,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(9) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:21

HC-FR2 having the amino acid sequence of SEQ ID NO:22

HC-FR3 having the amino acid sequence of SEQ ID NO:23

HC-FR4 having the amino acid sequence of SEQ ID NO:24,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VH region comprising the CDRs according to (1) or (2) above, and the FRs according to (3), (4), (5), (6), (7), (8) or (9) above.

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(10) a VH region comprising the CDRs according to (1) and the FRs according to (3).

(11) a VH region comprising the CDRs according to (1) and the FRs according to (4).

(12) a VH region comprising the CDRs according to (1) and the FRs according to (5).

(13) a VH region comprising the CDRs according to (1) and the FRs according to (6).

(14) a VH region comprising the CDRs according to (1) and the FRs according to (7).

(15) a VH region comprising the CDRs according to (1) and the FRs according to (8).

(16) a VH region comprising the CDRs according to (2) and the FRs according to (9).

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(17) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:112.

(18) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:117.

(19) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:1.

(20) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:94.

(21) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:98.

(22) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:174.

(23) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:17.

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(24) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:10
LC-CDR2 having the amino acid sequence of SEQ ID NO:11
LC-CDR3 having the amino acid sequence of SEQ ID NO:12,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(25) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:10
LC-CDR2 having the amino acid sequence of SEQ ID NO:149
LC-CDR3 having the amino acid sequence of SEQ ID NO:12,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(26) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:10

LC-CDR2 having the amino acid sequence of SEQ ID NO:162

LC-CDR3 having the amino acid sequence of SEQ ID NO:12,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(27) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:26

LC-CDR2 having the amino acid sequence of SEQ ID NO:27

LC-CDR3 having the amino acid sequence of SEQ ID NO:28,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(28) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:122

LC-FR2 having the amino acid sequence of SEQ ID NO:123

LC-FR3 having the amino acid sequence of SEQ ID NO:124

LC-FR4 having the amino acid sequence of SEQ ID NO:125,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(29) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:127

LC-FR2 having the amino acid sequence of SEQ ID NO:128

LC-FR3 having the amino acid sequence of SEQ ID NO:129

LC-FR4 having the amino acid sequence of SEQ ID NO:105,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(30) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:13

LC-FR2 having the amino acid sequence of SEQ ID NO:14

LC-FR3 having the amino acid sequence of SEQ ID NO:15
LC-FR4 having the amino acid sequence of SEQ ID NO:16,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(31) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:103
LC-FR2 having the amino acid sequence of SEQ ID NO:14
LC-FR3 having the amino acid sequence of SEQ ID NO:104
LC-FR4 having the amino acid sequence of SEQ ID NO:105,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(32) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:107
LC-FR2 having the amino acid sequence of SEQ ID NO:14
LC-FR3 having the amino acid sequence of SEQ ID NO:108
LC-FR4 having the amino acid sequence of SEQ ID NO:105,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(33) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:107
LC-FR2 having the amino acid sequence of SEQ ID NO:110
LC-FR3 having the amino acid sequence of SEQ ID NO:111
LC-FR4 having the amino acid sequence of SEQ ID NO:105,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(34) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:29
LC-FR2 having the amino acid sequence of SEQ ID NO:30
LC-FR3 having the amino acid sequence of SEQ ID NO:31
LC-FR4 having the amino acid sequence of SEQ ID NO:32,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VL region comprising the CDRs according to (24), (25), (26) or (27) above, and the FRs according to (28), (29), (30), (31), (32), (33) or (34) above.

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(35) a VL region comprising the CDRs according to (24) and the FRs according to (28).

(36) a VL region comprising the CDRs according to (24) and the FRs according to (29).

(37) a VL region comprising the CDRs according to (24) and the FRs according to (30).

(38) a VL region comprising the CDRs according to (24) and the FRs according to (31).

(39) a VL region comprising the CDRs according to (24) and the FRs according to (32).

(40) a VL region comprising the CDRs according to (24) and the FRs according to (33).

(41) a VL region comprising the CDRs according to (25) and the FRs according to (28).

(42) a VL region comprising the CDRs according to (25) and the FRs according to (29).

(43) a VL region comprising the CDRs according to (25) and the FRs according to (30).

(44) a VL region comprising the CDRs according to (25) and the FRs according to (31).

(45) a VL region comprising the CDRs according to (25) and the FRs according to (32).

(46) a VL region comprising the CDRs according to (25) and the FRs according to (33).

(47) a VL region comprising the CDRs according to (26) and the FRs according to (28).

(48) a VL region comprising the CDRs according to (26) and the FRs according to (29).

(49) a VL region comprising the CDRs according to (26) and the FRs according to (30).

(50) a VL region comprising the CDRs according to (26) and the FRs according to (31).

(51) a VL region comprising the CDRs according to (26) and the FRs according to (32).

(52) a VL region comprising the CDRs according to (26) and the FRs according to (33).

(53) a VL region comprising the CDRs according to (27) and the FRs according to (34).

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(54) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:121.

(55) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:126.

(56) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:9.

(57) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:102.

(58) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:106.

(59) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:109.

(60) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:147.

(61) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:148.

(62) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:143.

(63) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:144.

(64) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:145.

(65) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:146.

(66) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:160.

(67) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:161.

68) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:156.

(69) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:157.

(70) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:158.

(71) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:159.

(72) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:25.

In some embodiments, the antigen-binding molecule comprises a VH region according to any one of (1) to (23) above, and a VL region according to any one of (24) to (72) above.

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(73) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:240

HC-CDR2 having the amino acid sequence of SEQ ID NO:241
HC-CDR3 having the amino acid sequence of SEQ ID NO:242,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(74) a VH region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:380
HC-CDR3 having the amino acid sequence of SEQ ID NO:182,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(75) a VH region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:181
HC-CDR3 having the amino acid sequence of SEQ ID NO:182,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(76) a VH region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:375
HC-CDR3 having the amino acid sequence of SEQ ID NO:182,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(77) a VH region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:376
HC-CDR3 having the amino acid sequence of SEQ ID NO:182,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(78) a VH region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:377
HC-CDR3 having the amino acid sequence of SEQ ID NO:182,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(79) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180

HC-CDR2 having the amino acid sequence of SEQ ID NO:378

HC-CDR3 having the amino acid sequence of SEQ ID NO:182,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(80) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180

HC-CDR2 having the amino acid sequence of SEQ ID NO:379

HC-CDR3 having the amino acid sequence of SEQ ID NO:182,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(81) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:196

HC-CDR2 having the amino acid sequence of SEQ ID NO:197

HC-CDR3 having the amino acid sequence of SEQ ID NO:198,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(82) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:196

HC-CDR2 having the amino acid sequence of SEQ ID NO:197

HC-CDR3 having the amino acid sequence of SEQ ID NO:210,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(83) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:215

HC-CDR2 having the amino acid sequence of SEQ ID NO:216

HC-CDR3 having the amino acid sequence of SEQ ID NO:217,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

(84) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:230

HC-CDR2 having the amino acid sequence of SEQ ID NO:231

HC-CDR3 having the amino acid sequence of SEQ ID NO:232,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1, and/or in which 1 or 2 or 3 amino acids in HC-CDR2, and/or in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(85) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:246

HC-FR2 having the amino acid sequence of SEQ ID NO:184

HC-FR3 having the amino acid sequence of SEQ ID NO:247

HC-FR4 having the amino acid sequence of SEQ ID NO:186,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(86) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:281

HC-FR2 having the amino acid sequence of SEQ ID NO:282

HC-FR3 having the amino acid sequence of SEQ ID NO:283

HC-FR4 having the amino acid sequence of SEQ ID NO:257,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(87) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:254

HC-FR2 having the amino acid sequence of SEQ ID NO:184

HC-FR3 having the amino acid sequence of SEQ ID NO:255

HC-FR4 having the amino acid sequence of SEQ ID NO:257,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(88) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:254

HC-FR2 having the amino acid sequence of SEQ ID NO:259
HC-FR3 having the amino acid sequence of SEQ ID NO:260
HC-FR4 having the amino acid sequence of SEQ ID NO:257,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(89) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:262
HC-FR2 having the amino acid sequence of SEQ ID NO:259
HC-FR3 having the amino acid sequence of SEQ ID NO:263
HC-FR4 having the amino acid sequence of SEQ ID NO:257,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(90) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:254
HC-FR2 having the amino acid sequence of SEQ ID NO:259
HC-FR3 having the amino acid sequence of SEQ ID NO:255
HC-FR4 having the amino acid sequence of SEQ ID NO:257,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(91) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:254
HC-FR2 having the amino acid sequence of SEQ ID NO:184
HC-FR3 having the amino acid sequence of SEQ ID NO:260
HC-FR4 having the amino acid sequence of SEQ ID NO:257,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(92) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:183
HC-FR2 having the amino acid sequence of SEQ ID NO:184
HC-FR3 having the amino acid sequence of SEQ ID NO:185
HC-FR4 having the amino acid sequence of SEQ ID NO:186,
or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(93) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:199

HC-FR2 having the amino acid sequence of SEQ ID NO:184

HC-FR3 having the amino acid sequence of SEQ ID NO:200

HC-FR4 having the amino acid sequence of SEQ ID NO:186,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(94) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:199

HC-FR2 having the amino acid sequence of SEQ ID NO:184

HC-FR3 having the amino acid sequence of SEQ ID NO:211

HC-FR4 having the amino acid sequence of SEQ ID NO:186,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(95) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:218

HC-FR2 having the amino acid sequence of SEQ ID NO:219

HC-FR3 having the amino acid sequence of SEQ ID NO:220

HC-FR4 having the amino acid sequence of SEQ ID NO:221,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

(96) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:233

HC-FR2 having the amino acid sequence of SEQ ID NO:219

HC-FR3 having the amino acid sequence of SEQ ID NO:234

HC-FR4 having the amino acid sequence of SEQ ID NO:221,

or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1, and/or in which 1 or 2 or 3 amino acids in HC-FR2, and/or in which 1 or 2 or 3 amino acids in HC-FR3, and/or in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VH region comprising the CDRs according to one of (73) to (84) above, and the FRs according to any one of (85) to (96) above.

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(97) a VH region comprising the CDRs according to (73) and the FRs according to (85).

(98) a VH region comprising the CDRs according to (74) and the FRs according to (86).

(99) a VH region comprising the CDRs according to (75) and the FRs according to (86).

(100) a VH region comprising the CDRs according to (75) and the FRs according to (87).

(101) a VH region comprising the CDRs according to (75) and the FRs according to (88).

(102) a VH region comprising the CDRs according to (75) and the FRs according to (89).

(103) a VH region comprising the CDRs according to (75) and the FRs according to (90).

(104) a VH region comprising the CDRs according to (75) and the FRs according to (91).

(105) a VH region comprising the CDRs according to (75) and the FRs according to (92).

(106) a VH region comprising the CDRs according to (76) and the FRs according to (86).

(107) a VH region comprising the CDRs according to (76) and the FRs according to (87).

(108) a VH region comprising the CDRs according to (76) and the FRs according to (88).

(109) a VH region comprising the CDRs according to (76) and the FRs according to (89).

(110) a VH region comprising the CDRs according to (76) and the FRs according to (90).

(111) a VH region comprising the CDRs according to (76) and the FRs according to (91).

(112) a VH region comprising the CDRs according to (76) and the FRs according to (92).

(113) a VH region comprising the CDRs according to (77) and the FRs according to (86).

(114) a VH region comprising the CDRs according to (77) and the FRs according to (87).

(115) a VH region comprising the CDRs according to (77) and the FRs according to (88).

(116) a VH region comprising the CDRs according to (77) and the FRs according to (89).

(117) a VH region comprising the CDRs according to (77) and the FRs according to (90).

(118) a VH region comprising the CDRs according to (77) and the FRs according to (91).

(119) a VH region comprising the CDRs according to (77) and the FRs according to (92).

(120) a VH region comprising the CDRs according to (78) and the FRs according to (86).

(121) a VH region comprising the CDRs according to (78) and the FRs according to (87).

(122) a VH region comprising the CDRs according to (78) and the FRs according to (88).

(123) a VH region comprising the CDRs according to (78) and the FRs according to (89).

(124) a VH region comprising the CDRs according to (78) and the FRs according to (90).

(125) a VH region comprising the CDRs according to (78) and the FRs according to (91).

(126) a VH region comprising the CDRs according to (78) and the FRs according to (92).

(127) a VH region comprising the CDRs according to (79) and the FRs according to (86).

(128) a VH region comprising the CDRs according to (79) and the FRs according to (97).

(129) a VH region comprising the CDRs according to (79) and the FRs according to (88).

(130) a VH region comprising the CDRs according to (79) and the FRs according to (89).

(131) a VH region comprising the CDRs according to (79) and the FRs according to (90).

(132) a VH region comprising the CDRs according to (79) and the FRs according to (91).

(133) a VH region comprising the CDRs according to (79) and the FRs according to (92).

(134) a VH region comprising the CDRs according to (80) and the FRs according to (86).

(135) a VH region comprising the CDRs according to (80) and the FRs according to (87).

(136) a VH region comprising the CDRs according to (80) and the FRs according to (88).

(137) a VH region comprising the CDRs according to (80) and the FRs according to (89).

(138) a VH region comprising the CDRs according to (80) and the FRs according to (90).

(139) a VH region comprising the CDRs according to (80) and the FRs according to (91).

(140) a VH region comprising the CDRs according to (80) and the FRs according to (92).

(141) a VH region comprising the CDRs according to (81) and the FRs according to (93).

(142) a VH region comprising the CDRs according to (82) and the FRs according to (94).

(143) a VH region comprising the CDRs according to (83) and the FRs according to (95).

(144) a VH region comprising the CDRs according to (84) and the FRs according to (96).

In some embodiments, the antigen-binding molecule comprises a VH region according to one of:

(145) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:252.

(146) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:284.

(147) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:381.

(148) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:256.

(149) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:258.

(150) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:261.

(151) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:179.

(152) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:345.

(153) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:346.

(154) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:347.

(155) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:348.

(156) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:349.

(157) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:350.

(158) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:351.

(159) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:352.

(160) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:353.

(161) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:354.

(162) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:355.

(163) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:356.

(164) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:357.

(165) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:358.

(166) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:359.

(167) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:360.

(168) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:361.

(169) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:362.

(170) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:363.

(171) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:364.

(172) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:365.

(173) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:366.

(174) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:367.

(175) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:368.

(176) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:369.

(177) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:370.

(178) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:371.

(179) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:372.

(180) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:373.

(181) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:374.

(182) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:195.

(183) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:209.

(184) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:214.

(185) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:229.

(186) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:264.

(187) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:265.

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(188) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:243

LC-CDR2 having the amino acid sequence of SEQ ID NO:244

LC-CDR3 having the amino acid sequence of SEQ ID NO:245,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(189) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:417,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(190) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:190,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(191) a VL region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:412,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(192) a VL region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:413,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(193) a VL region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:414,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(194) a VL region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:415,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(195) a VL region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:416,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(196) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:202

LC-CDR2 having the amino acid sequence of SEQ ID NO:203

LC-CDR3 having the amino acid sequence of SEQ ID NO:204,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(197) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:202

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:190,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(198) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:223

LC-CDR2 having the amino acid sequence of SEQ ID NO:224

LC-CDR3 having the amino acid sequence of SEQ ID NO:225,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

(199) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:202

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:236,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1, and/or in which 1 or 2 or 3 amino acids in LC-CDR2, and/or in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(200) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:248

LC-FR2 having the amino acid sequence of SEQ ID NO:249

LC-FR3 having the amino acid sequence of SEQ ID NO:250

LC-FR4 having the amino acid sequence of SEQ ID NO:251,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(201) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:285

LC-FR2 having the amino acid sequence of SEQ ID NO:286

LC-FR3 having the amino acid sequence of SEQ ID NO:287

LC-FR4 having the amino acid sequence of SEQ ID NO:268,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(202) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:267

LC-FR2 having the amino acid sequence of SEQ ID NO:192

LC-FR3 having the amino acid sequence of SEQ ID NO:193

LC-FR4 having the amino acid sequence of SEQ ID NO:268,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(203) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:270

LC-FR2 having the amino acid sequence of SEQ ID NO:271

LC-FR3 having the amino acid sequence of SEQ ID NO:193

LC-FR4 having the amino acid sequence of SEQ ID NO:268,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(204) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:272

LC-FR2 having the amino acid sequence of SEQ ID NO:271

LC-FR3 having the amino acid sequence of SEQ ID NO:274

LC-FR4 having the amino acid sequence of SEQ ID NO:268,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(205) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:275
LC-FR2 having the amino acid sequence of SEQ ID NO:271
LC-FR3 having the amino acid sequence of SEQ ID NO:277
LC-FR4 having the amino acid sequence of SEQ ID NO:268,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(206) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:279
LC-FR2 having the amino acid sequence of SEQ ID NO:271
LC-FR3 having the amino acid sequence of SEQ ID NO:280
LC-FR4 having the amino acid sequence of SEQ ID NO:268,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(207) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:191
LC-FR2 having the amino acid sequence of SEQ ID NO:192
LC-FR3 having the amino acid sequence of SEQ ID NO:193
LC-FR4 having the amino acid sequence of SEQ ID NO:194,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(208) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:205
LC-FR2 having the amino acid sequence of SEQ ID NO:206
LC-FR3 having the amino acid sequence of SEQ ID NO:207
LC-FR4 having the amino acid sequence of SEQ ID NO:208,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(209) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:205
LC-FR2 having the amino acid sequence of SEQ ID NO:213
LC-FR3 having the amino acid sequence of SEQ ID NO:207
LC-FR4 having the amino acid sequence of SEQ ID NO:208,

or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(210) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:226
LC-FR2 having the amino acid sequence of SEQ ID NO:227
LC-FR3 having the amino acid sequence of SEQ ID NO:228
LC-FR4 having the amino acid sequence of SEQ ID NO:208,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

(211) a VL region incorporating the following FRs:
LC-FR1 having the amino acid sequence of SEQ ID NO:191
LC-FR2 having the amino acid sequence of SEQ ID NO:237
LC-FR3 having the amino acid sequence of SEQ ID NO:238
LC-FR4 having the amino acid sequence of SEQ ID NO:239,
or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1, and/or in which 1 or 2 or 3 amino acids in LC-FR2, and/or in which 1 or 2 or 3 amino acids in LC-FR3, and/or in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid.

In some embodiments, the antigen-binding molecule comprises a VL region comprising the CDRs according to any one of (188) to (199) above, and the FRs according to any one of (200) to (211) above.

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:
(212) a VL region comprising the CDRs according to (188) and the FRs according to (200).

(213) a VL region comprising the CDRs according to (189) and the FRs according to (200).

(214) a VL region comprising the CDRs according to (190) and the FRs according to (201).

(215) a VL region comprising the CDRs according to (190) and the FRs according to (202).

(216) a VL region comprising the CDRs according to (190) and the FRs according to (203).

(217) a VL region comprising the CDRs according to (190) and the FRs according to (204).

(218) a VL region comprising the CDRs according to (190) and the FRs according to (205).

(219) a VL region comprising the CDRs according to (190) and the FRs according to (206).

(220) a VL region comprising the CDRs according to (190) and the FRs according to (207).

(221) a VL region comprising the CDRs according to (191) and the FRs according to (201).

(222) a VL region comprising the CDRs according to (191) and the FRs according to (202).

(223) a VL region comprising the CDRs according to (191) and the FRs according to (203).

(224) a VL region comprising the CDRs according to (191) and the FRs according to (204).

(225) a VL region comprising the CDRs according to (191) and the FRs according to (205).

(226) a VL region comprising the CDRs according to (191) and the FRs according to (206).

(227) a VL region comprising the CDRs according to (191) and the FRs according to (207).

(228) a VL region comprising the CDRs according to (192) and the FRs according to (201).

(229) a VL region comprising the CDRs according to (192) and the FRs according to (202).

(230) a VL region comprising the CDRs according to (192) and the FRs according to (203).

(231) a VL region comprising the CDRs according to (192) and the FRs according to (204).

(232) a VL region comprising the CDRs according to (192) and the FRs according to (205).

(233) a VL region comprising the CDRs according to (192) and the FRs according to (206).

(234) a VL region comprising the CDRs according to (192) and the FRs according to (207).

(235) a VL region comprising the CDRs according to (193) and the FRs according to (201).

(236) a VL region comprising the CDRs according to (193) and the FRs according to (202).

(237) a VL region comprising the CDRs according to (193) and the FRs according to (203).

(238) a VL region comprising the CDRs according to (193) and the FRs according to (204).

(239) a VL region comprising the CDRs according to (193) and the FRs according to (205).

(240) a VL region comprising the CDRs according to (193) and the FRs according to (206).

(241) a VL region comprising the CDRs according to (193) and the FRs according to (207).

(242) a VL region comprising the CDRs according to (194) and the FRs according to (201).

(243) a VL region comprising the CDRs according to (194) and the FRs according to (202).

(244) a VL region comprising the CDRs according to (194) and the FRs according to (203).

(245) a VL region comprising the CDRs according to (194) and the FRs according to (204).

(246) a VL region comprising the CDRs according to (194) and the FRs according to (205).

(247) a VL region comprising the CDRs according to (194) and the FRs according to (206).

(248) a VL region comprising the CDRs according to (194) and the FRs according to (207).

(249) a VL region comprising the CDRs according to (195) and the FRs according to (201).

(250) a VL region comprising the CDRs according to (195) and the FRs according to (202).

(251) a VL region comprising the CDRs according to (195) and the FRs according to (203).

(252) a VL region comprising the CDRs according to (195) and the FRs according to (204).

(253) a VL region comprising the CDRs according to (195) and the FRs according to (205).

(254) a VL region comprising the CDRs according to (195) and the FRs according to (206).

(255) a VL region comprising the CDRs according to (195) and the FRs according to (207).

(256) a VL region comprising the CDRs according to (196) and the FRs according to (208).

(257) a VL region comprising the CDRs according to (197) and the FRs according to (209).

(258) a VL region comprising the CDRs according to (198) and the FRs according to (210).

(259) a VL region comprising the CDRs according to (199) and the FRs according to (211).

In some embodiments, the antigen-binding molecule comprises a VL region according to one of:

(260) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:253.

(261) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:288.

(262) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:266.

(263) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:269.

(264) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:273.

(265) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:276.

(266) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:278.

(267) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:187.

(268) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:382.

(269) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:383.

(270) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:384.

(271) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:385.

(272) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:386.

(273) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:387.

(274) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:388.

(275) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:389.

(276) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:390.

(277) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:391.

(278) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:392.

(279) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:393.

(280) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:394.

(281) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:395.

(282) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:396.

(283) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:397.

(284) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:398.

(285) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:399.

(286) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:400.

(287) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:401.

(288) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:402.

(289) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:403.

(290) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:404.

(291) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:405.

(292) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:406.

(293) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:407.

(294) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:408.

(295) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:409.

(296) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:410.

(297) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:411.

(298) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:201.

(299) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:212.

(300) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:222.

(301) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:235.

In some embodiments, the antigen-binding molecule comprises a VH region according to any one of (73) to (187) above, and a VL region according to any one of (188) to (301) above.

In some embodiments, a VH according to any one of (145) to (181) comprises an amino acid other than 'D' at the position corresponding to position 54 of SEQ ID NO:179. In some embodiments, the amino acid other than amino acid other than 'D' is selected from 'G', 'E', 'Q' and 'L'. In some embodiments, the amino acid other than 'D' is 'G' or 'Q'.

In some embodiments, a VH according to any one of (145) to (181) comprises an amino acid other than 'G' at the position corresponding to position 55 of SEQ ID NO:179. In some embodiments, the amino acid other than amino acid other than 'G' is selected from 'G', 'A', 'L' and 'T'. In some embodiments, the amino acid other than 'G' is 'A'.

In some embodiments, a VL according to any one of (260) to (297) comprises an amino acid other than 'N' at the position corresponding to position 93 of SEQ ID NO:187. In some embodiments, the amino acid other than amino acid other than 'N' is selected from 'G', 'E', 'Q', 'L' and 'T'. In some embodiments, the amino acid other than amino acid other than 'N' is selected from 'G', 'E', 'Q' and 'L'. In some embodiments, the amino acid other than 'N' is 'Q' or 'G'.

In some embodiments, a VL according to any one of (260) to (297) comprises an amino acid other than 'G' at the position corresponding to position 94 of SEQ ID NO:187. In some embodiments, the amino acid other than amino acid other than 'G' is 'A' or 'V'. In some embodiments, the amino acid other than 'G' is 'A'.

In embodiments in accordance with the present disclosure, one or more amino acids are substituted with another amino acid. A substitution comprises substitution of an amino acid residue with a non-identical 'replacement' amino acid residue. A replacement amino acid residue of a substitution according to the present disclosure may be a naturally-occurring amino acid residue (*i.e.* encoded by the genetic code) which is non-identical to the amino acid residue at the relevant position of the equivalent, unsubstituted amino acid sequence, selected from: alanine (Ala), arginine (Arg), asparagine (Asn), aspartic acid (Asp), cysteine (Cys), glutamine (Gln), glutamic acid (Glu), glycine (Gly), histidine (His), isoleucine (Ile): leucine (Leu), lysine (Lys), methionine (Met), phenylalanine (Phe), proline (Pro), serine (Ser), threonine (Thr), tryptophan (Trp), tyrosine (Tyr), and valine (Val). In some embodiments, a replacement amino acid may be a non-naturally occurring amino acid residue – *i.e.* an amino acid residue other than those recited in the preceding sentence. Examples of non-naturally occurring amino acid residues include norleucine, ornithine, norvaline, homoserine, aib, and other amino acid residue analogues such as those described in Ellman, *et al.*, Meth. Enzym. 202 (1991) 301-336.

In some embodiments, a substitution may be biochemically conservative. In some embodiments, where an amino acid to be substituted is provided in one of rows 1 to 5 of the table below, the replacement amino acid of the substitution is another, non-identical amino acid provided in the same row:

Row	Shared property	Amino acids
1	Hydrophobic	Met, Ala, Val, Leu, Ile, Trp, Tyr, Phe, Norleucine
2	Neutral hydrophilic	Cys, Ser, Thr, Asn, Gln
3	Acidic or negatively-charged	Asp, Glu
4	Basic or positively-charged	His, Lys, Arg
5	Orientation influencing	Gly, Pro

By way of illustration, in some embodiments wherein substitution is of a Met residue, the replacement amino acid may be selected from Ala, Val, Leu, Ile, Trp, Tyr, Phe and Norleucine.

In some embodiments, a replacement amino acid in a substitution may have the same side chain polarity as the amino acid residue it replaces. In some embodiments, a replacement amino acid in a substitution may have the same side chain charge (at pH 7.4) as the amino acid residue it replaces:

Amino Acid	Side-chain polarity	Side-chain charge (pH 7.4)
Alanine	nonpolar	neutral
Arginine	basic polar	positive
Asparagine	polar	neutral
Aspartic acid	acidic polar	negative
Cysteine	nonpolar	neutral
Glutamic acid	acidic polar	negative
Glutamine	polar	neutral
Glycine	nonpolar	neutral
Histidine	basic polar	positive (10%) neutral (90%)
Isoleucine	nonpolar	neutral
Leucine	nonpolar	neutral
Lysine	basic polar	positive
Methionine	nonpolar	neutral
Phenylalanine	nonpolar	neutral
Proline	nonpolar	neutral
Serine	polar	neutral
Threonine	polar	neutral
Tryptophan	nonpolar	neutral
Tyrosine	polar	neutral

Amino Acid	Side-chain polarity	Side-chain charge (pH 7.4)
Valine	nonpolar	neutral

That is, in some embodiments, a nonpolar amino acid is substituted with another, non-identical nonpolar amino acid. In some embodiments, a polar amino acid is substituted with another, non-identical polar amino acid. In some embodiments, an acidic polar amino acid is substituted with another, non-identical acidic polar amino acid. In some embodiments, a basic polar amino acid is substituted with another, non-identical basic polar amino acid. In some embodiments, a neutral amino acid is substituted with another, non-identical neutral amino acid. In some embodiments, a positive amino acid is substituted with another, non-identical positive amino acid. In some embodiments, a negative amino acid is substituted with another, non-identical negative amino acid.

In some embodiments, substitution(s) may be functionally conservative. That is, in some embodiments, the substitution may not affect (or may not substantially affect) one or more functional properties (*e.g.* target binding) of the antigen-binding molecule comprising the substitution as compared to the equivalent unsubstituted molecule.

In some embodiments, a VL region according to the present disclosure comprises a LC-CDR2 according to SEQ ID NO:11, comprising substitution of D at position 1 of SEQ ID NO:11 with another amino acid.

In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106 or 109, wherein the VL region comprises substitution of D at position 50 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 50 of SEQ ID NO:9) with another amino acid.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139 or 140, wherein the polypeptide comprises substitution of D at position 50 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 50 of SEQ ID NO:66) with another amino acid.

In some embodiments in accordance with the preceding three paragraphs, D is substituted with A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q. In some embodiments, D is substituted with A, E, N, C, G, I, L, M, F, P, S, T, W, Y or V. In some embodiments, D is substituted with A or E. In some embodiments, D is substituted with A.

In some embodiments, a VL region according to the present disclosure comprises a LC-FR3 having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or greater amino

acid sequence identity to SEQ ID NO:124, 129, 15, 104, 108 or 111, wherein the amino acid at the position corresponding to position 30 of SEQ ID NO:15 is D.

In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 147, 148, 143, 144, 145, 146, 160, 161, 156, 157, 158 or 159 (*e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, or 109; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:147, 148, 143, 144, 145 or 146; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:160, 161, 156, 157, 158 or 159), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:9) is D.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 154, 155, 150, 151, 152, 153, 167, 168, 163, 164, 165 or 166 (*e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139 or 140; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:154, 155, 150, 151, 152 or 153; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:167, 168, 163, 164, 165 or 166), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:66) is D.

In some embodiments, a VL region according to the present disclosure comprises a LC-FR3 having at least 60%, preferably one of 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or greater amino acid sequence identity to SEQ ID NO:124, 129, 15, 104, 108 or 111, wherein the amino acid at the position corresponding to position 30 of SEQ ID NO:15 is D, and wherein the amino acid sequence comprises one or more (*e.g.* one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14) amino acid substitutions relative to the reference amino acid sequence (*i.e.* the amino acid sequence selected from SEQ ID NO:124, 129, 15, 104, 108 and 111), wherein the one or more amino acid substitutions are provided at the position(s) corresponding to the following positions of the reference sequence: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36 (that is, the one or more amino acid substitutions are provided within the 8 positions immediately N-terminal to (in the context of the amino acid sequence of the LC-FR3) position 30, and/or are provided within the 6 positions immediately C-terminal to position 30).

In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 147, 148, 143, 144, 145, 146, 160, 161, 156, 157, 158 or 159 (*e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, or 109; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:147, 148, 143, 144, 145 or 146; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:160, 161, 156, 157, 158 or 159), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:9) is D, and wherein the amino acid sequence comprises one or more (*e.g.* one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16) amino acid substitutions relative to the reference amino acid sequence, wherein the one or more amino acid substitutions are provided at the position(s) corresponding to the following positions of the reference sequence: 74, 75, 76, 77, 78, 79, 80, 81, 83, 84, 85, 86, 87, 88, 89, 90 (that is, the one or more amino acid substitutions are provided within the 8 positions immediately N-terminal to (in the context of the amino acid sequence of the VL region) position 82, and/or are provided within the 8 positions immediately C-terminal to position 82).

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 154, 155, 150, 151, 152, 153, 167, 168, 163, 164, 165 or 166 (*e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139 or 140; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:154, 155, 150, 151, 152 or 153; *e.g.* comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:167, 168, 163, 164, 165 or 166), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:66) is D, and wherein the amino acid sequence comprises one or more (*e.g.* one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16) amino acid substitutions relative to the reference amino acid sequence, wherein the one or more amino acid substitutions are provided at the position(s) corresponding to the following positions of the reference sequence: 74, 75, 76, 77, 78, 79, 80, 81, 83, 84, 85, 86, 87, 88, 89, 90 (that is, the one or more amino acid substitutions are provided within the 8 positions immediately N-terminal to (in the context of the amino acid sequence of the polypeptide) position 82, and/or are provided within the 8 positions immediately C-terminal to position 82).

The VH and VL region of an antigen-binding region of an antibody together constitute the Fv region. In some embodiments, the antigen-binding molecule according to the present disclosure comprises, or

consists of, an Fv region that binds to gp130. In some embodiments, the VH and VL regions of the Fv are provided as single polypeptide joined by a linker sequence, *i.e.* a single chain Fv (scFv). In some embodiments, the VH and VL regions of the Fv are provided as separate polypeptides stabilised by the introduction of one or more cysteine residues for the formation of an interchain disulfide bond, *i.e.* a disulfide stabilised Fv (dsFv).

The VL and light chain constant (CL) region, and the VH region and heavy chain constant 1 (CH1) region of an antigen-binding region of an antibody together constitute the Fab region. In some embodiments, the antigen-binding molecule comprises a Fab region comprising a VH, a CH1, a VL and a CL (*e.g.* Cκ or Cλ). In some embodiments, the Fab region comprises a polypeptide comprising a VH and a CH1 (*e.g.* a VH-CH1 fusion polypeptide), and a polypeptide comprising a VL and a CL (*e.g.* a VL-CL fusion polypeptide). In some embodiments, the Fab region comprises a polypeptide comprising a VH and a CL (*e.g.* a VH-CL fusion polypeptide) and a polypeptide comprising a VL and a CH (*e.g.* a VL-CH1 fusion polypeptide); that is, in some embodiments, the Fab region is a CrossFab region. In some embodiments, the VH, CH1, VL and CL regions of the Fab or CrossFab are provided as single polypeptide joined by linker regions, *i.e.* as a single chain Fab (scFab) or a single chain CrossFab (scCrossFab).

In some embodiments, the antigen-binding molecule described herein comprises, or consists of, a whole antibody that binds to gp130. As used herein, 'whole antibody' refers to an antibody having a structure which is substantially similar to the structure of an immunoglobulin (Ig). Different kinds of immunoglobulins and their structures are described *e.g.* in Schroeder and Cavacini J Allergy Clin Immunol. (2010) 125(202): S41-S52, which is hereby incorporated by reference in its entirety.

Immunoglobulins of type G (*i.e.* IgG) are ~150 kDa glycoproteins comprising two heavy chains and two light chains. From N- to C-terminus, the heavy chains comprise a VH followed by a heavy chain constant region comprising three constant domains (CH1, CH2, and CH3), and similarly the light chains comprise a VL followed by a CL. Depending on the heavy chain, immunoglobulins may be classed as IgG (*e.g.* IgG1, IgG2, IgG3, IgG4), IgA (*e.g.* IgA1, IgA2), IgD, IgE, or IgM. The light chain may be kappa (κ) or lambda (λ).

Herein, a 'CH2 domain' refers to an amino acid sequence corresponding to the CH2 domain of an immunoglobulin (Ig). The CH2 domain is the region of an Ig formed by positions 231 to 340 of the immunoglobulin constant domain, according to the EU numbering system (described in Edelman *et al.*, Proc Natl Acad Sci USA (1969) 63(1): 78-85). A 'CH3 domain' refers to an amino acid sequence corresponding to the CH3 domain of an immunoglobulin (Ig). The CH3 domain is the region of an Ig formed by positions 341 to 447 of the immunoglobulin constant domain, according to the EU numbering system. A 'CH2-CH3 region' refers to an amino acid sequence corresponding to the CH2 and CH3 domains of an immunoglobulin (Ig). The CH2-CH3 region is the region of an Ig formed by positions 231 to 447 of the immunoglobulin constant domain, according to the EU numbering system.

In some embodiments, the antigen-binding molecule described herein comprises, or consists of, an IgG (*e.g.* IgG1, IgG2, IgG3, IgG4), IgA (*e.g.* IgA1, IgA2), IgD, IgE, or IgM that binds to gp130.

In some embodiments, the antigen-binding molecule of the present disclosure comprises one or more regions (*e.g.* CH1, CH2, CH3, *etc.*) of an immunoglobulin heavy chain constant sequence. In some embodiments, the immunoglobulin heavy chain constant sequence is, or is derived from, the heavy chain constant sequence of an IgG (*e.g.* IgG1, IgG2, IgG3, IgG4), IgA (*e.g.* IgA1, IgA2), IgD, IgE or IgM, *e.g.* a human IgG (*e.g.* hIgG1, hIgG2, hIgG3, hIgG4), hIgA (*e.g.* hIgA1, hIgA2), hIgD, hIgE or hIgM. In some embodiments, the immunoglobulin heavy chain constant sequence is, or is derived from, the heavy chain constant sequence of a human IgG1 allotype (*e.g.* G1m1, G1m2, G1m3 or G1m17).

In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:33 or 38. In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:48 or 49. In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:41 or 50.

In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:42, 43, 46 or 47. In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:44 or 57.

In some embodiments, the antigen-binding molecule comprises a CH1 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:34 or 39. In some embodiments, the antigen-binding molecule comprises a CH1 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:51.

In some embodiments, the antigen-binding molecule comprises a hinge region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:35. In some embodiments, the antigen-binding molecule comprises a hinge region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:52 or 53.

In some embodiments, the antigen-binding molecule comprises a CH2 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:36 or 45. In some embodiments, the antigen-binding molecule comprises a CH2 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:54 or 55.

In some embodiments, the antigen-binding molecule comprises a CH3 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:37 or 40. In some embodiments, the antigen-binding molecule comprises a CH3 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:56.

It will be appreciated that CH2 and/or CH3 regions may be provided with further substitutions in accordance with modification to an Fc region of the antigen-binding molecule as described herein.

In some embodiments, the antigen-binding molecule of the present disclosure comprises one or more regions of an immunoglobulin light chain constant sequence. In some embodiments, the immunoglobulin light chain constant sequence is human immunoglobulin kappa constant (IGKC; Cκ). In some embodiments, the immunoglobulin light chain constant sequence is a human immunoglobulin lambda constant (IGLC; Cλ), *e.g.* IGLC1, IGLC2, IGLC3, IGLC6 or IGLC7.

In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:58, 59, 60, 61, 62 or 63. In preferred embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:58.

In some embodiments, the antigen-binding molecule is or comprises a monoclonal antibody, or an antigen-binding fragment thereof.

In some embodiments, the antigen-binding molecule is or comprises a fully human antibody/antibody fragment. A fully human antibody/antibody fragment may be encoded by human nucleic acid sequence(s). A fully human antibody/antibody fragment may be devoid of non-human amino acid

sequences. Commonly employed techniques for the production of fully human antibodies include (i) phage display, in which human antibody genes are expressed in phage display libraries, and (ii) production of antibodies in transgenic mice engineered to have human antibody genes (described in Park and Smolen, Advances in Protein Chemistry (2001) 56: 369-421). Briefly, in the human antibody gene-phage display technique, genes encoding the VH and VL chains are generated by PCR amplification and cloning from 'naive' human lymphocytes, and assembled into a library from which they can be expressed either as disulfide-linked Fab fragments or as single-chain Fv (scFv) fragments. The Fab- or scFv-encoding genes are fused to a surface coat protein of filamentous bacteriophage and Fab or scFv capable of binding to the target of interest can then be identified by screening the library with antigen. Molecular evolution or affinity maturation procedures can be employed to enhance the affinity of the Fab/scFv fragment. In the transgenic mouse technique, mice in which the endogenous murine Ig gene loci have been replaced by homologous recombination with their human homologues are immunised with antigen, and monoclonal antibody is prepared by conventional hybridoma technology, to yield a fully human monoclonal antibody.

In some embodiments, the antigen-binding molecule of the present disclosure is a mouse antibody/antibody fragment. In some embodiments, the antibody/antibody fragment is obtained from phage display using a human naïve antibody gene library.

In some embodiments, the antigen-binding molecule is a mouse/human chimeric antigen-binding molecule (*i.e.* an antigen-binding molecule comprising mouse antibody variable domains and human antibody constant regions). In some embodiments, the antigen-binding molecule is a humanized antigen-binding molecule (*i.e.* an antigen-binding molecule comprising variable domains derived by humanization of the variable domains of an antibody from a non-human animal, *e.g.* a mouse) comprising mouse antibody variable domains and human antibody constant regions. In some embodiments, the antigen-binding molecule comprises mouse antibody CDRs and human antibody framework and constant regions.

Mouse/human chimeric antigen-binding molecules can be prepared from mouse antibodies by the process of chimerisation, *e.g.* as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 8 thereof, in particular section 3 of Chapter 8.

Humanized antigen-binding molecules can be prepared from mouse antibodies by the process of humanization, *e.g.* as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 7 thereof, in particular section 3.1 of Chapter 7 entitled 'Antibody Humanization'. Techniques for antibody humanization are also described *e.g.* in Safdari *et al.*, Biotechnol Genet Eng Rev (2013) 29:175-86.

Aspects of the present disclosure relate to multispecific antigen-binding molecules. By 'multispecific' it is meant that the antigen-binding molecule displays specific binding to more than one target. In some embodiments, the antigen-binding molecule is a bispecific antigen-binding molecule. In some

embodiments, the antigen-binding molecule comprises at least two different antigen-binding domains (*i.e.* at least two antigen-binding domains, *e.g.* comprising non-identical VHs and VLs).

In some embodiments, the antigen-binding molecule binds to gp130 and another target (*e.g.* an antigen other than gp130), and so is at least bispecific. The term 'bispecific' means that the antigen-binding molecule is able to bind specifically to at least two distinct antigenic determinants.

It will be appreciated that an antigen-binding molecule according to the present disclosure (*e.g.* a multispecific antigen-binding molecule) may comprise antigen-binding molecules capable of binding to the targets for which the antigen-binding molecule is specific. For example, an antigen-binding molecule that binds to gp130 and an antigen other than gp130 may comprise: (i) an antigen-binding molecule that binds to gp130, and (ii) an antigen-binding molecule that binds to an antigen other than gp130.

It will also be appreciated that an antigen-binding molecule according to the present disclosure (*e.g.* a multispecific antigen-binding molecule) may comprise antigen-binding polypeptides or antigen-binding polypeptide complexes capable of binding to the targets for which the antigen-binding molecule is specific.

In some embodiments, a component antigen-binding molecule of a larger antigen-binding molecule (*e.g.* a multispecific antigen-binding molecule) may be referred to *e.g.* as an 'antigen-binding domain' or 'antigen-binding region' of the larger antigen-binding molecule.

In some embodiments, the antigen other than gp130 in a multispecific antigen-binding molecule is an angiogenic factor as described herein. In some embodiments, the antigen is selected from: a member of the vascular endothelial growth factor (VEGF) family, a angiopoietin, a transforming growth factor (TGF), platelet-derived growth factor, tumour necrosis factor-α, an interleukins and a member of the fibroblast growth factor (FGF) family. In some embodiments the antigen other than gp130 is VEGF. In some embodiments, an antigen-binding molecule according to the present invention is a multispecific (e.g. bispecific) antigen-binding molecule comprising a gp130-binding domain, and an angiogenic factor-binding domain.

In some embodiments, the antigen-binding molecule is an immune cell engager. Immune cell engagers are reviewed *e.g.* in Goebeler and Bargou, Nat. Rev. Clin. Oncol. (2020) 17: 418–434 and Ellerman, Methods (2019) 154:102-117, both of which are hereby incorporated by reference in their entirety. Immune cell engager molecules comprise an antigen-binding region for a target antigen of interest, and an antigen-binding region for recruiting/engaging an immune cell of interest. Immune cell engagers recruit/engage immune cells through an antigen-binding region specific for an immune cell surface molecule.

The best studied immune cell engagers are bispecific T cell engagers (BiTEs), which comprise a target antigen binding domain, and a CD3 polypeptide (typically CD3ε)-binding domain, through which the BiTE recruits T cells. Binding of the BiTE to its target antigen and to the CD3 polypeptide expressed by the T

cell results in activation of the T cell, and ultimately directs T cell effector activity against cells expressing the target antigen. Other kinds of immune cell engagers are well known in the art, and include natural killer cell engagers such as bispecific killer engagers (BiKEs), which recruit and activate NK cells.

In some embodiments, the immune cell engaged by the immune cell engager is a T cell or an NK cell. In some embodiments, the immune cell engager is a T cell-engager.

Multispecific antigen-binding molecules according to the present disclosure may be provided in any suitable format, such as those formats described in described in Brinkmann and Kontermann, MAbs (2017) 9(2): 182-212, which is hereby incorporated by reference in its entirety. Suitable formats include those shown in Figure 2 of Brinkmann and Kontermann, MAbs (2017) 9(2): 182-212: antibody conjugates, *e.g.* IgG_2, $F(ab')_2$ or CovX-Body; IgG or IgG-like molecules, *e.g.* IgG, chimeric IgG, κλ-body common HC; CH1/CL fusion proteins, *e.g.* scFv2-CH1/CL, VHH2-CH1/CL; 'variable domain only' bispecific antigen-binding molecules, *e.g.* tandem scFv (taFV), triplebodies, diabodies (Db), dsDb, Db(kih), DART, scDB, dsFv-dsFv, tandAbs, triple heads, tandem dAb/VHH, tertravalent dAb.VHH; Non-Ig fusion proteins, *e.g.* $scFv_2$-albumin, scDb-albumin, taFv-albumin, taFv-toxin, miniantibody, DNL-Fab_2, DNL-Fab_2-scFv, DNL-Fab_2-IgG-$cytokine_2$, ImmTAC (TCR-scFv); modified Fc and CH3 fusion proteins, *e.g.* scFv-Fc(kih), scFv-Fc(CH3 charge pairs), scFv-Fc (EW-RVT), scFv-fc (HA-TF), scFv-Fc (SEEDbody), taFv-Fc(kih), scFv-Fc(kih)-Fv, Fab-Fc(kih)-scFv, Fab-scFv-Fc(kih), Fab-scFv-Fc(BEAT), Fab-scFv-Fc (SEEDbody), DART-Fc, scFv-CH3(kih), TriFabs; Fc fusions, *e.g.* Di-diabody, scDb-Fc, taFv-Fc, scFv-Fc-scFv, HCAb-VHH, Fab-scFv-Fc, $scFv_4$-Ig, $scFv_2$-Fcab; CH3 fusions, *e.g.* Dia-diabody, scDb-CH3; IgE/IgM CH2 fusions, *e.g.* scFv-EHD2-scFv, scFvMHD2-scFv; Fab fusion proteins, *e.g.* Fab-scFv (bibody), Fab-$scFv_2$ (tribody), Fab-Fv, Fab-dsFv, Fab-VHH, orthogonal Fab-Fab; non-Ig fusion proteins, *e.g.* DNL-Fab_3, DNL-Fab_2-scFv, DNL-Fab_2-IgG-$cytokine_2$; asymmetric IgG or IgG-like molecules, *e.g.* IgG(kih), IgG(kih) common LC, ZW1 IgG common LC, Biclonics common LC, CrossMab, CrossMab(kih), scFab-IgG(kih), Fab-scFab-IgG(kih), orthogonal Fab IgG(kih), DuetMab, CH3 charge pairs + CH1/CL charge pairs, hinge/CH3 charge pairs, SEED-body, Duobody, four-in-one-CrossMab(kih), LUZ-Y common LC; LUZ-Y scFab-IgG, FcFc*; appended and Fc-modified IgGs, *e.g.* IgG(kih)-Fv, IgG HA-TF-Fv, IgG(kih)scFab, scFab-Fc(kih)-scFv2, scFab-Fc(kih)-scFv, half DVD-Ig, DVI-Ig (four-in-one), CrossMab-Fab; modified Fc and CH3 fusion proteins, *e.g.* Fab-Fc(kih)-scFv, Fab-scFv-Fc(kih), Fab-scFv-Fc(BEAT), Fab-scFv-Fc-SEEDbody, TriFab; appended IgGs - HC fusions, *e.g.* IgG-HC, scFv, IgG-dAb, IgG-taFV, IgG-CrossFab, IgG-orthogonal Fab, IgG-(CαCβ) Fab, scFv-HC-IgG, tandem Fab-IgG (orthogonal Fab), Fab-IgG(CαCβ Fab), Fab-IgG(CR3), Fab-hinge-IgG(CR3); appended IgGs - LC fusions, *e.g.* IgG-scFv(LC), scFv(LC)-IgG, dAb-IgG; appended IgGs - HC and LC fusions, *e.g.* DVD-Ig, TVD-Ig, CODV-Ig, $scFv_4$-IgG, Zybody; Fc fusions, *e.g.* Fab-scFv-Fc, $scFv_4$-Ig; F(ab')2 fusions, *e.g.* $F(ab')_2$-$scFv_2$; CH1/CL fusion proteins *e.g.* $scFv_2$-CH1-hinge/CL; modified IgGs, *e.g.* DAF (two-in one-IgG), DutaMab, Mab^2; and non-Ig fusions, *e.g.* DNL-Fab_4-IgG. The skilled person is readily able to design and produce multispecific antigen-binding molecules.

The present disclosure also provides Chimeric Antigen Receptors (CARs). CARs are recombinant receptors that provide both antigen-binding and T cell activating functions. CAR structure and engineering is reviewed, for example, in Dotti *et al.*, Immunol Rev (2014) 257(1), hereby incorporated by reference in its entirety. CARs comprise an antigen-binding region linked to a cell membrane anchor region and a

signalling region. An optional hinge region may provide separation between the antigen-binding region and cell membrane anchor region, and may act as a flexible linker.

The antigen-binding domain of a CAR according to the present disclosure comprises or consists of an antigen-binding molecule that binds to gp130 as described herein. Accordingly, a CAR according to the present disclosure comprises an antigen-binding molecule as described herein.

It will be appreciated that an antigen-binding molecule according to the present disclosure forms, or is comprised in, the antigen-binding domain of the CAR. Accordingly, in some embodiments, the antigen-binding molecule of the present disclosure is comprised in a CAR.

It will also be appreciated that an antigen-binding molecule according to the present disclosure may be a CAR. A CAR having an antigen-binding domain comprising or consisting of an antigen-binding molecule of the present disclosure (*e.g.* a gp130-binding Fv) is an antigen-binding molecule. The antigen-binding domain of the CAR of the present disclosure may be provided with any suitable format, *e.g.* scFv, scFab, *etc.*

The cell membrane anchor region is provided between the antigen-binding region and the signalling region of the CAR and provides for anchoring the CAR to the cell membrane of a cell expressing a CAR, with the antigen-binding region in the extracellular space, and signalling region inside the cell. In some embodiments, the CAR comprises a cell membrane anchor region comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the transmembrane region amino acid sequence for one of CD3-ζ, CD4, CD8 or CD28. As used herein, a region which is 'derived from' a reference amino acid sequence comprises an amino acid sequence having at least 60%, *e.g.* one of at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the reference sequence.

The signalling region of a CAR allows for activation of the T cell. The CAR signalling regions may comprise the amino acid sequence of the intracellular domain of CD3-ζ, which provides immunoreceptor tyrosine-based activation motifs (ITAMs) for phosphorylation and activation of the CAR-expressing T cell. Signalling regions comprising sequences of other ITAM-containing proteins such as FcγRI have also been employed in CARs (Haynes *et al.*, 2001 J Immunol 166(1):182-187). Signalling regions of CARs may also comprise co-stimulatory sequences derived from the signalling region of co-stimulatory molecules, to facilitate activation of CAR-expressing T cells upon binding to the target protein. Suitable co-stimulatory molecules include CD28, OX40, 4-1BB, ICOS and CD27. In some cases CARs are engineered to provide for co-stimulation of different intracellular signalling pathways. For example, signalling associated with CD28 costimulation preferentially activates the phosphatidylinositol 3-kinase (PI3K) pathway, whereas the 4-1BB-mediated signalling is through TNF receptor associated factor (TRAF) adaptor proteins. Signalling regions of CARs therefore sometimes contain co-stimulatory sequences derived from signalling regions of more than one co-stimulatory molecule. In some embodiments, the CAR of the present disclosure comprises one or more co-stimulatory sequences

comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the amino acid sequence of the intracellular domain of one or more of CD28, OX40, 4-1BB, ICOS and CD27.

An optional hinge region may provide separation between the antigen-binding domain and the transmembrane domain, and may act as a flexible linker. Hinge regions may be derived from IgG1 or IgG4. In some embodiments, the CAR of the present disclosure comprises a hinge region comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the amino acid sequence of the hinge region of IgG1 or IgG4. In some embodiments, the hinge region of a CAR according to the present disclosure comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:35. In some embodiments, the hinge region of a CAR according to the present disclosure comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:52 or 53.

Also provided is a cell comprising a CAR according to the present disclosure. The CAR according to the present disclosure may be used to generate CAR-expressing immune cells, *e.g.* CAR-T or CAR-NK cells. Engineering of CARs into immune cells may be performed during culture, *in vitro*.

Fc regions

In some embodiments, the antigen-binding molecules of the present disclosure comprise an Fc region.

As used herein, an 'Fc region' refers to a polypeptide complex formed by interaction between two polypeptides, each polypeptide comprising the CH2-CH3 region of an immunoglobulin (Ig) heavy chain constant sequence.

Herein, a 'CH2 region' refers to an amino acid sequence corresponding to the CH2 region of an immunoglobulin (Ig). The CH2 region is the region of an Ig formed by positions 231 to 340 of the immunoglobulin constant region, according to the EU numbering system described in Edelman *et al.*, Proc Natl Acad Sci USA (1969) 63(1): 78-85. A 'CH3 region' refers to an amino acid sequence corresponding to the CH3 region of an immunoglobulin (Ig). The CH3 region is the region of an Ig formed by positions 341 to 447 of the immunoglobulin constant region, according to the EU numbering system described in Edelman *et al.*, Proc Natl Acad Sci USA (1969) 63(1): 78-85. A 'CH2-CH3 region' refers to an amino acid sequence corresponding to the CH2 and CH3 regions of an immunoglobulin (Ig). The CH2-CH3 region is the region of an Ig formed by positions 231 to 447 of the immunoglobulin constant region, according to the EU numbering system described in Edelman *et al.*, Proc Natl Acad Sci USA (1969) 63(1): 78-85.

In some embodiments, a CH2 region, CH3 region and/or a CH2-CH3 region according to the present disclosure corresponds to the CH2 region/CH3 region/CH2-CH3 region of an IgG (*e.g.* IgG1, IgG2, IgG3, IgG4), IgA (*e.g.* IgA1, IgA2), IgD, IgE or IgM. In some embodiments, the CH2 region, CH3 region and/or a

CH2-CH3 region corresponds to the CH2 region/CH3 region/CH2-CH3 region of a human IgG (*e.g.* hIgG1, hIgG2, hIgG3, hIgG4), hIgA (*e.g.* hIgA1, hIgA2), hIgD, hIgE or hIgM. In some embodiments, the CH2 region, CH3 region and/or a CH2-CH3 region corresponds to the CH2 region/CH3 region/CH2-CH3 region of a human IgG1 allotype (*e.g.* G1m1, G1m2, G1m3 or G1m17).

Fc regions provide for interaction with Fc receptors and other molecules of the immune system to bring about functional effects. Fc-mediated effector functions are reviewed *e.g.* in Jefferis *et al.*, Immunol Rev 1998 163:59-76 (hereby incorporated by reference in its entirety), and are brought about through Fc-mediated recruitment and activation of immune cells (*e.g.* macrophages, dendritic cells, neutrophils, basophils, eosinophils, platelets, mast cells, NK cells and T cells) through interaction between the Fc region and Fc receptors expressed by the immune cells, recruitment of complement pathway components through binding of the Fc region to complement protein C1q, and consequent activation of the complement cascade. Fc-mediated functions include Fc receptor binding, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), formation of the membrane attack complex (MAC), cell degranulation, cytokine and/or chemokine production, and antigen processing and presentation.

Modifications to antibody Fc regions that influence Fc-mediated functions are known in the art, such as those described *e.g.* in Wang *et al.*, Protein Cell (2018) 9(1):63-73, which is hereby incorporated by reference in its entirety. Exemplary Fc region modifications known to influence antibody effector function are summarised in Table 1 of Wang *et al.*, Protein Cell (2018) 9(1):63-73. In some embodiments, the antigen-binding molecule of the present disclosure comprises an Fc region comprising modification to increase or reduce an Fc-mediated function as compared to an antigen-binding molecule comprising the corresponding unmodified Fc region.

Where an Fc region/CH2/CH3 is described as comprising modification(s) 'corresponding to' reference substitution(s), equivalent substitution(s) in the homologous Fc/CH2/CH3 are contemplated. By way of illustration, L234A/L235A substitutions in human IgG1 (numbered according to the EU numbering system as described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991) correspond to L to A substitutions at positions 117 and 118 of the mouse Ig gamma-2A chain C region (UniProtKB: P01863-1, v1).

Where an Fc region is described as comprising a modification, the modification may be present in one or both of the polypeptide chains which together form the Fc region.

In some embodiments, the antigen-binding molecule of the present disclosure comprises an Fc region comprising modification. In some embodiments, the antigen-binding molecule of the present disclosure comprises an Fc region comprising modification in one or more of the CH2 and/or CH3 regions.

In some embodiments, the Fc region comprises modification to increase an Fc-mediated function. In some embodiments, the Fc region comprises modification to increase ADCC. In some embodiments, the Fc region comprises modification to increase ADCP. In some embodiments, the Fc region comprises

modification to increase CDC. An antigen-binding molecule comprising an Fc region comprising modification to increase an Fc-mediated function (*e.g.* ADCC, ADCP, CDC) induces an increased level of the relevant effector function as compared to an antigen-binding molecule comprising the corresponding unmodified Fc region.

In some embodiments, the Fc region comprises modification to increase binding to an Fc receptor. In some embodiments, the Fc region comprises modification to increase binding to an Fcγ receptor. In some embodiments, the Fc region comprises modification to increase binding to one or more of FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa and FcγRIIIb. In some embodiments, the Fc region comprises modification to increase binding to FcγRIIIa. In some embodiments, the Fc region comprises modification to increase binding to FcγRIIa. In some embodiments, the Fc region comprises modification to increase binding to FcγRIIb. In some embodiments, the Fc region comprises modification to increase binding to FcRn. In some embodiments, the Fc region comprises modification to increase binding to a complement protein. In some embodiments, the Fc region comprises modification to increase binding to C1q. In some embodiments, the Fc region comprises modification to promote hexamerisation of the antigen-binding molecule. In some embodiments, the Fc region comprises modification to increase antigen-binding molecule half-life. In some embodiments, the Fc region comprises modification to increase co-engagement.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions F243L/R292P/Y300L/V305I/P396L as described in Stavenhagen *et al.* Cancer Res. (2007) 67:8882–8890. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions S239D/I332E or S239D/I332E/A330L as described in Lazar *et al.*, Proc Natl Acad Sci USA. (2006)103:4005–4010. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions S298A/E333A/K334A as described in Shields *et al.*, J Biol Chem. (2001) 276:6591–6604. In some embodiments, the Fc region comprises modification to one of heavy chain polypeptides corresponding to the combination of substitutions L234Y/L235Q/G236W/S239M/H268D/D270E/S298A, and modification to the other heavy chain polypeptide corresponding to the combination of substitutions D270E/K326D/A330M/K334E, as described in Mimoto *et al.*, MAbs. (2013): 5:229–236. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions G236A/S239D/I332E as described in Richards *et al.*, Mol Cancer Ther. (2008) 7:2517–2527.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions K326W/E333S as described in Idusogie *et al.* J Immunol. (2001) 166(4):2571-5. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions S267E/H268F/S324T as described in Moore *et al.* MAbs. (2010) 2(2):181-9. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions described in Natsume *et al.*, Cancer Res. (2008) 68(10):3863-72. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions E345R/E430G/S440Y as described in Diebolder *et al.* Science (2014) 343(6176):1260-3.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions M252Y/S254T/T256E as described in Dall'Acqua *et al.* J Immunol. (2002) 169:5171–5180.

In some embodiments, the Fc region comprises a CH2-CH3 region comprising an amino acid difference at one or more of the following positions, relative to the amino acid sequence of a CH2-CH3 region of a reference Fc region: 252, 254 or 256 (according to the EU numbering system). In some embodiments, the Fc region comprises a CH2-CH3 region comprising one or more of the following specified amino acid residues: Y252, T254 or E256 (according to the EU numbering system). In some embodiments, the Fc region comprises a CH2-CH3 region comprising Y252, T254 and E256. In some embodiments, the Fc region comprises a CH2-CH3 region comprising one or more of the following amino acid substitutions, relative to the amino acid sequence of a CH2-CH3 region of the reference Fc region: M252Y, S254T or T256E (according to the EU numbering system).

These so called 'YTE' modifications located at the CH2-CH3 interface of the Fc region have been shown to increase the binding affinity at pH 6.0 to the MHC Class I neonatal Fc receptor (FcRn), localised within the acidic endosomes of endothelial and hematopoietic cells, which increases efficient recycling of administered mAb and longer half-life in the plasma.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions M428L/N434S as described in Zalevsky *et al.* Nat Biotechnol. (2010) 28:157–159. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions S267E/L328F as described in Chu *et al.*, Mol Immunol. (2008) 45:3926–3933. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions N325S/L328F as described in Shang *et al.* Biol Chem. (2014) 289:15309–15318.

In some embodiments, the Fc region comprises modification to reduce/prevent an Fc-mediated function. In some embodiments, the Fc region comprises modification to reduce/prevent ADCC. In some embodiments, the Fc region comprises modification to reduce/prevent ADCP. In some embodiments, the Fc region comprises modification to reduce/prevent CDC. An antigen-binding molecule comprising an Fc region comprising modification to reduce/prevent an Fc-mediated function (*e.g.* ADCC, ADCP, CDC) induces a reduced level of the relevant effector function as compared to an antigen-binding molecule comprising the corresponding unmodified Fc region.

In some embodiments, the Fc region comprises modification to reduce/prevent binding to an Fc receptor. In some embodiments, the Fc region comprises modification to reduce/prevent binding to an Fcγ receptor. In some embodiments, the Fc region comprises modification to reduce/prevent binding to one or more of FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa and FcγRIIIb. In some embodiments, the Fc region comprises modification to reduce/prevent binding to FcγRIIIa. In some embodiments, the Fc region comprises modification to reduce/prevent binding to FcγRIIa. In some embodiments, the Fc region comprises modification to reduce/prevent binding to FcγRIIb. In some embodiments, the Fc region comprises modification to reduce/prevent binding to a complement protein. In some embodiments, the Fc

region comprises modification to reduce/prevent binding to C1q. In some embodiments, the Fc region comprises modification to reduce/prevent glycosylation of the amino acid residue corresponding to N297.

In some embodiments, the Fc region is not able to induce one or more Fc-mediated functions (*i.e.* lacks the ability to elicit the relevant Fc-mediated function(s)). Accordingly, antigen-binding molecules comprising such Fc regions also lack the ability to induce the relevant function(s). Such antigen-binding molecules may be described as being devoid of the relevant function(s).

In some embodiments, the Fc region is not able to induce ADCC. In some embodiments, the Fc region is not able to induce ADCP. In some embodiments, the Fc region is not able to induce CDC. In some embodiments, the Fc region is not able to induce ADCC and/or is not able to induce ADCP and/or is not able to induce CDC.

In some embodiments, the Fc region is not able to bind to an Fc receptor. In some embodiments, the Fc region is not able to bind to an Fcγ receptor. In some embodiments, the Fc region is not able to bind to one or more of FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa and FcγRIIIb. In some embodiments, the Fc region is not able to bind to FcγRIIIa. In some embodiments, the Fc region is not able to bind to FcγRIIa. In some embodiments, the Fc region is not able to bind to FcγRIIb. In some embodiments, the Fc region is not able to bind to FcRn. In some embodiments, the Fc region is not able to bind to a complement protein. In some embodiments, the Fc region is not able to bind to C1q. In some embodiments, the Fc region is not glycosylated at the amino acid residue corresponding to N297.

In some embodiments, the Fc region comprises modification corresponding to N297A or N297Q or N297G as described in Leabman *et al.*, MAbs. (2013) 5:896–903. In some embodiments, the Fc region comprises modification corresponding to L235E as described in Alegre *et al.*, J Immunol. (1992) 148:3461–3468. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A or F234A/L235A as described in Xu *et al.*, Cell Immunol. (2000) 200:16–26. In some embodiments, the Fc region comprises modification corresponding to P329A or P329G as described in Schlothauer *et al.*, Protein Engineering, Design and Selection (2016), 29(10):457–466. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A/P329G as described in Lo *et al.* J. Biol. Chem (2017) 292(9):3900-3908. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions described in Rother *et al.*, Nat Biotechnol. (2007) 25:1256–1264. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions S228P/L235E as described in Newman *et al.*, Clin. Immunol. (2001) 98:164–174. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions H268Q/V309L/A330S/P331S as described in An *et al.*, MAbs. (2009) 1:572–579. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions V234A/G237A/P238S/H268A/V309L/A330S/P331S as described in Vafa *et al.*, Methods. (2014) 65:114–126. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235E/G237A/A330S/P331S as described in US 2015/0044231 A1.

The combination of substitutions 'L234A/L235A' and corresponding substitutions (such as *e.g.* F234A/L235A in human IgG4) are known to disrupt binding of Fc to Fcγ receptors and inhibit ADCC, ADCP, and also to reduce C1q binding and thus CDC (Schlothauer *et al.*, Protein Engineering, Design and Selection (2016), 29(10):457–466, hereby incorporated by reference in entirety). The substitutions 'P329G' and 'P329A' reduce C1q binding (and thereby CDC). Substitution of 'N297' with 'A', 'G' or 'Q' is known to eliminate glycosylation, and thereby reduce Fc binding to C1q and Fcγ receptors, and thus CDC and ADCC. Lo *et al.* J. Biol. Chem (2017) 292(9):3900-3908 (hereby incorporated by reference in its entirety) reports that the combination of substitutions L234A/L235A/P329G eliminated complement binding and fixation as well as Fc γ receptor dependent, antibody-dependent, cell-mediated cytotoxicity in both murine IgG2a and human IgG1.

The combination of substitutions L234A/L235E/G237A/A330S/P331S in IgG1 Fc is disclosed in US 2015/0044231 A1 to abolish induction of phagocytosis, ADCC and CDC.

In some embodiments, the Fc region comprises modification corresponding to the substitution S228P as described in Silva *et al.*, J Biol Chem. (2015) 290(9):5462-5469. The substitution S228P in IgG4 Fc reduces Fab-arm exchange (Fab-arm exchange can be undesirable).

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A. In some embodiments, the Fc region comprises modification corresponding to the substitution P329G. In some embodiments, the Fc region comprises modification corresponding to the substitution N297Q.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A/P329G.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A/P329G/N297Q.

In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235E/G237A/A330S/P331S.

In some embodiments, the Fc region comprises modification corresponding to the substitution S228P, *e.g.* in IgG4.

It may be desirable for the antigen-binding molecule to have a relatively-short half-life. Because the antigen-binding molecules of the present disclosure influence signalling mediated by multiple cytokines/through multiple cytokine receptors, it might be desirable for their functional effects to be relatively short-lived. Accordingly, in some embodiments the antigen-binding molecule of the present disclosure may comprise an Fc region comprising modification to decrease antigen-binding molecule half-life.

Fc modifications that reduce half-life include H345A, and the triple substitution I253A/H310A/H345A, which have been reported to reduce binding to FcRn and decrease half-life of antigen-binding molecules bearing Fc regions comprising such modifications relative to their unmodified wildtype counterparts (see *e.g.* Kruijsen *et al.*, J Virol. (2013) 87(13): 7550–7557, which is hereby incorporated by reference in its entirety.

In some embodiments, the Fc region comprises modification corresponding to the substitution H345A. In some embodiments, the Fc region comprises modification corresponding to the substitution I253A. In some embodiments, the Fc region comprises modification corresponding to the substitution H310A. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions I253A/H310A/H345A.

In some embodiments, the antigen-binding molecule does not comprise an Fc region. In some embodiments, the antigen-binding molecule consists essentially of an Fv moiety (*e.g.* is a scFv or a dsFv). In some embodiments, the antigen-binding molecule consists essentially of a Fab moiety (*e.g.* is a Fab, CrossFab, scFab, scCrossFab or $F(ab')_2$).

As used herein, an antigen-binding molecule that 'consists essentially of' a reference polypeptide domain(s)/amino acid sequence(s) either (i) consists of the reference domain(s)/amino acid sequence(s), or (ii) comprises the reference domain(s)/amino acid sequence(s), wherein the reference domain(s)/amino acid sequence(s) constitute at least 80% (*e.g.* one of ≥85% ≥86%, ≥87%, ≥88%, ≥89%, ≥90%, ≥91%, ≥92%, ≥93%, ≥94%, ≥95%, ≥96%, ≥97%, ≥98%, ≥99%) of the molecule. It will be appreciated that an antigen-binding molecule that 'consists essentially of' a reference polypeptide domain(s)/amino acid sequence(s) may comprise the reference domain(s)/amino acid sequence(s), and additional amino acid(s) at one or both of the N-terminal and C-terminal ends of the reference domain(s)/amino acid sequence(s), provided that the additional amino acid(s) constitute ≤20% of the molecule. By way of illustration, antigen-binding molecules that consist essentially of an Fv moiety include scFv molecules, which comprise a VH and VL connected via a linker moiety.

Antigen-binding molecules and polypeptides according to the present disclosure may be prepared according to methods for the production of polypeptides known to the skilled person. Antigen-binding molecules and polypeptides may be prepared by chemical synthesis, *e.g.* liquid or solid phase synthesis. For example, peptides/polypeptides can be synthesised using the methods described in, for example, Chandrudu *et al.*, Molecules (2013), 18: 4373-4388, which is hereby incorporated by reference in its entirety. Alternatively, antigen-binding molecules and polypeptides may be produced by recombinant expression. Molecular biology techniques suitable for recombinant production of polypeptides are well known in the art, such as those set out in Green and Sambrook, Molecular Cloning: A Laboratory Manual (4th Edition), Cold Spring Harbor Press, 2012, and in Nat Methods. (2008); 5(2): 135-146 both of which are hereby incorporated by reference in their entirety. Methods for the recombinant production of antigen-binding molecules are also described in Frenzel *et al.*, Front Immunol. (2013); 4: 217 and Kunert and Reinhart, Appl Microbiol Biotechnol. (2016) 100: 3451–3461, both of which are hereby incorporated by reference in their entirety.

In some embodiments – particularly embodiments in which the antigen-binding molecule is a multispecific (*e.g.* bispecific) antigen-binding molecule – the antigen-binding molecule comprises an Fc region comprising modification in one or more of the CH2 and CH3 regions promoting association of the Fc region. Recombinant co-expression of constituent polypeptides of an antigen-binding molecule and subsequent association leads to several possible combinations. To improve the yield of the desired combinations of polypeptides in antigen-binding molecules in recombinant production, it is advantageous to introduce in the Fc regions modification(s) promoting association of the desired combination of heavy chain polypeptides. Modifications may promote *e.g.* hydrophobic and/or electrostatic interaction between CH2 and/or CH3 regions of different polypeptide chains. Suitable modifications are described *e.g.* in Ha *et al.*, Front. Immnol (2016) 7:394, which is hereby incorporated by reference in its entirety.

In some embodiments, the antigen-binding molecule of the present disclosure comprises an Fc region comprising paired substitutions in the CH3 regions of the Fc region according to one of the following formats, as shown in Table 1 of Ha *et al.*, Front. Immnol (2016) 7:394: KiH, KiH$_{s-s}$, HA-TF, ZW1, 7.8.60, DD-KK, EW-RVT, EW-RVT$_{s-s}$, SEED or A107.

Particular exemplary polypeptides and antigen-binding molecules

The present disclosure also provides polypeptide constituents of antigen-binding molecules. The polypeptides may be provided in isolated or substantially purified form.

The antigen-binding molecule of the present disclosure may be, or may comprise, a complex of polypeptides.

In the present specification where a polypeptide comprises more than one domain or region, it will be appreciated that the plural domains/regions are preferably present in the same polypeptide chain. That is, the polypeptide comprising more than one domain or region is a fusion polypeptide comprising the domains/regions.

In some embodiments a polypeptide according to the present disclosure comprises, or consists of, a VH as described herein. In some embodiments a polypeptide according to the present disclosure comprises, or consists of, a VL as described herein.

In some embodiments, the polypeptide additionally comprises one or more antibody heavy chain constant regions (CH). In some embodiments, the polypeptide additionally comprises one or more antibody light chain constant regions (CL). In some embodiments, the polypeptide comprises a CH1, CH2 region and/or a CH3 region of an immunoglobulin (Ig).

In some embodiments, the polypeptide comprises one or more regions of an immunoglobulin heavy chain constant sequence. In some embodiments, the polypeptide comprises a CH1 region as described herein. In some embodiments, the polypeptide comprises a CH1-CH2 hinge region as described herein. In some

embodiments, the polypeptide comprises a CH2 region as described herein. In some embodiments, the polypeptide comprises a CH3 region as described herein.

In some embodiments, the polypeptide comprises one or more regions of an immunoglobulin light chain constant sequence. In some embodiments, the polypeptide comprises a CL region as described herein.

In some embodiments, the polypeptide according to the present disclosure comprises a structure from N- to C-terminus according to one of the following:

(i) VH
(ii) VL
(iii) VH-CH1
(iv) VL-CL
(v) VL-CH1
(vi) VH-CL
(vii) VH-CH1-CH2-CH3
(viii) VL-CL-CH2-CH3
(ix) VL-CH1-CH2-CH3
(x) VH-CL-CH2-CH3

Also provided by the present disclosure are antigen-binding molecules composed of the polypeptides of the present disclosure. In some embodiments, the antigen-binding molecule of the present disclosure comprises one of the following combinations of polypeptides:

(A) VH + VL
(B) VH-CH1 + VL-CL
(C) VL-CH1 + VH-CL
(D) VH-CH1-CH2-CH3 + VL-CL
(E) VH-CL-CH2-CH3 + VL-CH1
(F) VL-CH1-CH2-CH3 + VH-CL
(G) VL-CL-CH2-CH3 + VH-CH1
(H) VH-CH1-CH2-CH3 + VL-CL-CH2-CH3
(I) VH-CL-CH2-CH3 + VL-CH1-CH2-CH3

In some embodiments, the antigen-binding molecule comprises more than one of a polypeptide of the combinations shown in (A) to (I) above. By way of example, with reference to (D) above, in some embodiments, the antigen-binding molecule comprises two polypeptides comprising the structure VH-CH1-CH2-CH3, and two polypeptides comprising the structure VL-CL.

In some embodiments, the antigen-binding molecule of the present disclosure comprises one of the following combinations of polypeptides:

(J) VH (anti-gp130) + VL (anti-gp130)
(K) VH (anti-gp130)-CH1 + VL (anti-gp130)-CL
(L) VL (anti-gp130)-CH1 + VH (anti-gp130)-CL

(M) VH (anti-gp130)-CH1-CH2-CH3 + VL (anti-gp130)-CL

(N) VH (anti-gp130)-CL-CH2-CH3 + VL (anti-gp130)-CH1

(O) VL (anti-gp130)-CH1-CH2-CH3 + VH (anti-gp130)-CL

(P) VL (anti-gp130)-CL-CH2-CH3 + VH (anti-gp130)-CH1

(Q) VH (anti-gp130)-CH1-CH2-CH3 + VL (anti-gp130)-CL-CH2-CH3

Wherein: 'VH(anti-gp130)' refers to the VH of an antigen-binding molecule capable of binding to gp130 as described herein, *e.g.* as defined in one of (1) to (23); and 'VL(anti-gp130)' refers to the VL of an antigen-binding molecule capable of binding to gp130 as described herein, *e.g.* as defined in one of (24) to (72).

Alternatively, wherein: 'VH(anti-gp130)' refers to the VH of an antigen-binding molecule capable of binding to gp130 as described herein, *e.g.* as defined in one of (73) to (187); and 'VL(anti-gp130)' refers to the VL of an antigen-binding molecule capable of binding to gp130 as described herein, *e.g.* as defined in one of (188) to (301).

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:112, 117, 1, 94, 98 or 174.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:17.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 147, 148, 143, 144, 145, 146, 160, 161, 156, 157, 158 or 159. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, or 109. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:147, 148, 143, 144, 145 or 146. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:160, 161, 156, 157, 158 or 159.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:25.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:134, 135, 136, 137, 64, 65, 130, 131, 132, 133, 176 or 177.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:67 or 68.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 154, 155, 150, 151, 152, 153, 167, 168, 163, 164, 165 or 166. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139 or 140. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:154, 155, 150, 151, 152 or 153. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:167, 168, 163, 164, 165 or 166.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:69.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain CDRs, and a VL region comprising the light chain CDRs, of an antibody selected from an antibody as shown in Table A herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) a VH region comprising HC-CDR1, HC-CDR2 and HC-CDR3 as indicated in column A of Table A, and (ii) a VL

region comprising LC-CDR1, LC-CDR2 and LC-CDR3 as indicated in column B of Table A, wherein the sequences of columns A and B are selected from the same row of Table A.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain FRs, and a VL region comprising the light chain FRs, of an antibody selected from an antibody as shown in Table B herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) a VH region comprising HC-FR1, HC-FR2, HC-FR3 and HC-FR4 as indicated in column A of Table B, and (ii) a VL region comprising LC-FR1, LC-FR2, LC-FR3, and LC-FR4 as indicated in column B of Table B, wherein the sequences of columns A and B are selected from the same row of Table B.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising: (i) an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column A of Table C, and (ii) an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column B of Table C, wherein the sequences of columns A and B are selected from the same row of Table C.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region and a VL region of a clone selected from an antibody as shown in Table C herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) an amino acid sequence indicated in column A of Table C, and (ii) an amino acid sequence indicated in column B of Table C, wherein the sequences of columns A and B are selected from the same row of Table C.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column A of Table D, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column B of Table D, wherein the sequences of columns A and B are selected from the same row of Table D.

In some embodiments, the antigen-binding molecule of the present disclosure comprises the polypeptides of an antigen-binding molecule according to Table D herein. That is, in some embodiments, the antigen-binding molecule comprises: (i) a polypeptide comprising or consisting of an amino acid sequence indicated in column A of Table D, and (ii) a polypeptide comprising or consisting of an amino acid sequence indicated in column B of Table D, wherein the sequences of columns A and B are selected from the same row of Table D.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:179, 195, 209, 214, 229, 252, 256, 258, 261, 284, 264, 265, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374 or 382.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:352. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:350. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:372. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:370. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:351. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:371.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:187, 201, 212, 222, 235, 253, 266, 269, 273, 276, 278, 288, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411 or 418.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:402. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:400.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479 or 480.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:426. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:457. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:446. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:477. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:424. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:455. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:444. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:475. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:425. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID

NO:456. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:445. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:476.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510 or 511.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:504.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain CDRs, and a VL region comprising the light chain CDRs, of an antibody selected from an antibody as shown in Table E herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) a VH region comprising HC-CDR1, HC-CDR2 and HC-CDR3 as indicated in column A of Table E, and (ii) a VL region comprising LC-CDR1, LC-CDR2 and LC-CDR3 as indicated in column B of Table E, wherein the sequences of columns A and B are selected from the same row of Table E. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain CDRs, and a VL region comprising the light chain CDRs, of an antibody selected from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G (as shown in Table E). In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain CDRs, and a VL region comprising the light chain CDRs, of an antibody selected from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q and 4D4CVH2.2_D53G/4D4GVL3_N93Q (as shown in Table E).

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain FRs, and a VL region comprising the light chain FRs, of an antibody selected from an antibody as shown in Table F herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) a VH region comprising HC-FR1, HC-FR2, HC-FR3 and HC-FR4 as indicated in column A of Table F, and (ii) a VL region comprising LC-FR1, LC-FR2, LC-FR3, and LC-FR4 as indicated in column B of Table F, wherein the sequences of columns A and B are selected from the same row of Table F. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain FRs, and a VL region comprising the light chain FRs, of an antibody selected from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G (as shown in Table F). In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region comprising the heavy chain FRs, and a VL region comprising the light chain FRs, of an antibody selected from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q and 4D4CVH2.2_D53G/4D4GVL3_N93Q (as shown in Table F).

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising: (i) an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column A of Table G, and (ii) an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column B of Table G, wherein the sequences of columns A and B are selected from the same row of Table G.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region and a VL region of an antibody clone selected from an antibody as shown in Table G herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) an amino acid sequence indicated in column A of Table G, and (ii) an amino acid sequence indicated in column B of Table G, wherein the sequences of columns A and B are selected from the same row of Table G. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region and a VL region of an antibody clone selected from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G (as shown in Table G). In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region and a VL region of an antibody clone selected from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q and 4D4CVH2.2_D53G/4D4GVL3_N93Q (as shown in Table G).

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column A of Table H, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column B of Table H, wherein the sequences of columns A and B are selected from the same row of Table H.

In some embodiments, the antigen-binding molecule of the present disclosure comprises the polypeptides of an antigen-binding molecule according to Table H herein. That is, in some embodiments, the antigen-binding molecule comprises: (i) a polypeptide comprising or consisting of an amino acid sequence indicated in column A of Table H, and (ii) a polypeptide comprising or consisting of an amino acid sequence indicated in column B of Table H, wherein the sequences of columns A and B are selected from the same row of Table H.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:426, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:457, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:446, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:477, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:424, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:504. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:455, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:504.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:444, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:504. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:475, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:504.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:425, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:456, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501.

In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of

80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:445, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:476, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:501.

Functional properties of the antigen-binding molecules

The antigen-binding molecules described herein may be characterised by reference to certain functional properties. In some embodiments, the antigen-binding molecule described herein may possess one or more of the following properties:

binds to gp130 (*e.g.* human gp130, rhesus macaque gp130, mouse gp130 and/or rat gp130);
binds to gp130-expressing cells;
inhibits signalling mediated by a receptor comprising gp130;
inhibits signalling mediated by gp130:IL-6Rα, gp130:IL-11Rα, gp130:OSMRβ, gp130:LIFRβ, gp130:LIFRβ:CNTFRα, gp130:IL-27Rα and/or gp130:IL-12Rβ2;
inhibits signalling mediated by a cytokine that binds to a receptor comprising gp130;
inhibits IL-6-, IL-11-, OSM-, LIF-, CNTF-, CT-1-, CLC-, IL-27- and/or IL-35-mediated signalling;
does not inhibit OSM-, LIF-, CNTF-, CT-1-, CLC-, IL-27- and/or IL-35-mediated signalling;
reduces inflammation and/or fibrosis;
reduces the pathology of a disease/condition characterised by inflammation and/or fibrosis;
increases killing of cells expressing gp130;
reduces or inhibits angiogenesis;
reduces or inhibits choroidal neovascularization (*e.g.* reduces size of CNV lesions and/or reduces CNV leakage area); and/or
reduces or inhibits expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11.

It will be appreciated that a given antigen-binding molecule may display more than one of the properties recited in the preceding paragraph. A given antigen-binding molecule may be evaluated for the properties recited in the preceding paragraph using suitable assays. For example, the assays may be *e.g. in vitro* assays, optionally cell-based assays or cell-free assays. In some embodiments, the assays may be *e.g. in vivo* assays, *i.e.* performed in non-human animals. In some embodiments, the assays may be *e.g. ex vivo* assays, *i.e.* performed using cells/tissue/an organ obtained from a subject.

Where assays are cell-based assays, they may comprise treating cells with a given antigen-binding molecule in order to determine whether the antigen-binding molecule displays one or more of the recited properties. Assays may employ species labelled with detectable entities in order to facilitate their detection. Assays may comprise evaluating the recited properties following treatment of cells separately

with a range of quantities/concentrations of a given antigen-binding molecule (*e.g.* a dilution series). It will be appreciated that the cells preferably express the target antigen for the antigen-binding molecule (*i.e.* gp130).

Analysis of the results of such assays may comprise determining the concentration at which 50% of the maximal level of the relevant activity is attained. The concentration of a given agent at which 50% of the maximal level of the relevant activity is attained may be referred to as the 'half-maximal effective concentration' of the agent in relation to the relevant activity, which may also be referred to as the 'EC_{50}'. By way of illustration, the EC_{50} of a given antigen-binding molecule for binding to human gp130 may be the concentration of the antigen-binding molecule at which 50% of the maximal level of binding to human gp130 is achieved.

Depending on the property, the EC_{50} may also be referred to as the 'half-maximal inhibitory concentration' or 'IC_{50}', this being the concentration of the agent at which 50% of the maximal level of inhibition of a given property is observed.

The antigen-binding molecules described herein bind to gp130. In some embodiments, the antigen-binding molecule binds to human gp130. In some embodiments, the antigen-binding molecule binds to mouse gp130. In some embodiments, the antigen-binding molecule binds to rat gp130. In some embodiments, the antigen-binding molecule binds to rhesus macaque gp130. In some embodiments, the antigen-binding molecule binds to canine gp130.

In some embodiments, the antigen-binding molecules display cross-reactive binding to human gp130, and to one or more homologues of human gp130 (*e.g.* selected from rhesus macaque gp130, mouse gp130 and rat gp130). It will be appreciated that cross-reactive binding refers to the ability to bind independently to each antigen, and not simultaneous binding of an antigen-binding domain of the antigen-binding molecule to the two or more antigens.

In some embodiments, the antigen-binding molecule is cross-reactive for human gp130 and rhesus macaque gp130 (*i.e.* is capable of binding to human gp130, and is also capable of binding to rhesus macaque gp130). In some embodiments, the antigen-binding molecule is cross-reactive for human gp130 and mouse gp130. In some embodiments, the antigen-binding molecule is cross-reactive for human gp130 and rat gp130. In some embodiments, the antigen-binding molecule binds to human gp130, mouse gp130 and rat gp130. In some embodiments, the antigen-binding molecule is cross-reactive for human gp130 and rhesus macaque gp130 and mouse gp130 and rat gp130.

The antigen-binding molecules and antigen-binding domains described herein preferably display specific binding to gp130. As used herein, 'specific binding' refers to binding which is selective for the antigen, and which can be discriminated from non-specific binding to non-target antigen. An antigen-binding molecule/domain that specifically binds to a target molecule preferably binds the target with greater affinity, and/or with greater duration than it binds to other, non-target molecules.

The ability of a given polypeptide to bind specifically to a given molecule can be determined by analysis according to methods known in the art, such as by ELISA, Surface Plasmon Resonance (SPR; see *e.g.* Hearty *et al.*, Methods Mol Biol (2012) 907:411-442), Bio-Layer Interferometry (BLI; see *e.g.* Lad *et al.*, (2015) J Biomol Screen 20(4): 498-507), flow cytometry, or by a radiolabelled antigen-binding assay (RIA) enzyme-linked immunosorbent assay. Through such analysis binding to a given molecule can be measured and quantified. In some embodiments, the binding may be the response detected in a given assay.

In some embodiments, the extent of binding of the antigen-binding molecule to a non-target molecule is less than about 10% of the binding of the antibody to the target molecule as measured, *e.g.* by ELISA, SPR, BLI or by RIA. Alternatively, binding specificity may be reflected in terms of binding affinity where the antigen-binding molecule binds with a dissociation constant (K_D) that is at least 0.1 order of magnitude (*i.e.* 0.1 x 10^n, where n is an integer representing the order of magnitude) greater than the K_D of the antigen-binding molecule towards a non-target molecule. This may optionally be one of at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, or 2.0.

The affinity of binding to a given target antigen for an antigen-binding molecule described herein may be determined by SPR, *e.g.* as described in the Examples of the present disclosure.

In some embodiments, the antigen-binding molecule described herein binds to gp130 with an affinity in the micromolar range, *i.e.* K_D = 9.9 x 10^{-4} to 1 x 10^{-6} M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with sub-micromolar affinity, *i.e.* K_D < 1 x 10^{-6} M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with an affinity in the nanomolar range, *i.e.* K_D = 9.9 x 10^{-7} to 1 x 10^{-9} M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with sub-nanomolar affinity, *i.e.* K_D < 1 x 10^{-9} M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with an affinity in the picomolar range, *i.e.* K_D = 9.9 x 10^{-10} to 1 x 10^{-12} M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with sub-picomolar affinity, *i.e.* K_D < 1 x 10^{-12} M.

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of 10 μM or less, preferably one of ≤5 μM, ≤2 μM, ≤1 μM, ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM (*e.g.* as determined by analysis surface plasmon resonance analysis, *e.g.* performed as described in Example 5 and 31). In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of 100 nM or less, preferably one of ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM (*e.g.* as determined by analysis surface plasmon resonance analysis, *e.g.* performed as described in Example 5 herein). In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of 3 nM or less, preferably one of ≤2.5 nM, ≤2 nM, ≤1.5 nM, ≤1 nM, ≤750 pM, ≤500 pM, or ≤400 pM.

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of ≤200 nM, preferably one of ≤190 nM, ≤180 nM, ≤170 nM, ≤160 nM, ≤150 nM, ≤140 nM, ≤130 nM, ≤120 nM, ≤110 nM, ≤100 nM, ≤95 nM, ≤90 nM, ≤85 nM, ≤80 nM, ≤75 nM, ≤60 nM, ≤55 nM, ≤50 nM, ≤45 nM, ≤40 nM, ≤35 nM, ≤30 nM, ≤25 nM, ≤20 nM, ≤15 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM, ≤3 nM, ≤2 nM or ≤1 nM (*e.g.* as determined by analysis surface plasmon resonance analysis, *e.g.* performed as described in Example 5 and 31 herein). In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of ≤166 nM. In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of ≤2.91 nM.

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of 1 nM or less, preferably one of ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM or ≤100 pM (*e.g.* as determined by analysis as described in Example 31 and 52 herein).

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with an EC_{50} of 10 µM or less, preferably one of ≤5 µM, ≤2 µM, ≤1 µM, ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM.

The antigen-binding molecules of the present disclosure may bind to a particular region of interest of gp130. Antigen-binding molecules according to the present disclosure may bind to linear epitope of gp130, consisting of a contiguous sequence of amino acids (*i.e.* an amino acid primary sequence). In some embodiments, an antigen-binding molecules may bind to a conformational epitope of gp130, consisting of a discontinuous sequence of amino acids of the amino acid sequence.

The region of a given target molecule to which an antigen-binding molecule binds can be determined by the skilled person using various methods well known in the art, including X-ray co-crystallography analysis of antibody-antigen complexes, peptide scanning, mutagenesis mapping, hydrogen-deuterium exchange analysis by mass spectrometry, phage display, competition ELISA and proteolysis-based 'protection' methods. Such methods are described, for example, in Gershoni *et al.*, BioDrugs, 2007, 21(3):145-156, which is hereby incorporated by reference in its entirety.

In some embodiments, the antigen-binding molecule of the present disclosure binds to the extracellular domain of gp130. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:75. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:75.

In some embodiments, the antigen-binding molecule of the present disclosure binds to the cytokine binding module of gp130. In some embodiments, the antigen-binding molecule binds to the region of

gp130 shown in SEQ ID NO:85. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:85.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:89. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:89. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:89. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:89. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:89.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:86. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:86. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:86. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:86. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:87. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:87. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:87. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:87. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:88. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:88. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:88. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:88.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID NOs:86, 87 and 88. In some embodiments, the antigen-binding molecule contacts the regions of gp130 shown in SEQ ID NOs:86, 87 and 88. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:86, 87 and 88. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in SEQ ID NOs:86, 87 and 88.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:93. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:93. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:93. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:93. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:93.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:90. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:90. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:90. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:90. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:91. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:91. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:91. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:91. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:92. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:92. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:92. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:92.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID NOs:90, 91 and 92. In some embodiments, the antigen-binding molecule contacts the regions of gp130 shown in SEQ ID NOs:90, 91 and 92. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:90, 91 and 92. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in SEQ ID NOs:90, 91 and 92.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:169. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:169. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:169. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:169. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:170. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:170. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:170. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:170.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:171. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:171. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:171. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:171. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:172. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:172. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or

more amino acids of the region shown in SEQ ID NO:172. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:172.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID NOs:169 and 170. In some embodiments, the antigen-binding molecule contacts the regions of gp130 shown in SEQ ID NOs:169 and 170. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:169 and 170. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in SEQ ID NOs:169 and 170.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID NOs:171 and 172. In some embodiments, the antigen-binding molecule contacts the regions of gp130 shown in SEQ ID NOs:171 and 172. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:171 and 172. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in SEQ ID NOs:171 and 172.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:173. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:173. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:173. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:173. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:173.

In some embodiments, the antigen-binding molecule does not bind to the region of gp130 shown in SEQ ID NO:178. In some embodiments, the antigen-binding molecule does not contact the region of gp130 shown in SEQ ID NO:178. In some embodiments, the antigen-binding molecule does not bind to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:178. In some embodiments, the epitope of the antigen-binding molecule does not consist of the amino acid sequence shown in SEQ ID NO:178. In some embodiments, the antigen-binding molecule does not bind to a polypeptide consisting of the amino acid sequence shown in SEQ ID NO:178.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:313, SEQ ID NO:314 and/or SEQ ID NO:315. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:313, SEQ ID NO:314 and/or SEQ ID NO:315. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:313, SEQ ID NO:314 and/or SEQ ID NO:315. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:313, SEQ ID NO:314 and/or SEQ ID NO:315. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:313, SEQ ID NO:314 and/or SEQ ID NO:315. In some embodiments, the antigen-binding molecule binds to

the region of gp130 shown in SEQ ID NO:316. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:316. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:316. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:316. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:316.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:317 and/or SEQ ID NO:318. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:317 and/or SEQ ID NO:318. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:317 and/or SEQ ID NO:318. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:317 and/or SEQ ID NO:318. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:317 and/or SEQ ID NO:318. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:319. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:319. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:319. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:319. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:319.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:320, SEQ ID NO:321 and/or SEQ ID NO:322. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:320, SEQ ID NO:321 and/or SEQ ID NO:322. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:320, SEQ ID NO:321 and/or SEQ ID NO:322. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:320, SEQ ID NO:321 and/or SEQ ID NO:322. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:320, SEQ ID NO:321 and/or SEQ ID NO:322. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:323. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:323. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:323. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:323. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:323.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:513 and/or SEQ ID NO:516. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:324, SEQ ID NO:325, SEQ ID

NO:513 and/or SEQ ID NO:516. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:513 and/or SEQ ID NO:516. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:513 and/or SEQ ID NO:516. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:513 and/or SEQ ID NO:516. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:326. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:326. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:326. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:326. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:326. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:517. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:517. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:517. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:517. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:517.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:512 and/or SEQ ID NO:513. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:512 and/or SEQ ID NO:513. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:512 and/or SEQ ID NO:513. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:512 and/or SEQ ID NO:513. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:512 and/or SEQ ID NO:513. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:329. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:329. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:329. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:329. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:329. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:514. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:514. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:514. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:514. In

some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:514. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:515. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:515. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:515. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:515. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:515.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:330 and/or SEQ ID NO:331. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:330 and/or SEQ ID NO:331. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:330 and/or SEQ ID NO:331. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:330 and/or SEQ ID NO:331. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:330 and/or SEQ ID NO:331. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:332. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:332. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:332. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:332. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:332.

The ability of an antigen-binding molecule to bind to a given peptide/polypeptide can be analysed by methods well known to the skilled person, including analysis by ELISA, immunoblot (*e.g.* western blot), immunoprecipitation, SPR and BLI.

In some embodiments, the antigen-binding molecule is capable of binding the same region of gp130, or an overlapping region of gp130, to the region of gp130 which is bound by an antibody comprising the VH and VL regions (see *e.g.* Table C) of an antibody as indicated in Table C.

In some embodiments, the antigen-binding molecule is capable of binding the same region of gp130, or an overlapping region of gp130, to the region of gp130 which is bound by an antibody comprising the VH and VL regions (see *e.g.* Table G) of an antibody as indicated in Table G.

Whether a test antigen-binding molecule binds to the same or an overlapping region of a given target as a reference antigen-binding molecule can be evaluated, for example, by analysis of (i) interaction between the test antigen-binding molecule and the target in the absence of the reference binding molecule, and (ii) interaction between the test antigen-binding molecule in the presence of the reference antigen-binding molecule, or following incubation of the target with the reference antigen-binding molecule. Determination

of a reduced level of interaction between the test antigen-binding molecule and the target following analysis according to (ii) as compared to (i) might support an inference that the test and reference antigen-binding molecule bind to the same or an overlapping region of the target. Suitable assays for such analysis include *e.g.* competition ELISA assays and epitope binning assays.

In some embodiments, the antigen-binding molecule of the present disclosure binds to gp130 in a region which is accessible to an antigen-binding molecule (*i.e.*, an extracellular antigen-binding molecule) when gp130 is expressed at the cell surface (*i.e.* in or at the cell membrane). In some embodiments, the antigen-binding molecule binds to gp130 expressed at the cell surface of a cell expressing gp130. In some embodiments, the antigen-binding molecule binds to gp130-expressing cells (*e.g.* fibroblasts). In some embodiments, the antigen-binding molecule does not bind (*i.e.* does not substantially bind) to cells lacking surface expression of gp130.

The ability of an antigen-binding molecule to bind to a given cell type (*e.g.* cells expressing gp130, or cells not expressing gp130) can be analysed by contacting cells with the antigen-binding molecule, and detecting antigen-binding molecule bound to the cells, *e.g.* after a washing step to remove unbound antigen-binding molecule. The ability of an antigen-binding molecule to bind to a given cell type can be analysed by methods such as flow cytometry and immunofluorescence microscopy.

In some embodiments, the antigen-binding molecule of the present disclosure inhibits signalling mediated by a receptor comprising gp130. In some embodiments, the antigen-binding molecule inhibits gp130-mediated signalling (*e.g.* gp130-mediated signalling as described hereinabove). Signalling mediated by gp130 and/or by receptors comprising gp130 can be analysed using cells expressing gp130/the relevant receptor, *e.g.* using an assay for detecting and/or quantifying gp130-mediated signalling. Suitable assays include *e.g.* assays for detecting the phosphorylation/activity/expression of factors which are phosphorylated/activated/expressed as a consequence of signalling though gp130/receptors comprising gp130.

Such assays may comprise contacting cells expressing a given cytokine receptor comprising gp130 with an antigen-binding molecule according to the present disclosure, *e.g.* in the presence of a ligand for the cytokine receptor. By way of illustration, an assay for investigating the ability of an antigen-binding molecule to inhibit IL-6-mediated signalling and/or the ability of an antigen-binding molecule to inhibit signalling mediated by gp130:IL-6Rα may comprise contacting cells expressing gp130:IL-6Rα complexes with an antigen-binding molecule according to the present disclosure, *e.g.* in the presence of IL-6. By way of further illustration, an assay for investigating the ability of an antigen-binding molecule to inhibit IL-11-mediated signalling and/or the ability of an antigen-binding molecule to inhibit signalling mediated by gp130:IL-11Rα may comprise contacting cells expressing gp130:IL-11Rα complexes with an antigen-binding molecule according to the present disclosure, *e.g.* in the presence of IL-11.

For example, gp130-mediated signalling can be investigated by evaluating phosphorylation of one or more signal transduction molecules of a signal transduction pathway triggered by signalling through gp130/cytokine receptors comprising gp130 (*e.g.* the JAK/STAT, MAPK/ERK or PI3K/AKT pathways). For

example, the level of gp130-mediated signalling can be analysed by detection and/or quantification of the level of phosphorylation of JAK1, JAK2, STAT1, STAT3, STAT5 and/or ERK (*e.g.* STAT3 and/or ERK). By way of illustration, in the experimental examples of the present disclosure, gp130-mediated signalling (particularly gp130-mediated signalling in response to stimulation with IL-6, IL-11, OSM, LIF, CT-1 or CNTF) is analysed by evaluating phosphorylation of STAT3 or ERK1/2 by western blot.

The level of gp130-mediated signalling can also be evaluated by analysing one or more correlates of gp130-mediated signalling. For example, gp130-mediated signalling may be investigated by detecting and/or quantifying the expression or activity of a factor whose expression/activity is upregulated or downregulated as a consequence of gp130-mediated signalling. In some embodiments, gp130-mediated signalling may be investigated by detecting and/or quantifying the expression of a factor whose expression is upregulated as a consequence of gp130-mediated signalling, *e.g.* a proinflammatory/ profibrotic/profibroinflammatory factor. By way of illustration, gp130-mediated signalling may be analysed by evaluating the expression of αSMA and MMP2.

The level of gp130-mediated signalling can also be analysed using reporter-based methods. For example, gp130-mediated signalling can be investigated using a reporter cell line stably expressing a luciferase reporter driven by gp130-mediated signalling. By way of illustration, gp130-mediated signalling may be investigated using a HEK293 reporter cell line comprising a luciferase gene under the control of STAT3 response elements (STAT3 Reporter (Luc)-HEK293 cell line (puromycin), BPS Bioscience).

In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130 and/or signalling by a receptor comprising gp130 to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence signalling mediated by gp130 and/or signalling by a receptor comprising gp130).

In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-11-mediated signalling. In some embodiments, the antigen-binding molecule inhibits OSM-mediated signalling. In some embodiments, the antigen-binding molecule inhibits LIF-mediated signalling. In some embodiments, the antigen-binding molecule inhibits CNTF-mediated signalling. In some embodiments, the antigen-binding molecule inhibits CT-1-mediated signalling. In some embodiments, the antigen-binding molecule inhibits CLC-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-27-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-35-mediated signalling.

In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling and inhibits IL-11-mediated signalling and inhibits OSM-mediated signalling and inhibits LIF-mediated signalling and inhibits CNTF-mediated signalling and inhibits CT-1-mediated signalling.

In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling and inhibits IL-11-mediated signalling and inhibits OSM-mediated signalling and inhibits LIF-mediated signalling and inhibits CNTF-mediated signalling and inhibits CT-1-mediated signalling and inhibits CLC-mediated signalling and inhibits IL-27-mediated signalling and inhibits IL-35-mediated signalling.

In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-11-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling and inhibits IL-11-mediated signalling.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-11Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:OSMRβ. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:LIFRβ. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:LIFRβ:CNTFRα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-27Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-12Rβ2.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6Rα and inhibits signalling mediated by gp130:IL-11Rα and inhibits signalling mediated by gp130:OSMRβ and inhibits signalling mediated by gp130:LIFRβ and inhibits signalling mediated by gp130:LIFRβ:CNTFRα.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6Rα and inhibits signalling mediated by gp130:IL-11Rα and inhibits signalling mediated by gp130:OSMRβ and inhibits signalling mediated by gp130:LIFRβ and inhibits signalling mediated by gp130:LIFRβ:CNTFRα and inhibits signalling mediated by gp130:IL-27Rα and inhibits signalling mediated by gp130:IL-12Rβ2.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of OSM to cells expressing gp130:OSMRβ. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of OSM to cells expressing gp130:LIFRβ. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of LIF to cells expressing gp130:LIFRβ. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα and inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα and inhibits signalling mediated by binding of OSM to cells expressing gp130:OSMRβ and inhibits signalling mediated by binding of OSM to cells expressing gp130:LIFRβ and inhibits signalling mediated by binding of LIF to cells expressing gp130:LIFRβ and inhibits signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ and inhibits signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα and inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα and inhibits signalling mediated by binding of OSM to cells expressing gp130:OSMRβ and inhibits signalling mediated by binding of OSM to cells expressing gp130:LIFRβ and inhibits signalling mediated by binding of LIF to cells expressing gp130:LIFRβ and inhibits signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ and inhibits signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα and inhibits signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα and inhibits signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα and inhibits signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2.

In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα). In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα to

less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα). In some embodiments, the antigen-binding molecule inhibits IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ). In some embodiments, the antigen-binding molecule inhibits OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling

mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ). In some embodiments, the antigen-binding molecule inhibits LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in

the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ). In some embodiments, the antigen-binding molecule inhibits CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα). In some embodiments, the antigen-binding molecule inhibits CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of

CLC to cells expressing gp130:LIFRβ:CNTFRα). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα). In some embodiments, the antigen-binding molecule inhibits CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα). In some embodiments, the antigen-binding molecule inhibits IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule inhibits IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2 to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times,

≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2). In some embodiments, the antigen-binding molecule inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2 observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2). In some embodiments, the antigen-binding molecule inhibits IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2 with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule: (i) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα); (ii) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα); (iii) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ); (iv) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the LIF-mediated

signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ); (v) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ); and (vi) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα).

In some embodiments, the antigen-binding molecule: (i) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα); (ii) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα); (iii) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ/signalling mediated by gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ/signalling mediated by binding of OSM to cells expressing gp130:LIFRβ); (iv) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the LIF-mediated

signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ); (v) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ); (vi) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα); (vii) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CLC-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CLC to cells expressing gp130:LIFRβ:CNTFRα); (viii) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-27-mediated signalling/signalling mediated by gp130:IL-27Rα/signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα); and (ix) inhibits more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2 observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-35-mediated signalling/signalling mediated by gp130:IL-12Rβ2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2).

In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-11-mediated signalling. In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling and inhibits IL-11-mediated signalling.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-11Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6Rα, and inhibits signalling mediated by gp130:IL-11Rα.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα. In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα, and inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα).

In some embodiments, the antigen-binding molecule is capable of inhibiting more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα with an IC_{50} of less than 100 nM, preferably one of ≤70 nM, ≤60 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤10 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200

pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling. In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα with an IC_{50} of less than 15 µg/ml, preferably one of ≤11 µg/ml, ≤10 µg/ml, ≤9 µg/ml, ≤8 µg/ml, ≤7 µg/ml, ≤6 µg/ml, ≤5 µg/ml, ≤4 µg/ml, ≤3 µg/ml, ≤2 µg/ml, ≤1 µg/ml, ≤0.9 µg/ml, ≤0.8 µg/ml, ≤0.7 µg/ml, ≤0.6 µg/ml, ≤0.5 µg/ml, ≤0.4 µg/ml, ≤0.3 µg/ml, ≤0.2 µg/ml, ≤0.1 µg/ml, ≤0.09 µg/ml, ≤0.8 µg/ml, ≤0.07 µg/ml, ≤0.06 µg/ml, or ≤0.05 µg/ml, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα with an IC_{50} of less than 10 µg/ml, preferably one of ≤5 µg/ml, ≤4 µg/ml, ≤3 µg/ml, ≤2 µg/ml, ≤1 µg/ml, ≤0.9 µg/ml, ≤0.8 µg/ml, ≤0.7 µg/ml, ≤0.6 µg/ml or ≤0.5 µg/ml, *e.g.* as determined by analysis as described in Example 29 or 61 herein.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα).

In some embodiments, the antigen-binding molecule is capable of inhibiting more than 50%, *e.g.* ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule), and is capable of inhibiting IL-11-mediated

signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule).

In some embodiments, the antigen-binding molecule is capable of inhibiting more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα), *e.g.* as determined in an assay performed as described in Examples 1 and 11 herein, and is capable of inhibiting more than 50%, *e.g.* ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα with an IC_{50} of less than 1 μM, preferably one of ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling. In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα with an IC_{50} of less than 10 nM, preferably one of ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤900 pM, ≤800 pM, ≤700 pM, ≤600 pM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling. In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα with an IC_{50} of less than 1 μg/ml, preferably one of ≤0.9 μg/ml, ≤0.8 μg/ml, ≤0.7 μg/ml, ≤0.6 μg/ml, ≤0.5 μg/ml, ≤0.4 μg/ml, ≤0.3 μg/ml, ≤0.2 μg/ml, ≤0.1 μg/ml, ≤0.09 μg/ml, ≤0.8 μg/ml, ≤0.07 μg/ml, ≤0.06 μg/ml, or ≤0.05 μg/ml, *e.g.* as determined in an appropriate *in vitro* assay of the ability of an antigen-binding molecule to inhibit such signalling.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα with an IC_{50} of less than 10 μg/ml, preferably one of ≤5 μg/ml, ≤4 μg/ml, ≤3 μg/ml, ≤2 μg/ml, ≤1 μg/ml, ≤0.9 μg/ml, ≤0.8 μg/ml, ≤0.7 μg/ml, ≤0.6 μg/ml or ≤0.5 μg/ml, *e.g.* as determined by analysis as described in Example 29 or 61 herein.

In some embodiments, the antigen-binding molecule does not inhibit (*i.e.*, does not substantially inhibit) OSM-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit LIF-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit CNTF-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit CT-1-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit CLC-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit IL-27-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit IL-35-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit OSM-mediated signalling, does not inhibit LIF-mediated signalling, does not inhibit CNTF-mediated signalling, does not inhibit CT-1-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit OSM-mediated signalling, does not inhibit LIF-mediated signalling, does not inhibit CNTF-mediated signalling, does not inhibit CT-1-mediated signalling, does not inhibit IL-27-mediated signalling, does not inhibit IL-35-mediated signalling. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by a cytokine other than IL-6 or IL-11.

In some embodiments, the antigen-binding molecule does not inhibit (*i.e.*, does not substantially inhibit) signalling mediated by gp130:OSMRβ. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:LIFRβ. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:LIFRβ:CNTFRα. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:IL-27Rα. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:IL-12Rβ2. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMRβ, and does not inhibit signalling mediated by gp130:LIFRβ, and does not inhibit signalling mediated by gp130:LIFRβ:CNTFRα. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMRβ, and does not inhibit signalling mediated by gp130:LIFRβ, and does not inhibit signalling mediated by gp130:LIFRβ:CNTFRα, and does not inhibit signalling mediated by gp130:IL-27Rα, and does not inhibit signalling mediated by gp130:IL-12Rβ2. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by a gp130-containing polypeptide complex other than gp130:IL-6Rα or gp130:IL-11Rα.

In some embodiments, the antigen-binding molecule does not inhibit (*i.e.*, does not substantially inhibit) signalling mediated by binding of OSM to cells expressing gp130:OSMRβ. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of OSM, LIF or CT-1 to cells expressing gp130:LIFRβ. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of CNTF or CLC to cells expressing gp130:LIFRβ:CNTFRα. In some embodiments,

the antigen-binding molecule does not inhibit signalling mediated by binding of IL-27 to cells expressing gp130:IL-27Rα. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of IL-35 to cells expressing gp130:IL-12Rβ2. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of OSM to cells expressing gp130:OSMRβ, and does not inhibit signalling mediated by binding of OSM, LIF or CT-1 to cells expressing gp130:LIFRβ, and does not inhibit signalling mediated by binding of CNTF or CLC to cells expressing gp130:LIFRβ:CNTFRα. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of OSM to cells expressing gp130:OSMRβ, and does not inhibit signalling mediated by binding of OSM, LIF or CT-1 to cells expressing gp130:LIFRβ, and does not inhibit signalling mediated by binding of CNTF or CLC to cells expressing gp130:LIFRβ:CNTFRα, and does not inhibit signalling mediated by binding of IL-27 to cells expressing gp130:LIFRβ:IL-27Rα, and does not inhibit signalling mediated by binding of IL-35 to cells expressing gp130:LIFRβ:IL-12Rβ2.

In an assay of the ability of an antigen-binding molecule to inhibit signalling mediated by a given cytokine/gp130-containing receptor complex/binding of a given cytokine to cells expressing a given gp130-containing receptor complex, an antigen-binding molecule that 'does not inhibit' or that 'does not substantially inhibit' signalling may inhibit the relevant signalling with an IC50 greater than 1 μM, preferably one of ≥5 μM, ≥10 μM, ≥20 μM, ≥50 μM, ≥100 μM, ≥500 μM or ≥1 M.

In an assay of the ability of an antigen-binding molecule to inhibit signalling mediated by a given cytokine/gp130-containing receptor complex/binding of a given cytokine to cells expressing a given gp130-containing receptor complex, an antigen-binding molecule that 'does not inhibit' or that 'does not substantially inhibit' signalling may not inhibit the relevant signalling to less than 0.8 times, *e.g.* may not inhibit the relevant signalling to <0.85 times, <0.86 times, <0.87 times, <0.88 times, <0.89 times, <0.9 times, <0.91 times, <0.92 times, <0.93 times, <0.94 times, <0.95 times, <0.96 times, <0.97 times, <0.98 times, <0.99 times or <1 times the level of signalling observed in the relevant assay in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to affect signalling by the given cytokine/through the given gp130-containing receptor complex).

In an assay of the ability of an antigen-binding molecule to inhibit signalling mediated by a given cytokine/gp130-containing receptor complex/binding of a given cytokine to cells expressing a given gp130-containing receptor complex, the level of signalling observed in the presence of an antigen-binding molecule that 'does not inhibit' or that 'does not substantially inhibit' signalling may be similar to the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to affect signalling by the given cytokine/through the given gp130-containing receptor complex). In some embodiments, a 'similar' level of signalling in accordance with the preceding sentence may be ≥0.5 times and ≤2 times, *e.g.* one of ≥0.75 times and ≤1.5 times, ≥0.8 times and ≤1.4 times, ≥0.85 times and ≤1.3 times, ≥0.9 times and ≤1.2 times, ≥0.95 times and ≤1.1 times the reference level of signalling.

In some embodiments, the antigen-binding molecule inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein.

In some embodiments, the antigen-binding molecule inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the OSM-mediated signalling/signalling mediated by gp130:OSMRβ or gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ or gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ or gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ or gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein.

In some embodiments, the antigen-binding molecule: (i) is capable of inhibiting more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein; (ii) is capable of inhibiting more than 50%, *e.g.* ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein; (iii) inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein; and (iv) inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the OSM-mediated signalling/signalling mediated by gp130:OSMRβ or gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ

or gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ or gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ or gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein.

In some embodiments, the antigen-binding molecule inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 39 herein.

In some embodiments, the antigen-binding molecule inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα), *e.g.* as determined in an assay performed as described in Examples 28 and 39 herein.

In some embodiments, the antigen-binding molecule: (i) is capable of inhibiting more than 25%, *e.g.* ≥30%, ≥35%, ≥40%, ≥45%, ≥50%, ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-6-mediated signalling/signalling mediated by gp130:IL-6Rα/signalling mediated by binding of IL-6 to cells expressing gp130:IL-6Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein; (ii) is capable of inhibiting more than 50%, *e.g.* ≥55%, ≥60%, ≥65%, ≥70%, ≥75%, ≥80%, ≥85%, ≥90%, ≥95%, ≥96%, ≥97%, ≥98% or ≥99% of the IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence IL-11-mediated signalling/signalling mediated by gp130:IL-11Rα/signalling mediated by binding of IL-11 to cells expressing gp130:IL-11Rα), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein; (iii) inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an

appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence LIF-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of LIF to cells expressing gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein; (iv) inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the OSM-mediated signalling/signalling mediated by gp130:OSMRβ or gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ or gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMRβ or gp130:LIFRβ/signalling mediated by binding of OSM to cells expressing gp130:OSMRβ or gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 38 herein, (v) inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFRβ/signalling mediated by binding of CT-1 to cells expressing gp130:LIFRβ), *e.g.* as determined in an assay performed as described in Examples 28 and 39 herein, and (vi) inhibits less than 20%, *e.g.* ≤15%, ≤14%, ≤13%, ≤12%, ≤11%, ≤10%, ≤9%, ≤8%, ≤7%, ≤6%, ≤5%, ≤4%, ≤3%, ≤2% or ≤1% of the CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFRβ:CNTFRα/signalling mediated by binding of CNTF to cells expressing gp130:LIFRβ:CNTFRα), *e.g.* as determined in an assay performed as described in Examples 28 and 39 herein.

In some embodiments, an antigen-binding molecule according to the present disclosure reduces inflammation. In some embodiments, an antigen-binding molecule according to the present disclosure reduces fibrosis. In some embodiments, an antigen-binding molecule according to the present disclosure reduces inflammation and fibrosis.

The ability of, and extent to which, a given antigen-binding molecule/composition/combination to reduce inflammation and/or fibrosis can be evaluated in an appropriate *in vitro* or *in vivo* model of inflammation/fibrosis. For example, *in vitro* methods may comprise contacting cells (*e.g.* gp130-expressing cells) with a proinflammatory, profibrotic or profibroinflammatory stimulus (*e.g.* IL-6, IL-11, TGFβ1, *etc.*) in the presence of the antigen-binding molecule/composition/combination, and subsequently evaluating the cells to determine the level of one or more correlates of inflammation/fibrosis. By way of illustration, in the experimental examples of the present disclosure, gp130-specific antigen-binding molecules are evaluated for their ability to reduce fibrosis in *in vitro* assays in which cells are stimulated with TGFβ1 or IL-11, and in which the fibrotic response is subsequently analysed by evaluating the expression of MMP2. By way of illustration, in the experimental examples of the present disclosure, gp130-specific antigen-binding molecules are evaluated for their ability to reduce fibrosis in an *in vitro*

assay in which cells are stimulated with IL-6 or IL-11, and in which the fibrotic response is subsequently analysed by evaluating the expression of αSMA and MMP2.

Analysis *in vivo* of the ability of, and extent to which, a given antigen-binding molecule/composition/combination reduces inflammation and/or fibrosis may employ a non-human animal model of a disease characterised by inflammation and/or fibrosis. Such models are also useful to evaluate the ability of an antigen-binding molecule to reduce the pathology of a disease/condition characterised by inflammation and/or fibrosis. Such analysis may comprise administering the antigen-binding molecule/composition/combination to a subject having a disease characterised by inflammation and/or fibrosis, and subsequently evaluating one or more correlates of inflammation/fibrosis in the subject. By way of illustration, in the experimental examples of the present disclosure, gp130-specific antigen-binding molecules are evaluated for their ability to reduce inflammation and fibrosis *in vivo* in a folic acid-induced mouse model of acute kidney injury, by evaluating *e.g.* serum levels of IL-6, collagen content of the kidney, and renal expression of proinflammatory genes (*e.g. Ccl2, Ccl5, Il6, Tnfα* and *Il1β*), and profibrotic genes (*e.g. Col1a1, Col1a2, Col3a1, Fn, Acta2* and *Il11*).

In some embodiments, administration of an antigen-binding molecule according to the present disclosure may inhibit the development/progression of a disease/condition characterised by inflammation and/or fibrosis. In some embodiments, administration of the antigen-binding molecule may reduce the severity of the symptoms of a disease/condition characterised by inflammation and/or fibrosis, *e.g.* as determined in an appropriate model.

In some embodiments, the antigen-binding molecule of the present disclosure is capable of reducing the level of one of more correlates of inflammation and/or fibrosis (*e.g.* in an *in vitro* model of inflammation/fibrosis, or in an *in vivo* model of a disease/condition characterised by inflammation/fibrosis) to less than 1 times, *e.g.* ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times, ≤0.05 times, or ≤0.01 times the level observed in the absence of treatment with the antigen-binding molecule (or following treatment with an appropriate control antigen-binding molecule known not to influence the level of the relevant correlate(s)), in a given assay.

Antigen-binding molecules according to the present disclosure may comprise one or more moieties for potentiating cell killing of, or reducing the number/proportion of, cells expressing gp130. For example, an antigen-binding molecule according to the present disclosure may *e.g.* comprise an Fc region and/or a drug moiety.

In some embodiments, an antigen-binding molecule according to the present disclosure may potentiate (*i.e.* upregulate, enhance) cell killing of cells comprising/expressing gp130. In some embodiments, the antigen-binding molecule does not potentiate (*i.e.* does not substantially potentiate) cell killing of cells lacking surface expression of gp130.

Cell killing can be investigated, for example, using any of the methods reviewed in Zaritskaya *et al.,* Expert Rev Vaccines (2011), 9(6):601-616, hereby incorporated by reference in its entirety. Examples of *in vitro* assays of cytotoxicity/cell killing assays include release assays such as the 51Cr release assay, the lactate dehydrogenase (LDH) release assay, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) release assay, and the calcein-acetoxymethyl (calcein-AM) release assay. These assays measure cell killing based on the detection of factors released from lysed cells. Cell killing of a given test cell type by a given effector immune cell type can be analysed *e.g.* by co-culturing the test cells with the effector immune cells, and measuring the number/proportion of viable/dead (*e.g.* lysed) test cells after a suitable period of time. Other suitable assays include the xCELLigence real-time cytolytic *in vitro* potency assay described in Cerignoli *et al*., PLoS One. (2018) 13(3): e0193498 (hereby incorporated by reference in its entirety).

In some embodiments an antigen-binding molecule according to the present disclosure is capable of reducing the number/proportion of cells expressing gp130. In some embodiments an antigen-binding molecule according to the present disclosure is capable of reducing the number/proportion of cells expressing gp130. In some embodiments, an antigen-binding molecule according to the present disclosure is capable of depleting/enhancing depletion of such cells.

Fc regions provide for interaction with Fc receptors and other molecules of the immune system to bring about functional effects. IgG Fc-mediated effector functions are reviewed *e.g.* in Jefferis *et al*., Immunol Rev 1998 163:59-76 (hereby incorporated by reference in its entirety), and are brought about through Fc-mediated recruitment and activation of immune cells (*e.g.* macrophages, dendritic cells, neutrophils, basophils, eosinophils, platelets, mast cells, NK cells and T cells) through interaction between the Fc region and Fc receptors expressed by the immune cells, recruitment of complement pathway components through binding of the Fc region to complement protein C1q, and consequent activation of the complement cascade. Fc-mediated functions include Fc receptor binding, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), formation of the membrane attack complex (MAC), cell degranulation, cytokine and/or chemokine production, and antigen processing and presentation.

In some embodiments, an antigen-binding molecule according to the present disclosure comprises an Fc region capable of potentiating/directing one or more of ADCC, ADCP, CDC against, and/or potentiating formation of a MAC on or cell degranulation of, a cell expressing gp130 (*e.g.* a cell expressing gp130 at the cell surface).

In some embodiments, an antigen-binding molecule according to the present disclosure is capable of potentiating/directing ADCC against a cell expressing gp130.

The ability of, and extent to which, a given antigen-binding molecule is able to induce ADCC of a given target cell type can be analysed *e.g.* according to the method described in Yamashita *et al*., Scientific Reports (2016) 6:19772 (hereby incorporated by reference in its entirety), or by 51Cr release assay as described *e.g.* in Jedema *et al.,* Blood (2004) 103: 2677–82 (hereby incorporated by reference in its

entirety). The ability of, and extent to which, a given antigen-binding molecule is able to induce ADCP can be analysed *e.g.* according to the method described in Kamen *et al.*, J Immunol (2017) 198 (1 Supplement) 157.17 (hereby incorporated by reference in its entirety). The ability of, and extent to which, a given antigen-binding molecule is able to induce CDC can be analysed *e.g.* using a C1q binding assay, *e.g.* as described in Schlothauer *et al.*, Protein Engineering, Design and Selection (2016), 29(10):457–466 (hereby incorporated by reference in its entirety).

In some embodiments, an antigen-binding molecule according to the present disclosure comprises a drug moiety. The antigen-binding molecule may be conjugated to the drug moiety. Antibody-drug conjugates are reviewed *e.g.* in Parslow *et al.,* Biomedicines. 2016 Sep; 4(3):14 (hereby incorporated by reference in its entirety). In some embodiments, the drug moiety is or comprises a cytotoxic agent, such that the antigen-binding molecule displays cytotoxicity to a cell expressing gp130 (*e.g.* a cell expressing gp130 at the cell surface).

In some embodiments, an antigen-binding molecule according to the present disclosure is capable of reducing or inhibiting angiogenesis. In some embodiments, the antigen-binding molecule is capable of reducing or inhibiting choroidal neovascularization (*e.g.* reducing the size of CNV lesions and/or reducing CNV leakage area).

Antigen-binding molecules, compositions and combinations can be evaluated for their ability to reduce/inhibit angiogenesis and/or choroidal neovascularization using appropriate assays of angiogenesis and/or choroidal neovascularization. By way of illustration, the 'General Materials and Methods for Examples 1-3' and Example 2 herein describe evaluation of the ability of antigen-binding molecules to reduce/inhibit angiogenesis (particularly choroidal neovascularization) in a laser-induced mouse model of choroidal neovascularization. In the present disclosure, CNV is evaluated by fluorescein fundus angiogram (FFA) and/or posterior-segment Optical Coherence Tomography (PS-OCT). Example 2 herein further describes the assessment of fibrotic area of the retina via histopathological examination, or through immunofluorescence staining and examination. Further assays in which the ability of a given antigen-binding molecule/composition/combination to reduce/inhibit angiogenesis and/or choroidal neovascularization can be evaluated are described *e.g.* in Tahergorabi and Khazaei, Iran J Basic Med Sci. (2012) 15(6): 1110–1126.

In some embodiments, an antigen-binding molecule according to the present disclosure is capable of reducing the expression (*i.e.* gene and/or protein expression) of VEGF, TGF-β, TNF-α, IL-6, COL1A1 and/or IL-11.

Antigen-binding molecules, compositions and combinations may be analyzed for the ability to reduce the expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1 and/or IL-11 in appropriate assays. By way of illustration, the 'General Materials and Methods for Examples 1-3' and Example 3 herein describe evaluation of the ability of antigen-binding molecules/compositions to reduce/inhibit expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1 and IL-11 by qRT-PCR.

Assays for evaluating the ability of an antigen-binding molecule/composition/combination to reduce gene expression may comprise detecting the level of RNA encoding the relevant protein, *e.g.* by RT-qPCR. Such assays may comprise treating cells/tissue with the relevant agent, and subsequently comparing the level of RNA encoding the relevant protein in such cells/tissue to the level of RNA encoding the relevant protein in cells/tissue of an appropriate control condition (*e.g.* untreated/vehicle-treated cells/tissue). Assays for evaluating the ability of an antigen-binding molecule/composition/combination to reduce protein expression may comprise detecting the level of the relevant protein, *e.g.* using antibody/reporter-based methods (western blot, ELISA, immunohisto/cytochemistry, *etc.*). Such assays may comprise treating cells/tissue with the relevant agent, and subsequently comparing the level of the relevant protein in such cells/tissue to the level of the relevant protein in cells/tissue of an appropriate control condition (*e.g.* untreated/vehicle-treated cells/tissue).

Angiogenic factors

Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels. It is a vital process in growth and would healing. Dysregulation of angiogenesis has been linked to several diseases and conditions, including tumour malignancy, inflammation, and fibrosis. Upregulation of angiogenesis is a common feature in diseases of the eye, and especially in neovascular diseases of the retina, many of which result in fibrosis.

Numerous inducers of angiogenesis have been identified, including the members of the vascular endothelial growth factor (VEGF) family, angiopoietins, transforming growth factors (TGF), members of the platelet-derived growth factor family, tumour necrosis factor-α, interleukins and the members of the fibroblast growth factor (FGF) family. The cellular and molecular mechanisms of angiogenesis are described in Adams & Alitalo, Nature Reviews Molecular Cell Biology volume 8, pages 464–478 (2007), and Otrock *et al*, *Understanding the biology of angiogenesis: Review of the most important molecular mechanisms*, Blood Cells, Molecules, and Diseases, Volume 39, Issue 2, 2007, Pages 212-220, which are herein incorporated by reference in their entirety.

As used herein, an ‘angiogenic factor’ refers to any factor (*e.g.* peptide/polypeptide, glycoprotein, lipoprotein, glycan, glycolipid, lipid, nucleic acid or fragment thereof) capable of inducing/potentiating/promoting angiogenesis.

Factors capable of inducing/potentiating/promoting angiogenesis can be identified *e.g.* by analysis in an *in vitro* or *in vivo* assay of angiogenesis. Suitable assays for analysis of angiogenesis include endothelial cell migration assays, endothelial cell proliferation assays, and endothelial tube formation assays. Angiogenesis assays are described in detail in Adair TH, Montani JP. *Angiogenesis*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010, *Chapter 2, Angiogenesis Assays,* which is herein incorporated by reference in its entirety.

In some embodiments, an angiogenic factor is a polypeptide or a polypeptide complex capable of inducing/promoting angiogenesis. An angiogenic factor may be soluble or membrane-bound, and may be

a polypeptide or polypeptide complex ligand, or a polypeptide or polypeptide complex receptor for such a ligand. An angiogenic factor may be from any species, and includes isoforms, fragments, variants or homologues of an angiogenic factor from any species. In preferred embodiments the species is human (*Homo sapiens*). Isoforms, fragments, variants or homologues of an angiogenic factor may optionally be characterised as having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of immature or mature angiogenic factor from a given species, *e.g.* human. Isoforms, fragments, variants or homologues of an angiogenic factor may optionally be characterised by ability to bind to an interaction partner for the angiogenic factor (*e.g.* a receptor for the angiogenic factor, or a ligand for the angiogenic factor) and/or ability to induce/promote angiogenesis. For example, an angiogenic factor may be a VEGF, a VEGF receptor, an FGF, an FGF receptor, a PDGF, or a PDGF receptor, or a fragment, variant, isoform or homologue of a VEGF, a VEGF receptor, an FGF, an FGF receptor, a PDGF, or a PDGF receptor.

A fragment of a polypeptide of an angiogenic factor may be of any length (by number of amino acids), although may optionally be at least 25% of the length of mature angiogenic factor and may have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of the mature angiogenic factor. An angiogenic factor may be a complex comprising one or more subunits, such as a hetero or homodimer.

As used herein, an 'interaction partner for an angiogenic factor' refers to any factor (*e.g.* polypeptide or polypeptide complex) capable of interacting with (*e.g.* binding to) an angiogenic factor. The interaction may be non-covalent association.

An angiogenic factor and an interaction partner for the angiogenic factor preferably associate to form a biologically-functional complex, *e.g.* a receptor:ligand complex capable of initiating/promoting signalling (*e.g.* proangiogenic signalling). An interaction partner for an angiogenic factor may *e.g.* be a receptor for the angiogenic factor, or a ligand for the angiogenic factor. In some embodiments, interaction between an interaction partner for an angiogenic factor and the angiogenic factor induces/promotes proangiogenic signalling and/or angiogenesis. For example, binding of VEGF to a VEGF receptor is capable of triggering intracellular signalling by cells expressing the VEGF receptor, inducing/promoting angiogenic processes.

For example, an interaction partner for an angiogenic factor may be an angiogenic factor receptor. In some embodiments an angiogenic factor receptor may be a polypeptide or polypeptide complex capable of binding a VEGF, an FGF, a PDGF, or a fragment, variant, isoform or homologue of a VEGF, an FGF, or a PDGF. Angiogenic factor receptors include *e.g.* VEGF receptors, FGF receptors, and PDGF receptors. It will be appreciated that angiogenic factor receptors are angiogenic factors according to the present disclosure. For example, VEGFR is both an angiogenic factor (*i.e.* a factor capable of inducing/potentiating/promoting angiogenesis) and an angiogenic factor receptor (*i.e.* a receptor for VEGF).

Similarly, an interaction partner for an angiogenic factor may be a ligand for an angiogenic factor receptor. In some embodiments a ligand for an angiogenic factor receptor may be a polypeptide or

polypeptide complex capable of binding a VEGF receptor, an FGF receptor, a PDGF receptor, or a fragment, variant, isoform or homologue of a VEGF receptor, an FGF receptor, or a PDGF receptor. Angiogenic factor ligands include *e.g.* VEGF, FGF, and PDGF. It will be appreciated that angiogenic factor ligands are angiogenic factors according to the present disclosure. For example, VEGF is both an angiogenic factor (*i.e.* a factor capable of inducing/potentiating/promoting angiogenesis) and a ligand for an angiogenic factor receptor (*i.e.* a ligand for VEGF receptor).

In some embodiments herein, the angiogenic factor is a VEGF. VEGF is a growth factor, encoded by a gene family that includes placental growth factor (PlGF, AAD30179.1 GI: 4809334), VEGF-A (AAP86646.1 GI: 32699990), VEGF-B (AAC50721.1 GI: 1488259), VEGF-C (CAA63907.1 GI: 1182005), VEGF-D (BAA24264.1 GI: 2766190), and the orf virus encoded VEGF-E (ABA00650.1 GI: 74230845). In some embodiments, the VEGF is VEGF-A. Differences in exon splicing result in the generation of four main VEGF-A isoforms: VEGF121, VEGF165, VEGF189, and VEGF206, which have 121, 165, 189, and 206 amino acids after cleavage of the signal sequence, respectively (Alitalo *et al.* Nature. (2005) 438:946–953). VEGF165 appears to be the dominant isoform.

VEGF stimulates the growth of vascular endothelial cells derived from arteries, veins, and the lymphatic system, as well as inducing angiogenesis in a variety of *in vivo* models (*i.e.* the formation of thin-walled endothelium-lined structures), inducing rapid elevations in microvascular permeability (Lee *et al.* J Cell Biol. (2005)169:681–691; Leung *et al.* Science. (1989) 246:1306–1309; Alon *et al.* Nat Med. (1995) 1:1024–1028).

In this specification, 'VEGF' refers to a VEGF (*e.g.* VEGF-A, B, C, D or E) from any species and includes isoforms, fragments, variants or homologues of a VEGF from any species. In preferred embodiments the species is human (*Homo sapiens*). A fragment of VEGF may be of any length (by number of amino acids), although may optionally be at least 25% of the length of mature VEGF and may have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of mature VEGF. A fragment of VEGF may have a minimum length of 10 amino acids, and a maximum length of one of 15, 20, 25, 30, 40, 50, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220 or 225 amino acids.

VEGF exerts its biological effects through binding to three receptors – VEGFR1 (AAH39007.1 GI: 24660372), VEGFR2 (P35968.2 GI: 9087218) and VEGFR3 (AAA85215.1 GI: 1150991). Each receptor has extracellular binding domains for VEGF, a transmembrane sequence and intracellular tyrosine kinase moieties. VEGF binding to the extracellular receptor domain dimerizes the receptors and results in phosphorylation of the intracellular tyrosine kinase moieties.

In this specification, 'a receptor for VEGF' or 'a VEGF receptor' refers to a polypeptide or polypeptide complex capable of binding VEGF. In some embodiments a VEGF receptor is capable of binding VEGF and inducing signal transduction in cells expressing the receptor. In some embodiments, 'a receptor for VEGF' refers to a VEGFR. In this specification, unless otherwise stated, 'VEGFR' refers to VEGFR1, VEGFR2 and/or VEGFR3.

VEGFR may optionally be characterised as having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of VEGFR from a given species, *e.g.* human. Isoforms, fragments, variants or homologues of VEGFR may optionally be characterised by ability to bind VEGF (preferably from the same species) and stimulate signal transduction in cells expressing the VEGFR. A fragment of an VEGF receptor may be of any length (by number of amino acids), although may optionally be at least 25% of the length of the mature VEGFR and have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of the mature VEGFR. A fragment of an VEGF receptor fragment may have a minimum length of 10 amino acids, and a maximum length of one of 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, 1000, 1010, 1020, 1030, 1040, 1050, 1060, 1070, 1080, 1090, 1100, 1110, 1120, 1130, 1140, 1150, 1160, 1170, 1180, 1190, 1200, 1210, 1220, 1230, 1240, 1250, 1260, 1270, 1280, 1290, 1300, 1310, 1320, 1330, 1340, 1350, 1360, 1370, 1380, 1390, 1400, 1410, 1420, 1430, 1440, 1450, 1460, 1470, 1480, 1490, 1500, 1510, 1520, 1530, 1540, 1550, 1560, 1570, 1580, 1590, 1600, 1610, 1620, 1630, 1640, 1650, 1660, 1670, 1680, 1690, 1700, 1710, 1720, 1730, 1740, 1750, 1760, 1770, 1780, 1790, or 1795 amino acids.

In some embodiments, the angiogenic factor is an FGF. Acidic and basic fibroblast growth factors, aFGF and bFGF respectively, are heparin-binding protein mitogens that are thought to play an important role in angiogenesis. There are 22 distinct FGFs and four different tyrosine kinase receptors (FGFRs). FGF and its receptors are reviewed in Presta *et al*. Cytokine Growth Factor Rev. (2005), 16:159-178, which is herein incorporated by reference in its entirety.

As used herein, 'FGF' refers to an aFGF or bFGF from any species and includes isoforms, fragments, variants or homologues thereof. For example and FGF may be: FGF1 (AAH32697.1 GI: 21595687), FGF2 (P09038.3 GI: 261260095), FGF3 (P11487.1 GI: 122748), FGF4 (NP_001998.1 GI: 4503701), FGF5 (P12034.4 GI: 85700417), FGF6 (P10767.4 GI: 1169676), FGF7 (P21781.1 GI: 122756), FGF8 (NP_001193318.1 GI: 329755303), FGF9 (NP_002001.1 GI: 4503707), FGF10 (CAG46466.1 GI: 49456291), FGF11 (Q92914.1 GI: 2494457), FGF12 (P61328.1 GI: 47117683), FGF13 (Q92913.1 GI: 2494461), FGF14 (NP_001308867.1 GI: 1013165743), FGF15 (AAO13811.1 GI: 27448228), FGF16 (NP_003859.1 GI: 4503691), FGF17 (AAQ89228.1 GI: 37182856), FGF18 (AAQ89954.1 GI: 37222209), FGF19 (NP_005108.1 GI: 4826726), FGF20 (AAH98339.1 GI: 68226699), FGF21 (AAQ89444.1 GI: 37183289), or FGF22 (Q9HCT0.1 GI: 13626689), or isoforms, fragments, variants or homologues thereof. An 'FGF receptor' refers to a polypeptide or polypeptide complex capable of binding an FGF, and isoforms, fragments, variants or homologues thereof. FGF receptors include FGFR1 (AAH15035.1 GI: 21955340), FGFR2 (AAA61188.1 GI: 3397110), FGFR3 (P22607.1 GI: 120050), and FGFR4 (AAH11847.1 GI: 15080148), and isoforms, fragments, variants or homologues thereof. In some

embodiments, the FGF receptor is capable of binding FGF and inducing signal transduction in cells expressing the FGF receptor.

In some embodiments, the angiogenic factor is a PDGF. PDGF was initially purified from platelets and was then identified in fibroblasts, astrocytes, keratinocytes, epithelial cells and other cell types. PDGFs exist as heterodimers (PDGF-AB) or homodimers (PDGF-AA or -BB) composed of chains A (P04085.1 GI: 129719) and B (CAG46606.1 GI: 49456571). There are two forms of the PDGF-R, alpha (P16234.1 GI: 129892) and beta (P09619.1 GI: 129890) each encoded by a different gene. Depending on which growth factor is bound, PDGF-R homo- or heterodimerizes. PDGF and its receptors are described in Ross *et al*, Cell. (1986) 46:155-169, which is herein incorporated by reference in its entirety.

As used herein, 'PDGF' refers to PDGF-A, PDGF-B, PDGF-AB, PDGF-AA, PDGF-BA, or PDGF-BB from any species and includes isoforms, fragments, variants or homologues thereof. A 'PDGF receptor' refers to a polypeptide or polypeptide complex capable of binding a PDGF, or isoforms, fragments, variants or homologues thereof. In some embodiments, the PDGF receptor is PDGF-R alpha, PDGF-R beta, PDGF-R alpha-alpha homodimer, PDGF-R beta-beta homodimer, or the PDGF-R alpha-beta heterodimer. In some embodiments, the PDGF receptor is capable of binding PDGF and inducing signal transduction in cells expressing the PDGF receptor.

Other angiogenic factors include angiogenin (NP_001091046.1 GI: 148277046), angiopoietin (AAD19608.1 GI: 4378598), integrins (*e.g.* selected from NP_001004439.1 GI: 52485853, NP_002194.2 GI: 116295258, NP_002195.1 GI: 4504747, NP_000876.3 GI: 67191027, NP_002196.4 GI: 1017029567, NP_001303235.1 GI: 937834186, NP_001138468.1 GI: 222418613, NP_003629.2 GI: 612407851, NP_002198.2 GI: 52485941, NP_001273304.1 GI: 556503454, NP_001004439.1 GI: 52485853, NP_001305114.1 GI: 970949440, NP_001273304.1 GI: 556503454, NP_002200.2 GI: 167466215, NP_001139280.1 GI: 224831239, NP_002201.1 GI: 4504763, EAW51597.1 GI: 119571982, NP_001273304.1 GI: 556503454, NP_391988.1 GI: 19743819, NP_001120963.2 GI: 735367803, NP_000203.2 GI: 47078292, NP_000204.3 GI: 54607035, NP_001341694.1 GI: 1269208512, NP_001269282.1 GI: 538916664, NP_000880.1 GI: 4504777, NP_002205.1 GI: 4504779), TGF-β (AAA36738.1 GI: 339564) and TNFα (AQY77150.1 GI: 1159611449).

Antagonists of angiogenic factors

Aspects of the present invention involve antagonism (*i.e.* inhibition) of angiogenesis, *e.g.* by antagonism of one or more angiogenic factors.

Herein, 'inhibition' refers to a reduction, decrease or lessening relative to a control condition. For example, inhibition of angiogenic signalling by an antagonist of an angiogenic factor refers to a reduction, decrease or lessening of the extent/degree of angiogenic signalling in the presence of the agent, and/or in the absence of an appropriate control agent.

Inhibition may herein also be referred to as neutralisation or antagonism. An antagonist of an angiogenic factor (*e.g.* an antagonist of an activity mediated by an angiogenic factor, or an antagonist of angiogenic signalling) may be said to be a 'neutralising' or 'antagonist' agent with respect to the relevant function or process. For example, an agent which is capable of inhibiting an angiogenic factor may be referred to as an agent which is capable of neutralising an angiogenic factor or may be referred to as an antagonist of an angiogenic factor. Additionally, an agent which is capable of inhibiting angiogenic signalling may be referred to as an agent which is capable of neutralising angiogenic signalling or may be referred to as an antagonist of angiogenic signalling.

Angiogenic signalling pathways offer multiple routes for inhibition of signalling. An antagonist of angiogenic signalling may inhibit the action of an angiogenic factor through inhibiting the action of one or more factors involved in, or necessary for, signalling through a receptor for that factor.

For example, inhibition may be achieved by disrupting interaction between an angiogenic factor (*e.g.* VEGF) and a receptor for that factor (*e.g.* VEGFR1, 2 or 3). In some embodiments, inhibition of angiogenic signalling is achieved by inhibiting the gene or protein expression of one or more of *e.g.* VEGF, VEGFR1, VEGFR2, and VEGFR3.

Binding agents

In some embodiments, an antagonist of an angiogenic factor may bind to an angiogenic factor. In some embodiments, an antagonist of an angiogenic factor may bind to an interaction partner for an angiogenic factor. In some embodiments, an antagonist of an angiogenic factor may bind to a receptor for an angiogenic factor (*e.g.* VEGFR1, VEGFR2 or VEGFR3 for VEGF). Binding of such agents may inhibit angiogenic factor-mediated signalling by reducing/preventing the ability of an angiogenic factor ligand to bind to receptors, thereby inhibiting downstream signalling.

Agents capable of binding to an angiogenic factor or an interaction partner for an angiogenic factor may be of any kind, but in some embodiments the agent may be an antigen-binding molecule *e.g.* an antibody or an antigen-binding fragment thereof, a polypeptide, a peptide, a nucleic acid, an oligonucleotide, an aptamer or a small molecule. The agents may be provided in isolated or purified form, or may be formulated as a pharmaceutical composition or medicament.

In some embodiments, an antagonist of an angiogenic factor is an antigen-binding molecules (*e.g.* an antibody, or an antigen-binding fragment thereof). In some embodiments, an antagonist of an angiogenic factor is a polypeptide, *e.g.* a decoy binding partner molecule *e.g.* a decoy receptor. In some embodiments, an antagonist of an angiogenic factor may be an aptamer.

Agents capable of binding to an angiogenic factor or a complex comprising the angiogenic factor or an interaction partner for an angiogenic factor according to the present invention may exhibit one or more of the following properties:

Specific binding to an angiogenic factor or a complex comprising the angiogenic factor or an interaction partner for the angiogenic factor;

Binding to an angiogenic factor or a complex comprising the angiogenic factor or an interaction partner for the angiogenic factor, with a K_D of 10μM or less, preferably one of ≤ 5μM ≤ 1μM, ≤ 100nM, ≤10nM, ≤1nM or ≤100pM;

Inhibition of interaction between an angiogenic factor and an interaction partner for the angiogenic factor;

Reduction or inhibition of angiogenesis and/or

Reduction or inhibition of choroidal neovascularization (*e.g.* reduction in size of CNV lesions and/or reduction in CNV leakage area).

These properties can be determined by analysis of the relevant agent in a suitable assay, which may involve comparison of the performance of the agent to suitable control agents. The skilled person is able to identify appropriate control conditions for a given assay. As explained herein, an interaction partner for an angiogenic factor may *e.g.* be a ligand for an angiogenic factor (*e.g.* where the angiogenic factor is a receptor, *e.g.* a VEGF receptor, an FGF receptor or a PDGF receptor), or may be a receptor for an angiogenic factor (*e.g.* where the angiogenic factor is a ligand, *e.g.* a VEGF, an FGF or a PDGF).

For example, a suitable negative control for the analysis of the ability of a test antibody/antigen-binding fragment to bind to an angiogenic factor/a complex comprising the angiogenic factor /an interaction partner for the angiogenic factor may be an antibody/antigen-binding fragment directed against a non-target protein (*i.e.* which is not specific for an angiogenic factor/a complex comprising the angiogenic factor/interaction partner for the angiogenic factor). A suitable positive control may be a known, validated (*e.g.* commercially available) angiogenic factor- or angiogenic factor interaction partner-binding antibody. Controls may be of the same isotype as the putative an angiogenic factor/a complex comprising the angiogenic factor/interaction partner-binding antibody/antigen-binding fragment being analysed, and may *e.g.* have the same constant regions.

In some embodiments, the antagonist of an angiogenic factor may be capable of binding specifically to an angiogenic factor or a complex comprising the angiogenic factor, or an interaction partner for the angiogenic factor. An agent which specifically binds to a given target molecule preferably binds the target with greater affinity, and/or with greater duration than it binds to other, non-target molecules.

In some embodiments, the extent of binding of a binding agent to a non-target is less than about 10% of the binding of the agent to the target as measured, *e.g.*, by ELISA, SPR, Bio-Layer Interferometry (BLI), MicroScale Thermophoresis (MST), or by a radioimmunoassay (RIA). Alternatively, the binding specificity may be reflected in terms of binding affinity, where the binding agent binds to an angiogenic factor, a complex comprising the angiogenic factor or an interaction partner for an angiogenic factor with a K_D that is at least 0.1 order of magnitude (*i.e.* 0.1 x 10^n, where n is an integer representing the order of magnitude) greater than the K_D towards another, non-target molecule. This may optionally be one of at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, or 2.0.

Binding affinity for a given binding agent for its target is often described in terms of its dissociation constant (K_D). Binding affinity can be measured by methods known in the art, such as by ELISA, Surface Plasmon Resonance (SPR; see *e.g.* Hearty *et al.,* Methods Mol Biol (2012) 907:411-442; or Rich *et al.,* Anal Biochem. (2008) 1; 373(1):112-20), Bio-Layer Interferometry (see *e.g.* Lad *et al.*, J Biomol Screen (2015) 20(4):498-507; or Concepcion *et al.,* Comb Chem High Throughput Screen. (2009) 12(8):791-800), MicroScale Thermophoresis (MST) analysis (see *e.g.* Jerabek-Willemsen *et al.,* Assay Drug Dev Technol. (2011) 9(4):342–353), or by a radiolabelled antigen binding assay (RIA).

In some embodiments, the antagonist of an angiogenic factor binds to an angiogenic factor or a complex comprising the angiogenic factor, or an interaction partner for the angiogenic factor with a K_D of 50 μM or less, preferably one of ≤10 μM, ≤5 μM, ≤4 μM, ≤3 μM, ≤2 μM, ≤1 μM, ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, or ≤100 pM.

In some embodiments, the antagonist of an angiogenic factor binds to an angiogenic factor, a complex comprising the angiogenic factor or an interaction partner for the angiogenic factor with an affinity of binding (*e.g.* as determined by ELISA) of EC50 = 10,000 ng/mL or less, preferably one of ≤5,000 ng/mL, ≤1000 ng/mL, ≤900 ng/mL, ≤800 ng/mL, ≤700 ng/mL, ≤600 ng/mL, ≤500 ng/mL, ≤400 ng/mL, ≤300 ng/mL, ≤200 ng/mL, ≤100 ng/mL, ≤90 ng/mL, ≤80 ng/mL, ≤70 ng/mL, ≤60 ng/mL, ≤50 ng/mL, ≤40 ng/mL, ≤30 ng/mL, ≤20 ng/mL, ≤15 ng/mL, ≤10 ng/mL, ≤7.5 ng/mL, ≤5 ng/mL, ≤2.5 ng/mL, or ≤1 ng/mL. Such ELISAs can be performed *e.g.* as described in Antibody Engineering, vol. 1 (2nd Edn), Springer Protocols, Springer (2010), Part V, pp657-665.

In some embodiments, the antagonist of an angiogenic factor binds to an angiogenic factor or a complex comprising the angiogenic factor in a region which is important for binding to an interaction partner for the angiogenic factor or a complex comprising the angiogenic factor, and thereby inhibits interaction between an angiogenic factor or a complex comprising the angiogenic factor and an interaction partner for the angiogenic factor (*e.g.* inhibiting signalling through an angiogenic factor receptor). In some embodiments, the agent binds to an interaction partner for the angiogenic factor in a region which is important for binding to the angiogenic factor or a complex comprising the angiogenic factor, and thereby inhibits interaction between an angiogenic factor or a complex comprising the angiogenic factor and an interaction partner for the angiogenic factor (*e.g.* inhibiting signalling through an angiogenic factor receptor).

The ability of a given binding agent (*e.g.* an agent capable of binding an angiogenic factor/a complex comprising the angiogenic factor or an interaction partner for the angiogenic factor) to inhibit interaction between two proteins can be determined for example by analysis of interaction in the presence of, or following incubation of, one or both of the interaction partners with the binding agent. An example of a suitable assay to determine whether a given binding agent is capable of inhibiting interaction between two interaction partners is a competition ELISA.

A binding agent which is capable of inhibiting a given interaction (*e.g.* between an angiogenic factor and an interaction partner for the angiogenic factor, such as between VEGF and one or more of VEGFR1-3) is identified by the observation of a reduction/decrease in the level of interaction between the interaction partners in the presence of – or following incubation of one or both of the interaction partners with – the binding agent, as compared to the level of interaction in the absence of the binding agent (or in the presence of an appropriate control binding agent). Suitable analysis can be performed *in vitro*, *e.g.* using recombinant interaction partners or using cells expressing the interaction partners. Cells expressing interaction partners may do so endogenously, or may do so from nucleic acid introduced into the cell. For the purposes of such assays, one or both of the interaction partners and/or the binding agent may be labelled or used in conjunction with a detectable entity for the purposes of detecting and/or measuring the level of interaction. For example, the agent may be labelled with a radioactive atom or a coloured molecule or a fluorescent molecule or a molecule which can be readily detected in any other way. Suitable detectable molecules include fluorescent proteins, luciferase, enzyme substrates, and radiolabels. The binding agent may be directly labelled with a detectable label or it may be indirectly labelled. For example, the binding agent may be unlabelled, and detected by another binding agent which is itself labelled. Alternatively, the second binding agent may have bound to it biotin and binding of labelled streptavidin to the biotin may be used to indirectly label the first binding agent.

Ability of a binding agent to inhibit interaction between two binding partners can also be determined by analysis of the downstream functional consequences of such interaction, *e.g.* an angiogenic factor-mediated signalling.

In some embodiments, the binding agent may be capable of inhibiting interaction between an angiogenic factor and an interaction partner for the angiogenic factor to less than 100%, *e.g.* one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between the angiogenic factor and the interaction partner for the angiogenic factor in the absence of the binding agent (or in the presence of an appropriate control binding agent). In some embodiments, the binding agent may be capable of inhibiting interaction between an angiogenic factor and an interaction partner for the angiogenic factor to less than 1 times, *e.g.* one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of interaction between the angiogenic factor and the interaction partner for the angiogenic factor in the absence of the binding agent (or in the presence of an appropriate control binding agent).

In some embodiments, an agent capable of binding to an angiogenic factor or an interaction partner for the angiogenic factor is an antigen-binding molecule. In some embodiments, an antigen-binding molecule capable of binding to an angiogenic factor or an interaction partner for the angiogenic factor is an antibody or an antigen-binding fragment thereof.

Antibodies and antigen-binding fragments according to the present disclosure comprise the complementarity-determining regions (CDRs) of an antibody which is capable of binding to the relevant target molecule (*i.e.* an angiogenic factor/ an interaction partner of an angiogenic factor).

Antibodies capable of binding to an angiogenic factor or an interaction partner of an angiogenic factor include *e.g.* anti-VEGF/anti-VEGF-interaction partner antibodies (including *e.g.* anti-VEGF-A humanized monoclonal antibody Bevacizumab (also known as Avastin, drug bank accession No: #DB00112), anti-VEGF-A humanized monoclonal antibody Ranibizumab (also known as Lucentis, #DB01270), anti-VEGFR2 fully human monoclonal antibody Ramucirumab (also known as Cyramza, #DB05578)); anti-PDGF/anti-PDGF-interaction partner antibodies (including *e.g.* anti-PDGF-F fully human monoclonal antibody CR002 (#DB05139), anti-PDGF Rα monoclonal antibody Olaratumab (also known as Lartruvo, #DB06043), anti-PDGF-CC monoclonal antibody clone 6B3, disclosed in Li *et al.* PLoS One (2018) 13(7):e0201089); anti-FGF/anti-FGF-interaction partner antibodies (including *e.g.* anti-FGFR3 human monoclonal antibody Vofatamab (also known as MFGR1877S, #DB14781), anti-FGFR2 antibody Bemarituzumab (#DB16105)); anti-angiopoietin antibodies (including *e.g.* anti-angiopoietin-2 antibody clones LC06 and LC08, disclosed in WO2010069532A1, and anti-angiopoietin 1 and 2 fully human monoclonal antibody AMG 780, disclosed in Bready *et al.* Cancer Res. (2014) 74(19):1022)); anti-TGF/anti-TGF-interaction partner antibodies (including *e.g.* pan-TGFβ binding monoclonal antibody clones XPA.42.089, XPA.42.068, and XPA.42.681, disclosed in Bedinger *et al.* Mabs (2016) 8(2):389-404); anti-TNFα/interaction-partner for TNFα antibodies (including *e.g.* Infliximab (also known as Avsola, #DB00065), Adalimumab (also known as Humira, #DB00051), pegylated monoclonal antibody Certolizumab pegol (also known as Cimzia, #DB08904)).

The antibodies/fragments may be antagonist antibodies/fragments that inhibit or reduce a biological activity of an angiogenic factor. The antibodies/fragments may be neutralising antibodies that neutralise the biological effect of an angiogenic factor, *e.g.* its ability to stimulate productive signalling via an angiogenic factor receptor.

The antibody or antigen-binding fragment may be a multispecific. By 'multispecific' it is meant that the antigen-binding molecule displays specific binding to more than one target. In some embodiments, the antigen-binding molecule is a bispecific antigen-binding molecule. In some embodiments, the antigen-binding molecule comprises at least two different antigen-binding domains (*i.e.* at least two antigen-binding domains, *e.g.* comprising non-identical VHs and VLs).

In some embodiments, the antigen-binding molecule binds to an angiogenic factor and another target (*e.g.* an antigen other than an angiogenic factor), and so is at least bispecific. The term 'bispecific' means that the antigen-binding molecule is able to bind specifically to at least two distinct antigenic determinants. In some embodiments, the antigen other than an angiogenic factor is gp130. In some embodiments, a multispecific antibody according to the present invention binds to an angiogenic factor and gp130. In some embodiments, a multispecific antibody according to the present invention comprises an anti-gp130 antigen-binding region as described herein, and an anti-angiogenic factor antigen-binding region as described herein.

Peptide or polypeptide based agents capable of binding to an angiogenic factor or a complex comprising the angiogenic factor may be based on an angiogenic factor receptor, *e.g.* an angiogenic factor-binding fragment of an angiogenic factor receptor.

In some embodiments, the binding agent may comprise an angiogenic factor-binding fragment of the receptor extracellular domain, and may preferably be soluble and/or exclude one or more, or all, of the transmembrane domain(s). Such molecules may be described as decoy receptors. Decoy receptor technology is reviewed in, for example, Mantovani *et al.* Trends Immunol. (2001) 22(6):328-336.

In some embodiments a binding agent may be a decoy receptor, *e.g.* a soluble receptor for an angiogenic factor and/or complexes comprising the angiogenic factor.

Decoy angiogenic factor receptors preferably bind to an angiogenic factor and/or complexes comprising the angiogenic factor, and thereby make these species unavailable for binding to their receptors. As such, they act as 'decoy' receptors, and angiogenic signalling is reduced as compared to the level of signalling in the absence of the decoy receptor.

In some embodiments a decoy receptor may be able to bind an angiogenic factor, *e.g.* with binding affinity of at least 100 μM or less, optionally one of 10 μM or less, 1 μM or less, 100 nM or less, or about 1 to 100 nM. In some embodiments a decoy receptor may comprise all or part of the angiogenic factor binding domain and may optionally lack all or part of the transmembrane domains. The decoy receptor may optionally be fused to an immunoglobulin constant region, *e.g.* IgG Fc region.

Decoy receptors for targeting growth factor signalling are reviewed in, for example, Kefaloyianni *et al.* FEBS Lett. (2022) 596(5):589-606, which is hereby incorporated by reference in its entirety. Decoy receptors according to the present invention include *e.g.* VEGF decoy receptors (including *e.g.* FP3, a selective VEGF decoy receptor disclosed in Yu *et al.* American Society of Gene and Cell Therapy (2012) 20(5):938-947; sVEGFR3-Fc disclosed in Lin *et al.* Cancer Research. (2005) 65(15)6901-6909; sVEGFR1/R2 disclosed in Harding *et al.* Molecular Therapy. (2006) 13(5)956-966; and aflibercept (also known as Eylea, #DB08885)); PDGF decoy receptors; FGF decoy receptors (including FGF-2 decoy-receptor designated 'FGF-Trap' disclosed in Li *et al.* British Journal of Cancer. (2014) 111:68-77); angiopoietin decoy receptors (including *e.g.* angiopoietin-1 decoy receptor designated 'TIE2-Fc', disclosed in Davis *et al.* Cell. (1996) 87(7):1161-1169; and dual-targeting VEGF and angiopoietin decoy receptor designated 'DAAP', disclosed in Jun Koh *et al.* Cancer Cell. (2010) 18(2):171-184); TGF decoy receptors (including *e.g.* TGF-β decoy receptor based on TGF-β receptor II, disclosed in WO 2018/138003 A1); TNFα decoy receptors (including *e.g.* Etanercept (#DB00005)).

In some embodiments, the antagonist of an angiogenic factor is a VEGF decoy receptor. In some embodiments, the antagonist of an angiogenic factor may comprise a recombinant fusion protein of the second immunoglobulin (Ig) domain of VEGFR-1 and the third Ig domain of VEGFR-2, fused to the constant region (Fc) of human IgG1. Such agents include, for example, FP3 (disclosed in Yu *et al.*

American Society of Gene and Cell Therapy (2012) 20(5):938-947); sVEGFR1/R2 disclosed in Harding *et al.* Molecular Therapy. (2006) 13(5)956-966; and aflibercept (also known as Eylea, drug bank accession No: #DB08885).

In some embodiments, the antagonist of an angiogenic factor is, or comprises, a polypeptide comprising, or consisting of, an amino acid sequence having at least 70% sequence identity, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity, to the amino acid sequence of SEQ ID NO:524. In some embodiments, the antagonist of an angiogenic factor is aflibercept.

In some embodiments, the antagonist of an angiogenic factor is an aptamer.

Aptamers, also called nucleic acid/peptide ligands, are nucleic acid or peptide molecules characterised by the ability to bind to a target molecule with high specificity and high affinity. Almost every aptamer identified to date is a non-naturally occurring molecule.

Aptamers to a given target (*e.g.* VEGF, a VEGF containing complex or a receptor for VEGF) may be identified and/or produced by the method of Systematic Evolution of Ligands by EXponential enrichment (SELEXTM), or by developing SOMAmers (slow off-rate modified aptamers) (Gold L *et al.* (2010) *PLoS ONE* 5(12):e15004). Aptamers and SELEX are described in Tuerk and Gold, *Science* (1990) 249(4968):505-10, and in WO 91/19813. Applying the SELEX and the SOMAmer technology includes for instance adding functional groups that mimic amino acid side chains to expand the aptamer's chemical diversity. As a result high affinity aptamers for a target may be enriched and identified.

Aptamers may be DNA or RNA molecules and may be single stranded or double stranded. The aptamer may comprise chemically modified nucleic acids, for example in which the sugar and/or phosphate and/or base is chemically modified. Such modifications may improve the stability of the aptamer or make the aptamer more resistant to degradation and may include modification at the 2′ position of ribose.

Aptamers may be synthesised by methods which are well known to the skilled person. For example, aptamers may be chemically synthesised, *e.g.* on a solid support. Solid phase synthesis may use phosphoramidite chemistry. Briefly, a solid supported nucleotide is detritylated, then coupled with a suitably activated nucleoside phosphoramidite to form a phosphite triester linkage. Capping may then occur, followed by oxidation of the phosphite triester with an oxidant, typically iodine. The cycle may then be repeated to assemble the aptamer (*e.g.*, see Sinha, N. D.; Biernat, J.; McManus, J.; Köster, H. Nucleic Acids Res. 1984, 12, 4539; and Beaucage, S. L.; Lyer, R. P. (1992). Tetrahedron 48 (12): 2223).

Suitable nucleic acid aptamers may optionally have a minimum length of one of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 nucleotides. Suitable nucleic acid aptamers may optionally have a maximum length of one of 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80

nucleotides. Suitable nucleic acid aptamers may optionally have a length of one of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, or 80 nucleotides.

Aptamers may be peptides selected or engineered to bind specific target molecules. Peptide aptamers and methods for their generation and identification are reviewed in Reverdatto *et al.*, *Curr Top Med Chem*. (2015) 15(12):1082-101, which is hereby incorporated by reference in its entirety. Peptide aptamers may optionally have a minimum length of one of 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids. Peptide aptamers may optionally have a maximum length of one of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 amino acids. Suitable peptide aptamers may optionally have a length of one of 2-30, 2-25, 2-20, 5-30, 5-25 or 5-20 amino acids.

Aptamers may have K_D's in the nM or pM range, *e.g.* less than one of 500nM, 100nM, 50nM, 10nM, 1nM, 500pM, 100pM.

Aptamers according to the present invention include *e.g.* anti-VEGF/anti-VEGF interaction partner aptamers (including *e.g.* pegaptanib, which is disclosed in WO9818480 A1); anti-PDGF/anti-PDGF interaction partner aptamers (including *e.g.* the anti-PDGF-B aptamer designated 'PDGF-BB', disclosed in Quang Vu *et al.* J Mol Graph Model. (2018) 82:145-156); anti-FGF/anti-FGF interaction partner aptamers (including *e.g.* anti-FGF-2 aptamer designated RBM-007 disclosed in Matsuda *et al.* Molecular Therapy Nucleic Acids. (2019) 17:819-828); anti-angiopoietin/anti-angiopoietin interaction partner aptamers (including *e.g.* the anti-Ang2 aptamer disclosed in Sarraf-Yazdi *et al.* Journal of Surgical Research. (2008) 146(1):16-23); anti-TGF/anti-TGF interaction partner aptamers (including *e.g.* the anti-TGFβ aptamer designated 'APT-β1', disclosed in Takahashi *et al.* Molecular Therapy Nucleic Acids. (2022) 29:969-978); anti-TNFα/anti-TNFα interaction partner aptamers (including *e.g.* the anti-TNFα aptamer designated 'VR11', disclosed in Orava *et al.* ACS Chem Biol. (2013) 8(1):170-178; and aptTNF-α and its PEGylated-derivative, disclosed in Lai *et al.* Theranostics. (2019) 9(6):1741-1751).

In some embodiments, the antagonist of an angiogenic factor is the anti-VEGF aptamer pegaptanib, which is disclosed in WO 9818480 A1, herein incorporated by reference in its entirety.

In some embodiments, the antagonist of an angiogenic factor is an inhibitor capable of binding to one or more of an angiogenic factor, a complex comprising the angiogenic factor, or an interaction partner for an angiogenic factor, and inhibiting angiogenic signalling.

In some embodiments the agent is a peptide or polypeptide based binding agent based on an angiogenic factor, *e.g.* mutant, variant or binding fragment of an angiogenic factor. Suitable peptide or polypeptide based agents may bind to a receptor for an angiogenic factor (*e.g.* VEGFR1, 2 and/or 3) in a manner that does not lead to initiation of signal transduction, or which produces sub-optimal signalling. Mutants of this kind may act as competitive inhibitors of endogenous angiogenic factors.

In some embodiments a binding agent capable of antagonism of an angiogenic factor may take the form of a small molecule inhibitor.

Small molecule inhibitors of angiogenesis may be tyrosine kinase inhibitors. Multiple small-molecule tyrosine kinase inhibitors have been developed, and are reviewed in, for example Qin *et al.* J Hematol Oncol. (2019) 12:27; Gotink and Verheul, Angiogenesis. (2009) 13(1):1-14, and Roskoski Jr *et al.* Pharmacological Research (2020) 152:104609; which are hereby incorporated by reference in their entirety. Given the functional redundancy of angiogenic pathway components, these drugs target multiple kinases, such as VEGFRs, PDGFRs and FGFRs. They include pazopanib (Votrient®, #DB06589), an inhibitor of VEGF, platelet-derived growth factor receptor (PDGFR), and KIT; sorafenib (Nexavar®, #DB00398), an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, and RAF1; sunitinib (Sutent®, #DB01268), an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, and RET; vandetanib (Caprelsa®, #DB05294), an inhibitor of VEGFR and epidermal growth factor receptor; cabozantinib (Cometriq®, #DB08875), an inhibitor of MET and VEGFR2; axitinib (Inlyta®, #DB06626), an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3; vatalanib, an inhibitor of known VEGF receptors, as well as platelet-derived growth factor receptor-beta and c-kit, but is most selective for VEGFR-2; and regorafenib (Stivarga®, #DB08896), an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, TIE2, PDGFR, fibroblast growth factor receptor, KIT, RET, and RAFf; Nintedanib (Ofev®, #DB09079), an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, FGFR-1, FGFR-2; Imatinib (Gleevec®, #DB00619), an inhibitor of PDGF and c-KIT.

Other small molecule inhibitors of angiogenesis include anecortave acetate (#DB12081), and squalamine lactate (as discussed in Connolly *et al.* Ophthalmol Clin North Am. (2006) 19(3):381-391, which is hereby incorporated by reference in its entirety).

Agents capable of reducing expression of angiogenic factor or an angiogenic factor receptor

In aspects of the present invention the antagonist of an angiogenic factor-mediated signalling may be provided, which is capable of preventing or reducing the expression of one or more of an angiogenic factor, or an interaction partner for the angiogenic factor.

Expression may be gene or protein expression, and may be determined as described herein. Expression may be by a cell/tissue/organ/organ system of a subject.

Suitable agents may be of any kind, but in some embodiments an agent capable of preventing or reducing the expression of one or more of an angiogenic factor, or an interaction partner for the angiogenic factor may be a small molecule or an oligonucleotide.

An agent capable of preventing or reducing of the expression of one or more of an angiogenic factor, or an interaction partner for the angiogenic factor may do so *e.g.* through inhibiting transcription of the gene encoding an angiogenic factor, or interaction partner for the angiogenic factor, inhibiting post-transcriptional processing of RNA encoding an angiogenic factor, or interaction partner for the angiogenic

factor, reducing the stability of RNA encoding an angiogenic factor, or an interaction partner for the angiogenic factor, promoting degradation of RNA encoding an angiogenic factor, or an interaction partner for the angiogenic factor, inhibiting post-translational processing of an angiogenic factor, or an interaction partner for the angiogenic factor, reducing the stability of an angiogenic factor, or interaction partner for the angiogenic factor, or promoting degradation of an angiogenic factor, or an interaction partner for the angiogenic factor.

The present invention contemplates the use of antisense nucleic acid to prevent/reduce expression of an angiogenic factor, or an interaction partner for the angiogenic factor. In some embodiments, an agent capable of preventing or reducing the expression of an angiogenic factor, or an interaction partner for the angiogenic factor may cause reduced expression by RNA interference (RNAi).

In some embodiments, the agent may be an inhibitory nucleic acid, such as antisense or small interfering RNA, including but not limited to shRNA, dsRNA, miRNA or siRNA.

In some embodiments the inhibitory nucleic acid is provided in a vector. For example, in some embodiments the agent may be a lentiviral vector encoding shRNA for one or more of an angiogenic factor, or an interaction partner for the angiogenic factor.

In view of the known nucleic acid sequences for angiogenic factors and their interaction partners (*e.g.* the known mRNA sequences available from GenBank under Accession Nos: AY047581.1 GI: 15422108 (human VEGF-A), AF317892.1 GI: 12802453 (mouse VEGF), AY033508.1 GI: 15822724 (rat VEGF), NM_002253.3 GI: 1333881084 (human VEGF receptor), NM_025809.5 GI: 237512936 (mouse VEGF receptor), NM_019306.2 GI: 828178218 (rat VEGF receptor),) oligonucleotides may be designed to repress or silence the expression of an angiogenic factor, or an angiogenic factor receptor.

Such oligonucleotides may have any length, but may preferably be short, *e.g.* less than 100 nucleotides, *e.g.* 10-40 nucleotides, or 20-50 nucleotides, and may comprise a nucleotide sequence having complete- or near- complementarity (*e.g.* 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% complementarity) to a sequence of nucleotides of corresponding length in the target oligonucleotide, *e.g.* the mRNA of an angiogenic factor, or the mRNA of an interaction partner for the angiogenic factor. The complementary region of the nucleotide sequence may have any length, but is preferably at least 5, and optionally no more than 50, nucleotides long, *e.g.* one of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides.

Repression of expression of an angiogenic factor, or an interaction partner for the angiogenic factor will preferably result in a decrease in the quantity of an angiogenic factor, or an interaction partner for the angiogenic factor expressed by a cell/tissue/organ/organ system/subject. For example, in a given cell the repression of an angiogenic factor, or an interaction partner for the angiogenic factor by administration of a suitable nucleic acid will result in a decrease in the quantity of an angiogenic factor, or an interaction partner for the angiogenic factor expressed by that cell relative to an untreated cell. Repression may be

partial. Preferred degrees of repression are at least 50%, more preferably one of at least 60%, 70%, 80%, 85% or 90%. A level of repression between 90% and 100% is considered a 'silencing' of expression or function.

Another alternative is the expression of a short hairpin RNA molecule (shRNA) in the cell. Preferably, the shRNA molecule comprises a partial sequence of an angiogenic factor, or an interaction partner for the angiogenic factor. Preferably, the shRNA sequence is between 40 and 100 bases in length, more preferably between 40 and 70 bases in length. The stem of the hairpin is preferably between 19 and 30 base pairs in length. The stem may contain G-U pairings to stabilise the hairpin structure.

siRNA molecules, longer dsRNA molecules or miRNA molecules may be made recombinantly by transcription of a nucleic acid sequence, preferably contained within a vector. Preferably, the siRNA molecule, longer dsRNA molecule or miRNA molecule comprises a partial sequence of an angiogenic factor, or an interaction partner for the angiogenic factor.

In one embodiment, the siRNA, longer dsRNA or miRNA is produced endogenously (within a cell) by transcription from a vector. Suitable vectors may be oligonucleotide vectors configured to express the oligonucleotide agent capable of repression of an angiogenic factor, or an interaction partner for the angiogenic factor . Such vectors may be viral vectors or plasmid vectors.

In other embodiments, the invention provides nucleic acid that is capable, when suitably introduced into or expressed within a mammalian, *e.g.* human, cell that otherwise expresses an angiogenic factor, or an angiogenic factor receptor, of suppressing expression of an angiogenic factor, or an interaction partner for the angiogenic factor by RNAi.

In view of the known nucleic acid sequences for angiogenic factors and their interaction partners (*e.g.* the known mRNA sequences available from GenBank under Accession Nos: AF437895.1 GI: 16660685 (human VEGF), U41383.1 GI: 1134964 (mouse VEGF), NM_001287107.1 GI: 560186576 (rat VEGF), NM_002253.3 GI: 1333881084 (human VEGF receptor), NM_001001183.1 GI: 47564089 (mouse VEGF receptor), NM_019306.2 GI: 828178218 (rat VEGF receptor)) oligonucleotides may be designed to repress or silence the expression of an angiogenic factor, or an angiogenic factor receptor.

The nucleic acid may have substantial sequence identity to a portion of mRNA of an angiogenic factor, or an interaction partner for the angiogenic factor, *e.g.* as defined in GenBank accession M32977.1 GI: 181970 (VEGF), BC131822.1 GI: 124297527 (VEGF receptor) or the complementary sequence to said mRNA.

The nucleic acid may be a double-stranded siRNA. As the skilled person will appreciate, and as explained further below, a siRNA molecule may include a short 3' DNA sequence also.

Alternatively, the nucleic acid may be a DNA (usually double-stranded DNA) which, when transcribed in a mammalian cell, yields an RNA having two complementary portions joined via a spacer, such that the

RNA takes the form of a hairpin when the complementary portions hybridise with each other. In a mammalian cell, the hairpin structure may be cleaved from the molecule by the enzyme DICER, to yield two distinct, but hybridised, RNA molecules.

The invention also provides DNA that, when transcribed in a mammalian cell, yields an RNA (herein also referred to as an shRNA) having two complementary portions which are capable of self-hybridising to produce a double-stranded motif, *e.g.* including a sequence selected from the group consisting of SEQ ID NOs: 520 to 523 or a sequence that differs from any one of the aforementioned sequences by a single base pair substitution.

The complementary portions will generally be joined by a spacer, which has suitable length and sequence to allow the two complementary portions to hybridise with each other. Preferably the 5' end of the spacer (immediately 3' of the upstream complementary portion) consists of the nucleotides –UU- or –UG-, again preferably –UU- (though, again, the use of these particular dinucleotides is not essential). A suitable spacer, recommended for use in the pSuper system of OligoEngine (Seattle, Washington, USA) is UUCAAGAGA. In this and other cases, the ends of the spacer may hybridise with each other, *e.g.* elongating the double-stranded motif beyond the exact sequences of SEQ ID NOs: 520 to 523 by a small number (*e.g.* 1 or 2) of base pairs.

The double-stranded siRNAs of the invention may be introduced into mammalian cells *in vitro* or *in vivo* using known techniques, as described below, to suppress expression of an angiogenic factor or an interaction partner for the angiogenic factor.

Similarly, transcription vectors containing the DNAs of the invention may be introduced into tumour cells *in vitro* or *in vivo* using known techniques, as described below, for transient or stable expression of RNA, again to suppress expression of an angiogenic factor or an interaction partner for the angiogenic factor.

Accordingly, the invention also provides a method of suppressing expression of an angiogenic factor or an interaction partner for the angiogenic factor in a mammalian, *e.g.* human, cell, the method comprising administering to the cell a double-stranded siRNA of the invention or a transcription vector of the invention.

Similarly, the invention further provides a method of treating a disease/condition in which fibrosis, inflammation and/or angiogenesis is pathologically-implicated, the method comprising administering to a subject a double-stranded siRNA of the invention or a transcription vector of the invention in combination with an antagonist of an angiogenic factor.

The invention further provides the double-stranded siRNAs of the invention and the transcription vectors of the invention, for use in a method of treatment in combination with an antagonist of an angiogenic factor, preferably a method of treating a disease/condition in which fibrosis and/or angiogenesis and/or inflammation is pathologically implicated.

The invention further provides the use of the double-stranded siRNAs of the invention and the transcription vectors of the invention in combination with an antagonist of an angiogenic factor in the preparation of a medicament for the treatment of a disease/condition in which fibrosis and/or angiogenesis and/or inflammation is pathologically implicated.

Inhibition of angiogenic factor-mediated signalling

In embodiments of the present invention, agents capable of inhibiting the action of (*i.e.* antagonising) an angiogenic factor may possess one or more of the following functional properties:

- Inhibition of signalling mediated by an angiogenic factor;
- Inhibition of signalling mediated by binding of an angiogenic factor to an interaction partner for the angiogenic factor;
- Inhibition of a process mediated by an angiogenic factor;
- Inhibition of intussusception;
- Inhibition of capillary proliferation;
- Inhibition of edema.

These properties can be determined by analysis of the relevant agent in a suitable assay, which may involve comparison of the performance of the agent to suitable control agents. The skilled person is able to identify an appropriate control conditions for a given assay.

An angiogenic factor-mediated signalling and/or processes mediated by an angiogenic factor includes signalling mediated by fragments of an angiogenic factor and polypeptide complexes comprising an angiogenic factor or fragments thereof. Angiogenic factor-mediated signalling may be signalling mediated by human an angiogenic factor and/or mouse an angiogenic factor. Signalling mediated by an angiogenic factor may occur following binding of an angiogenic factor or an angiogenic factor containing complex to an interaction partner (*e.g.* receptor or ligand) to which an angiogenic factor or said complex binds.

In some embodiments, an agent may be capable of inhibiting the biological activity of an angiogenic factor or a complex comprising the angiogenic factor.

In some embodiments, the agent is an antagonist of one or more signalling pathways which are activated by signal transduction through receptors comprising an angiogenic factor receptor.

In some embodiments, the agent may be capable of inhibiting an angiogenic factor-mediated signalling to less than 100%, *e.g.* one of 99% or less, 95% or less, 90% or less, 85% or less, 80% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of signalling in the absence of the agent (or in the presence of an appropriate control agent). In some embodiments, the agent is capable of reducing an angiogenic factor-mediated signalling to less than 1 times, *e.g.* one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times,

≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of signalling in the absence of the agent (or in the presence of an appropriate control agent).

In some embodiments, the angiogenic factor-mediated signalling may be signalling mediated by binding of an angiogenic factor to an interaction partner for the angiogenic factor (*e.g.* a receptor or ligand for the angiogenic factor). Such signalling can be analysed *e.g.* by treating cells expressing an interaction partner for the angiogenic factor with the angiogenic factor, or by stimulating production of the angiogenic factor in cells which express an interaction partner for the angiogenic factor.

The IC_{50} for agent for inhibition of an angiogenic factor-mediated signalling may be determined, *e.g.* by culturing cells expressing an interaction partner for the angiogenic factor receptor in the presence of an angiogenic factor and the agent, and measuring a functional consequence of signalling mediated by the angiogenic factor. For example, in an assay of cell proliferation mediated by an angiogenic factor ^{3}H-thymidine incorporation into DNA may be analysed. In some embodiments, the agent may exhibit an IC_{50} of 10 µg/ml or less, preferably one of ≤ 5 µg/ml, ≤ 4 µg/ml, ≤ 3.5 µg/ml, ≤ 3 µg/ml, ≤ 2 µg/ml, ≤ 1 µg/ml, ≤ 0.9 µg/ml, ≤ 0.8 µg/ml, ≤ 0.7 µg/ml, ≤ 0.6 µg/ml, or ≤ 0.5 µg/ml in such an assay.

In some embodiments, the agent may be capable of inhibiting a process mediated by an angiogenic factor (*e.g.* following stimulation with VEGF). Processes mediated by an angiogenic factor include *e.g.* intussusception, capillary proliferation, and gene/protein expression of *e.g.* collagen and an angiogenic factor, and can be evaluated either *in vitro* or *in vivo*.

In some embodiments, the antagonist of an angiogenic factor is an angiogenesis inhibitor selected from: endostatin (NP_569711.2 GI: 206597445), prolactin (CAA38264.1 GI: 531103), T2-TrpRS (as described in Otani A *et al., A fragment of human TrpRS as a potent antagonist of ocular angiogenesis* Proceedings of the National Academy of Sciences of the United States of America. 2002;99(1):178-183, which is herein incorporated by reference in its entirety), or vasostatin (AAL13126.1 GI: 16151097), or a fragment, isoform, homologue or variant thereof.

Pharmaceutical combinations and compositions

The present disclosure also provides compositions comprising the agents described herein.

The present disclosure also provides a combination comprising (i) an antigen-binding molecule that binds to gp130, and (ii) an antagonist of an angiogenic factor. The present disclosure also provides a composition comprising (i) an antigen-binding molecule that binds to gp130, and (ii) an antagonist of an angiogenic factor.

It will be appreciated that the antigen-binding molecule that binds to gp130 may be an antigen-binding molecule that binds to gp130 according to any embodiment described herein, and that similarly the antagonist of an angiogenic factor may be an antagonist of an angiogenic factor according to any embodiment described herein. In preferred embodiments of the combinations and compositions of the

preceding paragraph, the antigen-binding molecule that binds to gp130 is selected from one of (1) to (72) above. In preferred embodiments of the combinations and compositions of the preceding paragraph, the antagonist of an angiogenic factor is an antagonist of VEGF.

In some aspects and embodiments, the combination is a pharmaceutical combination. As used herein, a 'pharmaceutical combination' refers to a product that comprises plural (herein typically two) different active (*i.e.* therapeutic/prophylactic) agents, which are intended to be used in combination. The agents of a pharmaceutical combination may be formulated together or separately, but will typically be packaged together, typically with a package insert bearing instructions for the use of the agents in combination.

In some embodiments, the agents of a pharmaceutical combination are comprised in a single composition, *e.g.* a pharmaceutical composition comprising both agents. In some embodiments, the agents of a pharmaceutical combination are comprised in separate compositions; for example, the pharmaceutical combination may be provided as (i) a pharmaceutical composition comprising an antigen-binding molecule that binds to gp130, and (ii) a pharmaceutical composition comprising an antagonist of an angiogenic factor.

The present disclosure also provides compositions (*e.g.* pharmaceutical compositions and medicaments) comprising the agents described herein (*i.e.* antigen-binding molecules that bind to gp130, antagonists of an angiogenic factor). Such compositions may comprise the relevant article in a formulation suitable for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

The compositions of the present disclosure may comprise one or more pharmaceutically-acceptable carriers (*e.g.* liposomes, micelles, microspheres, nanoparticles), diluents/excipients (*e.g.* starch, cellulose, a cellulose derivative, a polyol, dextrose, maltodextrin, magnesium stearate), adjuvants, fillers, buffers, preservatives (*e.g.* vitamin A, vitamin E, vitamin C, retinyl palmitate, selenium, cysteine, methionine, citric acid, sodium citrate, methyl paraben, propyl paraben), anti-oxidants (*e.g.* vitamin A, vitamin E, vitamin C, retinyl palmitate, selenium), lubricants (*e.g.* magnesium stearate, talc, silica, stearic acid, vegetable stearin), binders (*e.g.* sucrose, lactose, starch, cellulose, gelatin, polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), xylitol, sorbitol, mannitol), stabilizers, solubilizers, surfactants (*e.g.*, wetting agents), masking agents or coloring agents (*e.g.* titanium oxide).

The term 'pharmaceutically-acceptable' as used herein pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (*e.g.* a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, adjuvant, filler, buffer, preservative, anti-oxidant, lubricant, binder, stabilizer, solubilizer, surfactant, masking agent, coloring agent, flavoring agent or sweetening agent of a composition according to the present disclosure must also be 'acceptable' in the sense of being compatible with the other ingredients of the formulation. Suitable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, binders, stabilizers, solubilizers, surfactants, masking agents, coloring agents, flavoring agents or sweetening agents can be

found in standard pharmaceutical texts, for example, Remington's 'The Science and Practice of Pharmacy' (Ed. A. Adejare), 23rd Edition (2020), Academic Press.

The pharmaceutical compositions/medicaments according to the present disclosure may be formulated for administration to a subject, *e.g.* administration via a route of administration as appropriate for the nature of the composition/medicament and the disease/condition to be treated/prevented. In some embodiments, a pharmaceutical composition/medicament may be formulated for parenteral, systemic, topical, intracavitary, intravascular, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intraconjunctival, intratumoral, subcutaneous, intradermal, oral or transdermal administration. In some embodiments, a pharmaceutical composition/medicament may be formulated for administration by injection or infusion, or administration by ingestion.

Medicaments and pharmaceutical compositions may be formulated for injection or infusion, *e.g.* into a blood vessel, tissue/organ of interest, or a tumor (*e.g.* a tissue/organ affected by the disease/condition; *e.g.* a tissue/organ in which symptoms of the disease/condition manifest).

The pharmaceutical compositions/medicaments may comprise the agent(s) (*i.e.* the antigen-binding molecule that binds to gp130 and/or the antagonist of an angiogenic factor) in a sterile or isotonic medium. The pharmaceutical compositions/medicaments may be provided in fluid, including gel, form. Fluid formulations may be formulated for administration by injection or infusion (*e.g.* via cannula) to a blood vessel, or a selected region of the human or animal body, or to a tumor. The pharmaceutical compositions/medicaments may be provided in solid form, *e.g.* in lyophilized form.

Functional properties

The combinations and compositions described herein may be characterized by reference to certain functional properties. In some embodiments, a combination/composition described herein may possess one or more of the following properties:

reduces or inhibits inflammation and/or fibrosis (*e.g.* retinal inflammation and/or retinal fibrosis);

reduces the pathology of a disease/condition characterised by inflammation and/or fibrosis in a subject;

reduces or inhibits angiogenesis (*e.g.* in the eye);

reduces the pathology of a disease/condition characterised by angiogenesis (*i.e.* pathological angiogenesis) in a subject;

reduces or inhibits choroidal neovascularization (*e.g.* reduces size of CNV lesions and/or reduces CNV leakage area);

reduces or inhibits expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1 and/or IL-11;

improved ability to reduce/inhibit inflammation and/or fibrosis (*e.g.* retinal inflammation and/or retinal fibrosis) as compared to the ability to reduce/inhibit inflammation and/or fibrosis (*e.g.* retinal inflammation and/or retinal fibrosis) by either component used alone;

ability to reduce/inhibit inflammation and/or fibrosis (*e.g.* retinal inflammation and/or fibrosis) which is synergistic (*i.e.* super-additive) as compared to the ability to reduce/inhibit inflammation and/or fibrosis (*e.g.* retinal inflammation and/or fibrosis) by the components used alone;

improved ability to reduce/inhibit angiogenesis (*e.g.* in the eye) as compared to the ability to reduce/inhibit angiogenesis by either component used alone;

ability to reduce/inhibit angiogenesis (*e.g.* in the eye) which is synergistic (*i.e.* super-additive) as compared to the ability to reduce/inhibit angiogenesis by the components used alone;

improved ability to reduce/inhibit CNV (*e.g.* size of CNV lesions and/or CNV leakage area) as compared to the ability to reduce/inhibit CNV (*e.g.* size of CNV lesions and/or CNV leakage area) by either component used alone;

ability to reduce/inhibit CNV (*e.g.* size of CNV lesions and/or CNV leakage area) which is synergistic (*i.e.* super-additive) as compared to the ability to reduce/inhibit CNV (*e.g.* size of CNV lesions and/or CNV leakage area) by the components used alone;

improved ability to reduce/inhibit expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11 as compared to the ability to reduce/inhibit expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11 by either component used alone; and/or

ability to reduce/inhibit expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11 which is synergistic (*i.e.* super-additive) as compared to the ability to reduce/inhibit expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11 by the components used alone.

It will be appreciated that a given combination/composition may display more than one of the properties recited in the preceding paragraph. A given combination/composition may be evaluated for the properties recited in the preceding paragraph using suitable assays, *e.g.* as described herein.

As used herein, a 'synergistic' or 'super-additive' level of a relevant effect (*e.g.* reduction in fibrosis, reduction in angiogenesis, reduction in expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11, reduction in CNV) for a given combination/composition refers to a level of the effect which is greater than the sum of the effects observed for the individual components of the combination/composition.

Quantitative methods for assessing synergism are described *e.g.* in Tallarida, Genes Cancer. (2011) 2(11):1003–1008 and Chou, Cancer Res (2010) 70:440-446, both of which are hereby incorporated by reference in their entirety. Additive, synergistic and antagonistic effects may be evaluated in experiments in which a range of different doses of the combination/composition and the individual constituents thereof are evaluated for the relevant effect. Dose-response curves may be plotted, and evaluated in order to determine whether the combination/composition achieves a synergistic level of the relevant effect relative to the individual constituents of the combination/composition employed in isolation (*i.e.* as monotherapies). In some embodiments, synergy may be evaluated using combination index (CI) values calculated using the Chou-Talalay method described in Chou, Cancer Res (2010) 70:440-446. According

to the Chou-Talalay method, for a given combination CI = 1 indicates an additive effect, CI <1 indicates synergism, and CI >1 indicates antagonism.

In some embodiments, a combination/composition of the present disclosure achieves a synergistic (*i.e.* super-additive) reduction in fibroblast activation; reduction in angiogenesis; reduction in fibrosis; reduction in inflammation, reduction in the pathology of a disease/condition characterised by angiogenesis (*i.e.* pathological angiogenesis) in a subject; reduction in the pathology of a disease/condition characterised by fibrosis in a subject; reduction in the pathology of a disease/condition characterised by inflammation (*i.e.* pathological inflammation) in a subject; reduction in expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11; reduction in CNV (*e.g.* reduction in the size of CNV lesions and/or reduction in CNV leakage area); reduction in fibrous area relative to what is observed when either component of the combination/composition is employed alone. In some embodiments, a combination/composition achieves a synergistic (*i.e.* super-additive) reduction in fibroblast activation; reduction in angiogenesis; reduction in fibrosis; reduction in inflammation, reduction in the pathology of a disease/condition characterised by angiogenesis (*i.e.* pathological angiogenesis) in a subject; reduction in the pathology of a disease/condition characterised by fibrosis in a subject, reduction in the pathology of a disease/condition characterised by inflammation (*i.e.* pathological inflammation) reduction in expression of VEGF, TGF-β, TNF-α, IL-6, COL1A1, IL-11; reduction in CNV (*e.g.* reduction in the size of CNV lesions and/or reduction in CNV leakage area); reduction in fibrous area, relative to what is observed when the antigen-binding molecule that binds to gp130 constituent of the combination/composition is employed as a monotherapy, and/or relative to what is observed when the antagonist of an angiogenic factor constituent of the combination/composition is employed as a monotherapy.

Therapeutic and prophylactic applications

The present disclosure provides methods and articles (*e.g.* the agents, combinations and compositions of the present disclosure) for the treatment and/or prevention of disease, *e.g.* fibrosis, pathological angiogenesis, pathological inflammation, diseases/conditions characterised by fibrosis, diseases/conditions characterised by angiogenesis, and/or diseases/conditions characterised by inflammation.

Accordingly, the present disclosure provides an antigen-binding molecule that binds to gp130 for use in a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis, and/or a disease/condition characterised by inflammation wherein the method further comprises administering an antagonist of an angiogenic factor. Also provided is an antagonist of an angiogenic factor for use in a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis, and/or a disease/condition characterised by inflammation wherein the method further comprises administering an antigen-binding molecule that binds to gp130.

Also provided is the use of an antigen-binding molecule that binds to gp130 in the manufacture of a medicament for use in a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis, and/or a disease/condition characterised by inflammation wherein the method further comprises administering an antagonist of an angiogenic factor. Also provided is the use of an antagonist of an angiogenic factor in the manufacture of a medicament for use in a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis, a disease/condition characterised by inflammation wherein the method further comprises administering an antigen-binding molecule that binds to gp130.

Further provided is a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis, and/or a disease/condition characterised by inflammation the method comprising administering a therapeutically- or prophylactically-effective amount of (i) an antigen-binding molecule that binds to gp130 and (ii) an antagonist of an angiogenic factor to a subject in need of treatment. Also provided is a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis, and/or a disease/condition characterised by inflammation, the method comprising administering a therapeutically- or prophylactically-effective amount of (i) an antagonist of an angiogenic factor and (ii) an antigen-binding molecule that binds to gp130 to a subject in need of treatment.

The present disclosure also provides (i) an antigen-binding molecule that binds to gp130 and (ii) an antagonist of an angiogenic factor for use in a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis and/or a disease/condition characterised by inflammation in a subject. Also provided is the use of (i) an antigen-binding molecule that binds to gp130 and (ii) an antagonist of an angiogenic factor in the manufacture of a medicament for use in treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis and/or a disease/condition characterised by inflammation in a subject. Also provided is a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis and/or a disease/condition characterised by inflammation in a subject, comprising administering to the subject a therapeutically- or prophylactically-effective amount of (i) an antigen-binding molecule that binds to gp130 and (ii) an antagonist of an angiogenic factor.

The present disclosure also provides (i) an antagonist of an angiogenic factor and (ii) an antigen-binding molecule that binds to gp130 for use in a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis and/or a disease/condition characterised by inflammation in a subject. Also provided is the use of (i) an antagonist of an angiogenic factor and (ii) an

antigen-binding molecule that binds to gp130 in the manufacture of a medicament for use in treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis and/or a disease/condition characterised by inflammation in a subject. Also provided is a method of treating or preventing fibrosis, pathological angiogenesis, pathological inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by angiogenesis and/or a disease/condition characterised by inflammation in a subject, comprising administering to the subject a therapeutically- or prophylactically-effective amount of (i) an antagonist of an angiogenic factor and (ii) an antigen-binding molecule that binds to gp130.

In embodiments in accordance with aspects of the preceding paragraph, provision of (i) and (ii) may be as a combination therapy. In some embodiments, (i) and (ii) may be provided simultaneously, separately or sequentially.

The present disclosure is directed to methods and articles (*e.g.* the agents, combinations and compositions of the present disclosure) for the treatment and/or prevention of fibrosis, pathological angiogenesis, pathological inflammation, a disease or condition characterised by fibrosis, a disease or condition characterised by angiogenesis and/or a disease characterised by inflammation. In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of fibrosis. In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of pathological angiogenesis. In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of pathological inflammation. In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of a disease or condition characterised by fibrosis. In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of a disease or condition characterised by angiogenesis. In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of a disease or condition characterised by inflammation.

The fibrosis, pathological angiogenesis, pathological inflammation, disease or condition characterised by fibrosis, disease or condition characterised by angiogenesis and/or disease or condition characterised by inflammation may affect any tissue, or multiple tissues. Herein, where a given disease/condition is said to affect a given organ system/organ/tissue, it is to be understood that the symptoms of the disease/condition manifest in the relevant organ system/organ/tissue. For example, correlates of the disease/condition may be detectable in the relevant organ system/organ/tissue. By way of illustration, choroidal neovascularization (CNV) is an example of a disease/condition characterised by pathological angiogenesis that affects tissue of the eye, and CNV lesions are detected in the ocular tissue.

In some embodiments, the fibrosis, pathological angiogenesis, pathological inflammation, disease or condition characterised by fibrosis, disease or condition characterised by angiogenesis and/or disease or condition characterised by inflammation to be treated/prevented in accordance with the present disclosure affects tissue of one or more of: the eye, liver, lungs, kidney, heart, blood vessels, skin,

pancreas, intestine, brain, and bone marrow. In some embodiments, the fibrosis, pathological angiogenesis, pathological inflammation, disease or condition characterised by fibrosis, disease or condition characterised by angiogenesis and/or disease or condition characterised by inflammation to be treated/prevented in accordance with the present disclosure affects tissue of the eye.

In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of inflammation, particularly pathological inflammation.

As used herein, 'pathological inflammation' refers to inflammation (*i.e.* the biological response of the body to harmful stimuli), wherein the inflammation contributes to the development and/or progression of a disease.

Inflammation and its role in heath and disease is reviewed *e.g.* in Chen *et al.*, Oncotarget (2018) 9(6): 7204–7218, which is hereby incorporated by reference in its entirety. Inflammation refers to the bodily response to cellular/tissue injury, and is characterised by edema, erythema (redness), heat, pain, and loss of function (stiffness and immobility) resulting from local immune, vascular and inflammatory cell responses to infection or injury. The injury may result from *e.g.* of physical (*e.g.* mechanical) or chemical insult, trauma, infection, cancer or overactive/aberrant immune responses (*e.g.* autoimmune disease). Inflammation forms part of the innate immune response and plays an important physiological role in wound healing and the control of infection, and contributes to the restoration of tissue homeostasis.

However, many diseases are associated with an overactive inflammatory response (*i.e.* excessive inflammation and/or aberrantly activated inflammation), and/or chronic (prolonged) inflammation. Herein, excessive and/or chronic inflammation may be referred to as 'pathological inflammation'. Pathological inflammation may refer to inflammation which is implicated in (*i.e.* which positively contributes to) the pathology of a disease.

Inflammation to be treated/prevented in accordance with the present disclosure can be of any tissue/organ of the body. In some embodiments, the inflammation is of the lung (*e.g.* bronchioles, alveoli), airways (*e.g.* nasal cavity, oral cavity, pharynx, larynx, trachea, bronchi), heart, kidney, liver, skeletal muscle, blood vessels, eye, skin, pancreas, bowel, small intestine, large intestine, colon, joints, brain, or bone marrow. Inflammation may also occur in multiple tissues/organs at once.

In some embodiments, inflammation may be of an organ or tissue of the respiratory system, *e.g.* the lung (*e.g.* bronchioles, alveoli), or airways (*e.g.* nasal cavity, oral cavity, pharynx, larynx, trachea, bronchi). In some embodiments, inflammation may be of an organ or tissue of the cardiovascular system, *e.g.* the heart or blood vessels. In some embodiments, inflammation may be of an organ or tissue of the gastrointestinal system, *e.g.* of the liver, bowel, small intestine, large intestine, colon, or pancreas. In some embodiments, inflammation may be of the eye. In some embodiments, inflammation may be of the skin. In some embodiments, inflammation may be of an organ or tissue of the nervous system, *e.g.* the brain. In some embodiments, inflammation may be of the bone marrow. In some embodiments, inflammation may be of the joints. In some embodiments, inflammation may be of an organ or tissue of

the urinary system, *e.g.* the kidneys. In some embodiments, inflammation may be of an organ or tissue of the musculoskeletal system, *e.g.* muscle tissue. In some embodiments, inflammation may be of an organ or tissue of one or more organ systems.

Inflammation can promote angiogenesis (*i.e.* the growth and development of new blood vessels from existing vasculature), through multiple different pathways as described *e.g.* in Granger and Senchenkova, 'Chapter 6: Angiogenesis', in 'Inflammation and the Microcirculation', Morgan & Claypool Life Sciences; 2010. For example, inflammation can lead to hypoxic conditions in inflamed tissue, which in turn upregulates the expression of the potent angiogenic factor vascular endothelial growth factor (VEGF) which induces the growth of new blood vessels. Inflammatory cells such as macrophages, lymphocytes, mast cells and also fibroblasts produce angiogenic factors such as VEGF and FGF. Increased blood flow to inflamed tissue can stimulate angiogenesis through shear stresses on the endothelium of existing vessels, and extravasated plasma proteins, such as fibrinogen products, may also stimulate neovascularisation.

Angiogenesis is known to be dysregulated *e.g.* in systemic sclerosis, a chromic autoimmune connective tissue disease characterised by inflammation, vascular injury and fibrosis, and by an impaired angiogenesis response which cannot ensure efficient vascular recovery – reviewed *e.g.* in Cantatore *et al.*, Biomed Res Int. (2017) 2017:5345673, which is incorporated herein by reference in its entirety. Vascular injury in systemic sclerosis induces hypoxia and tissue ischemia (which are usually primary triggers for angiogenesis) due to avascularisation of tissue, and causes vascular occlusion and thrombosis in larger vessels due to endothelial proliferation, fibrin disoposition and smooth muscle cell hypertrophy. However, when angiogenesis is dysregulated, compensatory angiogenesis is not induced and vascular damage may induce avascular areas or morphological changes in the vessel walls, such as fibrosis. Angiogenic cytokines, such as VEGF, TGFβ and PDGF which are responsible for vessel formation and stabilisation, are also implicated in fibrosis, further contributing to vessel instability and loss of peripheral vascularisation.

Inflammatory reactions play an important part in triggering fibrosis in many different organ systems. Inflammation can lead to excess in deposition of ECM components in the affected tissues. Low-grade but persistent inflammation is also thought to contribute to the progression of fibrosis in cardiovascular disease and hypertension. In many fibrotic disorders, a persistent inflammatory trigger is crucial to upregulation of production of growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines, which stimulate the deposition of connective tissue elements that progressively remodel and destroy normal tissue architecture.

As used herein, a disease/condition which is 'characterised by inflammation' is a disease/condition in which inflammation is a symptom of the disease/condition. Diseases/conditions characterised by inflammation include, but are not limited to:

Diseases/conditions affecting the respiratory system, such as sinusitis, rhinitis, pharyngitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonitis, pleuritis and mediastinitis;

Diseases/conditions affecting the accessory digestive organs such as hepatitis, ascending cholangitis, cholecystitis, pancreatitis and peritonitis;

Diseases/conditions affecting the cardiovascular system such as carditis, endocarditis, myocarditis, pericarditis, vasculitis, arteritis, phlebitis, capillaritis and cardiogenic shock;

Diseases/conditions affecting the urinary system such as nephritis, glomerulonephritis, pyelonephritis, ureteritis, cystitis and urethritis;

Diseases/conditions affecting the nervous system such as encephalitis, myelitis, meningitis, arachnoiditis and neuritis;

Diseases/conditions affecting the musculoskeletal system such as arthritis, dermatomyositis, soft tissue, myositis, synovitis/tenosynovitis, bursitis, enthesitis, fasciitis, capsulitis, epicondylitis, tendinitis, panniculitis, osteochondritis: osteitis/osteomyelitis, spondylitis, periostitis and chondritis;

Diseases/conditions affecting the oral cavity and throat such as stomatitis, gingivitis, gingivostomatitis, periodontitis, glossitis, tonsillitis, sialadenitis, parotitis, cheilitis, pulpitis and gnathitis;

Diseases/conditions affecting the gastrointestinal system such as esophagitis, gastritis, gastroenteritis, enteritis, colitis, enterocolitis, duodenitis, ileitis, caecitis, appendicitis, proctitis and Peutz-Jeghers syndrome;

Diseases/conditions affecting the skin such as dermatitis, folliculitis, cellulitis and hidradenitis;

Diseases/conditions affecting the eye such as dacryoadenitis, scleritis, episcleritis, keratitis, retinitis, chorioretinitis, blepharitis, conjunctivitis, uveitis (including autoimmune uveitis and infectious uveitis), Bechet's disease, cataracts, keratic precipitates, conjunctival ulcers, corneal immune ring opacities, post-surgical inflammation (*e.g.* following glaucoma surgery), dry eye disease, retinitis pigmentosa, glaucoma, toxic anterior segment syndrome (TASS), Eales' disease, macular degeneration (*e.g.* wet age-related macular degeneration (AMD)), diabetic retinopathy, retinal dystrophy (*e.g.* retinitis pigmentosa) and Sjögrens syndrome;

Diseases/conditions affecting the ear such as otitis externa, otitis media, labyrinthitis and mastoiditis;

Diseases/conditions of the reproductive system such as oophoritis, salpingitis, endometritis, endometriosis, parametritis, cervicitis, vaginitis, vulvitis, mastitis, orchitis, epididymitis, prostatitis, seminal vesiculitis, balanitis, posthitis, balanoposthitis, chorioamnionitis, funisitis and omphalitis;

Diseases/conditions of the endocrine system such as insulitis, hypophysitis, thyroiditis, parathyroiditis and adrenalitis;

Diseases/conditions of the lymphatic system such as lymphangitis and lymphadenitis;

Cancers, including inflammation-induced and inflammation-associated cancers, such as lung cancer (*e.g.* lung adenocarcinoma, lung squamous cell carcinoma), prostate cancer, hematological malignancies (*e.g.* multiple myeloma), pancreatic cancer, cervical cancer, stomach cancer, oesophageal cancer, head and neck cancer, colorectal cancer, colon cancer, liver cancer (*e.g.* hepatocellular carcinoma) and bile duct cancer.

It will be appreciated that many of the diseases/conditions listed above are interrelated.

It will be appreciated that diseases/conditions characterised by inflammation may also exhibit further symptoms/pathologies. For example, a disease/condition characterised by inflammation may further be

characterised by angiogenesis (*e.g.* pathological angiogenesis as described herein) and/or fibrosis (*e.g.* fibrosis as described herein).

In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of pathological inflammation of the eye. Inflammation of the eye is described in detail in Perez and Caspi, Trends Immunol. (2015) 36(6):354-363, which is herein incorporated by reference in its entirety. The eye is an immune-privileged tissue, and multiple mechanisms have evolved to inhibit inflammation in the eye in order to protect vision. Nevertheless, the eye is subject to a number of inflammatory diseases and disorders, that can result in vision loss.

Inflammation of the eye may result from genetic factors, including aberrant expression of pro/anti-inflammatory factors. Genetic factors underlying inflammation of the eye are reviewed, for example, in Singh and Tyagi, Int J Ophthalmol. (2018) 11(1):117-134. Inflammation of the eye may also result from a number of non-genetic factors, including trauma/injury to the eye, infection, diabetes, age, and other lifestyle factors. Non-genetic factors underlying inflammation of the eye are discussed, for example, in Kaur and Singh, Neural Regen Res. (2023) 18(3):513-518.

Pathological inflammation of the eye may affect any anatomical location, substructure or tissue of the eye, including the anterior segment, intermediate segment and posterior (*i.e.* the retinal and choroidal) segment of the eye, and the lacrimal gland.

In some embodiments, pathological inflammation may affect the anterior segment of the eye. For example, pathological inflammation may affect the cornea, or the trabecular meshwork (the tracts through which the intraocular fluid leaves the eye).

In some embodiments, pathological inflammation may affect the posterior segment of the eye. Pathological inflammation may be retinal, epiretinal or subretinal inflammation. Pathological inflammation may be a result of or be associated with an ischemic retinopathy. Pathological inflammation may be inflammation associated with ischemia and/or neovascularisation on the surface of the retina. Pathological inflammation may be associated with subretinal neovascularisation, *e.g.* neovascularization originating from the choriocapillaris. Pathological inflammation may be associated with fibrovascular scarring, *e.g.* of the retina. Pathological inflammation may be associated with choroidal neovascularization (CNV).

In some embodiments, 'pathological inflammation' as used herein may refer to uveitis. Historically, the term 'uveitis' referred to inflammation of the uvea, however, uveitis may refer to inflammation in any area of the eye, including the anterior segment (*i.e.* anterior uveitis), intermediate segment (*i.e.* intermediate uveitis), posterior segment (*i.e.* posterior uveitis), or multiple areas (*i.e.* panuveitis). Uveitis is reviewed in, for example, Miller and Hanumunthadu, Clin Med (Lond). (2022). 22(2):100-103, which is hereby incorporated by reference in its entirety.

Uveitis may be caused by autoimmune conditions (*i.e.* 'autoimmune uveitis'). Autoimmune conditions associated with uveitis include AIDS, ankylosing spondylitis, Behcet's disease, lupus, multiple sclerosis, psoriasis, rheumatoid arthritis, sarcoidosis, ulcerative colitis, Vogt-Koyanagi-Harada (VKH) disease.
Uveitis may be caused by infection (*i.e.* 'infectious uveitis'). Infections associated with uveitis include viral infections (*e.g.* infection caused by cytomegalovirus, herpes simplex virus, or varicella zoster virus), fungal infections (*e.g.* infection caused by histoplasma), bacterial infection (*e.g.* infection caused by *Treponema*), parasitic infection (*e.g.* infection caused by *Toxoplasma*).

In some embodiments, pathological inflammation of the eye may be associated with a degenerative disease or condition affecting the eye. Pathological inflammation of the eye may be associated with retinal degeneration, for example, pathological inflammation may be associated with photoreceptor degeneration. In some embodiments, pathological inflammation may be associated with retinitis pigmentosa.

Pathological inflammation of the eye may be associated with fibrosis and/or disease/condition characterised by fibrosis, *e.g.* fibrosis and/or a disease/condition characterised by fibrosis as described herein. Pathological inflammation of the eye may be associated with pathological angiogenesis and/or a disease/condition characterised by angiogenesis, *e.g.* pathological angiogenesis and/or a disease/condition characterised by angiogenesis as described herein.

Pathological inflammation of the eye may be associated with a disease/condition including, but not limited to, dacryoadenitis, scleritis, episcleritis, keratitis, retinitis, chorioretinitis, blepharitis, conjunctivitis, uveitis, (including autoimmune uveitis and infectious uveitis), Bechet's disease, cataracts, keratic precipitates, conjunctival ulcers, corneal immune ring opacities, post-surgical inflammation (*e.g.* following glaucoma surgery), dry eye disease, retinitis pigmentosa, glaucoma, toxic anterior segment syndrome (TASS), Eales' disease, macular degeneration (*e.g.* wet age-related macular degeneration (AMD)), diabetic retinopathy, retinal dystrophy (*e.g.* retinitis pigmentosa) and Sjögrens syndrome.
In some embodiments, a disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition selected from: dacryoadenitis, uveitis, autoimmune uveitis, infectious uveitis, Bechet's disease, and dry eye disease. In some embodiments, pathological inflammation and/or a disease/condition characterised by inflammation in accordance with the present disclosure is selected from dacryoadenitis, uveitis, autoimmune uveitis, infectious uveitis, Bechet's disease, and dry eye disease.

As used herein, 'fibrosis' refers to the formation of excess fibrous connective tissue as a result of the excess deposition of extracellular matrix components, for example collagen. Fibrous connective tissue is characterised by having extracellular matrix (ECM) with a high collagen content. The collagen may be provided in strands or fibres, which may be arranged irregularly or aligned. The ECM of fibrous connective tissue may also include glycosaminoglycans.

As used herein, 'excess fibrous connective tissue' refers to an amount of connective tissue at a given location (*e.g.* a given tissue or organ, or part of a given tissue or organ) which is greater than the amount

of connective tissue present at that location in the absence of fibrosis, *e.g.* under normal, non-pathological conditions. As used herein, 'excess deposition of extracellular matrix components' refers to a level of deposition of one or more extracellular matrix components which is greater than the level of deposition in the absence of fibrosis, *e.g.* under normal, non-pathological conditions.

The cellular and molecular mechanisms of fibrosis are described in Wynn, J. Pathol. (2008) 214(2): 199-210, and Wynn and Ramalingam, Nature Medicine (2012) 18:1028-1040, which are hereby incorporated by reference in their entirety.

Damage to tissues can result from various stimuli, including infections, autoimmune reactions, toxins, radiation and mechanical injury. Repair typically involves replacement of injured cells by cells of the same type, and replacement of normal parenchymal tissue with connective tissue. Repair processes become pathologic when they are not controlled properly, resulting in excess deposition of ECM components in which normal parenchymal tissue is replaced with connective tissue. In diseases such as idiopathic pulmonary fibrosis, liver cirrhosis, cardiovascular fibrosis, systemic sclerosis and nephritis, extensive tissue remodelling and fibrosis can ultimately lead to organ failure and death.

The main cellular effectors of fibrosis are myofibroblasts. In response to tissue injury, damaged cells and leukocytes produce pro-fibroinflammafory factors such as TGFβ, IL-13 and PDGF, which activate fibroblasts (and other myofibroblast precursor cells) to become αSMA-expressing myofibroblasts, and recruit myofibroblasts to the site of injury. Myofibroblasts produce large amounts of extracellular matrix components such as collagen and periostin for wound contracture and closure, and also produce proinflammatory cytokines such as IL-6, and tissue remodelling factors such as MMP2 and TIMP1. Persistent/chronic infection and/or inflammation can result in the generation of too many myofibroblasts, and consequently the over-production of extracellular matrix, resulting in fibrosis. In many diseases and conditions characterised by fibrosis, a persistent inflammatory trigger is crucial to upregulation of production of growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines, which stimulate the deposition of connective tissue elements that progressively remodel and destroy normal tissue architecture.

In some embodiments fibrosis may be triggered by pathological conditions, *e.g.* conditions, infections or disease states that lead to production of pro-fibrotic factors such as TGFβ1. In some embodiments, fibrosis may be caused by physical injury/stimuli, chemical injury/stimuli or environmental injury/stimuli. Physical injury/stimuli may occur during surgery, *e.g.* iatrogenic causes. Chemical injury/stimuli may include drug induced fibrosis, *e.g.* following chronic administration of drugs such as bleomycin, cyclophosphamide, amiodarone, procainamide, penicillamine, gold and nitrofurantoin (Daba *et al.,* Saudi Med J 2004 Jun; 25(6): 700-6). Environmental injury/stimuli may include exposure to asbestos fibres or silica.

Fibrosis can occur in many tissues of the body. For example, fibrosis can occur in the liver (*e.g.* cirrhosis), lungs, kidney, heart, blood vessels, eye, skin, pancreas, intestine, brain, and bone marrow. Fibrosis may also occur in multiple organs at once.

In some embodiments, fibrosis may involve an organ of the gastrointestinal system, *e.g.* of the liver, small intestine, large intestine, or pancreas. In some embodiments, fibrosis may involve an organ of the respiratory system, *e.g.* the lungs. In some embodiments, fibrosis may involve an organ of the cardiovascular system, *e.g.* of the heart or blood vessels. In some embodiments, fibrosis may involve the skin. In some embodiments, fibrosis may involve an organ of the nervous system, *e.g.* the brain. In some embodiments, fibrosis may involve an organ of the urinary system, *e.g.* the kidneys. In some embodiments, fibrosis may involve an organ of the musculoskeletal system, *e.g.* muscle tissue.

In some embodiments fibrosis may be cardiac or myocardial fibrosis, hepatic fibrosis, or renal fibrosis. In some embodiments cardiac or myocardial fibrosis is associated with dysfunction of the musculature or electrical properties of the heart, or thickening of the walls of valves of the heart. In some embodiments fibrosis is of the atrium and/or ventricles of the heart. Treatment or prevention of atrial or ventricular fibrosis may help reduce risk or onset of atrial fibrillation, ventricular fibrillation, or myocardial infarction. In some embodiments hepatic fibrosis is associated with chronic liver disease or liver cirrhosis. In some embodiments renal fibrosis is associated with chronic kidney disease.

As used herein, a disease/condition which is 'characterised by fibrosis' is a disease/condition in which fibrosis is a symptom of the disease/condition. Diseases/conditions characterised by fibrosis in accordance with the present invention include but are not limited to:

Diseases/conditions affecting the respiratory system such as pulmonary fibrosis, fibrothorax, radiation-induced lung injury, interstitial lung disease (ILD), idiopathic interstitial pneumonia (IIP), idiopathic pulmonary fibrosis (IPF), cystic fibrosis, progressive massive fibrosis, scleroderma, obliterative bronchiolitis, Hermansky-Pudlak syndrome, asbestosis, silicosis, sarcoidosis, tumor stroma in lung disease, chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis and asthma;

Diseases/conditions affecting the liver such as chronic liver disease, liver fibrosis, bridging fibrosis, cirrhosis, non-alcoholic fatty liver disease (NAFLD), steatohepatitis, non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), alcoholic fatty liver (AFL), alcoholic hepatitis, alcoholic steatohepatitis (ASH), primary biliary cirrhosis (PBC), schistosomal liver disease and hepatocellular carcinoma (HCC);

Diseases/conditions affecting the cardiovascular system such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), fibrosis of the atrium, atrial fibrillation, fibrosis of the ventricle, ventricular fibrillation, myocardial fibrosis, interstitial fibrosis, replacement fibrosis Brugada syndrome, myocarditis, endomyocardial fibrosis, myocardial infarction, fibrotic vascular disease, hypertension, hypertensive heart disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), atherosclerosis, arterial stiffness, chronic pulmonary hypertension, AIDS-associated pulmonary hypertension, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), varicose veins and cerebral infarcts;

Diseases/conditions affecting the kidneys such as tubulointerstitial fibrosis, glomerular fibrosis, renal fibrosis, nephritic syndrome, Alport's syndrome, HIV-associated nephropathy, polycystic kidney disease, Fabry's disease, diabetic nephropathy, chronic glomerulonephritis and nephritis associated with systemic lupus;

Diseases/conditions affecting the pancreas such as pancreatic fibrosis, cystic fibrosis and chronic pancreatitis;

Diseases/conditions affecting the nervous system such as gliosis, Alzheimer's disease and multiple sclerosis;

Diseases/conditions affecting the musculoskeletal system such as muscular dystrophy, Duchenne muscular dystrophy (DMD), Becker's muscular dystrophy (BMD) and fibrotic myopathy;

Diseases/conditions affecting the gastrointestinal system such as inflammatory bowel disease (IBD), Crohn's disease, microscopic colitis and primary sclerosing cholangitis (PSC);

Diseases/conditions affecting the skin such as scleroderma, nephrogenic systemic fibrosis, Dupuytren's contracture and cutis keloid;

Diseases/conditions affecting the eye such as macular degeneration, Age-related Macular Degeneration (AMD), Geographic Atrophy ('dry' or non-exudative AMD), early AMD, early onset macular degeneration (EOMD), intermediate AMD, late/advanced AMD, 'wet' (neovascular or exudative) AMD, choroidal neovascularisation (CNV), retinal dystrophy, glaucoma (open-angle or closed-angle), neuromyelitis optica (neuromyelitis optica spectrum disorder (NMOSD)), diabetic retinopathy, macular edema, drusen formation, Grave's opthalmopathy, corneal opacification, subretinal fibrosis, corneal fibrosis, epiretinal fibrosis, post-surgical fibrosis (*e.g.* of the posterior capsule following cataract surgery, or the bleb following trabeculectomy for glaucoma), conjunctival fibrosis, subconjunctival fibrosis, macular fibrosis and preretinal fibrosis;

Diseases/conditions affecting the joints such as arthrofibrosis, arthritis and adhesive capsulitis;

Diseases/conditions affecting multiple tissues/organ systems, including progressive systemic sclerosis (PSS), chronic graft versus host disease (GVHD); fibrotic pre-neoplastic and fibrotic neoplastic disease, and fibrosis induced by chemical or environmental insult (*e.g.*, cancer chemotherapy, pesticides, radiation/cancer radiotherapy);

Cancers, such as hepatocellular carcinoma, gastric cancer, oesophageal cancer, head and neck cancer, colorectal cancer, pancreatic cancer, cervical cancer, and vulvar cancer;

Mediastinal fibrosis, retroperitoneal fibrosis, myelofibrosis and Peyronie's disease.

It will be appreciated that many of the diseases/conditions listed above are interrelated.

In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of fibrosis of the eye. Fibrosis of the eye is described in detail in Friedlander, *Fibrosis and diseases of the eye*, J Clin Invest. 2007 Mar 1; 117(3): 576–586, which is herein incorporated by reference.

Fibrosis of the eye may result from a mechanical wound or various metabolic malfunctions, including responses to inflammation, ischemia, and degenerative disease. Fibrosis of the eye may affect any anatomical location, substructure or tissue of the eye, including the anterior segment, intermediate segment and posterior (*i.e.* the retinal and choroidal) segment of the eye, and the lacrimal gland. Fibrosis of the eye may refer to wound-healing or disease events in the anterior segment of the eye, or within the posterior (*i.e.* retinal) segment of the eye.

Fibrosis of the eye may be a retinal, epiretinal or subretinal fibrosis. It may be a result of or be associated with an ischemic retinopathy. The fibrosis of the eye may be a fibrosis associated with ischemia and/or neovascularisation on the surface of the retina. The fibrosis of the eye may be associated with subretinal neovascularisation, *e.g.* neovascularization originating from the choriocapillaris. Fibrosis may be associated with fibrovascular scarring, *e.g.* of the retina. Fibrosis of the eye may be associated with choroidal neovascularization (CNV).

Fibrosis of the eye may also occur in the anterior segment of the eye. For example, fibrosis may affect the cornea, or the trabecular meshwork (the tracts through which the intraocular fluid leaves the eye). Fibrosis may be characterised by fibrovascular growths on the surface of the cornea, for example pingueculae and pterygia.

Fibrosis of the eye may be associated with a disease/condition such as an inflammatory or ischemic disorder. Such diseases/disorders include Grave's opthalmopathy, epiretinal fibrosis, retinal fibrosis, idiopathic premacular fibrosis, subretinal fibrosis (*e.g.* associated with retinal detachment or macular degeneration (*e.g.* wet age-related macular degeneration (AMD)), diabetic retinopathy, glaucoma, geographic atrophy (dry age-related macular degeneration (AMD)), corneal fibrosis, post-surgical fibrosis (*e.g.* of the posterior capsule following cataract surgery, or of the bleb following trabeculectomy for glaucoma), conjunctival fibrosis, or subconjunctival fibrosis.

As used herein ‘early AMD’ refers to a stage of AMD characterised by the presence of medium-sized drusen, commonly having a width of up to ~200 µm, within the Bruch’s membrane adjacent to the RPE layer. Subjects with early AMD typically do not present significant vision loss. As used herein ‘intermediate AMD’ refers to a stage of AMD characterised by large drusen and/or pigment changes in the retina. Intermediate AMD may be accompanied by some vision loss. As used herein ‘late AMD’ refers to a stage of AMD characterised by the presence of drusen and vision loss due to damage to the macula. In all stages of AMD, ‘reticular pseudodrusen’ (RPD) or ‘reticular drusen’ may be present, referring to the accumulation of extracellular material in the subretinal space between the neurosensory retina and RPE. ‘Late AMD’ encompasses ‘dry’ and ‘wet’ AMD. In ‘dry’ AMD (also known as geographic atrophy), there is a gradual breakdown of the light-sensitive cells in the macula that convey visual information to the brain and of the supporting tissue beneath the macula. In ‘wet’ AMD (also known as choroidal neovascularization AMD (nAMD) and exudative AMD), abnormal blood vessels grow underneath and into the retina. These vessels can leak fluid and blood which can lead to swelling and damage of the macula and subsequent fibrosis/scar formation. The damage may be rapid and severe.

Fibrosis of the eye and fibrotic diseases of the eye are reviewed *e.g.* in Mallone *et al.*, Int J Mol Sci. (2021) 22:11748 and Friedlander, J Clin Invest. (2007) 117(3):576-586 which are hereby incorporated by reference in their entirety. Neovascular AMD (nAMD) is reviewed *e.g.* in Pugazhendhi *et al.*, Int J Mol Sci. (2021) 22(3):1170, which is hereby incorporated by reference in its entirety.

It will be appreciated that diseases/conditions characterised by fibrosis may also exhibit further symptoms/pathologies. For example, a disease/condition characterised by fibrosis may further be

characterised by pathological angiogenesis (*e.g.* pathological angiogenesis as described herein) and/or pathological inflammation (*e.g.* pathological inflammation as described herein). In some embodiments, the methods may reduce the development or progression of one or more of: fibrosis, pathological angiogenesis and pathological inflammation. In some embodiments, the methods may be effective to prevent the progression (*e.g.* to prevent worsening, or the slow the rate of development) of one or more of: fibrosis, pathological angiogenesis and pathological inflammation. In some embodiments, the methods may lead to an improvement in the disease/condition, *e.g.* a reduction in one or more of: fibrosis, pathological angiogenesis and pathological inflammation; or a reduction in some correlate of the severity of one or more of: fibrosis, pathological angiogenesis and pathological inflammation. In some embodiments, the methods may prevent development of a later stage of one or more of: fibrosis, pathological angiogenesis and pathological inflammation. For example, the methods may reduce/prevent the development/progression of fibrosis, pathological angiogenesis and pathological inflammation. The methods may reduce/prevent the development/progression of fibrosis, pathological angiogenesis and pathological inflammation.

In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of pathological angiogenesis. As used herein, 'pathological angiogenesis' refers to angiogenesis (*i.e.* the growth of new blood vessels from an existing vascular plexus), wherein the angiogenesis contributes to the development and/or progression of a disease. The role of angiogenesis in disease is reviewed in, for example, La Mendola *et al.* Int J Mol Sci. (2022). 23(18):10962, which is hereby incorporated by reference in its entirety.

As used herein, a disease/condition which is 'characterised by angiogenesis' is a disease/condition in which angiogenesis is a symptom of the disease/condition. Diseases/conditions characterised by angiogenesis in accordance with the present invention include but are not limited to cancers, diabetic retinopathy, autoimmune diseases, rheumatoid arthritis, atherosclerosis, cerebral ischemia, cardiovascular diseases, delayed wound healing, macular degeneration (including Age-related Macular Degeneration (AMD), Geographic Atrophy ('dry' or non-exudative AMD), early AMD, early onset macular degeneration (EOMD), intermediate AMD, late/advanced AMD, 'wet' (neovascular or exudative) AMD), choroidal neovascularisation (CNV), fibrotic disease (including retinal fibrosis, liver fibrosis, lung fibrosis, cardiac fibrosis, kidney fibrosis).

As described herein, numerous inducers of angiogenesis have been identified, including the members of the vascular endothelial growth factor (VEGF) family, angiopoietins, transforming growth factors (TGF), members of the platelet-derived growth factor family, tumour necrosis factor-α, interleukins and the members of the fibroblast growth factor (FGF) family. As well as promoting new blood vessel growth, pro-angiogenic signalling can impact vascular permeability. Pro-angiogenic signalling may lead to vascular hyper-permeability, or vascular leakage. The association of pro-angiogenic signalling and vascular permeability is described in, for example, Nagy *et al.* J Exp Med. (2002) 196(11):1497-1506.

In some embodiments, a disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition characterised by vascular leakage and/or vascular hyper-permeability.

Herein, a disease/condition characterised by vascular leakage and/or vascular hyper-permeability may be a disease/condition in which vascular leakage and/or vascular hyper-permeability is a symptom of the disease/condition. In some embodiments, a disease/condition characterised by angiogenesis in accordance with the present disclosure is a disease/condition characterised by vascular leakage and/or vascular hyper-permeability.

Angiogenesis is closely related to fibrosis and plays a major role in the development/progression of fibrosis in various organs (see, for example, Matsuda *et al.* Molecular Therapy Nucleic Acids. (2019) 17:819-828; Wan *et al.* Respir Res. (2013) 14(1):56; Liu *et al.* Nature Materials. (2017) 16:1252-1261)).

Angiogenesis can also be induced by inflammation, as described herein.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition characterised by angiogenesis, (*e.g.* pathological angiogenesis). In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition characterised by inflammation-induced angiogenesis.

It will be appreciated that diseases/conditions characterised by angiogenesis may also exhibit further symptoms/pathologies. For example, a disease/condition characterised by angiogenesis may further be characterised by pathological inflammation (*e.g.* pathological inflammation as described herein) and/or fibrosis (*e.g.* fibrosis as described herein).

In some embodiments, the present disclosure is directed to methods and articles for the treatment and/or prevention of pathological angiogenesis affecting the eye (*i.e.* pathological angiogenesis of the eye, or ocular angiogenesis). Pathological angiogenesis of the eye may be associated with any anatomical location, structure or tissue of the eye, including the anterior segment, intermediate segment and posterior (*i.e.* the retinal and choroidal) segment of the eye, and the lacrimal gland.

Pathological angiogenesis of the eye may be associated with an ischemic retinopathy. Pathological angiogenesis of the eye may be associated with ischemia and/or neovascularisation on the surface of the retina. Pathological angiogenesis may be associated with subretinal neovascularisation, *e.g.* neovascularisation originating from the choriocapillaris. Pathological angiogenesis of the eye may be associated with choroidal neovascularisation (CNV).

Pathological angiogenesis of the eye may be associated with a disease/condition including, but not limited to, corneal neovascularisation, macular degeneration (*e.g.* wet age-related macular degeneration (AMD)), diabetic retinopathy, retinal vein occlusions, sickle cell retinopathy, hyperviscosity syndromes, pathologic myopia, retinal arterial occlusion, radiation retinopathy, ocular ischemic syndrome, retinopathy of prematurity, familial exudative vitreoretinopathy (FEVR), retinal vasculitis, uveitis (including autoimmune uveitis and infectious uveitis), pathological inflammation of the eye (*i.e.* ocular inflammation), tumors, retinal vascular tumors (including hemangiomas), retinal degeneration/retinal dystrophy (*e.g.* retinal pigmentosa), angioid streaks, choroidal rupture, Eales disease, sarcoidosis, chronic retinal

detachment, carotid-cavernous fistula, Coats' disease, retinal artery macroaneurysms, and incontinentia pigmenti.

Pathological angiogenesis of the eye may be associated with fibrosis and/or disease/condition characterised by fibrosis, *e.g.* as described herein. Pathological angiogenesis of the eye may be associated with pathological inflammation and/or a disease/condition characterised by inflammation, *e.g.* as described herein.

Fibrosis, pathological angiogenesis, and pathological inflammation are hallmarks of AMD. This is reviewed in *e.g.* Heloterä and Kaarniranta, Cells (2022) 11(21):3453, which is hereby incorporated by reference in its entirety.

As used herein 'choroidal neovascularization' or CNV refers to the creation of new blood vessels in the choroid layer of the eye. In CNV, new blood vessels grow from the choroid, through the Bruch's membrane into the subretinal space. The pathogenesis of CNV is described in, for example, Al-Sheikh, and Barthelmes, (2020). Pathogenesis of Choroidal Neovascularization. Choroidal Neovascularization. Springer, Singapore, which is hereby incorporated by reference in its entirety. The exact causes and stages of development of CNV are not well understood, although it is well established that pathological angiogenesis is a critical factor. Moreover, aberrant VEGF activity is known to play a crucial role in CNV. Imbalance in the secretion of VEGF from the retinal pigmented epithelium (as a result of abnormal conditions such as, for example, hypoxia) can promote angiogenesis, which in turn contributes to CNV development. In some embodiments, 'pathological angiogenesis' as used herein may refer to CNV. Inflammation is also closely associated with the pathogenesis of CNV. The recruitment of inflammatory cells, and activation of the complement system during inflammation promotes angiogenesis, as well as exacerbating damage to the Bruch's membrane. The role of inflammation in CNV is reviewed in, for example, Campa *et al.* Mediators Inflamm. (2010) e546826, which is hereby incorporated by reference in its entirety.

Another hallmark of CNV is fibrosis, specifically fibrosis in the tissue of the eye (*e.g.* subretinal fibrosis). Dysfunction of the retinal pigmented epithelium can lead to build-up of sub-retinal deposits, called drusen, which can result in fibrosis. This fibrosis can lead to damage to the Bruch's membrane, as well as generating conditions that promote angiogenesis. Both factors can contribute to the pathogenesis of CNV. The relationship between fibrosis and CNV is described in, for example, Friedlander, Journal of Clinical Investigation. (2007) 117(3):576-586, which is hereby incorporated by reference in its entirety.

CNV itself is a hallmark of 'wet' AMD, wherein the excessive growth of abnormal blood vessels in the eye can eventually lead to vision loss due to detachment of the retinal pigmented epithelium.

In some embodiments the disease/condition to be treated/prevented is choroidal neovascularization (CNV) and/or age-related macular degeneration (AMD), *e.g.* 'wet' AMD.

In some embodiments, the disease/condition to be treated in accordance with the present disclosure is systemic sclerosis. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is arthritis. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is idiopathic pulmonary fibrosis (IPF). In some embodiments, the disease/condition to be treated in accordance with the present disclosure is COVID-19. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is a cytokine storm syndrome (CSS), *e.g.* cytokine release syndrome (CRS). In some embodiments, the disease/condition to be treated in accordance with the present disclosure is kidney disease. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is kidney disease sepsis or septic shock. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is hypertrophic cardiomyopathy (HCM). In some embodiments, the disease/condition to be treated in accordance with the present disclosure is dilated cardiomyopathy (DCM). In some embodiments, the disease/condition to be treated in accordance with the present disclosure is cardiogenic shock. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is chronic inflammation, for example, chronic inflammation associated with ageing. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is cardiovascular disease.

In some embodiments, the disease/condition to be treated in accordance with the present disclosure is a disease/condition described in WO 2022/090509 A1, which is hereby incorporated by reference in its entirety. In some embodiments, the disease/condition to be treated is an age-related diseases/condition. Age-related diseases/conditions as referred to herein are diseases/conditions having an incidence which increases with age. Age-related diseases and conditions are described *e.g.* in Franceschi *et al.,* Front Med (Lausanne) (2018) 5: 61 and Jaul and Barron Front Public Health (2017) 5: 335, both of which are hereby incorporated by reference in their entirety.

Age-related diseases/conditions are typically characterised by progressive degeneration of tissue structure and/or the progressive decline of physiological tissue function. The molecular and cellular mechanisms underlying such diseases/conditions include one or more of deregulated autophagy, mitochondrial dysfunction, telomere shortening, oxidative stress, inflammation, metabolic dysfunction, and commonly cellular senescence.

Aging is a major risk factor for many chronic diseases. In the liver, aging increases the susceptibility towards acute liver injury and hepatic fibrotic response (Kim *et al.,* Curr Opin Gastroenterol (2015) 31(3): 184-191; Hunt *et al.,* Comput Struct Biotechnol J (2019) 17: 1151-1161, Ferrucci *et al*., Aging Cell (2020) 19(2): e13080). Moreover, aging has been positively associated with increased risk and poor prognosis of various liver diseases including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, hepatitis C, and negatively associated with hepatic regenerative capacity (Kim *et al*., Curr Opin Gastroenterol (2015) 31(3): 184-191; Papatheodoridi *et al.,* Hepatology (2020) 71(1): 363-374).

As used herein, an ‘age-related’ disease/condition or phenotype may also be referred to as being ‘aging-related’ or ‘age/aging-associated’. In aspects and embodiments of the present disclosure, a

disease/condition or phenotype which is described as being 'age-related' may arise as a consequence of the age of the subject having the relevant disease/condition or phenotype, rather than another etiological cause. In some aspects and embodiments, a disease/condition or phenotype which is 'age-related' may arise as a consequence of cellular senescence. By way of illustration, 'age-related' changes in body composition may refer to changes in body composition arising as a consequence of aging of the subject and/or of cellular senescence, rather than the subject's diet.

The accumulation of senescent cells is one of the hallmarks in aging (Hunt *et al.,* Comput Struct Biotechnol J (2019) 17: 1151-1161). Cellular senescence is characterised by reduced replicative capacity and producing senescence-associated secretory phenotype (SASPs) proteins, resulting in a chronic, low-grade inflammatory environment for neighbouring cells (Hunt *et al*., Comput Struct Biotechnol J (2019) 17: 1151-1161; Borghesan *et al*., Trends Cell Biol. (2020) 30(10):777-791). Under pathological stress conditions, excessive accumulation of senescence cells in affected tissues adversely affects the tissue's regenerative ability and chronic inflammation that can resemble various age-related disorders such as Alzheimer's disease, cancer, arthritis, cataracts, osteoporosis, atherosclerosis, hypertension, cardiovascular disease, type 2 diabetes, and chronic liver disorders (Baker and Haynes, Trends Biochem Sci (2011) 36(5): 254-261; Kim *et al*., Curr Opin Gastroenterol (2015) 31(3): 184-191; Hernandez-Segura *et al*., Trends Cell Biol (2018) 28(6): 436-453; Stahl et al. Front Immunol (2018) 9: 2795; Belikov, Ageing Res Rev (2019) 49: 11-26; Campisi *et al.,* Nature (2019) 571(7764): 183-192; Gorgoulis *et al.,* Cell (2019) 179(4): 813-827; Schmeer *et al*., Cells (2019) 8(11); Papatheodoridi *et al*., Hepatology (2020) 71(1): 363-374). Cellular senescence is therefore thought to be a key physiological process in the development and progression of age-related diseases (Borghesan *et al*., Trends Cell Biol. (2020) 30(10):777-791; Pignolo *et al.,* Trends Mol Med (2020) 26(7): 630-638).

In some aspects and embodiments the present disclosure contemplates treatment/prevention of cellular senescence, and diseases/conditions characterised by cellular senescence. In some aspects and embodiments, the methods of the present disclosure comprise inhibiting cellular senescence. In some aspects and embodiments, the methods of the present disclosure comprise inhibiting senescent cells. In some aspects and embodiments, the methods comprise reducing the number of senescent cells and/or inhibiting the activity of senescent cells.

In some embodiments, reducing the number of senescent cells comprises inhibiting the process of cellular senescence. That is, in some embodiments reducing the number of senescent cells comprises inhibiting the development of senescent cells from non-senescent precursor cells. In some embodiments, reducing the number of senescent cells comprises reversing the process of cellular senescence. That is, in some embodiments reducing the number of senescent cells comprises promoting reversion of senescent cells to a non-senescent phenotype. In some embodiments, reducing the number of senescent cells comprises depleting senescent cells.

Cellular senescence is described *e.g.* in Childs *et al.* Nat Med (2015) 21(12):1424-1435 and van Deursen, Nature (2014) 509(7501): 439-446, both of which are hereby incorporated by reference in their entirety. Cellular senescence is characterised by cessation of cell division (associated with activation of p16INK4a,

p21CIP1 and p53), chromatin remodelling (including *e.g.* DNA damage response (DDR), formation of promyelocytic leukemia protein (PML) bodies and senescence associated heterochromatic foci (SAHF)), senescence-associated β-galactosidase activity, and production of a mixture of proinflammatory factors termed the senescence-associated secretory phenotype (SASP).

In accordance with the present disclosure, a senescent cell may display one or more of the following relative to an equivalent non-senescent cell of the same cell type/from the same tissue: increased expression of p16INK4a, p21CIP1 and/or p53; increased level of DDR; increased number of PML bodies; increased number of SAHF, increased expression and/or activity of senescence-associated β-galactosidase; increased expression of one or more SASP factors (*e.g.* IL-1b or IL-8).

In particular aspects and embodiments, the present disclosure relates to the treatment of diseases/conditions comprising and/or characterised by cellular senescence, *i.e.* diseases/conditions in which cellular senescence is pathologically-implicated. A disease/condition in which cellular senescence is 'pathologically-implicated' is a disease/condition in which the number/proportion and/or activity of senescent cells is positively associated with the disease or condition.

A disease/condition in which cellular senescence is 'pathologically-implicated' may be a disease/condition for which an increase in the number/proportion and/or activity of senescent cells (relative to the non-diseased, healthy state) is positively associated with the onset, development and/or progression of the disease/condition. A disease/condition in which cellular senescence is 'pathologically-implicated' may be a disease/condition for which an increase in the number/proportion and/or activity of senescent cells (relative to the non-diseased, healthy state) is positively associated with the severity of one or more symptoms of the disease/condition. A disease/condition in which cellular senescence is 'pathologically-implicated' may be a disease/condition for which an increase in the number/proportion and/or activity of senescent cells (relative to the non-diseased, healthy state) is a risk factor for the onset, development and/or progression of the disease/condition.

Diseases/conditions (*e.g.* age-related diseases/conditions) contemplated to be treated/presented in accordance with the present disclosure include *e.g.* geriatric syndromes, Alzheimer's disease, cancer, hyperlipidaemia, hypertriglyceridemia, hypercholesterolemia, steatosis (*e.g.* of the liver), non-alcoholic fatty liver disease (NAFLD), non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), cardiovascular disease, hypertension (*e.g.* systolic, diastolic), heart failure with reduced or preserved ejection fraction, renal disease (*e.g.* chronic kidney disease), atherosclerosis, hypertension, maculopathy, age-related macular degeneration (AMD), cataracts, chronic obstructive pulmonary disease (COPD), arthritis, osteoarthritis, osteopenia, osteoporosis, Parkinson's disease, periodontitis, rheumatoid arthritis, diabetes mellitus, type II diabetes mellitus, chronic liver disease, sarcopenia, constipation, impotence, vaginal dryness, hair loss, skin disease and skin fragility.

Geriatric syndromes are conditions which are common in elderly patients, and include frailty, cognitive impairment, delirium, dementia, incontinence, hearing impairment, visual impairment, sarcopenia, metabolic syndrome, malnutrition, gait disturbance, falls and pressure ulcers.

Further exemplary diseases/conditions contemplated to be treated/presented in accordance with the present disclosure include frailty, age-related increase in fat mass, sarcopenia, age-related hyperlipidaemia, age-related hypertriglyceridemia, age-related hypercholesterolemia, age-related liver steatosis, age-related non-alcoholic fatty liver disease (NAFLD), age-related non-alcoholic fatty liver (NAFL), age-related non-alcoholic steatohepatitis (NASH), age-related cardiovascular disease, age-related hypertension, age-related renal disease and age-related skin disease.

Where a disease/condition is described herein as 'age-related', reference is made to the disease/condition arising as a consequence of the age of the subject as distinct from other possible etiological causes. For example, 'age-related steatosis' refers to the specific subtype of steatosis arising as a consequence of the aging process, which is distinct from steatosis arising *e.g.* as a consequence of diet.

In particular embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is selected from: osteoarthritis, osteopenia, osteoporosis, Parkinson's disease, periodontitis, frailty, cognitive impairment, delirium, dementia, incontinence, hearing impairment, visual impairment, malnutrition, gait disturbance, falls and pressure ulcers.

In some aspects and embodiments, the present disclosure contemplates the treatment/prevention of frailty.

Frailty may be determined in accordance with the phenotypic criteria established by Fried *et al*., J Gerontol A Biol Sci Med Sci (2001) 56(3):M146-56 (hereby incorporated by reference in its entirety), as subject having three or more of: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss, which may in turn be defined in accordance with the frailty-defining criteria of the Women's Health and Aging Studies (WHAS) or the Cardiovascular Health Study (CHS) as summarised in Table 1 of Xue, Clin Geriatr Med (2011) Feb; 27(1): 1–15 (hereby incorporated by reference in its entirety).

In some aspects and embodiments, the present disclosure contemplates the treatment/prevention of an age-related change in body composition.

Age-related changes in body composition are described *e.g.* in Santanasto *et al*., J Gerontol A Biol Sci Med Sci. (2017) 72(4): 513-519 and St-Onge and Gallagher, Nutrition (2010) 26(2): 152–155, both of which are hereby incorporated by reference in their entirety. Age-related changes in body composition include: reduction in muscle mass (*i.e.* sarcopenia), reduction in bone mass (*e.g.* leading to osteoporosis), increase in fat mass, degeneration of cartilage (*e.g.* leading to osteoarthritis), changes in the kidney (*e.g.* leading to renal dysfunction (*e.g.* age-dependent deterioration in glomerular filtration rate)), changes in the organs of the respiratory system (*e.g.* the lungs, *e.g.* leading to chronic obstructive pulmonary disease (COPD)), changes in the organs of the digestive system (*e.g.* leading to constipation), changes in the bladder (*e.g.* leading to urinary incontinence), degeneration of teeth and/or gums (*e.g.*

leading to periodontal disease), hair loss, skin fragility (*e.g.* leading to dryness and/or wrinkles), changes in the organs of the auditory system (*e.g.* leading to hearing loss), and changes to the reproductive organs (*e.g.* leading to impotence or vaginal dryness).

Age-related reduction in muscle mass may comprise a reduction in skeletal muscle mass. Skeletal muscle undergoes age-associated changes to the mitochondria, leading to the formation of inefficient mitochondria that release more reactive oxygen species (Johnson *et al.,* Trends Endocrinol Metab. (2013) 24(5):247-56). Mitochondrial dysfunction is in turn thought to give rise to activation of skeletal muscle apoptosis, resulting in atrophy of skeletal muscle (Lenk et al. J Cachexia Sarcopenia Muscle. (2010) 1(1):9-21).

Age-related reduction in bone mass is described *e.g.* in Demontiero *et al*. Ther Adv Musculoskelet Dis. (2012) 4(2): 61–76. Underlying mechanisms include bone resorption by osteoclasts and insufficient formation of bone tissue by osteoblasts. Reduction in bone mass may result in osteoporosis, which is defined as defined as deterioration in bone mass and micro-architecture, with increasing risk to fragility fractures (Raisz and Rodan, Endocrinol Metab Clin North Am. (2003) 32(1):15-24).

Aging is often characterised by increased in body total fat mass independent from general and physiological fluctuations in weight and body mass index (BMI) (Zong *et al.,* Obesity (2016) 24(11):2414-2421). In particular, accumulation of muscle fat, visceral fat and liver fat, in form of lipid droplets (LD), shows an age-dependent increase (Reinders *et al*., Curr Opin Clin Nutr Metab Care. (2017) 20(1):11-15).

In some embodiments, an age-related change in body composition in accordance with the present disclosure is selected from: age-related reduction in muscle mass, sarcopenia, age-related reduction in bone mass, osteoporosis, and age-related increase in fat mass. In some embodiments, an age-related change in body composition in accordance with the present disclosure is selected from: age-related reduction in muscle mass, sarcopenia and age-related increase in fat mass.

Aging is often associated with increases in serum lipid levels. Older adults display higher serum levels of triglycerides and cholesterol, and in some instances display hyperlipidaemia (*e.g.* hypertriglyceridemia, hypercholesterolemia or combined hyperlipidaemia (combination of hypertriglyceridemia and hypercholesterolemia). Hyperlipidaemia is in turn commonly associated *e.g.* with atherosclerosis and cardiovascular disease.

Hypertriglyceridemia is described *e.g.* in Berglund *et al.,* J. Clin. Endocrinol. Metab. (2012) 97(9):2969-89, and is defined by blood triglyceride level ≥150 mg/dL (≥1.7 mmol/L). Hypercholesterolemia is described *e.g.* in Bhatnagar *et al.,* BMJ (2008) 337:a993. The UK NHS defines hypercholesterolemia as blood total cholesterol level of ≥5 mmol/L or blood low-density lipoprotein (LDL) level of ≥3 mmol/L. The US NIH defines hypercholesterolemia as blood total cholesterol level of ≥240 mg/dL.

Aging is often associated with liver steatosis, *e.g.* as described in Nguyen *et al*., Cell Rep (2018) Aug 7;24(6):1597-1609. Steatosis refers to the abnormal retention of lipid within a cell/tissue/organ. Steatosis

may be macrovesicular or microvesicular, and commonly affects the liver. Age-related steatosis can lead to age-related non-alcoholic fatty liver disease (NAFLD). NAFLD is reviewed *e.g.* in Benedict and Zhang, World J Hepatol. (2017) 9(16): 715–732 and Albhaisi *et al.,* Version 1. F1000Res. (2018) 7: F1000 Faculty Rev-720, both of which are hereby incorporated by reference in their entirety. NAFLD is characterised by steatosis of the liver, and in particular of hepatocytes. NAFLD includes non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is characterized by steatosis of the liver, involving greater than 5% of parenchyma, with no evidence of hepatocyte injury. NAFL may progress to NASH, which is steatosis combined with inflammation and/or fibrosis (steatohepatitis).

In particular embodiments, a disease/condition to be treated in accordance with the present disclosure may comprise or be characterised by one or more of the following: frailty, a reduction in muscle mass, an increase in fat mass, an increase in serum lipids (*e.g.* hyperlipidaemia), an increase in serum triglycerides (*e.g.* hypertriglyceridemia), an increase in serum cholesterol (*e.g.* hypercholesterolemia), an increase in liver triglycerides (*e.g.* steatosis of the liver), and a reduction in serum β-hydroxybutyrate. It will be appreciated that a reduction/increase is determined relative to the non-diseased state, or in the absence of the condition.

In some embodiments, a disease/condition to be treated or prevented in accordance with the present disclosure may be, or may be associated with, one or more Hallmark of Ageing. The 'Hallmarks of Ageing', as described in López-Otín *et al.* 2013 consist of: telomere attrition, genomic instability, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, loss of proteostasis, deregulated nutrient sensing, epigenetic alterations, and altered intercellular communication. In some embodiments, the disease/condition to be treated or prevented in accordance with the present disclosure is, or is associated with, a Hallmark selected from deregulated nutrient sensing, loss of proteostasis and/or cellular senescence.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of signalling mediated by a gp130-containing complex. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130:IL-6Rα-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130:IL-11Rα-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130:OSMRβ-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130:LIFRβ-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130:LIFRβ:CNTFRα-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of

gp130:IL-27Rα-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of gp130:IL-12Rβ2-mediated signalling.

In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of signalling mediated by a cytokine that signals through a gp130-containing complex. In some embodiments, disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of IL-6-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of IL-11-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of OSM-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of LIF-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of CNTF-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of CT-1-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of CLC-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of IL-27-mediated signalling. In some embodiments, the disease/condition is a fibrosis, pathological angiogenesis, and/or pathological inflammation characterised by an increased level of IL-35-mediated signalling.

The level of gp130-mediated signalling/signalling mediated by a gp130-containing complex/signalling mediated by a cytokine that signals through a gp130-containing complex can be evaluated by means well known to the skilled person, with reference also to the experimental examples of the present disclosure.

In some embodiments, the disease/condition to be treated/prevented may be characterised by an increase in one or more of the following in an organ/tissue/subject affected by the disease, *e.g.* as compared to normal (*i.e.* non-diseased) organ/tissue/subject: IL-11, IL-11Rα, TGFβ, VEGF, FGF, PDGF, VEGFR, FGFR or PDGFR.

An 'increased' level of signalling in accordance with the present disclosure may by a level of signalling that is greater than a reference level of signalling, which may be the level of signalling detected in the absence of the disease/condition. For example, the reference level of signalling may be the level of signalling detected in a healthy (*e.g.* non-diseased) subject. In some embodiments, the increased level of signalling may be in cells of a tissue/organ affected by the disease/condition (*e.g.* cells of a tissue/organ in which one or more symptoms of the disease/condition manifest), or in cells of a cancer (*e.g.* cells of a tumor). In accordance with such embodiments, an increased level of signalling may be a level of signalling that is greater than the level of signalling detected in cells of the same type (*e.g.* cells from the same organ/tissue) in the absence of the disease/condition (*e.g.* the level of signalling detected in cells of

the same type from a healthy (*e.g.* non-diseased) subject), or a level of signalling that is greater than the level of signalling detected in equivalent non-cancerous cells (*e.g.* equivalent non-tumor tissue).

IL-6 signalling in health and disease is reviewed *e.g.* in Rose-John, F1000Res. (2020) 9:F1000 Faculty Rev-1013, Tanaka *et al.*, Cold Spring Harb Perspect Biol. (2014) 6(10): a016295, and Hirano *et al.* International Immunology (2021) 33(3): 127–148, all of which are hereby incorporated by reference in their entirety. IL-6/gp130:IL-6Rα-mediated signalling is implicated in the pathology of a wide range of diseases/conditions, including metabolic syndrome, neurodegenerative diseases, chronic inflammatory diseases, sepsis, septic shock, age-related diseases/conditions, arthritis (*e.g.* rheumatoid arthritis, juvenile arthritis), lupus, pancreatitis, thyroiditis, Graves' disease, diabetes (*e.g.* type 1 diabetes and type 2 diabetes), multiple sclerosis, cardiovascular diseases, cardiogenic shock, atherosclerosis, systemic sclerosis, Alzheimer's disease, hippocampal atrophy, pulmonary disease, asthma, cystic fibrosis, hepatitis, inflammatory bowel disease, colitis, stroke, nephropathy, glomerulonephritis and cancers, including hematologic malignancies (*e.g.* plasmacytoma), lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, breast cancer, stomach cancer and liver cancer (*e.g.* hepatocellular carcinoma). Diseases/conditions in which gp130:IL-6Rα/IL-6-mediated signalling is pathologically-implicated and/or characterised by an increased level of gp130:IL-6Rα-/IL-6-mediated signalling also include diseases/conditions characterised by pathological inflammation and/or fibrosis, *e.g.* as described herein.

Antagonists of IL-6/gp130:IL-6Rα-mediated signalling have been employed for the treatment of variety of different diseases/conditions (see *e.g.* Choy *et al.*, Nat. Rev. Rheumatol. (2020) 16: 335–345). Monoclonal antibodies targeting the IL-6 receptor such as tocilizumab and sarilumab, and monoclonal antibodies targeting IL-6 such as siltuximab and olokizumab, have been used for the treatment of diseases/conditions such as rheumatoid arthritis, juvenile arthritis (particularly systemic juvenile idiopathic arthritis), adult-onset Still's disease, Castleman's disease, giant cell (temporal) arteritis, Takayasu arteritis, cytokine release syndrome (CRS), COVID-19, renal cancer (particularly metastatic renal cell cancer) and prostate cancer.

Accordingly, in some embodiments, a disease/condition in which IL-6-mediated signalling is pathologically-implicated, or in which gp130:IL-6Rα-mediated signalling is pathologically-implicated, may be selected from: a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, metabolic syndrome, a neurodegenerative disease, a chronic inflammatory disease, arthritis, rheumatoid arthritis, juvenile arthritis, systemic juvenile idiopathic arthritis, lupus, pancreatitis, thyroiditis, Graves' disease, diabetes, type 1 diabetes, type 2 diabetes, multiple sclerosis, cardiovascular disease, atherosclerosis, systemic sclerosis, Alzheimer's disease, hippocampal atrophy, pulmonary disease, asthma, cystic fibrosis, hepatitis, inflammatory bowel disease, colitis, stroke, nephropathy, glomerulonephritis, adult-onset Still's disease, Castleman's disease, giant cell arteritis, Takayasu arteritis, cytokine release syndrome, sepsis, septic shock, COVID-19, a cancer, a hematologic malignancy, plasmacytoma, lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, breast cancer, stomach cancer, renal cancer, metastatic renal cell cancer, prostate cancer, liver cancer and hepatocellular carcinoma.

IL-11 signalling in health and disease is reviewed *e.g.* in Putoczki and Ernst, Immunotherapy (2015) 7(4): 441-453, Nguyen *et al.* Growth Factors (2019) 37(1-2):1-11, Cook and Schafer Annu. Rev. Med. (2020) 71:263-276 and Fung *et al.*, Cytokine (2022) 149:155750, all of which are hereby incorporated by reference in their entirety. IL-11/gp130:IL-11Rα-mediated signalling is implicated in the pathology of a wide range of diseases/conditions including autoimmune diseases, inflammatory conditions, cancers, fibrotic diseases and age-related diseases/conditions. Diseases/conditions contemplated to be treated in accordance with the present disclosure include those diseases/conditions described in WO 2017/103108 A1, WO 2019/238882 A1, WO 2019/073057 A1, WO 2019/207122 A1, WO 2020/152122 A1, WO 2020/169783 A1, WO 2020/225147 A1 and WO 2022/090509 A1, all of which are hereby incorporated by reference in their entirety.

For example, IL-11/gp130:IL-11Rα-mediated signalling is implicated in the pathology of arthritis (*e.g.* rheumatoid arthritis), multiple sclerosis, diabetes (*e.g.* type 1, type 2), metabolic syndrome, pregnancy-associated hyperglycemia, systemic sclerosis, keloid, scleroderma, periodontitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis (*e.g.* idiopathic pulmonary fibrosis), cystic fibrosis, dermatitis (*e.g.* atopic dermatitis), psoriasis, inflammatory bowel disease (*e.g.* Crohn's disease and ulcerative colitis), cirrhosis, hepatotoxicity (including acetaminophen-induced hepatotoxicity), hepatitis, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, Marfan syndrome, Hermansky-Pudlak syndrome, chronic kidney disease, Alport syndrome, retinal fibrosis, age-related macular degeneration (*e.g.* wet age-related macular degeneration), a cancer, breast cancer, stomach cancer, colorectal cancer, endometrial cancer, bone cancer, glioblastoma, liver cancer, leukemia, lung cancer, Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer and skin cancer. Diseases/conditions in which gp130:IL-11Rα/IL-11-mediated signalling is pathologically-implicated and/or characterised by an increased level of gp130:IL-11Rα-/IL-11-mediated signalling also include diseases/conditions characterised by pathological inflammation and/or fibrosis, *e.g.* as described herein.

Accordingly, in some embodiments, a disease/condition in which IL-11-mediated signalling is pathologically-implicated, or in which gp130:IL-11Rα-mediated signalling is pathologically-implicated, may be selected from: a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, arthritis, rheumatoid arthritis, multiple sclerosis, diabetes, type 1 diabetes, type 2 diabetes, metabolic syndrome, pregnancy-associated hyperglycemia, systemic sclerosis, keloid, scleroderma, periodontitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, dermatitis, atopic dermatitis, psoriasis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cirrhosis, hepatotoxicity, acetaminophen-induced hepatotoxicity, hepatitis, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy, dilated

cardiomyopathy, myocarditis, Marfan syndrome, Hermansky-Pudlak syndrome, chronic kidney disease, Alport syndrome, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, breast cancer, stomach cancer, colorectal cancer, endometrial cancer, bone cancer, glioblastoma, liver cancer, leukemia, lung cancer, Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer and skin cancer.

OSM signalling in health and disease is reviewed *e.g.* in Richards, ISRN Inflamm. (2013) 2013:512103 and Dey *et al.*, J Cell Commun Signal. (2013) 7(2):103-108, both of which are hereby incorporated by reference in their entirety. OSM/gp130:OSMRβ-mediated signalling and/or OSM/gp130:LIFRβ-mediated signalling is implicated in the pathology of: autoimmune diseases and inflammatory conditions (*e.g.* rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), psoriasis, systemic lupus erythematosus), cancers (breast cancer, lung cancer, ovarian cancer, pancreatic cancer, colorectal cancer, liver cancer), fibrotic diseases (*e.g.* pulmonary fibrosis, liver fibrosis, kidney fibrosis, systemic sclerosis, scleroderma), metabolic disorders (*e.g.* obesity, insulin resistance, type 2 diabetes), neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease), cardiovascular diseases (*e.g.* cardiac hypertrophy, heart failure, atherosclerosis).

LIF signalling in health and disease is reviewed *e.g.* in Wang *et al.*, Mol Ther. (2023) 31(2):331-343, which is hereby incorporated by reference in its entirety. LIF/gp130:LIFRβ-mediated signalling is implicated in the pathology of: neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), autoimmune diseases and inflammatory conditions (*e.g.* rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), psoriasis), metabolic disorders (*e.g.* obesity, insulin resistance), cancers (*e.g.* liver cancer, breast cancer, ovarian cancer, leukemia) and cardiovascular diseases (*e.g.* cardiac hypertrophy, heart failure, ischemic heart disease).

CT-1 signalling in health and disease is reviewed *e.g.* in Asrih, Mediators Inflamm. (2013) 2013:370715, which is hereby incorporated by reference in its entirety. CT-1/gp130:LIFRβ-mediated signalling is implicated in the pathology of: neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease, ischemic stroke), metabolic disorders (*e.g.* obesity, insulin resistance, diabetes), skeletal muscle disorders (*e.g.* muscular dystrophy, cachexia), inflammatory diseases (*e.g.* rheumatoid arthritis, systemic lupus erythematosus), cardiovascular diseases (*e.g.* heart failure, myocardial infarction, hypertrophic cardiomyopathy), liver diseases (*e.g.* alcoholic liver disease, non-alcoholic fatty liver disease) and renal diseases (*e.g.* renal fibrosis, chronic kidney disease).

CNTF signalling in health and disease is reviewed *e.g.* in Schuster *et al.*, J Biol Chem. (2003) 278(11):9528-35 and Sleeman *et al.*, Pharm Acta Helv. (2000) 74(2-3):265-72, both of which are hereby incorporated by reference in their entirety. CNTF/gp130:CNTFRα-mediated signalling is implicated in the pathology of: neurological disorders (*e.g.* Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis), retinal disorders (*e.g.* retinitis pigmentosa, age-related macular degeneration), metabolic disorders (*e.g.* obesity, insulin resistance), skeletal muscle disorders (*e.g.* muscular dystrophy, amyotrophy), inflammatory diseases (*e.g.* rheumatoid arthritis, inflammatory bowel disease (Crohn's

disease, ulcerative colitis)), cardiovascular diseases (*e.g.* heart failure, myocardial infarction) and endocrine disorders (*e.g.* polycystic ovary syndrome).

CLC/gp130:CNTFRα-mediated signalling is implicated in the pathology of: neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease, ischemic stroke), metabolic disorders (*e.g.* obesity, insulin resistance, diabetes), skeletal muscle disorders (*e.g.* muscular dystrophy, cachexia), inflammatory diseases (*e.g.* rheumatoid arthritis, systemic lupus erythematosus), cardiovascular diseases (*e.g.* heart failure, myocardial infarction, hypertrophic cardiomyopathy), liver diseases (*e.g.* alcoholic liver disease, non-alcoholic fatty liver disease) and renal diseases (*e.g.* kidney injury, renal fibrosis).

IL-27 signalling in health and disease is reviewed *e.g.* in Meka *et al.*, Autoimmun Rev. (2015) 14(12): 1131–1141, Shahi *et al.*, Int Immunopharmacol. (2020) 84:106538 and Yoshida and Hunter, Annu Rev Immunol. (2015) 33:417-43, all of which are hereby incorporated by reference in their entirety. IL-27/gp130:IL-27Rα-mediated signalling is implicated in the pathology of: autoimmune diseases (*e.g.* systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis), inflammatory bowel disease (*e.g.* Crohn's disease, ulcerative colitis), infectious disease (*e.g.* viral hepatitis, hepatitis B, HIV, influenza, malaria, tuberculosis), cancers (*e.g.* melanoma, lung cancer, breast cancer, hepatocellular carcinoma), allergic diseases (*e.g.* allergic rhinitis, atopic dermatitis asthma) and neurological disorders (*e.g.* multiple sclerosis, Alzheimer's disease, stroke).

IL-35 signalling in health and disease is reviewed *e.g.* in Ye *et al.*, J Interferon Cytokine Res. (2021) 41(11):391-406, which is hereby incorporated by reference in its entirety. IL-35/gp130:IL-12Rβ2-mediated signalling is implicated in the pathology of: autoimmune diseases (*e.g.* systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis), inflammatory bowel disease (*e.g.* Crohn's disease, ulcerative colitis), infectious disease (*e.g.* viral disease, malaria, tuberculosis), cancers (*e.g.* breast cancer, lung cancer, colorectal cancer, hepatocellular carcinoma), transplant rejection and graft-versus-host disease.

Treatment or alleviation of a disease/condition according to the present disclosure (*e.g.* fibrosis, pathological angiogenesis, a disease/condition associated with fibrosis, a disease/condition associated with angiogenesis, pathological inflammation and/or a disease/condition associated with inflammation) may be effective to prevent progression of the disease/condition, *e.g.* to prevent worsening of the disease/condition or to slow the rate of development of the disease/condition. In some embodiments treatment or alleviation may lead to an improvement in the disease/condition.

Prevention of disease/condition according to the present disclosure (*e.g.* fibrosis, pathological angiogenesis, a disease/condition associated with fibrosis, a disease/condition associated with angiogenesis, pathological inflammation and/or a disease/condition associated with inflammation) may refer to prevention of a worsening of the disease/condition or prevention of the development of the disease/condition, *e.g.* preventing an early stage of the disease/condition developing to a later and/or chronic stage.

Administration/dosages

Administration of the agents, pharmaceutical combinations and pharmaceutical compositions of the present disclosure is preferably in a 'therapeutically-effective' or 'prophylactically-effective' amount, this being sufficient to show therapeutic or prophylactic benefit to the subject. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the disease/condition and the particular article administered. Prescription of treatment, *e.g.* decisions on dosage *etc.*, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disease/condition to be treated, the condition of the individual subject, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's 'The Science and Practice of Pharmacy' (Ed. A. Adejare), 23rd Edition (2020), Academic Press.

Administration of the articles of the present disclosure may be *e.g.* parenteral, systemic, topical, intracavitary, intravascular, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intravitreal, intraconjunctival, intratumoral, subcutaneous, intradermal, oral or transdermal. Administration may be by any suitable mode of ocular delivery, including: topical (*e.g.* eye drops), intravitreal, intraocular, juxtascleral, subconjunctival, intracameral, subtenon, and retrobulbar. Administration may be by injection, infusion or ingestion.

In some aspects and embodiments, articles of the present disclosure may be administered to a tissue/organ of interest (*e.g.* a tissue/organ affected by the disease/condition) affected by the condition (*e.g.* a tissue/organ in which symptoms of the disease/condition manifest). In some aspects and embodiments, articles of the present disclosure may be administered to the blood (*i.e.* intravenous/intra-arterial administration) by injection or infusion (*e.g.* via cannula), or may be administered subcutaneously or orally.

In some embodiments, articles of the present disclosure may be administered topically to the eye or skin. In such embodiments, a micro-dose of the relevant article may be employed. In some embodiments, articles of the present disclosure may be administered to an immune-privileged site. In some embodiments, administration may be intrathecal or intraocular.

In some aspects and embodiments in accordance with the present disclosure there may be targeted delivery of articles of the present disclosure, *i.e.* wherein the concentration of the relevant agent in the subject is increased in some parts of the body relative to other parts of the body. In some embodiments, the methods comprise intravenous, intra-arterial, intramuscular or subcutaneous administration and wherein the relevant article is formulated in a targeted agent delivery system. Suitable targeted delivery systems include, for example, nanoparticles, liposomes, micelles, beads, polymers, metal particles, dendrimers, antibodies, aptamers, nanotubes or micro-sized silica rods. Such systems may comprise a magnetic element to direct the agent to the desired organ or tissue. Suitable nanocarriers and delivery systems will be apparent to one skilled in the art.
In some cases, the articles of the present disclosure are formulated for targeted delivery to specific cells, a tissue, an organ and/or a tumor.

Where two or more agents (*e.g.* an antigen-binding molecule that binds to gp130 and an antagonist of an angiogenic factor) are administered in combination, the agents may be administered simultaneously, sequentially or separately.

Simultaneous administration refers to administration of the two or more agents (*e.g.* an antigen-binding molecule that binds to gp130 and an antagonist of an angiogenic factor) together, for example as a pharmaceutical composition containing both agents (*i.e.* as a combined preparation), or immediately after each other (*e.g.* within 1, 4, 6, 8 or 12 hours), and optionally via the same route of administration, *e.g.* to the same artery, vein or other blood vessel.

Sequential administration refers to administration of one of the agents followed after a given time interval by separate administration of another agent. It is not required that the agents are administered by the same route, although this is the case in some embodiments. The time interval may be any time interval.

In some embodiments, therapeutic or prophylactic intervention according to the present disclosure comprises: (i) administering an antigen-binding molecule that binds to gp130 to a subject having fibrosis (*e.g.* fibrosis as described herein), and (ii) administering to the subject an antagonist of an angiogenic factor. In some embodiments, (i) and (ii) are performed simultaneously. In some embodiments, (i) and (ii) are performed sequentially (*e.g.* (i) may be followed by (ii), or (ii) may be followed by (i)).

Multiple doses of the agents, pharmaceutical combinations and pharmaceutical compositions may be provided. Multiple doses may be separated by a predetermined time interval, which may be selected to be one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days, or 1, 2, 3, 4, 5, or 6 months. By way of example, doses may be given once every 7, 14, 21 or 28 days (plus or minus 3, 2, or 1 days).

In some embodiments, therapeutic or prophylactic intervention according to the present disclosure may further comprise administering another agent for the treatment/prevention of the relevant disease/condition.

Methods of detection

The present disclosure also provides the articles of the present disclosure for use in methods for detecting, localising or imaging gp130, or cells expressing gp130.

The antigen-binding molecules described herein may be used in methods that involve detecting binding of the antigen-binding molecule to gp130. Such methods may involve detection of the bound complex of the antigen-binding molecule and gp130. It will be appreciated that the gp130 may be gp130 expressed by a cell, *e.g.* in or at the cell surface of a cell expressing gp130.

As such, a method is provided, comprising contacting a sample containing, or suspected to contain, gp130, and detecting the formation of a complex of the antigen-binding molecule and gp130. Also provided is a method comprising contacting a sample containing, or suspected to contain, a cell expressing gp130, and detecting the formation of a complex of the antigen-binding molecule and a cell expressing gp130.

Suitable method formats are well known in the art, including immunoassays such as sandwich assays, *e.g.* ELISA. The methods may involve labelling the antigen-binding molecule, or target(s), or both, with a detectable moiety, *e.g.* a fluorescent label, phosphorescent label, luminescent label, immuno-detectable label, radiolabel, chemical, nucleic acid or enzymatic label as described herein. Detection techniques are well known to those of skill in the art and can be selected to correspond with the labelling agent.

Methods comprising detecting gp130, or cells expressing gp130, include methods for diagnosing/prognosing a disease/condition described herein.

Methods of this kind may be performed *in vitro* on a patient sample, or following processing of a patient sample. Once the sample is collected, the patient is not required to be present for the *in vitro* method to be performed, and therefore the method may be one which is not practised on the human or animal body. In some embodiments, the method is performed *in vivo*.

Such methods may involve detecting or quantifying gp130 and/or cells expressing gp130, *e.g.* in a patient sample. Where the method comprises quantifying the relevant factor, the method may further comprise comparing the determined amount against a standard or reference value as part of the diagnostic or prognostic evaluation. Other diagnostic/prognostic tests may be used in conjunction with those described herein to enhance the accuracy of the diagnosis or prognosis or to confirm a result obtained by using the tests described herein.

Detection in a sample may be used for the purpose of diagnosis of a disease/condition (*e.g.* a cancer), predisposition to a disease/condition, or for providing a prognosis (prognosticating) for a disease/condition, *e.g.* a disease/condition described herein. The diagnosis or prognosis may relate to an existing (previously diagnosed) disease/condition.

A sample may be taken from any tissue or bodily fluid. The sample may comprise or may be derived from: a quantity of blood; a quantity of serum derived from the individual's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a tissue sample or biopsy; pleural fluid; cerebrospinal fluid (CSF); or cells isolated from said individual. In some embodiments, the sample may be obtained or derived from a tissue or tissues which are affected by the disease/condition (*e.g.* tissue or tissues in which symptoms of the disease manifest, or which are involved in the pathogenesis of the disease/condition).

A subject may be selected for diagnostic/prognostic evaluation based on the presence of symptoms indicative of a disease/condition described herein, or based on the subject being considered to be at risk of developing a disease/condition described herein.

The present disclosure also provides methods for selecting/stratifying a subject for treatment with a gp130-targeted agent. In some embodiments a subject is selected for treatment/prevention in accordance with the methods of the present disclosure, or is identified as a subject which would benefit from such treatment/prevention, based on detection/quantification of gp130, or cells expressing gp130, *e.g.* in a sample obtained from the individual.

Subjects

The subject in accordance with aspects described herein may be any animal or human. Therapeutic and prophylactic applications may be in human or animals (veterinary use).

The subject to be administered with an article of the present disclosure (*e.g.* in accordance with therapeutic or prophylactic intervention) may be a subject in need of such intervention. The subject is preferably mammalian, more preferably human. The subject may be a non-human mammal but is more preferably human. The subject may be male or female. The subject may be a patient. A subject may have been diagnosed with a disease or condition requiring treatment (*e.g.* fibrosis and/or pathological angiogenesis, *e.g.* fibrosis and/or pathological angiogenesis as described herein), may be suspected of having such a disease/condition, or may be at risk of developing/contracting such a disease/condition.

In some embodiments, the subject to be treated according to a therapeutic or prophylactic method of the present disclosure herein is a subject having, or at risk of developing, fibrosis and/or pathological angiogenesis, *e.g.* fibrosis and/or pathological angiogenesis as described herein. In embodiments according to the present disclosure, a subject may be selected for treatment according to the methods based on characterization for certain markers of such disease/condition.

In some embodiments, a subject may be selected for therapeutic or prophylactic intervention as described herein based on the detection of cells/tissue expressing gp130, cells/tissue overexpressing gp130, or cells having an increased level of an activity of gp130 (*e.g.* gp130-mediated signalling) *e.g.* in a sample obtained from the subject.

In some embodiments, a subject may be selected for therapeutic or prophylactic intervention as described herein based on the detection of cells/tissue expressing an angiogenic factor as described herein (*e.g.* VEGF), cells/tissue overexpressing an angiogenic factor as described herein (*e.g.* VEGF), or cells having an increased level of an activity of an angiogenic factor as described herein (*e.g.* VEGF-mediated signalling) *e.g.* in a sample obtained from the subject.

Kits

The present disclosure also provides kits of parts. A kit according to the present disclosure may comprise components for performing a method described herein, in whole or in part.

The kit may have at least one container having a predetermined quantity of a combination or composition described herein.

In some aspects of the present disclosure a kit of parts is provided. In some embodiments, the kit may comprise an antigen-binding molecule which binds to gp130 as described herein, and an antagonist of an angiogenic factor as described herein. The antigen-binding molecule which binds to gp130 and the antagonist of an angiogenic factor may be provided in a predetermined quantity. The antigen-binding molecule which binds to gp130 and the antagonist of an angiogenic factor may be provided in separate containers, or in the same container.

In some embodiments, the kit comprises a pharmaceutical combination or pharmaceutical composition according to the present disclosure.

The kit may provide the antigen-binding molecule which binds to gp130, antagonist of an angiogenic factor, pharmaceutical combination, or pharmaceutical composition together with instructions for administration to a patient in order to treat a specified disease/condition (*e.g.* a disease/condition described herein, *e.g.* fibrosis and/or pathological angiogenesis).

The kit may further comprise reagents, buffers and/or standards required for execution of a method according to the present disclosure. Kits according to the present disclosure may include instructions for use, *e.g.* in the form of an instruction booklet or leaflet. The instructions may include a protocol for performing any one or more of the methods described herein.

Sequence identity

As used herein, 'sequence identity' refers to the percent of nucleotides/amino acid residues in a subject sequence that are identical to nucleotides/amino acid residues in a reference sequence, after aligning the sequences and, if necessary, introducing gaps, to achieve the maximum percent sequence identity between the sequences. Pairwise and multiple sequence alignment for the purposes of determining percent sequence identity between two or more amino acid or nucleic acid sequences can be achieved in various ways known to a person of skill in the art, for instance, using publicly available computer software such as ClustalOmega (Söding, J. 2005, Bioinformatics 21, 951-960), T-coffee (Notredame *et al.* 2000, J. Mol. Biol. (2000) 302, 205-217), Kalign (Lassmann and Sonnhammer 2005, BMC Bioinformatics, 6(298)) and MAFFT (Katoh and Standley 2013, Molecular Biology and Evolution, 30(4) 772–780) software. When using such software, the default parameters, *e.g.* for gap penalty and extension penalty, are preferably used.

Sequences

SEQ ID NO:	DESCRIPTION	SEQUENCE
1	B035-C03-A3 VH	EVQLVESGGGLVQPGGSLKLSCAASGFTFSNYGIHWIRQAPTKGLEWVALISPSGYSTFYRDSV KGRFTISRDNANSTLYLQMDSLRSEDTATYYCATPMMAVITPYYFDYWGQGVMVTVSS
2	B035-C03-A3, A3_3.2, A3_4.2, A3_6.2 HC-CDR1	GFTFSNYG
3	B035-C03-A3, A3_3.2, A3_4.2, A3_6.2 HC-CDR2	ISPSGYST
4	B035-C03-A3, A3_3.2, A3_4.2, A3_6.2 HC-CDR3	ATPMMAVITPYYFDY
5	B035-C03-A3 HC-FR1	EVQLVESGGGLVQPGGSLKLSCAAS
6	B035-C03-A3 HC-FR2	IHWIRQAPTKGLEWVAL
7	B035-C03-A3 HC-FR3	FYRDSVKGRFTISRDNANSTLYLQMDSLRSEDTATYYC
8	B035-C03-A3 HC-FR4	WGQGVMVTVSS
9	B035-C03-A3 VL	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGS GSGTDFTLTIRSLEPEDFGLYYCQQHNEYPPTFGSGTKLEIK
10	B035-C03-A3, A3_3, A3_4, A3_5 LC-CDR1	KSISKY
11	B035-C03-A3, A3_3, A3_4, A3_5 LC-CDR2	DGS
12	B035-C03-A3, A3_3, A3_4, A3_5 LC-CDR3	QQHNEYPPT
13	B035-C03-A3 LC-FR1	DVQMTQSPYNLAASPGESVSINCKAS
14	B035-C03-A3, A3_3, A3_4 LC-FR2	LAWYQQKPGKANKLLIY
15	B035-C03-A3 LC-FR3	TLQSGIPSRFSGSGSGTDFTLTIRSLEPEDFGLYYC
16	B035-C03-A3 LC-FR4	FGSGTKLEIK
17	CSP-S-5H8 VH	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSGGSTDYDSAL KSRLTISRDTSKSQVFLKMNSLQAEDTAIYFCTKSFYDGGYYWLGYWGQGTLVTVSS
18	CSP-S-5H8 HC-CDR1	GFSLTNNN
19	CSP-S-5H8 HC-CDR2	IWSGGST
20	CSP-S-5H8 HC-CDR3	TKSFYDGGYYWLGY
21	CSP-S-5H8 HC-FR1	QVQLKESGPGLVQPSQTLSLTCTVS
22	CSP-S-5H8 HC-FR2	IHWVRQPPGKGLEWVGA
23	CSP-S-5H8 HC-FR3	DYDSALKSRLTISRDTSKSQVFLKMNSLQAEDTAIYFC
24	CSP-S-5H8, A3_3.2, A3_4.2, A3_6.2 HC-FR4	WGQGTLVTVSS
25	CSP-S-5H8 VL	ETVMTQSPTSMSTSIGERVTLNCKASQSVDINVDWYQQTPGQSPKLLIYGASNRHTGVPDRFTG SRFGKDFTLTISNVESEDLAVYYCLQYDSIPWTFGGGTKLELK
26	CSP-S-5H8 LC-CDR1	QSVDIN
27	CSP-S-5H8 LC-CDR2	GAS
28	CSP-S-5H8 LC-CDR3	LQYDSIPWT
29	CSP-S-5H8 LC-FR1	ETVMTQSPTSMSTSIGERVTLNCKAS
30	CSP-S-5H8 LC-FR2	VDWYQQTPGQSPKLLIY
31	CSP-S-5H8 LC-FR3	NRHTGVPDRFTGSRFGKDFTLTISNVESEDLAVYYC

32	CSP-S-5H8 LC-FR4	FGGGTKLELK
33	Human IgG1 constant region (IGHG1; UniProt:P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
34	CH1 IgG1 (positions 1-98 of P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV
35	Hinge IgG1 (positions 99-110 of P01857-1, v1)	EPKSCDKTHTCP
36	CH2 IgG1 (positions 111-223 of P01857-1, v1)	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
37	CH3 IgG1 (positions 224-330 of P01857-1, v1)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
38	Human IgG1 constant region G1m3 allotype (K214R, D356E and L358M (EU numbering) relative to P01857-1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
39	CH1 IgG1 G1m3 allotype	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
40	CH3 IgG1 G1m3 allotype	GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
41	Human IgG4 constant region (IGHG4; UniProt:P01861-1, v1)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK
42	Human IgG1 CH2-CH3 region	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
43	Human IgG1 G1m3 allotype CH2-CH3 region	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG
44	Human IgG4 CH2-CH3 region	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK
45	CH2 IgG1 (YTE)	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
46	Human IgG1 CH2-CH3 region (YTE)	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
47	Human IgG1 G1m3 allotype CH2-CH3 region (YTE)	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
48	Human IgG1 constant region (YTE)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
49	Human IgG1 constant region G1m3 allotype (YTE)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK

50	Human IgG4 constant region (S228P, L235E)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK
51	Human IgG4 CH1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRV
52	Human IgG4 hinge	ESKYGPPCPSCP
53	Human IgG4 hinge (S228P)	ESKYGPPCPPCP
54	Human IgG4 CH2	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
55	Human IgG4 CH2 (L235E)	APEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
56	Human IgG4 CH3	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
57	Human IgG4 CH2-CH3 (L235E)	APEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK
58	Cκ CL (IGKC; UniProt: P01834-1, v2)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
59	Cλ CL1 (IGLC1; UniProt: P0CG04-1, v1)	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
60	Cλ CL2 (IGLC2; UniProt: P0DOY2-1, v1)	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
61	Cλ CL3 (IGLC3; UniProt: P0DOY3-1, v1)	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
62	Cλ CL6 (IGLC6; UniProt: P0CF74-1, v1)	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS
63	Cλ CL7 (IGLC7; UniProt: A0M8Q6-1, v3)	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFNPGAVTVAWKADGSPVKVGVETTKPSKQSN NKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS
64	B035-C03-A3 hIgG1 HC	EVQLVESGGGLVQPGGSLKLSCAASGFTFSNYGIHWIRQAPTKGLEWVALISPSGYSTFYRDSV KGRFTISRDNANSTLYLQMDSLRSEDTATYYCATPMMAVITPYYFDYWGQGVMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
65	B035-C03-A3 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLKLSCAASGFTFSNYGIHWIRQAPTKGLEWVALISPSGYSTFYRDSV KGRFTISRDNANSTLYLQMDSLRSEDTATYYCATPMMAVITPYYFDYWGQGVMVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK
66	B035-C03-A3 K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGS GSGTDFTLTIRSLEPEDFGLYYCQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
67	CSP-S-5H8 hIgG1 HC	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSGGSTDYDSAL KSRLTISRDTSKSQVFLKMNSLQAEDTAIYFCTKSFYDGGYYWLGYWGQGTLVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK

68	CSP-S-5H8 hIgG4(S228P, L235E) HC	QVQLKESGPGLVQPSQTLSLTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSGGSTDYDSAL KSRLTISRDTSKSQVFLKMNSLQAEDTAIYFCTKSFYDGGYYWLGYWGQGTLVTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV PSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL GK
69	CSP-S-5H8 K LC	ETVMTQSPTSMSTSIGERVTLNCKASQSVDINVDWYQQTPGQSPKLLIYGASNRHTGVPDRFTG SRFGKDFTLTISNVESEDLAVYYCLQYDSIPWTFGGGTKLELKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
70	Human gp130 isoform 1 (UniProt: P40189-1, v2)	MLTLQTWLVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIV WKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCI VNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWV EAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDA STWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAP SFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTND RYLATLTVRNLVGKSDAAVLTIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWC VLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKG PTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLY MVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPN VPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEIEANDKKPFPEDLKSLDLFKKEK INTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQVFSRSES TQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESSPDISHFERSKQVSSVNEEDF VRLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEAATDEGMPKSYLP QTVRQGGYMPQ
71	Human gp130 isoform 2 (UniProt: P40189-2)	MLTLQTWLVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIV WKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCI VNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWV EAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDA STWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDNIASF
72	Human gp130 isoform 3 (UniProt: P40189-3)	MLTLQTWLVQALFIFLTTESTGELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIV WKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCI VNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWV EAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDA STWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAP SFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTND RYLATLTVRNLVGKSDAAVLTIPACDFQGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSK GPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTL YMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWP NVPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEIEANDKKPFPEDLKSLDLFKKE KINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQVFSRSE STQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESSPDISHFERSKQVSSVNEED FVRLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEAATDEGMPKSYL PQTVRQGGYMPQ
73	Human gp130 signal peptide	MLTLQTWLVQALFIFLTTESTG
74	Mature human gp130 isoform 1	ELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASS VTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLE TNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYK VKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTV QDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQL VWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL TIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTV HRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWDQ LPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEF TFTTPKFAQGEIEAIVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIAQWSPHTPPR HNFNSKDQMYSDGNFTDVSVVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSS RPSISSSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVD HVDGGDGILPRQQYFKQNCSQHESSPDISHFERSKQVSSVNEEDFVRLKQQISDHISQSCGSG QMKMFQEVSAADAFGPGTEGQVERFETVGMEAATDEGMPKSYLPQTVRQGGYMPQ
75	Human gp130 extracellular domain	ELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASS VTFTDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLE TNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYK VKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTV QDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQL VWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL TIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTV

		HRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEWDQ LPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEF TFTTPKFAQGEIE
76	Human gp130 transmembrane domain	AIVVPVCLAFLLTTLLGVLFCF
77	Human gp130 cytoplasmic domain	NKRDLIKKHIWPNVPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEIEANDKKPFP EDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSTVQYSTVVHSGYRH QVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSQHESSPDISHFE RSKQVSSVNEEDFVRLKQQISDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGME AATDEGMPKSYLPQTVRQGGYMPQ
78	Human gp130 Ig-like C2-type domain	DPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTF TDIASLNIQLTCNILTFGQLEQNVYGITI
79	Human gp130 FNIII domain 1	PPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYS TVYFVNIEVWVEAENALGKVTSDHINFDP
80	Human gp130 FNIII domain 2	PPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKP FTEYVFRIRCMKEDGKGYWSDWSEEASGITYED
81	WSXWS motif	WSDWS
82	Human gp130 FNIII domain 3	APSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLT NDRYLATLTVRNLVGKSDAAVLTIPACDFQAT
83	Human gp130 FNIII domain 4	PVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAE SKCYLITVTPVYADGPGSPESIKAYLKQA
84	Human gp130 FNIII domain 5	PPSKGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSL TSDTLYMVRMAAYTDEGGKDGPEFTFTTPKF
85	Human gp130 cytokine-binding module	DPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTF TDIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNF TLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVKP NPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLK PFTEYVFRIRCMKEDGKGYWSDWSEEASGITYED
86	CSP-S-5H8 epitope region 1	KPKNLSCIVNEGKKMR
87	CSP-S-5H8 epitope region 2	YRT
88	CSP-S-5H8 epitope region 3	RCMK
89	CSP-S-5H8 epitope region composite	KPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVY FVNIEVWVEAENALGKVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYN IQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMK
90	B035-C03-A3 epitope region A1	RCEWDGGR
91	B035-C03-A3 epitope region A2	KSEWATHKFADCK
92	B035-C03-A3 epitope region A3	KSVIILKYNIQYR
93	B035-C03-A3 epitope region composite 1	RCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDYSTVYFVNIEVWVEAENALG KVTSDHINFDPVYKVKPNPPHNLSVINSEELSSILKLTWTNPSIKSVIILKYNIQYR
94	A3_3.2 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDS VKGRFTISRDNSKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSS
95	A3_3.2 HC-FR1	EVQLLESGGGLVQPGGSLRLSCAAS
96	A3_3.2 HC-FR2	IHWVRQAPGKGLEWVSL
97	A3_3.2 HC-FR3	FYRDSVKGRFTISRDNSKNTLYLQMDSLRAEDTATYYC
98	A3_4.2 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSV KGRFTISRDNAKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSS
99	A3_4.2, A3_6.2 HC-FR1	EVQLVESGGGLVQPGGSLRLSCAAS
100	A3_4.2 HC-FR2	IHWIRQAPGKGLEWVSL
101	A3_4.2, A3_6.2 HC-FR3	FYRDSVKGRFTISRDNAKNTLYLQMDSLRAEDTATYYC
102	A3_3 VL	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIK
103	A3_3 LC-FR1	DVQMTQSPSSLSASVGDRVTITCKAS
104	A3_3 LC-FR3	TLQSGIPSRFSGSGSGTDFTLTISSLQPEDFATYYC
105	A3_3, A3_4, A3_5 LC-FR4	FGQGTKLEIK
106	A3_4 VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFGLYYCQQHNEYPPTFGQGTKLEIK
107	A3_4, A3_5 LC-FR1	DIQMTQSPSSLSASVGDRVTITCKAS
108	A3_4 LC-FR3	TLQSGVPSRFSGSGSGTDFTLTISSLQPEDFGLYYC

109	A3_5 VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYDGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIK
110	A3_5 LC-FR2	LAWYQQKPGKAPKLLIY
111	A3_5 LC-FR3	TLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
112	A3-derived VH CON	EVQLX$_1$ESGGGLVQPGGSLX$_2$LSCAASGFTFSNYGIHWX$_3$RQAPX$_4$KGLEWVX$_5$LISPSGYSTFYR DSVKGRFTISRDNX$_6$X$_7$X$_8$TLYLQMDSLRX$_9$EDTATYYCATPMMAVITPYYFDYWGQGX$_{10}$X$_{11}$VTV SS wherein X$_1$ = V or L, X$_2$ = R or K, X$_3$ = I or V, X$_4$ = G or T, X$_5$ = S or A, X$_6$ = A or S, X$_7$ = K or N, X$_8$ = N or S, X$_9$ = A or S, X$_{10}$ = T or V, X$_{11}$ = L or M
113	A3-derived HC-FR1 CON	EVQLX$_1$ESGGGLVQPGGSLX$_2$LSCAAS wherein X$_1$ = V or L, X$_2$ = R or K
114	A3-derived HC-FR2 CON	IHWX$_1$RQAPX$_2$KGLEWVX$_3$L wherein X$_1$ = I or V, X$_2$ = G or T, X$_3$ = S or A
115	A3-derived HC-FR3 CON	FYRDSVKGRFTISRDNX$_1$X$_2$X$_3$TLYLQMDSLRX$_4$EDTATYYC wherein X$_1$ = A or S, X$_2$ = K or N, X$_3$ = N or S, X$_4$ = A or S
116	A3-derived HC-FR4 CON	WGQGX$_1$X$_2$VTVSS wherein X$_1$ = T or V, X$_2$ = L or M
117	A3-Hum VH CON	EVQLX$_1$ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX$_2$RQAPGKGLEWVX$_3$LISPSGYSTFYR DSVKGRFTISRDNX$_4$KNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSS wherein X$_1$ = V or L, X$_2$ = I or V, X$_3$ = S or A, X$_4$ = A or S
118	A3-Hum HC-FR1 CON	EVQLX$_1$ESGGGLVQPGGSLRLSCAAS wherein X$_1$ = V or L
119	A3-Hum HC-FR2 CON	IHWX$_1$RQAPGKGLEWVX$_2$L wherein X$_1$ = I or V, X$_2$ = S or A
120	A3-Hum HC-FR3 CON	FYRDSVKGRFTISRDNX$_1$KNTLYLQMDSLRAEDTATYYC wherein X$_1$ = A or S
121	A3-derived VL CON	DX$_1$QMTQSPX$_2$X$_3$LX$_4$ASX$_5$GX$_6$X$_7$VX$_8$IX$_9$CKASKSISKYLAWYQQKPGKAX$_{10}$KLLIYDGSTLQSGX$_1$ $_1$PSRFSGSGSGTDFTLTIX$_{12}$SLX$_{13}$PEDFX$_{14}$X$_{15}$YYCQQHNEYPPTFGX$_{16}$GTKLEIK wherein X$_1$ = V or I, X$_2$ = S or Y, X$_3$ = S or N, X$_4$ = S or A, X$_5$ = V or P, X$_6$ = D or E, X$_7$ = R or S, X$_8$ = T or S, X$_9$ = N or T, X$_{10}$ = N or P, X$_{11}$ = V or I, X$_{12}$ = S or R, X$_{13}$ = Q or E, X$_{14}$ = A or G, X$_{15}$ = T or L, X$_{16}$ = Q or S
122	A3-derived LC-FR1 CON	DX$_1$QMTQSPX$_2$X$_3$LX$_4$ASX$_5$GX$_6$X$_7$VX$_8$IX$_9$CKAS wherein X$_1$ = V or I, X$_2$ = S or Y, X$_3$ = S or N, X$_4$ = S or A, X$_5$ = V or P, X$_6$ = D or E, X$_7$ = R or S, X$_8$ = T or S, X$_9$ = N or T
123	A3-derived LC-FR2 CON	LAWYQQKPGKAX$_1$KLLIY wherein X$_1$ = N or P
124	A3-derived LC-FR3 CON	TLQSGX$_1$PSRFSGSGSGTDFTLTIX$_2$SLX$_3$PEDFX$_4$X$_5$YYC wherein X$_1$ = V or I, X$_2$ = S or R, X$_3$ = Q or E, X$_4$ = A or G, X$_5$ = T or L
125	A3-derived LC-FR4 CON	FGX$_1$GTKLEIK wherein X$_1$ = Q or S
126	A3-Hum VL CON	DX$_1$QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX$_2$KLLIYDGSTLQSGX$_3$PSRFS GSGSGTDFTLTISSLQPEDX$_4$X$_5$LYYCQQHNEYPPTFGQGTKLEIK wherein X$_1$ = V or I, X$_2$ = N or P, X$_3$ = V or I, X$_4$ = A or G, X$_5$ = T or L
127	A3-Hum LC-FR1 CON	DX$_1$QMTQSPSSLSASVGDRVTITCKAS wherein X$_1$ = V or I
128	A3-Hum LC-FR2 CON	LAWYQQKPGKAX$_1$KLLIY wherein X$_1$ = N or P
129	A3-Hum LC-FR3 CON	TLQSGX$_1$PSRFSGSGSGTDFTLTISSLQPEDX$_2$X$_3$LYYC wherein X$_1$ = V or I, X$_2$ = A or G, X$_3$ = T or L
130	A3_3.2 hIgG1 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDS VKGRFTISRDNSKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSASTKG

		PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
131	A3_3.2 hIgG4(S228P, L235E) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDS VKGRFTISRDNSKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK
132	A3_4.2 hIgG1 HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSV KGRFTISRDNAKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
133	A3_4.2 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSV KGRFTISRDNAKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS LGK
134	A3-derived CON hIgG1 HC	EVQLX$_1$ESGGGLVQPGGSLX$_2$LSCAASGFTFSNYGIHWX$_3$RQAPX$_4$KGLEWVX$_5$LISPSGYSTFYR DSVKGRFTISRDNX$_6$X$_7$X$_8$TLYLQMDSLRX$_9$EDTATYYCATPMMAVITPYYFDYWGQGX$_{10}$X$_{11}$VTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK wherein X$_1$ = V or L, X$_2$ = R or K, X$_3$ = I or V, X$_4$ = G or T, X$_5$ = S or A, X$_6$ = A or S, X$_7$ = K or N, X$_8$ = N or S, X$_9$ = A or S, X$_{10}$ = T or V, X$_{11}$ = L or M
135	A3-derived hIgG4(S228P, L235E) HC	EVQLX$_1$ESGGGLVQPGGSLX$_2$LSCAASGFTFSNYGIHWX$_3$RQAPX$_4$KGLEWVX$_5$LISPSGYSTFYR DSVKGRFTISRDNX$_6$X$_7$X$_8$TLYLQMDSLRX$_9$EDTATYYCATPMMAVITPYYFDYWGQGX$_{10}$X$_{11}$VTV SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY TQKSLSLSLGK wherein X$_1$ = V or L, X$_2$ = R or K, X$_3$ = I or V, X$_4$ = G or T, X$_5$ = S or A, X$_6$ = A or S, X$_7$ = K or N, X$_8$ = N or S, X$_9$ = A or S, X$_{10}$ = T or V, X$_{11}$ = L or M
136	A3-Hum CON hIgG1 HC	EVQLX$_1$ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX$_2$RQAPGKGLEWVX$_3$LISPSGYSTFYR DSVKGRFTISRDNX$_4$KNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK wherein X$_1$ = V or L, X$_2$ = I or V, X$_3$ = S or A, X$_4$ = A or S
137	A3-Hum hIgG4(S228P, L235E) HC	EVQLX$_1$ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX$_2$RQAPGKGLEWVX$_3$LISPSGYSTFYR DSVKGRFTISRDNX$_4$KNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA

		VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK wherein X_1 = V or L, X_2 = I or V, X_3 = S or A, X_4 = A or S
138	A3_3 K LC	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
139	A3_4 K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFGLYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
140	A3_5 K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYDGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
141	A3-derived CON K LC	$DX_1QMTQSPX_2X_3LX_4ASX_5GX_6X_7VX_8IX_9CKASKSISKYLAWYQQKPGKAX_{10}KLLIYDGSTLQSGX_{11}PSRFSGSGSGTDFTLTIX_{12}SLX_{13}PEDFX_{14}X_{15}YYCQQHNEYPPTFGX_{16}GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC$ wherein X_1 = V or I, X_2 = S or Y, X_3 = S or N, X_4 = S or A, X_5 = V or P, X_6 = D or E, X_7 = R or S, X_8 = T or S, X_9 = N or T, X_{10} = N or P, X_{11} = V or I, X_{12} = S or R, X_{13} = Q or E, X_{14} = A or G, X_{15} = T or L, X_{16} = Q or S
142	A3-Hum K LC	$DX_1QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX_2KLLIYDGSTLQSGX_3PSRFSGSGSGTDFTLTISSLQPEDX_4X_5LYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC$ wherein X_1 = V or I, X_2 = N or P, X_3 = V or I, X_4 = A or G, X_5 = T or L
143	B035-C03-A3_D50X VL	$DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYX_1GSTLQSGIPSRFSGSGSGTDFTLTIRSLEPEDFGLYYCQQHNEYPPTFGSGTKLEIK$ wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
144	A3_3_D50X VL	$DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX_1GSTLQSGIPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIK$ wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
145	A3_4_D50X VL	$DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX_1GSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFGLYYCQQHNEYPPTFGQGTKLEIK$ wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
146	A3_5_D50X VL	$DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYX_1GSTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIK$ wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
147	A3-derived_ D50X VL CON	$DX_1QMTQSPX_2X_3LX_4ASX_5GX_6X_7VX_8IX_9CKASKSISKYLAWYQQKPGKAX_{10}KLLIYX_{11}GSTLQSGX_{12}PSRFSGSGSGTDFTLTIX_{13}SLX_{14}PEDFX_{15}X_{16}YYCQQHNEYPPTFGX_{17}GTKLEIK$ wherein X_1 = V or I, X_2 = S or Y, X_3 = S or N, X_4 = S or A, X_5 = V or P, X_6 = D or E, X_7 = R or S, X_8 = T or S, X_9 = N or T, X_{10} = N or P, X_{11} = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X_{12} = V or I, X_{13} = S or R, X_{14} = Q or E, X_{15} = A or G, X_{16} = T or L, X_{17} = Q or S
148	A3-Hum_D50X VL CON	$DX_1QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX_2KLLIYX_3GSTLQSGX_4PSRFSGSGSGTDFTLTISSLQPEDX_5X_6LYYCQQHNEYPPTFGQGTKLEIK$ wherein X_1 = V or I, X_2 = N or P, X_3 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X_4 = V or I, X_5 = A or G, X_6 = T or L
149	B035-C03-A3_D50X, A3_3_D50X, A3_4_D50X, A3_5_D50X LC-CDR2	X_1GS wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
150	B035-C03-A3_D50X K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYX1GSTLQSGIPSRFSGSGSGTDFTLTIRSLEPEDFGLYYCQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
151	A3_3_D50X K LC	$DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX_1GSTLQSGIPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT

		ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
152	A3_4_D50X K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX$_1$GSTLQSGVPSRFSG SGSGTDFTLTISSLQPEDFGLYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
153	A3_5_D50X K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYX$_1$GSTLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC wherein X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
154	A3-derived_D50X CON K LC	DX$_1$QMTQSPX$_2$X$_3$LX$_4$ASX$_5$GX$_6$X$_7$VX$_8$IX$_9$CKASKSISKYLAWYQQKPGKAX$_{10}$KLLIYX$_{11}$GSTLQSG X$_{12}$PSRFSGSGSGTDFTLTIX$_{13}$SLX$_{14}$PEDFX$_{15}$X$_{16}$YYCQQHNEYPPTFGX$_{17}$GTKLEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X_1 = V or I, X_2 = S or Y, X_3 = S or N, X_4 = S or A, X_5 = V or P, X_6 = D or E, X_7 = R or S, X_8 = T or S, X_9 = N or T, X_{10} = N or P, X_{11} = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X_{12} = V or I, X_{13} = S or R, X_{14} = Q or E, X_{15} = A or G, X_{16} = T or L, X_{17} = Q or S
155	A3-Hum_D50X K LC	X$_1$QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX$_2$KLLIYX$_3$GSTLQSGX$_4$PSRFS GSGSGTDFTLTISSLQPEDX$_5$X$_6$LYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC wherein X_1 = V or I, X_2 = N or P, X_3 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X_4 = V or I, X_5 = A or G, X_6 = T or L
156	B035-C03-A3_D50A VL	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGS GSGTDFTLTIRSLEPEDFGLYYCQQHNEYPPTFGSGTKLEIK
157	A3_3_D50A VL	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIK
158	A3_4_D50A VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFGLYYCQQHNEYPPTFGQGTKLEIK
159	A3_5_D50A VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYAGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIK
160	A3-derived_ D50A VL CON	DX$_1$QMTQSPX$_2$X$_3$LX$_4$ASX$_5$GX$_6$X$_7$VX$_8$IX$_9$CKASKSISKYLAWYQQKPGKAX$_{10}$KLLIYAGSTLQSGX$_{11}$PSRFSGSGSGTDFTLTIX$_{12}$SLX$_{13}$PEDFX$_{14}$X$_{15}$YYCQQHNEYPPTFGX$_{16}$GTKLEIK wherein X_1 = V or I, X_2 = S or Y, X_3 = S or N, X_4 = S or A, X_5 = V or P, X_6 = D or E, X_7 = R or S, X_8 = T or S, X_9 = N or T, X_{10} = N or P, X_{11} = V or I, X_{12} = S or R, X_{13} = Q or E, X_{14} = A or G, X_{15} = T or L, X_{16} = Q or S
161	A3-Hum_D50A VL CON	DX$_1$QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX$_2$KLLIYDGSTLQSGX$_3$PSRFS GSGSGTDFTLTISSLQPEDX$_4$X$_5$LYYCQQHNEYPPTFGQGTKLEIK wherein X_1 = V or I, X_2 = N or P, X_3 = V or I, X_4 = A or G, X_5 = T or L
162	B035-C03-A3_D50A, A3_3_D50A, A3_4_D50A, A3_5_D50A LC-CDR2	AGS
163	B035-C03-A3_D50A K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGS GSGTDFTLTIRSLEPEDFGLYYCQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
164	A3_3_D50A K LC	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
165	A3_4_D50A K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFGLYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
166	A3_5_D50A K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYAGSTLQSGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA

		SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
167	A3-derived_D50A CON K LC	DX1QMTQSPX2X3LX4ASX5GX6X7VX8IX9CKASKSISKYLAWYQQKPGKAX10KLLIYAGSTLQSGX1 1PSRFSGSGSGTDFTLTIX12SLX13PEDFX14X15YYCQQHNEYPPTFGX16GTKLEIKRTVAAPSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X1 = V or I, X2 = S or Y, X3 = S or N, X4 = S or A, X5 = V or P, X6 = D or E, X7 = R or S, X8 = T or S, X9 = N or T, X10 = N or P, X11 = V or I, X12 = S or R, X13 = Q or E, X14 = A or G, X15 = T or L, X16 = Q or S
168	A3-Hum_D50A K LC	DX1QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX2KLLIYDGSTLQSGX3PSRFS GSGSGTDFTLTISSLQPEDX4X5LYYCQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC wherein X1 = V or I, X2 = N or P, X3 = V or I, X4 = A or G, X5 = T or L
169	B035-C03-A3 epitope B1	CEWDGGRETHL
170	B035-C03-A3 epitope B2	EWATHKFADCKA
171	Residues common to B035-C03-A3 epitope A1 and B1	CEWDGGR
172	Residues common to B035-C03-A3 epitope A2 and B2	EWATHKFADCK
173	B035-C03-A3 epitope region composite 2	CEWDGGRETHLETNFTLKSEWATHKFADCK
174	A3_6.2 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSV KGRFTISRDNAKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSS
175	A3_6.2 HC-FR2	IHWIRQAPGKGLEWVAL
176	A3_6.2 hIgG1 HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSV KGRFTISRDNAKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK
177	A3_6.2 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSV KGRFTISRDNAKNTLYLQMDSLRAEDTATYYCATPMMAVITPYYFDYWGQGTLVTVSSASTKGP SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS LGK
178	B-R3 epitope	YSTVYF
179	4D4 VH	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSS
180	4D4, 4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-CDR1	GFTFSNYW
181	4D4, 4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-CDR2	INADGGST
182	4D4, 4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-CDR3	VKMGLYFGLLVPYVMDA
183	4D4 HC-FR1	EVQLVETGGGLVQPGRSLKLSCVVS

184	4D4, 3G9, 4A7/7D8, 4D4CVH2, 4D4CVH2.2 HC-FR2	MYWIRQAPGKGLEWVAS
185	4D4 HC-FR3	YYPDSVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYC
186	4D4, 3G9, 4A7/7D8, HC-FR4	WGQGASVTVSS
187	4D4 VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGTGTKLELK
188	4D4, 4D4C/GVL1, 4D4CVL2, 4D4CVL4, 4D4GVL3, 4D4GVL4, LC-CDR1	QNVNNY
189	4D4, 4A7/7D8, C03-A7, 4D4C/GVL1, 4D4CVL2, 4D4CVL4, 4D4CVL5, 4D4GVL2, 4D4GVL3, 4D4GVL4, LC-CDR2	NTN
190	4D4, 4A7/7D8, 4D4C/GVL1, 4D4CVL2, 4D4CVL4, 4D4GVL3, 4D4GVL4, LC-CDR3	YQYTNGYT
191	4D4, C03-A7 LC-FR1	NIQLTQSPSLLSASVGDRVTLSCKGS
192	4D4, 4D4C/GVL1 LC-FR2	LAWYQQKLGKTPKLLIY
193	4D4, 4D4C/GVL1, 4D4CVL2, LC-FR3	NLQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFC
194	4D4 LC-FR4	FGTGTKLELK
195	3G9 VH	EVQLAETGGGLVQPGRSLKLSCVASGFTFSRYWMYWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVYLQMNSLRSEDTATYYCVKMGVKYGLLLPYVMDAWGQGASVTVSS
196	3G9, 4A7/7D8 HC-CDR1	GFTFSRYW
197	3G9, 4A7/7D8 HC-CDR2	INTDGGST
198	3G9 HC-CDR3	VKMGVKYGLLLPYVMDA
199	3G9, 4A7/7D8 HC-FR1	EVQLAETGGGLVQPGRSLKLSCVAS
200	3G9 HC-FR3	YYPDSVQGRFTVSRDNAENTVYLQMNSLRSEDTATYYC
201	3G9 VL	NIQLTQSPSLLSTSVGDRVTLSCKGSQNINNYLAWFQQKLGEVPKLLIYHTNSLQTGIPSRFSGS GSGTDYTLTISSLQPEDVATYFCYQYTSGYTFGAGTKLELK
202	3G9, 4A7/7D8, C03-A7 LC-CDR1	QNINNY
203	3G9 LC-CDR2	HTN
204	3G9 LC-CDR3	YQYTSGYT
205	3G9, 4A7/7D8 LC-FR1	NIQLTQSPSLLSTSVGDRVTLSCKGS
206	3G9 LC-FR2	LAWFQQKLGEVPKLLIY
207	3G9, 4A7/7D8 LC-FR3	SLQTGIPSRFSGSGSGTDYTLTISSLQPEDVATYFC
208	3G9, 4A7/7D8, 8C6 LC-FR4	FGAGTKLELK
209	4A7/7D8 VH	EVQLAETGGGLVQPGRSLKLSCVASGFTFSRYWMYWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVFLQMNSLRSEDTATYYCVKMGLKYGLLLPYVMDAWGQGASVTVSS
210	4A7/7D8 HC-CDR3	VKMGLKYGLLLPYVMDA
211	4A7/7D8 HC-FR3	YYPDSVQGRFTVSRDNAENTVFLQMNSLRSEDTATYYC
212	4A7/7D8 VL	NIQLTQSPSLLSTSVGDRVTLSCKGSQNINNYLAWYQQKLGEVPKLLIYNTNSLQTGIPSRFSGS GSGTDYTLTISSLQPEDVATYFCYQYTNGYTFGAGTKLELK
213	4A7/7D8 LC-FR2	LAWYQQKLGEVPKLLIY
214	8C6 VH	EVQLVESGGGLVQPGRSLKLSCAASGFTFNNYYMAWVRQAPTKGLEWVASITKSGGSTNYRD SVRGRFTISRDDAKSTLSLQMDSLRSEDTATYYCARGGIYYGLFTGYFDYWGQGVMVTVSS
215	8C6 HC-CDR1	GFTFNNYY
216	8C6 HC-CDR2	ITKSGGST
217	8C6 HC-CDR3	ARGGIYYGLFTGYFDY
218	8C6 HC-FR1	EVQLVESGGGLVQPGRSLKLSCAAS
219	8C6, C03-A7 HC-FR2	MAWVRQAPTKGLEWVAS
220	8C6 HC-FR3	NYRDSVRGRFTISRDDAKSTLSLQMDSLRSEDTATYYC
221	8C6, C03-A7 HC-FR4	WGQGVMVTVSS

222	8C6 VL	DTVLTQSPTLAVSPGERVSISCRASEGVNSFMHWYQQNPGQQPKLLIYKASNLASGVPARFSG SGSGTDFTLTIDPVEADDTATYFCQQNWNDPFTFGAGTKLELK
223	8C6 LC-CDR1	EGVNSF
224	8C6 LC-CDR2	KAS
225	8C6 LC-CDR3	QQNWNDPFT
226	8C6 LC-FR1	DTVLTQSPTLAVSPGERVSISCRAS
227	8C6 LC-FR2	MHWYQQNPGQQPKLLIY
228	8C6 LC-FR3	NLASGVPARFSGSGSGTDFTLTIDPVEADDTATYFC
229	C03-A7 VH	EVQLVESGGGLVQPGRSLKLSCVGSGFTFSNYGMAWVRQAPTKGLEWVASISTGGDNTYYRD SVKGRFTISRDDAKNTQYLQMDSLRSEDTATYYCARLGIYYRLLVPYFHYWGQGVMVTVSS
230	C03-A7 HC-CDR1	GFTFSNYG
231	C03-A7 HC-CDR2	ISTGGDNT
232	C03-A7 HC-CDR3	ARLGIYYRLLVPYFHY
233	C03-A7 HC-FR1	EVQLVESGGGLVQPGRSLKLSCVGS
234	C03-A7 HC-FR3	YYRDSVKGRFTISRDDAKNTQYLQMDSLRSEDTATYYC
235	C03-A7 VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNINNYLAWYQQKLGEAPKLLIYNTNSFQTGIPSRFSGS GSGTDYTLTINSLQPEDVATYFCYQYNNGWTFGGGTKLDLK
236	C03-A7 LC-CDR3	YQYNNGWT
237	C03-A7 LC-FR2	LAWYQQKLGEAPKLLIY
238	C03-A7 LC-FR3	SFQTGIPSRFSGSGSGTDYTLTINSLQPEDVATYFC
239	C03-A7 LC-FR4	FGGGTKLDLK
240	CON'4'9'7/8 HC-CDR1	GFTFSX$_1$YW wherein X$_1$ = R or N
241	CON'4'9'7/8 HC-CDR2	INX$_1$DGGST wherein X$_1$ = T or A
242	CON'4'9'7/8 HC-CDR3	VKMGX$_1$X$_2$X$_3$GLLX$_4$PYVMDA wherein X$_1$ = L or V; X$_2$ = K or Y; X$_3$ = Y or F; X$_4$ = L or V
243	CON'4'9'7/8 LC-CDR1	QNX$_1$NNY wherein X$_1$ = I or V
244	CON'4'9'7/8 LC-CDR2	X$_1$TN wherein X$_1$ = N or H
245	CON'4'9'7/8 LC-CDR3	YQYTX$_1$GYT wherein X$_1$ = N or S
246	CON'4'9'7/8 HC-FR1	EVQLX$_1$ETGGGLVQPGRSLKLSCVX$_2$S wherein X$_1$ = A or V; X$_2$ = A or V
247	CON'4'9'7/8 HC-FR3	YYPDSVX$_1$GRFTX$_2$SRDNAEX$_3$TVYLQMNSLRSEDTATYYC wherein X$_1$ = K or Q; X$_2$ = I or V; X$_3$ = D or N
248	CON'4'9'7/8 LC-FR1	NIQLTQSPSLLSX$_1$SVGDRVTLSCKGS wherein X$_1$ = A or T
249	CON'4'9'7/8 LC-FR2	LAWX$_1$QQKLGEX$_2$PKLLIY wherein X$_1$ = Y or F; X$_2$ = V or T
250	CON'4'9'7/8 LC-FR3	X$_1$LQTGIPSRFSGSGSX$_2$TDYTLTISSLQPEDVATYFC wherein X$_1$ = N or S; X$_2$ = D or G
251	CON'4'9'7/8 LC-FR4	FGX$_1$GTKLELK wherein X$_1$ = T or A
252	CON'4'9'7/8 VH	EVQLX$_1$ETGGGLVQPGRSLKLSCVX$_2$SGFTFSX$_3$YWMYWIRQAPGKGLEWVASINX$_4$DGGSTYY PDSVX$_5$GRFTX$_6$SRDNAEX$_7$TVYLQMNSLRSEDTATYYCVKMGX$_8$X$_9$X$_{10}$GLLX$_{11}$PYVMDAWGQG ASVTVSS wherein X$_1$ = A or V; X$_2$ = A or V; X$_3$ = R or N; X$_4$ = T or A; X$_5$ = K or Q; X$_6$ = I or V; X$_7$ = D or N; X$_8$ = L or V; X$_9$ = K or Y; X$_{10}$ = Y or F; X$_{11}$ = L or V

253	CON'4'9'7/8 VL	NIQLTQSPSLLSX$_1$SVGDRVTLSCKGSQNX$_2$NNYLAWX$_3$QQKLGEX$_4$PKLLIYX$_5$TNX$_6$LQTGIPSRF SGSGSX$_7$TDYTLTISSLQPEDVATYFCYQYTX$_8$GYTFGX$_9$GTKLELK wherein X$_1$ = A or T; X$_2$ = I or V; X$_3$ = Y or F; X$_4$ = V or T; X$_5$ = N or H; X$_6$ = N or S; X$_7$ = D or G; X$_8$ = N or S; X$_9$ = T or A
254	4D4CVH2, 4D4CVH3, 4D4CVH2.1, 4D4CVH2.2 HC-FR1	EVQLVESGGGLVQPGRSLRLSCVVS
255	4D4CVH2, 4D4CVH2.1 HC-FR3	YYPDSVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYC
256	4D4CVH2	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
257	4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-FR4	WGQGTLVTVSS
258	4D4CVH3	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
259	4D4CVH3, 4D4CVH4, 4D4CVH2.1 HC-FR2	MYWVRQAPGKGLEWVAS
260	4D4CVH3, 4D4CVH2.2 HC-FR3	YYPDSVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYC
261	4D4CVH4	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
262	4D4CVH4, HC-FR1	EVQLVESGGGLVQPGRSLRLSCAAS
263	4D4CVH4 HC-FR3	YYPDSVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYC
264	4D4CVH2.1	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
265	4D4CVH2.2	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
266	4D4C/GVL1	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGQGTKLEIK
267	4D4C/GVL1 LC-FR1	NIQLTQSPSLLSASVGDRVTITCKGS
268	4D4C/GVL1, 4D4CVL2, 4D4CVL4, , 4D4GVL3, 4D4GVL4, LC-FR4	FGQGTKLEIK
269	4D4CVL2	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGQGTKLEIK
270	4D4CVL2 LC-FR1	NIQLTQSPSFLSASVGDRVTITCKGS
271	4D4CVL2, 4D4CVL4, 4D4GVL3, 4D4GVL4 LC-FR2	LAWYQQKPGKAPKLLIY
272	4D4CVL4, LC-FR1	DIQLTQSPSFLSASVGDRVTITCKGS
273	4D4CVL4	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTNGYTFGQGTKLEIK
274	4D4CVL4 LC-FR3	NLQTGVPSRFSGSGSDTDYTLTISSLQPEDVATYYC
275	4D4GVL3 LC-FR1	DIQLTQSPSSLSASVGDRVTITCKGS
276	4D4GVL3	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTNGYTFGQGTKLEIK
277	4D4GVL3 LC-FR3	NLQTGVPSRFSGSGSDTDYTLTISSLQPEDFATYYC
278	4D4GVL4	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTNGYTFGQGTKLEIK
279	4D4GVL4 LC-FR1	DIQMTQSPSSLSASVGDRVTITCKGS
280	4D4GVL4 LC-FR3	NLQTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
281	CON4D4P/Hu HC-FR1	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$S wherein X$_1$ = V or A; X$_2$ = V or A
282	CON4D4P/Hu HC-FR2	MYWX$_1$RQAPGKGLEWVAS wherein X$_1$ = V or I
283	CON4D4P/Hu HC-FR3	YYPDSVKGRFTISRDNX$_1$X$_2$X$_3$TVYLQMNSLRAEDTATYYC wherein X$_1$ = S or A; X$_2$ = K or E; X$_3$ = D or N

284	CON4D4P/Hu VH	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$SGFTFSNYWMYWX$_3$RQAPGKGLEWVASINADGGSTYY PDSVKGRFTISRDNX$_4$X$_5$X$_6$TVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVT VSS wherein X$_1$ = V or A; X$_2$ = V or A; X$_3$ = V or I; X$_4$ = S or A; X$_5$ = K or E; X$_6$ = D or N
285	CON4D4P/Hu LC-FR1	X$_1$IQX$_2$TQSPSX$_3$LSASVGDRVTITCKGS wherein X$_1$ = D or N; X$_2$ = L or M; X$_3$ = F, L or S
286	CON4D4P/Hu LC-FR2	LAWYQQKX$_1$GKX$_2$PKLLIY wherein X$_1$ = P or L; X$_2$ = A or T
287	CON4D4P/Hu LC-FR3	NLQTGX$_1$PSRFSGSGSX$_2$TDX$_3$TLTISSLQPEDX$_4$ATYX$_5$C wherein X$_1$ = I or V; X$_2$ = D or G; X$_3$ = Y or F; X$_4$ = V or F; X$_5$ = F or Y
288	CON4D4P/Hu VL	X$_1$IQX$_2$TQSPSX$_3$LSASVGDRVTITCKGSQNVNNYLAWYQQKX$_4$GKX$_5$PKLLIYNTNNLQTGX$_6$PSR FSGSGSX$_7$TDX$_8$TLTISSLQPEDX$_9$ATYX$_{10}$CYQYTNGYTFGQGTKLEIK wherein X$_1$ = D or N; X$_2$ = L or M; X$_3$ = F, L or S; X$_4$ = P or L; X$_5$ = A or T; X$_6$ = I or V; X$_7$ = D or G; X$_8$ = Y or F; X$_9$ = V or F; X$_{10}$ = F or Y
289	4D4 hIgG1 HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
290	3G9 hIgG1 HC	EVQLAETGGGLVQPGRSLKLSCVASGFTFSRYWMYWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVYLQMNSLRSEDTATYYCVKMGVKYGLLLPYVMDAWGQGASVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
291	4A7/7D8 hIgG1 HC	EVQLAETGGGLVQPGRSLKLSCVASGFTFSRYWMYWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVFLQMNSLRSEDTATYYCVKMGLKYGLLLPYVMDAWGQGASVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
292	8C6 hIgG1 HC	EVQLVESGGGLVQPGRSLKLSCAASGFTFNNYYMAWVRQAPTKGLEWVASITKSGGSTNYRD SVRGRFTISRDDAKSTLSLQMDSLRSEDTATYYCARGGIYYGLFTGYFDYWGQGVMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
293	C03-A7 hIgG1 HC	EVQLVESGGGLVQPGRSLKLSCVGSGFTFSNYGMAWVRQAPTKGLEWVASISTGGDNTYYRD SVKGRFTISRDDAKNTQYLQMDSLRSEDTATYYCARLGIYYRLLVPYFHYWGQGVMVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
294	CON'4'9'7/8 hIgG1 HC	EVQLX$_1$ETGGGLVQPGRSLKLSCVX$_2$SGFTFSX$_3$YWMYWIRQAPGKGLEWVASINX$_4$DGGSTYY PDSVX$_5$GRFTX$_6$SRDNAEX$_7$TVYLQMNSLRSEDTATYYCVKMGX$_8$X$_9$X$_{10}$GLLX$_{11}$PYVMDAWGQG ASVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK

		wherein X_1 = A or V; X_2 = A or V; X_3 = R or N; X_4 = T or A; X_5 = K or Q; X_6 = I or V; X_7 = D or N; X_8 = L or V; X_9 = K or Y; X_{10} = Y or F; X_{11} = L or V
295	4D4CVH2 hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
296	4D4CVH3 hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
297	4D4CVH4 hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
298	4D4CVH2.1 hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
299	4D4CVH2.2 hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
300	CON4D4P/Hu hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$SGFTFSNYWMYWX$_3$RQAPGKGLEWVASINADGGSTYY PDSVKGRFTISRDNX$_4$X$_5$X$_6$TVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK wherein X_1 = V or A; X_2 = V or A; X_3 = V or I; X_4 = S or A; X_5 = K or E; X_6 = D or N
301	4D4 K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGTGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
302	3G9 K LC	NIQLTQSPSLLSTSVGDRVTLSCKGSQNINNYLAWFQQKLGEVPKLLIYHTNSLQTGIPSRFSGS GSGTDYTLTISSLQPEDVATYFCYQYTSGYTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
303	4A7/7D8 K LC	NIQLTQSPSLLSTSVGDRVTLSCKGSQNINNYLAWYQQKLGEVPKLLIYNTNSLQTGIPSRFSGS GSGTDYTLTISSLQPEDVATYFCYQYTNGYTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
304	8C6 K LC	DTVLTQSPTLAVSPGERVSISCRASEGVNSFMHWYQQNPGQQPKLLIYKASNLASGVPARFSG SGSGTDFTLTIDPVEADDTATYFCQQNWNDPFTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC

305	C03-A7 K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNINNYLAWYQQKLGEAPKLLIYNTNSFQTGIPSRFSGS GSGTDYTLTINSLQPEDVATYFCYQYNNGWTFGGGTKLDLKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
306	CON'4'9'7/8 K LC	NIQLTQSPSLLSX_1SVGDRVTLSCKGSQNX_2NNYLAWX_3QQKLGEX_4PKLLIYX_5TNX_6LQTGIPSRF SGSGSX_7TDYTLTISSLQPEDVATYFCYQYTX_8GYTFGX_9GTKLELKRTVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNRGEC wherein X_1 = A or T; X_2 = I or V; X_3 = Y or F; X_4 = V or T; X_5 = N or H; X_6 = N or S; X_7 = D or G; X_8 = N or S; X_9 = T or A
307	4D4C/GVL1 K LC	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
308	4D4CVL2 K LC	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
309	4D4CVL4 K LC	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTNGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
310	4D4GVL3 K LC	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTNGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
311	4D4GVL4 K LC	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTNGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
312	CON4D4P/Hu K LC	X_1IQX_2TQSPSX_3LSASVGDRVTITCKGSQNVNNYLAWYQQKX$_4$GKX$_5$PKLLIYNTNNLQTGX_6PSR FSGSGSX_7TDX_8TLTISSLQPEDX_9ATYX_{10}CYQYTNGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK HKVYACEVTHQGLSSPVTKSFNRGEC wherein X_1 = D or N; X_2 = L or M; X_3 = F, L or S; X_4 = P or L; X_5 = A or T; X_6 = I or V; X_7 = D or G; X_8 = Y or F; X_9 = V or F; X_{10} = F or Y
313	3G9 region a	SKGPTVRTK
314	3G9 region b	RNYTIFY
315	3G9 region c	TDEGGK
316	3G9 region composite	SKGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTS DTLYMVRMAAYTDEGGK
317	4A7/7D8 region 1a	KEKCMDY
318	4A7/7D8 region 1b	THLETNFT
319	4A7/7D8 region 1 composite	KEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNIQLTCNILTFGQLEQNVYGI TIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFT
320	4A7/7D8 region 2a	SEELSSILK
321	4A7/7D8 region 2b	YNIQYRT
322	4A7/7D8 region 2c	RYLATLTVR
323	4A7/7D8 region 2 composite	SEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIR CMKEDGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKI LDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVR
324	4D4 region a	YTVNATKLT
325	4D4 region b	KSDAAVLT
326	4D4 region a+b composite	YTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLT
327	8C6 region a	KILDYEVT
328	8C6 region b	RWKSHLQNY
329	8C6 region a+b composite	KILDYEVTLTRWKSHLQNY
330	C03-A7 region a	RETH
331	C03-A7 region b	KAKRDTPTSCTVDY
332	C03-A7 region a+b composite	RETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDY
333	4D4 hIgG4(S228P, L235E) HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL

		SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
334	3G9 hIgG4(S228P, L235E) HC	EVQLAETGGGLVQPGRSLKLSCVASGFTFSRYWMYWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVYLQMNSLRSEDTATYYCVKMGVKYGLLLPYVMDAWGQGASVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK
335	4A7/7D8 hIgG4(S228P, L235E) HC	EVQLAETGGGLVQPGRSLKLSCVASGFTFSRYWMYWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVFLQMNSLRSEDTATYYCVKMGLKYGLLLPYVMDAWGQGASVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK
336	8C6 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLKLSCAASGFTFNNYYMAWVRQAPTKGLEWVASITKSGGSTNYRD SVRGRFTISRDDAKSTLSLQMDSLRSEDTATYYCARGGIYYGLFTGYFDYWGQGVMVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK
337	C03-A7 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLKLSCVGSGFTFSNYGMAWVRQAPTKGLEWVASISTGGDNTYYRD SVKGRFTISRDDAKNTQYLQMDSLRSEDTATYYCARLGIYYRLLVPYFHYWGQGVMVTVSSAST KGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLGK
338	CON'4'9'7/8 hIgG4(S228P, L235E) HC	EVQLX$_1$ETGGGLVQPGRSLKLSCVX$_2$SGFTFSX$_3$YWMYWIRQAPGKGLEWVASINX$_4$DGGSTYY PDSVX$_5$GRFTX$_6$SRDNAEX$_7$TVYLQMNSLRSEDTATYYCVKMGX$_8$X$_9$X$_{10}$GLLX$_{11}$PYVMDAWGQG ASVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE ALHNHYTQKSLSLSLGK wherein X$_1$ = A or V; X$_2$ = A or V; X$_3$ = R or N; X$_4$ = T or A; X$_5$ = K or Q; X$_6$ = I or V; X$_7$ = D or N; X$_8$ = L or V; X$_9$ = K or Y; X$_{10}$ = Y or F; X$_{11}$ = L or V
339	4D4CVH2 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
340	4D4CVH3 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
341	4D4CVH4 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD

		WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
342	4D4CVH2.1 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
343	4D4CVH2.2 hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
344	CON4D4P/Hu hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$SGFTFSNYWMYWX$_3$RQAPGKGLEWVASINADGGSTYY PDSVKGRFTISRDNX$_4$X$_5$X$_6$TVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVT VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH YTQKSLSLSLGK wherein X$_1$ = V or A; X$_2$ = V or A; X$_3$ = V or I; X$_4$ = S or A; X$_5$ = K or E; X$_6$ = D or N
345	4D4_D53G VH	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSS
346	4D4_D53E VH	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSS
347	4D4_D53Q VH	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSS
348	4D4_D53L VH	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPDS VKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSS
349	4D4_G54A VH	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPDS VKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSS
350	4D4CVH2_D53G VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
351	4D4CVH2_D53E VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
352	4D4CVH2_D53Q VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
353	4D4CVH2_D53L VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
354	4D4CVH2_G54A VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
355	4D4CVH3_D53G VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
356	4D4CVH3_D53E VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
357	4D4CVH3_D53Q VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
358	4D4CVH3_D53L VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
359	4D4CVH3_G54A VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
360	4D4CVH4_D53G VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
361	4D4CVH4_D53E VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
362	4D4CVH4_D53Q VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
363	4D4CVH4_D53L VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS

364	4D4CVH4_G54A VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
365	4D4CVH2.1_D53G VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
366	4D4CVH2.1_D53E VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
367	4D4CVH2.1_D53Q VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
368	4D4CVH2.1_D53L VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
369	4D4CVH2.1_G54A VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
370	4D4CVH2.2_D53G VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
371	4D4CVH2.2_D53E VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
372	4D4CVH2.2_D53Q VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
373	4D4CVH2.2_D53L VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
374	4D4CVH2.2_G54A VH	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSS
375	4D4_D53G, 4D4CVH2_D53G, 4D4CVH3_D53G, 4D4CVH4_D53G, 4D4CVH2.1_D53G, 4D4CVH2.2_D53G HC-CDR2	INAGGGST
376	4D4_D53E, 4D4CVH2_D53E, 4D4CVH3_D53E, 4D4CVH4_D53E, 4D4CVH2.1_D53E, 4D4CVH2.2_D53E HC-CDR2	INAEGGST
377	4D4_D53Q, 4D4CVH2_D53Q, 4D4CVH3_D53Q, 4D4CVH4_D53Q, 4D4CVH2.1_D53Q, 4D4CVH2.2_D53Q HC-CDR2	INAQGGST
378	4D4_D53L, 4D4CVH2_D53L, 4D4CVH3_D53L, 4D4CVH4_D53L, 4D4CVH2.1_D53L, 4D4CVH2.2_D53L HC-CDR2	INALGGST
379	4D4_G54A, 4D4CVH2_G54A, 4D4CVH3_G54A, 4D4CVH4_G54A, 4D4CVH2.1_G54A, 4D4CVH2.2_G54A HC-CDR2	INADAGST
380	CON4D4P/Hu_D53var_G53var HC-CDR2	INAX$_1$X$_2$GST wherein X$_1$ = D, G, E, Q or L; X$_2$ = G or A
381	CON4D4P/Hu_D53var_G53var VH	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$SGFTFSNYWMYWX$_3$RQAPGKGLEWVASINAX$_4$X$_5$GSTY YPDSVKGRFTISRDNX$_6$X$_7$X$_8$TVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLV TVSS wherein X$_1$ = V or A; X$_2$ = V or A; X$_3$ = V or I; X$_4$ = D, G, E, Q or L; X$_5$ = G or A; X$_6$ = S or A; X$_7$ = K or E; X$_8$ = D or N
382	4D4_N93G VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGGYTFGTGTKLELK

383	4D4_N93E VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGTGTKLELK
384	4D4_N93L VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGTGTKLELK
385	4D4_N93Q VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTQGYTFGTGTKLELK
386	4D4_G94A VL	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGTGTKLELK
387	4D4C/GVL1_N93G VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGGYTFGQGTKLEIK
388	4D4C/GVL1_N93E VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIK
389	4D4C/GVL1_N93L VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIK
390	4D4C/GVL1_N93Q VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTQGYTFGQGTKLEIK
391	4D4C/GVL1_G94A VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIK
392	4D4CVL2_N93G VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGGYTFGQGTKLEIK
393	4D4CVL2_N93E VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIK
394	4D4CVL2_N93L VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIK
395	4D4CVL2_N93Q VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTQGYTFGQGTKLEIK
396	4D4CVL2_G94A VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIK
397	4D4CVL4_N93G VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTGGYTFGQGTKLEIK
398	4D4CVL4_N93E VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTEGYTFGQGTKLEIK
399	4D4CVL4_N93L VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTLGYTFGQGTKLEIK
400	4D4CVL4_N93Q VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTQGYTFGQGTKLEIK
401	4D4CVL4_G94A VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTNAYTFGQGTKLEIK
402	4D4GVL3_N93G VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTGGYTFGQGTKLEIK
403	4D4GVL3_N93E VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTEGYTFGQGTKLEIK
404	4D4GVL3_N93L VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTLGYTFGQGTKLEIK
405	4D4GVL3_N93Q VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTQGYTFGQGTKLEIK
406	4D4GVL3_G94A VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTNAYTFGQGTKLEIK
407	4D4GVL4_N93G VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTGGYTFGQGTKLEIK
408	4D4GVL4_N93E VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTEGYTFGQGTKLEIK
409	4D4GVL4_N93L VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTLGYTFGQGTKLEIK
410	4D4GVL4_N93Q VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTQGYTFGQGTKLEIK
411	4D4GVL4_G94A VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTNAYTFGQGTKLEIK
412	4D4_N93G, 4D4C/GVL1_N93G, 4D4CVL2_N93G, 4D4CVL4_N93G, 4D4GVL3_N93G, 4D4GVL4_N93G LC-CDR3	YQYTGGYT
413	4D4_N93E, 4A7/7D8_N93E, 4D4C/GVL1_N93E,	YQYTEGYT

	4D4CVL2_N93E, 4D4CVL4_N93E, 4D4GVL3_N93E, 4D4GVL4_N93E LC-CDR3	
414	4D4_N93L, 4A7/7D8_N93L, 4D4C/GVL1_N93L, 4D4CVL2_N93L, 4D4CVL4_N93L, 4D4GVL3_N93L, 4D4GVL4_N93L LC-CDR3	YQYTLGYT
415	4D4_N93Q, 4D4C/GVL1_N93Q, 4D4CVL2_N93Q, 4D4CVL4_N93Q, 4D4GVL3_N93Q, 4D4GVL4_N93Q LC-CDR3	YQYTQGYT
416	4D4_G94A, 4D4C/GVL1_G94A, 4D4CVL2_G94A, 4D4CVL4_G94A, 4D4GVL3_G94A, 4D4GVL4_G94A LC-CDR3	YQYTNAYT
417	CON4D4P/Hu_N93var_G94var LC-CDR3	YQYTX$_1$X$_2$YT wherein X$_1$ = N, G, E, L or Q; X$_2$ = G or A
418	CON4D4P/Hu_N93var_G94var VL	X$_1$IQX$_2$TQSPSX$_3$LSASVGDRVTITCKGSQNVNNYLAWYQQKX$_4$GKX$_5$PKLLIYNTNNLQTGX$_6$PSRFSGSGSX$_7$TDX$_8$TLTISSLQPEDX$_9$ATYX$_{10}$CYQYTX$_{11}$X$_{12}$YTFGQGTKLEIK wherein X$_1$ = D or N; X$_2$ = L or M; X$_3$ = F, L or S; X$_4$ = P or L; X$_5$ = A or T; X$_6$ = I or V; X$_7$ = D or G; X$_8$ = Y or F; X$_9$ = V or F; X$_{10}$ = F or Y; X$_{11}$ = N, G, E, L or Q; X$_{12}$ = G or A
419	4D4_D53G hIgG1 HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPDSVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
420	4D4_D53E hIgG1 HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPDSVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
421	4D4_D53Q hIgG1 HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPDSVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
422	4D4_D53L hIgG1 HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPDSVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
423	4D4_G54A hIgG1 HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPDSVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSAS

		TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
424	4D4CVH2_D53G hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
425	4D4CVH2_D53E hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
426	4D4CVH2_D53Q hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
427	4D4CVH2_D53L hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
428	4D4CVH2_G54A hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
429	4D4CVH3_D53G hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
430	4D4CVH3_D53E hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
431	4D4CVH3_D53Q hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP

		SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
432	4D4CVH3_D53L hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
433	4D4CVH3_G54A hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
434	4D4CVH4_D53G hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
435	4D4CVH4_D53E hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
436	4D4CVH4_D53Q hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
437	4D4CVH4_D53L hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
438	4D4CVH4_G54A hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
439	4D4CVH2.1_D53G hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
440	4D4CVH2.1_D53E hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL

		SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
441	4D4CVH2.1_D53Q hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
442	4D4CVH2.1_D53L hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
443	4D4CVH2.1_G54A hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
444	4D4CVH2.2_D53G hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
445	4D4CVH2.2_D53E hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
446	4D4CVH2.2_D53Q hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
447	4D4CVH2.2_D53L hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
448	4D4CVH2.2_G54A hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK

449	CON4D4P/Hu_D53var_G53var hIgG1 HC	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$SGFTFSNYWMYWX$_3$RQAPGKGLEWVASINAX$_4$X$_5$GSTY YPDSVKGRFTISRDNX$_6$X$_7$X$_8$TVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK wherein X$_1$ = V or A; X$_2$ = V or A; X$_3$ = V or I; X$_4$ = D, G, E, Q or L; X$_5$ = G or A; X$_6$ = S or A; X$_7$ = K or E; X$_8$ = D or N
450	4D4_D53G hIgG4(S228P, L235E) HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
451	4D4_D53E hIgG4(S228P, L235E) HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
452	4D4_D53Q hIgG4(S228P, L235E) HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
453	4D4_D53L hIgG4(S228P, L235E) HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPDS VKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK
454	4D4_G54A hIgG4(S228P, L235E) HC	EVQLVETGGGLVQPGRSLKLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPDS VKGRFTISRDNAEDTVYLQMNSLRSEDTATYYCVKMGLYFGLLVPYVMDAWGQGASVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS LSLSLGK
455	4D4CVH2_D53G hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
456	4D4CVH2_D53E hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK

457	4D4CVH2_D53Q hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
458	4D4CVH2_D53L hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
459	4D4CVH2_G54A hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
460	4D4CVH3_D53G hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
461	4D4CVH3_D53E hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
462	4D4CVH3_D53Q hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
463	4D4CVH3_D53L hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
464	4D4CVH3_G54A hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
465	4D4CVH4_D53G hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD

		WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
466	4D4CVH4_D53E hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
467	4D4CVH4_D53Q hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
468	4D4CVH4_D53L hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
469	4D4CVH4_G54A hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
470	4D4CVH2.1_D53G hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
471	4D4CVH2.1_D53E hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
472	4D4CVH2.1_D53Q hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
473	4D4CVH2.1_D53L hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK

474	4D4CVH2.1_G54A hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWVRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNAEDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
475	4D4CVH2.2_D53G hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
476	4D4CVH2.2_D53E hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
477	4D4CVH2.2_D53Q hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
478	4D4CVH2.2_D53L hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
479	4D4CVH2.2_G54A hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSGFTFSNYWMYWIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNSKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK SLSLSLGK
480	CON4D4P/Hu_D53var_G53var hIgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCX$_1$X$_2$SGFTFSNYWMYWX$_3$RQAPGKGLEWVASINAX$_4$X$_5$GSTY YPDSVKGRFTISRDNX$_6$X$_7$X$_8$TVYLQMNSLRAEDTATYYCVKMGLYFGLLVPYVMDAWGQGTLV TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN HYTQKSLSLSLGK wherein X$_1$ = V or A; X$_2$ = V or A; X$_3$ = V or I; X$_4$ = D, G, E, Q or L; X$_5$ = G or A; X$_6$ = S or A; X$_7$ = K or E; X$_8$ = D or N
481	4D4_N93G K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGGYTFGTGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
482	4D4_N93E K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGTGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
483	4D4_N93L K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGTGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV

		VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
484	4D4_N93Q K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTQGYTFGTGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
485	4D4_G94A K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGTGTKLELKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
486	4D4C/GVL1_N93G K LC	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
487	4D4C/GVL1_N93E K LC	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
488	4D4C/GVL1_N93L K LC	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
489	4D4C/GVL1_N93Q K LC	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTQGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
490	4D4C/GVL1_G94A K LC	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
491	4D4CVL2_N93G K LC	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
492	4D4CVL2_N93E K LC	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
493	4D4CVL2_N93L K LC	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
494	4D4CVL2_N93Q K LC	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTQGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
495	4D4CVL2_G94A K LC	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGEC
496	4D4CVL4_N93G K LC	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTGGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
497	4D4CVL4_N93E K LC	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
498	4D4CVL4_N93L K LC	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
499	4D4CVL4_N93Q K LC	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTQGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
500	4D4CVL4_G94A K LC	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYYCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS

		VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
501	4D4GVL3_N93G K LC	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTGGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
502	4D4GVL3_N93E K LC	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
503	4D4GVL3_N93L K LC	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
504	4D4GVL3_N93Q K LC	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTQGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
505	4D4GVL3_G94A K LC	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYYCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
506	4D4GVL4_N93G K LC	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTGGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
507	4D4GVL4_N93E K LC	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
508	4D4GVL4_N93L K LC	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
509	4D4GVL4_N93Q K LC	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTQGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC
510	4D4GVL4_G94A K LC	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGEC
511	CON4D4P/Hu_N93var_G94var K LC	X_1IQX_2TQSPSX_3LSASVGDRVTITCKGSQNVNNYLAWYQQKX_4GKX_5PKLLIYNTNNLQTGX_6PSR FSGSGSX_7TDX_8TLTISSLQPEDX_9ATYX_{10}CYQYT$X_{11}X_{12}$YTFGQGTKLEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X_1 = D or N; X_2 = L or M; X_3 = F, L or S; X_4 = P or L; X_5 = A or T; X_6 = I or V; X_7 = D or G; X_8 = Y or F; X_9 = V or F; X_{10} = F or Y; X_{11} = N, G, E, L or Q; X_{12} = G or A
512	8C6 region c	EVTL
513	8C6 region d, 4D4 region c	LQNYTVNATKLTV
514	8C6 region c+d composite	EVTLTRWKSHLQNYTVNATKLTV
515	8C6 region a+b+c+d composite	KILDYEVTLTRWKSHLQNYTVNATKLTV
516	4D4 region d	LTIPACDFQATHPVM
517	4D4 region a+b+c+d composite	EVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQATHPVM
518	Ab343315 region	YSTVYF
519	Human gp130 membrane proximal region	APSFWYKIDPSHTQGYRTVQLVWKTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLT NDRYLATLTVRNLVGKSDAAVLTIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILE WCVLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPS KGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSD TLYMVRMAAYTDEGGKDGPEFTFTTPKF
520	Human VEGF-A (UniProtKB - P15692)	MNFLLSWVHWSLALLLYLHHAKWSQAAPMAEGGGQNHHEVVKFMDVYQRSYCHPIETLVD IFQEYPDEIEYIFKPSCVPLMRCGGCCNDEGLECVPTEESNITMQIMRIKPHQGQHIGEM SFLQHNKCECRPKKDRARQEKKSVRGKGKGQKRKRKKSRYKSWSVYVGARCCLMPWSLPG PHPCGPCSERRKHLFVQDPQTCKCSCKNTDSRCKARQLELNERTCRCDKPRR

521	Human VEGFR-1 (UniProtKB - P17948)	MVSYWDTGVLLCALLSCLLLTGSSSGSKLKDPELSLKGTQHIMQAGQTLHLQCRGEAAHK WSLPEMVSKESERLSITKSACGRNGKQFCSTLTLNTAQANHTGFYSCKYLAVPTSKKKET ESAIYIFISDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPD GKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVQISTPRPV KLLRGHTLVLNCTATTPLNTRVQMTWSYPDEKNKRASVRRRIDQSNSHANIFYSVLTIDK MQNKDKGLYTCRVRSGPSFKSVNTSVHIYDKAFITVKHRKQQVLETVAGKRSYRLSMKVK AFPSPEVVWLKDGLPATEKSARYLTRGYSLIIKDVTEEDAGNYTILLSIKQSNVFKNLTA TLIVNVKPQIYEKAVSSFPDPALYPLGSRQILTCTAYGIPQPTIKWFWHPCNHNHSEARC DFCSNNEESFILDADSNMGNRIESITQRMAIIEGKNKMASTLVVADSRISGIYICIASNK VGTVGRNISFYITDVPNGFHVNLEKMPTEGEDLKLSCTVNKFLYRDVTWILLRTVNNRTM HYSISKQKMAITKEHSITLNLTIMNVSLQDSGTYACRARNVYTGEEILQKKEITIRDQEA PYLLRNLSDHTVAISSSTTLDCHANGVPEPQITWFKNNHKIQQEPGIILGPGSSTLFIER VTEEDEGVYHCKATNQKGSVESSAYLTVQGTSDKSNLELITLTCTCVAATLFWLLLTLFI RKMKRSSSEIKTDYLSIIMDPDEVPLDEQCERLPYDASKWEFARERLKLGKSLGRGAFGK VVQASAFGIKKSPTCRTVAVKMLKEGATASEYKALMTELKILTHIGHHLNVVNLLGACTK QGGPLMVIVEYCKYGNLSNYLKSKRDLFFLNKDAALHMEPKKEKMEPGLEQGKKPRLDSV TSSESFASSGFQEDKSLSDVEEEEDSDGFYKEPITMEDLISYSFQVARGMEFLSSRKCIH RDLAARNILLSENNVVKICDFGLARDIYKNPDYVRKGDTRLPLKWMAPESIFDKIYSTKS DVWSYGVLLWEIFSLGGSPYPGVQMDEDFCSRLREGMRMRAPEYSTPEIYQIMLDCWHRD PKERPRFAELVEKLGDLLQANVQQDGKDYIPINAILTGNSGFTYSTPAFSEDFFKESISA PKFNSGSSDDVRYVNAFKFMSLERIKTFEELLPNATSMFDDYQGDSSTLLASPMLKRFTW TDSKPKASLKIDLRVTSKSKESGLSDVSRPSFCHSSCGHVSEGKRRFTYDHAELERKIAC CSPPPDYNSVVLYSTPPI
522	Human VEGFR-2 (UniProtKB - P35968)	MQSKVLLAVALWLCVETRAASVGLPSVSLDLPRLSIQKDILTIKANTTLQITCRGQRDLD WLWPNNQSGSEQRVEVTECSDGLFCKTLTIPKVIGNDTGAYKCFYRETDLASVIYVYVQD YRSPFIASVSDQHGVVYITENKNKTVVIPCLGSISNLNVSLCARYPEKRFVPDGNRISWD SKKGFTIPSYMISYAGMVFCEAKINDESYQSIMYIVVVVGYRIYDVVLSPSHGIELSVGE KLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRS DQGLYTCAASSGLMTKKNSTFVRVHEKPFVAFGSGMESLVEATVGERVRIPAKYLGYPPP EIKWYKNGIPLESNHTIKAGHVLTIMEVSERDTGNYTVILTNPISKEKQSHVVSLVVYVP PQIGEKSLISPVDSYQYGTTQTLTCTVYAIPPPHHIHWYWQLEEECANEPSQAVSVTNPY PCEEWRSVEDFQGGNKIEVNKNQFALIEGKNKTVSTLVIQAANVSALYKCEAVNKVGRGE RVISFHVTRGPEITLQPDMQPTEQESVSLWCTADRSTFENLTWYKLGPQPLPIHVGELPT PVCKNLDTLWKLNATMFSNSTNDILIMELKNASLQDQGDYVCLAQDRKTKKRHCVVRQLT VLERVAPTITGNLENQTTSIGESIEVSCTASGNPPPQIMWFKDNETLVEDSGIVLKDGNR NLTIRRVRKEDEGLYTCQACSVLGCAKVEAFFIIEGAQEKTNLEIIILVGTAVIAMFFWL LLVIILRTVKRANGGELKTGYLSIVMDPDELPLDEHCERLPYDASKWEFPRDRLKLGKPL GRGAFGQVIEADAFGIDKTATCRTVAVKMLKEGATHSEHRALMSELKILIHIGHHLNVVN LLGACTKPGGPLMVIVEFCKFGNLSTYLRSKRNEFVPYKTKGARFRQGKDYVGAIPVDLK RRLDSITSSQSSASSGFVEEKSLSDVEEEEAPEDLYKDFLTLEHLICYSFQVAKGMEFLA SRKCIHRDLAARNILLSEKNVVKICDFGLARDIYKDPDYVRKGDARLPLKWMAPETIFDR VYTIQSDVWSFGVLLWEIFSLGASPYPGVKIDEEFCRRLKEGTRMRAPDYTTPEMYQTML DCWHGEPSQRPTFSELVEHLGNLLQANAQQDGKDYIVLPISETLSMEEDSGLSLPTSPVS CMEEEEVCDPKFHYDNTAGISQYLQNSKRKSRPVSVKTFEDIPLEEPEVKVIPDDNQTDS GMVLASEELKTLEDRTKLSPSFGGMVPSKSRESVASEGSNQTSGYQSGYHSDDTDTTVYS SEEAELLKLIEIGVQTGSTAQILQPDSGTTLSSPPV
523	Human VEGFR-3 (UniProtKB - P35916)	MQRGAALCLRLWLCLGLLDGLVSGYSMTPPTLNITEESHVIDTGDSLSISCRGQHPLEWA WPGAQEAPATGDKDSEDTGVVRDCEGTDARPYCKVLLLHEVHANDTGSYVCYYKYIKARI EGTTAASSYVFVRDFEQPFINKPDTLLVNRKDAMWVPCLVSIPGLNVTLRSQSSVLWPDG QEVVWDDRRGMLVSTPLLHDALYLQCETTWGDQDFLSNPFLVHITGNELYDIQLLPRKSL ELLVGEKLVLNCTVWAEFNSGVTFDWDYPGKQAERGKWVPERRSQQTHTELSSILTIHNV SQHDLGSYVCKANNGIQRFRESTEVIVHENPFISVEWLKGPILEATAGDELVKLPVKLAA YPPPEFQWYKDGKALSGRHSPHALVLKEVTEASTGTYTLALWNSAAGLRRNISLELVVNV PPQIHEKEASSPSIYSRHSRQALTCTAYGVPLPLSIQWHWRPWTPCKMFAQRSLRRRQQQ DLMPQCRDWRAVTTQDAVNPIESLDTWTEFVEGKNKTVSKLVIQNANVSAMYKCVVSNKV GQDERLIYFYVTTIPDGFTIESKPSEELLEGQPVLLSCQADSYKYEHLRWYRLNLSTLHD AHGNPLLLDCKNVHLFATPLAASLEEVAPGARHATLSLSIPRVAPEHEGHYVCEVQDRRS HDKHCHKKYLSVQALEAPRLTQNLTDLLVNVSDSLEMQCLVAGAHAPSIVWYKDERLLEE KSGVDLADSNQKLSIQRVREEDAGRYLCSVCNAKGCVNSSASVAVEGSEDKGSMEIVILV GTGVIAVFFWVLLLLIFCNMRRPAHADIKTGYLSIIMDPGEVPLEEQCEYLSYDASQWEF PRERLHLGRVLGYGAFGKVVEASAFGIHKGSSCDTVAVKMLKEGATASEHRALMSELKIL IHIGNHLNVVNLLGACTKPQGPLMVIVEFCKYGNLSNFLRAKRDAFSPCAEKSPEQRGRF RAMVELARLDRRRPGSSDRVLFARFSKTEGGARRASPDQEAEDLWLSPLTMEDLVCYSFQ VARGMEFLASRKCIHRDLAARNILLSESDVVKICDFGLARDIYKDPDYVRKGSARLPLKW MAPESIFDKVYTTQSDVWSFGVLLWEIFSLGASPYPGVQINEEFCQRLRDGTRMRAPELA TPAIRRIMLNCWSGDPKARPAFSELVEILGDLLQGRGLQEEEEVCMAPRSSQSSEEGSFS QVSTMALHIAQADAEDSPPSLQRHSLAARYYNWVSFPGCLARGAETRGSSRMKTFEEFPM TPTTYKGSVDNQTDSGMVLASEEFEQIESRHRQESGFSCKGPGQNVAVTRAHPDSQGRRR RPERGARGGQVFYNSEYGELSEPSEEDHCSPSARVTFFTDNSY

524	Aflibercept (DB08885)	SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNA TYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDF NWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTF VRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

Table A

	Column A			Column B		
Antibody	**VH**			**VL**		
	HC-CDR1	**HC-CDR2**	**HC-CDR3**	**LC-CDR1**	**LC-CDR2**	**LC-CDR3**
B035-C03-A3	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
CSP-S-5H8	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
A3_3.2 VH / A3_3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_3.2 VH / A3_4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_3.2 VH / A3_5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_4.2 VH / A3_3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_4.2 VH / A3_4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_4.2 VH / A3_5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_6.2 VH / A3_3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_6.2 VH / A3_4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3_6.2 VH / A3_5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3-derived VH CON / A3-derived VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
A3-Hum VH CON / A3-Hum VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
B035-C03-A3_D50X	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_3.2 VH / A3_3_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_3.2 VH / A3_4_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_3.2 VH / A3_5_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_4.2 VH / A3_3_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_4.2 VH / A3_4_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_4.2 VH / A3_5_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_6.2 VH / A3_3_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_6.2 VH / A3_4_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_6.2 VH / A3_5_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3-derived VH CON / A3-derived VL_D50X CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3-Hum VH CON / A3-Hum VL_D50X CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
B035-C03-A3_D50A	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3_3.2 VH / A3_3_D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3_3.2 VH / A3_4_D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3_3.2 VH / A3_5_D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3_4.2 VH / A3_3_D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3_4.2 VH / A3_4_D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12

A3_4.2 VH / A3_5_D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3_6.2 VH / A3_3_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_6.2 VH / A3_4_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3_6.2 VH / A3_5_D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
A3-derived VH CON / A3-derived VL_D50A CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
A3-Hum VH CON / A3-Hum VL_D50A CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12

Table B

	Column A				Column B			
Antibody	**VH**				**VL**			
	HC-FR1	**HC-FR2**	**HC-FR3**	**HC-FR4**	**LC-FR1**	**LC-FR2**	**LC-FR3**	**LC-FR4**
B035-C03-A3	SEQ ID NO:5	SEQ ID NO:6	SEQ ID NO:7	SEQ ID NO:8	SEQ ID NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16
CSP-S-5H8	SEQ ID NO:21	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32
A3_3.2 VH / A3_3 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_3.2 VH / A3_4 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_3.2 VH / A3_5 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3_4.2 VH / A3_3 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_4.2 VH / A3_4 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_4.2 VH / A3_5 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3_6.2 VH / A3_3 VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_6.2 VH / A3_4 VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_6.2 VH / A3_5 VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3-derived VH CON / A3-derived VL CON	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
A3-Hum VH CON / A3-Hum VL CON	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
B035-C03-A3_D50X	SEQ ID NO:5	SEQ ID NO:6	SEQ ID NO:7	SEQ ID NO:8	SEQ ID NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16
A3_3.2 VH / A3_3_D50X VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_3.2 VH / A3_4_D50X VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_3.2 VH / A3_5_D50X VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3_4.2 VH / A3_3_D50X VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_4.2 VH / A3_4_D50X VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_4.2 VH / A3_5_D50X VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3_6.2 VH / A3_3_D50X VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_6.2 VH / A3_4_D50X VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_6.2 VH / A3_5_D50X VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3-derived VH CON / A3-derived VL_D50X CON	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
A3-Hum VH CON / A3-Hum VL_D50X CON	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
B035-C03-A3_D50A	SEQ ID NO:5	SEQ ID NO:6	SEQ ID NO:7	SEQ ID NO:8	SEQ ID NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16
A3_3.2 VH / A3_3_D50A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_3.2 VH / A3_4_D50A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_3.2 VH / A3_5_D50A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105

A3_4.2 VH / A3_3_D50A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_4.2 VH / A3_4_D50A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_4.2 VH / A3_5_D50A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3_6.2 VH / A3_3_D50A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
A3_6.2 VH / A3_4_D50A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
A3_6.2 VH / A3_5_D50A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
A3-derived VH CON / A3-derived VL_D50A CON	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
A3-Hum VH CON / A3-Hum VL_D50A CON	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105

Table C

	Column A	Column B
Antibody	**VH**	**VL**
B035-C03-A3	SEQ ID NO:1	SEQ ID NO:9
CSP-S-5H8	SEQ ID NO:17	SEQ ID NO:25
A3_3.2 VH / A3_3 VL	SEQ ID NO:94	SEQ ID NO:102
A3_3.2 VH / A3_4 VL	SEQ ID NO:94	SEQ ID NO:106
A3_3.2 VH / A3_5 VL	SEQ ID NO:94	SEQ ID NO:109
A3_4.2 VH / A3_3 VL	SEQ ID NO:98	SEQ ID NO:102
A3_4.2 VH / A3_4 VL	SEQ ID NO:98	SEQ ID NO:106
A3_4.2 VH / A3_5 VL	SEQ ID NO:98	SEQ ID NO:109
A3_6.2 VH / A3_3 VL	SEQ ID NO:174	SEQ ID NO:102
A3_6.2 VH / A3_4 VL	SEQ ID NO:174	SEQ ID NO:106
A3_6.2 VH / A3_5 VL	SEQ ID NO:174	SEQ ID NO:109
A3-derived VH CON / A3-derived VL CON	SEQ ID NO:112	SEQ ID NO:121
A3-Hum VH CON / A3-Hum VL CON	SEQ ID NO:117	SEQ ID NO:126
B035-C03-A3_D50X	SEQ ID NO:1	SEQ ID NO:143
A3_3.2 VH / A3_3_D50X VL	SEQ ID NO:94	SEQ ID NO:144
A3_3.2 VH / A3_4_D50X VL	SEQ ID NO:94	SEQ ID NO:145
A3_3.2 VH / A3_5_D50X VL	SEQ ID NO:94	SEQ ID NO:146
A3_4.2 VH / A3_3_D50X VL	SEQ ID NO:98	SEQ ID NO:144
A3_4.2 VH / A3_4_D50X VL	SEQ ID NO:98	SEQ ID NO:145
A3_4.2 VH / A3_5_D50X VL	SEQ ID NO:98	SEQ ID NO:146
A3_6.2 VH / A3_3_D50X VL	SEQ ID NO:174	SEQ ID NO:144
A3_6.2 VH / A3_4_D50X VL	SEQ ID NO:174	SEQ ID NO:145
A3_6.2 VH / A3_5_D50X VL	SEQ ID NO:174	SEQ ID NO:146
A3-derived VH CON / A3-derived VL_D50X CON	SEQ ID NO:112	SEQ ID NO:147
A3-Hum VH CON / A3-Hum VL_D50X CON	SEQ ID NO:117	SEQ ID NO:148
B035-C03-A3_D50A	SEQ ID NO:1	SEQ ID NO:156
A3_3.2 VH / A3_3_D50A VL	SEQ ID NO:94	SEQ ID NO:157
A3_3.2 VH / A3_4_D50A VL	SEQ ID NO:94	SEQ ID NO:158
A3_3.2 VH / A3_5_D50A VL	SEQ ID NO:94	SEQ ID NO:159
A3_4.2 VH / A3_3_D50A VL	SEQ ID NO:98	SEQ ID NO:157
A3_4.2 VH / A3_4_D50A VL	SEQ ID NO:98	SEQ ID NO:158
A3_4.2 VH / A3_5_D50A VL	SEQ ID NO:98	SEQ ID NO:159
A3_6.2 VH / A3_3_D50A VL	SEQ ID NO:174	SEQ ID NO:157
A3_6.2 VH / A3_4_D50A VL	SEQ ID NO:174	SEQ ID NO:158
A3_6.2 VH / A3_5_D50A VL	SEQ ID NO:174	SEQ ID NO:159
A3-derived VH CON / A3-derived VL_D50A CON	SEQ ID NO:112	SEQ ID NO:160
A3-Hum VH CON / A3-Hum VL_D50A CON	SEQ ID NO:117	SEQ ID NO:161

Table D

	Column A	Column B
Name	**Heavy Chain**	**Light Chain**
B035-C03-A3 hIgG1	SEQ ID NO:64	SEQ ID NO:66
CSP-S-5H8 hIgG1	SEQ ID NO:67	SEQ ID NO:69
B035-C03-A3 hIgG4(S228P, L235E)	SEQ ID NO:65	SEQ ID NO:66
CSP-S-5H8 hIgG4(S228P, L235E)	SEQ ID NO:68	SEQ ID NO:69
A3_3.2 VH / A3_3 VL hIgG1	SEQ ID NO:130	SEQ ID NO:138
A3_3.2 VH / A3_4 VL hIgG1	SEQ ID NO:130	SEQ ID NO:139
A3_3.2 VH / A3_5 VL hIgG1	SEQ ID NO:130	SEQ ID NO:140
A3_4.2 VH / A3_3 VL hIgG1	SEQ ID NO:132	SEQ ID NO:138
A3_4.2 VH / A3_4 VL hIgG1	SEQ ID NO:132	SEQ ID NO:139
A3_4.2 VH / A3_5 VL hIgG1	SEQ ID NO:132	SEQ ID NO:140
A3_6.2 VH / A3_3 VL hIgG1	SEQ ID NO:176	SEQ ID NO:138
A3_6.2 VH / A3_4 VL hIgG1	SEQ ID NO:176	SEQ ID NO:139
A3_6.2 VH / A3_5 VL hIgG1	SEQ ID NO:176	SEQ ID NO:140
A3-derived VH CON / A3-derived VL CON hIgG1	SEQ ID NO:134	SEQ ID NO:141
A3-Hum VH CON / A3-Hum VL CON hIgG1	SEQ ID NO:136	SEQ ID NO:142
A3_3.2 VH / A3_3 VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:138
A3_3.2 VH / A3_4 VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:139
A3_3.2 VH / A3_5 VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:140
A3_4.2 VH / A3_3 VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:138
A3_4.2 VH / A3_4 VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:139
A3_4.2 VH / A3_5 VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:140
A3_6.2 VH / A3_3 VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:138
A3_6.2 VH / A3_4 VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:139
A3_6.2 VH / A3_5 VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:140
A3-derived VH CON / A3-derived VL CON hIgG4(S228P, L235E)	SEQ ID NO:135	SEQ ID NO:141
A3-Hum VH CON / A3-Hum VL CON hIgG4(S228P, L235E)	SEQ ID NO:137	SEQ ID NO:142
B035-C03-A3_D50X hIgG1	SEQ ID NO:64	SEQ ID NO:150
B035-C03-A3_D50X hIgG4(S228P, L235E)	SEQ ID NO:65	SEQ ID NO:150
A3_3.2 VH / A3_3_D50X VL hIgG1	SEQ ID NO:130	SEQ ID NO:151
A3_3.2 VH / A3_4_D50X VL hIgG1	SEQ ID NO:130	SEQ ID NO:152
A3_3.2 VH / A3_5_D50X VL hIgG1	SEQ ID NO:130	SEQ ID NO:153
A3_4.2 VH / A3_3_D50X VL hIgG1	SEQ ID NO:132	SEQ ID NO:151
A3_4.2 VH / A3_4_D50X VL hIgG1	SEQ ID NO:132	SEQ ID NO:152
A3_4.2 VH / A3_5_D50X VL hIgG1	SEQ ID NO:132	SEQ ID NO:153
A3_6.2 VH / A3_3_D50X VL hIgG1	SEQ ID NO:176	SEQ ID NO:151
A3_6.2 VH / A3_4_D50X VL hIgG1	SEQ ID NO:176	SEQ ID NO:152
A3_6.2 VH / A3_5_D50X VL hIgG1	SEQ ID NO:176	SEQ ID NO:153
A3-derived VH CON / A3-derived_D50X VL CON hIgG1	SEQ ID NO:134	SEQ ID NO:154
A3-Hum VH CON / A3-Hum_D50X VL CON hIgG1	SEQ ID NO:136	SEQ ID NO:155
A3_3.2 VH / A3_3_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:151
A3_3.2 VH / A3_4_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:152
A3_3.2 VH / A3_5_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:153
A3_4.2 VH / A3_3_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:151
A3_4.2 VH / A3_4_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:152
A3_4.2 VH / A3_5_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:153
A3_6.2 VH / A3_3_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:151
A3_6.2 VH / A3_4_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:152
A3_6.2 VH / A3_5_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:153
A3-derived VH CON / A3-derived_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:135	SEQ ID NO:154
A3-Hum VH CON / A3-Hum_D50X VL hIgG4(S228P, L235E)	SEQ ID NO:137	SEQ ID NO:155
B035-C03-A3_D50A hIgG1	SEQ ID NO:64	SEQ ID NO:163
B035-C03-A3_D50A hIgG4(S228P, L235E)	SEQ ID NO:65	SEQ ID NO:163
A3_3.2 VH / A3_3_D50A VL hIgG1	SEQ ID NO:130	SEQ ID NO:164
A3_3.2 VH / A3_4_D50A VL hIgG1	SEQ ID NO:130	SEQ ID NO:165
A3_3.2 VH / A3_5_D50A VL hIgG1	SEQ ID NO:130	SEQ ID NO:166
A3_4.2 VH / A3_3_D50A VL hIgG1	SEQ ID NO:132	SEQ ID NO:164
A3_4.2 VH / A3_4_D50A VL hIgG1	SEQ ID NO:132	SEQ ID NO:165
A3_4.2 VH / A3_5_D50A VL hIgG1	SEQ ID NO:132	SEQ ID NO:166
A3_6.2 VH / A3_3_D50A VL hIgG1	SEQ ID NO:176	SEQ ID NO:164

A3_6.2 VH / A3_4_D50A VL hIgG1	SEQ ID NO:176	SEQ ID NO:165
A3_6.2 VH / A3_5_D50A VL hIgG1	SEQ ID NO:176	SEQ ID NO:166
A3-derived VH CON / A3-derived_D50A VL CON hIgG1	SEQ ID NO:134	SEQ ID NO:167
A3-Hum VH CON / A3-Hum_D50A VL CON hIgG1	SEQ ID NO:136	SEQ ID NO:168
A3_3.2 VH / A3_3_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:164
A3_3.2 VH / A3_4_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:165
A3_3.2 VH / A3_5_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:166
A3_4.2 VH / A3_3_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:164
A3_4.2 VH / A3_4_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:165
A3_4.2 VH / A3_5_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:166
A3_6.2 VH / A3_3_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:164
A3_6.2 VH / A3_4_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:165
A3_6.2 VH / A3_5_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:166
A3-derived VH CON / A3-derived_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:135	SEQ ID NO:167
A3-Hum VH CON / A3-Hum_D50A VL hIgG4(S228P, L235E)	SEQ ID NO:137	SEQ ID NO:168

Table E

Antibody	Column A			Column B		
	VH			VL		
	HC-CDR1	HC-CDR2	HC-CDR3	LC-CDR1	LC-CDR2	LC-CDR3
4D4, 4D4CVH2/4D4C/GVL1, 4D4CVH2/4D4CVL2, 4D4CVH2/4D4CVL4, 4D4CVH2/4D4GVL3, 4D4CVH2/4D4GVL4, 4D4CVH3/4D4C/GVL1, 4D4CVH3/4D4CVL2, 4D4CVH3/4D4CVL4, 4D4CVH3/4D4GVL3, 4D4CVH3/4D4GVL4, 4D4CVH4/4D4C/GVL1, 4D4CVH4/4D4CVL2, 4D4CVH4/4D4CVL4, 4D4CVH4/4D4GVL3, 4D4CVH4/4D4GVL4, 4D4CVH2.1/4D4C/GVL1, 4D4CVH2.1/4D4CVL2, 4D4CVH2.1/4D4CVL4, 4D4CVH2.1/4D4GVL3, 4D4CVH2.1/4D4GVL4, 4D4CVH2.2/4D4C/GVL1, 4D4CVH2.2/4D4CVL2, 4D4CVH2.2/4D4CVL4, 4D4CVH2.2/4D4GVL3, 4D4CVH2.2/4D4GVL4, CON4D4P/Hu	SEQ ID NO:180	SEQ ID NO:181	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:190
3G9	SEQ ID NO:196	SEQ ID NO:197	SEQ ID NO:198	SEQ ID NO:202	SEQ ID NO:203	SEQ ID NO:204
4A7/7D8	SEQ ID NO:196	SEQ ID NO:197	SEQ ID NO:210	SEQ ID NO:202	SEQ ID NO:189	SEQ ID NO:190
8C6	SEQ ID NO:215	SEQ ID NO:216	SEQ ID NO:217	SEQ ID NO:223	SEQ ID NO:224	SEQ ID NO:225
C03-A7	SEQ ID NO:230	SEQ ID NO:231	SEQ ID NO:232	SEQ ID NO:202	SEQ ID NO:189	SEQ ID NO:236
CON'4'9'7/8	SEQ ID NO:240	SEQ ID NO:241	SEQ ID NO:242	SEQ ID NO:243	SEQ ID NO:244	SEQ ID NO:245
4D4/4D4_N93G, 4D4CVH2/4D4C/GVL1_N93G, 4D4CVH3/4D4C/GVL1_N93G, 4D4CVH4/4D4C/GVL1_N93G, 4D4CVH2.1/4D4C/GVL1_N93G, 4D4CVH2.2/4D4C/GVL1_N93G, 4D4CVH2/4D4CVL2_N93G, 4D4CVH3/4D4CVL2_N93G, 4D4CVH4/4D4CVL2_N93G, 4D4CVH2.1/4D4CVL2_N93G, 4D4CVH2.2/4D4CVL2_N93G, 4D4CVH2/4D4CVL4_N93G, 4D4CVH3/4D4CVL4_N93G, 4D4CVH4/4D4CVL4_N93G, 4D4CVH2.1/4D4CVL4_N93G, 4D4CVH2.2/4D4CVL4_N93G, 4D4CVH2/4D4GVL3_N93G, 4D4CVH3/4D4GVL3_N93G, 4D4CVH4/4D4GVL3_N93G, 4D4CVH2.1/4D4GVL3_N93G, 4D4CVH2.2/4D4GVL3_N93G, 4D4CVH2/4D4GVL4_N93G, 4D4CVH3/4D4GVL4_N93G, 4D4CVH4/4D4GVL4_N93G, 4D4CVH2.1/4D4GVL4_N93G, 4D4CVH2.2/4D4GVL4_N93G	SEQ ID NO:180	SEQ ID NO:181	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:412
4D4/4D4_N93E, 4D4CVH2/4D4C/GVL1_N93E, 4D4CVH3/4D4C/GVL1_N93E, 4D4CVH4/4D4C/GVL1_N93E, 4D4CVH2.1/4D4C/GVL1_N93E, 4D4CVH2.2/4D4C/GVL1_N93E, 4D4CVH2/4D4CVL2_N93E, 4D4CVH3/4D4CVL2_N93E, 4D4CVH4/4D4CVL2_N93E, 4D4CVH2.1/4D4CVL2_N93E, 4D4CVH2.2/4D4CVL2_N93E, 4D4CVH2/4D4CVL4_N93E, 4D4CVH3/4D4CVL4_N93E, 4D4CVH4/4D4CVL4_N93E, 4D4CVH2.1/4D4CVL4_N93E, 4D4CVH2.2/4D4CVL4_N93E,	SEQ ID NO:180	SEQ ID NO:181	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:413

4D4CVH2/4D4GVL3_N93E, 4D4CVH3/4D4GVL3_N93E, 4D4CVH4/4D4GVL3_N93E, 4D4CVH2.1/4D4GVL3_N93E, 4D4CVH2.2/4D4GVL3_N93E, 4D4CVH2/4D4GVL4_N93E, 4D4CVH3/4D4GVL4_N93E, 4D4CVH4/4D4GVL4_N93E, 4D4CVH2.1/4D4GVL4_N93E, 4D4CVH2.2/4D4GVL4_N93E						
4D4/4D4_N93L, 4D4CVH2/4D4C/GVL1_N93L, 4D4CVH3/4D4C/GVL1_N93L, 4D4CVH4/4D4C/GVL1_N93L, 4D4CVH2.1/4D4C/GVL1_N93L, 4D4CVH2.2/4D4C/GVL1_N93L, 4D4CVH2/4D4CVL2_N93L, 4D4CVH3/4D4CVL2_N93L, 4D4CVH4/4D4CVL2_N93L, 4D4CVH2.1/4D4CVL2_N93L, 4D4CVH2.2/4D4CVL2_N93L, 4D4CVH2/4D4CVL4_N93L, 4D4CVH3/4D4CVL4_N93L, 4D4CVH4/4D4CVL4_N93L, 4D4CVH2.1/4D4CVL4_N93L, 4D4CVH2.2/4D4CVL4_N93L, 4D4CVH2/4D4GVL3_N93L, 4D4CVH3/4D4GVL3_N93L, 4D4CVH4/4D4GVL3_N93L, 4D4CVH2.1/4D4GVL3_N93L, 4D4CVH2.2/4D4GVL3_N93L, 4D4CVH2/4D4GVL4_N93L, 4D4CVH3/4D4GVL4_N93L, 4D4CVH4/4D4GVL4_N93L, 4D4CVH2.1/4D4GVL4_N93L, 4D4CVH2.2/4D4GVL4_N93L	SEQ ID NO:180	SEQ ID NO:181	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:414
4D4/4D4_N93Q, 4D4CVH2/4D4C/GVL1_N93Q, 4D4CVH3/4D4C/GVL1_N93Q, 4D4CVH4/4D4C/GVL1_N93Q, 4D4CVH2.1/4D4C/GVL1_N93Q, 4D4CVH2.2/4D4C/GVL1_N93Q, 4D4CVH2/4D4CVL2_N93Q, 4D4CVH3/4D4CVL2_N93Q, 4D4CVH4/4D4CVL2_N93Q, 4D4CVH2.1/4D4CVL2_N93Q, 4D4CVH2.2/4D4CVL2_N93Q, 4D4CVH2/4D4CVL4_N93Q, 4D4CVH3/4D4CVL4_N93Q, 4D4CVH4/4D4CVL4_N93Q, 4D4CVH2.1/4D4CVL4_N93Q, 4D4CVH2.2/4D4CVL4_N93Q, 4D4CVH2/4D4GVL3_N93Q, 4D4CVH3/4D4GVL3_N93Q, 4D4CVH4/4D4GVL3_N93Q, 4D4CVH2.1/4D4GVL3_N93Q, 4D4CVH2.2/4D4GVL3_N93Q, 4D4CVH2/4D4GVL4_N93Q, 4D4CVH3/4D4GVL4_N93Q, 4D4CVH4/4D4GVL4_N93Q, 4D4CVH2.1/4D4GVL4_N93Q, 4D4CVH2.2/4D4GVL4_N93Q	SEQ ID NO:180	SEQ ID NO:181	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:415
4D4/4D4_G94A, 4D4CVH2/4D4C/GVL1_G94A, 4D4CVH3/4D4C/GVL1_G94A, 4D4CVH4/4D4C/GVL1_G94A, 4D4CVH2.1/4D4C/GVL1_G94A, 4D4CVH2.2/4D4C/GVL1_G94A, 4D4CVH2/4D4CVL2_G94A, 4D4CVH3/4D4CVL2_G94A, 4D4CVH4/4D4CVL2_G94A, 4D4CVH2.1/4D4CVL2_G94A, 4D4CVH2.2/4D4CVL2_G94A, 4D4CVH2/4D4CVL4_G94A, 4D4CVH3/4D4CVL4_G94A,	SEQ ID NO:180	SEQ ID NO:181	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:416

4D4CVH4/4D4CVL4_G94A, 4D4CVH2.1/4D4CVL4_G94A, 4D4CVH2.2/4D4CVL4_G94A, 4D4CVH2/4D4GVL3_G94A, 4D4CVH3/4D4GVL3_G94A, 4D4CVH4/4D4GVL3_G94A, 4D4CVH2.1/4D4GVL3_G94A, 4D4CVH2.2/4D4GVL3_G94A, 4D4CVH2/4D4GVL4_G94A, 4D4CVH3/4D4GVL4_G94A, 4D4CVH4/4D4GVL4_G94A, 4D4CVH2.1/4D4GVL4_G94A, 4D4CVH2.2/4D4GVL4_G94A						
4D4_D53G/4D4, 4D4CVH2_D53G/4D4C/GVL1, 4D4CVH2_D53G/4D4CVL2, 4D4CVH2_D53G/4D4CVL4, 4D4CVH2_D53G/4D4GVL3, 4D4CVH2_D53G/4D4GVL4, 4D4CVH3_D53G/4D4C/GVL1, 4D4CVH3_D53G/4D4CVL2, 4D4CVH3_D53G/4D4CVL4, 4D4CVH3_D53G/4D4GVL3, 4D4CVH3_D53G/4D4GVL4 4D4CVH4_D53G/4D4C/GVL1, 4D4CVH4_D53G/4D4CVL2, 4D4CVH4_D53G/4D4CVL4, 4D4CVH4_D53G/4D4GVL3, 4D4CVH4_D53G/4D4GVL4, 4D4CVH2.1_D53G/4D4C/GVL1, 4D4CVH2.1_D53G/4D4CVL2, 4D4CVH2.1_D53G/4D4CVL4, 4D4CVH2.1_D53G/4D4GVL3, 4D4CVH2.1_D53G/4D4GVL4, 4D4CVH2.2_D53G/4D4C/GVL1, 4D4CVH2.2_D53G/4D4CVL2, 4D4CVH2.2_D53G/4D4CVL4, 4D4CVH2.2_D53G/4D4GVL3, 4D4CVH2.2_D53G/4D4GVL4	SEQ ID NO:180	SEQ ID NO:375	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:190
4D4_D53E/4D4, 4D4CVH2_D53E/4D4C/GVL1, 4D4CVH2_D53E/4D4CVL2, 4D4CVH2_D53E/4D4CVL4, 4D4CVH2_D53E/4D4GVL3, 4D4CVH2_D53E/4D4GVL4, 4D4CVH3_D53E/4D4C/GVL1, 4D4CVH3_D53E/4D4CVL2, 4D4CVH3_D53E/4D4CVL4, 4D4CVH3_D53E/4D4GVL3, 4D4CVH3_D53E/4D4GVL4 4D4CVH4_D53E/4D4C/GVL1, 4D4CVH4_D53E/4D4CVL2, 4D4CVH4_D53E/4D4CVL4, 4D4CVH4_D53E/4D4GVL3, 4D4CVH4_D53E/4D4GVL4, 4D4CVH2.1_D53E/4D4C/GVL1, 4D4CVH2.1_D53E/4D4CVL2, 4D4CVH2.1_D53E/4D4CVL4, 4D4CVH2.1_D53E/4D4GVL3, 4D4CVH2.1_D53E/4D4GVL4, 4D4CVH2.2_D53E/4D4C/GVL1, 4D4CVH2.2_D53E/4D4CVL2, 4D4CVH2.2_D53E/4D4CVL4, 4D4CVH2.2_D53E/4D4GVL3, 4D4CVH2.2_D53E/4D4GVL4	SEQ ID NO:180	SEQ ID NO:376	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:190
4D4_D53Q/4D4, 4D4CVH2_D53Q/4D4C/GVL1, 4D4CVH2_D53Q/4D4CVL2, 4D4CVH2_D53Q/4D4CVL4, 4D4CVH2_D53Q/4D4GVL3, 4D4CVH2_D53Q/4D4GVL4, 4D4CVH3_D53Q/4D4C/GVL1, 4D4CVH3_D53Q/4D4CVL2, 4D4CVH3_D53Q/4D4CVL4,	SEQ ID NO:180	SEQ ID NO:377	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:190

4D4CVH3_D53Q/4D4GVL3, 4D4CVH3_D53Q/4D4GVL4 4D4CVH4_D53Q/4D4C/GVL1, 4D4CVH4_D53Q/4D4CVL2, 4D4CVH4_D53Q/4D4CVL4, 4D4CVH4_D53Q/4D4GVL3, 4D4CVH4_D53Q/4D4GVL4, 4D4CVH2.1_D53Q/4D4C/GVL1, 4D4CVH2.1_D53Q/4D4CVL2, 4D4CVH2.1_D53Q/4D4CVL4, 4D4CVH2.1_D53Q/4D4GVL3, 4D4CVH2.1_D53Q/4D4GVL4, 4D4CVH2.2_D53Q/4D4C/GVL1, 4D4CVH2.2_D53Q/4D4CVL2, 4D4CVH2.2_D53Q/4D4CVL4, 4D4CVH2.2_D53Q/4D4GVL3, 4D4CVH2.2_D53Q/4D4GVL4						
4D4_D53L/4D4, 4D4CVH2_D53L/4D4C/GVL1, 4D4CVH2_D53L/4D4CVL2, 4D4CVH2_D53L/4D4CVL4, 4D4CVH2_D53L/4D4GVL3, 4D4CVH2_D53L/4D4GVL4, 4D4CVH3_D53L/4D4C/GVL1, 4D4CVH3_D53L/4D4CVL2, 4D4CVH3_D53L/4D4CVL4, 4D4CVH3_D53L/4D4GVL3, 4D4CVH3_D53L/4D4GVL4 4D4CVH4_D53L/4D4C/GVL1, 4D4CVH4_D53L/4D4CVL2, 4D4CVH4_D53L/4D4CVL4, 4D4CVH4_D53L/4D4GVL3, 4D4CVH4_D53L/4D4GVL4, 4D4CVH2.1_D53L/4D4C/GVL1, 4D4CVH2.1_D53L/4D4CVL2, 4D4CVH2.1_D53L/4D4CVL4, 4D4CVH2.1_D53L/4D4GVL3, 4D4CVH2.1_D53L/4D4GVL4, 4D4CVH2.2_D53L/4D4C/GVL1, 4D4CVH2.2_D53L/4D4CVL2, 4D4CVH2.2_D53L/4D4CVL4, 4D4CVH2.2_D53L/4D4GVL3, 4D4CVH2.2_D53L/4D4GVL4	SEQ ID NO:180	SEQ ID NO:378	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:190
4D4_G54A/4D4, 4D4CVH2_G54A/4D4C/GVL1, 4D4CVH2_G54A/4D4CVL2, 4D4CVH2_G54A/4D4CVL4, 4D4CVH2_G54A/4D4GVL3, 4D4CVH2_G54A/4D4GVL4, 4D4CVH3_G54A/4D4C/GVL1, 4D4CVH3_G54A/4D4CVL2, 4D4CVH3_G54A/4D4CVL4, 4D4CVH3_G54A/4D4GVL3, 4D4CVH3_G54A/4D4GVL4 4D4CVH4_G54A/4D4C/GVL1, 4D4CVH4_G54A/4D4CVL2, 4D4CVH4_G54A/4D4CVL4, 4D4CVH4_G54A/4D4GVL3, 4D4CVH4_G54A/4D4GVL4, 4D4CVH2.1_G54A/4D4C/GVL1, 4D4CVH2.1_G54A/4D4CVL2, 4D4CVH2.1_G54A/4D4CVL4, 4D4CVH2.1_G54A/4D4GVL3, 4D4CVH2.1_G54A/4D4GVL4, 4D4CVH2.2_G54A/4D4C/GVL1, 4D4CVH2.2_G54A/4D4CVL2, 4D4CVH2.2_G54A/4D4CVL4, 4D4CVH2.2_G54A/4D4GVL3, 4D4CVH2.2_G54A/4D4GVL4	SEQ ID NO:180	SEQ ID NO:379	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:190
4D4_D53G/4D4_N93G, 4D4CVH2_D53G/4D4C/GVL1_N93G, 4D4CVH2_D53G/4D4CVL2_N93G, 4D4CVH2_D53G/4D4CVL4_N93G, 4D4CVH2_D53G/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL4_N93G,	SEQ ID NO:180	SEQ ID NO:375	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:412

4D4CVH3_D53G/4D4C/GVL1_N93G, 4D4CVH3_D53G/4D4CVL2_N93G, 4D4CVH3_D53G/4D4CVL4_N93G, 4D4CVH3_D53G/4D4GVL3_N93G, 4D4CVH3_D53G/4D4GVL4_N93G, 4D4CVH4_D53G/4D4C/GVL1_N93G, 4D4CVH4_D53G/4D4CVL2_N93G, 4D4CVH4_D53G/4D4CVL4_N93G, 4D4CVH4_D53G/4D4GVL3_N93G, 4D4CVH4_D53G/4D4GVL4_N93G, 4D4CVH2.1_D53G/4D4C/GVL1_N93G, 4D4CVH2.1_D53G/4D4CVL2_N93G, 4D4CVH2.1_D53G/4D4CVL4_N93G, 4D4CVH2.1_D53G/4D4GVL3_N93G, 4D4CVH2.1_D53G/4D4GVL4_N93G, 4D4CVH2.2_D53G/4D4C/GVL1_N93G, 4D4CVH2.2_D53G/4D4CVL2_N93G, 4D4CVH2.2_D53G/4D4CVL4_N93G, 4D4CVH2.2_D53G/4D4GVL3_N93G, 4D4CVH2.2_D53G/4D4GVL4_N93G,						
4D4_D53E/4D4_N93G, 4D4CVH2_D53E/4D4C/GVL1_N93G, 4D4CVH2_D53E/4D4CVL2_N93G, 4D4CVH2_D53E/4D4CVL4_N93G, 4D4CVH2_D53E/4D4GVL3_N93G, 4D4CVH2_D53E/4D4GVL4_N93G, 4D4CVH3_D53E/4D4C/GVL1_N93G, 4D4CVH3_D53E/4D4CVL2_N93G, 4D4CVH3_D53E/4D4CVL4_N93G, 4D4CVH3_D53E/4D4GVL3_N93G, 4D4CVH3_D53E/4D4GVL4_N93G, 4D4CVH4_D53E/4D4C/GVL1_N93G, 4D4CVH4_D53E/4D4CVL2_N93G, 4D4CVH4_D53E/4D4CVL4_N93G, 4D4CVH4_D53E/4D4GVL3_N93G, 4D4CVH4_D53E/4D4GVL4_N93G, 4D4CVH2.1_D53E/4D4C/GVL1_N93G, 4D4CVH2.1_D53E/4D4CVL2_N93G, 4D4CVH2.1_D53E/4D4CVL4_N93G, 4D4CVH2.1_D53E/4D4GVL3_N93G, 4D4CVH2.1_D53E/4D4GVL4_N93G, 4D4CVH2.2_D53E/4D4C/GVL1_N93G, 4D4CVH2.2_D53E/4D4CVL2_N93G, 4D4CVH2.2_D53E/4D4CVL4_N93G, 4D4CVH2.2_D53E/4D4GVL3_N93G, 4D4CVH2.2_D53E/4D4GVL4_N93G,	SEQ ID NO:180	SEQ ID NO:376	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:412
4D4_D53Q/4D4_N93G, 4D4CVH2_D53Q/4D4C/GVL1_N93G, 4D4CVH2_D53Q/4D4CVL2_N93G, 4D4CVH2_D53Q/4D4CVL4_N93G, 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53Q/4D4GVL4_N93G, 4D4CVH3_D53Q/4D4C/GVL1_N93G, 4D4CVH3_D53Q/4D4CVL2_N93G, 4D4CVH3_D53Q/4D4CVL4_N93G, 4D4CVH3_D53Q/4D4GVL3_N93G, 4D4CVH3_D53Q/4D4GVL4_N93G, 4D4CVH4_D53Q/4D4C/GVL1_N93G, 4D4CVH4_D53Q/4D4CVL2_N93G, 4D4CVH4_D53Q/4D4CVL4_N93G, 4D4CVH4_D53Q/4D4GVL3_N93G, 4D4CVH4_D53Q/4D4GVL4_N93G, 4D4CVH2.1_D53Q/4D4C/GVL1_N93G, 4D4CVH2.1_D53Q/4D4CVL2_N93G, 4D4CVH2.1_D53Q/4D4CVL4_N93G, 4D4CVH2.1_D53Q/4D4GVL3_N93G, 4D4CVH2.1_D53Q/4D4GVL4_N93G, 4D4CVH2.2_D53Q/4D4C/GVL1_N93G, 4D4CVH2.2_D53Q/4D4CVL2_N93G, 4D4CVH2.2_D53Q/4D4CVL4_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL4_N93G,	SEQ ID NO:180	SEQ ID NO:377	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:412
4D4_D53L/4D4_N93G, 4D4CVH2_D53L/4D4C/GVL1_N93G,	SEQ ID NO:180	SEQ ID NO:378	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:412

4D4CVH2_D53L/4D4CVL2_N93G, 4D4CVH2_D53L/4D4CVL4_N93G, 4D4CVH2_D53L/4D4GVL3_N93G, 4D4CVH2_D53L/4D4GVL4_N93G, 4D4CVH3_D53L/4D4C/GVL1_N93G, 4D4CVH3_D53L/4D4CVL2_N93G, 4D4CVH3_D53L/4D4CVL4_N93G, 4D4CVH3_D53L/4D4GVL3_N93G, 4D4CVH3_D53L/4D4GVL4_N93G, 4D4CVH4_D53L/4D4C/GVL1_N93G, 4D4CVH4_D53L/4D4CVL2_N93G, 4D4CVH4_D53L/4D4CVL4_N93G, 4D4CVH4_D53L/4D4GVL3_N93G, 4D4CVH4_D53L/4D4GVL4_N93G, 4D4CVH2.1_D53L/4D4C/GVL1_N93G, 4D4CVH2.1_D53L/4D4CVL2_N93G, 4D4CVH2.1_D53L/4D4CVL4_N93G, 4D4CVH2.1_D53L/4D4GVL3_N93G, 4D4CVH2.1_D53L/4D4GVL4_N93G, 4D4CVH2.2_D53L/4D4C/GVL1_N93G, 4D4CVH2.2_D53L/4D4CVL2_N93G, 4D4CVH2.2_D53L/4D4CVL4_N93G, 4D4CVH2.2_D53L/4D4GVL3_N93G, 4D4CVH2.2_D53L/4D4GVL4_N93G,						
4D4_G54A/4D4_N93G, 4D4CVH2_G54A/4D4C/GVL1_N93G, 4D4CVH2_G54A/4D4CVL2_N93G, 4D4CVH2_G54A/4D4CVL4_N93G, 4D4CVH2_G54A/4D4GVL3_N93G, 4D4CVH2_G54A/4D4GVL4_N93G, 4D4CVH3_G54A/4D4C/GVL1_N93G, 4D4CVH3_G54A/4D4CVL2_N93G, 4D4CVH3_G54A/4D4CVL4_N93G, 4D4CVH3_G54A/4D4GVL3_N93G, 4D4CVH3_G54A/4D4GVL4_N93G, 4D4CVH4_G54A/4D4C/GVL1_N93G, 4D4CVH4_G54A/4D4CVL2_N93G, 4D4CVH4_G54A/4D4CVL4_N93G, 4D4CVH4_G54A/4D4GVL3_N93G, 4D4CVH4_G54A/4D4GVL4_N93G, 4D4CVH2.1_G54A/4D4C/GVL1_N93G, 4D4CVH2.1_G54A/4D4CVL2_N93G, 4D4CVH2.1_G54A/4D4CVL4_N93G, 4D4CVH2.1_G54A/4D4GVL3_N93G, 4D4CVH2.1_G54A/4D4GVL4_N93G, 4D4CVH2.2_G54A/4D4C/GVL1_N93G, 4D4CVH2.2_G54A/4D4CVL2_N93G, 4D4CVH2.2_G54A/4D4CVL4_N93G, 4D4CVH2.2_G54A/4D4GVL3_N93G, 4D4CVH2.2_G54A/4D4GVL4_N93G,	SEQ ID NO:180	SEQ ID NO:379	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:412
4D4_D53G/4D4_N93E, 4D4CVH2_D53G/4D4C/GVL1_N93E, 4D4CVH2_D53G/4D4CVL2_N93E, 4D4CVH2_D53G/4D4CVL4_N93E, 4D4CVH2_D53G/4D4GVL3_N93E, 4D4CVH2_D53G/4D4GVL4_N93E, 4D4CVH3_D53G/4D4C/GVL1_N93E, 4D4CVH3_D53G/4D4CVL2_N93E, 4D4CVH3_D53G/4D4CVL4_N93E, 4D4CVH3_D53G/4D4GVL3_N93E, 4D4CVH3_D53G/4D4GVL4_N93E, 4D4CVH4_D53G/4D4C/GVL1_N93E, 4D4CVH4_D53G/4D4CVL2_N93E, 4D4CVH4_D53G/4D4CVL4_N93E, 4D4CVH4_D53G/4D4GVL3_N93E, 4D4CVH4_D53G/4D4GVL4_N93E, 4D4CVH2.1_D53G/4D4C/GVL1_N93E, 4D4CVH2.1_D53G/4D4CVL2_N93E, 4D4CVH2.1_D53G/4D4CVL4_N93E, 4D4CVH2.1_D53G/4D4GVL3_N93E, 4D4CVH2.1_D53G/4D4GVL4_N93E, 4D4CVH2.2_D53G/4D4C/GVL1_N93E, 4D4CVH2.2_D53G/4D4CVL2_N93E, 4D4CVH2.2_D53G/4D4CVL4_N93E,	SEQ ID NO:180	SEQ ID NO:375	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:413

4D4CVH2.2_D53G/4D4GVL3_N93E, 4D4CVH2.2_D53G/4D4GVL4_N93E,						
4D4_D53E/4D4_N93E, 4D4CVH2_D53E/4D4C/GVL1_N93E, 4D4CVH2_D53E/4D4CVL2_N93E, 4D4CVH2_D53E/4D4CVL4_N93E, 4D4CVH2_D53E/4D4GVL3_N93E, 4D4CVH2_D53E/4D4GVL4_N93E, 4D4CVH3_D53E/4D4C/GVL1_N93E, 4D4CVH3_D53E/4D4CVL2_N93E, 4D4CVH3_D53E/4D4CVL4_N93E, 4D4CVH3_D53E/4D4GVL3_N93E, 4D4CVH3_D53E/4D4GVL4_N93E, 4D4CVH4_D53E/4D4C/GVL1_N93E, 4D4CVH4_D53E/4D4CVL2_N93E, 4D4CVH4_D53E/4D4CVL4_N93E, 4D4CVH4_D53E/4D4GVL3_N93E, 4D4CVH4_D53E/4D4GVL4_N93E, 4D4CVH2.1_D53E/4D4C/GVL1_N93E, 4D4CVH2.1_D53E/4D4CVL2_N93E, 4D4CVH2.1_D53E/4D4CVL4_N93E, 4D4CVH2.1_D53E/4D4GVL3_N93E, 4D4CVH2.1_D53E/4D4GVL4_N93E, 4D4CVH2.2_D53E/4D4C/GVL1_N93E, 4D4CVH2.2_D53E/4D4CVL2_N93E, 4D4CVH2.2_D53E/4D4CVL4_N93E, 4D4CVH2.2_D53E/4D4GVL3_N93E, 4D4CVH2.2_D53E/4D4GVL4_N93E,	SEQ ID NO:180	SEQ ID NO:376	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:413
4D4_D53Q/4D4_N93E, 4D4CVH2_D53Q/4D4C/GVL1_N93E, 4D4CVH2_D53Q/4D4CVL2_N93E, 4D4CVH2_D53Q/4D4CVL4_N93E, 4D4CVH2_D53Q/4D4GVL3_N93E, 4D4CVH2_D53Q/4D4GVL4_N93E, 4D4CVH3_D53Q/4D4C/GVL1_N93E, 4D4CVH3_D53Q/4D4CVL2_N93E, 4D4CVH3_D53Q/4D4CVL4_N93E, 4D4CVH3_D53Q/4D4GVL3_N93E, 4D4CVH3_D53Q/4D4GVL4_N93E, 4D4CVH4_D53Q/4D4C/GVL1_N93E, 4D4CVH4_D53Q/4D4CVL2_N93E, 4D4CVH4_D53Q/4D4CVL4_N93E, 4D4CVH4_D53Q/4D4GVL3_N93E, 4D4CVH4_D53Q/4D4GVL4_N93E, 4D4CVH2.1_D53Q/4D4C/GVL1_N93E, 4D4CVH2.1_D53Q/4D4CVL2_N93E, 4D4CVH2.1_D53Q/4D4CVL4_N93E, 4D4CVH2.1_D53Q/4D4GVL3_N93E, 4D4CVH2.1_D53Q/4D4GVL4_N93E, 4D4CVH2.2_D53Q/4D4C/GVL1_N93E, 4D4CVH2.2_D53Q/4D4CVL2_N93E, 4D4CVH2.2_D53Q/4D4CVL4_N93E, 4D4CVH2.2_D53Q/4D4GVL3_N93E, 4D4CVH2.2_D53Q/4D4GVL4_N93E,	SEQ ID NO:180	SEQ ID NO:377	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:413
4D4_D53L/4D4_N93E, 4D4CVH2_D53L/4D4C/GVL1_N93E, 4D4CVH2_D53L/4D4CVL2_N93E, 4D4CVH2_D53L/4D4CVL4_N93E, 4D4CVH2_D53L/4D4GVL3_N93E, 4D4CVH2_D53L/4D4GVL4_N93E, 4D4CVH3_D53L/4D4C/GVL1_N93E, 4D4CVH3_D53L/4D4CVL2_N93E, 4D4CVH3_D53L/4D4CVL4_N93E, 4D4CVH3_D53L/4D4GVL3_N93E, 4D4CVH3_D53L/4D4GVL4_N93E, 4D4CVH4_D53L/4D4C/GVL1_N93E, 4D4CVH4_D53L/4D4CVL2_N93E, 4D4CVH4_D53L/4D4CVL4_N93E, 4D4CVH4_D53L/4D4GVL3_N93E, 4D4CVH4_D53L/4D4GVL4_N93E, 4D4CVH2.1_D53L/4D4C/GVL1_N93E, 4D4CVH2.1_D53L/4D4CVL2_N93E, 4D4CVH2.1_D53L/4D4CVL4_N93E, 4D4CVH2.1_D53L/4D4GVL3_N93E,	SEQ ID NO:180	SEQ ID NO:378	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:413

4D4CVH2.1_D53L/4D4GVL4_N93E, 4D4CVH2.2_D53L/4D4C/GVL1_N93E, 4D4CVH2.2_D53L/4D4CVL2_N93E, 4D4CVH2.2_D53L/4D4CVL4_N93E, 4D4CVH2.2_D53L/4D4GVL3_N93E, 4D4CVH2.2_D53L/4D4GVL4_N93E,						
4D4_G54A/4D4_N93E, 4D4CVH2_G54A/4D4C/GVL1_N93E, 4D4CVH2_G54A/4D4CVL2_N93E, 4D4CVH2_G54A/4D4CVL4_N93E, 4D4CVH2_G54A/4D4GVL3_N93E, 4D4CVH2_G54A/4D4GVL4_N93E, 4D4CVH3_G54A/4D4C/GVL1_N93E, 4D4CVH3_G54A/4D4CVL2_N93E, 4D4CVH3_G54A/4D4CVL4_N93E, 4D4CVH3_G54A/4D4GVL3_N93E, 4D4CVH3_G54A/4D4GVL4_N93E, 4D4CVH4_G54A/4D4C/GVL1_N93E, 4D4CVH4_G54A/4D4CVL2_N93E, 4D4CVH4_G54A/4D4CVL4_N93E, 4D4CVH4_G54A/4D4GVL3_N93E, 4D4CVH4_G54A/4D4GVL4_N93E, 4D4CVH2.1_G54A/4D4C/GVL1_N93E, 4D4CVH2.1_G54A/4D4CVL2_N93E, 4D4CVH2.1_G54A/4D4CVL4_N93E, 4D4CVH2.1_G54A/4D4GVL3_N93E, 4D4CVH2.1_G54A/4D4GVL4_N93E, 4D4CVH2.2_G54A/4D4C/GVL1_N93E, 4D4CVH2.2_G54A/4D4CVL2_N93E, 4D4CVH2.2_G54A/4D4CVL4_N93E, 4D4CVH2.2_G54A/4D4GVL3_N93E, 4D4CVH2.2_G54A/4D4GVL4_N93E,	SEQ ID NO:180	SEQ ID NO:379	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:413
4D4_D53G/4D4_N93L, 4D4CVH2_D53G/4D4C/GVL1_N93L, 4D4CVH2_D53G/4D4CVL2_N93L, 4D4CVH2_D53G/4D4CVL4_N93L, 4D4CVH2_D53G/4D4GVL3_N93L, 4D4CVH2_D53G/4D4GVL4_N93L, 4D4CVH3_D53G/4D4C/GVL1_N93L, 4D4CVH3_D53G/4D4CVL2_N93L, 4D4CVH3_D53G/4D4CVL4_N93L, 4D4CVH3_D53G/4D4GVL3_N93L, 4D4CVH3_D53G/4D4GVL4_N93L, 4D4CVH4_D53G/4D4C/GVL1_N93L, 4D4CVH4_D53G/4D4CVL2_N93L, 4D4CVH4_D53G/4D4CVL4_N93L, 4D4CVH4_D53G/4D4GVL3_N93L, 4D4CVH4_D53G/4D4GVL4_N93L, 4D4CVH2.1_D53G/4D4C/GVL1_N93L, 4D4CVH2.1_D53G/4D4CVL2_N93L, 4D4CVH2.1_D53G/4D4CVL4_N93L, 4D4CVH2.1_D53G/4D4GVL3_N93L, 4D4CVH2.1_D53G/4D4GVL4_N93L, 4D4CVH2.2_D53G/4D4C/GVL1_N93L, 4D4CVH2.2_D53G/4D4CVL2_N93L, 4D4CVH2.2_D53G/4D4CVL4_N93L, 4D4CVH2.2_D53G/4D4GVL3_N93L, 4D4CVH2.2_D53G/4D4GVL4_N93L,	SEQ ID NO:180	SEQ ID NO:375	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:414
4D4_D53E/4D4_N93L, 4D4CVH2_D53E/4D4C/GVL1_N93L, 4D4CVH2_D53E/4D4CVL2_N93L, 4D4CVH2_D53E/4D4CVL4_N93L, 4D4CVH2_D53E/4D4GVL3_N93L, 4D4CVH2_D53E/4D4GVL4_N93L, 4D4CVH3_D53E/4D4C/GVL1_N93L, 4D4CVH3_D53E/4D4CVL2_N93L, 4D4CVH3_D53E/4D4CVL4_N93L, 4D4CVH3_D53E/4D4GVL3_N93L, 4D4CVH3_D53E/4D4GVL4_N93L, 4D4CVH4_D53E/4D4C/GVL1_N93L, 4D4CVH4_D53E/4D4CVL2_N93L, 4D4CVH4_D53E/4D4CVL4_N93L, 4D4CVH4_D53E/4D4GVL3_N93L, 4D4CVH4_D53E/4D4GVL4_N93L,	SEQ ID NO:180	SEQ ID NO:376	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:414

4D4CVH2.1_D53E/4D4C/GVL1_N93L, 4D4CVH2.1_D53E/4D4CVL2_N93L, 4D4CVH2.1_D53E/4D4CVL4_N93L, 4D4CVH2.1_D53E/4D4GVL3_N93L, 4D4CVH2.1_D53E/4D4GVL4_N93L, 4D4CVH2.2_D53E/4D4C/GVL1_N93L, 4D4CVH2.2_D53E/4D4CVL2_N93L, 4D4CVH2.2_D53E/4D4CVL4_N93L, 4D4CVH2.2_D53E/4D4GVL3_N93L, 4D4CVH2.2_D53E/4D4GVL4_N93L,						
4D4_D53Q/4D4_N93L, 4D4CVH2_D53Q/4D4C/GVL1_N93L, 4D4CVH2_D53Q/4D4CVL2_N93L, 4D4CVH2_D53Q/4D4CVL4_N93L, 4D4CVH2_D53Q/4D4GVL3_N93L, 4D4CVH2_D53Q/4D4GVL4_N93L, 4D4CVH3_D53Q/4D4C/GVL1_N93L, 4D4CVH3_D53Q/4D4CVL2_N93L, 4D4CVH3_D53Q/4D4CVL4_N93L, 4D4CVH3_D53Q/4D4GVL3_N93L, 4D4CVH3_D53Q/4D4GVL4_N93L, 4D4CVH4_D53Q/4D4C/GVL1_N93L, 4D4CVH4_D53Q/4D4CVL2_N93L, 4D4CVH4_D53Q/4D4CVL4_N93L, 4D4CVH4_D53Q/4D4GVL3_N93L, 4D4CVH4_D53Q/4D4GVL4_N93L, 4D4CVH2.1_D53Q/4D4C/GVL1_N93L, 4D4CVH2.1_D53Q/4D4CVL2_N93L, 4D4CVH2.1_D53Q/4D4CVL4_N93L, 4D4CVH2.1_D53Q/4D4GVL3_N93L, 4D4CVH2.1_D53Q/4D4GVL4_N93L, 4D4CVH2.2_D53Q/4D4C/GVL1_N93L, 4D4CVH2.2_D53Q/4D4CVL2_N93L, 4D4CVH2.2_D53Q/4D4CVL4_N93L, 4D4CVH2.2_D53Q/4D4GVL3_N93L, 4D4CVH2.2_D53Q/4D4GVL4_N93L,	SEQ ID NO:180	SEQ ID NO:377	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:414
4D4_D53L/4D4_N93L, 4D4CVH2_D53L/4D4C/GVL1_N93L, 4D4CVH2_D53L/4D4CVL2_N93L, 4D4CVH2_D53L/4D4CVL4_N93L, 4D4CVH2_D53L/4D4GVL3_N93L, 4D4CVH2_D53L/4D4GVL4_N93L, 4D4CVH3_D53L/4D4C/GVL1_N93L, 4D4CVH3_D53L/4D4CVL2_N93L, 4D4CVH3_D53L/4D4CVL4_N93L, 4D4CVH3_D53L/4D4GVL3_N93L, 4D4CVH3_D53L/4D4GVL4_N93L, 4D4CVH4_D53L/4D4C/GVL1_N93L, 4D4CVH4_D53L/4D4CVL2_N93L, 4D4CVH4_D53L/4D4CVL4_N93L, 4D4CVH4_D53L/4D4GVL3_N93L, 4D4CVH4_D53L/4D4GVL4_N93L, 4D4CVH2.1_D53L/4D4C/GVL1_N93L, 4D4CVH2.1_D53L/4D4CVL2_N93L, 4D4CVH2.1_D53L/4D4CVL4_N93L, 4D4CVH2.1_D53L/4D4GVL3_N93L, 4D4CVH2.1_D53L/4D4GVL4_N93L, 4D4CVH2.2_D53L/4D4C/GVL1_N93L, 4D4CVH2.2_D53L/4D4CVL2_N93L, 4D4CVH2.2_D53L/4D4CVL4_N93L, 4D4CVH2.2_D53L/4D4GVL3_N93L, 4D4CVH2.2_D53L/4D4GVL4_N93L,	SEQ ID NO:180	SEQ ID NO:378	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:414
4D4_G54A/4D4_N93L, 4D4CVH2_G54A/4D4C/GVL1_N93L, 4D4CVH2_G54A/4D4CVL2_N93L, 4D4CVH2_G54A/4D4CVL4_N93L, 4D4CVH2_G54A/4D4GVL3_N93L, 4D4CVH2_G54A/4D4GVL4_N93L, 4D4CVH3_G54A/4D4C/GVL1_N93L, 4D4CVH3_G54A/4D4CVL2_N93L, 4D4CVH3_G54A/4D4CVL4_N93L, 4D4CVH3_G54A/4D4GVL3_N93L, 4D4CVH3_G54A/4D4GVL4_N93L, 4D4CVH4_G54A/4D4C/GVL1_N93L,	SEQ ID NO:180	SEQ ID NO:379	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:414

4D4CVH4_G54A/4D4CVL2_N93L, 4D4CVH4_G54A/4D4CVL4_N93L, 4D4CVH4_G54A/4D4GVL3_N93L, 4D4CVH4_G54A/4D4GVL4_N93L, 4D4CVH2.1_G54A/4D4C/GVL1_N93L, 4D4CVH2.1_G54A/4D4CVL2_N93L, 4D4CVH2.1_G54A/4D4CVL4_N93L, 4D4CVH2.1_G54A/4D4GVL3_N93L, 4D4CVH2.1_G54A/4D4GVL4_N93L, 4D4CVH2.2_G54A/4D4C/GVL1_N93L, 4D4CVH2.2_G54A/4D4CVL2_N93L, 4D4CVH2.2_G54A/4D4CVL4_N93L, 4D4CVH2.2_G54A/4D4GVL3_N93L, 4D4CVH2.2_G54A/4D4GVL4_N93L,						
4D4_D53G/4D4_N93Q, 4D4CVH2_D53G/4D4C/GVL1_N93Q, 4D4CVH2_D53G/4D4CVL2_N93Q, 4D4CVH2_D53G/4D4CVL4_N93Q, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2_D53G/4D4GVL4_N93Q, 4D4CVH3_D53G/4D4C/GVL1_N93Q, 4D4CVH3_D53G/4D4CVL2_N93Q, 4D4CVH3_D53G/4D4CVL4_N93Q, 4D4CVH3_D53G/4D4GVL3_N93Q, 4D4CVH3_D53G/4D4GVL4_N93Q, 4D4CVH4_D53G/4D4C/GVL1_N93Q, 4D4CVH4_D53G/4D4CVL2_N93Q, 4D4CVH4_D53G/4D4CVL4_N93Q, 4D4CVH4_D53G/4D4GVL3_N93Q, 4D4CVH4_D53G/4D4GVL4_N93Q, 4D4CVH2.1_D53G/4D4C/GVL1_N93Q, 4D4CVH2.1_D53G/4D4CVL2_N93Q, 4D4CVH2.1_D53G/4D4CVL4_N93Q, 4D4CVH2.1_D53G/4D4GVL3_N93Q, 4D4CVH2.1_D53G/4D4GVL4_N93Q, 4D4CVH2.2_D53G/4D4C/GVL1_N93Q, 4D4CVH2.2_D53G/4D4CVL2_N93Q, 4D4CVH2.2_D53G/4D4CVL4_N93Q, 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53G/4D4GVL4_N93Q,	SEQ ID NO:180	SEQ ID NO:375	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:415
4D4_D53E/4D4_N93Q, 4D4CVH2_D53E/4D4C/GVL1_N93Q, 4D4CVH2_D53E/4D4CVL2_N93Q, 4D4CVH2_D53E/4D4CVL4_N93Q, 4D4CVH2_D53E/4D4GVL3_N93Q, 4D4CVH2_D53E/4D4GVL4_N93Q, 4D4CVH3_D53E/4D4C/GVL1_N93Q, 4D4CVH3_D53E/4D4CVL2_N93Q, 4D4CVH3_D53E/4D4CVL4_N93Q, 4D4CVH3_D53E/4D4GVL3_N93Q, 4D4CVH3_D53E/4D4GVL4_N93Q, 4D4CVH4_D53E/4D4C/GVL1_N93Q, 4D4CVH4_D53E/4D4CVL2_N93Q, 4D4CVH4_D53E/4D4CVL4_N93Q, 4D4CVH4_D53E/4D4GVL3_N93Q, 4D4CVH4_D53E/4D4GVL4_N93Q, 4D4CVH2.1_D53E/4D4C/GVL1_N93Q, 4D4CVH2.1_D53E/4D4CVL2_N93Q, 4D4CVH2.1_D53E/4D4CVL4_N93Q, 4D4CVH2.1_D53E/4D4GVL3_N93Q, 4D4CVH2.1_D53E/4D4GVL4_N93Q, 4D4CVH2.2_D53E/4D4C/GVL1_N93Q, 4D4CVH2.2_D53E/4D4CVL2_N93Q, 4D4CVH2.2_D53E/4D4CVL4_N93Q, 4D4CVH2.2_D53E/4D4GVL3_N93Q, 4D4CVH2.2_D53E/4D4GVL4_N93Q,	SEQ ID NO:180	SEQ ID NO:376	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:415
4D4_D53Q/4D4_N93Q, 4D4CVH2_D53Q/4D4C/GVL1_N93Q, 4D4CVH2_D53Q/4D4CVL2_N93Q, 4D4CVH2_D53Q/4D4CVL4_N93Q, 4D4CVH2_D53Q/4D4GVL3_N93Q, 4D4CVH2_D53Q/4D4GVL4_N93Q, 4D4CVH3_D53Q/4D4C/GVL1_N93Q, 4D4CVH3_D53Q/4D4CVL2_N93Q,	SEQ ID NO:180	SEQ ID NO:377	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:415

4D4CVH3_D53Q/4D4CVL4_N93Q, 4D4CVH3_D53Q/4D4GVL3_N93Q, 4D4CVH3_D53Q/4D4GVL4_N93Q, 4D4CVH4_D53Q/4D4C/GVL1_N93Q, 4D4CVH4_D53Q/4D4CVL2_N93Q, 4D4CVH4_D53Q/4D4CVL4_N93Q, 4D4CVH4_D53Q/4D4GVL3_N93Q, 4D4CVH4_D53Q/4D4GVL4_N93Q, 4D4CVH2.1_D53Q/4D4C/GVL1_N93Q, 4D4CVH2.1_D53Q/4D4CVL2_N93Q, 4D4CVH2.1_D53Q/4D4CVL4_N93Q, 4D4CVH2.1_D53Q/4D4GVL3_N93Q, 4D4CVH2.1_D53Q/4D4GVL4_N93Q, 4D4CVH2.2_D53Q/4D4C/GVL1_N93Q, 4D4CVH2.2_D53Q/4D4CVL2_N93Q, 4D4CVH2.2_D53Q/4D4CVL4_N93Q, 4D4CVH2.2_D53Q/4D4GVL3_N93Q, 4D4CVH2.2_D53Q/4D4GVL4_N93Q,						
4D4_D53L/4D4_N93Q, 4D4CVH2_D53L/4D4C/GVL1_N93Q, 4D4CVH2_D53L/4D4CVL2_N93Q, 4D4CVH2_D53L/4D4CVL4_N93Q, 4D4CVH2_D53L/4D4GVL3_N93Q, 4D4CVH2_D53L/4D4GVL4_N93Q, 4D4CVH3_D53L/4D4C/GVL1_N93Q, 4D4CVH3_D53L/4D4CVL2_N93Q, 4D4CVH3_D53L/4D4CVL4_N93Q, 4D4CVH3_D53L/4D4GVL3_N93Q, 4D4CVH3_D53L/4D4GVL4_N93Q, 4D4CVH4_D53L/4D4C/GVL1_N93Q, 4D4CVH4_D53L/4D4CVL2_N93Q, 4D4CVH4_D53L/4D4CVL4_N93Q, 4D4CVH4_D53L/4D4GVL3_N93Q, 4D4CVH4_D53L/4D4GVL4_N93Q, 4D4CVH2.1_D53L/4D4C/GVL1_N93Q, 4D4CVH2.1_D53L/4D4CVL2_N93Q, 4D4CVH2.1_D53L/4D4CVL4_N93Q, 4D4CVH2.1_D53L/4D4GVL3_N93Q, 4D4CVH2.1_D53L/4D4GVL4_N93Q, 4D4CVH2.2_D53L/4D4C/GVL1_N93Q, 4D4CVH2.2_D53L/4D4CVL2_N93Q, 4D4CVH2.2_D53L/4D4CVL4_N93Q, 4D4CVH2.2_D53L/4D4GVL3_N93Q, 4D4CVH2.2_D53L/4D4GVL4_N93Q,	SEQ ID NO:180	SEQ ID NO:378	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:415
4D4_G54A/4D4_N93Q, 4D4CVH2_G54A/4D4C/GVL1_N93Q, 4D4CVH2_G54A/4D4CVL2_N93Q, 4D4CVH2_G54A/4D4CVL4_N93Q, 4D4CVH2_G54A/4D4GVL3_N93Q, 4D4CVH2_G54A/4D4GVL4_N93Q, 4D4CVH3_G54A/4D4C/GVL1_N93Q, 4D4CVH3_G54A/4D4CVL2_N93Q, 4D4CVH3_G54A/4D4CVL4_N93Q, 4D4CVH3_G54A/4D4GVL3_N93Q, 4D4CVH3_G54A/4D4GVL4_N93Q, 4D4CVH4_G54A/4D4C/GVL1_N93Q, 4D4CVH4_G54A/4D4CVL2_N93Q, 4D4CVH4_G54A/4D4CVL4_N93Q, 4D4CVH4_G54A/4D4GVL3_N93Q, 4D4CVH4_G54A/4D4GVL4_N93Q, 4D4CVH2.1_G54A/4D4C/GVL1_N93Q, 4D4CVH2.1_G54A/4D4CVL2_N93Q, 4D4CVH2.1_G54A/4D4CVL4_N93Q, 4D4CVH2.1_G54A/4D4GVL3_N93Q, 4D4CVH2.1_G54A/4D4GVL4_N93Q, 4D4CVH2.2_G54A/4D4C/GVL1_N93Q, 4D4CVH2.2_G54A/4D4CVL2_N93Q, 4D4CVH2.2_G54A/4D4CVL4_N93Q, 4D4CVH2.2_G54A/4D4GVL3_N93Q, 4D4CVH2.2_G54A/4D4GVL4_N93Q,	SEQ ID NO:180	SEQ ID NO:379	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:415
4D4_D53G/4D4_G94A, 4D4CVH2_D53G/4D4C/GVL1_G94A, 4D4CVH2_D53G/4D4CVL2_G94A, 4D4CVH2_D53G/4D4CVL4_G94A,	SEQ ID NO:180	SEQ ID NO:375	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:416

4D4CVH2_D53G/4D4GVL3_G94A, 4D4CVH2_D53G/4D4GVL4_G94A, 4D4CVH3_D53G/4D4C/GVL1_G94A, 4D4CVH3_D53G/4D4CVL2_G94A, 4D4CVH3_D53G/4D4CVL4_G94A, 4D4CVH3_D53G/4D4GVL3_G94A, 4D4CVH3_D53G/4D4GVL4_G94A, 4D4CVH4_D53G/4D4C/GVL1_G94A, 4D4CVH4_D53G/4D4CVL2_G94A, 4D4CVH4_D53G/4D4CVL4_G94A, 4D4CVH4_D53G/4D4GVL3_G94A, 4D4CVH4_D53G/4D4GVL4_G94A, 4D4CVH2.1_D53G/4D4C/GVL1_G94A, 4D4CVH2.1_D53G/4D4CVL2_G94A, 4D4CVH2.1_D53G/4D4CVL4_G94A, 4D4CVH2.1_D53G/4D4GVL3_G94A, 4D4CVH2.1_D53G/4D4GVL4_G94A, 4D4CVH2.2_D53G/4D4C/GVL1_G94A, 4D4CVH2.2_D53G/4D4CVL2_G94A, 4D4CVH2.2_D53G/4D4CVL4_G94A, 4D4CVH2.2_D53G/4D4GVL3_G94A, 4D4CVH2.2_D53G/4D4GVL4_G94A,						
4D4_D53E/4D4_G94A, 4D4CVH2_D53E/4D4C/GVL1_G94A, 4D4CVH2_D53E/4D4CVL2_G94A, 4D4CVH2_D53E/4D4CVL4_G94A, 4D4CVH2_D53E/4D4GVL3_G94A, 4D4CVH2_D53E/4D4GVL4_G94A, 4D4CVH3_D53E/4D4C/GVL1_G94A, 4D4CVH3_D53E/4D4CVL2_G94A, 4D4CVH3_D53E/4D4CVL4_G94A, 4D4CVH3_D53E/4D4GVL3_G94A, 4D4CVH3_D53E/4D4GVL4_G94A, 4D4CVH4_D53E/4D4C/GVL1_G94A, 4D4CVH4_D53E/4D4CVL2_G94A, 4D4CVH4_D53E/4D4CVL4_G94A, 4D4CVH4_D53E/4D4GVL3_G94A, 4D4CVH4_D53E/4D4GVL4_G94A, 4D4CVH2.1_D53E/4D4C/GVL1_G94A, 4D4CVH2.1_D53E/4D4CVL2_G94A, 4D4CVH2.1_D53E/4D4CVL4_G94A, 4D4CVH2.1_D53E/4D4GVL3_G94A, 4D4CVH2.1_D53E/4D4GVL4_G94A, 4D4CVH2.2_D53E/4D4C/GVL1_G94A, 4D4CVH2.2_D53E/4D4CVL2_G94A, 4D4CVH2.2_D53E/4D4CVL4_G94A, 4D4CVH2.2_D53E/4D4GVL3_G94A, 4D4CVH2.2_D53E/4D4GVL4_G94A,	SEQ ID NO:180	SEQ ID NO:376	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:416
4D4_D53Q/4D4_G94A, 4D4CVH2_D53Q/4D4C/GVL1_G94A, 4D4CVH2_D53Q/4D4CVL2_G94A, 4D4CVH2_D53Q/4D4CVL4_G94A, 4D4CVH2_D53Q/4D4GVL3_G94A, 4D4CVH2_D53Q/4D4GVL4_G94A, 4D4CVH3_D53Q/4D4C/GVL1_G94A, 4D4CVH3_D53Q/4D4CVL2_G94A, 4D4CVH3_D53Q/4D4CVL4_G94A, 4D4CVH3_D53Q/4D4GVL3_G94A, 4D4CVH3_D53Q/4D4GVL4_G94A, 4D4CVH4_D53Q/4D4C/GVL1_G94A, 4D4CVH4_D53Q/4D4CVL2_G94A, 4D4CVH4_D53Q/4D4CVL4_G94A, 4D4CVH4_D53Q/4D4GVL3_G94A, 4D4CVH4_D53Q/4D4GVL4_G94A, 4D4CVH2.1_D53Q/4D4C/GVL1_G94A, 4D4CVH2.1_D53Q/4D4CVL2_G94A, 4D4CVH2.1_D53Q/4D4CVL4_G94A, 4D4CVH2.1_D53Q/4D4GVL3_G94A, 4D4CVH2.1_D53Q/4D4GVL4_G94A, 4D4CVH2.2_D53Q/4D4C/GVL1_G94A, 4D4CVH2.2_D53Q/4D4CVL2_G94A, 4D4CVH2.2_D53Q/4D4CVL4_G94A, 4D4CVH2.2_D53Q/4D4GVL3_G94A, 4D4CVH2.2_D53Q/4D4GVL4_G94A,	SEQ ID NO:180	SEQ ID NO:377	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:416

4D4_D53L/4D4_G94A, 4D4CVH2_D53L/4D4C/GVL1_G94A, 4D4CVH2_D53L/4D4CVL2_G94A, 4D4CVH2_D53L/4D4CVL4_G94A, 4D4CVH2_D53L/4D4GVL3_G94A, 4D4CVH2_D53L/4D4GVL4_G94A, 4D4CVH3_D53L/4D4C/GVL1_G94A, 4D4CVH3_D53L/4D4CVL2_G94A, 4D4CVH3_D53L/4D4CVL4_G94A, 4D4CVH3_D53L/4D4GVL3_G94A, 4D4CVH3_D53L/4D4GVL4_G94A, 4D4CVH4_D53L/4D4C/GVL1_G94A, 4D4CVH4_D53L/4D4CVL2_G94A, 4D4CVH4_D53L/4D4CVL4_G94A, 4D4CVH4_D53L/4D4GVL3_G94A, 4D4CVH4_D53L/4D4GVL4_G94A, 4D4CVH2.1_D53L/4D4C/GVL1_G94A, 4D4CVH2.1_D53L/4D4CVL2_G94A, 4D4CVH2.1_D53L/4D4CVL4_G94A, 4D4CVH2.1_D53L/4D4GVL3_G94A, 4D4CVH2.1_D53L/4D4GVL4_G94A, 4D4CVH2.2_D53L/4D4C/GVL1_G94A, 4D4CVH2.2_D53L/4D4CVL2_G94A, 4D4CVH2.2_D53L/4D4CVL4_G94A, 4D4CVH2.2_D53L/4D4GVL3_G94A, 4D4CVH2.2_D53L/4D4GVL4_G94A,	SEQ ID NO:180	SEQ ID NO:378	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:416
4D4_G54A/4D4_G94A, 4D4CVH2_G54A/4D4C/GVL1_G94A, 4D4CVH2_G54A/4D4CVL2_G94A, 4D4CVH2_G54A/4D4CVL4_G94A, 4D4CVH2_G54A/4D4GVL3_G94A, 4D4CVH2_G54A/4D4GVL4_G94A, 4D4CVH3_G54A/4D4C/GVL1_G94A, 4D4CVH3_G54A/4D4CVL2_G94A, 4D4CVH3_G54A/4D4CVL4_G94A, 4D4CVH3_G54A/4D4GVL3_G94A, 4D4CVH3_G54A/4D4GVL4_G94A, 4D4CVH4_G54A/4D4C/GVL1_G94A, 4D4CVH4_G54A/4D4CVL2_G94A, 4D4CVH4_G54A/4D4CVL4_G94A, 4D4CVH4_G54A/4D4GVL3_G94A, 4D4CVH4_G54A/4D4GVL4_G94A, 4D4CVH2.1_G54A/4D4C/GVL1_G94A, 4D4CVH2.1_G54A/4D4CVL2_G94A, 4D4CVH2.1_G54A/4D4CVL4_G94A, 4D4CVH2.1_G54A/4D4GVL3_G94A, 4D4CVH2.1_G54A/4D4GVL4_G94A, 4D4CVH2.2_G54A/4D4C/GVL1_G94A, 4D4CVH2.2_G54A/4D4CVL2_G94A, 4D4CVH2.2_G54A/4D4CVL4_G94A, 4D4CVH2.2_G54A/4D4GVL3_G94A, 4D4CVH2.2_G54A/4D4GVL4_G94A,	SEQ ID NO:180	SEQ ID NO:379	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:416
CON4D4P/Hu_D53var_G53var /CON4D4P/Hu_N93var_G94var	SEQ ID NO:180	SEQ ID NO:380	SEQ ID NO:182	SEQ ID NO:188	SEQ ID NO:189	SEQ ID NO:417

Table F

	Column A				Column B			
Antibody	**VH**				**VL**			
	HC-FR1	**HC-FR2**	**HC-FR3**	**HC-FR4**	**LC-FR1**	**LC-FR2**	**LC-FR3**	**LC-FR4**
4D4, 4D4/4D4_N93G, 4D4/4D4_N93E, 4D4/4D4_N93L, 4D4/4D4_N93Q, 4D4/4D4_G94A, 4D4_D53G/4D4, 4D4_D53G/4D4_N93G, 4D4_D53G/4D4_N93E, 4D4_D53G/4D4_N93L, 4D4_D53G/4D4_N93Q, 4D4_D53G/4D4_G94A, 4D4_D53E/4D4, 4D4_D53E/4D4_N93G, 4D4_D53E/4D4_N93E, 4D4_D53E/4D4_N93L, 4D4_D53E/4D4_N93Q, 4D4_D53E/4D4_G94A, 4D4_D53Q/4D4, 4D4_D53Q/4D4_N93G, 4D4_D53Q/4D4_N93E, 4D4_D53Q/4D4_N93L, 4D4_D53Q/4D4_N93Q, 4D4_D53Q/4D4_G94A, 4D4_D53L/4D4, 4D4_D53L/4D4_N93G, 4D4_D53L/4D4_N93E, 4D4_D53L/4D4_N93L, 4D4_D53L/4D4_N93Q, 4D4_D53L/4D4_G94A, 4D4_G54A/4D4, 4D4_G54A/4D4_N93G, 4D4_G54A/4D4_N93E, 4D4_G54A/4D4_N93L, 4D4_G54A/4D4_N93Q, 4D4_G54A/4D4_G94A	SEQ ID NO:183	SEQ ID NO:184	SEQ ID NO:185	SEQ ID NO:186	SEQ ID NO:191	SEQ ID NO:192	SEQ ID NO:193	SEQ ID NO:194
3G9	SEQ ID NO:199	SEQ ID NO:184	SEQ ID NO:200	SEQ ID NO:186	SEQ ID NO:205	SEQ ID NO:206	SEQ ID NO:207	SEQ ID NO:208
4A7/7D8	SEQ ID NO:199	SEQ ID NO:184	SEQ ID NO:211	SEQ ID NO:186	SEQ ID NO:205	SEQ ID NO:213	SEQ ID NO:207	SEQ ID NO:208
8C6	SEQ ID NO:218	SEQ ID NO:219	SEQ ID NO:220	SEQ ID NO:221	SEQ ID NO:226	SEQ ID NO:227	SEQ ID NO:228	SEQ ID NO:208
C03-A7	SEQ ID NO:233	SEQ ID NO:219	SEQ ID NO:234	SEQ ID NO:221	SEQ ID NO:191	SEQ ID NO:237	SEQ ID NO:238	SEQ ID NO:239
CON'4'9'7/8	SEQ ID NO:246	SEQ ID NO:184	SEQ ID NO:247	SEQ ID NO:186	SEQ ID NO:248	SEQ ID NO:249	SEQ ID NO:250	SEQ ID NO:251
4D4CVH2/4D4C/GVL1, 4D4CVH2/4D4C/GVL1_N93G, 4D4CVH2/4D4C/GVL1_N93E, 4D4CVH2/4D4C/GVL1_N93L, 4D4CVH2/4D4C/GVL1_N93Q, 4D4CVH2/4D4C/GVL1_G94A, 4D4CVH2_D53G/4D4C/GVL1, 4D4CVH2_D53G/4D4C/GVL1_N93G, 4D4CVH2_D53G/4D4C/GVL1_N93E, 4D4CVH2_D53G/4D4C/GVL1_N93L, 4D4CVH2_D53G/4D4C/GVL1_N93Q, 4D4CVH2_D53G/4D4C/GVL1_G94A, 4D4CVH2_D53E/4D4C/GVL1, 4D4CVH2_D53E/4D4C/GVL1_N93G, 4D4CVH2_D53E/4D4C/GVL1_N93E, 4D4CVH2_D53E/4D4C/GVL1_N93L, 4D4CVH2_D53E/4D4C/GVL1_N93Q, 4D4CVH2_D53E/4D4C/GVL1_G94A, 4D4CVH2_D53Q/4D4C/GVL1, 4D4CVH2_D53Q/4D4C/GVL1_N93G, 4D4CVH2_D53Q/4D4C/GVL1_N93E, 4D4CVH2_D53Q/4D4C/GVL1_N93L, 4D4CVH2_D53Q/4D4C/GVL1_N93Q, 4D4CVH2_D53Q/4D4C/GVL1_G94A,	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:267	SEQ ID NO:192	SEQ ID NO:193	SEQ ID NO:268

4D4CVH2_D53L/4D4C/GVL1, 4D4CVH2_D53L/4D4C/GVL1_N93G, 4D4CVH2_D53L/4D4C/GVL1_N93E, 4D4CVH2_D53L/4D4C/GVL1_N93L, 4D4CVH2_D53L/4D4C/GVL1_N93Q, 4D4CVH2_D53L/4D4C/GVL1_G94A, 4D4CVH2_G54A/4D4C/GVL1, 4D4CVH2_G54A/4D4C/GVL1_N93G, 4D4CVH2_G54A/4D4C/GVL1_N93E, 4D4CVH2_G54A/4D4C/GVL1_N93L, 4D4CVH2_G54A/4D4C/GVL1_N93Q, 4D4CVH2_G54A/4D4C/GVL1_G94A								
4D4CVH2/4D4CVL2, 4D4CVH2/4D4CVL2_N93G, 4D4CVH2/4D4CVL2_N93E, 4D4CVH2/4D4CVL2_N93L, 4D4CVH2/4D4CVL2_N93Q, 4D4CVH2/4D4CVL2_G94A, 4D4CVH2_D53G/4D4CVL2 4D4CVH2_D53G/4D4CVL2_N93G, 4D4CVH2_D53G/4D4CVL2_N93E, 4D4CVH2_D53G/4D4CVL2_N93L, 4D4CVH2_D53G/4D4CVL2_N93Q, 4D4CVH2_D53G/4D4CVL2_G94A, 4D4CVH2_D53E/4D4CVL2, 4D4CVH2_D53E/4D4CVL2_N93G, 4D4CVH2_D53E/4D4CVL2_N93E, 4D4CVH2_D53E/4D4CVL2_N93L, 4D4CVH2_D53E/4D4CVL2_N93Q, 4D4CVH2_D53E/4D4CVL2_G94A, 4D4CVH2_D53Q/4D4CVL2, 4D4CVH2_D53Q/4D4CVL2_N93G, 4D4CVH2_D53Q/4D4CVL2_N93E, 4D4CVH2_D53Q/4D4CVL2_N93L, 4D4CVH2_D53Q/4D4CVL2_N93Q, 4D4CVH2_D53Q/4D4CVL2_G94A, 4D4CVH2_D53L/4D4CVL2 4D4CVH2_D53L/4D4CVL2_N93G, 4D4CVH2_D53L/4D4CVL2_N93E, 4D4CVH2_D53L/4D4CVL2_N93L, 4D4CVH2_D53L/4D4CVL2_N93Q, 4D4CVH2_D53L/4D4CVL2_G94A, 4D4CVH2_G54A/4D4CVL2 4D4CVH2_G54A/4D4CVL2_N93G, 4D4CVH2_G54A/4D4CVL2_N93E, 4D4CVH2_G54A/4D4CVL2_N93L, 4D4CVH2_G54A/4D4CVL2_N93Q, 4D4CVH2_G54A/4D4CVL2_G94A	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:270	SEQ ID NO:271	SEQ ID NO:193	SEQ ID NO:268
4D4CVH2/4D4CVL4, 4D4CVH2/4D4CVL4_N93G, 4D4CVH2/4D4CVL4_N93E, 4D4CVH2/4D4CVL4_N93L, 4D4CVH2/4D4CVL4_N93Q, 4D4CVH2/4D4CVL4_G94A, 4D4CVH2_D53G/4D4CVL4, 4D4CVH2_D53G/4D4CVL4_N93G, 4D4CVH2_D53G/4D4CVL4_N93E, 4D4CVH2_D53G/4D4CVL4_N93L, 4D4CVH2_D53G/4D4CVL4_N93Q, 4D4CVH2_D53G/4D4CVL4_G94A, 4D4CVH2_D53E/4D4CVL4, 4D4CVH2_D53E/4D4CVL4_N93G, 4D4CVH2_D53E/4D4CVL4_N93E, 4D4CVH2_D53E/4D4CVL4_N93L, 4D4CVH2_D53E/4D4CVL4_N93Q, 4D4CVH2_D53E/4D4CVL4_G94A, 4D4CVH2_D53Q/4D4CVL4 4D4CVH2_D53Q/4D4CVL4_N93G, 4D4CVH2_D53Q/4D4CVL4_N93E, 4D4CVH2_D53Q/4D4CVL4_N93L, 4D4CVH2_D53Q/4D4CVL4_N93Q, 4D4CVH2_D53Q/4D4CVL4_G94A, 4D4CVH2_D53L/4D4CVL4, 4D4CVH2_D53L/4D4CVL4_N93G,	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:272	SEQ ID NO:271	SEQ ID NO:274	SEQ ID NO:268

4D4CVH2_D53L/4D4CVL4_N93E, 4D4CVH2_D53L/4D4CVL4_N93L, 4D4CVH2_D53L/4D4CVL4_N93Q, 4D4CVH2_D53L/4D4CVL4_G94A, 4D4CVH2_G54A/4D4CVL4, 4D4CVH2_G54A/4D4CVL4_N93G, 4D4CVH2_G54A/4D4CVL4_N93E, 4D4CVH2_G54A/4D4CVL4_N93L, 4D4CVH2_G54A/4D4CVL4_N93Q, 4D4CVH2_G54A/4D4CVL4_G94A								
4D4CVH2/4D4GVL3, 4D4CVH2/4D4GVL3_N93G, 4D4CVH2/4D4GVL3_N93E, 4D4CVH2/4D4GVL3_N93L, 4D4CVH2/4D4GVL3_N93Q, 4D4CVH2/4D4GVL3_G94A, 4D4CVH2_D53G/4D4GVL3, 4D4CVH2_D53G/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93E, 4D4CVH2_D53G/4D4GVL3_N93L, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2_D53G/4D4GVL3_G94A, 4D4CVH2_D53E/4D4GVL3, 4D4CVH2_D53E/4D4GVL3_N93G, 4D4CVH2_D53E/4D4GVL3_N93E, 4D4CVH2_D53E/4D4GVL3_N93L, 4D4CVH2_D53E/4D4GVL3_N93Q, 4D4CVH2_D53E/4D4GVL3_G94A, 4D4CVH2_D53Q/4D4GVL3, 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53Q/4D4GVL3_N93E, 4D4CVH2_D53Q/4D4GVL3_N93L, 4D4CVH2_D53Q/4D4GVL3_N93Q, 4D4CVH2_D53Q/4D4GVL3_G94A, 4D4CVH2_D53L/4D4GVL3, 4D4CVH2_D53L/4D4GVL3_N93G, 4D4CVH2_D53L/4D4GVL3_N93E, 4D4CVH2_D53L/4D4GVL3_N93L, 4D4CVH2_D53L/4D4GVL3_N93Q, 4D4CVH2_D53L/4D4GVL3_G94A, 4D4CVH2_G54A/4D4GVL3, 4D4CVH2_G54A/4D4GVL3_N93G, 4D4CVH2_G54A/4D4GVL3_N93E, 4D4CVH2_G54A/4D4GVL3_N93L, 4D4CVH2_G54A/4D4GVL3_N93Q, 4D4CVH2_G54A/4D4GVL3_G94A	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:275	SEQ ID NO:271	SEQ ID NO:277	SEQ ID NO:268
4D4CVH2/4D4GVL4, 4D4CVH2/4D4GVL4_N93G, 4D4CVH2/4D4GVL4_N93E, 4D4CVH2/4D4GVL4_N93L, 4D4CVH2/4D4GVL4_N93Q, 4D4CVH2/4D4GVL4_G94A, 4D4CVH2_D53G/4D4GVL4, 4D4CVH2_D53G/4D4GVL4_N93G, 4D4CVH2_D53G/4D4GVL4_N93E, 4D4CVH2_D53G/4D4GVL4_N93L, 4D4CVH2_D53G/4D4GVL4_N93Q, 4D4CVH2_D53G/4D4GVL4_G94A, 4D4CVH2_D53E/4D4GVL4, 4D4CVH2_D53E/4D4GVL4_N93G, 4D4CVH2_D53E/4D4GVL4_N93E, 4D4CVH2_D53E/4D4GVL4_N93L, 4D4CVH2_D53E/4D4GVL4_N93Q, 4D4CVH2_D53E/4D4GVL4_G94A, 4D4CVH2_D53Q/4D4GVL4 4D4CVH2_D53Q/4D4GVL4_N93G, 4D4CVH2_D53Q/4D4GVL4_N93E, 4D4CVH2_D53Q/4D4GVL4_N93L, 4D4CVH2_D53Q/4D4GVL4_N93Q, 4D4CVH2_D53Q/4D4GVL4_G94A, 4D4CVH2_D53L/4D4GVL4, 4D4CVH2_D53L/4D4GVL4_N93G, 4D4CVH2_D53L/4D4GVL4_N93E, 4D4CVH2_D53L/4D4GVL4_N93L,	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:279	SEQ ID NO:271	SEQ ID NO:280	SEQ ID NO:268

4D4CVH2_D53L/4D4GVL4_N93Q, 4D4CVH2_D53L/4D4GVL4_G94A 4D4CVH2_G54A/4D4GVL4, 4D4CVH2_G54A/4D4GVL4_N93G, 4D4CVH2_G54A/4D4GVL4_N93E, 4D4CVH2_G54A/4D4GVL4_N93L, 4D4CVH2_G54A/4D4GVL4_N93Q, 4D4CVH2_G54A/4D4GVL4_G94A								
4D4CVH3/4D4C/GVL1, 4D4CVH3/4D4C/GVL1_N93G, 4D4CVH3/4D4C/GVL1_N93E, 4D4CVH3/4D4C/GVL1_N93L, 4D4CVH3/4D4C/GVL1_N93Q, 4D4CVH3/4D4C/GVL1_G94A, 4D4CVH3_D53G/4D4C/GVL1, 4D4CVH3_D53G/4D4C/GVL1_N93G, 4D4CVH3_D53G/4D4C/GVL1_N93E, 4D4CVH3_D53G/4D4C/GVL1_N93L, 4D4CVH3_D53G/4D4C/GVL1_N93Q, 4D4CVH3_D53G/4D4C/GVL1_G94A, 4D4CVH3_D53E/4D4C/GVL1, 4D4CVH3_D53E/4D4C/GVL1_N93G, 4D4CVH3_D53E/4D4C/GVL1_N93E, 4D4CVH3_D53E/4D4C/GVL1_N93L, 4D4CVH3_D53E/4D4C/GVL1_N93Q, 4D4CVH3_D53E/4D4C/GVL1_G94A, 4D4CVH3_D53Q/4D4C/GVL1, 4D4CVH3_D53Q/4D4C/GVL1_N93G, 4D4CVH3_D53Q/4D4C/GVL1_N93E, 4D4CVH3_D53Q/4D4C/GVL1_N93L, 4D4CVH3_D53Q/4D4C/GVL1_N93Q, 4D4CVH3_D53Q/4D4C/GVL1_G94A, 4D4CVH3_D53L/4D4C/GVL1, 4D4CVH3_D53L/4D4C/GVL1_N93G, 4D4CVH3_D53L/4D4C/GVL1_N93E, 4D4CVH3_D53L/4D4C/GVL1_N93L, 4D4CVH3_D53L/4D4C/GVL1_N93Q, 4D4CVH3_D53L/4D4C/GVL1_G94A, 4D4CVH3_G54A/4D4C/GVL1, 4D4CVH3_G54A/4D4C/GVL1_N93G, 4D4CVH3_G54A/4D4C/GVL1_N93E, 4D4CVH3_G54A/4D4C/GVL1_N93L, 4D4CVH3_G54A/4D4C/GVL1_N93Q, 4D4CVH3_G54A/4D4C/GVL1_G94A	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:267	SEQ ID NO:192	SEQ ID NO:193	SEQ ID NO:268
4D4CVH3/4D4CVL2, 4D4CVH3/4D4CVL2_N93G, 4D4CVH3/4D4CVL2_N93E, 4D4CVH3/4D4CVL2_N93L, 4D4CVH3/4D4CVL2_N93Q, 4D4CVH3/4D4CVL2_G94A, 4D4CVH3_D53G/4D4CVL2, 4D4CVH3_D53G/4D4CVL2_N93G, 4D4CVH3_D53G/4D4CVL2_N93E, 4D4CVH3_D53G/4D4CVL2_N93L, 4D4CVH3_D53G/4D4CVL2_N93Q, 4D4CVH3_D53G/4D4CVL2_G94A, 4D4CVH3_D53E/4D4CVL2, 4D4CVH3_D53E/4D4CVL2_N93G, 4D4CVH3_D53E/4D4CVL2_N93E, 4D4CVH3_D53E/4D4CVL2_N93L, 4D4CVH3_D53E/4D4CVL2_N93Q, 4D4CVH3_D53E/4D4CVL2_G94A, 4D4CVH3_D53Q/4D4CVL2, 4D4CVH3_D53Q/4D4CVL2_N93G, 4D4CVH3_D53Q/4D4CVL2_N93E, 4D4CVH3_D53Q/4D4CVL2_N93L, 4D4CVH3_D53Q/4D4CVL2_N93Q, 4D4CVH3_D53Q/4D4CVL2_G94A, 4D4CVH3_D53L/4D4CVL2 4D4CVH3_D53L/4D4CVL2_N93G, 4D4CVH3_D53L/4D4CVL2_N93E, 4D4CVH3_D53L/4D4CVL2_N93L, 4D4CVH3_D53L/4D4CVL2_N93Q, 4D4CVH3_D53L/4D4CVL2_G94A,	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:270	SEQ ID NO:271	SEQ ID NO:193	SEQ ID NO:268

4D4CVH3_G54A/4D4CVL2 4D4CVH3_G54A/4D4CVL2_N93G, 4D4CVH3_G54A/4D4CVL2_N93E, 4D4CVH3_G54A/4D4CVL2_N93L, 4D4CVH3_G54A/4D4CVL2_N93Q, 4D4CVH3_G54A/4D4CVL2_G94A								
4D4CVH3/4D4CVL4, 4D4CVH3/4D4CVL4_N93G, 4D4CVH3/4D4CVL4_N93E, 4D4CVH3/4D4CVL4_N93L, 4D4CVH3/4D4CVL4_N93Q, 4D4CVH3/4D4CVL4_G94A, 4D4CVH3_D53G/4D4CVL4, 4D4CVH3_D53G/4D4CVL4_N93G, 4D4CVH3_D53G/4D4CVL4_N93E, 4D4CVH3_D53G/4D4CVL4_N93L, 4D4CVH3_D53G/4D4CVL4_N93Q, 4D4CVH3_D53G/4D4CVL4_G94A, 4D4CVH3_D53E/4D4CVL4, 4D4CVH3_D53E/4D4CVL4_N93G, 4D4CVH3_D53E/4D4CVL4_N93E, 4D4CVH3_D53E/4D4CVL4_N93L, 4D4CVH3_D53E/4D4CVL4_N93Q, 4D4CVH3_D53E/4D4CVL4_G94A, 4D4CVH3_D53Q/4D4CVL4, 4D4CVH3_D53Q/4D4CVL4_N93G, 4D4CVH3_D53Q/4D4CVL4_N93E, 4D4CVH3_D53Q/4D4CVL4_N93L, 4D4CVH3_D53Q/4D4CVL4_N93Q, 4D4CVH3_D53Q/4D4CVL4_G94A, 4D4CVH3_D53L/4D4CVL4 4D4CVH3_D53L/4D4CVL4_N93G, 4D4CVH3_D53L/4D4CVL4_N93E, 4D4CVH3_D53L/4D4CVL4_N93L, 4D4CVH3_D53L/4D4CVL4_N93Q, 4D4CVH3_D53L/4D4CVL4_G94A, 4D4CVH3_G54A/4D4CVL4 4D4CVH3_G54A/4D4CVL4_N93G, 4D4CVH3_G54A/4D4CVL4_N93E, 4D4CVH3_G54A/4D4CVL4_N93L, 4D4CVH3_G54A/4D4CVL4_N93Q, 4D4CVH3_G54A/4D4CVL4_G94A,	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:272	SEQ ID NO:271	SEQ ID NO:274	SEQ ID NO:268
4D4CVH3/4D4GVL3, 4D4CVH3/4D4GVL3_N93G, 4D4CVH3/4D4GVL3_N93E, 4D4CVH3/4D4GVL3_N93L, 4D4CVH3/4D4GVL3_N93Q, 4D4CVH3/4D4GVL3_G94A, 4D4CVH3_D53G/4D4GVL3, 4D4CVH3_D53G/4D4GVL3_N93G, 4D4CVH3_D53G/4D4GVL3_N93E, 4D4CVH3_D53G/4D4GVL3_N93L, 4D4CVH3_D53G/4D4GVL3_N93Q, 4D4CVH3_D53G/4D4GVL3_G94A, 4D4CVH3_D53E/4D4GVL3, 4D4CVH3_D53E/4D4GVL3_N93G, 4D4CVH3_D53E/4D4GVL3_N93E, 4D4CVH3_D53E/4D4GVL3_N93L, 4D4CVH3_D53E/4D4GVL3_N93Q, 4D4CVH3_D53E/4D4GVL3_G94A, 4D4CVH3_D53Q/4D4GVL3, 4D4CVH3_D53Q/4D4GVL3_N93G, 4D4CVH3_D53Q/4D4GVL3_N93E, 4D4CVH3_D53Q/4D4GVL3_N93L, 4D4CVH3_D53Q/4D4GVL3_N93Q, 4D4CVH3_D53Q/4D4GVL3_G94A, 4D4CVH3_D53L/4D4GVL3, 4D4CVH3_D53L/4D4GVL3_N93G, 4D4CVH3_D53L/4D4GVL3_N93E, 4D4CVH3_D53L/4D4GVL3_N93L, 4D4CVH3_D53L/4D4GVL3_N93Q, 4D4CVH3_D53L/4D4GVL3_G94, 4D4CVH3_G54A/4D4GVL3, 4D4CVH3_G54A/4D4GVL3_N93G,	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:275	SEQ ID NO:271	SEQ ID NO:277	SEQ ID NO:268

4D4CVH3_G54A/4D4GVL3_N93E, 4D4CVH3_G54A/4D4GVL3_N93L, 4D4CVH3_G54A/4D4GVL3_N93Q, 4D4CVH3_G54A/4D4GVL3_G94A								
4D4CVH3/4D4GVL4, 4D4CVH3/4D4GVL4_N93G, 4D4CVH3/4D4GVL4_N93E, 4D4CVH3/4D4GVL4_N93L, 4D4CVH3/4D4GVL4_N93Q, 4D4CVH3/4D4GVL4_G94A, 4D4CVH3_D53G/4D4GVL4, 4D4CVH3_D53G/4D4GVL4_N93G, 4D4CVH3_D53G/4D4GVL4_N93E, 4D4CVH3_D53G/4D4GVL4_N93L, 4D4CVH3_D53G/4D4GVL4_N93Q, 4D4CVH3_D53G/4D4GVL4_G94A, 4D4CVH3_D53E/4D4GVL4, 4D4CVH3_D53E/4D4GVL4_N93G, 4D4CVH3_D53E/4D4GVL4_N93E, 4D4CVH3_D53E/4D4GVL4_N93L, 4D4CVH3_D53E/4D4GVL4_N93Q, 4D4CVH3_D53E/4D4GVL4_G94A, 4D4CVH3_D53Q/4D4GVL4, 4D4CVH3_D53Q/4D4GVL4_N93G, 4D4CVH3_D53Q/4D4GVL4_N93E, 4D4CVH3_D53Q/4D4GVL4_N93L, 4D4CVH3_D53Q/4D4GVL4_N93Q, 4D4CVH3_D53Q/4D4GVL4_G94A, 4D4CVH3_D53L/4D4GVL4, 4D4CVH3_D53L/4D4GVL4_N93G, 4D4CVH3_D53L/4D4GVL4_N93E, 4D4CVH3_D53L/4D4GVL4_N93L, 4D4CVH3_D53L/4D4GVL4_N93Q, 4D4CVH3_D53L/4D4GVL4_G94A, 4D4CVH3_G54A/4D4GVL4, 4D4CVH3_G54A/4D4GVL4_N93G, 4D4CVH3_G54A/4D4GVL4_N93E, 4D4CVH3_G54A/4D4GVL4_N93L, 4D4CVH3_G54A/4D4GVL4_N93Q, 4D4CVH3_G54A/4D4GVL4_G94A	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:279	SEQ ID NO:271	SEQ ID NO:280	SEQ ID NO:268
4D4CVH4/4D4C/GVL1, 4D4CVH4/4D4C/GVL1_N93G, 4D4CVH4/4D4C/GVL1_N93E, 4D4CVH4/4D4C/GVL1_N93L, 4D4CVH4/4D4C/GVL1_N93Q, 4D4CVH4/4D4C/GVL1_G94A, 4D4CVH4_D53G/4D4C/GVL1, 4D4CVH4_D53G/4D4C/GVL1_N93G, 4D4CVH4_D53G/4D4C/GVL1_N93E, 4D4CVH4_D53G/4D4C/GVL1_N93L, 4D4CVH4_D53G/4D4C/GVL1_N93Q, 4D4CVH4_D53G/4D4C/GVL1_G94A, 4D4CVH4_D53E/4D4C/GVL1, 4D4CVH4_D53E/4D4C/GVL1_N93G, 4D4CVH4_D53E/4D4C/GVL1_N93E, 4D4CVH4_D53E/4D4C/GVL1_N93L, 4D4CVH4_D53E/4D4C/GVL1_N93Q, 4D4CVH4_D53E/4D4C/GVL1_G94A, 4D4CVH4_D53Q/4D4C/GVL1, 4D4CVH4_D53Q/4D4C/GVL1_N93G, 4D4CVH4_D53Q/4D4C/GVL1_N93E, 4D4CVH4_D53Q/4D4C/GVL1_N93L, 4D4CVH4_D53Q/4D4C/GVL1_N93Q, 4D4CVH4_D53Q/4D4C/GVL1_G94A, 4D4CVH4_D53L/4D4C/GVL1, 4D4CVH4_D53L/4D4C/GVL1_N93G, 4D4CVH4_D53L/4D4C/GVL1_N93E, 4D4CVH4_D53L/4D4C/GVL1_N93L, 4D4CVH4_D53L/4D4C/GVL1_N93Q, 4D4CVH4_D53L/4D4C/GVL1_G94A, 4D4CVH4_G54A/4D4C/GVL1, 4D4CVH4_G54A/4D4C/GVL1_N93G, 4D4CVH4_G54A/4D4C/GVL1_N93E, 4D4CVH4_G54A/4D4C/GVL1_N93L,	SEQ ID NO:262	SEQ ID NO:259	SEQ ID NO:263	SEQ ID NO:257	SEQ ID NO:267	SEQ ID NO:192	SEQ ID NO:193	SEQ ID NO:268

4D4CVH4_G54A/4D4C/GVL1_N93Q, 4D4CVH4_G54A/4D4C/GVL1_G94A								
4D4CVH4/4D4CVL2, 4D4CVH4/4D4CVL2_N93G, 4D4CVH4/4D4CVL2_N93E, 4D4CVH4/4D4CVL2_N93L, 4D4CVH4/4D4CVL2_N93Q, 4D4CVH4/4D4CVL2_G94A, 4D4CVH4_D53G/4D4CVL2, 4D4CVH4_D53G/4D4CVL2_N93G, 4D4CVH4_D53G/4D4CVL2_N93E, 4D4CVH4_D53G/4D4CVL2_N93L, 4D4CVH4_D53G/4D4CVL2_N93Q, 4D4CVH4_D53G/4D4CVL2_G94A, 4D4CVH4_D53E/4D4CVL2, 4D4CVH4_D53E/4D4CVL2_N93G, 4D4CVH4_D53E/4D4CVL2_N93E, 4D4CVH4_D53E/4D4CVL2_N93L, 4D4CVH4_D53E/4D4CVL2_N93Q, 4D4CVH4_D53E/4D4CVL2_G94A, 4D4CVH4_D53Q/4D4CVL2, 4D4CVH4_D53Q/4D4CVL2_N93G, 4D4CVH4_D53Q/4D4CVL2_N93E, 4D4CVH4_D53Q/4D4CVL2_N93L, 4D4CVH4_D53Q/4D4CVL2_N93Q, 4D4CVH4_D53Q/4D4CVL2_G94A, 4D4CVH4_D53L/4D4CVL2 4D4CVH4_D53L/4D4CVL2_N93G, 4D4CVH4_D53L/4D4CVL2_N93E, 4D4CVH4_D53L/4D4CVL2_N93L, 4D4CVH4_D53L/4D4CVL2_N93Q, 4D4CVH4_D53L/4D4CVL2_G94A, 4D4CVH4_G54A/4D4CVL2 4D4CVH4_G54A/4D4CVL2_N93G, 4D4CVH4_G54A/4D4CVL2_N93E, 4D4CVH4_G54A/4D4CVL2_N93L, 4D4CVH4_G54A/4D4CVL2_N93Q, 4D4CVH4_G54A/4D4CVL2_G94A	SEQ ID NO:262	SEQ ID NO:259	SEQ ID NO:263	SEQ ID NO:257	SEQ ID NO:270	SEQ ID NO:271	SEQ ID NO:193	SEQ ID NO:268
4D4CVH4/4D4CVL4, 4D4CVH4/4D4CVL4_N93G, 4D4CVH4/4D4CVL4_N93E, 4D4CVH4/4D4CVL4_N93L, 4D4CVH4/4D4CVL4_N93Q, 4D4CVH4/4D4CVL4_G94A, 4D4CVH4_D53G/4D4CVL4, 4D4CVH4_D53G/4D4CVL4_N93G, 4D4CVH4_D53G/4D4CVL4_N93E, 4D4CVH4_D53G/4D4CVL4_N93L, 4D4CVH4_D53G/4D4CVL4_N93Q, 4D4CVH4_D53G/4D4CVL4_G94A, 4D4CVH4_D53E/4D4CVL4, 4D4CVH4_D53E/4D4CVL4_N93G, 4D4CVH4_D53E/4D4CVL4_N93E, 4D4CVH4_D53E/4D4CVL4_N93L, 4D4CVH4_D53E/4D4CVL4_N93Q, 4D4CVH4_D53E/4D4CVL4_G94A, 4D4CVH4_D53Q/4D4CVL4 4D4CVH4_D53Q/4D4CVL4_N93G, 4D4CVH4_D53Q/4D4CVL4_N93E, 4D4CVH4_D53Q/4D4CVL4_N93L, 4D4CVH4_D53Q/4D4CVL4_N93Q, 4D4CVH4_D53Q/4D4CVL4_G94A, 4D4CVH4_D53L/4D4CVL4, 4D4CVH4_D53L/4D4CVL4_N93G, 4D4CVH4_D53L/4D4CVL4_N93E, 4D4CVH4_D53L/4D4CVL4_N93L, 4D4CVH4_D53L/4D4CVL4_N93Q, 4D4CVH4_D53L/4D4CVL4_G94A, 4D4CVH4_G54A/4D4CVL4, 4D4CVH4_G54A/4D4CVL4_N93G, 4D4CVH4_G54A/4D4CVL4_N93E, 4D4CVH4_G54A/4D4CVL4_N93L, 4D4CVH4_G54A/4D4CVL4_N93Q, 4D4CVH4_G54A/4D4CVL4_G94A	SEQ ID NO:262	SEQ ID NO:259	SEQ ID NO:263	SEQ ID NO:257	SEQ ID NO:272	SEQ ID NO:271	SEQ ID NO:274	SEQ ID NO:268

4D4CVH4/4D4GVL3, 4D4CVH4/4D4GVL3_N93G, 4D4CVH4/4D4GVL3_N93E, 4D4CVH4/4D4GVL3_N93L, 4D4CVH4/4D4GVL3_N93Q, 4D4CVH4/4D4GVL3_G94A, 4D4CVH4_D53G/4D4GVL3, 4D4CVH4_D53G/4D4GVL3_N93G, 4D4CVH4_D53G/4D4GVL3_N93E, 4D4CVH4_D53G/4D4GVL3_N93L, 4D4CVH4_D53G/4D4GVL3_N93Q, 4D4CVH4_D53G/4D4GVL3_G94A, 4D4CVH4_D53E/4D4GVL3, 4D4CVH4_D53E/4D4GVL3_N93G, 4D4CVH4_D53E/4D4GVL3_N93E, 4D4CVH4_D53E/4D4GVL3_N93L, 4D4CVH4_D53E/4D4GVL3_N93Q, 4D4CVH4_D53E/4D4GVL3_G94A, 4D4CVH4_D53Q/4D4GVL3, 4D4CVH4_D53Q/4D4GVL3_N93G, 4D4CVH4_D53Q/4D4GVL3_N93E, 4D4CVH4_D53Q/4D4GVL3_N93L, 4D4CVH4_D53Q/4D4GVL3_N93Q, 4D4CVH4_D53Q/4D4GVL3_G94A, 4D4CVH4_D53L/4D4GVL3, 4D4CVH4_D53L/4D4GVL3_N93G, 4D4CVH4_D53L/4D4GVL3_N93E, 4D4CVH4_D53L/4D4GVL3_N93L, 4D4CVH4_D53L/4D4GVL3_N93Q, 4D4CVH4_D53L/4D4GVL3_G94A, 4D4CVH4_G54A/4D4GVL3, 4D4CVH4_G54A/4D4GVL3_N93G, 4D4CVH4_G54A/4D4GVL3_N93E, 4D4CVH4_G54A/4D4GVL3_N93L, 4D4CVH4_G54A/4D4GVL3_N93Q, 4D4CVH4_G54A/4D4GVL3_G94A	SEQ ID NO:262	SEQ ID NO:259	SEQ ID NO:263	SEQ ID NO:257	SEQ ID NO:275	SEQ ID NO:271	SEQ ID NO:277	SEQ ID NO:268
4D4CVH4/4D4GVL4, 4D4CVH4/4D4GVL4_N93G, 4D4CVH4/4D4GVL4_N93E, 4D4CVH4/4D4GVL4_N93L, 4D4CVH4/4D4GVL4_N93Q, 4D4CVH4/4D4GVL4_G94A, 4D4CVH4_D53G/4D4GVL4, 4D4CVH4_D53G/4D4GVL4_N93G, 4D4CVH4_D53G/4D4GVL4_N93E, 4D4CVH4_D53G/4D4GVL4_N93L, 4D4CVH4_D53G/4D4GVL4_N93Q, 4D4CVH4_D53G/4D4GVL4_G94A, 4D4CVH4_D53E/4D4GVL4, 4D4CVH4_D53E/4D4GVL4_N93G, 4D4CVH4_D53E/4D4GVL4_N93E, 4D4CVH4_D53E/4D4GVL4_N93L, 4D4CVH4_D53E/4D4GVL4_N93Q, 4D4CVH4_D53E/4D4GVL4_G94A, 4D4CVH4_D53Q/4D4GVL4, 4D4CVH4_D53Q/4D4GVL4_N93G, 4D4CVH4_D53Q/4D4GVL4_N93E, 4D4CVH4_D53Q/4D4GVL4_N93L, 4D4CVH4_D53Q/4D4GVL4_N93Q, 4D4CVH4_D53Q/4D4GVL4_G94A, 4D4CVH4_D53L/4D4GVL4, 4D4CVH4_D53L/4D4GVL4_N93G, 4D4CVH4_D53L/4D4GVL4_N93E, 4D4CVH4_D53L/4D4GVL4_N93L, 4D4CVH4_D53L/4D4GVL4_N93Q, 4D4CVH4_D53L/4D4GVL4_G94A, 4D4CVH4_G54A/4D4GVL4, 4D4CVH4_G54A/4D4GVL4_N93G, 4D4CVH4_G54A/4D4GVL4_N93E, 4D4CVH4_G54A/4D4GVL4_N93L, 4D4CVH4_G54A/4D4GVL4_N93Q, 4D4CVH4_G54A/4D4GVL4_G94A	SEQ ID NO:262	SEQ ID NO:259	SEQ ID NO:263	SEQ ID NO:257	SEQ ID NO:279	SEQ ID NO:271	SEQ ID NO:280	SEQ ID NO:268
4D4CVH2.1/4D4C/GVL1, 4D4CVH2.1/4D4C/GVL1_N93G,	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:267	SEQ ID NO:192	SEQ ID NO:193	SEQ ID NO:268

4D4CVH2.1/4D4C/GVL1_N93E, 4D4CVH2.1/4D4C/GVL1_N93L, 4D4CVH2.1/4D4C/GVL1_N93Q, 4D4CVH2.1/4D4C/GVL1_G94A, 4D4CVH2.1_D53G/4D4C/GVL1 4D4CVH2.1_D53G/4D4C/GVL1_N93G, 4D4CVH2.1_D53G/4D4C/GVL1_N93E, 4D4CVH2.1_D53G/4D4C/GVL1_N93L, 4D4CVH2.1_D53G/4D4C/GVL1_N93Q, 4D4CVH2.1_D53G/4D4C/GVL1_G94A, 4D4CVH2.1_D53E/4D4C/GVL1, 4D4CVH2.1_D53E/4D4C/GVL1_N93G, 4D4CVH2.1_D53E/4D4C/GVL1_N93E, 4D4CVH2.1_D53E/4D4C/GVL1_N93L, 4D4CVH2.1_D53E/4D4C/GVL1_N93Q, 4D4CVH2.1_D53E/4D4C/GVL1_G94A, 4D4CVH2.1_D53Q/4D4C/GVL1, 4D4CVH2.1_D53Q/4D4C/GVL1_N93G, 4D4CVH2.1_D53Q/4D4C/GVL1_N93E, 4D4CVH2.1_D53Q/4D4C/GVL1_N93L, 4D4CVH2.1_D53Q/4D4C/GVL1_N93Q, 4D4CVH2.1_D53Q/4D4C/GVL1_G94A, 4D4CVH2.1_D53L/4D4C/GVL1, 4D4CVH2.1_D53L/4D4C/GVL1_N93G, 4D4CVH2.1_D53L/4D4C/GVL1_N93E, 4D4CVH2.1_D53L/4D4C/GVL1_N93L, 4D4CVH2.1_D53L/4D4C/GVL1_N93Q, 4D4CVH2.1_D53L/4D4C/GVL1_G94A, 4D4CVH2.1_G54A/4D4C/GVL1, 4D4CVH2.1_G54A/4D4C/GVL1_N93G, 4D4CVH2.1_G54A/4D4C/GVL1_N93E, 4D4CVH2.1_G54A/4D4C/GVL1_N93L, 4D4CVH2.1_G54A/4D4C/GVL1_N93Q, 4D4CVH2.1_G54A/4D4C/GVL1_G94A								
4D4CVH2.1/4D4CVL2, 4D4CVH2.1/4D4CVL2_N93G, 4D4CVH2.1/4D4CVL2_N93E, 4D4CVH2.1/4D4CVL2_N93L, 4D4CVH2.1/4D4CVL2_N93Q, 4D4CVH2.1/4D4CVL2_G94A, 4D4CVH2.1_D53G/4D4CVL2, 4D4CVH2.1_D53G/4D4CVL2_N93G, 4D4CVH2.1_D53G/4D4CVL2_N93E, 4D4CVH2.1_D53G/4D4CVL2_N93L, 4D4CVH2.1_D53G/4D4CVL2_N93Q, 4D4CVH2.1_D53G/4D4CVL2_G94A, 4D4CVH2.1_D53E/4D4CVL2, 4D4CVH2.1_D53E/4D4CVL2_N93G, 4D4CVH2.1_D53E/4D4CVL2_N93E, 4D4CVH2.1_D53E/4D4CVL2_N93L, 4D4CVH2.1_D53E/4D4CVL2_N93Q, 4D4CVH2.1_D53E/4D4CVL2_G94A,	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:270	SEQ ID NO:271	SEQ ID NO:193	SEQ ID NO:268

4D4CVH2.1_D53Q/4D4CVL2, 4D4CVH2.1_D53Q/4D4CVL2_N93G, 4D4CVH2.1_D53Q/4D4CVL2_N93E, 4D4CVH2.1_D53Q/4D4CVL2_N93L, 4D4CVH2.1_D53Q/4D4CVL2_N93Q, 4D4CVH2.1_D53Q/4D4CVL2_G94A, 4D4CVH2.1_D53L/4D4CVL2, 4D4CVH2.1_D53L/4D4CVL2_N93G, 4D4CVH2.1_D53L/4D4CVL2_N93E, 4D4CVH2.1_D53L/4D4CVL2_N93L, 4D4CVH2.1_D53L/4D4CVL2_N93Q, 4D4CVH2.1_D53L/4D4CVL2_G94A, 4D4CVH2.1_G54A/4D4CVL2, 4D4CVH2.1_G54A/4D4CVL2_N93G, 4D4CVH2.1_G54A/4D4CVL2_N93E, 4D4CVH2.1_G54A/4D4CVL2_N93L, 4D4CVH2.1_G54A/4D4CVL2_N93Q, 4D4CVH2.1_G54A/4D4CVL2_G94A								
4D4CVH2.1/4D4CVL4, 4D4CVH2.1/4D4CVL4_N93G, 4D4CVH2.1/4D4CVL4_N93E, 4D4CVH2.1/4D4CVL4_N93L, 4D4CVH2.1/4D4CVL4_N93Q, 4D4CVH2.1/4D4CVL4_G94A, 4D4CVH2.1_D53G/4D4CVL4, 4D4CVH2.1_D53G/4D4CVL4_N93G, 4D4CVH2.1_D53G/4D4CVL4_N93E, 4D4CVH2.1_D53G/4D4CVL4_N93L, 4D4CVH2.1_D53G/4D4CVL4_N93Q, 4D4CVH2.1_D53G/4D4CVL4_G94A, 4D4CVH2.1_D53E/4D4CVL4 4D4CVH2.1_D53E/4D4CVL4_N93G, 4D4CVH2.1_D53E/4D4CVL4_N93E, 4D4CVH2.1_D53E/4D4CVL4_N93L, 4D4CVH2.1_D53E/4D4CVL4_N93Q, 4D4CVH2.1_D53E/4D4CVL4_G94A, 4D4CVH2.1_D53Q/4D4CVL4, 4D4CVH2.1_D53Q/4D4CVL4_N93G, 4D4CVH2.1_D53Q/4D4CVL4_N93E, 4D4CVH2.1_D53Q/4D4CVL4_N93L, 4D4CVH2.1_D53Q/4D4CVL4_N93Q, 4D4CVH2.1_D53Q/4D4CVL4_G94A, 4D4CVH2.1_D53L/4D4CVL4 4D4CVH2.1_D53L/4D4CVL4_N93G, 4D4CVH2.1_D53L/4D4CVL4_N93E, 4D4CVH2.1_D53L/4D4CVL4_N93L, 4D4CVH2.1_D53L/4D4CVL4_N93Q, 4D4CVH2.1_D53L/4D4CVL4_G94A, 4D4CVH2.1_G54A/4D4CVL4 4D4CVH2.1_G54A/4D4CVL4_N93G, 4D4CVH2.1_G54A/4D4CVL4_N93E, 4D4CVH2.1_G54A/4D4CVL4_N93L, 4D4CVH2.1_G54A/4D4CVL4_N93Q, 4D4CVH2.1_G54A/4D4CVL4_G94A	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:272	SEQ ID NO:271	SEQ ID NO:274	SEQ ID NO:268
4D4CVH2.1/4D4GVL3, 4D4CVH2.1/4D4GVL3_N93G, 4D4CVH2.1/4D4GVL3_N93E, 4D4CVH2.1/4D4GVL3_N93L, 4D4CVH2.1/4D4GVL3_N93Q, 4D4CVH2.1/4D4GVL3_G94A, 4D4CVH2.1_D53G/4D4GVL3, 4D4CVH2.1_D53G/4D4GVL3_N93G, 4D4CVH2.1_D53G/4D4GVL3_N93E, 4D4CVH2.1_D53G/4D4GVL3_N93L, 4D4CVH2.1_D53G/4D4GVL3_N93Q, 4D4CVH2.1_D53G/4D4GVL3_G94A, 4D4CVH2.1_D53E/4D4GVL3, 4D4CVH2.1_D53E/4D4GVL3_N93G, 4D4CVH2.1_D53E/4D4GVL3_N93E, 4D4CVH2.1_D53E/4D4GVL3_N93L, 4D4CVH2.1_D53E/4D4GVL3_N93Q, 4D4CVH2.1_D53E/4D4GVL3_G94A, 4D4CVH2.1_D53Q/4D4GVL3, 4D4CVH2.1_D53Q/4D4GVL3_N93G,	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:275	SEQ ID NO:271	SEQ ID NO:277	SEQ ID NO:268

4D4CVH2.1_D53Q/4D4GVL3_N93E, 4D4CVH2.1_D53Q/4D4GVL3_N93L, 4D4CVH2.1_D53Q/4D4GVL3_N93Q, 4D4CVH2.1_D53Q/4D4GVL3_G94A, 4D4CVH2.1_D53L/4D4GVL3, 4D4CVH2.1_D53L/4D4GVL3_N93G, 4D4CVH2.1_D53L/4D4GVL3_N93E, 4D4CVH2.1_D53L/4D4GVL3_N93L, 4D4CVH2.1_D53L/4D4GVL3_N93Q, 4D4CVH2.1_D53L/4D4GVL3_G94A, 4D4CVH2.1_G54A/4D4GVL3, 4D4CVH2.1_G54A/4D4GVL3_N93G, 4D4CVH2.1_G54A/4D4GVL3_N93E, 4D4CVH2.1_G54A/4D4GVL3_N93L, 4D4CVH2.1_G54A/4D4GVL3_N93Q, 4D4CVH2.1_G54A/4D4GVL3_G94A								
4D4CVH2.1/4D4GVL4, 4D4CVH2.1/4D4GVL4_N93G, 4D4CVH2.1/4D4GVL4_N93E, 4D4CVH2.1/4D4GVL4_N93L, 4D4CVH2.1/4D4GVL4_N93Q, 4D4CVH2.1/4D4GVL4_G94A, 4D4CVH2.1_D53G/4D4GVL4, 4D4CVH2.1_D53G/4D4GVL4_N93G, 4D4CVH2.1_D53G/4D4GVL4_N93E, 4D4CVH2.1_D53G/4D4GVL4_N93L, 4D4CVH2.1_D53G/4D4GVL4_N93Q, 4D4CVH2.1_D53G/4D4GVL4_G94A, 4D4CVH2.1_D53E/4D4GVL4, 4D4CVH2.1_D53E/4D4GVL4_N93G, 4D4CVH2.1_D53E/4D4GVL4_N93E, 4D4CVH2.1_D53E/4D4GVL4_N93L, 4D4CVH2.1_D53E/4D4GVL4_N93Q, 4D4CVH2.1_D53E/4D4GVL4_G94A, 4D4CVH2.1_D53Q/4D4GVL4, 4D4CVH2.1_D53Q/4D4GVL4_N93G, 4D4CVH2.1_D53Q/4D4GVL4_N93E, 4D4CVH2.1_D53Q/4D4GVL4_N93L, 4D4CVH2.1_D53Q/4D4GVL4_N93Q, 4D4CVH2.1_D53Q/4D4GVL4_G94A, 4D4CVH2.1_D53L/4D4GVL4, 4D4CVH2.1_D53L/4D4GVL4_N93G, 4D4CVH2.1_D53L/4D4GVL4_N93E, 4D4CVH2.1_D53L/4D4GVL4_N93L, 4D4CVH2.1_D53L/4D4GVL4_N93Q, 4D4CVH2.1_D53L/4D4GVL4_G94A, 4D4CVH2.1_G54A/4D4GVL4, 4D4CVH2.1_G54A/4D4GVL4_N93G, 4D4CVH2.1_G54A/4D4GVL4_N93E, 4D4CVH2.1_G54A/4D4GVL4_N93L, 4D4CVH2.1_G54A/4D4GVL4_N93Q, 4D4CVH2.1_G54A/4D4GVL4_G94A	SEQ ID NO:254	SEQ ID NO:259	SEQ ID NO:255	SEQ ID NO:257	SEQ ID NO:279	SEQ ID NO:271	SEQ ID NO:280	SEQ ID NO:268
4D4CVH2.2/4D4C/GVL1, 4D4CVH2.2/4D4C/GVL1_N93G, 4D4CVH2.2/4D4C/GVL1_N93E, 4D4CVH2.2/4D4C/GVL1_N93L, 4D4CVH2.2/4D4C/GVL1_N93Q, 4D4CVH2.2/4D4C/GVL1_G94A, 4D4CVH2.2_D53G/4D4C/GVL1, 4D4CVH2.2_D53G/4D4C/GVL1_N93G, 4D4CVH2.2_D53G/4D4C/GVL1_N93E, 4D4CVH2.2_D53G/4D4C/GVL1_N93L, 4D4CVH2.2_D53G/4D4C/GVL1_N93Q, 4D4CVH2.2_D53G/4D4C/GVL1_G94A, 4D4CVH2.2_D53E/4D4C/GVL1, 4D4CVH2.2_D53E/4D4C/GVL1_N93G, 4D4CVH2.2_D53E/4D4C/GVL1_N93E, 4D4CVH2.2_D53E/4D4C/GVL1_N93L	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:267	SEQ ID NO:192	SEQ ID NO:193	SEQ ID NO:268

, 4D4CVH2.2_D53E/4D4C/GVL1_N93Q, 4D4CVH2.2_D53E/4D4C/GVL1_G94A, 4D4CVH2.2_D53Q/4D4C/GVL1, 4D4CVH2.2_D53Q/4D4C/GVL1_N93G, 4D4CVH2.2_D53Q/4D4C/GVL1_N93E, 4D4CVH2.2_D53Q/4D4C/GVL1_N93L, 4D4CVH2.2_D53Q/4D4C/GVL1_N93Q, 4D4CVH2.2_D53Q/4D4C/GVL1_G94A, 4D4CVH2.2_D53L/4D4C/GVL1, 4D4CVH2.2_D53L/4D4C/GVL1_N93G, 4D4CVH2.2_D53L/4D4C/GVL1_N93E, 4D4CVH2.2_D53L/4D4C/GVL1_N93L, 4D4CVH2.2_D53L/4D4C/GVL1_N93Q, 4D4CVH2.2_D53L/4D4C/GVL1_G94A, 4D4CVH2.2_G54A/4D4C/GVL1, 4D4CVH2.2_G54A/4D4C/GVL1_N93G, 4D4CVH2.2_G54A/4D4C/GVL1_N93E, 4D4CVH2.2_G54A/4D4C/GVL1_N93L, 4D4CVH2.2_G54A/4D4C/GVL1_N93Q, 4D4CVH2.2_G54A/4D4C/GVL1_G94A								
4D4CVH2.2/4D4CVL2, 4D4CVH2.2/4D4CVL2_N93G, 4D4CVH2.2/4D4CVL2_N93E, 4D4CVH2.2/4D4CVL2_N93L, 4D4CVH2.2/4D4CVL2_N93Q, 4D4CVH2.2/4D4CVL2_G94A, 4D4CVH2.2_D53G/4D4CVL2, 4D4CVH2.2_D53G/4D4CVL2_N93G, 4D4CVH2.2_D53G/4D4CVL2_N93E, 4D4CVH2.2_D53G/4D4CVL2_N93L, 4D4CVH2.2_D53G/4D4CVL2_N93Q, 4D4CVH2.2_D53G/4D4CVL2_G94A, 4D4CVH2.2_D53E/4D4CVL2, 4D4CVH2.2_D53E/4D4CVL2_N93G, 4D4CVH2.2_D53E/4D4CVL2_N93E, 4D4CVH2.2_D53E/4D4CVL2_N93L, 4D4CVH2.2_D53E/4D4CVL2_N93Q, 4D4CVH2.2_D53E/4D4CVL2_G94A, 4D4CVH2.2_D53Q/4D4CVL2, 4D4CVH2.2_D53Q/4D4CVL2_N93G, 4D4CVH2.2_D53Q/4D4CVL2_N93E, 4D4CVH2.2_D53Q/4D4CVL2_N93L, 4D4CVH2.2_D53Q/4D4CVL2_N93Q, 4D4CVH2.2_D53Q/4D4CVL2_G94A, 4D4CVH2.2_D53L/4D4CVL2, 4D4CVH2.2_D53L/4D4CVL2_N93G, 4D4CVH2.2_D53L/4D4CVL2_N93E, 4D4CVH2.2_D53L/4D4CVL2_N93L, 4D4CVH2.2_D53L/4D4CVL2_N93Q, 4D4CVH2.2_D53L/4D4CVL2_G94A, 4D4CVH2.2_G54A/4D4CVL2, 4D4CVH2.2_G54A/4D4CVL2_N93G, 4D4CVH2.2_G54A/4D4CVL2_N93E, 4D4CVH2.2_G54A/4D4CVL2_N93L, 4D4CVH2.2_G54A/4D4CVL2_N93Q, 4D4CVH2.2_G54A/4D4CVL2_G94A	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:270	SEQ ID NO:271	SEQ ID NO:193	SEQ ID NO:268
4D4CVH2.2/4D4CVL4, 4D4CVH2.2/4D4CVL4_N93G, 4D4CVH2.2/4D4CVL4_N93E,	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:272	SEQ ID NO:271	SEQ ID NO:274	SEQ ID NO:268

4D4CVH2.2/4D4CVL4_N93L, 4D4CVH2.2/4D4CVL4_N93Q, 4D4CVH2.2/4D4CVL4_G94A, 4D4CVH2.2_D53G/4D4CVL4, 4D4CVH2.2_D53G/4D4CVL4_N93G, 4D4CVH2.2_D53G/4D4CVL4_N93E, 4D4CVH2.2_D53G/4D4CVL4_N93L, 4D4CVH2.2_D53G/4D4CVL4_N93Q, 4D4CVH2.2_D53G/4D4CVL4_G94A, 4D4CVH2.2_D53E/4D4CVL4, 4D4CVH2.2_D53E/4D4CVL4_N93G, 4D4CVH2.2_D53E/4D4CVL4_N93E, 4D4CVH2.2_D53E/4D4CVL4_N93L, 4D4CVH2.2_D53E/4D4CVL4_N93Q, 4D4CVH2.2_D53E/4D4CVL4_G94A, 4D4CVH2.2_D53Q/4D4CVL4, 4D4CVH2.2_D53Q/4D4CVL4_N93G, 4D4CVH2.2_D53Q/4D4CVL4_N93E, 4D4CVH2.2_D53Q/4D4CVL4_N93L, 4D4CVH2.2_D53Q/4D4CVL4_N93Q, 4D4CVH2.2_D53Q/4D4CVL4_G94A, 4D4CVH2.2_D53L/4D4CVL4, 4D4CVH2.2_D53L/4D4CVL4_N93G, 4D4CVH2.2_D53L/4D4CVL4_N93E, 4D4CVH2.2_D53L/4D4CVL4_N93L, 4D4CVH2.2_D53L/4D4CVL4_N93Q, 4D4CVH2.2_D53L/4D4CVL4_G94A, 4D4CVH2.2_G54A/4D4CVL4, 4D4CVH2.2_G54A/4D4CVL4_N93G, 4D4CVH2.2_G54A/4D4CVL4_N93E, 4D4CVH2.2_G54A/4D4CVL4_N93L, 4D4CVH2.2_G54A/4D4CVL4_N93Q, 4D4CVH2.2_G54A/4D4CVL4_G94A								
4D4CVH2.2/4D4GVL3, 4D4CVH2.2/4D4GVL3_N93G, 4D4CVH2.2/4D4GVL3_N93E, 4D4CVH2.2/4D4GVL3_N93L, 4D4CVH2.2/4D4GVL3_N93Q, 4D4CVH2.2/4D4GVL3_G94A, 4D4CVH2.2_D53G/4D4GVL3, 4D4CVH2.2_D53G/4D4GVL3_N93G, 4D4CVH2.2_D53G/4D4GVL3_N93E, 4D4CVH2.2_D53G/4D4GVL3_N93L, 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53G/4D4GVL3_G94A, 4D4CVH2.2_D53E/4D4GVL3, 4D4CVH2.2_D53E/4D4GVL3_N93G, 4D4CVH2.2_D53E/4D4GVL3_N93E, 4D4CVH2.2_D53E/4D4GVL3_N93L, 4D4CVH2.2_D53E/4D4GVL3_N93Q, 4D4CVH2.2_D53E/4D4GVL3_G94A, 4D4CVH2.2_D53Q/4D4GVL3, 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93E, 4D4CVH2.2_D53Q/4D4GVL3_N93L, 4D4CVH2.2_D53Q/4D4GVL3_N93Q, 4D4CVH2.2_D53Q/4D4GVL3_G94A, 4D4CVH2.2_D53L/4D4GVL3, 4D4CVH2.2_D53L/4D4GVL3_N93G, 4D4CVH2.2_D53L/4D4GVL3_N93E, 4D4CVH2.2_D53L/4D4GVL3_N93L, 4D4CVH2.2_D53L/4D4GVL3_N93Q, 4D4CVH2.2_D53L/4D4GVL3_G94A, 4D4CVH2.2_G54A/4D4GVL3, 4D4CVH2.2_G54A/4D4GVL3_N93G, 4D4CVH2.2_G54A/4D4GVL3_N93E, 4D4CVH2.2_G54A/4D4GVL3_N93L, 4D4CVH2.2_G54A/4D4GVL3_N93Q, 4D4CVH2.2_G54A/4D4GVL3_G94A	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:275	SEQ ID NO:271	SEQ ID NO:277	SEQ ID NO:268
4D4CVH2.2/4D4GVL4, 4D4CVH2.2/4D4GVL4_N93G, 4D4CVH2.2/4D4GVL4_N93E, 4D4CVH2.2/4D4GVL4_N93L, 4D4CVH2.2/4D4GVL4_N93Q,	SEQ ID NO:254	SEQ ID NO:184	SEQ ID NO:260	SEQ ID NO:257	SEQ ID NO:279	SEQ ID NO:271	SEQ ID NO:280	SEQ ID NO:268

4D4CVH2.2/4D4GVL4_G94A, 4D4CVH2.2_D53G/4D4GVL4, 4D4CVH2.2_D53G/4D4GVL4_N93G, 4D4CVH2.2_D53G/4D4GVL4_N93E, 4D4CVH2.2_D53G/4D4GVL4_N93L, 4D4CVH2.2_D53G/4D4GVL4_N93Q, 4D4CVH2.2_D53G/4D4GVL4_G94A, 4D4CVH2.2_D53E/4D4GVL4, 4D4CVH2.2_D53E/4D4GVL4_N93G, 4D4CVH2.2_D53E/4D4GVL4_N93E, 4D4CVH2.2_D53E/4D4GVL4_N93L, 4D4CVH2.2_D53E/4D4GVL4_N93Q, 4D4CVH2.2_D53E/4D4GVL4_G94A, 4D4CVH2.2_D53Q/4D4GVL4, 4D4CVH2.2_D53Q/4D4GVL4_N93G, 4D4CVH2.2_D53Q/4D4GVL4_N93E, 4D4CVH2.2_D53Q/4D4GVL4_N93L, 4D4CVH2.2_D53Q/4D4GVL4_N93Q, 4D4CVH2.2_D53Q/4D4GVL4_G94A, 4D4CVH2.2_D53L/4D4GVL4, 4D4CVH2.2_D53L/4D4GVL4_N93G, 4D4CVH2.2_D53L/4D4GVL4_N93E, 4D4CVH2.2_D53L/4D4GVL4_N93L, 4D4CVH2.2_D53L/4D4GVL4_N93Q, 4D4CVH2.2_D53L/4D4GVL4_G94A, 4D4CVH2.2_G54A/4D4GVL4, 4D4CVH2.2_G54A/4D4GVL4_N93G, 4D4CVH2.2_G54A/4D4GVL4_N93E, 4D4CVH2.2_G54A/4D4GVL4_N93L, 4D4CVH2.2_G54A/4D4GVL4_N93Q, 4D4CVH2.2_G54A/4D4GVL4_G94A								
CON4D4P/Hu CON4D4P/Hu_D53var_G53var	SEQ ID NO:281	SEQ ID NO:282	SEQ ID NO:283	SEQ ID NO:257	SEQ ID NO:285	SEQ ID NO:286	SEQ ID NO:287	SEQ ID NO:268

Table G

	Column A	Column B
Antibody	**VH**	**VL**
4D4	SEQ ID NO:179	SEQ ID NO:187
3G9	SEQ ID NO:195	SEQ ID NO:201
4A7/7D8	SEQ ID NO:209	SEQ ID NO:212
8C6	SEQ ID NO:214	SEQ ID NO:222
C03-A7	SEQ ID NO:229	SEQ ID NO:235
CON'4'9'7/8	SEQ ID NO:252	SEQ ID NO:253
4D4CVH2/4D4C/GVL1	SEQ ID NO:256	SEQ ID NO:266
4D4CVH2/4D4CVL2	SEQ ID NO:256	SEQ ID NO:269
4D4CVH2/4D4CVL4	SEQ ID NO:256	SEQ ID NO:273
4D4CVH2/4D4GVL3	SEQ ID NO:256	SEQ ID NO:276
4D4CVH2/4D4GVL4	SEQ ID NO:256	SEQ ID NO:278
4D4CVH3/4D4C/GVL1	SEQ ID NO:258	SEQ ID NO:266
4D4CVH3/4D4CVL2	SEQ ID NO:258	SEQ ID NO:269
4D4CVH3/4D4CVL4	SEQ ID NO:258	SEQ ID NO:273
4D4CVH3/4D4GVL3	SEQ ID NO:258	SEQ ID NO:276
4D4CVH3/4D4GVL4	SEQ ID NO:258	SEQ ID NO:278
4D4CVH4/4D4C/GVL1	SEQ ID NO:261	SEQ ID NO:266
4D4CVH4/4D4CVL2	SEQ ID NO:261	SEQ ID NO:269
4D4CVH4/4D4CVL4	SEQ ID NO:261	SEQ ID NO:273
4D4CVH4/4D4GVL3	SEQ ID NO:261	SEQ ID NO:276
4D4CVH4/4D4GVL4	SEQ ID NO:261	SEQ ID NO:278
4D4CVH2.1/4D4C/GVL1	SEQ ID NO:264	SEQ ID NO:266
4D4CVH2.1/4D4CVL2	SEQ ID NO:264	SEQ ID NO:269
4D4CVH2.1/4D4CVL4	SEQ ID NO:264	SEQ ID NO:273
4D4CVH2.1/4D4GVL3	SEQ ID NO:264	SEQ ID NO:276
4D4CVH2.1/4D4GVL4	SEQ ID NO:264	SEQ ID NO:278
4D4CVH2.2/4D4C/GVL1	SEQ ID NO:265	SEQ ID NO:266
4D4CVH2.2/4D4CVL2	SEQ ID NO:265	SEQ ID NO:269
4D4CVH2.2/4D4CVL4	SEQ ID NO:265	SEQ ID NO:273
4D4CVH2.2/4D4GVL3	SEQ ID NO:265	SEQ ID NO:276
4D4CVH2.2/4D4GVL4	SEQ ID NO:265	SEQ ID NO:278
CON4D4P/Hu	SEQ ID NO:284	SEQ ID NO:288
4D4/4D4_N93G	SEQ ID NO:179	SEQ ID NO:382
4D4/4D4_N93E	SEQ ID NO:179	SEQ ID NO:383
4D4/4D4_N93L	SEQ ID NO:179	SEQ ID NO:384
4D4/4D4_N93Q	SEQ ID NO:179	SEQ ID NO:385
4D4/4D4_G94A	SEQ ID NO:179	SEQ ID NO:386
4D4_D53G/4D4	SEQ ID NO:345	SEQ ID NO:187
4D4_D53E/4D4	SEQ ID NO:346	SEQ ID NO:187
4D4_D53Q/4D4	SEQ ID NO:347	SEQ ID NO:187
4D4_D53L/4D4	SEQ ID NO:348	SEQ ID NO:187
4D4_G54A/4D4	SEQ ID NO:349	SEQ ID NO:187
4D4_D53G/4D4_N93G	SEQ ID NO:345	SEQ ID NO:382
4D4_D53E/4D4_N93G	SEQ ID NO:346	SEQ ID NO:382
4D4_D53Q/4D4_N93G	SEQ ID NO:347	SEQ ID NO:382
4D4_D53L/4D4_N93G	SEQ ID NO:348	SEQ ID NO:382
4D4_G54A/4D4_N93G	SEQ ID NO:349	SEQ ID NO:382
4D4_D53G/4D4_N93E	SEQ ID NO:345	SEQ ID NO:383
4D4_D53E/4D4_N93E	SEQ ID NO:346	SEQ ID NO:383
4D4_D53Q/4D4_N93E	SEQ ID NO:347	SEQ ID NO:383
4D4_D53L/4D4_N93E	SEQ ID NO:348	SEQ ID NO:383
4D4_G54A/4D4_N93E	SEQ ID NO:349	SEQ ID NO:383
4D4_D53G/4D4_N93L	SEQ ID NO:345	SEQ ID NO:384
4D4_D53E/4D4_N93L	SEQ ID NO:346	SEQ ID NO:384
4D4_D53Q/4D4_N93L	SEQ ID NO:347	SEQ ID NO:384
4D4_D53L/4D4_N93L	SEQ ID NO:348	SEQ ID NO:384
4D4_G54A/4D4_N93L	SEQ ID NO:349	SEQ ID NO:384
4D4_D53G/4D4_N93Q	SEQ ID NO:345	SEQ ID NO:385
4D4_D53E/4D4_N93Q	SEQ ID NO:346	SEQ ID NO:385
4D4_D53Q/4D4_N93Q	SEQ ID NO:347	SEQ ID NO:385
4D4_D53L/4D4_N93Q	SEQ ID NO:348	SEQ ID NO:385
4D4_G54A/4D4_N93Q	SEQ ID NO:349	SEQ ID NO:385
4D4_D53G/4D4_G94A	SEQ ID NO:345	SEQ ID NO:386
4D4_D53E/4D4_G94A	SEQ ID NO:346	SEQ ID NO:386
4D4_D53Q/4D4_G94A	SEQ ID NO:347	SEQ ID NO:386
4D4_D53L/4D4_G94A	SEQ ID NO:348	SEQ ID NO:386

4D4_G54A/4D4_G94A	SEQ ID NO:349	SEQ ID NO:386
4D4CVH2/4D4C/GVL1_N93G	SEQ ID NO:256	SEQ ID NO:387
4D4CVH2/4D4C/GVL1_N93E	SEQ ID NO:256	SEQ ID NO:388
4D4CVH2/4D4C/GVL1_N93L	SEQ ID NO:256	SEQ ID NO:389
4D4CVH2/4D4C/GVL1_N93Q	SEQ ID NO:256	SEQ ID NO:390
4D4CVH2/4D4C/GVL1_G94A	SEQ ID NO:256	SEQ ID NO:391
4D4CVH2_D53G/4D4C/GVL1	SEQ ID NO:350	SEQ ID NO:266
4D4CVH2_D53E/4D4C/GVL1	SEQ ID NO:351	SEQ ID NO:266
4D4CVH2_D53Q/4D4C/GVL1	SEQ ID NO:352	SEQ ID NO:266
4D4CVH2_D53L/4D4C/GVL1	SEQ ID NO:353	SEQ ID NO:266
4D4CVH2_G54A/4D4C/GVL1	SEQ ID NO:354	SEQ ID NO:266
4D4CVH2_D53G/4D4C/GVL1_N93G	SEQ ID NO:350	SEQ ID NO:387
4D4CVH2_D53E/4D4C/GVL1_N93G	SEQ ID NO:351	SEQ ID NO:387
4D4CVH2_D53Q/4D4C/GVL1_N93G	SEQ ID NO:352	SEQ ID NO:387
4D4CVH2_D53L/4D4C/GVL1_N93G	SEQ ID NO:353	SEQ ID NO:387
4D4CVH2_G54A/4D4C/GVL1_N93G	SEQ ID NO:354	SEQ ID NO:387
4D4CVH2_D53G/4D4C/GVL1_N93E	SEQ ID NO:350	SEQ ID NO:388
4D4CVH2_D53E/4D4C/GVL1_N93E	SEQ ID NO:351	SEQ ID NO:388
4D4CVH2_D53Q/4D4C/GVL1_N93E	SEQ ID NO:352	SEQ ID NO:388
4D4CVH2_D53L/4D4C/GVL1_N93E	SEQ ID NO:353	SEQ ID NO:388
4D4CVH2_G54A/4D4C/GVL1_N93E	SEQ ID NO:354	SEQ ID NO:388
4D4CVH2_D53G/4D4C/GVL1_N93L	SEQ ID NO:350	SEQ ID NO:389
4D4CVH2_D53E/4D4C/GVL1_N93L	SEQ ID NO:351	SEQ ID NO:389
4D4CVH2_D53Q/4D4C/GVL1_N93L	SEQ ID NO:352	SEQ ID NO:389
4D4CVH2_D53L/4D4C/GVL1_N93L	SEQ ID NO:353	SEQ ID NO:389
4D4CVH2_G54A/4D4C/GVL1_N93L	SEQ ID NO:354	SEQ ID NO:389
4D4CVH2_D53G/4D4C/GVL1_N93Q	SEQ ID NO:350	SEQ ID NO:390
4D4CVH2_D53E/4D4C/GVL1_N93Q	SEQ ID NO:351	SEQ ID NO:390
4D4CVH2_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:352	SEQ ID NO:390
4D4CVH2_D53L/4D4C/GVL1_N93Q	SEQ ID NO:353	SEQ ID NO:390
4D4CVH2_G54A/4D4C/GVL1_N93Q	SEQ ID NO:354	SEQ ID NO:390
4D4CVH2_D53G/4D4C/GVL1_G94A	SEQ ID NO:350	SEQ ID NO:391
4D4CVH2_D53E/4D4C/GVL1_G94A	SEQ ID NO:351	SEQ ID NO:391
4D4CVH2_D53Q/4D4C/GVL1_G94A	SEQ ID NO:352	SEQ ID NO:391
4D4CVH2_D53L/4D4C/GVL1_G94A	SEQ ID NO:353	SEQ ID NO:391
4D4CVH2_G54A/4D4C/GVL1_G94A	SEQ ID NO:354	SEQ ID NO:391
4D4CVH2/4D4CVL2_N93G	SEQ ID NO:256	SEQ ID NO:392
4D4CVH2/4D4CVL2_N93E	SEQ ID NO:256	SEQ ID NO:393
4D4CVH2/4D4CVL2_N93L	SEQ ID NO:256	SEQ ID NO:394
4D4CVH2/4D4CVL2_N93Q	SEQ ID NO:256	SEQ ID NO:395
4D4CVH2/4D4CVL2_G94A	SEQ ID NO:256	SEQ ID NO:396
4D4CVH2_D53G/4D4CVL2	SEQ ID NO:350	SEQ ID NO:269
4D4CVH2_D53E/4D4CVL2	SEQ ID NO:351	SEQ ID NO:269
4D4CVH2_D53Q/4D4CVL2	SEQ ID NO:352	SEQ ID NO:269
4D4CVH2_D53L/4D4CVL2	SEQ ID NO:353	SEQ ID NO:269
4D4CVH2_G54A/4D4CVL2	SEQ ID NO:354	SEQ ID NO:269
4D4CVH2_D53G/4D4CVL2_N93G	SEQ ID NO:350	SEQ ID NO:392
4D4CVH2_D53E/4D4CVL2_N93G	SEQ ID NO:351	SEQ ID NO:392
4D4CVH2_D53Q/4D4CVL2_N93G	SEQ ID NO:352	SEQ ID NO:392
4D4CVH2_D53L/4D4CVL2_N93G	SEQ ID NO:353	SEQ ID NO:392
4D4CVH2_G54A/4D4CVL2_N93G	SEQ ID NO:354	SEQ ID NO:392
4D4CVH2_D53G/4D4CVL2_N93E	SEQ ID NO:350	SEQ ID NO:393
4D4CVH2_D53E/4D4CVL2_N93E	SEQ ID NO:351	SEQ ID NO:393
4D4CVH2_D53Q/4D4CVL2_N93E	SEQ ID NO:352	SEQ ID NO:393
4D4CVH2_D53L/4D4CVL2_N93E	SEQ ID NO:353	SEQ ID NO:393
4D4CVH2_G54A/4D4CVL2_N93E	SEQ ID NO:354	SEQ ID NO:393
4D4CVH2_D53G/4D4CVL2_N93L	SEQ ID NO:350	SEQ ID NO:394
4D4CVH2_D53E/4D4CVL2_N93L	SEQ ID NO:351	SEQ ID NO:394
4D4CVH2_D53Q/4D4CVL2_N93L	SEQ ID NO:352	SEQ ID NO:394
4D4CVH2_D53L/4D4CVL2_N93L	SEQ ID NO:353	SEQ ID NO:394
4D4CVH2_G54A/4D4CVL2_N93L	SEQ ID NO:354	SEQ ID NO:394
4D4CVH2_D53G/4D4CVL2_N93Q	SEQ ID NO:350	SEQ ID NO:395
4D4CVH2_D53E/4D4CVL2_N93Q	SEQ ID NO:351	SEQ ID NO:395
4D4CVH2_D53Q/4D4CVL2_N93Q	SEQ ID NO:352	SEQ ID NO:395
4D4CVH2_D53L/4D4CVL2_N93Q	SEQ ID NO:353	SEQ ID NO:395
4D4CVH2_G54A/4D4CVL2_N93Q	SEQ ID NO:354	SEQ ID NO:395
4D4CVH2_D53G/4D4CVL2_G94A	SEQ ID NO:350	SEQ ID NO:396
4D4CVH2_D53E/4D4CVL2_G94A	SEQ ID NO:351	SEQ ID NO:396
4D4CVH2_D53Q/4D4CVL2_G94A	SEQ ID NO:352	SEQ ID NO:396
4D4CVH2_D53L/4D4CVL2_G94A	SEQ ID NO:353	SEQ ID NO:396

4D4CVH2_G54A/4D4CVL2_G94A	SEQ ID NO:354	SEQ ID NO:396
4D4CVH2/4D4CVL4_N93G	SEQ ID NO:256	SEQ ID NO:397
4D4CVH2/4D4CVL4_N93E	SEQ ID NO:256	SEQ ID NO:398
4D4CVH2/4D4CVL4_N93L	SEQ ID NO:256	SEQ ID NO:399
4D4CVH2/4D4CVL4_N93Q	SEQ ID NO:256	SEQ ID NO:400
4D4CVH2/4D4CVL4_G94A	SEQ ID NO:256	SEQ ID NO:401
4D4CVH2_D53G/4D4CVL4	SEQ ID NO:350	SEQ ID NO:273
4D4CVH2_D53E/4D4CVL4	SEQ ID NO:351	SEQ ID NO:273
4D4CVH2_D53Q/4D4CVL4	SEQ ID NO:352	SEQ ID NO:273
4D4CVH2_D53L/4D4CVL4	SEQ ID NO:353	SEQ ID NO:273
4D4CVH2_G54A/4D4CVL4	SEQ ID NO:354	SEQ ID NO:273
4D4CVH2_D53G/4D4CVL4_N93G	SEQ ID NO:350	SEQ ID NO:397
4D4CVH2_D53E/4D4CVL4_N93G	SEQ ID NO:351	SEQ ID NO:397
4D4CVH2_D53Q/4D4CVL4_N93G	SEQ ID NO:352	SEQ ID NO:397
4D4CVH2_D53L/4D4CVL4_N93G	SEQ ID NO:353	SEQ ID NO:397
4D4CVH2_G54A/4D4CVL4_N93G	SEQ ID NO:354	SEQ ID NO:397
4D4CVH2_D53G/4D4CVL4_N93E	SEQ ID NO:350	SEQ ID NO:398
4D4CVH2_D53E/4D4CVL4_N93E	SEQ ID NO:351	SEQ ID NO:398
4D4CVH2_D53Q/4D4CVL4_N93E	SEQ ID NO:352	SEQ ID NO:398
4D4CVH2_D53L/4D4CVL4_N93E	SEQ ID NO:353	SEQ ID NO:398
4D4CVH2_G54A/4D4CVL4_N93E	SEQ ID NO:354	SEQ ID NO:398
4D4CVH2_D53G/4D4CVL4_N93L	SEQ ID NO:350	SEQ ID NO:399
4D4CVH2_D53E/4D4CVL4_N93L	SEQ ID NO:351	SEQ ID NO:399
4D4CVH2_D53Q/4D4CVL4_N93L	SEQ ID NO:352	SEQ ID NO:399
4D4CVH2_D53L/4D4CVL4_N93L	SEQ ID NO:353	SEQ ID NO:399
4D4CVH2_G54A/4D4CVL4_N93L	SEQ ID NO:354	SEQ ID NO:399
4D4CVH2_D53G/4D4CVL4_N93Q	SEQ ID NO:350	SEQ ID NO:400
4D4CVH2_D53E/4D4CVL4_N93Q	SEQ ID NO:351	SEQ ID NO:400
4D4CVH2_D53Q/4D4CVL4_N93Q	SEQ ID NO:352	SEQ ID NO:400
4D4CVH2_D53L/4D4CVL4_N93Q	SEQ ID NO:353	SEQ ID NO:400
4D4CVH2_G54A/4D4CVL4_N93Q	SEQ ID NO:354	SEQ ID NO:400
4D4CVH2_D53G/4D4CVL4_G94A	SEQ ID NO:350	SEQ ID NO:401
4D4CVH2_D53E/4D4CVL4_G94A	SEQ ID NO:351	SEQ ID NO:401
4D4CVH2_D53Q/4D4CVL4_G94A	SEQ ID NO:352	SEQ ID NO:401
4D4CVH2_D53L/4D4CVL4_G94A	SEQ ID NO:353	SEQ ID NO:401
4D4CVH2_G54A/4D4CVL4_G94A	SEQ ID NO:354	SEQ ID NO:401
4D4CVH2/4D4GVL3_N93G	SEQ ID NO:256	SEQ ID NO:402
4D4CVH2/4D4GVL3_N93E	SEQ ID NO:256	SEQ ID NO:403
4D4CVH2/4D4GVL3_N93L	SEQ ID NO:256	SEQ ID NO:404
4D4CVH2/4D4GVL3_N93Q	SEQ ID NO:256	SEQ ID NO:405
4D4CVH2/4D4GVL3_G94A	SEQ ID NO:256	SEQ ID NO:406
4D4CVH2_D53G/4D4GVL3	SEQ ID NO:350	SEQ ID NO:276
4D4CVH2_D53E/4D4GVL3	SEQ ID NO:351	SEQ ID NO:276
4D4CVH2_D53Q/4D4GVL3	SEQ ID NO:352	SEQ ID NO:276
4D4CVH2_D53L/4D4GVL3	SEQ ID NO:353	SEQ ID NO:276
4D4CVH2_G54A/4D4GVL3	SEQ ID NO:354	SEQ ID NO:276
4D4CVH2_D53G/4D4GVL3_N93G	SEQ ID NO:350	SEQ ID NO:402
4D4CVH2_D53E/4D4GVL3_N93G	SEQ ID NO:351	SEQ ID NO:402
4D4CVH2_D53Q/4D4GVL3_N93G	SEQ ID NO:352	SEQ ID NO:402
4D4CVH2_D53L/4D4GVL3_N93G	SEQ ID NO:353	SEQ ID NO:402
4D4CVH2_G54A/4D4GVL3_N93G	SEQ ID NO:354	SEQ ID NO:402
4D4CVH2_D53G/4D4GVL3_N93E	SEQ ID NO:350	SEQ ID NO:403
4D4CVH2_D53E/4D4GVL3_N93E	SEQ ID NO:351	SEQ ID NO:403
4D4CVH2_D53Q/4D4GVL3_N93E	SEQ ID NO:352	SEQ ID NO:403
4D4CVH2_D53L/4D4GVL3_N93E	SEQ ID NO:353	SEQ ID NO:403
4D4CVH2_G54A/4D4GVL3_N93E	SEQ ID NO:354	SEQ ID NO:403
4D4CVH2_D53G/4D4GVL3_N93L	SEQ ID NO:350	SEQ ID NO:404
4D4CVH2_D53E/4D4GVL3_N93L	SEQ ID NO:351	SEQ ID NO:404
4D4CVH2_D53Q/4D4GVL3_N93L	SEQ ID NO:352	SEQ ID NO:404
4D4CVH2_D53L/4D4GVL3_N93L	SEQ ID NO:353	SEQ ID NO:404
4D4CVH2_G54A/4D4GVL3_N93L	SEQ ID NO:354	SEQ ID NO:404
4D4CVH2_D53G/4D4GVL3_N93Q	SEQ ID NO:350	SEQ ID NO:405
4D4CVH2_D53E/4D4GVL3_N93Q	SEQ ID NO:351	SEQ ID NO:405
4D4CVH2_D53Q/4D4GVL3_N93Q	SEQ ID NO:352	SEQ ID NO:405
4D4CVH2_D53L/4D4GVL3_N93Q	SEQ ID NO:353	SEQ ID NO:405
4D4CVH2_G54A/4D4GVL3_N93Q	SEQ ID NO:354	SEQ ID NO:405
4D4CVH2_D53G/4D4GVL3_G94A	SEQ ID NO:350	SEQ ID NO:406
4D4CVH2_D53E/4D4GVL3_G94A	SEQ ID NO:351	SEQ ID NO:406
4D4CVH2_D53Q/4D4GVL3_G94A	SEQ ID NO:352	SEQ ID NO:406
4D4CVH2_D53L/4D4GVL3_G94A	SEQ ID NO:353	SEQ ID NO:406

4D4CVH2_G54A/4D4GVL3_G94A	SEQ ID NO:354	SEQ ID NO:406
4D4CVH2/4D4GVL4_N93G	SEQ ID NO:256	SEQ ID NO:407
4D4CVH2/4D4GVL4_N93E	SEQ ID NO:256	SEQ ID NO:408
4D4CVH2/4D4GVL4_N93L	SEQ ID NO:256	SEQ ID NO:409
4D4CVH2/4D4GVL4_N93Q	SEQ ID NO:256	SEQ ID NO:410
4D4CVH2/4D4GVL4_G94A	SEQ ID NO:256	SEQ ID NO:411
4D4CVH2_D53G/4D4GVL4	SEQ ID NO:350	SEQ ID NO:278
4D4CVH2_D53E/4D4GVL4	SEQ ID NO:351	SEQ ID NO:278
4D4CVH2_D53Q/4D4GVL4	SEQ ID NO:352	SEQ ID NO:278
4D4CVH2_D53L/4D4GVL4	SEQ ID NO:353	SEQ ID NO:278
4D4CVH2_G54A/4D4GVL4	SEQ ID NO:354	SEQ ID NO:278
4D4CVH2_D53G/4D4GVL4_N93G	SEQ ID NO:350	SEQ ID NO:407
4D4CVH2_D53E/4D4GVL4_N93G	SEQ ID NO:351	SEQ ID NO:407
4D4CVH2_D53Q/4D4GVL4_N93G	SEQ ID NO:352	SEQ ID NO:407
4D4CVH2_D53L/4D4GVL4_N93G	SEQ ID NO:353	SEQ ID NO:407
4D4CVH2_G54A/4D4GVL4_N93G	SEQ ID NO:354	SEQ ID NO:407
4D4CVH2_D53G/4D4GVL4_N93E	SEQ ID NO:350	SEQ ID NO:408
4D4CVH2_D53E/4D4GVL4_N93E	SEQ ID NO:351	SEQ ID NO:408
4D4CVH2_D53Q/4D4GVL4_N93E	SEQ ID NO:352	SEQ ID NO:408
4D4CVH2_D53L/4D4GVL4_N93E	SEQ ID NO:353	SEQ ID NO:408
4D4CVH2_G54A/4D4GVL4_N93E	SEQ ID NO:354	SEQ ID NO:408
4D4CVH2_D53G/4D4GVL4_N93L	SEQ ID NO:350	SEQ ID NO:409
4D4CVH2_D53E/4D4GVL4_N93L	SEQ ID NO:351	SEQ ID NO:409
4D4CVH2_D53Q/4D4GVL4_N93L	SEQ ID NO:352	SEQ ID NO:409
4D4CVH2_D53L/4D4GVL4_N93L	SEQ ID NO:353	SEQ ID NO:409
4D4CVH2_G54A/4D4GVL4_N93L	SEQ ID NO:354	SEQ ID NO:409
4D4CVH2_D53G/4D4GVL4_N93Q	SEQ ID NO:350	SEQ ID NO:410
4D4CVH2_D53E/4D4GVL4_N93Q	SEQ ID NO:351	SEQ ID NO:410
4D4CVH2_D53Q/4D4GVL4_N93Q	SEQ ID NO:352	SEQ ID NO:410
4D4CVH2_D53L/4D4GVL4_N93Q	SEQ ID NO:353	SEQ ID NO:410
4D4CVH2_G54A/4D4GVL4_N93Q	SEQ ID NO:354	SEQ ID NO:410
4D4CVH2_D53G/4D4GVL4_G94A	SEQ ID NO:350	SEQ ID NO:411
4D4CVH2_D53E/4D4GVL4_G94A	SEQ ID NO:351	SEQ ID NO:411
4D4CVH2_D53Q/4D4GVL4_G94A	SEQ ID NO:352	SEQ ID NO:411
4D4CVH2_D53L/4D4GVL4_G94A	SEQ ID NO:353	SEQ ID NO:411
4D4CVH2_G54A/4D4GVL4_G94A	SEQ ID NO:354	SEQ ID NO:411
4D4CVH3/4D4C/GVL1_N93G	SEQ ID NO:258	SEQ ID NO:387
4D4CVH3/4D4C/GVL1_N93E	SEQ ID NO:258	SEQ ID NO:388
4D4CVH3/4D4C/GVL1_N93L	SEQ ID NO:258	SEQ ID NO:389
4D4CVH3/4D4C/GVL1_N93Q	SEQ ID NO:258	SEQ ID NO:390
4D4CVH3/4D4C/GVL1_G94A	SEQ ID NO:258	SEQ ID NO:391
4D4CVH3_D53G/4D4C/GVL1	SEQ ID NO:355	SEQ ID NO:266
4D4CVH3_D53E/4D4C/GVL1	SEQ ID NO:356	SEQ ID NO:266
4D4CVH3_D53Q/4D4C/GVL1	SEQ ID NO:357	SEQ ID NO:266
4D4CVH3_D53L/4D4C/GVL1	SEQ ID NO:358	SEQ ID NO:266
4D4CVH3_G54A/4D4C/GVL1	SEQ ID NO:359	SEQ ID NO:266
4D4CVH3_D53G/4D4C/GVL1_N93G	SEQ ID NO:355	SEQ ID NO:387
4D4CVH3_D53E/4D4C/GVL1_N93G	SEQ ID NO:356	SEQ ID NO:387
4D4CVH3_D53Q/4D4C/GVL1_N93G	SEQ ID NO:357	SEQ ID NO:387
4D4CVH3_D53L/4D4C/GVL1_N93G	SEQ ID NO:358	SEQ ID NO:387
4D4CVH3_G54A/4D4C/GVL1_N93G	SEQ ID NO:359	SEQ ID NO:387
4D4CVH3_D53G/4D4C/GVL1_N93E	SEQ ID NO:355	SEQ ID NO:388
4D4CVH3_D53E/4D4C/GVL1_N93E	SEQ ID NO:356	SEQ ID NO:388
4D4CVH3_D53Q/4D4C/GVL1_N93E	SEQ ID NO:357	SEQ ID NO:388
4D4CVH3_D53L/4D4C/GVL1_N93E	SEQ ID NO:358	SEQ ID NO:388
4D4CVH3_G54A/4D4C/GVL1_N93E	SEQ ID NO:359	SEQ ID NO:388
4D4CVH3_D53G/4D4C/GVL1_N93L	SEQ ID NO:355	SEQ ID NO:389
4D4CVH3_D53E/4D4C/GVL1_N93L	SEQ ID NO:356	SEQ ID NO:389
4D4CVH3_D53Q/4D4C/GVL1_N93L	SEQ ID NO:357	SEQ ID NO:389
4D4CVH3_D53L/4D4C/GVL1_N93L	SEQ ID NO:358	SEQ ID NO:389
4D4CVH3_G54A/4D4C/GVL1_N93L	SEQ ID NO:359	SEQ ID NO:389
4D4CVH3_D53G/4D4C/GVL1_N93Q	SEQ ID NO:355	SEQ ID NO:390
4D4CVH3_D53E/4D4C/GVL1_N93Q	SEQ ID NO:356	SEQ ID NO:390
4D4CVH3_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:357	SEQ ID NO:390
4D4CVH3_D53L/4D4C/GVL1_N93Q	SEQ ID NO:358	SEQ ID NO:390
4D4CVH3_G54A/4D4C/GVL1_N93Q	SEQ ID NO:359	SEQ ID NO:390
4D4CVH3_D53G/4D4C/GVL1_G94A	SEQ ID NO:355	SEQ ID NO:391
4D4CVH3_D53E/4D4C/GVL1_G94A	SEQ ID NO:356	SEQ ID NO:391
4D4CVH3_D53Q/4D4C/GVL1_G94A	SEQ ID NO:357	SEQ ID NO:391
4D4CVH3_D53L/4D4C/GVL1_G94A	SEQ ID NO:358	SEQ ID NO:391

4D4CVH3_G54A/4D4C/GVL1_G94A	SEQ ID NO:359	SEQ ID NO:391
4D4CVH3/4D4CVL2_N93G	SEQ ID NO:258	SEQ ID NO:392
4D4CVH3/4D4CVL2_N93E	SEQ ID NO:258	SEQ ID NO:393
4D4CVH3/4D4CVL2_N93L	SEQ ID NO:258	SEQ ID NO:394
4D4CVH3/4D4CVL2_N93Q	SEQ ID NO:258	SEQ ID NO:395
4D4CVH3/4D4CVL2_G94A	SEQ ID NO:258	SEQ ID NO:396
4D4CVH3_D53G/4D4CVL2	SEQ ID NO:355	SEQ ID NO:269
4D4CVH3_D53E/4D4CVL2	SEQ ID NO:356	SEQ ID NO:269
4D4CVH3_D53Q/4D4CVL2	SEQ ID NO:357	SEQ ID NO:269
4D4CVH3_D53L/4D4CVL2	SEQ ID NO:358	SEQ ID NO:269
4D4CVH3_G54A/4D4CVL2	SEQ ID NO:359	SEQ ID NO:269
4D4CVH3_D53G/4D4CVL2_N93G	SEQ ID NO:355	SEQ ID NO:392
4D4CVH3_D53E/4D4CVL2_N93G	SEQ ID NO:356	SEQ ID NO:392
4D4CVH3_D53Q/4D4CVL2_N93G	SEQ ID NO:357	SEQ ID NO:392
4D4CVH3_D53L/4D4CVL2_N93G	SEQ ID NO:358	SEQ ID NO:392
4D4CVH3_G54A/4D4CVL2_N93G	SEQ ID NO:359	SEQ ID NO:392
4D4CVH3_D53G/4D4CVL2_N93E	SEQ ID NO:355	SEQ ID NO:393
4D4CVH3_D53E/4D4CVL2_N93E	SEQ ID NO:356	SEQ ID NO:393
4D4CVH3_D53Q/4D4CVL2_N93E	SEQ ID NO:357	SEQ ID NO:393
4D4CVH3_D53L/4D4CVL2_N93E	SEQ ID NO:358	SEQ ID NO:393
4D4CVH3_G54A/4D4CVL2_N93E	SEQ ID NO:359	SEQ ID NO:393
4D4CVH3_D53G/4D4CVL2_N93L	SEQ ID NO:355	SEQ ID NO:394
4D4CVH3_D53E/4D4CVL2_N93L	SEQ ID NO:356	SEQ ID NO:394
4D4CVH3_D53Q/4D4CVL2_N93L	SEQ ID NO:357	SEQ ID NO:394
4D4CVH3_D53L/4D4CVL2_N93L	SEQ ID NO:358	SEQ ID NO:394
4D4CVH3_G54A/4D4CVL2_N93L	SEQ ID NO:359	SEQ ID NO:394
4D4CVH3_D53G/4D4CVL2_N93Q	SEQ ID NO:355	SEQ ID NO:395
4D4CVH3_D53E/4D4CVL2_N93Q	SEQ ID NO:356	SEQ ID NO:395
4D4CVH3_D53Q/4D4CVL2_N93Q	SEQ ID NO:357	SEQ ID NO:395
4D4CVH3_D53L/4D4CVL2_N93Q	SEQ ID NO:358	SEQ ID NO:395
4D4CVH3_G54A/4D4CVL2_N93Q	SEQ ID NO:359	SEQ ID NO:395
4D4CVH3_D53G/4D4CVL2_G94A	SEQ ID NO:355	SEQ ID NO:396
4D4CVH3_D53E/4D4CVL2_G94A	SEQ ID NO:356	SEQ ID NO:396
4D4CVH3_D53Q/4D4CVL2_G94A	SEQ ID NO:357	SEQ ID NO:396
4D4CVH3_D53L/4D4CVL2_G94A	SEQ ID NO:358	SEQ ID NO:396
4D4CVH3_G54A/4D4CVL2_G94A	SEQ ID NO:359	SEQ ID NO:396
4D4CVH3/4D4CVL4_N93G	SEQ ID NO:258	SEQ ID NO:397
4D4CVH3/4D4CVL4_N93E	SEQ ID NO:258	SEQ ID NO:398
4D4CVH3/4D4CVL4_N93L	SEQ ID NO:258	SEQ ID NO:399
4D4CVH3/4D4CVL4_N93Q	SEQ ID NO:258	SEQ ID NO:400
4D4CVH3/4D4CVL4_G94A	SEQ ID NO:258	SEQ ID NO:401
4D4CVH3_D53G/4D4CVL4	SEQ ID NO:355	SEQ ID NO:273
4D4CVH3_D53E/4D4CVL4	SEQ ID NO:356	SEQ ID NO:273
4D4CVH3_D53Q/4D4CVL4	SEQ ID NO:357	SEQ ID NO:273
4D4CVH3_D53L/4D4CVL4	SEQ ID NO:358	SEQ ID NO:273
4D4CVH3_G54A/4D4CVL4	SEQ ID NO:359	SEQ ID NO:273
4D4CVH3_D53G/4D4CVL4_N93G	SEQ ID NO:355	SEQ ID NO:397
4D4CVH3_D53E/4D4CVL4_N93G	SEQ ID NO:356	SEQ ID NO:397
4D4CVH3_D53Q/4D4CVL4_N93G	SEQ ID NO:357	SEQ ID NO:397
4D4CVH3_D53L/4D4CVL4_N93G	SEQ ID NO:358	SEQ ID NO:397
4D4CVH3_G54A/4D4CVL4_N93G	SEQ ID NO:359	SEQ ID NO:397
4D4CVH3_D53G/4D4CVL4_N93E	SEQ ID NO:355	SEQ ID NO:398
4D4CVH3_D53E/4D4CVL4_N93E	SEQ ID NO:356	SEQ ID NO:398
4D4CVH3_D53Q/4D4CVL4_N93E	SEQ ID NO:357	SEQ ID NO:398
4D4CVH3_D53L/4D4CVL4_N93E	SEQ ID NO:358	SEQ ID NO:398
4D4CVH3_G54A/4D4CVL4_N93E	SEQ ID NO:359	SEQ ID NO:398
4D4CVH3_D53G/4D4CVL4_N93L	SEQ ID NO:355	SEQ ID NO:399
4D4CVH3_D53E/4D4CVL4_N93L	SEQ ID NO:356	SEQ ID NO:399
4D4CVH3_D53Q/4D4CVL4_N93L	SEQ ID NO:357	SEQ ID NO:399
4D4CVH3_D53L/4D4CVL4_N93L	SEQ ID NO:358	SEQ ID NO:399
4D4CVH3_G54A/4D4CVL4_N93L	SEQ ID NO:359	SEQ ID NO:399
4D4CVH3_D53G/4D4CVL4_N93Q	SEQ ID NO:355	SEQ ID NO:400
4D4CVH3_D53E/4D4CVL4_N93Q	SEQ ID NO:356	SEQ ID NO:400
4D4CVH3_D53Q/4D4CVL4_N93Q	SEQ ID NO:357	SEQ ID NO:400
4D4CVH3_D53L/4D4CVL4_N93Q	SEQ ID NO:358	SEQ ID NO:400
4D4CVH3_G54A/4D4CVL4_N93Q	SEQ ID NO:359	SEQ ID NO:400
4D4CVH3_D53G/4D4CVL4_G94A	SEQ ID NO:355	SEQ ID NO:401
4D4CVH3_D53E/4D4CVL4_G94A	SEQ ID NO:356	SEQ ID NO:401
4D4CVH3_D53Q/4D4CVL4_G94A	SEQ ID NO:357	SEQ ID NO:401
4D4CVH3_D53L/4D4CVL4_G94A	SEQ ID NO:358	SEQ ID NO:401

4D4CVH3_G54A/4D4CVL4_G94A	SEQ ID NO:359	SEQ ID NO:401
4D4CVH3/4D4GVL3_N93G	SEQ ID NO:258	SEQ ID NO:402
4D4CVH3/4D4GVL3_N93E	SEQ ID NO:258	SEQ ID NO:403
4D4CVH3/4D4GVL3_N93L	SEQ ID NO:258	SEQ ID NO:404
4D4CVH3/4D4GVL3_N93Q	SEQ ID NO:258	SEQ ID NO:405
4D4CVH3/4D4GVL3_G94A	SEQ ID NO:258	SEQ ID NO:406
4D4CVH3_D53G/4D4GVL3	SEQ ID NO:355	SEQ ID NO:276
4D4CVH3_D53E/4D4GVL3	SEQ ID NO:356	SEQ ID NO:276
4D4CVH3_D53Q/4D4GVL3	SEQ ID NO:357	SEQ ID NO:276
4D4CVH3_D53L/4D4GVL3	SEQ ID NO:358	SEQ ID NO:276
4D4CVH3_G54A/4D4GVL3	SEQ ID NO:359	SEQ ID NO:276
4D4CVH3_D53G/4D4GVL3_N93G	SEQ ID NO:355	SEQ ID NO:402
4D4CVH3_D53E/4D4GVL3_N93G	SEQ ID NO:356	SEQ ID NO:402
4D4CVH3_D53Q/4D4GVL3_N93G	SEQ ID NO:357	SEQ ID NO:402
4D4CVH3_D53L/4D4GVL3_N93G	SEQ ID NO:358	SEQ ID NO:402
4D4CVH3_G54A/4D4GVL3_N93G	SEQ ID NO:359	SEQ ID NO:402
4D4CVH3_D53G/4D4GVL3_N93E	SEQ ID NO:355	SEQ ID NO:403
4D4CVH3_D53E/4D4GVL3_N93E	SEQ ID NO:356	SEQ ID NO:403
4D4CVH3_D53Q/4D4GVL3_N93E	SEQ ID NO:357	SEQ ID NO:403
4D4CVH3_D53L/4D4GVL3_N93E	SEQ ID NO:358	SEQ ID NO:403
4D4CVH3_G54A/4D4GVL3_N93E	SEQ ID NO:359	SEQ ID NO:403
4D4CVH3_D53G/4D4GVL3_N93L	SEQ ID NO:355	SEQ ID NO:404
4D4CVH3_D53E/4D4GVL3_N93L	SEQ ID NO:356	SEQ ID NO:404
4D4CVH3_D53Q/4D4GVL3_N93L	SEQ ID NO:357	SEQ ID NO:404
4D4CVH3_D53L/4D4GVL3_N93L	SEQ ID NO:358	SEQ ID NO:404
4D4CVH3_G54A/4D4GVL3_N93L	SEQ ID NO:359	SEQ ID NO:404
4D4CVH3_D53G/4D4GVL3_N93Q	SEQ ID NO:355	SEQ ID NO:405
4D4CVH3_D53E/4D4GVL3_N93Q	SEQ ID NO:356	SEQ ID NO:405
4D4CVH3_D53Q/4D4GVL3_N93Q	SEQ ID NO:357	SEQ ID NO:405
4D4CVH3_D53L/4D4GVL3_N93Q	SEQ ID NO:358	SEQ ID NO:405
4D4CVH3_G54A/4D4GVL3_N93Q	SEQ ID NO:359	SEQ ID NO:405
4D4CVH3_D53G/4D4GVL3_G94A	SEQ ID NO:355	SEQ ID NO:406
4D4CVH3_D53E/4D4GVL3_G94A	SEQ ID NO:356	SEQ ID NO:406
4D4CVH3_D53Q/4D4GVL3_G94A	SEQ ID NO:357	SEQ ID NO:406
4D4CVH3_D53L/4D4GVL3_G94A	SEQ ID NO:358	SEQ ID NO:406
4D4CVH3_G54A/4D4GVL3_G94A	SEQ ID NO:359	SEQ ID NO:406
4D4CVH3/4D4GVL4_N93G	SEQ ID NO:258	SEQ ID NO:407
4D4CVH3/4D4GVL4_N93E	SEQ ID NO:258	SEQ ID NO:408
4D4CVH3/4D4GVL4_N93L	SEQ ID NO:258	SEQ ID NO:409
4D4CVH3/4D4GVL4_N93Q	SEQ ID NO:258	SEQ ID NO:410
4D4CVH3/4D4GVL4_G94A	SEQ ID NO:258	SEQ ID NO:411
4D4CVH3_D53G/4D4GVL4	SEQ ID NO:355	SEQ ID NO:278
4D4CVH3_D53E/4D4GVL4	SEQ ID NO:356	SEQ ID NO:278
4D4CVH3_D53Q/4D4GVL4	SEQ ID NO:357	SEQ ID NO:278
4D4CVH3_D53L/4D4GVL4	SEQ ID NO:358	SEQ ID NO:278
4D4CVH3_G54A/4D4GVL4	SEQ ID NO:359	SEQ ID NO:278
4D4CVH3_D53G/4D4GVL4_N93G	SEQ ID NO:355	SEQ ID NO:407
4D4CVH3_D53E/4D4GVL4_N93G	SEQ ID NO:356	SEQ ID NO:407
4D4CVH3_D53Q/4D4GVL4_N93G	SEQ ID NO:357	SEQ ID NO:407
4D4CVH3_D53L/4D4GVL4_N93G	SEQ ID NO:358	SEQ ID NO:407
4D4CVH3_G54A/4D4GVL4_N93G	SEQ ID NO:359	SEQ ID NO:407
4D4CVH3_D53G/4D4GVL4_N93E	SEQ ID NO:355	SEQ ID NO:408
4D4CVH3_D53E/4D4GVL4_N93E	SEQ ID NO:356	SEQ ID NO:408
4D4CVH3_D53Q/4D4GVL4_N93E	SEQ ID NO:357	SEQ ID NO:408
4D4CVH3_D53L/4D4GVL4_N93E	SEQ ID NO:358	SEQ ID NO:408
4D4CVH3_G54A/4D4GVL4_N93E	SEQ ID NO:359	SEQ ID NO:408
4D4CVH3_D53G/4D4GVL4_N93L	SEQ ID NO:355	SEQ ID NO:409
4D4CVH3_D53E/4D4GVL4_N93L	SEQ ID NO:356	SEQ ID NO:409
4D4CVH3_D53Q/4D4GVL4_N93L	SEQ ID NO:357	SEQ ID NO:409
4D4CVH3_D53L/4D4GVL4_N93L	SEQ ID NO:358	SEQ ID NO:409
4D4CVH3_G54A/4D4GVL4_N93L	SEQ ID NO:359	SEQ ID NO:409
4D4CVH3_D53G/4D4GVL4_N93Q	SEQ ID NO:355	SEQ ID NO:410
4D4CVH3_D53E/4D4GVL4_N93Q	SEQ ID NO:356	SEQ ID NO:410
4D4CVH3_D53Q/4D4GVL4_N93Q	SEQ ID NO:357	SEQ ID NO:410
4D4CVH3_D53L/4D4GVL4_N93Q	SEQ ID NO:358	SEQ ID NO:410
4D4CVH3_G54A/4D4GVL4_N93Q	SEQ ID NO:359	SEQ ID NO:410
4D4CVH3_D53G/4D4GVL4_G94A	SEQ ID NO:355	SEQ ID NO:411
4D4CVH3_D53E/4D4GVL4_G94A	SEQ ID NO:356	SEQ ID NO:411
4D4CVH3_D53Q/4D4GVL4_G94A	SEQ ID NO:357	SEQ ID NO:411
4D4CVH3_D53L/4D4GVL4_G94A	SEQ ID NO:358	SEQ ID NO:411

4D4CVH3_G54A/4D4GVL4_G94A	SEQ ID NO:359	SEQ ID NO:411
4D4CVH4/4D4C/GVL1_N93G	SEQ ID NO:261	SEQ ID NO:387
4D4CVH4/4D4C/GVL1_N93E	SEQ ID NO:261	SEQ ID NO:388
4D4CVH4/4D4C/GVL1_N93L	SEQ ID NO:261	SEQ ID NO:389
4D4CVH4/4D4C/GVL1_N93Q	SEQ ID NO:261	SEQ ID NO:390
4D4CVH4/4D4C/GVL1_G94A	SEQ ID NO:261	SEQ ID NO:391
4D4CVH4_D53G/4D4C/GVL1	SEQ ID NO:360	SEQ ID NO:266
4D4CVH4_D53E/4D4C/GVL1	SEQ ID NO:361	SEQ ID NO:266
4D4CVH4_D53Q/4D4C/GVL1	SEQ ID NO:362	SEQ ID NO:266
4D4CVH4_D53L/4D4C/GVL1	SEQ ID NO:363	SEQ ID NO:266
4D4CVH4_G54A/4D4C/GVL1	SEQ ID NO:364	SEQ ID NO:266
4D4CVH4_D53G/4D4C/GVL1_N93G	SEQ ID NO:360	SEQ ID NO:387
4D4CVH4_D53E/4D4C/GVL1_N93G	SEQ ID NO:361	SEQ ID NO:387
4D4CVH4_D53Q/4D4C/GVL1_N93G	SEQ ID NO:362	SEQ ID NO:387
4D4CVH4_D53L/4D4C/GVL1_N93G	SEQ ID NO:363	SEQ ID NO:387
4D4CVH4_G54A/4D4C/GVL1_N93G	SEQ ID NO:364	SEQ ID NO:387
4D4CVH4_D53G/4D4C/GVL1_N93E	SEQ ID NO:360	SEQ ID NO:388
4D4CVH4_D53E/4D4C/GVL1_N93E	SEQ ID NO:361	SEQ ID NO:388
4D4CVH4_D53Q/4D4C/GVL1_N93E	SEQ ID NO:362	SEQ ID NO:388
4D4CVH4_D53L/4D4C/GVL1_N93E	SEQ ID NO:363	SEQ ID NO:388
4D4CVH4_G54A/4D4C/GVL1_N93E	SEQ ID NO:364	SEQ ID NO:388
4D4CVH4_D53G/4D4C/GVL1_N93L	SEQ ID NO:360	SEQ ID NO:389
4D4CVH4_D53E/4D4C/GVL1_N93L	SEQ ID NO:361	SEQ ID NO:389
4D4CVH4_D53Q/4D4C/GVL1_N93L	SEQ ID NO:362	SEQ ID NO:389
4D4CVH4_D53L/4D4C/GVL1_N93L	SEQ ID NO:363	SEQ ID NO:389
4D4CVH4_G54A/4D4C/GVL1_N93L	SEQ ID NO:364	SEQ ID NO:389
4D4CVH4_D53G/4D4C/GVL1_N93Q	SEQ ID NO:360	SEQ ID NO:390
4D4CVH4_D53E/4D4C/GVL1_N93Q	SEQ ID NO:361	SEQ ID NO:390
4D4CVH4_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:362	SEQ ID NO:390
4D4CVH4_D53L/4D4C/GVL1_N93Q	SEQ ID NO:363	SEQ ID NO:390
4D4CVH4_G54A/4D4C/GVL1_N93Q	SEQ ID NO:364	SEQ ID NO:390
4D4CVH4_D53G/4D4C/GVL1_G94A	SEQ ID NO:360	SEQ ID NO:391
4D4CVH4_D53E/4D4C/GVL1_G94A	SEQ ID NO:361	SEQ ID NO:391
4D4CVH4_D53Q/4D4C/GVL1_G94A	SEQ ID NO:362	SEQ ID NO:391
4D4CVH4_D53L/4D4C/GVL1_G94A	SEQ ID NO:363	SEQ ID NO:391
4D4CVH4_G54A/4D4C/GVL1_G94A	SEQ ID NO:364	SEQ ID NO:391
4D4CVH4/4D4CVL2_N93G	SEQ ID NO:261	SEQ ID NO:392
4D4CVH4/4D4CVL2_N93E	SEQ ID NO:261	SEQ ID NO:393
4D4CVH4/4D4CVL2_N93L	SEQ ID NO:261	SEQ ID NO:394
4D4CVH4/4D4CVL2_N93Q	SEQ ID NO:261	SEQ ID NO:395
4D4CVH4/4D4CVL2_G94A	SEQ ID NO:261	SEQ ID NO:396
4D4CVH4_D53G/4D4CVL2	SEQ ID NO:360	SEQ ID NO:269
4D4CVH4_D53E/4D4CVL2	SEQ ID NO:361	SEQ ID NO:269
4D4CVH4_D53Q/4D4CVL2	SEQ ID NO:362	SEQ ID NO:269
4D4CVH4_D53L/4D4CVL2	SEQ ID NO:363	SEQ ID NO:269
4D4CVH4_G54A/4D4CVL2	SEQ ID NO:364	SEQ ID NO:269
4D4CVH4_D53G/4D4CVL2_N93G	SEQ ID NO:360	SEQ ID NO:392
4D4CVH4_D53E/4D4CVL2_N93G	SEQ ID NO:361	SEQ ID NO:392
4D4CVH4_D53Q/4D4CVL2_N93G	SEQ ID NO:362	SEQ ID NO:392
4D4CVH4_D53L/4D4CVL2_N93G	SEQ ID NO:363	SEQ ID NO:392
4D4CVH4_G54A/4D4CVL2_N93G	SEQ ID NO:364	SEQ ID NO:392
4D4CVH4_D53G/4D4CVL2_N93E	SEQ ID NO:360	SEQ ID NO:393
4D4CVH4_D53E/4D4CVL2_N93E	SEQ ID NO:361	SEQ ID NO:393
4D4CVH4_D53Q/4D4CVL2_N93E	SEQ ID NO:362	SEQ ID NO:393
4D4CVH4_D53L/4D4CVL2_N93E	SEQ ID NO:363	SEQ ID NO:393
4D4CVH4_G54A/4D4CVL2_N93E	SEQ ID NO:364	SEQ ID NO:393
4D4CVH4_D53G/4D4CVL2_N93L	SEQ ID NO:360	SEQ ID NO:394
4D4CVH4_D53E/4D4CVL2_N93L	SEQ ID NO:361	SEQ ID NO:394
4D4CVH4_D53Q/4D4CVL2_N93L	SEQ ID NO:362	SEQ ID NO:394
4D4CVH4_D53L/4D4CVL2_N93L	SEQ ID NO:363	SEQ ID NO:394
4D4CVH4_G54A/4D4CVL2_N93L	SEQ ID NO:364	SEQ ID NO:394
4D4CVH4_D53G/4D4CVL2_N93Q	SEQ ID NO:360	SEQ ID NO:395
4D4CVH4_D53E/4D4CVL2_N93Q	SEQ ID NO:361	SEQ ID NO:395
4D4CVH4_D53Q/4D4CVL2_N93Q	SEQ ID NO:362	SEQ ID NO:395
4D4CVH4_D53L/4D4CVL2_N93Q	SEQ ID NO:363	SEQ ID NO:395
4D4CVH4_G54A/4D4CVL2_N93Q	SEQ ID NO:364	SEQ ID NO:395
4D4CVH4_D53G/4D4CVL2_G94A	SEQ ID NO:360	SEQ ID NO:396
4D4CVH4_D53E/4D4CVL2_G94A	SEQ ID NO:361	SEQ ID NO:396
4D4CVH4_D53Q/4D4CVL2_G94A	SEQ ID NO:362	SEQ ID NO:396
4D4CVH4_D53L/4D4CVL2_G94A	SEQ ID NO:363	SEQ ID NO:396

4D4CVH4_G54A/4D4CVL2_G94A	SEQ ID NO:364	SEQ ID NO:396
4D4CVH4/4D4CVL4_N93G	SEQ ID NO:261	SEQ ID NO:397
4D4CVH4/4D4CVL4_N93E	SEQ ID NO:261	SEQ ID NO:398
4D4CVH4/4D4CVL4_N93L	SEQ ID NO:261	SEQ ID NO:399
4D4CVH4/4D4CVL4_N93Q	SEQ ID NO:261	SEQ ID NO:400
4D4CVH4/4D4CVL4_G94A	SEQ ID NO:261	SEQ ID NO:401
4D4CVH4_D53G/4D4CVL4	SEQ ID NO:360	SEQ ID NO:273
4D4CVH4_D53E/4D4CVL4	SEQ ID NO:361	SEQ ID NO:273
4D4CVH4_D53Q/4D4CVL4	SEQ ID NO:362	SEQ ID NO:273
4D4CVH4_D53L/4D4CVL4	SEQ ID NO:363	SEQ ID NO:273
4D4CVH4_G54A/4D4CVL4	SEQ ID NO:364	SEQ ID NO:273
4D4CVH4_D53G/4D4CVL4_N93G	SEQ ID NO:360	SEQ ID NO:397
4D4CVH4_D53E/4D4CVL4_N93G	SEQ ID NO:361	SEQ ID NO:397
4D4CVH4_D53Q/4D4CVL4_N93G	SEQ ID NO:362	SEQ ID NO:397
4D4CVH4_D53L/4D4CVL4_N93G	SEQ ID NO:363	SEQ ID NO:397
4D4CVH4_G54A/4D4CVL4_N93G	SEQ ID NO:364	SEQ ID NO:397
4D4CVH4_D53G/4D4CVL4_N93E	SEQ ID NO:360	SEQ ID NO:398
4D4CVH4_D53E/4D4CVL4_N93E	SEQ ID NO:361	SEQ ID NO:398
4D4CVH4_D53Q/4D4CVL4_N93E	SEQ ID NO:362	SEQ ID NO:398
4D4CVH4_D53L/4D4CVL4_N93E	SEQ ID NO:363	SEQ ID NO:398
4D4CVH4_G54A/4D4CVL4_N93E	SEQ ID NO:364	SEQ ID NO:398
4D4CVH4_D53G/4D4CVL4_N93L	SEQ ID NO:360	SEQ ID NO:399
4D4CVH4_D53E/4D4CVL4_N93L	SEQ ID NO:361	SEQ ID NO:399
4D4CVH4_D53Q/4D4CVL4_N93L	SEQ ID NO:362	SEQ ID NO:399
4D4CVH4_D53L/4D4CVL4_N93L	SEQ ID NO:363	SEQ ID NO:399
4D4CVH4_G54A/4D4CVL4_N93L	SEQ ID NO:364	SEQ ID NO:399
4D4CVH4_D53G/4D4CVL4_N93Q	SEQ ID NO:360	SEQ ID NO:400
4D4CVH4_D53E/4D4CVL4_N93Q	SEQ ID NO:361	SEQ ID NO:400
4D4CVH4_D53Q/4D4CVL4_N93Q	SEQ ID NO:362	SEQ ID NO:400
4D4CVH4_D53L/4D4CVL4_N93Q	SEQ ID NO:363	SEQ ID NO:400
4D4CVH4_G54A/4D4CVL4_N93Q	SEQ ID NO:364	SEQ ID NO:400
4D4CVH4_D53G/4D4CVL4_G94A	SEQ ID NO:360	SEQ ID NO:401
4D4CVH4_D53E/4D4CVL4_G94A	SEQ ID NO:361	SEQ ID NO:401
4D4CVH4_D53Q/4D4CVL4_G94A	SEQ ID NO:362	SEQ ID NO:401
4D4CVH4_D53L/4D4CVL4_G94A	SEQ ID NO:363	SEQ ID NO:401
4D4CVH4_G54A/4D4CVL4_G94A	SEQ ID NO:364	SEQ ID NO:401
4D4CVH4/4D4GVL3_N93G	SEQ ID NO:261	SEQ ID NO:402
4D4CVH4/4D4GVL3_N93E	SEQ ID NO:261	SEQ ID NO:403
4D4CVH4/4D4GVL3_N93L	SEQ ID NO:261	SEQ ID NO:404
4D4CVH4/4D4GVL3_N93Q	SEQ ID NO:261	SEQ ID NO:405
4D4CVH4/4D4GVL3_G94A	SEQ ID NO:261	SEQ ID NO:406
4D4CVH4_D53G/4D4GVL3	SEQ ID NO:360	SEQ ID NO:276
4D4CVH4_D53E/4D4GVL3	SEQ ID NO:361	SEQ ID NO:276
4D4CVH4_D53Q/4D4GVL3	SEQ ID NO:362	SEQ ID NO:276
4D4CVH4_D53L/4D4GVL3	SEQ ID NO:363	SEQ ID NO:276
4D4CVH4_G54A/4D4GVL3	SEQ ID NO:364	SEQ ID NO:276
4D4CVH4_D53G/4D4GVL3_N93G	SEQ ID NO:360	SEQ ID NO:402
4D4CVH4_D53E/4D4GVL3_N93G	SEQ ID NO:361	SEQ ID NO:402
4D4CVH4_D53Q/4D4GVL3_N93G	SEQ ID NO:362	SEQ ID NO:402
4D4CVH4_D53L/4D4GVL3_N93G	SEQ ID NO:363	SEQ ID NO:402
4D4CVH4_G54A/4D4GVL3_N93G	SEQ ID NO:364	SEQ ID NO:402
4D4CVH4_D53G/4D4GVL3_N93E	SEQ ID NO:360	SEQ ID NO:403
4D4CVH4_D53E/4D4GVL3_N93E	SEQ ID NO:361	SEQ ID NO:403
4D4CVH4_D53Q/4D4GVL3_N93E	SEQ ID NO:362	SEQ ID NO:403
4D4CVH4_D53L/4D4GVL3_N93E	SEQ ID NO:363	SEQ ID NO:403
4D4CVH4_G54A/4D4GVL3_N93E	SEQ ID NO:364	SEQ ID NO:403
4D4CVH4_D53G/4D4GVL3_N93L	SEQ ID NO:360	SEQ ID NO:404
4D4CVH4_D53E/4D4GVL3_N93L	SEQ ID NO:361	SEQ ID NO:404
4D4CVH4_D53Q/4D4GVL3_N93L	SEQ ID NO:362	SEQ ID NO:404
4D4CVH4_D53L/4D4GVL3_N93L	SEQ ID NO:363	SEQ ID NO:404
4D4CVH4_G54A/4D4GVL3_N93L	SEQ ID NO:364	SEQ ID NO:404
4D4CVH4_D53G/4D4GVL3_N93Q	SEQ ID NO:360	SEQ ID NO:405
4D4CVH4_D53E/4D4GVL3_N93Q	SEQ ID NO:361	SEQ ID NO:405
4D4CVH4_D53Q/4D4GVL3_N93Q	SEQ ID NO:362	SEQ ID NO:405
4D4CVH4_D53L/4D4GVL3_N93Q	SEQ ID NO:363	SEQ ID NO:405
4D4CVH4_G54A/4D4GVL3_N93Q	SEQ ID NO:364	SEQ ID NO:405
4D4CVH4_D53G/4D4GVL3_G94A	SEQ ID NO:360	SEQ ID NO:406
4D4CVH4_D53E/4D4GVL3_G94A	SEQ ID NO:361	SEQ ID NO:406
4D4CVH4_D53Q/4D4GVL3_G94A	SEQ ID NO:362	SEQ ID NO:406
4D4CVH4_D53L/4D4GVL3_G94A	SEQ ID NO:363	SEQ ID NO:406

4D4CVH4_G54A/4D4GVL3_G94A	SEQ ID NO:364	SEQ ID NO:406
4D4CVH4/4D4GVL4_N93G	SEQ ID NO:261	SEQ ID NO:407
4D4CVH4/4D4GVL4_N93E	SEQ ID NO:261	SEQ ID NO:408
4D4CVH4/4D4GVL4_N93L	SEQ ID NO:261	SEQ ID NO:409
4D4CVH4/4D4GVL4_N93Q	SEQ ID NO:261	SEQ ID NO:410
4D4CVH4/4D4GVL4_G94A	SEQ ID NO:261	SEQ ID NO:411
4D4CVH4_D53G/4D4GVL4	SEQ ID NO:360	SEQ ID NO:278
4D4CVH4_D53E/4D4GVL4	SEQ ID NO:361	SEQ ID NO:278
4D4CVH4_D53Q/4D4GVL4	SEQ ID NO:362	SEQ ID NO:278
4D4CVH4_D53L/4D4GVL4	SEQ ID NO:363	SEQ ID NO:278
4D4CVH4_G54A/4D4GVL4	SEQ ID NO:364	SEQ ID NO:278
4D4CVH4_D53G/4D4GVL4_N93G	SEQ ID NO:360	SEQ ID NO:407
4D4CVH4_D53E/4D4GVL4_N93G	SEQ ID NO:361	SEQ ID NO:407
4D4CVH4_D53Q/4D4GVL4_N93G	SEQ ID NO:362	SEQ ID NO:407
4D4CVH4_D53L/4D4GVL4_N93G	SEQ ID NO:363	SEQ ID NO:407
4D4CVH4_G54A/4D4GVL4_N93G	SEQ ID NO:364	SEQ ID NO:407
4D4CVH4_D53G/4D4GVL4_N93E	SEQ ID NO:360	SEQ ID NO:408
4D4CVH4_D53E/4D4GVL4_N93E	SEQ ID NO:361	SEQ ID NO:408
4D4CVH4_D53Q/4D4GVL4_N93E	SEQ ID NO:362	SEQ ID NO:408
4D4CVH4_D53L/4D4GVL4_N93E	SEQ ID NO:363	SEQ ID NO:408
4D4CVH4_G54A/4D4GVL4_N93E	SEQ ID NO:364	SEQ ID NO:408
4D4CVH4_D53G/4D4GVL4_N93L	SEQ ID NO:360	SEQ ID NO:409
4D4CVH4_D53E/4D4GVL4_N93L	SEQ ID NO:361	SEQ ID NO:409
4D4CVH4_D53Q/4D4GVL4_N93L	SEQ ID NO:362	SEQ ID NO:409
4D4CVH4_D53L/4D4GVL4_N93L	SEQ ID NO:363	SEQ ID NO:409
4D4CVH4_G54A/4D4GVL4_N93L	SEQ ID NO:364	SEQ ID NO:409
4D4CVH4_D53G/4D4GVL4_N93Q	SEQ ID NO:360	SEQ ID NO:410
4D4CVH4_D53E/4D4GVL4_N93Q	SEQ ID NO:361	SEQ ID NO:410
4D4CVH4_D53Q/4D4GVL4_N93Q	SEQ ID NO:362	SEQ ID NO:410
4D4CVH4_D53L/4D4GVL4_N93Q	SEQ ID NO:363	SEQ ID NO:410
4D4CVH4_G54A/4D4GVL4_N93Q	SEQ ID NO:364	SEQ ID NO:410
4D4CVH4_D53G/4D4GVL4_G94A	SEQ ID NO:360	SEQ ID NO:411
4D4CVH4_D53E/4D4GVL4_G94A	SEQ ID NO:361	SEQ ID NO:411
4D4CVH4_D53Q/4D4GVL4_G94A	SEQ ID NO:362	SEQ ID NO:411
4D4CVH4_D53L/4D4GVL4_G94A	SEQ ID NO:363	SEQ ID NO:411
4D4CVH4_G54A/4D4GVL4_G94A	SEQ ID NO:364	SEQ ID NO:411
4D4CVH2.1/4D4C/GVL1_N93G	SEQ ID NO:264	SEQ ID NO:387
4D4CVH2.1/4D4C/GVL1_N93E	SEQ ID NO:264	SEQ ID NO:388
4D4CVH2.1/4D4C/GVL1_N93L	SEQ ID NO:264	SEQ ID NO:389
4D4CVH2.1/4D4C/GVL1_N93Q	SEQ ID NO:264	SEQ ID NO:390
4D4CVH2.1/4D4C/GVL1_G94A	SEQ ID NO:264	SEQ ID NO:391
4D4CVH2.1_D53G/4D4C/GVL1	SEQ ID NO:365	SEQ ID NO:266
4D4CVH2.1_D53E/4D4C/GVL1	SEQ ID NO:366	SEQ ID NO:266
4D4CVH2.1_D53Q/4D4C/GVL1	SEQ ID NO:367	SEQ ID NO:266
4D4CVH2.1_D53L/4D4C/GVL1	SEQ ID NO:368	SEQ ID NO:266
4D4CVH2.1_G54A/4D4C/GVL1	SEQ ID NO:369	SEQ ID NO:266
4D4CVH2.1_D53G/4D4C/GVL1_N93G	SEQ ID NO:365	SEQ ID NO:387
4D4CVH2.1_D53E/4D4C/GVL1_N93G	SEQ ID NO:366	SEQ ID NO:387
4D4CVH2.1_D53Q/4D4C/GVL1_N93G	SEQ ID NO:367	SEQ ID NO:387
4D4CVH2.1_D53L/4D4C/GVL1_N93G	SEQ ID NO:368	SEQ ID NO:387
4D4CVH2.1_G54A/4D4C/GVL1_N93G	SEQ ID NO:369	SEQ ID NO:387
4D4CVH2.1_D53G/4D4C/GVL1_N93E	SEQ ID NO:365	SEQ ID NO:388
4D4CVH2.1_D53E/4D4C/GVL1_N93E	SEQ ID NO:366	SEQ ID NO:388
4D4CVH2.1_D53Q/4D4C/GVL1_N93E	SEQ ID NO:367	SEQ ID NO:388
4D4CVH2.1_D53L/4D4C/GVL1_N93E	SEQ ID NO:368	SEQ ID NO:388
4D4CVH2.1_G54A/4D4C/GVL1_N93E	SEQ ID NO:369	SEQ ID NO:388
4D4CVH2.1_D53G/4D4C/GVL1_N93L	SEQ ID NO:365	SEQ ID NO:389
4D4CVH2.1_D53E/4D4C/GVL1_N93L	SEQ ID NO:366	SEQ ID NO:389
4D4CVH2.1_D53Q/4D4C/GVL1_N93L	SEQ ID NO:367	SEQ ID NO:389
4D4CVH2.1_D53L/4D4C/GVL1_N93L	SEQ ID NO:368	SEQ ID NO:389
4D4CVH2.1_G54A/4D4C/GVL1_N93L	SEQ ID NO:369	SEQ ID NO:389
4D4CVH2.1_D53G/4D4C/GVL1_N93Q	SEQ ID NO:365	SEQ ID NO:390
4D4CVH2.1_D53E/4D4C/GVL1_N93Q	SEQ ID NO:366	SEQ ID NO:390
4D4CVH2.1_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:367	SEQ ID NO:390
4D4CVH2.1_D53L/4D4C/GVL1_N93Q	SEQ ID NO:368	SEQ ID NO:390
4D4CVH2.1_G54A/4D4C/GVL1_N93Q	SEQ ID NO:369	SEQ ID NO:390
4D4CVH2.1_D53G/4D4C/GVL1_G94A	SEQ ID NO:365	SEQ ID NO:391
4D4CVH2.1_D53E/4D4C/GVL1_G94A	SEQ ID NO:366	SEQ ID NO:391
4D4CVH2.1_D53Q/4D4C/GVL1_G94A	SEQ ID NO:367	SEQ ID NO:391
4D4CVH2.1_D53L/4D4C/GVL1_G94A	SEQ ID NO:368	SEQ ID NO:391

4D4CVH2.1_G54A/4D4C/GVL1_G94A	SEQ ID NO:369	SEQ ID NO:391
4D4CVH2.1/4D4CVL2_N93G	SEQ ID NO:264	SEQ ID NO:392
4D4CVH2.1/4D4CVL2_N93E	SEQ ID NO:264	SEQ ID NO:393
4D4CVH2.1/4D4CVL2_N93L	SEQ ID NO:264	SEQ ID NO:394
4D4CVH2.1/4D4CVL2_N93Q	SEQ ID NO:264	SEQ ID NO:395
4D4CVH2.1/4D4CVL2_G94A	SEQ ID NO:264	SEQ ID NO:396
4D4CVH2.1_D53G/4D4CVL2	SEQ ID NO:365	SEQ ID NO:269
4D4CVH2.1_D53E/4D4CVL2	SEQ ID NO:366	SEQ ID NO:269
4D4CVH2.1_D53Q/4D4CVL2	SEQ ID NO:367	SEQ ID NO:269
4D4CVH2.1_D53L/4D4CVL2	SEQ ID NO:368	SEQ ID NO:269
4D4CVH2.1_G54A/4D4CVL2	SEQ ID NO:369	SEQ ID NO:269
4D4CVH2.1_D53G/4D4CVL2_N93G	SEQ ID NO:365	SEQ ID NO:392
4D4CVH2.1_D53E/4D4CVL2_N93G	SEQ ID NO:366	SEQ ID NO:392
4D4CVH2.1_D53Q/4D4CVL2_N93G	SEQ ID NO:367	SEQ ID NO:392
4D4CVH2.1_D53L/4D4CVL2_N93G	SEQ ID NO:368	SEQ ID NO:392
4D4CVH2.1_G54A/4D4CVL2_N93G	SEQ ID NO:369	SEQ ID NO:392
4D4CVH2.1_D53G/4D4CVL2_N93E	SEQ ID NO:365	SEQ ID NO:393
4D4CVH2.1_D53E/4D4CVL2_N93E	SEQ ID NO:366	SEQ ID NO:393
4D4CVH2.1_D53Q/4D4CVL2_N93E	SEQ ID NO:367	SEQ ID NO:393
4D4CVH2.1_D53L/4D4CVL2_N93E	SEQ ID NO:368	SEQ ID NO:393
4D4CVH2.1_G54A/4D4CVL2_N93E	SEQ ID NO:369	SEQ ID NO:393
4D4CVH2.1_D53G/4D4CVL2_N93L	SEQ ID NO:365	SEQ ID NO:394
4D4CVH2.1_D53E/4D4CVL2_N93L	SEQ ID NO:366	SEQ ID NO:394
4D4CVH2.1_D53Q/4D4CVL2_N93L	SEQ ID NO:367	SEQ ID NO:394
4D4CVH2.1_D53L/4D4CVL2_N93L	SEQ ID NO:368	SEQ ID NO:394
4D4CVH2.1_G54A/4D4CVL2_N93L	SEQ ID NO:369	SEQ ID NO:394
4D4CVH2.1_D53G/4D4CVL2_N93Q	SEQ ID NO:365	SEQ ID NO:395
4D4CVH2.1_D53E/4D4CVL2_N93Q	SEQ ID NO:366	SEQ ID NO:395
4D4CVH2.1_D53Q/4D4CVL2_N93Q	SEQ ID NO:367	SEQ ID NO:395
4D4CVH2.1_D53L/4D4CVL2_N93Q	SEQ ID NO:368	SEQ ID NO:395
4D4CVH2.1_G54A/4D4CVL2_N93Q	SEQ ID NO:369	SEQ ID NO:395
4D4CVH2.1_D53G/4D4CVL2_G94A	SEQ ID NO:365	SEQ ID NO:396
4D4CVH2.1_D53E/4D4CVL2_G94A	SEQ ID NO:366	SEQ ID NO:396
4D4CVH2.1_D53Q/4D4CVL2_G94A	SEQ ID NO:367	SEQ ID NO:396
4D4CVH2.1_D53L/4D4CVL2_G94A	SEQ ID NO:368	SEQ ID NO:396
4D4CVH2.1_G54A/4D4CVL2_G94A	SEQ ID NO:369	SEQ ID NO:396
4D4CVH2.1/4D4CVL4_N93G	SEQ ID NO:264	SEQ ID NO:397
4D4CVH2.1/4D4CVL4_N93E	SEQ ID NO:264	SEQ ID NO:398
4D4CVH2.1/4D4CVL4_N93L	SEQ ID NO:264	SEQ ID NO:399
4D4CVH2.1/4D4CVL4_N93Q	SEQ ID NO:264	SEQ ID NO:400
4D4CVH2.1/4D4CVL4_G94A	SEQ ID NO:264	SEQ ID NO:401
4D4CVH2.1_D53G/4D4CVL4	SEQ ID NO:365	SEQ ID NO:273
4D4CVH2.1_D53E/4D4CVL4	SEQ ID NO:366	SEQ ID NO:273
4D4CVH2.1_D53Q/4D4CVL4	SEQ ID NO:367	SEQ ID NO:273
4D4CVH2.1_D53L/4D4CVL4	SEQ ID NO:368	SEQ ID NO:273
4D4CVH2.1_G54A/4D4CVL4	SEQ ID NO:369	SEQ ID NO:273
4D4CVH2.1_D53G/4D4CVL4_N93G	SEQ ID NO:365	SEQ ID NO:397
4D4CVH2.1_D53E/4D4CVL4_N93G	SEQ ID NO:366	SEQ ID NO:397
4D4CVH2.1_D53Q/4D4CVL4_N93G	SEQ ID NO:367	SEQ ID NO:397
4D4CVH2.1_D53L/4D4CVL4_N93G	SEQ ID NO:368	SEQ ID NO:397
4D4CVH2.1_G54A/4D4CVL4_N93G	SEQ ID NO:369	SEQ ID NO:397
4D4CVH2.1_D53G/4D4CVL4_N93E	SEQ ID NO:365	SEQ ID NO:398
4D4CVH2.1_D53E/4D4CVL4_N93E	SEQ ID NO:366	SEQ ID NO:398
4D4CVH2.1_D53Q/4D4CVL4_N93E	SEQ ID NO:367	SEQ ID NO:398
4D4CVH2.1_D53L/4D4CVL4_N93E	SEQ ID NO:368	SEQ ID NO:398
4D4CVH2.1_G54A/4D4CVL4_N93E	SEQ ID NO:369	SEQ ID NO:398
4D4CVH2.1_D53G/4D4CVL4_N93L	SEQ ID NO:365	SEQ ID NO:399
4D4CVH2.1_D53E/4D4CVL4_N93L	SEQ ID NO:366	SEQ ID NO:399
4D4CVH2.1_D53Q/4D4CVL4_N93L	SEQ ID NO:367	SEQ ID NO:399
4D4CVH2.1_D53L/4D4CVL4_N93L	SEQ ID NO:368	SEQ ID NO:399
4D4CVH2.1_G54A/4D4CVL4_N93L	SEQ ID NO:369	SEQ ID NO:399
4D4CVH2.1_D53G/4D4CVL4_N93Q	SEQ ID NO:365	SEQ ID NO:400
4D4CVH2.1_D53E/4D4CVL4_N93Q	SEQ ID NO:366	SEQ ID NO:400
4D4CVH2.1_D53Q/4D4CVL4_N93Q	SEQ ID NO:367	SEQ ID NO:400
4D4CVH2.1_D53L/4D4CVL4_N93Q	SEQ ID NO:368	SEQ ID NO:400
4D4CVH2.1_G54A/4D4CVL4_N93Q	SEQ ID NO:369	SEQ ID NO:400
4D4CVH2.1_D53G/4D4CVL4_G94A	SEQ ID NO:365	SEQ ID NO:401
4D4CVH2.1_D53E/4D4CVL4_G94A	SEQ ID NO:366	SEQ ID NO:401
4D4CVH2.1_D53Q/4D4CVL4_G94A	SEQ ID NO:367	SEQ ID NO:401
4D4CVH2.1_D53L/4D4CVL4_G94A	SEQ ID NO:368	SEQ ID NO:401

4D4CVH2.1_G54A/4D4CVL4_G94A	SEQ ID NO:369	SEQ ID NO:401
4D4CVH2.1/4D4GVL3_N93G	SEQ ID NO:264	SEQ ID NO:402
4D4CVH2.1/4D4GVL3_N93E	SEQ ID NO:264	SEQ ID NO:403
4D4CVH2.1/4D4GVL3_N93L	SEQ ID NO:264	SEQ ID NO:404
4D4CVH2.1/4D4GVL3_N93Q	SEQ ID NO:264	SEQ ID NO:405
4D4CVH2.1/4D4GVL3_G94A	SEQ ID NO:264	SEQ ID NO:406
4D4CVH2.1_D53G/4D4GVL3	SEQ ID NO:365	SEQ ID NO:276
4D4CVH2.1_D53E/4D4GVL3	SEQ ID NO:366	SEQ ID NO:276
4D4CVH2.1_D53Q/4D4GVL3	SEQ ID NO:367	SEQ ID NO:276
4D4CVH2.1_D53L/4D4GVL3	SEQ ID NO:368	SEQ ID NO:276
4D4CVH2.1_G54A/4D4GVL3	SEQ ID NO:369	SEQ ID NO:276
4D4CVH2.1_D53G/4D4GVL3_N93G	SEQ ID NO:365	SEQ ID NO:402
4D4CVH2.1_D53E/4D4GVL3_N93G	SEQ ID NO:366	SEQ ID NO:402
4D4CVH2.1_D53Q/4D4GVL3_N93G	SEQ ID NO:367	SEQ ID NO:402
4D4CVH2.1_D53L/4D4GVL3_N93G	SEQ ID NO:368	SEQ ID NO:402
4D4CVH2.1_G54A/4D4GVL3_N93G	SEQ ID NO:369	SEQ ID NO:402
4D4CVH2.1_D53G/4D4GVL3_N93E	SEQ ID NO:365	SEQ ID NO:403
4D4CVH2.1_D53E/4D4GVL3_N93E	SEQ ID NO:366	SEQ ID NO:403
4D4CVH2.1_D53Q/4D4GVL3_N93E	SEQ ID NO:367	SEQ ID NO:403
4D4CVH2.1_D53L/4D4GVL3_N93E	SEQ ID NO:368	SEQ ID NO:403
4D4CVH2.1_G54A/4D4GVL3_N93E	SEQ ID NO:369	SEQ ID NO:403
4D4CVH2.1_D53G/4D4GVL3_N93L	SEQ ID NO:365	SEQ ID NO:404
4D4CVH2.1_D53E/4D4GVL3_N93L	SEQ ID NO:366	SEQ ID NO:404
4D4CVH2.1_D53Q/4D4GVL3_N93L	SEQ ID NO:367	SEQ ID NO:404
4D4CVH2.1_D53L/4D4GVL3_N93L	SEQ ID NO:368	SEQ ID NO:404
4D4CVH2.1_G54A/4D4GVL3_N93L	SEQ ID NO:369	SEQ ID NO:404
4D4CVH2.1_D53G/4D4GVL3_N93Q	SEQ ID NO:365	SEQ ID NO:405
4D4CVH2.1_D53E/4D4GVL3_N93Q	SEQ ID NO:366	SEQ ID NO:405
4D4CVH2.1_D53Q/4D4GVL3_N93Q	SEQ ID NO:367	SEQ ID NO:405
4D4CVH2.1_D53L/4D4GVL3_N93Q	SEQ ID NO:368	SEQ ID NO:405
4D4CVH2.1_G54A/4D4GVL3_N93Q	SEQ ID NO:369	SEQ ID NO:405
4D4CVH2.1_D53G/4D4GVL3_G94A	SEQ ID NO:365	SEQ ID NO:406
4D4CVH2.1_D53E/4D4GVL3_G94A	SEQ ID NO:366	SEQ ID NO:406
4D4CVH2.1_D53Q/4D4GVL3_G94A	SEQ ID NO:367	SEQ ID NO:406
4D4CVH2.1_D53L/4D4GVL3_G94A	SEQ ID NO:368	SEQ ID NO:406
4D4CVH2.1_G54A/4D4GVL3_G94A	SEQ ID NO:369	SEQ ID NO:406
4D4CVH2.1/4D4GVL4_N93G	SEQ ID NO:264	SEQ ID NO:407
4D4CVH2.1/4D4GVL4_N93E	SEQ ID NO:264	SEQ ID NO:408
4D4CVH2.1/4D4GVL4_N93L	SEQ ID NO:264	SEQ ID NO:409
4D4CVH2.1/4D4GVL4_N93Q	SEQ ID NO:264	SEQ ID NO:410
4D4CVH2.1/4D4GVL4_G94A	SEQ ID NO:264	SEQ ID NO:411
4D4CVH2.1_D53G/4D4GVL4	SEQ ID NO:365	SEQ ID NO:278
4D4CVH2.1_D53E/4D4GVL4	SEQ ID NO:366	SEQ ID NO:278
4D4CVH2.1_D53Q/4D4GVL4	SEQ ID NO:367	SEQ ID NO:278
4D4CVH2.1_D53L/4D4GVL4	SEQ ID NO:368	SEQ ID NO:278
4D4CVH2.1_G54A/4D4GVL4	SEQ ID NO:369	SEQ ID NO:278
4D4CVH2.1_D53G/4D4GVL4_N93G	SEQ ID NO:365	SEQ ID NO:407
4D4CVH2.1_D53E/4D4GVL4_N93G	SEQ ID NO:366	SEQ ID NO:407
4D4CVH2.1_D53Q/4D4GVL4_N93G	SEQ ID NO:367	SEQ ID NO:407
4D4CVH2.1_D53L/4D4GVL4_N93G	SEQ ID NO:368	SEQ ID NO:407
4D4CVH2.1_G54A/4D4GVL4_N93G	SEQ ID NO:369	SEQ ID NO:407
4D4CVH2.1_D53G/4D4GVL4_N93E	SEQ ID NO:365	SEQ ID NO:408
4D4CVH2.1_D53E/4D4GVL4_N93E	SEQ ID NO:366	SEQ ID NO:408
4D4CVH2.1_D53Q/4D4GVL4_N93E	SEQ ID NO:367	SEQ ID NO:408
4D4CVH2.1_D53L/4D4GVL4_N93E	SEQ ID NO:368	SEQ ID NO:408
4D4CVH2.1_G54A/4D4GVL4_N93E	SEQ ID NO:369	SEQ ID NO:408
4D4CVH2.1_D53G/4D4GVL4_N93L	SEQ ID NO:365	SEQ ID NO:409
4D4CVH2.1_D53E/4D4GVL4_N93L	SEQ ID NO:366	SEQ ID NO:409
4D4CVH2.1_D53Q/4D4GVL4_N93L	SEQ ID NO:367	SEQ ID NO:409
4D4CVH2.1_D53L/4D4GVL4_N93L	SEQ ID NO:368	SEQ ID NO:409
4D4CVH2.1_G54A/4D4GVL4_N93L	SEQ ID NO:369	SEQ ID NO:409
4D4CVH2.1_D53G/4D4GVL4_N93Q	SEQ ID NO:365	SEQ ID NO:410
4D4CVH2.1_D53E/4D4GVL4_N93Q	SEQ ID NO:366	SEQ ID NO:410
4D4CVH2.1_D53Q/4D4GVL4_N93Q	SEQ ID NO:367	SEQ ID NO:410
4D4CVH2.1_D53L/4D4GVL4_N93Q	SEQ ID NO:368	SEQ ID NO:410
4D4CVH2.1_G54A/4D4GVL4_N93Q	SEQ ID NO:369	SEQ ID NO:410
4D4CVH2.1_D53G/4D4GVL4_G94A	SEQ ID NO:365	SEQ ID NO:411
4D4CVH2.1_D53E/4D4GVL4_G94A	SEQ ID NO:366	SEQ ID NO:411
4D4CVH2.1_D53Q/4D4GVL4_G94A	SEQ ID NO:367	SEQ ID NO:411
4D4CVH2.1_D53L/4D4GVL4_G94A	SEQ ID NO:368	SEQ ID NO:411

4D4CVH2.1_G54A/4D4GVL4_G94A	SEQ ID NO:369	SEQ ID NO:411
4D4CVH2.2/4D4C/GVL1_N93G	SEQ ID NO:265	SEQ ID NO:387
4D4CVH2.2/4D4C/GVL1_N93E	SEQ ID NO:265	SEQ ID NO:388
4D4CVH2.2/4D4C/GVL1_N93L	SEQ ID NO:265	SEQ ID NO:389
4D4CVH2.2/4D4C/GVL1_N93Q	SEQ ID NO:265	SEQ ID NO:390
4D4CVH2.2/4D4C/GVL1_G94A	SEQ ID NO:265	SEQ ID NO:391
4D4CVH2.2_D53G/4D4C/GVL1	SEQ ID NO:370	SEQ ID NO:266
4D4CVH2.2_D53E/4D4C/GVL1	SEQ ID NO:371	SEQ ID NO:266
4D4CVH2.2_D53Q/4D4C/GVL1	SEQ ID NO:372	SEQ ID NO:266
4D4CVH2.2_D53L/4D4C/GVL1	SEQ ID NO:373	SEQ ID NO:266
4D4CVH2.2_G54A/4D4C/GVL1	SEQ ID NO:374	SEQ ID NO:266
4D4CVH2.2_D53G/4D4C/GVL1_N93G	SEQ ID NO:370	SEQ ID NO:387
4D4CVH2.2_D53E/4D4C/GVL1_N93G	SEQ ID NO:371	SEQ ID NO:387
4D4CVH2.2_D53Q/4D4C/GVL1_N93G	SEQ ID NO:372	SEQ ID NO:387
4D4CVH2.2_D53L/4D4C/GVL1_N93G	SEQ ID NO:373	SEQ ID NO:387
4D4CVH2.2_G54A/4D4C/GVL1_N93G	SEQ ID NO:374	SEQ ID NO:387
4D4CVH2.2_D53G/4D4C/GVL1_N93E	SEQ ID NO:370	SEQ ID NO:388
4D4CVH2.2_D53E/4D4C/GVL1_N93E	SEQ ID NO:371	SEQ ID NO:388
4D4CVH2.2_D53Q/4D4C/GVL1_N93E	SEQ ID NO:372	SEQ ID NO:388
4D4CVH2.2_D53L/4D4C/GVL1_N93E	SEQ ID NO:373	SEQ ID NO:388
4D4CVH2.2_G54A/4D4C/GVL1_N93E	SEQ ID NO:374	SEQ ID NO:388
4D4CVH2.2_D53G/4D4C/GVL1_N93L	SEQ ID NO:370	SEQ ID NO:389
4D4CVH2.2_D53E/4D4C/GVL1_N93L	SEQ ID NO:371	SEQ ID NO:389
4D4CVH2.2_D53Q/4D4C/GVL1_N93L	SEQ ID NO:372	SEQ ID NO:389
4D4CVH2.2_D53L/4D4C/GVL1_N93L	SEQ ID NO:373	SEQ ID NO:389
4D4CVH2.2_G54A/4D4C/GVL1_N93L	SEQ ID NO:374	SEQ ID NO:389
4D4CVH2.2_D53G/4D4C/GVL1_N93Q	SEQ ID NO:370	SEQ ID NO:390
4D4CVH2.2_D53E/4D4C/GVL1_N93Q	SEQ ID NO:371	SEQ ID NO:390
4D4CVH2.2_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:372	SEQ ID NO:390
4D4CVH2.2_D53L/4D4C/GVL1_N93Q	SEQ ID NO:373	SEQ ID NO:390
4D4CVH2.2_G54A/4D4C/GVL1_N93Q	SEQ ID NO:374	SEQ ID NO:390
4D4CVH2.2_D53G/4D4C/GVL1_G94A	SEQ ID NO:370	SEQ ID NO:391
4D4CVH2.2_D53E/4D4C/GVL1_G94A	SEQ ID NO:371	SEQ ID NO:391
4D4CVH2.2_D53Q/4D4C/GVL1_G94A	SEQ ID NO:372	SEQ ID NO:391
4D4CVH2.2_D53L/4D4C/GVL1_G94A	SEQ ID NO:373	SEQ ID NO:391
4D4CVH2.2_G54A/4D4C/GVL1_G94A	SEQ ID NO:374	SEQ ID NO:391
4D4CVH2.2/4D4CVL2_N93G	SEQ ID NO:265	SEQ ID NO:392
4D4CVH2.2/4D4CVL2_N93E	SEQ ID NO:265	SEQ ID NO:393
4D4CVH2.2/4D4CVL2_N93L	SEQ ID NO:265	SEQ ID NO:394
4D4CVH2.2/4D4CVL2_N93Q	SEQ ID NO:265	SEQ ID NO:395
4D4CVH2.2/4D4CVL2_G94A	SEQ ID NO:265	SEQ ID NO:396
4D4CVH2.2_D53G/4D4CVL2	SEQ ID NO:370	SEQ ID NO:269
4D4CVH2.2_D53E/4D4CVL2	SEQ ID NO:371	SEQ ID NO:269
4D4CVH2.2_D53Q/4D4CVL2	SEQ ID NO:372	SEQ ID NO:269
4D4CVH2.2_D53L/4D4CVL2	SEQ ID NO:373	SEQ ID NO:269
4D4CVH2.2_G54A/4D4CVL2	SEQ ID NO:374	SEQ ID NO:269
4D4CVH2.2_D53G/4D4CVL2_N93G	SEQ ID NO:370	SEQ ID NO:392
4D4CVH2.2_D53E/4D4CVL2_N93G	SEQ ID NO:371	SEQ ID NO:392
4D4CVH2.2_D53Q/4D4CVL2_N93G	SEQ ID NO:372	SEQ ID NO:392
4D4CVH2.2_D53L/4D4CVL2_N93G	SEQ ID NO:373	SEQ ID NO:392
4D4CVH2.2_G54A/4D4CVL2_N93G	SEQ ID NO:374	SEQ ID NO:392
4D4CVH2.2_D53G/4D4CVL2_N93E	SEQ ID NO:370	SEQ ID NO:393
4D4CVH2.2_D53E/4D4CVL2_N93E	SEQ ID NO:371	SEQ ID NO:393
4D4CVH2.2_D53Q/4D4CVL2_N93E	SEQ ID NO:372	SEQ ID NO:393
4D4CVH2.2_D53L/4D4CVL2_N93E	SEQ ID NO:373	SEQ ID NO:393
4D4CVH2.2_G54A/4D4CVL2_N93E	SEQ ID NO:374	SEQ ID NO:393
4D4CVH2.2_D53G/4D4CVL2_N93L	SEQ ID NO:370	SEQ ID NO:394
4D4CVH2.2_D53E/4D4CVL2_N93L	SEQ ID NO:371	SEQ ID NO:394
4D4CVH2.2_D53Q/4D4CVL2_N93L	SEQ ID NO:372	SEQ ID NO:394
4D4CVH2.2_D53L/4D4CVL2_N93L	SEQ ID NO:373	SEQ ID NO:394
4D4CVH2.2_G54A/4D4CVL2_N93L	SEQ ID NO:374	SEQ ID NO:394
4D4CVH2.2_D53G/4D4CVL2_N93Q	SEQ ID NO:370	SEQ ID NO:395
4D4CVH2.2_D53E/4D4CVL2_N93Q	SEQ ID NO:371	SEQ ID NO:395
4D4CVH2.2_D53Q/4D4CVL2_N93Q	SEQ ID NO:372	SEQ ID NO:395
4D4CVH2.2_D53L/4D4CVL2_N93Q	SEQ ID NO:373	SEQ ID NO:395
4D4CVH2.2_G54A/4D4CVL2_N93Q	SEQ ID NO:374	SEQ ID NO:395
4D4CVH2.2_D53G/4D4CVL2_G94A	SEQ ID NO:370	SEQ ID NO:396
4D4CVH2.2_D53E/4D4CVL2_G94A	SEQ ID NO:371	SEQ ID NO:396
4D4CVH2.2_D53Q/4D4CVL2_G94A	SEQ ID NO:372	SEQ ID NO:396
4D4CVH2.2_D53L/4D4CVL2_G94A	SEQ ID NO:373	SEQ ID NO:396

4D4CVH2.2_G54A/4D4CVL2_G94A	SEQ ID NO:374	SEQ ID NO:396
4D4CVH2.2/4D4CVL4_N93G	SEQ ID NO:265	SEQ ID NO:397
4D4CVH2.2/4D4CVL4_N93E	SEQ ID NO:265	SEQ ID NO:398
4D4CVH2.2/4D4CVL4_N93L	SEQ ID NO:265	SEQ ID NO:399
4D4CVH2.2/4D4CVL4_N93Q	SEQ ID NO:265	SEQ ID NO:400
4D4CVH2.2/4D4CVL4_G94A	SEQ ID NO:265	SEQ ID NO:401
4D4CVH2.2_D53G/4D4CVL4	SEQ ID NO:370	SEQ ID NO:273
4D4CVH2.2_D53E/4D4CVL4	SEQ ID NO:371	SEQ ID NO:273
4D4CVH2.2_D53Q/4D4CVL4	SEQ ID NO:372	SEQ ID NO:273
4D4CVH2.2_D53L/4D4CVL4	SEQ ID NO:373	SEQ ID NO:273
4D4CVH2.2_G54A/4D4CVL4	SEQ ID NO:374	SEQ ID NO:273
4D4CVH2.2_D53G/4D4CVL4_N93G	SEQ ID NO:370	SEQ ID NO:397
4D4CVH2.2_D53E/4D4CVL4_N93G	SEQ ID NO:371	SEQ ID NO:397
4D4CVH2.2_D53Q/4D4CVL4_N93G	SEQ ID NO:372	SEQ ID NO:397
4D4CVH2.2_D53L/4D4CVL4_N93G	SEQ ID NO:373	SEQ ID NO:397
4D4CVH2.2_G54A/4D4CVL4_N93G	SEQ ID NO:374	SEQ ID NO:397
4D4CVH2.2_D53G/4D4CVL4_N93E	SEQ ID NO:370	SEQ ID NO:398
4D4CVH2.2_D53E/4D4CVL4_N93E	SEQ ID NO:371	SEQ ID NO:398
4D4CVH2.2_D53Q/4D4CVL4_N93E	SEQ ID NO:372	SEQ ID NO:398
4D4CVH2.2_D53L/4D4CVL4_N93E	SEQ ID NO:373	SEQ ID NO:398
4D4CVH2.2_G54A/4D4CVL4_N93E	SEQ ID NO:374	SEQ ID NO:398
4D4CVH2.2_D53G/4D4CVL4_N93L	SEQ ID NO:370	SEQ ID NO:399
4D4CVH2.2_D53E/4D4CVL4_N93L	SEQ ID NO:371	SEQ ID NO:399
4D4CVH2.2_D53Q/4D4CVL4_N93L	SEQ ID NO:372	SEQ ID NO:399
4D4CVH2.2_D53L/4D4CVL4_N93L	SEQ ID NO:373	SEQ ID NO:399
4D4CVH2.2_G54A/4D4CVL4_N93L	SEQ ID NO:374	SEQ ID NO:399
4D4CVH2.2_D53G/4D4CVL4_N93Q	SEQ ID NO:370	SEQ ID NO:400
4D4CVH2.2_D53E/4D4CVL4_N93Q	SEQ ID NO:371	SEQ ID NO:400
4D4CVH2.2_D53Q/4D4CVL4_N93Q	SEQ ID NO:372	SEQ ID NO:400
4D4CVH2.2_D53L/4D4CVL4_N93Q	SEQ ID NO:373	SEQ ID NO:400
4D4CVH2.2_G54A/4D4CVL4_N93Q	SEQ ID NO:374	SEQ ID NO:400
4D4CVH2.2_D53G/4D4CVL4_G94A	SEQ ID NO:370	SEQ ID NO:401
4D4CVH2.2_D53E/4D4CVL4_G94A	SEQ ID NO:371	SEQ ID NO:401
4D4CVH2.2_D53Q/4D4CVL4_G94A	SEQ ID NO:372	SEQ ID NO:401
4D4CVH2.2_D53L/4D4CVL4_G94A	SEQ ID NO:373	SEQ ID NO:401
4D4CVH2.2_G54A/4D4CVL4_G94A	SEQ ID NO:374	SEQ ID NO:401
4D4CVH2.2/4D4GVL3_N93G	SEQ ID NO:265	SEQ ID NO:402
4D4CVH2.2/4D4GVL3_N93E	SEQ ID NO:265	SEQ ID NO:403
4D4CVH2.2/4D4GVL3_N93L	SEQ ID NO:265	SEQ ID NO:404
4D4CVH2.2/4D4GVL3_N93Q	SEQ ID NO:265	SEQ ID NO:405
4D4CVH2.2/4D4GVL3_G94A	SEQ ID NO:265	SEQ ID NO:406
4D4CVH2.2_D53G/4D4GVL3	SEQ ID NO:370	SEQ ID NO:276
4D4CVH2.2_D53E/4D4GVL3	SEQ ID NO:371	SEQ ID NO:276
4D4CVH2.2_D53Q/4D4GVL3	SEQ ID NO:372	SEQ ID NO:276
4D4CVH2.2_D53L/4D4GVL3	SEQ ID NO:373	SEQ ID NO:276
4D4CVH2.2_G54A/4D4GVL3	SEQ ID NO:374	SEQ ID NO:276
4D4CVH2.2_D53G/4D4GVL3_N93G	SEQ ID NO:370	SEQ ID NO:402
4D4CVH2.2_D53E/4D4GVL3_N93G	SEQ ID NO:371	SEQ ID NO:402
4D4CVH2.2_D53Q/4D4GVL3_N93G	SEQ ID NO:372	SEQ ID NO:402
4D4CVH2.2_D53L/4D4GVL3_N93G	SEQ ID NO:373	SEQ ID NO:402
4D4CVH2.2_G54A/4D4GVL3_N93G	SEQ ID NO:374	SEQ ID NO:402
4D4CVH2.2_D53G/4D4GVL3_N93E	SEQ ID NO:370	SEQ ID NO:403
4D4CVH2.2_D53E/4D4GVL3_N93E	SEQ ID NO:371	SEQ ID NO:403
4D4CVH2.2_D53Q/4D4GVL3_N93E	SEQ ID NO:372	SEQ ID NO:403
4D4CVH2.2_D53L/4D4GVL3_N93E	SEQ ID NO:373	SEQ ID NO:403
4D4CVH2.2_G54A/4D4GVL3_N93E	SEQ ID NO:374	SEQ ID NO:403
4D4CVH2.2_D53G/4D4GVL3_N93L	SEQ ID NO:370	SEQ ID NO:404
4D4CVH2.2_D53E/4D4GVL3_N93L	SEQ ID NO:371	SEQ ID NO:404
4D4CVH2.2_D53Q/4D4GVL3_N93L	SEQ ID NO:372	SEQ ID NO:404
4D4CVH2.2_D53L/4D4GVL3_N93L	SEQ ID NO:373	SEQ ID NO:404
4D4CVH2.2_G54A/4D4GVL3_N93L	SEQ ID NO:374	SEQ ID NO:404
4D4CVH2.2_D53G/4D4GVL3_N93Q	SEQ ID NO:370	SEQ ID NO:405
4D4CVH2.2_D53E/4D4GVL3_N93Q	SEQ ID NO:371	SEQ ID NO:405
4D4CVH2.2_D53Q/4D4GVL3_N93Q	SEQ ID NO:372	SEQ ID NO:405
4D4CVH2.2_D53L/4D4GVL3_N93Q	SEQ ID NO:373	SEQ ID NO:405
4D4CVH2.2_G54A/4D4GVL3_N93Q	SEQ ID NO:374	SEQ ID NO:405
4D4CVH2.2_D53G/4D4GVL3_G94A	SEQ ID NO:370	SEQ ID NO:406
4D4CVH2.2_D53E/4D4GVL3_G94A	SEQ ID NO:371	SEQ ID NO:406
4D4CVH2.2_D53Q/4D4GVL3_G94A	SEQ ID NO:372	SEQ ID NO:406
4D4CVH2.2_D53L/4D4GVL3_G94A	SEQ ID NO:373	SEQ ID NO:406

4D4CVH2.2_G54A/4D4GVL3_G94A	SEQ ID NO:374	SEQ ID NO:406
4D4CVH2.2/4D4GVL4_N93G	SEQ ID NO:265	SEQ ID NO:407
4D4CVH2.2/4D4GVL4_N93E	SEQ ID NO:265	SEQ ID NO:408
4D4CVH2.2/4D4GVL4_N93L	SEQ ID NO:265	SEQ ID NO:409
4D4CVH2.2/4D4GVL4_N93Q	SEQ ID NO:265	SEQ ID NO:410
4D4CVH2.2/4D4GVL4_G94A	SEQ ID NO:265	SEQ ID NO:411
4D4CVH2.2_D53G/4D4GVL4	SEQ ID NO:370	SEQ ID NO:278
4D4CVH2.2_D53E/4D4GVL4	SEQ ID NO:371	SEQ ID NO:278
4D4CVH2.2_D53Q/4D4GVL4	SEQ ID NO:372	SEQ ID NO:278
4D4CVH2.2_D53L/4D4GVL4	SEQ ID NO:373	SEQ ID NO:278
4D4CVH2.2_G54A/4D4GVL4	SEQ ID NO:374	SEQ ID NO:278
4D4CVH2.2_D53G/4D4GVL4_N93G	SEQ ID NO:370	SEQ ID NO:407
4D4CVH2.2_D53E/4D4GVL4_N93G	SEQ ID NO:371	SEQ ID NO:407
4D4CVH2.2_D53Q/4D4GVL4_N93G	SEQ ID NO:372	SEQ ID NO:407
4D4CVH2.2_D53L/4D4GVL4_N93G	SEQ ID NO:373	SEQ ID NO:407
4D4CVH2.2_G54A/4D4GVL4_N93G	SEQ ID NO:374	SEQ ID NO:407
4D4CVH2.2_D53G/4D4GVL4_N93E	SEQ ID NO:370	SEQ ID NO:408
4D4CVH2.2_D53E/4D4GVL4_N93E	SEQ ID NO:371	SEQ ID NO:408
4D4CVH2.2_D53Q/4D4GVL4_N93E	SEQ ID NO:372	SEQ ID NO:408
4D4CVH2.2_D53L/4D4GVL4_N93E	SEQ ID NO:373	SEQ ID NO:408
4D4CVH2.2_G54A/4D4GVL4_N93E	SEQ ID NO:374	SEQ ID NO:408
4D4CVH2.2_D53G/4D4GVL4_N93L	SEQ ID NO:370	SEQ ID NO:409
4D4CVH2.2_D53E/4D4GVL4_N93L	SEQ ID NO:371	SEQ ID NO:409
4D4CVH2.2_D53Q/4D4GVL4_N93L	SEQ ID NO:372	SEQ ID NO:409
4D4CVH2.2_D53L/4D4GVL4_N93L	SEQ ID NO:373	SEQ ID NO:409
4D4CVH2.2_G54A/4D4GVL4_N93L	SEQ ID NO:374	SEQ ID NO:409
4D4CVH2.2_D53G/4D4GVL4_N93Q	SEQ ID NO:370	SEQ ID NO:410
4D4CVH2.2_D53E/4D4GVL4_N93Q	SEQ ID NO:371	SEQ ID NO:410
4D4CVH2.2_D53Q/4D4GVL4_N93Q	SEQ ID NO:372	SEQ ID NO:410
4D4CVH2.2_D53L/4D4GVL4_N93Q	SEQ ID NO:373	SEQ ID NO:410
4D4CVH2.2_G54A/4D4GVL4_N93Q	SEQ ID NO:374	SEQ ID NO:410
4D4CVH2.2_D53G/4D4GVL4_G94A	SEQ ID NO:370	SEQ ID NO:411
4D4CVH2.2_D53E/4D4GVL4_G94A	SEQ ID NO:371	SEQ ID NO:411
4D4CVH2.2_D53Q/4D4GVL4_G94A	SEQ ID NO:372	SEQ ID NO:411
4D4CVH2.2_D53L/4D4GVL4_G94A	SEQ ID NO:373	SEQ ID NO:411
4D4CVH2.2_G54A/4D4GVL4_G94A	SEQ ID NO:374	SEQ ID NO:411
CON4D4P/Hu_D53var_G53var /CON4D4P/Hu_N93var_G94var	SEQ ID NO:381	SEQ ID NO:418

Table H

	Column A	Column B
Name	**Heavy Chain**	**Light Chain**
4D4 hIgG1	SEQ ID NO:289	SEQ ID NO:301
3G9 hIgG1	SEQ ID NO:290	SEQ ID NO:302
4A7/7D8 hIgG1	SEQ ID NO:291	SEQ ID NO:303
8C6 hIgG1	SEQ ID NO:292	SEQ ID NO:304
C03-A7 hIgG1	SEQ ID NO:293	SEQ ID NO:305
CON'4'9'7/8 hIgG1	SEQ ID NO:294	SEQ ID NO:306
4D4CVH2/4D4C/GVL1 hIgG1	SEQ ID NO:295	SEQ ID NO:307
4D4CVH2/4D4CVL2 hIgG1	SEQ ID NO:295	SEQ ID NO:308
4D4CVH2/4D4CVL4 hIgG1	SEQ ID NO:295	SEQ ID NO:309
4D4CVH2/4D4GVL3 hIgG1	SEQ ID NO:295	SEQ ID NO:310
4D4CVH2/4D4GVL4 hIgG1	SEQ ID NO:295	SEQ ID NO:311
4D4CVH3/4D4C/GVL1 hIgG1	SEQ ID NO:296	SEQ ID NO:307
4D4CVH3/4D4CVL2 hIgG1	SEQ ID NO:296	SEQ ID NO:308
4D4CVH3/4D4CVL4 hIgG1	SEQ ID NO:296	SEQ ID NO:309
4D4CVH3/4D4GVL3 hIgG1	SEQ ID NO:296	SEQ ID NO:310
4D4CVH3/4D4GVL4 hIgG1	SEQ ID NO:296	SEQ ID NO:311
4D4CVH4/4D4C/GVL1 hIgG1	SEQ ID NO:297	SEQ ID NO:307
4D4CVH4/4D4CVL2 hIgG1	SEQ ID NO:297	SEQ ID NO:308
4D4CVH4/4D4CVL4 hIgG1	SEQ ID NO:297	SEQ ID NO:309
4D4CVH4/4D4GVL3 hIgG1	SEQ ID NO:297	SEQ ID NO:310
4D4CVH4/4D4GVL4 hIgG1	SEQ ID NO:297	SEQ ID NO:311
4D4CVH2.1/4D4C/GVL1 hIgG1	SEQ ID NO:298	SEQ ID NO:307
4D4CVH2.1/4D4CVL2 hIgG1	SEQ ID NO:298	SEQ ID NO:308
4D4CVH2.1/4D4CVL4 hIgG1	SEQ ID NO:298	SEQ ID NO:309
4D4CVH2.1/4D4GVL3 hIgG1	SEQ ID NO:298	SEQ ID NO:310
4D4CVH2.1/4D4GVL4 hIgG1	SEQ ID NO:298	SEQ ID NO:311
4D4CVH2.2/4D4C/GVL1 hIgG1	SEQ ID NO:299	SEQ ID NO:307
4D4CVH2.2/4D4CVL2 hIgG1	SEQ ID NO:299	SEQ ID NO:308
4D4CVH2.2/4D4CVL4 hIgG1	SEQ ID NO:299	SEQ ID NO:309
4D4CVH2.2/4D4GVL3 hIgG1	SEQ ID NO:299	SEQ ID NO:310
4D4CVH2.2/4D4GVL4 hIgG1	SEQ ID NO:299	SEQ ID NO:311
CON4D4P/Hu hIgG1	SEQ ID NO:300	SEQ ID NO:312
4D4 hIgG4(S228P, L235E)	SEQ ID NO:333	SEQ ID NO:301
3G9 hIgG4(S228P, L235E)	SEQ ID NO:334	SEQ ID NO:302
4A7/7D8 hIgG4(S228P, L235E)	SEQ ID NO:335	SEQ ID NO:303
8C6 hIgG4(S228P, L235E)	SEQ ID NO:336	SEQ ID NO:304
C03-A7 hIgG4(S228P, L235E)	SEQ ID NO:337	SEQ ID NO:305
CON'4'9'7/8 hIgG4(S228P, L235E)	SEQ ID NO:338	SEQ ID NO:306
4D4CVH2/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:307
4D4CVH2/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:308
4D4CVH2/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:309
4D4CVH2/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:310
4D4CVH2/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:311
4D4CVH3/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:307
4D4CVH3/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:308
4D4CVH3/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:309
4D4CVH3/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:310
4D4CVH3/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:311
4D4CVH4/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:307
4D4CVH4/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:308
4D4CVH4/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:309
4D4CVH4/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:310
4D4CVH4/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:311
4D4CVH2.1/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:307
4D4CVH2.1/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:308
4D4CVH2.1/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:309
4D4CVH2.1/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:310
4D4CVH2.1/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:311
4D4CVH2.2/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:307
4D4CVH2.2/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:308
4D4CVH2.2/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:309
4D4CVH2.2/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:310
4D4CVH2.2/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:311
CON4D4P/Hu hIgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:312

4D4/4D4_N93G hIgG1	SEQ ID NO:289	SEQ ID NO:481
4D4/4D4_N93E hIgG1	SEQ ID NO:289	SEQ ID NO:482
4D4/4D4_N93L hIgG1	SEQ ID NO:289	SEQ ID NO:483
4D4/4D4_N93Q hIgG1	SEQ ID NO:289	SEQ ID NO:484
4D4/4D4_G94A hIgG1	SEQ ID NO:289	SEQ ID NO:485
4D4_D53G/4D4 hIgG1	SEQ ID NO:419	SEQ ID NO:301
4D4_D53E/4D4 hIgG1	SEQ ID NO:420	SEQ ID NO:301
4D4_D53Q/4D4 hIgG1	SEQ ID NO:421	SEQ ID NO:301
4D4_D53L/4D4 hIgG1	SEQ ID NO:422	SEQ ID NO:301
4D4_G54A/4D4 hIgG1	SEQ ID NO:423	SEQ ID NO:301
4D4_D53G/4D4_N93G hIgG1	SEQ ID NO:419	SEQ ID NO:481
4D4_D53E/4D4_N93G hIgG1	SEQ ID NO:420	SEQ ID NO:481
4D4_D53Q/4D4_N93G hIgG1	SEQ ID NO:421	SEQ ID NO:481
4D4_D53L/4D4_N93G hIgG1	SEQ ID NO:422	SEQ ID NO:481
4D4_G54A/4D4_N93G hIgG1	SEQ ID NO:423	SEQ ID NO:481
4D4_D53G/4D4_N93E hIgG1	SEQ ID NO:419	SEQ ID NO:482
4D4_D53E/4D4_N93E hIgG1	SEQ ID NO:420	SEQ ID NO:482
4D4_D53Q/4D4_N93E hIgG1	SEQ ID NO:421	SEQ ID NO:482
4D4_D53L/4D4_N93E hIgG1	SEQ ID NO:422	SEQ ID NO:482
4D4_G54A/4D4_N93E hIgG1	SEQ ID NO:423	SEQ ID NO:482
4D4_D53G/4D4_N93L hIgG1	SEQ ID NO:419	SEQ ID NO:483
4D4_D53E/4D4_N93L hIgG1	SEQ ID NO:420	SEQ ID NO:483
4D4_D53Q/4D4_N93L hIgG1	SEQ ID NO:421	SEQ ID NO:483
4D4_D53L/4D4_N93L hIgG1	SEQ ID NO:422	SEQ ID NO:483
4D4_G54A/4D4_N93L hIgG1	SEQ ID NO:423	SEQ ID NO:483
4D4_D53G/4D4_N93Q hIgG1	SEQ ID NO:419	SEQ ID NO:484
4D4_D53E/4D4_N93Q hIgG1	SEQ ID NO:420	SEQ ID NO:484
4D4_D53Q/4D4_N93Q hIgG1	SEQ ID NO:421	SEQ ID NO:484
4D4_D53L/4D4_N93Q hIgG1	SEQ ID NO:422	SEQ ID NO:484
4D4_G54A/4D4_N93Q hIgG1	SEQ ID NO:423	SEQ ID NO:484
4D4_D53G/4D4_G94A hIgG1	SEQ ID NO:419	SEQ ID NO:485
4D4_D53E/4D4_G94A hIgG1	SEQ ID NO:420	SEQ ID NO:485
4D4_D53Q/4D4_G94A hIgG1	SEQ ID NO:421	SEQ ID NO:485
4D4_D53L/4D4_G94A hIgG1	SEQ ID NO:422	SEQ ID NO:485
4D4_G54A/4D4_G94A hIgG1	SEQ ID NO:423	SEQ ID NO:485
4D4CVH2/4D4C/GVL1_N93G hIgG1	SEQ ID NO:295	SEQ ID NO:486
4D4CVH2/4D4C/GVL1_N93E hIgG1	SEQ ID NO:295	SEQ ID NO:487
4D4CVH2/4D4C/GVL1_N93L hIgG1	SEQ ID NO:295	SEQ ID NO:488
4D4CVH2/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:295	SEQ ID NO:489
4D4CVH2/4D4C/GVL1_G94A hIgG1	SEQ ID NO:295	SEQ ID NO:490
4D4CVH2_D53G/4D4C/GVL1 hIgG1	SEQ ID NO:424	SEQ ID NO:307
4D4CVH2_D53E/4D4C/GVL1 hIgG1	SEQ ID NO:425	SEQ ID NO:307
4D4CVH2_D53Q/4D4C/GVL1 hIgG1	SEQ ID NO:426	SEQ ID NO:307
4D4CVH2_D53L/4D4C/GVL1 hIgG1	SEQ ID NO:427	SEQ ID NO:307
4D4CVH2_G54A/4D4C/GVL1 hIgG1	SEQ ID NO:428	SEQ ID NO:307
4D4CVH2_D53G/4D4C/GVL1_N93G hIgG1	SEQ ID NO:424	SEQ ID NO:486
4D4CVH2_D53E/4D4C/GVL1_N93G hIgG1	SEQ ID NO:425	SEQ ID NO:486
4D4CVH2_D53Q/4D4C/GVL1_N93G hIgG1	SEQ ID NO:426	SEQ ID NO:486
4D4CVH2_D53L/4D4C/GVL1_N93G hIgG1	SEQ ID NO:427	SEQ ID NO:486
4D4CVH2_G54A/4D4C/GVL1_N93G hIgG1	SEQ ID NO:428	SEQ ID NO:486
4D4CVH2_D53G/4D4C/GVL1_N93E hIgG1	SEQ ID NO:424	SEQ ID NO:487
4D4CVH2_D53E/4D4C/GVL1_N93E hIgG1	SEQ ID NO:425	SEQ ID NO:487
4D4CVH2_D53Q/4D4C/GVL1_N93E hIgG1	SEQ ID NO:426	SEQ ID NO:487
4D4CVH2_D53L/4D4C/GVL1_N93E hIgG1	SEQ ID NO:427	SEQ ID NO:487
4D4CVH2_G54A/4D4C/GVL1_N93E hIgG1	SEQ ID NO:428	SEQ ID NO:487
4D4CVH2_D53G/4D4C/GVL1_N93L hIgG1	SEQ ID NO:424	SEQ ID NO:488
4D4CVH2_D53E/4D4C/GVL1_N93L hIgG1	SEQ ID NO:425	SEQ ID NO:488
4D4CVH2_D53Q/4D4C/GVL1_N93L hIgG1	SEQ ID NO:426	SEQ ID NO:488
4D4CVH2_D53L/4D4C/GVL1_N93L hIgG1	SEQ ID NO:427	SEQ ID NO:488
4D4CVH2_G54A/4D4C/GVL1_N93L hIgG1	SEQ ID NO:428	SEQ ID NO:488
4D4CVH2_D53G/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:424	SEQ ID NO:489
4D4CVH2_D53E/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:425	SEQ ID NO:489
4D4CVH2_D53Q/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:426	SEQ ID NO:489
4D4CVH2_D53L/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:427	SEQ ID NO:489
4D4CVH2_G54A/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:428	SEQ ID NO:489
4D4CVH2_D53G/4D4C/GVL1_G94A hIgG1	SEQ ID NO:424	SEQ ID NO:490
4D4CVH2_D53E/4D4C/GVL1_G94A hIgG1	SEQ ID NO:425	SEQ ID NO:490
4D4CVH2_D53Q/4D4C/GVL1_G94A hIgG1	SEQ ID NO:426	SEQ ID NO:490
4D4CVH2_D53L/4D4C/GVL1_G94A hIgG1	SEQ ID NO:427	SEQ ID NO:490
4D4CVH2_G54A/4D4C/GVL1_G94A hIgG1	SEQ ID NO:428	SEQ ID NO:490

4D4CVH2/4D4CVL2_N93G hIgG1	SEQ ID NO:295	SEQ ID NO:491
4D4CVH2/4D4CVL2_N93E hIgG1	SEQ ID NO:295	SEQ ID NO:492
4D4CVH2/4D4CVL2_N93L hIgG1	SEQ ID NO:295	SEQ ID NO:493
4D4CVH2/4D4CVL2_N93Q hIgG1	SEQ ID NO:295	SEQ ID NO:494
4D4CVH2/4D4CVL2_G94A hIgG1	SEQ ID NO:295	SEQ ID NO:495
4D4CVH2_D53G/4D4CVL2 hIgG1	SEQ ID NO:424	SEQ ID NO:308
4D4CVH2_D53E/4D4CVL2 hIgG1	SEQ ID NO:425	SEQ ID NO:308
4D4CVH2_D53Q/4D4CVL2 hIgG1	SEQ ID NO:426	SEQ ID NO:308
4D4CVH2_D53L/4D4CVL2 hIgG1	SEQ ID NO:427	SEQ ID NO:308
4D4CVH2_G54A/4D4CVL2 hIgG1	SEQ ID NO:428	SEQ ID NO:308
4D4CVH2_D53G/4D4CVL2_N93G hIgG1	SEQ ID NO:424	SEQ ID NO:491
4D4CVH2_D53E/4D4CVL2_N93G hIgG1	SEQ ID NO:425	SEQ ID NO:491
4D4CVH2_D53Q/4D4CVL2_N93G hIgG1	SEQ ID NO:426	SEQ ID NO:491
4D4CVH2_D53L/4D4CVL2_N93G hIgG1	SEQ ID NO:427	SEQ ID NO:491
4D4CVH2_G54A/4D4CVL2_N93G hIgG1	SEQ ID NO:428	SEQ ID NO:491
4D4CVH2_D53G/4D4CVL2_N93E hIgG1	SEQ ID NO:424	SEQ ID NO:492
4D4CVH2_D53E/4D4CVL2_N93E hIgG1	SEQ ID NO:425	SEQ ID NO:492
4D4CVH2_D53Q/4D4CVL2_N93E hIgG1	SEQ ID NO:426	SEQ ID NO:492
4D4CVH2_D53L/4D4CVL2_N93E hIgG1	SEQ ID NO:427	SEQ ID NO:492
4D4CVH2_G54A/4D4CVL2_N93E hIgG1	SEQ ID NO:428	SEQ ID NO:492
4D4CVH2_D53G/4D4CVL2_N93L hIgG1	SEQ ID NO:424	SEQ ID NO:493
4D4CVH2_D53E/4D4CVL2_N93L hIgG1	SEQ ID NO:425	SEQ ID NO:493
4D4CVH2_D53Q/4D4CVL2_N93L hIgG1	SEQ ID NO:426	SEQ ID NO:493
4D4CVH2_D53L/4D4CVL2_N93L hIgG1	SEQ ID NO:427	SEQ ID NO:493
4D4CVH2_G54A/4D4CVL2_N93L hIgG1	SEQ ID NO:428	SEQ ID NO:493
4D4CVH2_D53G/4D4CVL2_N93Q hIgG1	SEQ ID NO:424	SEQ ID NO:494
4D4CVH2_D53E/4D4CVL2_N93Q hIgG1	SEQ ID NO:425	SEQ ID NO:494
4D4CVH2_D53Q/4D4CVL2_N93Q hIgG1	SEQ ID NO:426	SEQ ID NO:494
4D4CVH2_D53L/4D4CVL2_N93Q hIgG1	SEQ ID NO:427	SEQ ID NO:494
4D4CVH2_G54A/4D4CVL2_N93Q hIgG1	SEQ ID NO:428	SEQ ID NO:494
4D4CVH2_D53G/4D4CVL2_G94A hIgG1	SEQ ID NO:424	SEQ ID NO:495
4D4CVH2_D53E/4D4CVL2_G94A hIgG1	SEQ ID NO:425	SEQ ID NO:495
4D4CVH2_D53Q/4D4CVL2_G94A hIgG1	SEQ ID NO:426	SEQ ID NO:495
4D4CVH2_D53L/4D4CVL2_G94A hIgG1	SEQ ID NO:427	SEQ ID NO:495
4D4CVH2_G54A/4D4CVL2_G94A hIgG1	SEQ ID NO:428	SEQ ID NO:495
4D4CVH2/4D4CVL4_N93G hIgG1	SEQ ID NO:295	SEQ ID NO:496
4D4CVH2/4D4CVL4_N93E hIgG1	SEQ ID NO:295	SEQ ID NO:497
4D4CVH2/4D4CVL4_N93L hIgG1	SEQ ID NO:295	SEQ ID NO:498
4D4CVH2/4D4CVL4_N93Q hIgG1	SEQ ID NO:295	SEQ ID NO:499
4D4CVH2/4D4CVL4_G94A hIgG1	SEQ ID NO:295	SEQ ID NO:500
4D4CVH2_D53G/4D4CVL4 hIgG1	SEQ ID NO:424	SEQ ID NO:309
4D4CVH2_D53E/4D4CVL4 hIgG1	SEQ ID NO:425	SEQ ID NO:309
4D4CVH2_D53Q/4D4CVL4 hIgG1	SEQ ID NO:426	SEQ ID NO:309
4D4CVH2_D53L/4D4CVL4 hIgG1	SEQ ID NO:427	SEQ ID NO:309
4D4CVH2_G54A/4D4CVL4 hIgG1	SEQ ID NO:428	SEQ ID NO:309
4D4CVH2_D53G/4D4CVL4_N93G hIgG1	SEQ ID NO:424	SEQ ID NO:496
4D4CVH2_D53E/4D4CVL4_N93G hIgG1	SEQ ID NO:425	SEQ ID NO:496
4D4CVH2_D53Q/4D4CVL4_N93G hIgG1	SEQ ID NO:426	SEQ ID NO:496
4D4CVH2_D53L/4D4CVL4_N93G hIgG1	SEQ ID NO:427	SEQ ID NO:496
4D4CVH2_G54A/4D4CVL4_N93G hIgG1	SEQ ID NO:428	SEQ ID NO:496
4D4CVH2_D53G/4D4CVL4_N93E hIgG1	SEQ ID NO:424	SEQ ID NO:497
4D4CVH2_D53E/4D4CVL4_N93E hIgG1	SEQ ID NO:425	SEQ ID NO:497
4D4CVH2_D53Q/4D4CVL4_N93E hIgG1	SEQ ID NO:426	SEQ ID NO:497
4D4CVH2_D53L/4D4CVL4_N93E hIgG1	SEQ ID NO:427	SEQ ID NO:497
4D4CVH2_G54A/4D4CVL4_N93E hIgG1	SEQ ID NO:428	SEQ ID NO:497
4D4CVH2_D53G/4D4CVL4_N93L hIgG1	SEQ ID NO:424	SEQ ID NO:498
4D4CVH2_D53E/4D4CVL4_N93L hIgG1	SEQ ID NO:425	SEQ ID NO:498
4D4CVH2_D53Q/4D4CVL4_N93L hIgG1	SEQ ID NO:426	SEQ ID NO:498
4D4CVH2_D53L/4D4CVL4_N93L hIgG1	SEQ ID NO:427	SEQ ID NO:498
4D4CVH2_G54A/4D4CVL4_N93L hIgG1	SEQ ID NO:428	SEQ ID NO:498
4D4CVH2_D53G/4D4CVL4_N93Q hIgG1	SEQ ID NO:424	SEQ ID NO:499
4D4CVH2_D53E/4D4CVL4_N93Q hIgG1	SEQ ID NO:425	SEQ ID NO:499
4D4CVH2_D53Q/4D4CVL4_N93Q hIgG1	SEQ ID NO:426	SEQ ID NO:499
4D4CVH2_D53L/4D4CVL4_N93Q hIgG1	SEQ ID NO:427	SEQ ID NO:499
4D4CVH2_G54A/4D4CVL4_N93Q hIgG1	SEQ ID NO:428	SEQ ID NO:499
4D4CVH2_D53G/4D4CVL4_G94A hIgG1	SEQ ID NO:424	SEQ ID NO:500
4D4CVH2_D53E/4D4CVL4_G94A hIgG1	SEQ ID NO:425	SEQ ID NO:500
4D4CVH2_D53Q/4D4CVL4_G94A hIgG1	SEQ ID NO:426	SEQ ID NO:500
4D4CVH2_D53L/4D4CVL4_G94A hIgG1	SEQ ID NO:427	SEQ ID NO:500
4D4CVH2_G54A/4D4CVL4_G94A hIgG1	SEQ ID NO:428	SEQ ID NO:500

4D4CVH2/4D4GVL3_N93G hIgG1	SEQ ID NO:295	SEQ ID NO:501
4D4CVH2/4D4GVL3_N93E hIgG1	SEQ ID NO:295	SEQ ID NO:502
4D4CVH2/4D4GVL3_N93L hIgG1	SEQ ID NO:295	SEQ ID NO:503
4D4CVH2/4D4GVL3_N93Q hIgG1	SEQ ID NO:295	SEQ ID NO:504
4D4CVH2/4D4GVL3_G94A hIgG1	SEQ ID NO:295	SEQ ID NO:505
4D4CVH2_D53G/4D4GVL3 hIgG1	SEQ ID NO:424	SEQ ID NO:310
4D4CVH2_D53E/4D4GVL3 hIgG1	SEQ ID NO:425	SEQ ID NO:310
4D4CVH2_D53Q/4D4GVL3 hIgG1	SEQ ID NO:426	SEQ ID NO:310
4D4CVH2_D53L/4D4GVL3 hIgG1	SEQ ID NO:427	SEQ ID NO:310
4D4CVH2_G54A/4D4GVL3 hIgG1	SEQ ID NO:428	SEQ ID NO:310
4D4CVH2_D53G/4D4GVL3_N93G hIgG1	SEQ ID NO:424	SEQ ID NO:501
4D4CVH2_D53E/4D4GVL3_N93G hIgG1	SEQ ID NO:425	SEQ ID NO:501
4D4CVH2_D53Q/4D4GVL3_N93G hIgG1	SEQ ID NO:426	SEQ ID NO:501
4D4CVH2_D53L/4D4GVL3_N93G hIgG1	SEQ ID NO:427	SEQ ID NO:501
4D4CVH2_G54A/4D4GVL3_N93G hIgG1	SEQ ID NO:428	SEQ ID NO:501
4D4CVH2_D53G/4D4GVL3_N93E hIgG1	SEQ ID NO:424	SEQ ID NO:502
4D4CVH2_D53E/4D4GVL3_N93E hIgG1	SEQ ID NO:425	SEQ ID NO:502
4D4CVH2_D53Q/4D4GVL3_N93E hIgG1	SEQ ID NO:426	SEQ ID NO:502
4D4CVH2_D53L/4D4GVL3_N93E hIgG1	SEQ ID NO:427	SEQ ID NO:502
4D4CVH2_G54A/4D4GVL3_N93E hIgG1	SEQ ID NO:428	SEQ ID NO:502
4D4CVH2_D53G/4D4GVL3_N93L hIgG1	SEQ ID NO:424	SEQ ID NO:503
4D4CVH2_D53E/4D4GVL3_N93L hIgG1	SEQ ID NO:425	SEQ ID NO:503
4D4CVH2_D53Q/4D4GVL3_N93L hIgG1	SEQ ID NO:426	SEQ ID NO:503
4D4CVH2_D53L/4D4GVL3_N93L hIgG1	SEQ ID NO:427	SEQ ID NO:503
4D4CVH2_G54A/4D4GVL3_N93L hIgG1	SEQ ID NO:428	SEQ ID NO:503
4D4CVH2_D53G/4D4GVL3_N93Q hIgG1	SEQ ID NO:424	SEQ ID NO:504
4D4CVH2_D53E/4D4GVL3_N93Q hIgG1	SEQ ID NO:425	SEQ ID NO:504
4D4CVH2_D53Q/4D4GVL3_N93Q hIgG1	SEQ ID NO:426	SEQ ID NO:504
4D4CVH2_D53L/4D4GVL3_N93Q hIgG1	SEQ ID NO:427	SEQ ID NO:504
4D4CVH2_G54A/4D4GVL3_N93Q hIgG1	SEQ ID NO:428	SEQ ID NO:504
4D4CVH2_D53G/4D4GVL3_G94A hIgG1	SEQ ID NO:424	SEQ ID NO:505
4D4CVH2_D53E/4D4GVL3_G94A hIgG1	SEQ ID NO:425	SEQ ID NO:505
4D4CVH2_D53Q/4D4GVL3_G94A hIgG1	SEQ ID NO:426	SEQ ID NO:505
4D4CVH2_D53L/4D4GVL3_G94A hIgG1	SEQ ID NO:427	SEQ ID NO:505
4D4CVH2_G54A/4D4GVL3_G94A hIgG1	SEQ ID NO:428	SEQ ID NO:505
4D4CVH2/4D4GVL4_N93G hIgG1	SEQ ID NO:295	SEQ ID NO:506
4D4CVH2/4D4GVL4_N93E hIgG1	SEQ ID NO:295	SEQ ID NO:507
4D4CVH2/4D4GVL4_N93L hIgG1	SEQ ID NO:295	SEQ ID NO:508
4D4CVH2/4D4GVL4_N93Q hIgG1	SEQ ID NO:295	SEQ ID NO:509
4D4CVH2/4D4GVL4_G94A hIgG1	SEQ ID NO:295	SEQ ID NO:510
4D4CVH2_D53G/4D4GVL4 hIgG1	SEQ ID NO:424	SEQ ID NO:311
4D4CVH2_D53E/4D4GVL4 hIgG1	SEQ ID NO:425	SEQ ID NO:311
4D4CVH2_D53Q/4D4GVL4 hIgG1	SEQ ID NO:426	SEQ ID NO:311
4D4CVH2_D53L/4D4GVL4 hIgG1	SEQ ID NO:427	SEQ ID NO:311
4D4CVH2_G54A/4D4GVL4 hIgG1	SEQ ID NO:428	SEQ ID NO:311
4D4CVH2_D53G/4D4GVL4_N93G hIgG1	SEQ ID NO:424	SEQ ID NO:506
4D4CVH2_D53E/4D4GVL4_N93G hIgG1	SEQ ID NO:425	SEQ ID NO:506
4D4CVH2_D53Q/4D4GVL4_N93G hIgG1	SEQ ID NO:426	SEQ ID NO:506
4D4CVH2_D53L/4D4GVL4_N93G hIgG1	SEQ ID NO:427	SEQ ID NO:506
4D4CVH2_G54A/4D4GVL4_N93G hIgG1	SEQ ID NO:428	SEQ ID NO:506
4D4CVH2_D53G/4D4GVL4_N93E hIgG1	SEQ ID NO:424	SEQ ID NO:507
4D4CVH2_D53E/4D4GVL4_N93E hIgG1	SEQ ID NO:425	SEQ ID NO:507
4D4CVH2_D53Q/4D4GVL4_N93E hIgG1	SEQ ID NO:426	SEQ ID NO:507
4D4CVH2_D53L/4D4GVL4_N93E hIgG1	SEQ ID NO:427	SEQ ID NO:507
4D4CVH2_G54A/4D4GVL4_N93E hIgG1	SEQ ID NO:428	SEQ ID NO:507
4D4CVH2_D53G/4D4GVL4_N93L hIgG1	SEQ ID NO:424	SEQ ID NO:508
4D4CVH2_D53E/4D4GVL4_N93L hIgG1	SEQ ID NO:425	SEQ ID NO:508
4D4CVH2_D53Q/4D4GVL4_N93L hIgG1	SEQ ID NO:426	SEQ ID NO:508
4D4CVH2_D53L/4D4GVL4_N93L hIgG1	SEQ ID NO:427	SEQ ID NO:508
4D4CVH2_G54A/4D4GVL4_N93L hIgG1	SEQ ID NO:428	SEQ ID NO:508
4D4CVH2_D53G/4D4GVL4_N93Q hIgG1	SEQ ID NO:424	SEQ ID NO:509
4D4CVH2_D53E/4D4GVL4_N93Q hIgG1	SEQ ID NO:425	SEQ ID NO:509
4D4CVH2_D53Q/4D4GVL4_N93Q hIgG1	SEQ ID NO:426	SEQ ID NO:509
4D4CVH2_D53L/4D4GVL4_N93Q hIgG1	SEQ ID NO:427	SEQ ID NO:509
4D4CVH2_G54A/4D4GVL4_N93Q hIgG1	SEQ ID NO:428	SEQ ID NO:509
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4D4CVH2_D53Q/4D4GVL4_G94A hIgG1	SEQ ID NO:426	SEQ ID NO:510
4D4CVH2_D53L/4D4GVL4_G94A hIgG1	SEQ ID NO:427	SEQ ID NO:510
4D4CVH2_G54A/4D4GVL4_G94A hIgG1	SEQ ID NO:428	SEQ ID NO:510

4D4CVH3/4D4C/GVL1_N93G hIgG1	SEQ ID NO:296	SEQ ID NO:486
4D4CVH3/4D4C/GVL1_N93E hIgG1	SEQ ID NO:296	SEQ ID NO:487
4D4CVH3/4D4C/GVL1_N93L hIgG1	SEQ ID NO:296	SEQ ID NO:488
4D4CVH3/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:296	SEQ ID NO:489
4D4CVH3/4D4C/GVL1_G94A hIgG1	SEQ ID NO:296	SEQ ID NO:490
4D4CVH3_D53G/4D4C/GVL1 hIgG1	SEQ ID NO:429	SEQ ID NO:307
4D4CVH3_D53E/4D4C/GVL1 hIgG1	SEQ ID NO:430	SEQ ID NO:307
4D4CVH3_D53Q/4D4C/GVL1 hIgG1	SEQ ID NO:431	SEQ ID NO:307
4D4CVH3_D53L/4D4C/GVL1 hIgG1	SEQ ID NO:432	SEQ ID NO:307
4D4CVH3_G54A/4D4C/GVL1 hIgG1	SEQ ID NO:433	SEQ ID NO:307
4D4CVH3_D53G/4D4C/GVL1_N93G hIgG1	SEQ ID NO:429	SEQ ID NO:486
4D4CVH3_D53E/4D4C/GVL1_N93G hIgG1	SEQ ID NO:430	SEQ ID NO:486
4D4CVH3_D53Q/4D4C/GVL1_N93G hIgG1	SEQ ID NO:431	SEQ ID NO:486
4D4CVH3_D53L/4D4C/GVL1_N93G hIgG1	SEQ ID NO:432	SEQ ID NO:486
4D4CVH3_G54A/4D4C/GVL1_N93G hIgG1	SEQ ID NO:433	SEQ ID NO:486
4D4CVH3_D53G/4D4C/GVL1_N93E hIgG1	SEQ ID NO:429	SEQ ID NO:487
4D4CVH3_D53E/4D4C/GVL1_N93E hIgG1	SEQ ID NO:430	SEQ ID NO:487
4D4CVH3_D53Q/4D4C/GVL1_N93E hIgG1	SEQ ID NO:431	SEQ ID NO:487
4D4CVH3_D53L/4D4C/GVL1_N93E hIgG1	SEQ ID NO:432	SEQ ID NO:487
4D4CVH3_G54A/4D4C/GVL1_N93E hIgG1	SEQ ID NO:433	SEQ ID NO:487
4D4CVH3_D53G/4D4C/GVL1_N93L hIgG1	SEQ ID NO:429	SEQ ID NO:488
4D4CVH3_D53E/4D4C/GVL1_N93L hIgG1	SEQ ID NO:430	SEQ ID NO:488
4D4CVH3_D53Q/4D4C/GVL1_N93L hIgG1	SEQ ID NO:431	SEQ ID NO:488
4D4CVH3_D53L/4D4C/GVL1_N93L hIgG1	SEQ ID NO:432	SEQ ID NO:488
4D4CVH3_G54A/4D4C/GVL1_N93L hIgG1	SEQ ID NO:433	SEQ ID NO:488
4D4CVH3_D53G/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:429	SEQ ID NO:489
4D4CVH3_D53E/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:430	SEQ ID NO:489
4D4CVH3_D53Q/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:431	SEQ ID NO:489
4D4CVH3_D53L/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:432	SEQ ID NO:489
4D4CVH3_G54A/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:433	SEQ ID NO:489
4D4CVH3_D53G/4D4C/GVL1_G94A hIgG1	SEQ ID NO:429	SEQ ID NO:490
4D4CVH3_D53E/4D4C/GVL1_G94A hIgG1	SEQ ID NO:430	SEQ ID NO:490
4D4CVH3_D53Q/4D4C/GVL1_G94A hIgG1	SEQ ID NO:431	SEQ ID NO:490
4D4CVH3_D53L/4D4C/GVL1_G94A hIgG1	SEQ ID NO:432	SEQ ID NO:490
4D4CVH3_G54A/4D4C/GVL1_G94A hIgG1	SEQ ID NO:433	SEQ ID NO:490
4D4CVH3/4D4CVL2_N93G hIgG1	SEQ ID NO:296	SEQ ID NO:491
4D4CVH3/4D4CVL2_N93E hIgG1	SEQ ID NO:296	SEQ ID NO:492
4D4CVH3/4D4CVL2_N93L hIgG1	SEQ ID NO:296	SEQ ID NO:493
4D4CVH3/4D4CVL2_N93Q hIgG1	SEQ ID NO:296	SEQ ID NO:494
4D4CVH3/4D4CVL2_G94A hIgG1	SEQ ID NO:296	SEQ ID NO:495
4D4CVH3_D53G/4D4CVL2 hIgG1	SEQ ID NO:429	SEQ ID NO:308
4D4CVH3_D53E/4D4CVL2 hIgG1	SEQ ID NO:430	SEQ ID NO:308
4D4CVH3_D53Q/4D4CVL2 hIgG1	SEQ ID NO:431	SEQ ID NO:308
4D4CVH3_D53L/4D4CVL2 hIgG1	SEQ ID NO:432	SEQ ID NO:308
4D4CVH3_G54A/4D4CVL2 hIgG1	SEQ ID NO:433	SEQ ID NO:308
4D4CVH3_D53G/4D4CVL2_N93G hIgG1	SEQ ID NO:429	SEQ ID NO:491
4D4CVH3_D53E/4D4CVL2_N93G hIgG1	SEQ ID NO:430	SEQ ID NO:491
4D4CVH3_D53Q/4D4CVL2_N93G hIgG1	SEQ ID NO:431	SEQ ID NO:491
4D4CVH3_D53L/4D4CVL2_N93G hIgG1	SEQ ID NO:432	SEQ ID NO:491
4D4CVH3_G54A/4D4CVL2_N93G hIgG1	SEQ ID NO:433	SEQ ID NO:491
4D4CVH3_D53G/4D4CVL2_N93E hIgG1	SEQ ID NO:429	SEQ ID NO:492
4D4CVH3_D53E/4D4CVL2_N93E hIgG1	SEQ ID NO:430	SEQ ID NO:492
4D4CVH3_D53Q/4D4CVL2_N93E hIgG1	SEQ ID NO:431	SEQ ID NO:492
4D4CVH3_D53L/4D4CVL2_N93E hIgG1	SEQ ID NO:432	SEQ ID NO:492
4D4CVH3_G54A/4D4CVL2_N93E hIgG1	SEQ ID NO:433	SEQ ID NO:492
4D4CVH3_D53G/4D4CVL2_N93L hIgG1	SEQ ID NO:429	SEQ ID NO:493
4D4CVH3_D53E/4D4CVL2_N93L hIgG1	SEQ ID NO:430	SEQ ID NO:493
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4D4CVH3_D53L/4D4CVL2_N93L hIgG1	SEQ ID NO:432	SEQ ID NO:493
4D4CVH3_G54A/4D4CVL2_N93L hIgG1	SEQ ID NO:433	SEQ ID NO:493
4D4CVH3_D53G/4D4CVL2_N93Q hIgG1	SEQ ID NO:429	SEQ ID NO:494
4D4CVH3_D53E/4D4CVL2_N93Q hIgG1	SEQ ID NO:430	SEQ ID NO:494
4D4CVH3_D53Q/4D4CVL2_N93Q hIgG1	SEQ ID NO:431	SEQ ID NO:494
4D4CVH3_D53L/4D4CVL2_N93Q hIgG1	SEQ ID NO:432	SEQ ID NO:494
4D4CVH3_G54A/4D4CVL2_N93Q hIgG1	SEQ ID NO:433	SEQ ID NO:494
4D4CVH3_D53G/4D4CVL2_G94A hIgG1	SEQ ID NO:429	SEQ ID NO:495
4D4CVH3_D53E/4D4CVL2_G94A hIgG1	SEQ ID NO:430	SEQ ID NO:495
4D4CVH3_D53Q/4D4CVL2_G94A hIgG1	SEQ ID NO:431	SEQ ID NO:495
4D4CVH3_D53L/4D4CVL2_G94A hIgG1	SEQ ID NO:432	SEQ ID NO:495
4D4CVH3_G54A/4D4CVL2_G94A hIgG1	SEQ ID NO:433	SEQ ID NO:495

4D4CVH3/4D4CVL4_N93G hIgG1	SEQ ID NO:296	SEQ ID NO:496
4D4CVH3/4D4CVL4_N93E hIgG1	SEQ ID NO:296	SEQ ID NO:497
4D4CVH3/4D4CVL4_N93L hIgG1	SEQ ID NO:296	SEQ ID NO:498
4D4CVH3/4D4CVL4_N93Q hIgG1	SEQ ID NO:296	SEQ ID NO:499
4D4CVH3/4D4CVL4_G94A hIgG1	SEQ ID NO:296	SEQ ID NO:500
4D4CVH3_D53G/4D4CVL4 hIgG1	SEQ ID NO:429	SEQ ID NO:309
4D4CVH3_D53E/4D4CVL4 hIgG1	SEQ ID NO:430	SEQ ID NO:309
4D4CVH3_D53Q/4D4CVL4 hIgG1	SEQ ID NO:431	SEQ ID NO:309
4D4CVH3_D53L/4D4CVL4 hIgG1	SEQ ID NO:432	SEQ ID NO:309
4D4CVH3_G54A/4D4CVL4 hIgG1	SEQ ID NO:433	SEQ ID NO:309
4D4CVH3_D53G/4D4CVL4_N93G hIgG1	SEQ ID NO:429	SEQ ID NO:496
4D4CVH3_D53E/4D4CVL4_N93G hIgG1	SEQ ID NO:430	SEQ ID NO:496
4D4CVH3_D53Q/4D4CVL4_N93G hIgG1	SEQ ID NO:431	SEQ ID NO:496
4D4CVH3_D53L/4D4CVL4_N93G hIgG1	SEQ ID NO:432	SEQ ID NO:496
4D4CVH3_G54A/4D4CVL4_N93G hIgG1	SEQ ID NO:433	SEQ ID NO:496
4D4CVH3_D53G/4D4CVL4_N93E hIgG1	SEQ ID NO:429	SEQ ID NO:497
4D4CVH3_D53E/4D4CVL4_N93E hIgG1	SEQ ID NO:430	SEQ ID NO:497
4D4CVH3_D53Q/4D4CVL4_N93E hIgG1	SEQ ID NO:431	SEQ ID NO:497
4D4CVH3_D53L/4D4CVL4_N93E hIgG1	SEQ ID NO:432	SEQ ID NO:497
4D4CVH3_G54A/4D4CVL4_N93E hIgG1	SEQ ID NO:433	SEQ ID NO:497
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4D4CVH3_D53L/4D4CVL4_N93L hIgG1	SEQ ID NO:432	SEQ ID NO:498
4D4CVH3_G54A/4D4CVL4_N93L hIgG1	SEQ ID NO:433	SEQ ID NO:498
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4D4CVH3_G54A/4D4CVL4_N93Q hIgG1	SEQ ID NO:433	SEQ ID NO:499
4D4CVH3_D53G/4D4CVL4_G94A hIgG1	SEQ ID NO:429	SEQ ID NO:500
4D4CVH3_D53E/4D4CVL4_G94A hIgG1	SEQ ID NO:430	SEQ ID NO:500
4D4CVH3_D53Q/4D4CVL4_G94A hIgG1	SEQ ID NO:431	SEQ ID NO:500
4D4CVH3_D53L/4D4CVL4_G94A hIgG1	SEQ ID NO:432	SEQ ID NO:500
4D4CVH3_G54A/4D4CVL4_G94A hIgG1	SEQ ID NO:433	SEQ ID NO:500
4D4CVH3/4D4GVL3_N93G hIgG1	SEQ ID NO:296	SEQ ID NO:501
4D4CVH3/4D4GVL3_N93E hIgG1	SEQ ID NO:296	SEQ ID NO:502
4D4CVH3/4D4GVL3_N93L hIgG1	SEQ ID NO:296	SEQ ID NO:503
4D4CVH3/4D4GVL3_N93Q hIgG1	SEQ ID NO:296	SEQ ID NO:504
4D4CVH3/4D4GVL3_G94A hIgG1	SEQ ID NO:296	SEQ ID NO:505
4D4CVH3_D53G/4D4GVL3 hIgG1	SEQ ID NO:429	SEQ ID NO:310
4D4CVH3_D53E/4D4GVL3 hIgG1	SEQ ID NO:430	SEQ ID NO:310
4D4CVH3_D53Q/4D4GVL3 hIgG1	SEQ ID NO:431	SEQ ID NO:310
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4D4CVH3_D53L/4D4GVL3_N93G hIgG1	SEQ ID NO:432	SEQ ID NO:501
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4D4CVH3_D53L/4D4GVL3_N93E hIgG1	SEQ ID NO:432	SEQ ID NO:502
4D4CVH3_G54A/4D4GVL3_N93E hIgG1	SEQ ID NO:433	SEQ ID NO:502
4D4CVH3_D53G/4D4GVL3_N93L hIgG1	SEQ ID NO:429	SEQ ID NO:503
4D4CVH3_D53E/4D4GVL3_N93L hIgG1	SEQ ID NO:430	SEQ ID NO:503
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4D4CVH3_G54A/4D4GVL3_N93L hIgG1	SEQ ID NO:433	SEQ ID NO:503
4D4CVH3_D53G/4D4GVL3_N93Q hIgG1	SEQ ID NO:429	SEQ ID NO:504
4D4CVH3_D53E/4D4GVL3_N93Q hIgG1	SEQ ID NO:430	SEQ ID NO:504
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4D4CVH3_D53L/4D4GVL3_N93Q hIgG1	SEQ ID NO:432	SEQ ID NO:504
4D4CVH3_G54A/4D4GVL3_N93Q hIgG1	SEQ ID NO:433	SEQ ID NO:504
4D4CVH3_D53G/4D4GVL3_G94A hIgG1	SEQ ID NO:429	SEQ ID NO:505
4D4CVH3_D53E/4D4GVL3_G94A hIgG1	SEQ ID NO:430	SEQ ID NO:505
4D4CVH3_D53Q/4D4GVL3_G94A hIgG1	SEQ ID NO:431	SEQ ID NO:505
4D4CVH3_D53L/4D4GVL3_G94A hIgG1	SEQ ID NO:432	SEQ ID NO:505
4D4CVH3_G54A/4D4GVL3_G94A hIgG1	SEQ ID NO:433	SEQ ID NO:505

4D4CVH3/4D4GVL4_N93G hIgG1	SEQ ID NO:296	SEQ ID NO:506
4D4CVH3/4D4GVL4_N93E hIgG1	SEQ ID NO:296	SEQ ID NO:507
4D4CVH3/4D4GVL4_N93L hIgG1	SEQ ID NO:296	SEQ ID NO:508
4D4CVH3/4D4GVL4_N93Q hIgG1	SEQ ID NO:296	SEQ ID NO:509
4D4CVH3/4D4GVL4_G94A hIgG1	SEQ ID NO:296	SEQ ID NO:510
4D4CVH3_D53G/4D4GVL4 hIgG1	SEQ ID NO:429	SEQ ID NO:311
4D4CVH3_D53E/4D4GVL4 hIgG1	SEQ ID NO:430	SEQ ID NO:311
4D4CVH3_D53Q/4D4GVL4 hIgG1	SEQ ID NO:431	SEQ ID NO:311
4D4CVH3_D53L/4D4GVL4 hIgG1	SEQ ID NO:432	SEQ ID NO:311
4D4CVH3_G54A/4D4GVL4 hIgG1	SEQ ID NO:433	SEQ ID NO:311
4D4CVH3_D53G/4D4GVL4_N93G hIgG1	SEQ ID NO:429	SEQ ID NO:506
4D4CVH3_D53E/4D4GVL4_N93G hIgG1	SEQ ID NO:430	SEQ ID NO:506
4D4CVH3_D53Q/4D4GVL4_N93G hIgG1	SEQ ID NO:431	SEQ ID NO:506
4D4CVH3_D53L/4D4GVL4_N93G hIgG1	SEQ ID NO:432	SEQ ID NO:506
4D4CVH3_G54A/4D4GVL4_N93G hIgG1	SEQ ID NO:433	SEQ ID NO:506
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4D4CVH3_D53G/4D4GVL4_N93L hIgG1	SEQ ID NO:429	SEQ ID NO:508
4D4CVH3_D53E/4D4GVL4_N93L hIgG1	SEQ ID NO:430	SEQ ID NO:508
4D4CVH3_D53Q/4D4GVL4_N93L hIgG1	SEQ ID NO:431	SEQ ID NO:508
4D4CVH3_D53L/4D4GVL4_N93L hIgG1	SEQ ID NO:432	SEQ ID NO:508
4D4CVH3_G54A/4D4GVL4_N93L hIgG1	SEQ ID NO:433	SEQ ID NO:508
4D4CVH3_D53G/4D4GVL4_N93Q hIgG1	SEQ ID NO:429	SEQ ID NO:509
4D4CVH3_D53E/4D4GVL4_N93Q hIgG1	SEQ ID NO:430	SEQ ID NO:509
4D4CVH3_D53Q/4D4GVL4_N93Q hIgG1	SEQ ID NO:431	SEQ ID NO:509
4D4CVH3_D53L/4D4GVL4_N93Q hIgG1	SEQ ID NO:432	SEQ ID NO:509
4D4CVH3_G54A/4D4GVL4_N93Q hIgG1	SEQ ID NO:433	SEQ ID NO:509
4D4CVH3_D53G/4D4GVL4_G94A hIgG1	SEQ ID NO:429	SEQ ID NO:510
4D4CVH3_D53E/4D4GVL4_G94A hIgG1	SEQ ID NO:430	SEQ ID NO:510
4D4CVH3_D53Q/4D4GVL4_G94A hIgG1	SEQ ID NO:431	SEQ ID NO:510
4D4CVH3_D53L/4D4GVL4_G94A hIgG1	SEQ ID NO:432	SEQ ID NO:510
4D4CVH3_G54A/4D4GVL4_G94A hIgG1	SEQ ID NO:433	SEQ ID NO:510
4D4CVH4/4D4C/GVL1_N93G hIgG1	SEQ ID NO:297	SEQ ID NO:486
4D4CVH4/4D4C/GVL1_N93E hIgG1	SEQ ID NO:297	SEQ ID NO:487
4D4CVH4/4D4C/GVL1_N93L hIgG1	SEQ ID NO:297	SEQ ID NO:488
4D4CVH4/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:297	SEQ ID NO:489
4D4CVH4/4D4C/GVL1_G94A hIgG1	SEQ ID NO:297	SEQ ID NO:490
4D4CVH4_D53G/4D4C/GVL1 hIgG1	SEQ ID NO:434	SEQ ID NO:307
4D4CVH4_D53E/4D4C/GVL1 hIgG1	SEQ ID NO:435	SEQ ID NO:307
4D4CVH4_D53Q/4D4C/GVL1 hIgG1	SEQ ID NO:436	SEQ ID NO:307
4D4CVH4_D53L/4D4C/GVL1 hIgG1	SEQ ID NO:437	SEQ ID NO:307
4D4CVH4_G54A/4D4C/GVL1 hIgG1	SEQ ID NO:438	SEQ ID NO:307
4D4CVH4_D53G/4D4C/GVL1_N93G hIgG1	SEQ ID NO:434	SEQ ID NO:486
4D4CVH4_D53E/4D4C/GVL1_N93G hIgG1	SEQ ID NO:435	SEQ ID NO:486
4D4CVH4_D53Q/4D4C/GVL1_N93G hIgG1	SEQ ID NO:436	SEQ ID NO:486
4D4CVH4_D53L/4D4C/GVL1_N93G hIgG1	SEQ ID NO:437	SEQ ID NO:486
4D4CVH4_G54A/4D4C/GVL1_N93G hIgG1	SEQ ID NO:438	SEQ ID NO:486
4D4CVH4_D53G/4D4C/GVL1_N93E hIgG1	SEQ ID NO:434	SEQ ID NO:487
4D4CVH4_D53E/4D4C/GVL1_N93E hIgG1	SEQ ID NO:435	SEQ ID NO:487
4D4CVH4_D53Q/4D4C/GVL1_N93E hIgG1	SEQ ID NO:436	SEQ ID NO:487
4D4CVH4_D53L/4D4C/GVL1_N93E hIgG1	SEQ ID NO:437	SEQ ID NO:487
4D4CVH4_G54A/4D4C/GVL1_N93E hIgG1	SEQ ID NO:438	SEQ ID NO:487
4D4CVH4_D53G/4D4C/GVL1_N93L hIgG1	SEQ ID NO:434	SEQ ID NO:488
4D4CVH4_D53E/4D4C/GVL1_N93L hIgG1	SEQ ID NO:435	SEQ ID NO:488
4D4CVH4_D53Q/4D4C/GVL1_N93L hIgG1	SEQ ID NO:436	SEQ ID NO:488
4D4CVH4_D53L/4D4C/GVL1_N93L hIgG1	SEQ ID NO:437	SEQ ID NO:488
4D4CVH4_G54A/4D4C/GVL1_N93L hIgG1	SEQ ID NO:438	SEQ ID NO:488
4D4CVH4_D53G/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:434	SEQ ID NO:489
4D4CVH4_D53E/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:435	SEQ ID NO:489
4D4CVH4_D53Q/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:436	SEQ ID NO:489
4D4CVH4_D53L/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:437	SEQ ID NO:489
4D4CVH4_G54A/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:438	SEQ ID NO:489
4D4CVH4_D53G/4D4C/GVL1_G94A hIgG1	SEQ ID NO:434	SEQ ID NO:490
4D4CVH4_D53E/4D4C/GVL1_G94A hIgG1	SEQ ID NO:435	SEQ ID NO:490
4D4CVH4_D53Q/4D4C/GVL1_G94A hIgG1	SEQ ID NO:436	SEQ ID NO:490
4D4CVH4_D53L/4D4C/GVL1_G94A hIgG1	SEQ ID NO:437	SEQ ID NO:490
4D4CVH4_G54A/4D4C/GVL1_G94A hIgG1	SEQ ID NO:438	SEQ ID NO:490

4D4CVH4/4D4CVL2_N93G hIgG1	SEQ ID NO:297	SEQ ID NO:491
4D4CVH4/4D4CVL2_N93E hIgG1	SEQ ID NO:297	SEQ ID NO:492
4D4CVH4/4D4CVL2_N93L hIgG1	SEQ ID NO:297	SEQ ID NO:493
4D4CVH4/4D4CVL2_N93Q hIgG1	SEQ ID NO:297	SEQ ID NO:494
4D4CVH4/4D4CVL2_G94A hIgG1	SEQ ID NO:297	SEQ ID NO:495
4D4CVH4_D53G/4D4CVL2 hIgG1	SEQ ID NO:434	SEQ ID NO:308
4D4CVH4_D53E/4D4CVL2 hIgG1	SEQ ID NO:435	SEQ ID NO:308
4D4CVH4_D53Q/4D4CVL2 hIgG1	SEQ ID NO:436	SEQ ID NO:308
4D4CVH4_D53L/4D4CVL2 hIgG1	SEQ ID NO:437	SEQ ID NO:308
4D4CVH4_G54A/4D4CVL2 hIgG1	SEQ ID NO:438	SEQ ID NO:308
4D4CVH4_D53G/4D4CVL2_N93G hIgG1	SEQ ID NO:434	SEQ ID NO:491
4D4CVH4_D53E/4D4CVL2_N93G hIgG1	SEQ ID NO:435	SEQ ID NO:491
4D4CVH4_D53Q/4D4CVL2_N93G hIgG1	SEQ ID NO:436	SEQ ID NO:491
4D4CVH4_D53L/4D4CVL2_N93G hIgG1	SEQ ID NO:437	SEQ ID NO:491
4D4CVH4_G54A/4D4CVL2_N93G hIgG1	SEQ ID NO:438	SEQ ID NO:491
4D4CVH4_D53G/4D4CVL2_N93E hIgG1	SEQ ID NO:434	SEQ ID NO:492
4D4CVH4_D53E/4D4CVL2_N93E hIgG1	SEQ ID NO:435	SEQ ID NO:492
4D4CVH4_D53Q/4D4CVL2_N93E hIgG1	SEQ ID NO:436	SEQ ID NO:492
4D4CVH4_D53L/4D4CVL2_N93E hIgG1	SEQ ID NO:437	SEQ ID NO:492
4D4CVH4_G54A/4D4CVL2_N93E hIgG1	SEQ ID NO:438	SEQ ID NO:492
4D4CVH4_D53G/4D4CVL2_N93L hIgG1	SEQ ID NO:434	SEQ ID NO:493
4D4CVH4_D53E/4D4CVL2_N93L hIgG1	SEQ ID NO:435	SEQ ID NO:493
4D4CVH4_D53Q/4D4CVL2_N93L hIgG1	SEQ ID NO:436	SEQ ID NO:493
4D4CVH4_D53L/4D4CVL2_N93L hIgG1	SEQ ID NO:437	SEQ ID NO:493
4D4CVH4_G54A/4D4CVL2_N93L hIgG1	SEQ ID NO:438	SEQ ID NO:493
4D4CVH4_D53G/4D4CVL2_N93Q hIgG1	SEQ ID NO:434	SEQ ID NO:494
4D4CVH4_D53E/4D4CVL2_N93Q hIgG1	SEQ ID NO:435	SEQ ID NO:494
4D4CVH4_D53Q/4D4CVL2_N93Q hIgG1	SEQ ID NO:436	SEQ ID NO:494
4D4CVH4_D53L/4D4CVL2_N93Q hIgG1	SEQ ID NO:437	SEQ ID NO:494
4D4CVH4_G54A/4D4CVL2_N93Q hIgG1	SEQ ID NO:438	SEQ ID NO:494
4D4CVH4_D53G/4D4CVL2_G94A hIgG1	SEQ ID NO:434	SEQ ID NO:495
4D4CVH4_D53E/4D4CVL2_G94A hIgG1	SEQ ID NO:435	SEQ ID NO:495
4D4CVH4_D53Q/4D4CVL2_G94A hIgG1	SEQ ID NO:436	SEQ ID NO:495
4D4CVH4_D53L/4D4CVL2_G94A hIgG1	SEQ ID NO:437	SEQ ID NO:495
4D4CVH4_G54A/4D4CVL2_G94A hIgG1	SEQ ID NO:438	SEQ ID NO:495
4D4CVH4/4D4CVL4_N93G hIgG1	SEQ ID NO:297	SEQ ID NO:496
4D4CVH4/4D4CVL4_N93E hIgG1	SEQ ID NO:297	SEQ ID NO:497
4D4CVH4/4D4CVL4_N93L hIgG1	SEQ ID NO:297	SEQ ID NO:498
4D4CVH4/4D4CVL4_N93Q hIgG1	SEQ ID NO:297	SEQ ID NO:499
4D4CVH4/4D4CVL4_G94A hIgG1	SEQ ID NO:297	SEQ ID NO:500
4D4CVH4_D53G/4D4CVL4 hIgG1	SEQ ID NO:434	SEQ ID NO:309
4D4CVH4_D53E/4D4CVL4 hIgG1	SEQ ID NO:435	SEQ ID NO:309
4D4CVH4_D53Q/4D4CVL4 hIgG1	SEQ ID NO:436	SEQ ID NO:309
4D4CVH4_D53L/4D4CVL4 hIgG1	SEQ ID NO:437	SEQ ID NO:309
4D4CVH4_G54A/4D4CVL4 hIgG1	SEQ ID NO:438	SEQ ID NO:309
4D4CVH4_D53G/4D4CVL4_N93G hIgG1	SEQ ID NO:434	SEQ ID NO:496
4D4CVH4_D53E/4D4CVL4_N93G hIgG1	SEQ ID NO:435	SEQ ID NO:496
4D4CVH4_D53Q/4D4CVL4_N93G hIgG1	SEQ ID NO:436	SEQ ID NO:496
4D4CVH4_D53L/4D4CVL4_N93G hIgG1	SEQ ID NO:437	SEQ ID NO:496
4D4CVH4_G54A/4D4CVL4_N93G hIgG1	SEQ ID NO:438	SEQ ID NO:496
4D4CVH4_D53G/4D4CVL4_N93E hIgG1	SEQ ID NO:434	SEQ ID NO:497
4D4CVH4_D53E/4D4CVL4_N93E hIgG1	SEQ ID NO:435	SEQ ID NO:497
4D4CVH4_D53Q/4D4CVL4_N93E hIgG1	SEQ ID NO:436	SEQ ID NO:497
4D4CVH4_D53L/4D4CVL4_N93E hIgG1	SEQ ID NO:437	SEQ ID NO:497
4D4CVH4_G54A/4D4CVL4_N93E hIgG1	SEQ ID NO:438	SEQ ID NO:497
4D4CVH4_D53G/4D4CVL4_N93L hIgG1	SEQ ID NO:434	SEQ ID NO:498
4D4CVH4_D53E/4D4CVL4_N93L hIgG1	SEQ ID NO:435	SEQ ID NO:498
4D4CVH4_D53Q/4D4CVL4_N93L hIgG1	SEQ ID NO:436	SEQ ID NO:498
4D4CVH4_D53L/4D4CVL4_N93L hIgG1	SEQ ID NO:437	SEQ ID NO:498
4D4CVH4_G54A/4D4CVL4_N93L hIgG1	SEQ ID NO:438	SEQ ID NO:498
4D4CVH4_D53G/4D4CVL4_N93Q hIgG1	SEQ ID NO:434	SEQ ID NO:499
4D4CVH4_D53E/4D4CVL4_N93Q hIgG1	SEQ ID NO:435	SEQ ID NO:499
4D4CVH4_D53Q/4D4CVL4_N93Q hIgG1	SEQ ID NO:436	SEQ ID NO:499
4D4CVH4_D53L/4D4CVL4_N93Q hIgG1	SEQ ID NO:437	SEQ ID NO:499
4D4CVH4_G54A/4D4CVL4_N93Q hIgG1	SEQ ID NO:438	SEQ ID NO:499
4D4CVH4_D53G/4D4CVL4_G94A hIgG1	SEQ ID NO:434	SEQ ID NO:500
4D4CVH4_D53E/4D4CVL4_G94A hIgG1	SEQ ID NO:435	SEQ ID NO:500
4D4CVH4_D53Q/4D4CVL4_G94A hIgG1	SEQ ID NO:436	SEQ ID NO:500
4D4CVH4_D53L/4D4CVL4_G94A hIgG1	SEQ ID NO:437	SEQ ID NO:500
4D4CVH4_G54A/4D4CVL4_G94A hIgG1	SEQ ID NO:438	SEQ ID NO:500

4D4CVH4/4D4GVL3_N93G hIgG1	SEQ ID NO:297	SEQ ID NO:501
4D4CVH4/4D4GVL3_N93E hIgG1	SEQ ID NO:297	SEQ ID NO:502
4D4CVH4/4D4GVL3_N93L hIgG1	SEQ ID NO:297	SEQ ID NO:503
4D4CVH4/4D4GVL3_N93Q hIgG1	SEQ ID NO:297	SEQ ID NO:504
4D4CVH4/4D4GVL3_G94A hIgG1	SEQ ID NO:297	SEQ ID NO:505
4D4CVH4_D53G/4D4GVL3 hIgG1	SEQ ID NO:434	SEQ ID NO:310
4D4CVH4_D53E/4D4GVL3 hIgG1	SEQ ID NO:435	SEQ ID NO:310
4D4CVH4_D53Q/4D4GVL3 hIgG1	SEQ ID NO:436	SEQ ID NO:310
4D4CVH4_D53L/4D4GVL3 hIgG1	SEQ ID NO:437	SEQ ID NO:310
4D4CVH4_G54A/4D4GVL3 hIgG1	SEQ ID NO:438	SEQ ID NO:310
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4D4CVH4_D53E/4D4GVL3_N93G hIgG1	SEQ ID NO:435	SEQ ID NO:501
4D4CVH4_D53Q/4D4GVL3_N93G hIgG1	SEQ ID NO:436	SEQ ID NO:501
4D4CVH4_D53L/4D4GVL3_N93G hIgG1	SEQ ID NO:437	SEQ ID NO:501
4D4CVH4_G54A/4D4GVL3_N93G hIgG1	SEQ ID NO:438	SEQ ID NO:501
4D4CVH4_D53G/4D4GVL3_N93E hIgG1	SEQ ID NO:434	SEQ ID NO:502
4D4CVH4_D53E/4D4GVL3_N93E hIgG1	SEQ ID NO:435	SEQ ID NO:502
4D4CVH4_D53Q/4D4GVL3_N93E hIgG1	SEQ ID NO:436	SEQ ID NO:502
4D4CVH4_D53L/4D4GVL3_N93E hIgG1	SEQ ID NO:437	SEQ ID NO:502
4D4CVH4_G54A/4D4GVL3_N93E hIgG1	SEQ ID NO:438	SEQ ID NO:502
4D4CVH4_D53G/4D4GVL3_N93L hIgG1	SEQ ID NO:434	SEQ ID NO:503
4D4CVH4_D53E/4D4GVL3_N93L hIgG1	SEQ ID NO:435	SEQ ID NO:503
4D4CVH4_D53Q/4D4GVL3_N93L hIgG1	SEQ ID NO:436	SEQ ID NO:503
4D4CVH4_D53L/4D4GVL3_N93L hIgG1	SEQ ID NO:437	SEQ ID NO:503
4D4CVH4_G54A/4D4GVL3_N93L hIgG1	SEQ ID NO:438	SEQ ID NO:503
4D4CVH4_D53G/4D4GVL3_N93Q hIgG1	SEQ ID NO:434	SEQ ID NO:504
4D4CVH4_D53E/4D4GVL3_N93Q hIgG1	SEQ ID NO:435	SEQ ID NO:504
4D4CVH4_D53Q/4D4GVL3_N93Q hIgG1	SEQ ID NO:436	SEQ ID NO:504
4D4CVH4_D53L/4D4GVL3_N93Q hIgG1	SEQ ID NO:437	SEQ ID NO:504
4D4CVH4_G54A/4D4GVL3_N93Q hIgG1	SEQ ID NO:438	SEQ ID NO:504
4D4CVH4_D53G/4D4GVL3_G94A hIgG1	SEQ ID NO:434	SEQ ID NO:505
4D4CVH4_D53E/4D4GVL3_G94A hIgG1	SEQ ID NO:435	SEQ ID NO:505
4D4CVH4_D53Q/4D4GVL3_G94A hIgG1	SEQ ID NO:436	SEQ ID NO:505
4D4CVH4_D53L/4D4GVL3_G94A hIgG1	SEQ ID NO:437	SEQ ID NO:505
4D4CVH4_G54A/4D4GVL3_G94A hIgG1	SEQ ID NO:438	SEQ ID NO:505
4D4CVH4/4D4GVL4_N93G hIgG1	SEQ ID NO:297	SEQ ID NO:506
4D4CVH4/4D4GVL4_N93E hIgG1	SEQ ID NO:297	SEQ ID NO:507
4D4CVH4/4D4GVL4_N93L hIgG1	SEQ ID NO:297	SEQ ID NO:508
4D4CVH4/4D4GVL4_N93Q hIgG1	SEQ ID NO:297	SEQ ID NO:509
4D4CVH4/4D4GVL4_G94A hIgG1	SEQ ID NO:297	SEQ ID NO:510
4D4CVH4_D53G/4D4GVL4 hIgG1	SEQ ID NO:434	SEQ ID NO:311
4D4CVH4_D53E/4D4GVL4 hIgG1	SEQ ID NO:435	SEQ ID NO:311
4D4CVH4_D53Q/4D4GVL4 hIgG1	SEQ ID NO:436	SEQ ID NO:311
4D4CVH4_D53L/4D4GVL4 hIgG1	SEQ ID NO:437	SEQ ID NO:311
4D4CVH4_G54A/4D4GVL4 hIgG1	SEQ ID NO:438	SEQ ID NO:311
4D4CVH4_D53G/4D4GVL4_N93G hIgG1	SEQ ID NO:434	SEQ ID NO:506
4D4CVH4_D53E/4D4GVL4_N93G hIgG1	SEQ ID NO:435	SEQ ID NO:506
4D4CVH4_D53Q/4D4GVL4_N93G hIgG1	SEQ ID NO:436	SEQ ID NO:506
4D4CVH4_D53L/4D4GVL4_N93G hIgG1	SEQ ID NO:437	SEQ ID NO:506
4D4CVH4_G54A/4D4GVL4_N93G hIgG1	SEQ ID NO:438	SEQ ID NO:506
4D4CVH4_D53G/4D4GVL4_N93E hIgG1	SEQ ID NO:434	SEQ ID NO:507
4D4CVH4_D53E/4D4GVL4_N93E hIgG1	SEQ ID NO:435	SEQ ID NO:507
4D4CVH4_D53Q/4D4GVL4_N93E hIgG1	SEQ ID NO:436	SEQ ID NO:507
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4D4CVH4_G54A/4D4GVL4_N93E hIgG1	SEQ ID NO:438	SEQ ID NO:507
4D4CVH4_D53G/4D4GVL4_N93L hIgG1	SEQ ID NO:434	SEQ ID NO:508
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4D4CVH4_G54A/4D4GVL4_N93L hIgG1	SEQ ID NO:438	SEQ ID NO:508
4D4CVH4_D53G/4D4GVL4_N93Q hIgG1	SEQ ID NO:434	SEQ ID NO:509
4D4CVH4_D53E/4D4GVL4_N93Q hIgG1	SEQ ID NO:435	SEQ ID NO:509
4D4CVH4_D53Q/4D4GVL4_N93Q hIgG1	SEQ ID NO:436	SEQ ID NO:509
4D4CVH4_D53L/4D4GVL4_N93Q hIgG1	SEQ ID NO:437	SEQ ID NO:509
4D4CVH4_G54A/4D4GVL4_N93Q hIgG1	SEQ ID NO:438	SEQ ID NO:509
4D4CVH4_D53G/4D4GVL4_G94A hIgG1	SEQ ID NO:434	SEQ ID NO:510
4D4CVH4_D53E/4D4GVL4_G94A hIgG1	SEQ ID NO:435	SEQ ID NO:510
4D4CVH4_D53Q/4D4GVL4_G94A hIgG1	SEQ ID NO:436	SEQ ID NO:510
4D4CVH4_D53L/4D4GVL4_G94A hIgG1	SEQ ID NO:437	SEQ ID NO:510
4D4CVH4_G54A/4D4GVL4_G94A hIgG1	SEQ ID NO:438	SEQ ID NO:510

4D4CVH2.1/4D4C/GVL1_N93G hIgG1	SEQ ID NO:298	SEQ ID NO:486
4D4CVH2.1/4D4C/GVL1_N93E hIgG1	SEQ ID NO:298	SEQ ID NO:487
4D4CVH2.1/4D4C/GVL1_N93L hIgG1	SEQ ID NO:298	SEQ ID NO:488
4D4CVH2.1/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:298	SEQ ID NO:489
4D4CVH2.1/4D4C/GVL1_G94A hIgG1	SEQ ID NO:298	SEQ ID NO:490
4D4CVH2.1_D53G/4D4C/GVL1 hIgG1	SEQ ID NO:439	SEQ ID NO:307
4D4CVH2.1_D53E/4D4C/GVL1 hIgG1	SEQ ID NO:440	SEQ ID NO:307
4D4CVH2.1_D53Q/4D4C/GVL1 hIgG1	SEQ ID NO:441	SEQ ID NO:307
4D4CVH2.1_D53L/4D4C/GVL1 hIgG1	SEQ ID NO:442	SEQ ID NO:307
4D4CVH2.1_G54A/4D4C/GVL1 hIgG1	SEQ ID NO:443	SEQ ID NO:307
4D4CVH2.1_D53G/4D4C/GVL1_N93G hIgG1	SEQ ID NO:439	SEQ ID NO:486
4D4CVH2.1_D53E/4D4C/GVL1_N93G hIgG1	SEQ ID NO:440	SEQ ID NO:486
4D4CVH2.1_D53Q/4D4C/GVL1_N93G hIgG1	SEQ ID NO:441	SEQ ID NO:486
4D4CVH2.1_D53L/4D4C/GVL1_N93G hIgG1	SEQ ID NO:442	SEQ ID NO:486
4D4CVH2.1_G54A/4D4C/GVL1_N93G hIgG1	SEQ ID NO:443	SEQ ID NO:486
4D4CVH2.1_D53G/4D4C/GVL1_N93E hIgG1	SEQ ID NO:439	SEQ ID NO:487
4D4CVH2.1_D53E/4D4C/GVL1_N93E hIgG1	SEQ ID NO:440	SEQ ID NO:487
4D4CVH2.1_D53Q/4D4C/GVL1_N93E hIgG1	SEQ ID NO:441	SEQ ID NO:487
4D4CVH2.1_D53L/4D4C/GVL1_N93E hIgG1	SEQ ID NO:442	SEQ ID NO:487
4D4CVH2.1_G54A/4D4C/GVL1_N93E hIgG1	SEQ ID NO:443	SEQ ID NO:487
4D4CVH2.1_D53G/4D4C/GVL1_N93L hIgG1	SEQ ID NO:439	SEQ ID NO:488
4D4CVH2.1_D53E/4D4C/GVL1_N93L hIgG1	SEQ ID NO:440	SEQ ID NO:488
4D4CVH2.1_D53Q/4D4C/GVL1_N93L hIgG1	SEQ ID NO:441	SEQ ID NO:488
4D4CVH2.1_D53L/4D4C/GVL1_N93L hIgG1	SEQ ID NO:442	SEQ ID NO:488
4D4CVH2.1_G54A/4D4C/GVL1_N93L hIgG1	SEQ ID NO:443	SEQ ID NO:488
4D4CVH2.1_D53G/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:439	SEQ ID NO:489
4D4CVH2.1_D53E/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:440	SEQ ID NO:489
4D4CVH2.1_D53Q/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:441	SEQ ID NO:489
4D4CVH2.1_D53L/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:442	SEQ ID NO:489
4D4CVH2.1_G54A/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:443	SEQ ID NO:489
4D4CVH2.1_D53G/4D4C/GVL1_G94A hIgG1	SEQ ID NO:439	SEQ ID NO:490
4D4CVH2.1_D53E/4D4C/GVL1_G94A hIgG1	SEQ ID NO:440	SEQ ID NO:490
4D4CVH2.1_D53Q/4D4C/GVL1_G94A hIgG1	SEQ ID NO:441	SEQ ID NO:490
4D4CVH2.1_D53L/4D4C/GVL1_G94A hIgG1	SEQ ID NO:442	SEQ ID NO:490
4D4CVH2.1_G54A/4D4C/GVL1_G94A hIgG1	SEQ ID NO:443	SEQ ID NO:490
4D4CVH2.1/4D4CVL2_N93G hIgG1	SEQ ID NO:298	SEQ ID NO:491
4D4CVH2.1/4D4CVL2_N93E hIgG1	SEQ ID NO:298	SEQ ID NO:492
4D4CVH2.1/4D4CVL2_N93L hIgG1	SEQ ID NO:298	SEQ ID NO:493
4D4CVH2.1/4D4CVL2_N93Q hIgG1	SEQ ID NO:298	SEQ ID NO:494
4D4CVH2.1/4D4CVL2_G94A hIgG1	SEQ ID NO:298	SEQ ID NO:495
4D4CVH2.1_D53G/4D4CVL2 hIgG1	SEQ ID NO:439	SEQ ID NO:308
4D4CVH2.1_D53E/4D4CVL2 hIgG1	SEQ ID NO:440	SEQ ID NO:308
4D4CVH2.1_D53Q/4D4CVL2 hIgG1	SEQ ID NO:441	SEQ ID NO:308
4D4CVH2.1_D53L/4D4CVL2 hIgG1	SEQ ID NO:442	SEQ ID NO:308
4D4CVH2.1_G54A/4D4CVL2 hIgG1	SEQ ID NO:443	SEQ ID NO:308
4D4CVH2.1_D53G/4D4CVL2_N93G hIgG1	SEQ ID NO:439	SEQ ID NO:491
4D4CVH2.1_D53E/4D4CVL2_N93G hIgG1	SEQ ID NO:440	SEQ ID NO:491
4D4CVH2.1_D53Q/4D4CVL2_N93G hIgG1	SEQ ID NO:441	SEQ ID NO:491
4D4CVH2.1_D53L/4D4CVL2_N93G hIgG1	SEQ ID NO:442	SEQ ID NO:491
4D4CVH2.1_G54A/4D4CVL2_N93G hIgG1	SEQ ID NO:443	SEQ ID NO:491
4D4CVH2.1_D53G/4D4CVL2_N93E hIgG1	SEQ ID NO:439	SEQ ID NO:492
4D4CVH2.1_D53E/4D4CVL2_N93E hIgG1	SEQ ID NO:440	SEQ ID NO:492
4D4CVH2.1_D53Q/4D4CVL2_N93E hIgG1	SEQ ID NO:441	SEQ ID NO:492
4D4CVH2.1_D53L/4D4CVL2_N93E hIgG1	SEQ ID NO:442	SEQ ID NO:492
4D4CVH2.1_G54A/4D4CVL2_N93E hIgG1	SEQ ID NO:443	SEQ ID NO:492
4D4CVH2.1_D53G/4D4CVL2_N93L hIgG1	SEQ ID NO:439	SEQ ID NO:493
4D4CVH2.1_D53E/4D4CVL2_N93L hIgG1	SEQ ID NO:440	SEQ ID NO:493
4D4CVH2.1_D53Q/4D4CVL2_N93L hIgG1	SEQ ID NO:441	SEQ ID NO:493
4D4CVH2.1_D53L/4D4CVL2_N93L hIgG1	SEQ ID NO:442	SEQ ID NO:493
4D4CVH2.1_G54A/4D4CVL2_N93L hIgG1	SEQ ID NO:443	SEQ ID NO:493
4D4CVH2.1_D53G/4D4CVL2_N93Q hIgG1	SEQ ID NO:439	SEQ ID NO:494
4D4CVH2.1_D53E/4D4CVL2_N93Q hIgG1	SEQ ID NO:440	SEQ ID NO:494
4D4CVH2.1_D53Q/4D4CVL2_N93Q hIgG1	SEQ ID NO:441	SEQ ID NO:494
4D4CVH2.1_D53L/4D4CVL2_N93Q hIgG1	SEQ ID NO:442	SEQ ID NO:494
4D4CVH2.1_G54A/4D4CVL2_N93Q hIgG1	SEQ ID NO:443	SEQ ID NO:494
4D4CVH2.1_D53G/4D4CVL2_G94A hIgG1	SEQ ID NO:439	SEQ ID NO:495
4D4CVH2.1_D53E/4D4CVL2_G94A hIgG1	SEQ ID NO:440	SEQ ID NO:495
4D4CVH2.1_D53Q/4D4CVL2_G94A hIgG1	SEQ ID NO:441	SEQ ID NO:495
4D4CVH2.1_D53L/4D4CVL2_G94A hIgG1	SEQ ID NO:442	SEQ ID NO:495
4D4CVH2.1_G54A/4D4CVL2_G94A hIgG1	SEQ ID NO:443	SEQ ID NO:495

4D4CVH2.1/4D4CVL4_N93G hIgG1	SEQ ID NO:298	SEQ ID NO:496
4D4CVH2.1/4D4CVL4_N93E hIgG1	SEQ ID NO:298	SEQ ID NO:497
4D4CVH2.1/4D4CVL4_N93L hIgG1	SEQ ID NO:298	SEQ ID NO:498
4D4CVH2.1/4D4CVL4_N93Q hIgG1	SEQ ID NO:298	SEQ ID NO:499
4D4CVH2.1/4D4CVL4_G94A hIgG1	SEQ ID NO:298	SEQ ID NO:500
4D4CVH2.1_D53G/4D4CVL4 hIgG1	SEQ ID NO:439	SEQ ID NO:309
4D4CVH2.1_D53E/4D4CVL4 hIgG1	SEQ ID NO:440	SEQ ID NO:309
4D4CVH2.1_D53Q/4D4CVL4 hIgG1	SEQ ID NO:441	SEQ ID NO:309
4D4CVH2.1_D53L/4D4CVL4 hIgG1	SEQ ID NO:442	SEQ ID NO:309
4D4CVH2.1_G54A/4D4CVL4 hIgG1	SEQ ID NO:443	SEQ ID NO:309
4D4CVH2.1_D53G/4D4CVL4_N93G hIgG1	SEQ ID NO:439	SEQ ID NO:496
4D4CVH2.1_D53E/4D4CVL4_N93G hIgG1	SEQ ID NO:440	SEQ ID NO:496
4D4CVH2.1_D53Q/4D4CVL4_N93G hIgG1	SEQ ID NO:441	SEQ ID NO:496
4D4CVH2.1_D53L/4D4CVL4_N93G hIgG1	SEQ ID NO:442	SEQ ID NO:496
4D4CVH2.1_G54A/4D4CVL4_N93G hIgG1	SEQ ID NO:443	SEQ ID NO:496
4D4CVH2.1_D53G/4D4CVL4_N93E hIgG1	SEQ ID NO:439	SEQ ID NO:497
4D4CVH2.1_D53E/4D4CVL4_N93E hIgG1	SEQ ID NO:440	SEQ ID NO:497
4D4CVH2.1_D53Q/4D4CVL4_N93E hIgG1	SEQ ID NO:441	SEQ ID NO:497
4D4CVH2.1_D53L/4D4CVL4_N93E hIgG1	SEQ ID NO:442	SEQ ID NO:497
4D4CVH2.1_G54A/4D4CVL4_N93E hIgG1	SEQ ID NO:443	SEQ ID NO:497
4D4CVH2.1_D53G/4D4CVL4_N93L hIgG1	SEQ ID NO:439	SEQ ID NO:498
4D4CVH2.1_D53E/4D4CVL4_N93L hIgG1	SEQ ID NO:440	SEQ ID NO:498
4D4CVH2.1_D53Q/4D4CVL4_N93L hIgG1	SEQ ID NO:441	SEQ ID NO:498
4D4CVH2.1_D53L/4D4CVL4_N93L hIgG1	SEQ ID NO:442	SEQ ID NO:498
4D4CVH2.1_G54A/4D4CVL4_N93L hIgG1	SEQ ID NO:443	SEQ ID NO:498
4D4CVH2.1_D53G/4D4CVL4_N93Q hIgG1	SEQ ID NO:439	SEQ ID NO:499
4D4CVH2.1_D53E/4D4CVL4_N93Q hIgG1	SEQ ID NO:440	SEQ ID NO:499
4D4CVH2.1_D53Q/4D4CVL4_N93Q hIgG1	SEQ ID NO:441	SEQ ID NO:499
4D4CVH2.1_D53L/4D4CVL4_N93Q hIgG1	SEQ ID NO:442	SEQ ID NO:499
4D4CVH2.1_G54A/4D4CVL4_N93Q hIgG1	SEQ ID NO:443	SEQ ID NO:499
4D4CVH2.1_D53G/4D4CVL4_G94A hIgG1	SEQ ID NO:439	SEQ ID NO:500
4D4CVH2.1_D53E/4D4CVL4_G94A hIgG1	SEQ ID NO:440	SEQ ID NO:500
4D4CVH2.1_D53Q/4D4CVL4_G94A hIgG1	SEQ ID NO:441	SEQ ID NO:500
4D4CVH2.1_D53L/4D4CVL4_G94A hIgG1	SEQ ID NO:442	SEQ ID NO:500
4D4CVH2.1_G54A/4D4CVL4_G94A hIgG1	SEQ ID NO:443	SEQ ID NO:500
4D4CVH2.1/4D4GVL3_N93G hIgG1	SEQ ID NO:298	SEQ ID NO:501
4D4CVH2.1/4D4GVL3_N93E hIgG1	SEQ ID NO:298	SEQ ID NO:502
4D4CVH2.1/4D4GVL3_N93L hIgG1	SEQ ID NO:298	SEQ ID NO:503
4D4CVH2.1/4D4GVL3_N93Q hIgG1	SEQ ID NO:298	SEQ ID NO:504
4D4CVH2.1/4D4GVL3_G94A hIgG1	SEQ ID NO:298	SEQ ID NO:505
4D4CVH2.1_D53G/4D4GVL3 hIgG1	SEQ ID NO:439	SEQ ID NO:310
4D4CVH2.1_D53E/4D4GVL3 hIgG1	SEQ ID NO:440	SEQ ID NO:310
4D4CVH2.1_D53Q/4D4GVL3 hIgG1	SEQ ID NO:441	SEQ ID NO:310
4D4CVH2.1_D53L/4D4GVL3 hIgG1	SEQ ID NO:442	SEQ ID NO:310
4D4CVH2.1_G54A/4D4GVL3 hIgG1	SEQ ID NO:443	SEQ ID NO:310
4D4CVH2.1_D53G/4D4GVL3_N93G hIgG1	SEQ ID NO:439	SEQ ID NO:501
4D4CVH2.1_D53E/4D4GVL3_N93G hIgG1	SEQ ID NO:440	SEQ ID NO:501
4D4CVH2.1_D53Q/4D4GVL3_N93G hIgG1	SEQ ID NO:441	SEQ ID NO:501
4D4CVH2.1_D53L/4D4GVL3_N93G hIgG1	SEQ ID NO:442	SEQ ID NO:501
4D4CVH2.1_G54A/4D4GVL3_N93G hIgG1	SEQ ID NO:443	SEQ ID NO:501
4D4CVH2.1_D53G/4D4GVL3_N93E hIgG1	SEQ ID NO:439	SEQ ID NO:502
4D4CVH2.1_D53E/4D4GVL3_N93E hIgG1	SEQ ID NO:440	SEQ ID NO:502
4D4CVH2.1_D53Q/4D4GVL3_N93E hIgG1	SEQ ID NO:441	SEQ ID NO:502
4D4CVH2.1_D53L/4D4GVL3_N93E hIgG1	SEQ ID NO:442	SEQ ID NO:502
4D4CVH2.1_G54A/4D4GVL3_N93E hIgG1	SEQ ID NO:443	SEQ ID NO:502
4D4CVH2.1_D53G/4D4GVL3_N93L hIgG1	SEQ ID NO:439	SEQ ID NO:503
4D4CVH2.1_D53E/4D4GVL3_N93L hIgG1	SEQ ID NO:440	SEQ ID NO:503
4D4CVH2.1_D53Q/4D4GVL3_N93L hIgG1	SEQ ID NO:441	SEQ ID NO:503
4D4CVH2.1_D53L/4D4GVL3_N93L hIgG1	SEQ ID NO:442	SEQ ID NO:503
4D4CVH2.1_G54A/4D4GVL3_N93L hIgG1	SEQ ID NO:443	SEQ ID NO:503
4D4CVH2.1_D53G/4D4GVL3_N93Q hIgG1	SEQ ID NO:439	SEQ ID NO:504
4D4CVH2.1_D53E/4D4GVL3_N93Q hIgG1	SEQ ID NO:440	SEQ ID NO:504
4D4CVH2.1_D53Q/4D4GVL3_N93Q hIgG1	SEQ ID NO:441	SEQ ID NO:504
4D4CVH2.1_D53L/4D4GVL3_N93Q hIgG1	SEQ ID NO:442	SEQ ID NO:504
4D4CVH2.1_G54A/4D4GVL3_N93Q hIgG1	SEQ ID NO:443	SEQ ID NO:504
4D4CVH2.1_D53G/4D4GVL3_G94A hIgG1	SEQ ID NO:439	SEQ ID NO:505
4D4CVH2.1_D53E/4D4GVL3_G94A hIgG1	SEQ ID NO:440	SEQ ID NO:505
4D4CVH2.1_D53Q/4D4GVL3_G94A hIgG1	SEQ ID NO:441	SEQ ID NO:505
4D4CVH2.1_D53L/4D4GVL3_G94A hIgG1	SEQ ID NO:442	SEQ ID NO:505
4D4CVH2.1_G54A/4D4GVL3_G94A hIgG1	SEQ ID NO:443	SEQ ID NO:505

4D4CVH2.1/4D4GVL4_N93G hIgG1	SEQ ID NO:298	SEQ ID NO:506
4D4CVH2.1/4D4GVL4_N93E hIgG1	SEQ ID NO:298	SEQ ID NO:507
4D4CVH2.1/4D4GVL4_N93L hIgG1	SEQ ID NO:298	SEQ ID NO:508
4D4CVH2.1/4D4GVL4_N93Q hIgG1	SEQ ID NO:298	SEQ ID NO:509
4D4CVH2.1/4D4GVL4_G94A hIgG1	SEQ ID NO:298	SEQ ID NO:510
4D4CVH2.1_D53G/4D4GVL4 hIgG1	SEQ ID NO:439	SEQ ID NO:311
4D4CVH2.1_D53E/4D4GVL4 hIgG1	SEQ ID NO:440	SEQ ID NO:311
4D4CVH2.1_D53Q/4D4GVL4 hIgG1	SEQ ID NO:441	SEQ ID NO:311
4D4CVH2.1_D53L/4D4GVL4 hIgG1	SEQ ID NO:442	SEQ ID NO:311
4D4CVH2.1_G54A/4D4GVL4 hIgG1	SEQ ID NO:443	SEQ ID NO:311
4D4CVH2.1_D53G/4D4GVL4_N93G hIgG1	SEQ ID NO:439	SEQ ID NO:506
4D4CVH2.1_D53E/4D4GVL4_N93G hIgG1	SEQ ID NO:440	SEQ ID NO:506
4D4CVH2.1_D53Q/4D4GVL4_N93G hIgG1	SEQ ID NO:441	SEQ ID NO:506
4D4CVH2.1_D53L/4D4GVL4_N93G hIgG1	SEQ ID NO:442	SEQ ID NO:506
4D4CVH2.1_G54A/4D4GVL4_N93G hIgG1	SEQ ID NO:443	SEQ ID NO:506
4D4CVH2.1_D53G/4D4GVL4_N93E hIgG1	SEQ ID NO:439	SEQ ID NO:507
4D4CVH2.1_D53E/4D4GVL4_N93E hIgG1	SEQ ID NO:440	SEQ ID NO:507
4D4CVH2.1_D53Q/4D4GVL4_N93E hIgG1	SEQ ID NO:441	SEQ ID NO:507
4D4CVH2.1_D53L/4D4GVL4_N93E hIgG1	SEQ ID NO:442	SEQ ID NO:507
4D4CVH2.1_G54A/4D4GVL4_N93E hIgG1	SEQ ID NO:443	SEQ ID NO:507
4D4CVH2.1_D53G/4D4GVL4_N93L hIgG1	SEQ ID NO:439	SEQ ID NO:508
4D4CVH2.1_D53E/4D4GVL4_N93L hIgG1	SEQ ID NO:440	SEQ ID NO:508
4D4CVH2.1_D53Q/4D4GVL4_N93L hIgG1	SEQ ID NO:441	SEQ ID NO:508
4D4CVH2.1_D53L/4D4GVL4_N93L hIgG1	SEQ ID NO:442	SEQ ID NO:508
4D4CVH2.1_G54A/4D4GVL4_N93L hIgG1	SEQ ID NO:443	SEQ ID NO:508
4D4CVH2.1_D53G/4D4GVL4_N93Q hIgG1	SEQ ID NO:439	SEQ ID NO:509
4D4CVH2.1_D53E/4D4GVL4_N93Q hIgG1	SEQ ID NO:440	SEQ ID NO:509
4D4CVH2.1_D53Q/4D4GVL4_N93Q hIgG1	SEQ ID NO:441	SEQ ID NO:509
4D4CVH2.1_D53L/4D4GVL4_N93Q hIgG1	SEQ ID NO:442	SEQ ID NO:509
4D4CVH2.1_G54A/4D4GVL4_N93Q hIgG1	SEQ ID NO:443	SEQ ID NO:509
4D4CVH2.1_D53G/4D4GVL4_G94A hIgG1	SEQ ID NO:439	SEQ ID NO:510
4D4CVH2.1_D53E/4D4GVL4_G94A hIgG1	SEQ ID NO:440	SEQ ID NO:510
4D4CVH2.1_D53Q/4D4GVL4_G94A hIgG1	SEQ ID NO:441	SEQ ID NO:510
4D4CVH2.1_D53L/4D4GVL4_G94A hIgG1	SEQ ID NO:442	SEQ ID NO:510
4D4CVH2.1_G54A/4D4GVL4_G94A hIgG1	SEQ ID NO:443	SEQ ID NO:510
4D4CVH2.2/4D4C/GVL1_N93G hIgG1	SEQ ID NO:299	SEQ ID NO:486
4D4CVH2.2/4D4C/GVL1_N93E hIgG1	SEQ ID NO:299	SEQ ID NO:487
4D4CVH2.2/4D4C/GVL1_N93L hIgG1	SEQ ID NO:299	SEQ ID NO:488
4D4CVH2.2/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:299	SEQ ID NO:489
4D4CVH2.2/4D4C/GVL1_G94A hIgG1	SEQ ID NO:299	SEQ ID NO:490
4D4CVH2.2_D53G/4D4C/GVL1 hIgG1	SEQ ID NO:444	SEQ ID NO:307
4D4CVH2.2_D53E/4D4C/GVL1 hIgG1	SEQ ID NO:445	SEQ ID NO:307
4D4CVH2.2_D53Q/4D4C/GVL1 hIgG1	SEQ ID NO:446	SEQ ID NO:307
4D4CVH2.2_D53L/4D4C/GVL1 hIgG1	SEQ ID NO:447	SEQ ID NO:307
4D4CVH2.2_G54A/4D4C/GVL1 hIgG1	SEQ ID NO:448	SEQ ID NO:307
4D4CVH2.2_D53G/4D4C/GVL1_N93G hIgG1	SEQ ID NO:444	SEQ ID NO:486
4D4CVH2.2_D53E/4D4C/GVL1_N93G hIgG1	SEQ ID NO:445	SEQ ID NO:486
4D4CVH2.2_D53Q/4D4C/GVL1_N93G hIgG1	SEQ ID NO:446	SEQ ID NO:486
4D4CVH2.2_D53L/4D4C/GVL1_N93G hIgG1	SEQ ID NO:447	SEQ ID NO:486
4D4CVH2.2_G54A/4D4C/GVL1_N93G hIgG1	SEQ ID NO:448	SEQ ID NO:486
4D4CVH2.2_D53G/4D4C/GVL1_N93E hIgG1	SEQ ID NO:444	SEQ ID NO:487
4D4CVH2.2_D53E/4D4C/GVL1_N93E hIgG1	SEQ ID NO:445	SEQ ID NO:487
4D4CVH2.2_D53Q/4D4C/GVL1_N93E hIgG1	SEQ ID NO:446	SEQ ID NO:487
4D4CVH2.2_D53L/4D4C/GVL1_N93E hIgG1	SEQ ID NO:447	SEQ ID NO:487
4D4CVH2.2_G54A/4D4C/GVL1_N93E hIgG1	SEQ ID NO:448	SEQ ID NO:487
4D4CVH2.2_D53G/4D4C/GVL1_N93L hIgG1	SEQ ID NO:444	SEQ ID NO:488
4D4CVH2.2_D53E/4D4C/GVL1_N93L hIgG1	SEQ ID NO:445	SEQ ID NO:488
4D4CVH2.2_D53Q/4D4C/GVL1_N93L hIgG1	SEQ ID NO:446	SEQ ID NO:488
4D4CVH2.2_D53L/4D4C/GVL1_N93L hIgG1	SEQ ID NO:447	SEQ ID NO:488
4D4CVH2.2_G54A/4D4C/GVL1_N93L hIgG1	SEQ ID NO:448	SEQ ID NO:488
4D4CVH2.2_D53G/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:444	SEQ ID NO:489
4D4CVH2.2_D53E/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:445	SEQ ID NO:489
4D4CVH2.2_D53Q/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:446	SEQ ID NO:489
4D4CVH2.2_D53L/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:447	SEQ ID NO:489
4D4CVH2.2_G54A/4D4C/GVL1_N93Q hIgG1	SEQ ID NO:448	SEQ ID NO:489
4D4CVH2.2_D53G/4D4C/GVL1_G94A hIgG1	SEQ ID NO:444	SEQ ID NO:490
4D4CVH2.2_D53E/4D4C/GVL1_G94A hIgG1	SEQ ID NO:445	SEQ ID NO:490
4D4CVH2.2_D53Q/4D4C/GVL1_G94A hIgG1	SEQ ID NO:446	SEQ ID NO:490
4D4CVH2.2_D53L/4D4C/GVL1_G94A hIgG1	SEQ ID NO:447	SEQ ID NO:490
4D4CVH2.2_G54A/4D4C/GVL1_G94A hIgG1	SEQ ID NO:448	SEQ ID NO:490

4D4CVH2.2/4D4CVL2_N93G hIgG1	SEQ ID NO:299	SEQ ID NO:491
4D4CVH2.2/4D4CVL2_N93E hIgG1	SEQ ID NO:299	SEQ ID NO:492
4D4CVH2.2/4D4CVL2_N93L hIgG1	SEQ ID NO:299	SEQ ID NO:493
4D4CVH2.2/4D4CVL2_N93Q hIgG1	SEQ ID NO:299	SEQ ID NO:494
4D4CVH2.2/4D4CVL2_G94A hIgG1	SEQ ID NO:299	SEQ ID NO:495
4D4CVH2.2_D53G/4D4CVL2 hIgG1	SEQ ID NO:444	SEQ ID NO:308
4D4CVH2.2_D53E/4D4CVL2 hIgG1	SEQ ID NO:445	SEQ ID NO:308
4D4CVH2.2_D53Q/4D4CVL2 hIgG1	SEQ ID NO:446	SEQ ID NO:308
4D4CVH2.2_D53L/4D4CVL2 hIgG1	SEQ ID NO:447	SEQ ID NO:308
4D4CVH2.2_G54A/4D4CVL2 hIgG1	SEQ ID NO:448	SEQ ID NO:308
4D4CVH2.2_D53G/4D4CVL2_N93G hIgG1	SEQ ID NO:444	SEQ ID NO:491
4D4CVH2.2_D53E/4D4CVL2_N93G hIgG1	SEQ ID NO:445	SEQ ID NO:491
4D4CVH2.2_D53Q/4D4CVL2_N93G hIgG1	SEQ ID NO:446	SEQ ID NO:491
4D4CVH2.2_D53L/4D4CVL2_N93G hIgG1	SEQ ID NO:447	SEQ ID NO:491
4D4CVH2.2_G54A/4D4CVL2_N93G hIgG1	SEQ ID NO:448	SEQ ID NO:491
4D4CVH2.2_D53G/4D4CVL2_N93E hIgG1	SEQ ID NO:444	SEQ ID NO:492
4D4CVH2.2_D53E/4D4CVL2_N93E hIgG1	SEQ ID NO:445	SEQ ID NO:492
4D4CVH2.2_D53Q/4D4CVL2_N93E hIgG1	SEQ ID NO:446	SEQ ID NO:492
4D4CVH2.2_D53L/4D4CVL2_N93E hIgG1	SEQ ID NO:447	SEQ ID NO:492
4D4CVH2.2_G54A/4D4CVL2_N93E hIgG1	SEQ ID NO:448	SEQ ID NO:492
4D4CVH2.2_D53G/4D4CVL2_N93L hIgG1	SEQ ID NO:444	SEQ ID NO:493
4D4CVH2.2_D53E/4D4CVL2_N93L hIgG1	SEQ ID NO:445	SEQ ID NO:493
4D4CVH2.2_D53Q/4D4CVL2_N93L hIgG1	SEQ ID NO:446	SEQ ID NO:493
4D4CVH2.2_D53L/4D4CVL2_N93L hIgG1	SEQ ID NO:447	SEQ ID NO:493
4D4CVH2.2_G54A/4D4CVL2_N93L hIgG1	SEQ ID NO:448	SEQ ID NO:493
4D4CVH2.2_D53G/4D4CVL2_N93Q hIgG1	SEQ ID NO:444	SEQ ID NO:494
4D4CVH2.2_D53E/4D4CVL2_N93Q hIgG1	SEQ ID NO:445	SEQ ID NO:494
4D4CVH2.2_D53Q/4D4CVL2_N93Q hIgG1	SEQ ID NO:446	SEQ ID NO:494
4D4CVH2.2_D53L/4D4CVL2_N93Q hIgG1	SEQ ID NO:447	SEQ ID NO:494
4D4CVH2.2_G54A/4D4CVL2_N93Q hIgG1	SEQ ID NO:448	SEQ ID NO:494
4D4CVH2.2_D53G/4D4CVL2_G94A hIgG1	SEQ ID NO:444	SEQ ID NO:495
4D4CVH2.2_D53E/4D4CVL2_G94A hIgG1	SEQ ID NO:445	SEQ ID NO:495
4D4CVH2.2_D53Q/4D4CVL2_G94A hIgG1	SEQ ID NO:446	SEQ ID NO:495
4D4CVH2.2_D53L/4D4CVL2_G94A hIgG1	SEQ ID NO:447	SEQ ID NO:495
4D4CVH2.2_G54A/4D4CVL2_G94A hIgG1	SEQ ID NO:448	SEQ ID NO:495
4D4CVH2.2/4D4CVL4_N93G hIgG1	SEQ ID NO:299	SEQ ID NO:496
4D4CVH2.2/4D4CVL4_N93E hIgG1	SEQ ID NO:299	SEQ ID NO:497
4D4CVH2.2/4D4CVL4_N93L hIgG1	SEQ ID NO:299	SEQ ID NO:498
4D4CVH2.2/4D4CVL4_N93Q hIgG1	SEQ ID NO:299	SEQ ID NO:499
4D4CVH2.2/4D4CVL4_G94A hIgG1	SEQ ID NO:299	SEQ ID NO:500
4D4CVH2.2_D53G/4D4CVL4 hIgG1	SEQ ID NO:444	SEQ ID NO:309
4D4CVH2.2_D53E/4D4CVL4 hIgG1	SEQ ID NO:445	SEQ ID NO:309
4D4CVH2.2_D53Q/4D4CVL4 hIgG1	SEQ ID NO:446	SEQ ID NO:309
4D4CVH2.2_D53L/4D4CVL4 hIgG1	SEQ ID NO:447	SEQ ID NO:309
4D4CVH2.2_G54A/4D4CVL4 hIgG1	SEQ ID NO:448	SEQ ID NO:309
4D4CVH2.2_D53G/4D4CVL4_N93G hIgG1	SEQ ID NO:444	SEQ ID NO:496
4D4CVH2.2_D53E/4D4CVL4_N93G hIgG1	SEQ ID NO:445	SEQ ID NO:496
4D4CVH2.2_D53Q/4D4CVL4_N93G hIgG1	SEQ ID NO:446	SEQ ID NO:496
4D4CVH2.2_D53L/4D4CVL4_N93G hIgG1	SEQ ID NO:447	SEQ ID NO:496
4D4CVH2.2_G54A/4D4CVL4_N93G hIgG1	SEQ ID NO:448	SEQ ID NO:496
4D4CVH2.2_D53G/4D4CVL4_N93E hIgG1	SEQ ID NO:444	SEQ ID NO:497
4D4CVH2.2_D53E/4D4CVL4_N93E hIgG1	SEQ ID NO:445	SEQ ID NO:497
4D4CVH2.2_D53Q/4D4CVL4_N93E hIgG1	SEQ ID NO:446	SEQ ID NO:497
4D4CVH2.2_D53L/4D4CVL4_N93E hIgG1	SEQ ID NO:447	SEQ ID NO:497
4D4CVH2.2_G54A/4D4CVL4_N93E hIgG1	SEQ ID NO:448	SEQ ID NO:497
4D4CVH2.2_D53G/4D4CVL4_N93L hIgG1	SEQ ID NO:444	SEQ ID NO:498
4D4CVH2.2_D53E/4D4CVL4_N93L hIgG1	SEQ ID NO:445	SEQ ID NO:498
4D4CVH2.2_D53Q/4D4CVL4_N93L hIgG1	SEQ ID NO:446	SEQ ID NO:498
4D4CVH2.2_D53L/4D4CVL4_N93L hIgG1	SEQ ID NO:447	SEQ ID NO:498
4D4CVH2.2_G54A/4D4CVL4_N93L hIgG1	SEQ ID NO:448	SEQ ID NO:498
4D4CVH2.2_D53G/4D4CVL4_N93Q hIgG1	SEQ ID NO:444	SEQ ID NO:499
4D4CVH2.2_D53E/4D4CVL4_N93Q hIgG1	SEQ ID NO:445	SEQ ID NO:499
4D4CVH2.2_D53Q/4D4CVL4_N93Q hIgG1	SEQ ID NO:446	SEQ ID NO:499
4D4CVH2.2_D53L/4D4CVL4_N93Q hIgG1	SEQ ID NO:447	SEQ ID NO:499
4D4CVH2.2_G54A/4D4CVL4_N93Q hIgG1	SEQ ID NO:448	SEQ ID NO:499
4D4CVH2.2_D53G/4D4CVL4_G94A hIgG1	SEQ ID NO:444	SEQ ID NO:500
4D4CVH2.2_D53E/4D4CVL4_G94A hIgG1	SEQ ID NO:445	SEQ ID NO:500
4D4CVH2.2_D53Q/4D4CVL4_G94A hIgG1	SEQ ID NO:446	SEQ ID NO:500
4D4CVH2.2_D53L/4D4CVL4_G94A hIgG1	SEQ ID NO:447	SEQ ID NO:500
4D4CVH2.2_G54A/4D4CVL4_G94A hIgG1	SEQ ID NO:448	SEQ ID NO:500

4D4CVH2.2/4D4GVL3_N93G hIgG1	SEQ ID NO:299	SEQ ID NO:501
4D4CVH2.2/4D4GVL3_N93E hIgG1	SEQ ID NO:299	SEQ ID NO:502
4D4CVH2.2/4D4GVL3_N93L hIgG1	SEQ ID NO:299	SEQ ID NO:503
4D4CVH2.2/4D4GVL3_N93Q hIgG1	SEQ ID NO:299	SEQ ID NO:504
4D4CVH2.2/4D4GVL3_G94A hIgG1	SEQ ID NO:299	SEQ ID NO:505
4D4CVH2.2_D53G/4D4GVL3 hIgG1	SEQ ID NO:444	SEQ ID NO:310
4D4CVH2.2_D53E/4D4GVL3 hIgG1	SEQ ID NO:445	SEQ ID NO:310
4D4CVH2.2_D53Q/4D4GVL3 hIgG1	SEQ ID NO:446	SEQ ID NO:310
4D4CVH2.2_D53L/4D4GVL3 hIgG1	SEQ ID NO:447	SEQ ID NO:310
4D4CVH2.2_G54A/4D4GVL3 hIgG1	SEQ ID NO:448	SEQ ID NO:310
4D4CVH2.2_D53G/4D4GVL3_N93G hIgG1	SEQ ID NO:444	SEQ ID NO:501
4D4CVH2.2_D53E/4D4GVL3_N93G hIgG1	SEQ ID NO:445	SEQ ID NO:501
4D4CVH2.2_D53Q/4D4GVL3_N93G hIgG1	SEQ ID NO:446	SEQ ID NO:501
4D4CVH2.2_D53L/4D4GVL3_N93G hIgG1	SEQ ID NO:447	SEQ ID NO:501
4D4CVH2.2_G54A/4D4GVL3_N93G hIgG1	SEQ ID NO:448	SEQ ID NO:501
4D4CVH2.2_D53G/4D4GVL3_N93E hIgG1	SEQ ID NO:444	SEQ ID NO:502
4D4CVH2.2_D53E/4D4GVL3_N93E hIgG1	SEQ ID NO:445	SEQ ID NO:502
4D4CVH2.2_D53Q/4D4GVL3_N93E hIgG1	SEQ ID NO:446	SEQ ID NO:502
4D4CVH2.2_D53L/4D4GVL3_N93E hIgG1	SEQ ID NO:447	SEQ ID NO:502
4D4CVH2.2_G54A/4D4GVL3_N93E hIgG1	SEQ ID NO:448	SEQ ID NO:502
4D4CVH2.2_D53G/4D4GVL3_N93L hIgG1	SEQ ID NO:444	SEQ ID NO:503
4D4CVH2.2_D53E/4D4GVL3_N93L hIgG1	SEQ ID NO:445	SEQ ID NO:503
4D4CVH2.2_D53Q/4D4GVL3_N93L hIgG1	SEQ ID NO:446	SEQ ID NO:503
4D4CVH2.2_D53L/4D4GVL3_N93L hIgG1	SEQ ID NO:447	SEQ ID NO:503
4D4CVH2.2_G54A/4D4GVL3_N93L hIgG1	SEQ ID NO:448	SEQ ID NO:503
4D4CVH2.2_D53G/4D4GVL3_N93Q hIgG1	SEQ ID NO:444	SEQ ID NO:504
4D4CVH2.2_D53E/4D4GVL3_N93Q hIgG1	SEQ ID NO:445	SEQ ID NO:504
4D4CVH2.2_D53Q/4D4GVL3_N93Q hIgG1	SEQ ID NO:446	SEQ ID NO:504
4D4CVH2.2_D53L/4D4GVL3_N93Q hIgG1	SEQ ID NO:447	SEQ ID NO:504
4D4CVH2.2_G54A/4D4GVL3_N93Q hIgG1	SEQ ID NO:448	SEQ ID NO:504
4D4CVH2.2_D53G/4D4GVL3_G94A hIgG1	SEQ ID NO:444	SEQ ID NO:505
4D4CVH2.2_D53E/4D4GVL3_G94A hIgG1	SEQ ID NO:445	SEQ ID NO:505
4D4CVH2.2_D53Q/4D4GVL3_G94A hIgG1	SEQ ID NO:446	SEQ ID NO:505
4D4CVH2.2_D53L/4D4GVL3_G94A hIgG1	SEQ ID NO:447	SEQ ID NO:505
4D4CVH2.2_G54A/4D4GVL3_G94A hIgG1	SEQ ID NO:448	SEQ ID NO:505
4D4CVH2.2/4D4GVL4_N93G hIgG1	SEQ ID NO:299	SEQ ID NO:506
4D4CVH2.2/4D4GVL4_N93E hIgG1	SEQ ID NO:299	SEQ ID NO:507
4D4CVH2.2/4D4GVL4_N93L hIgG1	SEQ ID NO:299	SEQ ID NO:508
4D4CVH2.2/4D4GVL4_N93Q hIgG1	SEQ ID NO:299	SEQ ID NO:509
4D4CVH2.2/4D4GVL4_G94A hIgG1	SEQ ID NO:299	SEQ ID NO:510
4D4CVH2.2_D53G/4D4GVL4 hIgG1	SEQ ID NO:444	SEQ ID NO:311
4D4CVH2.2_D53E/4D4GVL4 hIgG1	SEQ ID NO:445	SEQ ID NO:311
4D4CVH2.2_D53Q/4D4GVL4 hIgG1	SEQ ID NO:446	SEQ ID NO:311
4D4CVH2.2_D53L/4D4GVL4 hIgG1	SEQ ID NO:447	SEQ ID NO:311
4D4CVH2.2_G54A/4D4GVL4 hIgG1	SEQ ID NO:448	SEQ ID NO:311
4D4CVH2.2_D53G/4D4GVL4_N93G hIgG1	SEQ ID NO:444	SEQ ID NO:506
4D4CVH2.2_D53E/4D4GVL4_N93G hIgG1	SEQ ID NO:445	SEQ ID NO:506
4D4CVH2.2_D53Q/4D4GVL4_N93G hIgG1	SEQ ID NO:446	SEQ ID NO:506
4D4CVH2.2_D53L/4D4GVL4_N93G hIgG1	SEQ ID NO:447	SEQ ID NO:506
4D4CVH2.2_G54A/4D4GVL4_N93G hIgG1	SEQ ID NO:448	SEQ ID NO:506
4D4CVH2.2_D53G/4D4GVL4_N93E hIgG1	SEQ ID NO:444	SEQ ID NO:507
4D4CVH2.2_D53E/4D4GVL4_N93E hIgG1	SEQ ID NO:445	SEQ ID NO:507
4D4CVH2.2_D53Q/4D4GVL4_N93E hIgG1	SEQ ID NO:446	SEQ ID NO:507
4D4CVH2.2_D53L/4D4GVL4_N93E hIgG1	SEQ ID NO:447	SEQ ID NO:507
4D4CVH2.2_G54A/4D4GVL4_N93E hIgG1	SEQ ID NO:448	SEQ ID NO:507
4D4CVH2.2_D53G/4D4GVL4_N93L hIgG1	SEQ ID NO:444	SEQ ID NO:508
4D4CVH2.2_D53E/4D4GVL4_N93L hIgG1	SEQ ID NO:445	SEQ ID NO:508
4D4CVH2.2_D53Q/4D4GVL4_N93L hIgG1	SEQ ID NO:446	SEQ ID NO:508
4D4CVH2.2_D53L/4D4GVL4_N93L hIgG1	SEQ ID NO:447	SEQ ID NO:508
4D4CVH2.2_G54A/4D4GVL4_N93L hIgG1	SEQ ID NO:448	SEQ ID NO:508
4D4CVH2.2_D53G/4D4GVL4_N93Q hIgG1	SEQ ID NO:444	SEQ ID NO:509
4D4CVH2.2_D53E/4D4GVL4_N93Q hIgG1	SEQ ID NO:445	SEQ ID NO:509
4D4CVH2.2_D53Q/4D4GVL4_N93Q hIgG1	SEQ ID NO:446	SEQ ID NO:509
4D4CVH2.2_D53L/4D4GVL4_N93Q hIgG1	SEQ ID NO:447	SEQ ID NO:509
4D4CVH2.2_G54A/4D4GVL4_N93Q hIgG1	SEQ ID NO:448	SEQ ID NO:509
4D4CVH2.2_D53G/4D4GVL4_G94A hIgG1	SEQ ID NO:444	SEQ ID NO:510
4D4CVH2.2_D53E/4D4GVL4_G94A hIgG1	SEQ ID NO:445	SEQ ID NO:510
4D4CVH2.2_D53Q/4D4GVL4_G94A hIgG1	SEQ ID NO:446	SEQ ID NO:510
4D4CVH2.2_D53L/4D4GVL4_G94A hIgG1	SEQ ID NO:447	SEQ ID NO:510
4D4CVH2.2_G54A/4D4GVL4_G94A hIgG1	SEQ ID NO:448	SEQ ID NO:510

CON4D4P/Hu_D53var_G53var /CON4D4P/Hu_N93var_G94var hIgG1	SEQ ID NO:449	SEQ ID NO:511
4D4/4D4_N93G hIgG4(S228P, L235E)	SEQ ID NO:333	SEQ ID NO:481
4D4/4D4_N93E hIgG4(S228P, L235E)	SEQ ID NO:333	SEQ ID NO:482
4D4/4D4_N93L hIgG4(S228P, L235E)	SEQ ID NO:333	SEQ ID NO:483
4D4/4D4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:333	SEQ ID NO:484
4D4/4D4_G94A hIgG4(S228P, L235E)	SEQ ID NO:333	SEQ ID NO:485
4D4_D53G/4D4 hIgG4(S228P, L235E)	SEQ ID NO:450	SEQ ID NO:301
4D4_D53E/4D4 hIgG4(S228P, L235E)	SEQ ID NO:451	SEQ ID NO:301
4D4_D53Q/4D4 hIgG4(S228P, L235E)	SEQ ID NO:452	SEQ ID NO:301
4D4_D53L/4D4 hIgG4(S228P, L235E)	SEQ ID NO:453	SEQ ID NO:301
4D4_G54A/4D4 hIgG4(S228P, L235E)	SEQ ID NO:454	SEQ ID NO:301
4D4_D53G/4D4_N93G hIgG4(S228P, L235E)	SEQ ID NO:450	SEQ ID NO:481
4D4_D53E/4D4_N93G hIgG4(S228P, L235E)	SEQ ID NO:451	SEQ ID NO:481
4D4_D53Q/4D4_N93G hIgG4(S228P, L235E)	SEQ ID NO:452	SEQ ID NO:481
4D4_D53L/4D4_N93G hIgG4(S228P, L235E)	SEQ ID NO:453	SEQ ID NO:481
4D4_G54A/4D4_N93G hIgG4(S228P, L235E)	SEQ ID NO:454	SEQ ID NO:481
4D4_D53G/4D4_N93E hIgG4(S228P, L235E)	SEQ ID NO:450	SEQ ID NO:482
4D4_D53E/4D4_N93E hIgG4(S228P, L235E)	SEQ ID NO:451	SEQ ID NO:482
4D4_D53Q/4D4_N93E hIgG4(S228P, L235E)	SEQ ID NO:452	SEQ ID NO:482
4D4_D53L/4D4_N93E hIgG4(S228P, L235E)	SEQ ID NO:453	SEQ ID NO:482
4D4_G54A/4D4_N93E hIgG4(S228P, L235E)	SEQ ID NO:454	SEQ ID NO:482
4D4_D53G/4D4_N93L hIgG4(S228P, L235E)	SEQ ID NO:450	SEQ ID NO:483
4D4_D53E/4D4_N93L hIgG4(S228P, L235E)	SEQ ID NO:451	SEQ ID NO:483
4D4_D53Q/4D4_N93L hIgG4(S228P, L235E)	SEQ ID NO:452	SEQ ID NO:483
4D4_D53L/4D4_N93L hIgG4(S228P, L235E)	SEQ ID NO:453	SEQ ID NO:483
4D4_G54A/4D4_N93L hIgG4(S228P, L235E)	SEQ ID NO:454	SEQ ID NO:483
4D4_D53G/4D4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:450	SEQ ID NO:484
4D4_D53E/4D4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:451	SEQ ID NO:484
4D4_D53Q/4D4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:452	SEQ ID NO:484
4D4_D53L/4D4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:453	SEQ ID NO:484
4D4_G54A/4D4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:454	SEQ ID NO:484
4D4_D53G/4D4_G94A hIgG4(S228P, L235E)	SEQ ID NO:450	SEQ ID NO:485
4D4_D53E/4D4_G94A hIgG4(S228P, L235E)	SEQ ID NO:451	SEQ ID NO:485
4D4_D53Q/4D4_G94A hIgG4(S228P, L235E)	SEQ ID NO:452	SEQ ID NO:485
4D4_D53L/4D4_G94A hIgG4(S228P, L235E)	SEQ ID NO:453	SEQ ID NO:485
4D4_G54A/4D4_G94A hIgG4(S228P, L235E)	SEQ ID NO:454	SEQ ID NO:485
4D4CVH2/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:486
4D4CVH2/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:487
4D4CVH2/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:488
4D4CVH2/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:489
4D4CVH2/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:490
4D4CVH2_D53G/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:307
4D4CVH2_D53E/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:307
4D4CVH2_D53Q/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:307
4D4CVH2_D53L/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:307
4D4CVH2_G54A/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:307
4D4CVH2_D53G/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:486
4D4CVH2_D53E/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:486
4D4CVH2_D53Q/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:486
4D4CVH2_D53L/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:486
4D4CVH2_G54A/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:486
4D4CVH2_D53G/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:487
4D4CVH2_D53E/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:487
4D4CVH2_D53Q/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:487
4D4CVH2_D53L/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:487
4D4CVH2_G54A/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:487
4D4CVH2_D53G/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:488
4D4CVH2_D53E/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:488
4D4CVH2_D53Q/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:488
4D4CVH2_D53L/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:488
4D4CVH2_G54A/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:488
4D4CVH2_D53G/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:489
4D4CVH2_D53E/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:489
4D4CVH2_D53Q/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:489
4D4CVH2_D53L/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:489
4D4CVH2_G54A/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:489
4D4CVH2_D53G/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:490
4D4CVH2_D53E/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:490
4D4CVH2_D53Q/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:490
4D4CVH2_D53L/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:490

4D4CVH2_G54A/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:490
4D4CVH2/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:491
4D4CVH2/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:492
4D4CVH2/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:493
4D4CVH2/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:494
4D4CVH2/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:495
4D4CVH2_D53G/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:308
4D4CVH2_D53E/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:308
4D4CVH2_D53Q/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:308
4D4CVH2_D53L/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:308
4D4CVH2_G54A/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:308
4D4CVH2_D53G/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:491
4D4CVH2_D53E/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:491
4D4CVH2_D53Q/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:491
4D4CVH2_D53L/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:491
4D4CVH2_G54A/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:491
4D4CVH2_D53G/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:492
4D4CVH2_D53E/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:492
4D4CVH2_D53Q/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:492
4D4CVH2_D53L/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:492
4D4CVH2_G54A/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:492
4D4CVH2_D53G/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:493
4D4CVH2_D53E/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:493
4D4CVH2_D53Q/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:493
4D4CVH2_D53L/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:493
4D4CVH2_G54A/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:493
4D4CVH2_D53G/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:494
4D4CVH2_D53E/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:494
4D4CVH2_D53Q/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:494
4D4CVH2_D53L/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:494
4D4CVH2_G54A/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:494
4D4CVH2_D53G/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:495
4D4CVH2_D53E/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:495
4D4CVH2_D53Q/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:495
4D4CVH2_D53L/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:495
4D4CVH2_G54A/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:495
4D4CVH2/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:496
4D4CVH2/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:497
4D4CVH2/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:498
4D4CVH2/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:499
4D4CVH2/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:500
4D4CVH2_D53G/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:309
4D4CVH2_D53E/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:309
4D4CVH2_D53Q/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:309
4D4CVH2_D53L/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:309
4D4CVH2_G54A/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:309
4D4CVH2_D53G/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:496
4D4CVH2_D53E/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:496
4D4CVH2_D53Q/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:496
4D4CVH2_D53L/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:496
4D4CVH2_G54A/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:496
4D4CVH2_D53G/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:497
4D4CVH2_D53E/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:497
4D4CVH2_D53Q/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:497
4D4CVH2_D53L/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:497
4D4CVH2_G54A/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:497
4D4CVH2_D53G/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:498
4D4CVH2_D53E/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:498
4D4CVH2_D53Q/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:498
4D4CVH2_D53L/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:498
4D4CVH2_G54A/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:498
4D4CVH2_D53G/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:499
4D4CVH2_D53E/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:499
4D4CVH2_D53Q/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:499
4D4CVH2_D53L/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:499
4D4CVH2_G54A/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:499
4D4CVH2_D53G/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:500
4D4CVH2_D53E/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:500
4D4CVH2_D53Q/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:500
4D4CVH2_D53L/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:500

4D4CVH2_G54A/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:500
4D4CVH2/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:501
4D4CVH2/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:502
4D4CVH2/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:503
4D4CVH2/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:504
4D4CVH2/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:505
4D4CVH2_D53G/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:310
4D4CVH2_D53E/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:310
4D4CVH2_D53Q/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:310
4D4CVH2_D53L/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:310
4D4CVH2_G54A/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:310
4D4CVH2_D53G/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:501
4D4CVH2_D53E/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:501
4D4CVH2_D53Q/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:501
4D4CVH2_D53L/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:501
4D4CVH2_G54A/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:501
4D4CVH2_D53G/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:502
4D4CVH2_D53E/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:502
4D4CVH2_D53Q/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:502
4D4CVH2_D53L/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:502
4D4CVH2_G54A/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:502
4D4CVH2_D53G/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:503
4D4CVH2_D53E/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:503
4D4CVH2_D53Q/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:503
4D4CVH2_D53L/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:503
4D4CVH2_G54A/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:503
4D4CVH2_D53G/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:504
4D4CVH2_D53E/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:504
4D4CVH2_D53Q/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:504
4D4CVH2_D53L/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:504
4D4CVH2_G54A/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:504
4D4CVH2_D53G/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:505
4D4CVH2_D53E/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:505
4D4CVH2_D53Q/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:505
4D4CVH2_D53L/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:505
4D4CVH2_G54A/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:505
4D4CVH2/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:506
4D4CVH2/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:507
4D4CVH2/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:508
4D4CVH2/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:509
4D4CVH2/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:339	SEQ ID NO:510
4D4CVH2_D53G/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:311
4D4CVH2_D53E/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:311
4D4CVH2_D53Q/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:311
4D4CVH2_D53L/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:311
4D4CVH2_G54A/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:311
4D4CVH2_D53G/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:506
4D4CVH2_D53E/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:506
4D4CVH2_D53Q/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:506
4D4CVH2_D53L/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:506
4D4CVH2_G54A/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:506
4D4CVH2_D53G/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:507
4D4CVH2_D53E/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:507
4D4CVH2_D53Q/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:507
4D4CVH2_D53L/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:507
4D4CVH2_G54A/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:507
4D4CVH2_D53G/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:508
4D4CVH2_D53E/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:508
4D4CVH2_D53Q/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:508
4D4CVH2_D53L/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:508
4D4CVH2_G54A/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:508
4D4CVH2_D53G/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:509
4D4CVH2_D53E/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:509
4D4CVH2_D53Q/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:509
4D4CVH2_D53L/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:509
4D4CVH2_G54A/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:509
4D4CVH2_D53G/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:455	SEQ ID NO:510
4D4CVH2_D53E/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:456	SEQ ID NO:510
4D4CVH2_D53Q/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:457	SEQ ID NO:510
4D4CVH2_D53L/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:458	SEQ ID NO:510

4D4CVH2_G54A/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:459	SEQ ID NO:510
4D4CVH3/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:486
4D4CVH3/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:487
4D4CVH3/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:488
4D4CVH3/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:489
4D4CVH3/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:490
4D4CVH3_D53G/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:307
4D4CVH3_D53E/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:307
4D4CVH3_D53Q/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:307
4D4CVH3_D53L/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:307
4D4CVH3_G54A/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:307
4D4CVH3_D53G/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:486
4D4CVH3_D53E/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:486
4D4CVH3_D53Q/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:486
4D4CVH3_D53L/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:486
4D4CVH3_G54A/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:486
4D4CVH3_D53G/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:487
4D4CVH3_D53E/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:487
4D4CVH3_D53Q/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:487
4D4CVH3_D53L/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:487
4D4CVH3_G54A/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:487
4D4CVH3_D53G/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:488
4D4CVH3_D53E/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:488
4D4CVH3_D53Q/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:488
4D4CVH3_D53L/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:488
4D4CVH3_G54A/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:488
4D4CVH3_D53G/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:489
4D4CVH3_D53E/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:489
4D4CVH3_D53Q/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:489
4D4CVH3_D53L/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:489
4D4CVH3_G54A/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:489
4D4CVH3_D53G/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:490
4D4CVH3_D53E/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:490
4D4CVH3_D53Q/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:490
4D4CVH3_D53L/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:490
4D4CVH3_G54A/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:490
4D4CVH3/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:491
4D4CVH3/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:492
4D4CVH3/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:493
4D4CVH3/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:494
4D4CVH3/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:495
4D4CVH3_D53G/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:308
4D4CVH3_D53E/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:308
4D4CVH3_D53Q/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:308
4D4CVH3_D53L/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:308
4D4CVH3_G54A/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:308
4D4CVH3_D53G/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:491
4D4CVH3_D53E/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:491
4D4CVH3_D53Q/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:491
4D4CVH3_D53L/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:491
4D4CVH3_G54A/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:491
4D4CVH3_D53G/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:492
4D4CVH3_D53E/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:492
4D4CVH3_D53Q/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:492
4D4CVH3_D53L/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:492
4D4CVH3_G54A/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:492
4D4CVH3_D53G/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:493
4D4CVH3_D53E/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:493
4D4CVH3_D53Q/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:493
4D4CVH3_D53L/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:493
4D4CVH3_G54A/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:493
4D4CVH3_D53G/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:494
4D4CVH3_D53E/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:494
4D4CVH3_D53Q/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:494
4D4CVH3_D53L/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:494
4D4CVH3_G54A/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:494
4D4CVH3_D53G/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:495
4D4CVH3_D53E/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:495
4D4CVH3_D53Q/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:495
4D4CVH3_D53L/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:495

4D4CVH3_G54A/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:495
4D4CVH3/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:496
4D4CVH3/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:497
4D4CVH3/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:498
4D4CVH3/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:499
4D4CVH3/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:500
4D4CVH3_D53G/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:309
4D4CVH3_D53E/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:309
4D4CVH3_D53Q/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:309
4D4CVH3_D53L/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:309
4D4CVH3_G54A/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:309
4D4CVH3_D53G/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:496
4D4CVH3_D53E/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:496
4D4CVH3_D53Q/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:496
4D4CVH3_D53L/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:496
4D4CVH3_G54A/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:496
4D4CVH3_D53G/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:497
4D4CVH3_D53E/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:497
4D4CVH3_D53Q/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:497
4D4CVH3_D53L/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:497
4D4CVH3_G54A/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:497
4D4CVH3_D53G/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:498
4D4CVH3_D53E/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:498
4D4CVH3_D53Q/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:498
4D4CVH3_D53L/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:498
4D4CVH3_G54A/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:498
4D4CVH3_D53G/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:499
4D4CVH3_D53E/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:499
4D4CVH3_D53Q/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:499
4D4CVH3_D53L/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:499
4D4CVH3_G54A/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:499
4D4CVH3_D53G/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:500
4D4CVH3_D53E/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:500
4D4CVH3_D53Q/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:500
4D4CVH3_D53L/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:500
4D4CVH3_G54A/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:500
4D4CVH3/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:501
4D4CVH3/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:502
4D4CVH3/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:503
4D4CVH3/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:504
4D4CVH3/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:505
4D4CVH3_D53G/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:310
4D4CVH3_D53E/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:310
4D4CVH3_D53Q/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:310
4D4CVH3_D53L/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:310
4D4CVH3_G54A/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:310
4D4CVH3_D53G/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:501
4D4CVH3_D53E/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:501
4D4CVH3_D53Q/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:501
4D4CVH3_D53L/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:501
4D4CVH3_G54A/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:501
4D4CVH3_D53G/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:502
4D4CVH3_D53E/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:502
4D4CVH3_D53Q/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:502
4D4CVH3_D53L/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:502
4D4CVH3_G54A/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:502
4D4CVH3_D53G/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:503
4D4CVH3_D53E/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:503
4D4CVH3_D53Q/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:503
4D4CVH3_D53L/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:503
4D4CVH3_G54A/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:503
4D4CVH3_D53G/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:504
4D4CVH3_D53E/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:504
4D4CVH3_D53Q/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:504
4D4CVH3_D53L/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:504
4D4CVH3_G54A/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:504
4D4CVH3_D53G/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:505
4D4CVH3_D53E/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:505
4D4CVH3_D53Q/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:505
4D4CVH3_D53L/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:505

4D4CVH3_G54A/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:505
4D4CVH3/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:506
4D4CVH3/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:507
4D4CVH3/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:508
4D4CVH3/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:509
4D4CVH3/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:340	SEQ ID NO:510
4D4CVH3_D53G/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:311
4D4CVH3_D53E/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:311
4D4CVH3_D53Q/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:311
4D4CVH3_D53L/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:311
4D4CVH3_G54A/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:311
4D4CVH3_D53G/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:506
4D4CVH3_D53E/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:506
4D4CVH3_D53Q/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:506
4D4CVH3_D53L/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:506
4D4CVH3_G54A/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:506
4D4CVH3_D53G/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:507
4D4CVH3_D53E/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:507
4D4CVH3_D53Q/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:507
4D4CVH3_D53L/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:507
4D4CVH3_G54A/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:507
4D4CVH3_D53G/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:508
4D4CVH3_D53E/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:508
4D4CVH3_D53Q/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:508
4D4CVH3_D53L/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:508
4D4CVH3_G54A/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:508
4D4CVH3_D53G/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:509
4D4CVH3_D53E/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:509
4D4CVH3_D53Q/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:509
4D4CVH3_D53L/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:509
4D4CVH3_G54A/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:509
4D4CVH3_D53G/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:460	SEQ ID NO:510
4D4CVH3_D53E/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:461	SEQ ID NO:510
4D4CVH3_D53Q/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:462	SEQ ID NO:510
4D4CVH3_D53L/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:463	SEQ ID NO:510
4D4CVH3_G54A/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:464	SEQ ID NO:510
4D4CVH4/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:486
4D4CVH4/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:487
4D4CVH4/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:488
4D4CVH4/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:489
4D4CVH4/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:490
4D4CVH4_D53G/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:307
4D4CVH4_D53E/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:307
4D4CVH4_D53Q/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:307
4D4CVH4_D53L/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:307
4D4CVH4_G54A/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:307
4D4CVH4_D53G/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:486
4D4CVH4_D53E/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:486
4D4CVH4_D53Q/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:486
4D4CVH4_D53L/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:486
4D4CVH4_G54A/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:486
4D4CVH4_D53G/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:487
4D4CVH4_D53E/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:487
4D4CVH4_D53Q/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:487
4D4CVH4_D53L/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:487
4D4CVH4_G54A/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:487
4D4CVH4_D53G/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:488
4D4CVH4_D53E/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:488
4D4CVH4_D53Q/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:488
4D4CVH4_D53L/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:488
4D4CVH4_G54A/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:488
4D4CVH4_D53G/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:489
4D4CVH4_D53E/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:489
4D4CVH4_D53Q/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:489
4D4CVH4_D53L/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:489
4D4CVH4_G54A/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:489
4D4CVH4_D53G/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:490
4D4CVH4_D53E/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:490
4D4CVH4_D53Q/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:490
4D4CVH4_D53L/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:490

4D4CVH4_G54A/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:490
4D4CVH4/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:491
4D4CVH4/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:492
4D4CVH4/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:493
4D4CVH4/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:494
4D4CVH4/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:495
4D4CVH4_D53G/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:308
4D4CVH4_D53E/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:308
4D4CVH4_D53Q/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:308
4D4CVH4_D53L/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:308
4D4CVH4_G54A/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:308
4D4CVH4_D53G/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:491
4D4CVH4_D53E/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:491
4D4CVH4_D53Q/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:491
4D4CVH4_D53L/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:491
4D4CVH4_G54A/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:491
4D4CVH4_D53G/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:492
4D4CVH4_D53E/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:492
4D4CVH4_D53Q/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:492
4D4CVH4_D53L/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:492
4D4CVH4_G54A/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:492
4D4CVH4_D53G/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:493
4D4CVH4_D53E/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:493
4D4CVH4_D53Q/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:493
4D4CVH4_D53L/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:493
4D4CVH4_G54A/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:493
4D4CVH4_D53G/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:494
4D4CVH4_D53E/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:494
4D4CVH4_D53Q/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:494
4D4CVH4_D53L/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:494
4D4CVH4_G54A/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:494
4D4CVH4_D53G/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:495
4D4CVH4_D53E/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:495
4D4CVH4_D53Q/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:495
4D4CVH4_D53L/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:495
4D4CVH4_G54A/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:495
4D4CVH4/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:496
4D4CVH4/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:497
4D4CVH4/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:498
4D4CVH4/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:499
4D4CVH4/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:500
4D4CVH4_D53G/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:309
4D4CVH4_D53E/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:309
4D4CVH4_D53Q/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:309
4D4CVH4_D53L/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:309
4D4CVH4_G54A/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:309
4D4CVH4_D53G/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:496
4D4CVH4_D53E/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:496
4D4CVH4_D53Q/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:496
4D4CVH4_D53L/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:496
4D4CVH4_G54A/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:496
4D4CVH4_D53G/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:497
4D4CVH4_D53E/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:497
4D4CVH4_D53Q/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:497
4D4CVH4_D53L/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:497
4D4CVH4_G54A/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:497
4D4CVH4_D53G/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:498
4D4CVH4_D53E/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:498
4D4CVH4_D53Q/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:498
4D4CVH4_D53L/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:498
4D4CVH4_G54A/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:498
4D4CVH4_D53G/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:499
4D4CVH4_D53E/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:499
4D4CVH4_D53Q/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:499
4D4CVH4_D53L/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:499
4D4CVH4_G54A/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:499
4D4CVH4_D53G/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:500
4D4CVH4_D53E/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:500
4D4CVH4_D53Q/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:500
4D4CVH4_D53L/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:500

4D4CVH4_G54A/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:500
4D4CVH4/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:501
4D4CVH4/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:502
4D4CVH4/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:503
4D4CVH4/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:504
4D4CVH4/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:505
4D4CVH4_D53G/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:310
4D4CVH4_D53E/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:310
4D4CVH4_D53Q/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:310
4D4CVH4_D53L/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:310
4D4CVH4_G54A/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:310
4D4CVH4_D53G/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:501
4D4CVH4_D53E/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:501
4D4CVH4_D53Q/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:501
4D4CVH4_D53L/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:501
4D4CVH4_G54A/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:501
4D4CVH4_D53G/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:502
4D4CVH4_D53E/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:502
4D4CVH4_D53Q/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:502
4D4CVH4_D53L/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:502
4D4CVH4_G54A/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:502
4D4CVH4_D53G/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:503
4D4CVH4_D53E/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:503
4D4CVH4_D53Q/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:503
4D4CVH4_D53L/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:503
4D4CVH4_G54A/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:503
4D4CVH4_D53G/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:504
4D4CVH4_D53E/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:504
4D4CVH4_D53Q/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:504
4D4CVH4_D53L/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:504
4D4CVH4_G54A/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:504
4D4CVH4_D53G/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:505
4D4CVH4_D53E/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:505
4D4CVH4_D53Q/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:505
4D4CVH4_D53L/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:505
4D4CVH4_G54A/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:505
4D4CVH4/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:506
4D4CVH4/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:507
4D4CVH4/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:508
4D4CVH4/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:509
4D4CVH4/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:341	SEQ ID NO:510
4D4CVH4_D53G/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:311
4D4CVH4_D53E/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:311
4D4CVH4_D53Q/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:311
4D4CVH4_D53L/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:311
4D4CVH4_G54A/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:311
4D4CVH4_D53G/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:506
4D4CVH4_D53E/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:506
4D4CVH4_D53Q/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:506
4D4CVH4_D53L/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:506
4D4CVH4_G54A/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:506
4D4CVH4_D53G/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:507
4D4CVH4_D53E/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:507
4D4CVH4_D53Q/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:507
4D4CVH4_D53L/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:507
4D4CVH4_G54A/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:507
4D4CVH4_D53G/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:508
4D4CVH4_D53E/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:508
4D4CVH4_D53Q/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:508
4D4CVH4_D53L/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:508
4D4CVH4_G54A/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:508
4D4CVH4_D53G/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:509
4D4CVH4_D53E/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:509
4D4CVH4_D53Q/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:509
4D4CVH4_D53L/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:509
4D4CVH4_G54A/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:509
4D4CVH4_D53G/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:465	SEQ ID NO:510
4D4CVH4_D53E/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:466	SEQ ID NO:510
4D4CVH4_D53Q/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:467	SEQ ID NO:510
4D4CVH4_D53L/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:468	SEQ ID NO:510

4D4CVH4_G54A/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:469	SEQ ID NO:510
4D4CVH2.1/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:486
4D4CVH2.1/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:487
4D4CVH2.1/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:488
4D4CVH2.1/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:489
4D4CVH2.1/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:490
4D4CVH2.1_D53G/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:307
4D4CVH2.1_D53E/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:307
4D4CVH2.1_D53Q/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:307
4D4CVH2.1_D53L/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:307
4D4CVH2.1_G54A/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:307
4D4CVH2.1_D53G/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:486
4D4CVH2.1_D53E/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:486
4D4CVH2.1_D53Q/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:486
4D4CVH2.1_D53L/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:486
4D4CVH2.1_G54A/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:486
4D4CVH2.1_D53G/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:487
4D4CVH2.1_D53E/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:487
4D4CVH2.1_D53Q/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:487
4D4CVH2.1_D53L/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:487
4D4CVH2.1_G54A/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:487
4D4CVH2.1_D53G/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:488
4D4CVH2.1_D53E/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:488
4D4CVH2.1_D53Q/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:488
4D4CVH2.1_D53L/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:488
4D4CVH2.1_G54A/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:488
4D4CVH2.1_D53G/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:489
4D4CVH2.1_D53E/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:489
4D4CVH2.1_D53Q/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:489
4D4CVH2.1_D53L/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:489
4D4CVH2.1_G54A/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:489
4D4CVH2.1_D53G/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:490
4D4CVH2.1_D53E/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:490
4D4CVH2.1_D53Q/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:490
4D4CVH2.1_D53L/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:490
4D4CVH2.1_G54A/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:490
4D4CVH2.1/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:491
4D4CVH2.1/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:492
4D4CVH2.1/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:493
4D4CVH2.1/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:494
4D4CVH2.1/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:495
4D4CVH2.1_D53G/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:308
4D4CVH2.1_D53E/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:308
4D4CVH2.1_D53Q/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:308
4D4CVH2.1_D53L/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:308
4D4CVH2.1_G54A/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:308
4D4CVH2.1_D53G/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:491
4D4CVH2.1_D53E/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:491
4D4CVH2.1_D53Q/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:491
4D4CVH2.1_D53L/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:491
4D4CVH2.1_G54A/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:491
4D4CVH2.1_D53G/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:492
4D4CVH2.1_D53E/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:492
4D4CVH2.1_D53Q/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:492
4D4CVH2.1_D53L/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:492
4D4CVH2.1_G54A/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:492
4D4CVH2.1_D53G/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:493
4D4CVH2.1_D53E/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:493
4D4CVH2.1_D53Q/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:493
4D4CVH2.1_D53L/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:493
4D4CVH2.1_G54A/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:493
4D4CVH2.1_D53G/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:494
4D4CVH2.1_D53E/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:494
4D4CVH2.1_D53Q/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:494
4D4CVH2.1_D53L/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:494
4D4CVH2.1_G54A/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:494
4D4CVH2.1_D53G/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:495
4D4CVH2.1_D53E/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:495
4D4CVH2.1_D53Q/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:495
4D4CVH2.1_D53L/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:495

4D4CVH2.1_G54A/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:495
4D4CVH2.1/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:496
4D4CVH2.1/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:497
4D4CVH2.1/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:498
4D4CVH2.1/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:499
4D4CVH2.1/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:500
4D4CVH2.1_D53G/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:309
4D4CVH2.1_D53E/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:309
4D4CVH2.1_D53Q/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:309
4D4CVH2.1_D53L/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:309
4D4CVH2.1_G54A/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:309
4D4CVH2.1_D53G/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:496
4D4CVH2.1_D53E/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:496
4D4CVH2.1_D53Q/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:496
4D4CVH2.1_D53L/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:496
4D4CVH2.1_G54A/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:496
4D4CVH2.1_D53G/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:497
4D4CVH2.1_D53E/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:497
4D4CVH2.1_D53Q/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:497
4D4CVH2.1_D53L/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:497
4D4CVH2.1_G54A/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:497
4D4CVH2.1_D53G/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:498
4D4CVH2.1_D53E/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:498
4D4CVH2.1_D53Q/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:498
4D4CVH2.1_D53L/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:498
4D4CVH2.1_G54A/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:498
4D4CVH2.1_D53G/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:499
4D4CVH2.1_D53E/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:499
4D4CVH2.1_D53Q/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:499
4D4CVH2.1_D53L/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:499
4D4CVH2.1_G54A/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:499
4D4CVH2.1_D53G/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:500
4D4CVH2.1_D53E/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:500
4D4CVH2.1_D53Q/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:500
4D4CVH2.1_D53L/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:500
4D4CVH2.1_G54A/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:500
4D4CVH2.1/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:501
4D4CVH2.1/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:502
4D4CVH2.1/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:503
4D4CVH2.1/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:504
4D4CVH2.1/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:505
4D4CVH2.1_D53G/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:310
4D4CVH2.1_D53E/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:310
4D4CVH2.1_D53Q/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:310
4D4CVH2.1_D53L/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:310
4D4CVH2.1_G54A/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:310
4D4CVH2.1_D53G/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:501
4D4CVH2.1_D53E/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:501
4D4CVH2.1_D53Q/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:501
4D4CVH2.1_D53L/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:501
4D4CVH2.1_G54A/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:501
4D4CVH2.1_D53G/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:502
4D4CVH2.1_D53E/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:502
4D4CVH2.1_D53Q/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:502
4D4CVH2.1_D53L/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:502
4D4CVH2.1_G54A/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:502
4D4CVH2.1_D53G/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:503
4D4CVH2.1_D53E/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:503
4D4CVH2.1_D53Q/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:503
4D4CVH2.1_D53L/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:503
4D4CVH2.1_G54A/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:503
4D4CVH2.1_D53G/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:504
4D4CVH2.1_D53E/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:504
4D4CVH2.1_D53Q/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:504
4D4CVH2.1_D53L/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:504
4D4CVH2.1_G54A/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:504
4D4CVH2.1_D53G/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:505
4D4CVH2.1_D53E/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:505
4D4CVH2.1_D53Q/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:505
4D4CVH2.1_D53L/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:505

4D4CVH2.1_G54A/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:505
4D4CVH2.1/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:506
4D4CVH2.1/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:507
4D4CVH2.1/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:508
4D4CVH2.1/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:509
4D4CVH2.1/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:342	SEQ ID NO:510
4D4CVH2.1_D53G/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:311
4D4CVH2.1_D53E/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:311
4D4CVH2.1_D53Q/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:311
4D4CVH2.1_D53L/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:311
4D4CVH2.1_G54A/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:311
4D4CVH2.1_D53G/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:506
4D4CVH2.1_D53E/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:506
4D4CVH2.1_D53Q/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:506
4D4CVH2.1_D53L/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:506
4D4CVH2.1_G54A/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:506
4D4CVH2.1_D53G/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:507
4D4CVH2.1_D53E/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:507
4D4CVH2.1_D53Q/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:507
4D4CVH2.1_D53L/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:507
4D4CVH2.1_G54A/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:507
4D4CVH2.1_D53G/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:508
4D4CVH2.1_D53E/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:508
4D4CVH2.1_D53Q/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:508
4D4CVH2.1_D53L/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:508
4D4CVH2.1_G54A/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:508
4D4CVH2.1_D53G/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:509
4D4CVH2.1_D53E/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:509
4D4CVH2.1_D53Q/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:509
4D4CVH2.1_D53L/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:509
4D4CVH2.1_G54A/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:509
4D4CVH2.1_D53G/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:470	SEQ ID NO:510
4D4CVH2.1_D53E/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:471	SEQ ID NO:510
4D4CVH2.1_D53Q/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:472	SEQ ID NO:510
4D4CVH2.1_D53L/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:473	SEQ ID NO:510
4D4CVH2.1_G54A/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:474	SEQ ID NO:510
4D4CVH2.2/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:486
4D4CVH2.2/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:487
4D4CVH2.2/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:488
4D4CVH2.2/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:489
4D4CVH2.2/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:490
4D4CVH2.2_D53G/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:307
4D4CVH2.2_D53E/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:307
4D4CVH2.2_D53Q/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:307
4D4CVH2.2_D53L/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:307
4D4CVH2.2_G54A/4D4C/GVL1 hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:307
4D4CVH2.2_D53G/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:486
4D4CVH2.2_D53E/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:486
4D4CVH2.2_D53Q/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:486
4D4CVH2.2_D53L/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:486
4D4CVH2.2_G54A/4D4C/GVL1_N93G hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:486
4D4CVH2.2_D53G/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:487
4D4CVH2.2_D53E/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:487
4D4CVH2.2_D53Q/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:487
4D4CVH2.2_D53L/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:487
4D4CVH2.2_G54A/4D4C/GVL1_N93E hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:487
4D4CVH2.2_D53G/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:488
4D4CVH2.2_D53E/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:488
4D4CVH2.2_D53Q/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:488
4D4CVH2.2_D53L/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:488
4D4CVH2.2_G54A/4D4C/GVL1_N93L hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:488
4D4CVH2.2_D53G/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:489
4D4CVH2.2_D53E/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:489
4D4CVH2.2_D53Q/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:489
4D4CVH2.2_D53L/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:489
4D4CVH2.2_G54A/4D4C/GVL1_N93Q hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:489
4D4CVH2.2_D53G/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:490
4D4CVH2.2_D53E/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:490
4D4CVH2.2_D53Q/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:490
4D4CVH2.2_D53L/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:490

4D4CVH2.2_G54A/4D4C/GVL1_G94A hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:490
4D4CVH2.2/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:491
4D4CVH2.2/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:492
4D4CVH2.2/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:493
4D4CVH2.2/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:494
4D4CVH2.2/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:495
4D4CVH2.2_D53G/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:308
4D4CVH2.2_D53E/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:308
4D4CVH2.2_D53Q/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:308
4D4CVH2.2_D53L/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:308
4D4CVH2.2_G54A/4D4CVL2 hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:308
4D4CVH2.2_D53G/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:491
4D4CVH2.2_D53E/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:491
4D4CVH2.2_D53Q/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:491
4D4CVH2.2_D53L/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:491
4D4CVH2.2_G54A/4D4CVL2_N93G hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:491
4D4CVH2.2_D53G/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:492
4D4CVH2.2_D53E/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:492
4D4CVH2.2_D53Q/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:492
4D4CVH2.2_D53L/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:492
4D4CVH2.2_G54A/4D4CVL2_N93E hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:492
4D4CVH2.2_D53G/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:493
4D4CVH2.2_D53E/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:493
4D4CVH2.2_D53Q/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:493
4D4CVH2.2_D53L/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:493
4D4CVH2.2_G54A/4D4CVL2_N93L hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:493
4D4CVH2.2_D53G/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:494
4D4CVH2.2_D53E/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:494
4D4CVH2.2_D53Q/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:494
4D4CVH2.2_D53L/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:494
4D4CVH2.2_G54A/4D4CVL2_N93Q hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:494
4D4CVH2.2_D53G/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:495
4D4CVH2.2_D53E/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:495
4D4CVH2.2_D53Q/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:495
4D4CVH2.2_D53L/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:495
4D4CVH2.2_G54A/4D4CVL2_G94A hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:495
4D4CVH2.2/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:496
4D4CVH2.2/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:497
4D4CVH2.2/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:498
4D4CVH2.2/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:499
4D4CVH2.2/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:500
4D4CVH2.2_D53G/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:309
4D4CVH2.2_D53E/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:309
4D4CVH2.2_D53Q/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:309
4D4CVH2.2_D53L/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:309
4D4CVH2.2_G54A/4D4CVL4 hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:309
4D4CVH2.2_D53G/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:496
4D4CVH2.2_D53E/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:496
4D4CVH2.2_D53Q/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:496
4D4CVH2.2_D53L/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:496
4D4CVH2.2_G54A/4D4CVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:496
4D4CVH2.2_D53G/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:497
4D4CVH2.2_D53E/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:497
4D4CVH2.2_D53Q/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:497
4D4CVH2.2_D53L/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:497
4D4CVH2.2_G54A/4D4CVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:497
4D4CVH2.2_D53G/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:498
4D4CVH2.2_D53E/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:498
4D4CVH2.2_D53Q/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:498
4D4CVH2.2_D53L/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:498
4D4CVH2.2_G54A/4D4CVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:498
4D4CVH2.2_D53G/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:499
4D4CVH2.2_D53E/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:499
4D4CVH2.2_D53Q/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:499
4D4CVH2.2_D53L/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:499
4D4CVH2.2_G54A/4D4CVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:499
4D4CVH2.2_D53G/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:500
4D4CVH2.2_D53E/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:500
4D4CVH2.2_D53Q/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:500
4D4CVH2.2_D53L/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:500

4D4CVH2.2_G54A/4D4CVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:500
4D4CVH2.2/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:501
4D4CVH2.2/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:502
4D4CVH2.2/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:503
4D4CVH2.2/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:504
4D4CVH2.2/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:505
4D4CVH2.2_D53G/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:310
4D4CVH2.2_D53E/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:310
4D4CVH2.2_D53Q/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:310
4D4CVH2.2_D53L/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:310
4D4CVH2.2_G54A/4D4GVL3 hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:310
4D4CVH2.2_D53G/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:501
4D4CVH2.2_D53E/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:501
4D4CVH2.2_D53Q/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:501
4D4CVH2.2_D53L/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:501
4D4CVH2.2_G54A/4D4GVL3_N93G hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:501
4D4CVH2.2_D53G/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:502
4D4CVH2.2_D53E/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:502
4D4CVH2.2_D53Q/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:502
4D4CVH2.2_D53L/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:502
4D4CVH2.2_G54A/4D4GVL3_N93E hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:502
4D4CVH2.2_D53G/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:503
4D4CVH2.2_D53E/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:503
4D4CVH2.2_D53Q/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:503
4D4CVH2.2_D53L/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:503
4D4CVH2.2_G54A/4D4GVL3_N93L hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:503
4D4CVH2.2_D53G/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:504
4D4CVH2.2_D53E/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:504
4D4CVH2.2_D53Q/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:504
4D4CVH2.2_D53L/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:504
4D4CVH2.2_G54A/4D4GVL3_N93Q hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:504
4D4CVH2.2_D53G/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:505
4D4CVH2.2_D53E/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:505
4D4CVH2.2_D53Q/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:505
4D4CVH2.2_D53L/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:505
4D4CVH2.2_G54A/4D4GVL3_G94A hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:505
4D4CVH2.2/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:506
4D4CVH2.2/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:507
4D4CVH2.2/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:508
4D4CVH2.2/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:509
4D4CVH2.2/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:343	SEQ ID NO:510
4D4CVH2.2_D53G/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:311
4D4CVH2.2_D53E/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:311
4D4CVH2.2_D53Q/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:311
4D4CVH2.2_D53L/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:311
4D4CVH2.2_G54A/4D4GVL4 hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:311
4D4CVH2.2_D53G/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:506
4D4CVH2.2_D53E/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:506
4D4CVH2.2_D53Q/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:506
4D4CVH2.2_D53L/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:506
4D4CVH2.2_G54A/4D4GVL4_N93G hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:506
4D4CVH2.2_D53G/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:507
4D4CVH2.2_D53E/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:507
4D4CVH2.2_D53Q/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:507
4D4CVH2.2_D53L/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:507
4D4CVH2.2_G54A/4D4GVL4_N93E hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:507
4D4CVH2.2_D53G/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:508
4D4CVH2.2_D53E/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:508
4D4CVH2.2_D53Q/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:508
4D4CVH2.2_D53L/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:508
4D4CVH2.2_G54A/4D4GVL4_N93L hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:508
4D4CVH2.2_D53G/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:509
4D4CVH2.2_D53E/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:509
4D4CVH2.2_D53Q/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:509
4D4CVH2.2_D53L/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:509
4D4CVH2.2_G54A/4D4GVL4_N93Q hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:509
4D4CVH2.2_D53G/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:475	SEQ ID NO:510
4D4CVH2.2_D53E/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:476	SEQ ID NO:510
4D4CVH2.2_D53Q/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:477	SEQ ID NO:510
4D4CVH2.2_D53L/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:478	SEQ ID NO:510

4D4CVH2.2_G54A/4D4GVL4_G94A hIgG4(S228P, L235E)	SEQ ID NO:479	SEQ ID NO:510
CON4D4P/Hu_D53var_G53var /CON4D4P/Hu_N93var_G94var hIgG4(S228P, L235E)	SEQ ID NO:480	SEQ ID NO:511

***

The present disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

The section headings used herein are for organisational purposes only and are not to be construed as limiting the subject matter described.

Aspects and embodiments of the present disclosure will now be illustrated, by way of example, with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word 'comprise,' and variations such as 'comprises' and 'comprising,' will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

As used herein, an amino acid sequence, or a region of a polypeptide which 'corresponds' to a specified reference amino acid sequence or region of a polypeptide has at least 60%, *e.g.* one of at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the amino acid sequence of the amino acid sequence/polypeptide/region. An amino acid sequence/region/position of a polypeptide/amino acid sequence which 'corresponds' to a specified reference amino acid sequence/region/position of a polypeptide/amino acid sequence can be identified by sequence alignment of the subject sequence to the reference sequence, *e.g.* using sequence alignment software such as ClustalOmega (Söding, J. 2005, Bioinformatics 21, 951-960).

It must be noted that, as used in the specification and the appended claims, the singular forms 'a,' 'an,' and 'the' include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from 'about' one particular value, and/or to 'about' another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent 'about,' it will be understood that the particular value forms another embodiment.

Where a nucleic acid sequence is disclosed herein, the reverse complement thereof is also expressly contemplated.

Methods described herein may preferably be performed *in vitro*. The term '*in vitro*' is intended to encompass procedures performed with cells in culture whereas the term '*in vivo*' is intended to encompass procedures with/on intact multi-cellular organisms.

Antigen-binding molecules, peptides/polypeptides, peptide/polypeptide complexes, nucleic acids/polynucleotides, vectors, compositions or cells according to the present disclosure may optionally be provided in isolated or purified form. For example, articles according to the present disclosure may be isolated/purified from naturally-occurring biological material.

Brief Description of the Figures

Embodiments and experiments illustrating the principles of the present disclosure will now be discussed with reference to the accompanying figures.

Figure 1A-1B. **Intra-Vitreal Treatment Effects on Laser-Induced CNV in Mice Model.** (A) Representative CNV lesions in mouse eyes treated with the vehicle, test compound, and Eylea were identified through Fluorescein Angiography (FFA). (B) Choroidal vascularity of laser-induced CNV lesions was investigated through FFA. The mean (± SEM) CNV lesions from fluorescein angiography were assessed for each timepoint across all groups. *p < 0.05; n = 20 per group.

Figure 2A-2B. **Impact of Intra-Vitreal Administration on CNV Volume Area.** (A) Representative CNV lesion area scans in mouse eyes treated with the vehicle, test compound, and Eylea were identified by PS-OCT (Polarization-Sensitive Optical Coherence Tomography). (B) Choroidal vascularity of laser-induced CNV lesion volume area was examined through PS-OCT scans. The mean (± SEM) CNV lesions from optical coherence tomography for the four groups were measured. *p < 0.05; n = 20 per group.

Figure 3A-3B. **Retinal Immunostaining of CNV Lesions. (**A) Retinal/RPE/Choroid Complex immunostaining was performed to validate the size of choroidal neovascularization (CNV) lesions in mouse eyes that was stained with antibodies of IB-4 in purple, Col-1 in green and alpha-SMA in red. DAPI stains nuclei in blue. (B) Provides a quantitative analysis of CNV lesion sizes, visually confirming the efficacy of different treatment modalities.

Figure 4. **Gene Expression Analysis in Treated Samples.** Gene expression analysis was conducted to assess transcript levels in response to intra-vitreal treatments. Data are expressed as mean ± SEM. Unpaired, two-tailed t-test was used for statistical analysis; * p < 0.05.

Examples

General Materials and Methods for Examples 1-3

Animals: 40 mice (*Mus musculus*) used in the study were C57BL/6J strain, male, aged 7-9 weeks old, weighing 25-30 g on Day 1 of the study (In-Vivos, Singapore). Mice were purpose-bred and experimentally naïve at the outset of the study.

Experimental Conditions: Animals were housed in standard cages with free access to food and water under a 12-hour light and 12-hour dark cycle. Mice were housed in groups of five in individually ventilated cages (IVCs, Tecniplast, USA). The holding room temperature and humidity were controlled according to

NCLAR guidelines. The temperature in the mice holding room was maintained between 20-26°C, with a relative humidity range of 55-65% and 10-15 air changes per hour, using 100% fresh air.

Reagents: B035-C03-A3 used at a concentration of 15 mg/mL. Commercially available Aflibercept (Eylea; Regeneron) used a concentration of 2 mg/0.05 mL

Dose Preparation: The test articles were supplied in terminally sterilized vials with a volume of 2 mL per vial. These formulations were prepared for dosing and required no subsequent dilution. Eylea was procured from Bayer Pharma and used as the positive control for injections. The dosing materials were stored refrigerated (2-8°C) and shielded from light. Documentation of test article usage was recorded in the raw data. Before administration, the test articles were allowed to reach room temperature for a minimum of 30 minutes. Dosing syringes were filled directly from the provided test article vials using aseptic technique.

Study Design:

Animals were allocated to study groups at least one day before the initiation of dosing. Random assignment to groups was performed using a selection method designed to ensure comparable group mean body weights and levels of laser-induced CNV severity.

Study design is outlined in Table1 below.

Table 1

Group	Drug Dose (µg/eye/dose)	Drug Dosing Conc. (mg/mL)	Dose Volume (µL/eye/dose)	Number of Animals	
				Dosing Day 3/10/17/24/31	Day 35 Sac
1. PBS	-	-	2 µL	10 (20 eyes)	10
2. B035-C03-A3	30µg	5 mg/mL	2 µL	10 (20 eyes)	10
3. Eylea	Equivalent for B035-C03-A3	2 mg/0.05 mL	2 µL	10 (20 eyes)	10
4. Combo (B035-C03-A3 + Eylea)	Equivalent for B035-C03-A3	5 mg/mL (B035-C03-A3) + 2 mg/0.05 mL (Eylea)	1 µL + 1 µL	10 (20 eyes)	10

Anaesthesia: For all experiments, mice were anesthetized using a combination of ketamine (20 mg/kg body weight) and xylazine (2 mg/kg body weight). Pupils were dilated by applying 1 drop of 1% tropicamide followed by 1 drop of 2.5% phenylephrine. The entire procedure took approximately 15-20 minutes per mouse.

Clinical examination: Visual inspection of all eyes for signs of conjunctival irritation, inflammation, or corneal infection was conducted daily after treatment. Additionally, animal behaviour and well-being were closely monitored. Animals were observed twice daily for potential adverse events, and food consumption was qualitatively assessed once daily. Body weights of the animals were recorded on the day of transfer,

at the time of animal selection for experiments based on the disease phenotype, and at the end of the study.

Treatment Groups: For this study, 40 male B6J wild-type mice were utilized and randomly assigned to five groups, each consisting of 10 mice, as outlined in Table 1.

Retinal Imaging: Fundus photography and fluorescein fundus angiography (FFA) were captured using a MICRON IV fundus camera from Phoenix Laboratories USA to analyze retinal pathological changes and the extent of leakage. For FFA, animals received intraperitoneal injections of 10% sodium fluorescein at a dosage of 0.01 mL per 5-6 g of body weight.

Real-time monitoring of retinal structure was conducted using posterior-segment Optical Coherence Topography (PS-OCT) to analyze retinal thickness and fibrous area.

The frequency of ophthalmic imaging and dosing is outlined in Table 2.

Table 2

	Day											
Activity	-7	0	3	7	10	14	17	21	24	28	31	35
CFP	X		X	X		X		X		X		
OCT	X		X	X		X		X		X		
FFA		X	X	X		X		X		X		
Induction of CNV												
Treatment			X		X		X		X		X	
Sacrifice												X

OCT: Optical coherence tomography; CFP: color fundus photograph; FFA: fundus fluoresceine angiography.

Slit lamp Biomicroscopy Examination: Corneal examination was conducted weekly through slit-lamp biomicroscopy before retinal imaging to monitor for any signs of conjunctival irritation, inflammation, or corneal infection.

Mouse model of laser-induced CNV/Retinal Fibrosis: C57BL/6J mice were anesthetized using a combination of Ketamine (20 mg/kg body weight) and Xylazine (2 mg/kg body weight). Pupil dilation was achieved through the topical administration of 1% tropicamide (Alcon Laboratories, Fort Worth, TX, USA) and 2.5% phenylephrine (Bausch and Lomb Pharmaceuticals, Inc., Tampa, FL, USA) ophthalmic solutions.

Laser photocoagulation was performed with the image-guided laser system (Micron IV, Phoenix Research Laboratories, Pleasanton, CA, USA). In each eye, four laser burns were placed at the 3, 6, 9, and 12 o'clock positions, equidistant from the optic disc. A green Argon laser pulse with a wavelength of

532 nm, a fixed diameter of 50 µm, a duration of 50 ms, and a power of 120 mW was used for the procedure. After laser treatment, mice were kept warm under infrared light until they recovered from anesthesia.

Route of Treatment: Intra-Vitreal (IVT) Injection
Animals received injections in both eyes, with each eye receiving either PBS (vehicle control), the novel antibody (B035-C03-A3, monotherapy), aflibercept (positive control), or a combination of the novel antibody and aflibercept (combination therapy). The injection volume for all groups was 1 µL, with a single injection at 1 µg. A 32-gauge needle was utilized to inject all test articles at a volume of 2 µL into the vitreal space via intravitreal (IVT) injection in both eyes, as specified above.

Clinical Observations: Daily cage-side observations were conducted twice a day during the experimental period. All mice underwent physical restraint for clinical examinations. Slit-lamp biomicroscopy (qualitative analysis), fundus, and PS-OCT examinations of the eyes were performed one week before and from post-laser treatment day 3 to day 35, as outlined in Table 2, to document the development of neovascularization and retinal fibrosis.
Visual inspection of all eyes after topical application and assessment for any conjunctival irritation, ocular inflammation, or infection was conducted daily. Clinical observations were made prior to dose administration after laser injury on Day 3, Day 10, Day 17, Day 24, and Day 31. Additional observations were documented as necessary.

Animals in Groups 1-4 were weighed before randomization and assignment to study groups (Day -7 and Day 0, respectively). Animals in Groups 1-4 were also weighed at the end of the study.

Full feeder weights and/or feeder weigh-backs were recorded daily throughout the dosing and recovery periods for the determination of food consumption.

Readouts: The primary variables under evaluation were the leakage and fibrosis areas. FFA (Fluorescein Fundus Angiography) images and OCT (Optical Coherence Tomography) images were analyzed using ImageJ software to quantify the area of leakage and retinal thickness/area, respectively.

On day 35 (5 weeks post-treatment), animals were euthanized with an overdose of pentobarbital for the collection of eye tissues.

Immunofluorescent Staining: Retinal cryosections (n = 10 from each group) were fixed in acetone for 10 minutes and subsequently incubated with antibodies against IB-4, α-SMA, and Collagen-I (Abcam, Cambridge, United Kingdom) at 4°C overnight. Following three washes with PBS, the retinal sections underwent an additional incubation with DAPI to stain nuclei for 1 hour. Subsequently, the sections were mounted using mounting medium (Vector Laboratories, Burlingame, CA, USA) and captured under a fluorescent microscope (DM2500; Leica Microsystems, Wetzlar, Germany).

Molecular biology analysis (RNA Extraction and Quantitative Real-Time PCR): At the study endpoint, 10 eyes from each group were promptly enucleated and meticulously dissected to extract the retina and RPE/Choroid complex, which were then snap-frozen in liquid nitrogen. Total RNA was extracted from homogenized mouse tissues using the NucleoSpin RNA Mini kit (Macherey-Nagel, Düren, Germany) following the manufacturer's instructions. For cDNA synthesis, the qScript cDNA Supermix (Quanta BioSciences, Beverly, MA, USA) was employed according to the manufacturer's guidelines.

Additionally, total RNA was extracted specifically from retinas using TRIzol Reagent (Invitrogen, Carlsbad, CA, USA), and reverse transcription was performed following the manufacturer's protocol (TaKaRa Bio, Inc., Shiga, Japan). The quantitative RT-PCR procedure was conducted as previously described (Murray AR, *et al*., IOVS; 2013; 54: 1689–1697).

Gene expression levels of relevant fibrotic genes such as TNF-alpha, VEGF, IL-6, IL-11, TGF-Beta, and Colagen-1a11 were quantified relative to GAPDH, serving as an internal control in the quantitative real-time polymerase chain reaction (RT-qPCR) analysis.

Statistical analysis: Statistical analyses were performed using Prism 10 software (GraphPad, San Diego, CA, USA), employing either a one-way ANOVA or a Student's t-test, as appropriate. All values are presented as mean ± SEM, with a minimum of three independent measurements conducted for each analysis. A significance threshold of $P < 0.05$ was applied to determine statistical significance.

Example 1: Safety and tolerability of combination therapy

Animal Mortality: Each animal in Groups 1-4 was monitored for signs of death or impending death, following the SEMC SOP. Throughout the study period, all animals remained healthy until the point of sacrifice.

Effects of IVT Administration of Mono or Combo Eye formulations in Body Weight: Forty mice were utilized in this experiment, and no significant changes in body weight (25-30g) were observed before and after drug dosing. Throughout the study period, all animals maintained normal eating habits, and there were no noticeable behavioural changes.

Clinical observation and Examination for Safety: The anterior segment was examined to assess the cornea, and any adverse clinical signs in the anterior chamber were noted for the evaluation of inflammation both pre- and post-dosing. The test compound demonstrated safety when delivered via intravitreal (IVT) injection, either as monotherapy or in combination.

Fundus examination and posterior segment optical coherence tomography (PS-OCT) were conducted to document the visualization of vitreous and retinal layers, capturing any adverse clinical signs in the vitreous body, fundus, and retinal layers. Additionally, these examinations quantified the choroidal neovascularization (CNV) leakage and area.

All test articles exhibited non-toxicity when administered via IVT, whether in monotherapy or combination therapy, with no observed ocular toxicity or irritation/inflammation in any of the groups.

Example 2: Analysis of the impact of an anti-gp130 and anti-VEGF combination therapy on Laser-Induced Choroidal Neovascularization in Mice Model

To assess the therapeutic potential of test compositions in reducing/preventing angiogenesis, inflammation and/or fibrosis, a mouse model of laser-induced CNV was employed. Test compounds, administered either as monotherapy or in combination, were delivered via the intra-vitreal route.

On Day 3 post-laser injury, IgG control, B035-C03-A3, and Eylea (positive control) were injected intravitreally (IVT) to assess their efficacy in reducing pathological angiogenesis, pathological inflammation and fibrosis in CNV mice. A total of five injections were administered on Day 3, Day 10, Day 17, Day 24, and Day 31 post-laser injury.

Fundus fluorescein angiography (FFA) as described in 'General Materials and Methods for Examples 1-3' was used to examine the extent of choroidal vascularization on post-laser days 3, 7, 14, 21, 28, and 35. Additionally, fibrosis area was examined by posterior-segment optical coherence tomography (PS-OCT) on the same days. Images of CNV lesions were acquired at different time points following fluorescein injection, and the choroidal vascularization area was validated in-vitro at the study endpoint.

Quantification revealed that compared to vehicle-injected eyes, test compound (IVT formulation) and Eylea-treated eyes exhibited significantly reduced CNV leakage at the study endpoint (Table 2).

The leakage area was significantly reduced from post-day 3 to post-day 35 in all three treatment groups. Leakage area significantly increased from post-day 3 to post-day 21 in PBS-treated eyes; however, this increase was mitigated after 21 days post-laser, confirming that the leakage area became fibrotic by post-day 28 and post-day 35 after laser injury. Both Eylea and the test compound, when delivered as monotherapy, exhibited similar efficacy with 5 injections. However, superior efficacy was achieved in eyes treated with combination therapy. The most significant reduction was observed in Combo (Test IVT formulation + Eylea) treated eyes (Figure 1A-B).

The fibrotic area was significantly reduced from post-day 3 to post-day 35 in all three treatment groups. Lesion volume area significantly increased from post-day 3 to post-day 35 in PBS-treated eyes compared to treated groups; however, this increase was mitigated after 21 days post-laser as compared to post-day 3, confirming that the lesion area became fibrotic by post-day 28 and post-day 35 after laser injury.

Both Eylea and the test compound, when delivered as combo-therapy, showed similar efficacy with 5 injections in terms of the impact on fibrosis (*i.e.* similar reductions in fibrotic area were observed compared to vehicle-injected eyes). However, a lower efficacy was observed in the test compound delivered as monotherapy (Figure 2A-B).

Retinal immunostaining confirmed smaller CNV lesions in eyes treated with test compound as monotherapy or Eylea, with the most significant reduction in eyes receiving Combo therapy (Figure 3A-B). The results demonstrate smaller CNV lesions in eyes treated with the test compound as monotherapy or Eylea. The most substantial reduction in CNV lesion size was observed in eyes receiving combination therapy.

The data demonstrates that both the test compound and Eylea causes reduction in CNV lesion size when used as monotherapy. The data further shows a synergistic (*i.e.* super-additive) impact on CNV lesion sizes when the test compound and Eylea are administered as a combination therapy, with a significant reduction in CNV lesion sizes seen. These data illustrate the therapeutic potential of combination treatments targeting gp130 alongside targeting of angiogenic factors for the treatment of pathological angiogenesis. In particular, the synergistic impact on CNV lesion size and CNV leakage area seen in the combination treatment group in comparison to either mono-therapy alone demonstrates the particular efficacy of the combination in the treatment of angiogenesis.

Furthermore, the reduction in fibrotic area seen following use of the combination treatment illustrates the efficacy of using anti-gp130 antibodies in conjunction with an antagonist of an angiogenic factor for the treatment of pathological inflammation and fibrosis. In particular, the synergistic impact on fibrotic area seen in the combination treatment group in comparison to either mono-therapy alone demonstrates the particular efficacy of the combination in the treatment of pathological inflammation and fibrosis.

Example 3: Analysis of the impact of an anti-gp130 antibody and anti-VEGF combination therapy on gene expression of fibrosis markers

To assess the therapeutic potential of test compositions in preventing angiogenesis, inflammation and/or fibrosis, a mouse model of laser-induced CNV was employed. Test compounds, administered either as monotherapy or in combination, were delivered via the intra-vitreal route.

On Day 3 post-laser injury, IgG control, B035-C03-A3, and Eylea (positive control) were injected intravitreally (IVT) to assess their efficacy in anti-angiogenesis and fibrosis in CNV mice. A total of five injections were administered on Day 3, Day 10, Day 17, Day 24, and Day 31 post-laser injury.

Retinal tissues from five eyes in each group were immunofluorescently stained with Isolectin B4, Collagen-I, and alpha-SMA, as described in 'General Materials and Methods for Examples 1-3'. RNA was extracted for gene expression analysis, focusing on TNF-α, TGF-β, VEGF, IL-6, IL-11, and Col1-a1, normalized with GAPDH as the internal control.

Gene expression analysis indicated lower VEGF transcript levels in all treated samples compared with control. The results show a synergistic (*i.e.* super-additive) impact of the combination therapy on VEGF expression compared with either monotherapy alone.

These data demonstrate the therapeutic potential of targeting gp130 alongside antagonising an angiogenic factor for the treatment of diseases/conditions having VEGF over-expression. In particular, these results demonstrate the therapeutic potential of targeting gp130 alongside antagonising an angiogenic factor for the treatment of pathological angiogenesis (including CNV), pathological inflammation, and fibrosis. The synergistic impact on VEGF expression seen following treatment with the combination therapy compared to either monotherapy alone demonstrates the particular efficacy of the combination for the treatment of diseases/conditions having VEGF over-expression, in particular pathological angiogenesis, pathological inflammation, and fibrosis.

Furthermore, TNF-alpha transcript levels were lower in all treated samples, especially in the Eylea group. TGF-Beta transcript levels were lower in B035-C03-A3 and combo-treated samples. IL-6 transcript levels were higher in combo and Eylea-treated samples. Col-1a1 and IL-11 transcript levels showed slight reductions in all three treatment samples. However, none of the gene expressions were statistically significant compared to vehicle-treated samples (Figure 4).

Conclusions

This comprehensive analysis indicates the efficacy ofB035-C03-A3 and combination therapy comprising anti-gp130 antibody and VEGF antagonist in reducing CNV lesions and fibrosis in the studied mouse model.

The results demonstrate the synergistic impact of combining anti-gp130 antibody with an antagonist of an angiogenic factor in the treatment of angiogenesis, including CNV, compared to either agent alone, as shown by reduction in CNV lesion size and CNV leakage area.

The results further demonstrate the utility of B035-C03-A3 for treating pathological inflammation and fibrosis, particularly in combination with an antagonist of an angiogenic factor (for example, anti-VEGF therapy such as Eylea). The data shows a synergistic impact of combining anti-gp130 antibody with an antagonist of an angiogenic factor on fibrosis/correlates of fibrosis, when compared to either agent alone.

Example 4: Characterisation of anti-gp130 clones in WO 2025/017127 A1

Antibodies which bind to gp130 are described and characterised in WO 2025/017127 A1 (which is hereby incorporated by reference in its entirety). The materials and methods used in Examples 1-18 of WO 2025/017127 A1 are described in “General Materials and Methods for Examples 1-18” on pages 150-151 of WO 2025/017127 A1.

Example 1 and Figure 1 and 2 of WO 2025/017127 A1 show that CSP-S-5H8 binds to human gp130 by ELISA binding assays. They also show that B-R3 binds to human gp130, but not to mouse gp130.

Example 2 of WO 2025/017127 A1 shows that B035-C03-A3 and CSP-S-5H8 bind to human gp130 and rhesus macaque gp130 with nanomolar affinity by SPR (Biacore) binding assays.

Example 3 and Figures 3 and 4 of WO 2025/017127 A1 show dose-dependent inhibition of hIL-6- and hIL11-mediated activation in a STAT3 Reporter (Luc)-HEK293 cell line by B035-C03-A3 and CSP-S-5H8. They also show inhibitory activity of B035-C03-A3 and CSP-S-5H8 on cells treated with hOSM, hLIF, hCT-1 and hCNTF.

Example 4 and Figure 5 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits IL-11Rα:gp130-mediated signalling in human cardiac fibroblasts, following stimulation with recombinant human IL-11.

Example 5 and Figure 6 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits signalling mediated by all of IL-6, IL-11, LIF, OSM and CTGF in human lung epithelial carcinoma (A549) cells. They also show that none of anti-gp130 antibodies MAB628, MA5-23817 or PA5-47650 are able to inhibit signalling mediated by each of IL-6, IL-11, LIF, OSM and CTGF.

Example 6 and Figure 7 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits IL-6-mediated signalling and OSM-mediated signalling in mouse atrial fibroblasts (MAFs) as determined by pSTAT3/STAT3 and pERK/ERK levels, and to potently inhibit IL-11-mediated signalling, as determined by inhibition of MMP2 expression.

Example 7 and Figure 8 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits signalling mediated by each of human IL-6 (hIL-6), IL-11 (hIL11), LIF (hLIF), OSM (hOSM) or CTGF (hCTGF) in human lung epithelial carcinoma (A549) cells. In contrast, B-R3 does not block IL-mediated signalling, and is therefore not a 'pan' inhibitor of gp130-mediated signalling.

Example 8 and Figure 9 of WO 2025/017127 A1 show that CSP-S-5H8 potently inhibits TGFβ1-stimulated, IL-6 family cytokine-mediated signalling through gp130 in primary rat atrial fibroblasts, with an IC_{50} value of 19.72 ng/ml, as determined by inhibition of MMP2 expression.

Example 9 and Figure 10 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits signalling mediated by all of IL-6, IL-11, CT-1, CNTF, OSM and LIF in human lung epithelial carcinoma (A549) cells, as determined by measurement of pSTAT3/STAT3 levels

Example 10 and Figure 11 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits IL-6-mediated STAT3 signalling with an IC_{50} of 16.85 ng/ml, and inhibits IL-11-mediated ERK signalling with an IC_{50} of 54.97 ng/ml in A549 cells. Together, these results show that clone CSP-S-5H8 strongly inhibits signalling mediated by IL-6/gp130:IL-6Rα and IL-11/gp130:IL-11Rα.

Example 11 and Figure 12 of WO 2025/017127 A1 show that CSP-S-5H8 inhibits LIF-mediated STAT3 signalling in A549 cells with an IC_{50} of 31.36 ng/ml, whereas B-R3 did not inhibit LIF-mediated signalling.

Example 12 and Figure 13 of WO 2025/017127 A1 show that B035-C03-A3 potently inhibits IL-11-mediated signalling in human cardiac fibroblasts (HCFs) with an IC_{50} of 1.88 ng/ml, and in mouse atrial

fibroblasts (MAFs) with an IC_{50} of 18.35 ng/ml. They also show that CSP-S-5H8 potently inhibits IL-11-mediated signalling in HCFs with an IC_{50} of 0.73 ng/ml and in MAFs with an IC_{50} of 41.94 ng/ml.

Example 13 and Figure 14 of WO 2025/017127 A1 show that both B035-C03-A3 (A3) and CSP-S-5H8 (5H8) inhibit signalling mediated by all of IL-6, IL-11, OSM, CNTF, CT-1 and LIF in human epithelial carcinoma (A549) cells as determined by analysis of pSTAT3/STAT3 levels. For B035-C03-A3, full inhibition was observed at 250 ng/ml for CNTF, CT-1, IL-11 and OSM and appears to be a more potent PAN-inhibitor compared to CSP-S-5H8. CSP-S-5H8 appeared to be slightly more potent at inhibiting IL-6 mediated signalling than B035-C03-A3.

Example 14 and Figure 15 of WO 2025/017127 A1 show that B035-C03-A3 (A3) inhibits signalling mediated by all of mIL-6, mIL-11, mLIF, mOSM, mCNTF and mCT1 in primary mouse atrial fibroblasts as determined by analysis of pSTAT3/STAT3 levels.

Example 15 and Figure 16 of WO 2025/017127 A1 show that both B035-C03-A3 and CSP-S-5H8 strongly inhibit Hyper IL-6- and Hyper IL-11-induced STAT3 signalling in HCFs.

Example 16 and Figure 17 of WO 2025/017127 A1 show that CSP-S-5H8 (5H8) inhibits signalling mediated by CNTF, CT1 and LIF in Primary mouse atrial fibroblasts as determined by analysis of pSTAT3/STAT3 levels.

Example 17 and Figure 18 of WO 2025/017127 A1 show that B035-C03-A3 inhibits LIF-mediated signalling in human primary cardiac fibroblasts as determined by analysis of pSTAT3/STAT3 levels and MMP2 levels, while B-R3 does not.

Example 18 and Figure 19 of WO 2025/017127 A1 show that CSP-S-5H8 and B035-C03-A3 inhibit mIL-11-, mIL-6- and Hyper mIL-6-induced STAT3 activity in mouse primary atrial fibroblasts.

Example 19 and Figure 20 of WO 2025/017127 A1 show that CSP-S-5H8 and B035-C03-A3 bind to gp130 in WT mouse tissue samples, but do not bind to mouse tissue samples in which gp130 had been knocked-out. The results demonstrate CSP-S-5H8 and B035-C03-A3 bind specifically to gp130, and can be successfully used for the detection of mouse gp130 immunoblotting and immunohistochemistry of tissue samples.

Example 20 and Figure 21 of WO 2025/017127 A1 show that CSP-S-5H8 reduces the concentration of ALT and AST in a mouse model of acetaminophen-induced liver injury (AILI), as compared to mice treated with a control antibody. These results demonstrate that CSP-A-5H8 is effective at preventing/protecting against/ameliorating the symptoms of APAP-induced liver injury

Example 21 and Figure 22 of WO 2025/017127 A1 demonstrate that CSP-S-5H8 is effective in preventing the consequences of acute kidney injury (AKI) in a folic acid-induced mouse model of nephrotoxicity. The effect was compared with the effect of a neutralising anti-IL-11 antibody.

Treatment with CSP-S-5H8 was shown to reduce/inhibit various effects which are observed in mice following AKI, as compared to the negative control antibody. For example, treatment with CSP-S-5H8 was shown to : abolish weight loss in the mouse model; reduce weight loss observed in the kidneys of mice; inhibit the increase in renal collagen content observed;inhibit the increase in markers of compromised kidney function (blood urea nitrogen (BUN) and creatine); inhibit the increase in serum IL-6 levels observed in mice following acute kidney injury; inhibit the increase in renal expression of pro-fibrotic markers (*Col1a1, Col1a2, Col3a1, Fn, Acta2* and *Il11* RNA); inhibit the increase in renal expression of pro-inflammatory markers (*Ccl2, Ccl5, Il6, Tnfα* and *Il1β* RNA); reduced the increase in the expression of markers of kidney injury (*Ngal* and *Kim1* RNA); reduce downstream effects of gp130 mediated signalling (phosphorylation of ERK, STAT3 and NFκB, and expression of αSMA). Treatment with CSP-S-5H8 was also shown to exhibit a stronger treatment effect than the neutralising IL-11 antibody for many of the tested parameters.

Together, these data show that CSP-S-5H8 strongly inhibited gp130-mediated signalling *in vivo* and significantly reduced the pathology of acute kidney injury, as determined by a reduction in the level of correlates of acute kidney injury. They furthermore demonstrate that CSP-S-5H8 is more effective at reducing the pathology of acute kidney injury than a neutralising anti-IL-11 antibody.

Example 22 and Figure 23 of WO 2025/017127 A1 demonstrate the effects of CSP-S-5H8 in a mouse model of inflammatory bowel disease (DSS-induced colitis model). Treatment with CSP-S-5H8 reduced correlates of Inflammatory Bowel Disease pathology *in vivo* in mouse model of colitis, and did not display negative side effects, *e.g.* did not lead to a significant increase in serum level of IL-6.

Example 23 and Figure 24 of WO 2025/017127 A1 shows the region(s) of gp130 to which B035-C03-A3, CSP-S-5H8 and known anti-gp130 antibody B-R3 bind as analysed by hydrogen-deuterium exchange mass spectrometry (HDX-MS) and/or cross-linking mass spectrometry (XL-MS).

While B35-C03-A3, CSP-S-5H8 and B-R3 were all found to bind to gp130 in the cytokine-binding module of human gp130 (SEQ ID NO:85 of WO 2025/017127 A1), B-R3 was found to bind to a distinct and non-overlapping region of human gp130 as the region bound by B35-C03-A3 and CSP-S-5H8. The fact that it binds to the cytokine-binding module of human gp130, but to a region distinct from B35-C03-A3, might explain why it displays inhibition of signalling mediated by some but not all of the cytokines whose signalling is inhibited by B35-C03-A3.

Furthermore, alignment of the amino acid sequences for human gp130 and mouse gp130 reveals that they share only 33% sequence identity in the region of human gp130 bound by B-R3 (SEQ ID NO:178 of WO 2025/017127 A1; *i.e.* 2/6 residues). By contrast, across SEQ ID NOs:171 and 172 of WO 2025/017127 A1, human gp130 and mouse gp130 share 72% sequence identity (5/7 and 8/11 residues, respectively). This might explain why B-R3 does not bind to mouse gp130, whereas B35-C03-A3 does bind to mouse gp130.

Example 24 and Figure 25 of WO 2025/017127 A1 show the characterisation of multiple humanized antibody variants of B035-C03-A3 which were designed based on both composite human antibody (CHAb) and CDR grafting technology. All of the humanized variants of B035-C03-A3 retained the ability to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM and LIF, in a dose-dependent manner. The humanized variants moreover inhibited signalling mediated by the various different IL-6 family cytokines with similar (*i.e.* IC_{50} value within ~2-fold) or improved (lower IC_{50} value) potency, relative to B035-C03-A3.

Example 25 of WO 2025/017127 A1 shows the thermal stability of B035-C03-A3, A3_6.2_I100T / A3_3_G51A, and A3_3.2_I100T / A3_4_G51A. The thermal stability of the variants is similar to that of the parent B035-C03-A3.

Example 26 of WO 2025/017127 A1 shows the binding affinity of B035-C03-A3, A3_3.2 / A3_4_G51A, A3_3.2_I100Q / A3_4_G51A, A3_3.2_I100K / A3_4_G51A, A3_3.2_I100T / A3_4_G51A and A3_6.2_I100T / A3_3_G51A to human gp130, as assessed by SPR using Biacore 8K. The variants show good binding to human gp130. A3_6.2_I100T / A3_3_G51A and A3_3.2_I100T / A3_4_G51A retained a K_D within three-fold and four-fold of chimeric antibody respectively.

Example 27 and Figure 26 of WO 2025/017127 A1 shows the abilty of B035-C03-A3, A3_6.2_I100T / A3_3_G51A and A3_3.2_I100T / A3_4_G51A to inhibit signalling induced by IL-6, IL-11, CT-1, CNTF, OSM or LIF through gp130 as evaluated using a STAT3 reporter cell line. Figure 26 of WO 2025/017127 A1 shows that all of B035-C03-A3, A3_6.2_I100T / A3_3_G51A, and A3_3.2_I100T / A3_4_G51A retained the ability to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM and LIF, in a dose-dependent manner. These data indicate that the humanised B035-C03-A3 antibodies comprising VH I100T and VL G51A retain the ability to inhibit signalling mediated by all of IL-6, IL-11, LIF, OSM and CTGF and are ‘pan’ inhibitors of gp130-mediated signalling.

Example 28 of WO 2025/017127 A1 shows binding of CSP-S-5H8 and humanised CSP-S-5H8 antibodies comprising VH D98 or VH G99 variations to human gp130 as assessed by SPR using Biacore 8K. Variations were introduced at VH D98 or VH G99 of the chimeric antibody CSP-S-5H8. The variants (CSP-S-5H8_D98A VH / CSP-S-5H8 VL; CSP-S-5H8_D98E VH / CSP-S-5H8 VL; CSP-S-5H8_D98G VH / CSP-S-5H8 VL; CSP-S-5H8_D98S VH / CSP-S-5H8 VL; CSP-S-5H8_G99A VH / CSP-S-5H8 VL; CSP-S-5H8_G99Y VH / CSP-S-5H8 VL) show good binding to human gp130. All variants retained a K_D within three-fold of the parent chimeric antibody, with the exception of CSP-S-5H8_G99A VH / CSP-S-5H8 VL which retained a K_D just over 4-fold of the parent chimeric antibody.

The VH D98G variation was introduced into each of 5H8CVH4 / 5H8CVL3, 5H8CVH4 / 5H8CVL4, 5H8CVH4 / 5H8GVL3, 5H8GVH4 / 5H8CVL4, and 5H8GVH4 / 5H8GVL3. The variants show good binding to human gp130, with all variants retaining a K_D within three-fold of the parent chimeric antibody. The VH D98S variation was introduced into each of 5H8CVH4 / 5H8CVL3, 5H8CVH4 / 5H8CVL4, 5H8CVH4 / 5H8GVL3, 5H8GVH4 / 5H8CVL4, and 5H8GVH4 / 5H8GVL3. The variants show good

binding to human gp130 with all VH D98S variants retaining a K_D within three-fold and four-fold of chimeric antibody respectively.

Example 29 and Figure 27 of WO 2025/017127 A1 show the ability of the antibodies (CSP-S-5H8, 5H8CVH4_D98G / 5H8CVL3, 5H8CVH4_D98G / 5H8CVL4, 5H8CVH4_D98G / 5H8GVL3, 5H8GVH4_D98G / 5H8CVL4 and 5H8GVH4_D98G / 5H8GVL3) provided in hIgG4(S228P, L235E) format to inhibit signalling induced by IL-6, IL-11, CT-1, CNTF, OSM or LIF through gp130, as evaluated using a STAT3 reporter cell line. Figure 27A and Figure 27B of WO 2025/017127 A1 show that all of CSP-S-5H8, 5H8CVH4_D98G/5H8CVL3, 5H8CVH4_D98G/5H8CVL4, 5H8CVH4_D98G/5H8GVL3, 5H8GVH4_D98G/5H8CVL4 and 5H8GVH4_D98G/5H8GVL3 retained the ability to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM and LIF, in a dose-dependent manner. These data indicate that the humanised CSP-S-5H8 antibodies retain the ability to inhibit signalling mediated by all of IL-6, IL-11, LIF, OSM and CTGF and are 'pan' inhibitors of gp130-mediated signalling.

Example 30 and Figure 28 of WO 2025/017127 A1 show that each of mAb16618, mAb16636 and mAb16673 did not inhibit signalling through gp130 induced by IL-6 and CNTF, as assessed in a STAT3 reporter cell line. These data indicate that mAb16618, mAb16636 and mAb16673 do not inhibit signalling mediated by gp130:IL-6Rα and gp130:LIFRβ:CNTFRα, and are therefore not 'pan' inhibitors of gp130-mediated signalling.

Example 5: Characterisation of anti-gp130 clones in WO 2024/121233 A1

Antibodies which bind to gp130 are described and characterised in WO 2024/121233 A1 (which is hereby incorporated by reference in its entirety). The materials and methods used in Examples 1-13 of WO 2024/121233 A1 are described in Example 1 of WO 2024/121233 A1.

Examples 3, 4, 19, 25, 29, 31 and Figures 14 and 17 of WO 2024/121233 A1 show binding of anti-gp130 clones (and variants thereof) to human, mouse and/or Rhesus monkey gp130 by ELISA and/or SPR (Biacore) binding assays. Various antibodies showed high affinity binding.

Examples 2, 27, 32 and 34 and Figures 13, 22, 23, 24 of WO 2024/121233 A1 show the ability of anti-gp130 clones (and variants thereof) to inhibit cytokine-mediated gp130 signalling as assessed by assays in STAT3 reporter cell lines. Examples 5, 6, 10, 11, 12, 21 and Figures 1, 2, 5, 6, 7, 19 of WO 2024/121233 A1 show the ability of anti-gp130 clones (and variants thereof) to inhibit cytokine-mediated gp130 signalling in various cell lines (mouse atrial fibroblasts, human cardiac fibroblasts, and A549) following stimulation with given cytokines. The results show that anti-gp130 clones (and variants thereof) are able to inhibit IL6-mediated signalling though IL-6Rα:gp130 and IL11-mediated signalling though IL-11Rα:gp130, but do not inhibit signalling mediated by other IL-6 family cytokines OSM, LIF, hCT-1, CNTF.

Examples 7, 8, 9 and Figures 3, 4, 15 of WO 2024/121233 A1 show in vitro IC50 screening of anti-gp130 clones (and variants thereof) in various cell lines (mouse atrial fibroblasts, rat atrial fibroblasts, canine

dermal fibroblasts). Clones were determined to inhibit IL-11-mediated signalling, following stimulation of cells with recombinant IL-11 or TGFβ1, with IC50 ranging from 14 ng/ml to 46 ng/ml. Examples 13 and Figures 8 of WO 2024/121233 A1 show in vitro IC50 screening in A549 cell line and demonstrate strong inhibition of signalling mediated by IL-6/gp130:IL-6Rα and IL-11/gp130:IL-11Rα.

Immunoblotting and immunohistochemistry assays in Example 14 and 20 and Figure 9 and 18 of WO 2024/121233 A1 show binding of anti-gp130 clones to WT mouse liver tissue samples, but no binding to gp130 conditional knock out samples. Thus demonstrating that the antibodies can be successfully used in immunoblotting and immunohistochemistry of tissue samples.

Examples 15, 16 and 17 and Figures 10, 11, and 16 of WO 2024/121233 A1 demonstrate that the anti-gp130 clones strongly inhibit gp130 signalling *in vivo*, significantly reduce the pathology of acute kidney injury, are an effective treatment in a mouse model of arthritis, and are an effective treatment in a mouse model of IBD.

Example 18 of WO 2024/121233 A1 describes the epitopes of anti-gp130 clones on gp130 as determined by peptide cross linking and hydrogen/deuterium exchange mass spectrometry analyses. The analyses found that the gp130-binding molecules that inhibit signalling mediated by IL-6 and IL-11, but not by the other IL-6 family cytokines CNTF, CT-1, LIF and OSM, are shown not to bind to regions of gp130 involved in cytokine binding (*i.e.* do not bind to the cytokine binding module of gp130 shown in SEQ ID NO:144 of WO 2024/121233 A1), and instead bind to the membrane-proximal region of gp130 (shown in SEQ ID NO:388 of WO 2024/121233 A1). Figure 12 of WO 2024/121233 A1 shows schematic representations of the interaction between gp130 and various anti-gp130 antibody clones.

Examples 22 and 23 and Figures 20 and 21 of WO 2024/121233 A1 show the ability of anti-gp130 clones to inhibited HyperIL-6- and Hyper IL-11-induced gp130-mediated signalling in human cardiac fibroblasts and mouse atrial fibroblasts.

Example 24 of WO 2024/121233 A1 demonstrates the ability to produce the anti-gp130 clones (and variants thereof) by large scale expression. Examples 26, 33 and 35 of WO 2024/121233 A1 show the results of thermal stability studies (UNcle biostability analysis) and freeze-thaw stability studies of anti-gp130 clones (and variants thereof), demonstrating that the anti-gp130 clones (and variants thereof) have good characteristics in terms of stability.

Example 28 of WO 2024/121233 A1 describes the identification of sequence liabilities within the anti-gp130 antibody 4D4 clone and the substitutions selected for further characterization. Example 30 of WO 2024/121233 A1 describes analysis to determine preferred humanised 4D4 VH and VL sequences for further characterization.

Claims:

1. An antigen-binding molecule that binds to gp130 for use in a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation wherein the method comprises administering to a subject an antagonist of an angiogenic factor.

2. Use of an antigen-binding molecule that binds to gp130 in the manufacture of a medicament for use in a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation wherein the method comprises administering an antagonist of an angiogenic factor.

3. A method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation comprising administering to a subject a therapeutically- or prophylactically-effective amount of (i) an antigen-binding molecule that binds to gp130 and (ii) an antagonist of an angiogenic factor.

4. A combination comprising an antigen-binding molecule that binds to gp130 and an antagonist of an angiogenic factor.

5. A combination according to claim 4, for use in a method of treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation.

6. Use of a combination according to claim 4, in the manufacture of a medicament for treating or preventing fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation.

7. A method of treating or preventing fibrosis, a disease characterised by fibrosis, a disease/condition characterised by fibrosis, pathological angiogenesis, a disease/condition characterised by angiogenesis, pathological inflammation and/or a disease/condition characterised by inflammation comprising administering to a subject a therapeutically- or prophylactically-effective amount of a combination according to claim 4.

8. The antigen-binding molecule for use according to claim 1, the combination for use according to claim 5, the use according to claim 2 or claim 6, or the method according to claim 3 or claim 7, wherein the fibrosis, disease/condition characterised by fibrosis, pathological angiogenesis, disease/condition characterised by angiogenesis, pathological inflammation and/or disease/condition characterised by inflammation affects tissue of the eye.

9. The antigen-binding molecule for use according to claim 1 or claim 8, the combination for use according to claim 5 or claim 8, the use according to any one of claims 2, 6 or 8, or the method according to any one of claims 3, 7 or 8, wherein the fibrosis, disease/condition characterised by fibrosis, pathological angiogenesis, disease/condition characterised by angiogenesis, pathological inflammation and/or disease/condition characterised by inflammation is selected from: choroidal neovascularization, retinal fibrosis, epiretinal fibrosis, idiopathic pre-macular fibrosis, retinal detachment, macular degeneration, subretinal fibrosis associated with wet age-related macular degeneration, diabetic retinopathy, glaucoma, geographic atrophy, corneal fibrosis, post-surgical fibrosis, post-surgical fibrosis of the posterior capsule following cataract surgery, post-surgical fibrosis of the bleb following trabeculectomy for glaucoma, conjunctival fibrosis, subconjunctival fibrosis, proliferative retinal vasculopathy, dacryoadenitis, scleritis, episcleritis, keratitis, retinitis, chorioretinitis, blepharitis, conjunctivitis, uveitis, autoimmune uveitis, infectious uveitis, Bechet's disease, cataracts, keratic precipitates, conjunctival ulcers, corneal immune ring opacities, post-surgical inflammation, dry eye disease, retinitis pigmentosa, glaucoma, toxic anterior segment syndrome (TASS), Eales' disease, diabetic retinopathy, retinal dystrophy (*e.g.* retinitis pigmentosa) and Sjögrens syndrome.

10. The antigen-binding molecule or combination for use, the use, or the method according to claim 9, wherein the fibrosis, disease/condition characterised by fibrosis, pathological angiogenesis, disease/condition characterised by angiogenesis, pathological inflammation and/or disease/condition characterised by inflammation is selected from: choroidal neovascularization, retinal fibrosis, epiretinal fibrosis, subretinal fibrosis, dacryoadenitis, uveitis, autoimmune uveitis, infectious uveitis, Bechet's disease, and dry eye disease.

11. A kit of parts, comprising predetermined quantities of: (i) an antigen-binding molecule that binds to gp130, and (ii) an antagonist of an angiogenic factor.

12. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, wherein the antigen-binding molecule that binds to gp130 inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling.

13. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 12, wherein the antigen-binding molecule that binds to gp130 comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:2

HC-CDR2 having the amino acid sequence of SEQ ID NO:3

HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:10

LC-CDR2 having the amino acid sequence of SEQ ID NO:11

LC-CDR3 having the amino acid sequence of SEQ ID NO:12.

14. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 13, wherein the antigen-binding molecule that binds to gp130 comprises:

(a)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:112, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:121; or

(b)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:117, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:126; or

(c)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or

(d)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

(e)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or

(f)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or

(g)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

(h)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or

(i)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or

(j)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

(k)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or

(l)

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:1, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:9.

15. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 12, wherein the antigen-binding molecule that binds to gp130 comprises:

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:18

HC-CDR2 having the amino acid sequence of SEQ ID NO:19

HC-CDR3 having the amino acid sequence of SEQ ID NO:20; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:26

LC-CDR2 having the amino acid sequence of SEQ ID NO:27

LC-CDR3 having the amino acid sequence of SEQ ID NO:28.

16. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 12 or claim 15, wherein the antigen-binding molecule that binds to gp130 comprises:

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:17, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:25.

17. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, wherein the antigen-binding molecule that binds to gp130 inhibits signalling mediated by gp130:IL-6Rα and/or gp130:IL-11Rα, and wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMRβ, gp130:LIFRβ, gp130:LIFRβ:CNTFRα, gp130:IL-27Rα and gp130:IL-12Rβ2.

18. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11 or 17, wherein the antigen-binding molecule that binds to gp130 inhibits signalling mediated by gp130:IL-6Rα and gp130:IL-11Rα.

19. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, 17 or 18, wherein the antigen-binding molecule that binds to gp130 does not inhibit signalling mediated by gp130:OSMRβ, and does not inhibit signalling mediated by gp130:LIFRβ, and does not inhibit signalling mediated by gp130:LIFRβ:CNTFRα.

20. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, or 17 to 19, wherein the antigen-binding molecule that binds to gp130 contacts the region of gp130 shown in SEQ ID NO:517.

21. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, or 17 to 20, wherein the antigen-binding molecule that binds to gp130 comprises:

(a)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:380
HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:417; or

(b)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:377
HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:412; or

(c)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:375
HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:415; or

(d)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:376
HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:412; or

(e)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:240
HC-CDR2 having the amino acid sequence of SEQ ID NO:241
HC-CDR3 having the amino acid sequence of SEQ ID NO:242; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:243
LC-CDR2 having the amino acid sequence of SEQ ID NO:244
LC-CDR3 having the amino acid sequence of SEQ ID NO:245; or

(f)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:180
HC-CDR2 having the amino acid sequence of SEQ ID NO:181
HC-CDR3 having the amino acid sequence of SEQ ID NO:182; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:188
LC-CDR2 having the amino acid sequence of SEQ ID NO:189
LC-CDR3 having the amino acid sequence of SEQ ID NO:190; or

(g)

(i) a heavy chain variable (VH) region incorporating the following CDRs:
HC-CDR1 having the amino acid sequence of SEQ ID NO:196
HC-CDR2 having the amino acid sequence of SEQ ID NO:197
HC-CDR3 having the amino acid sequence of SEQ ID NO:198; and
(ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:202
LC-CDR2 having the amino acid sequence of SEQ ID NO:203

LC-CDR3 having the amino acid sequence of SEQ ID NO:204; or

(h)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:196

HC-CDR2 having the amino acid sequence of SEQ ID NO:197

HC-CDR3 having the amino acid sequence of SEQ ID NO:210; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:202

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:190; or

(i)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:215

HC-CDR2 having the amino acid sequence of SEQ ID NO:216

HC-CDR3 having the amino acid sequence of SEQ ID NO:217; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:223

LC-CDR2 having the amino acid sequence of SEQ ID NO:224

LC-CDR3 having the amino acid sequence of SEQ ID NO:225; or

(j)

(i) a heavy chain variable (VH) region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:230

HC-CDR2 having the amino acid sequence of SEQ ID NO:231

HC-CDR3 having the amino acid sequence of SEQ ID NO:232; and

(ii) a light chain variable (VL) region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:202

LC-CDR2 having the amino acid sequence of SEQ ID NO:189

LC-CDR3 having the amino acid sequence of SEQ ID NO:236.

22. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, or 17 to 21, wherein the antigen-binding molecule that binds to gp130 comprises:

a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:352, 372, 350, 370, 351, 371, 252, 284, 256, 258, 261, 179, 195, 209, 214, 229, 264 or 265; and

a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:402, 405, 253, 288, 266, 269, 273, 276, 278, 187, 201, 212, 222 or 235.

23. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 11, or 17 to 22, wherein the antigen-binding molecule that binds to gp130 comprises:

a VH region having an amino acid sequence having at least 70% amino acid sequence identity to an amino acid sequence indicated in column A of Table G, and

a VL region having an amino acid sequence having at least 70% amino acid sequence identity to an amino acid sequence indicated in column B of Table G;

wherein the sequences of columns A and B are selected from the same row of Table G.

24. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 23, wherein the angiogenic factor is selected from vascular endothelial growth factor (VEGF), a fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).

25. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 24, wherein the angiogenic factor is VEGF.

26. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 25, wherein the antagonist of an angiogenic factor is selected from: a VEGF decoy receptor, an antigen-binding molecule that binds to VEGF, or an antigen-binding molecule that binds to a VEGF receptor.

27. The antigen-binding molecule or combination for use, the use, the method or the kit of parts according to any one of claims 1 to 26, wherein the antagonist of an angiogenic factor is aflibercept.