

Gp130 Antigen-Binding Molecules

This application claims priority from GB 2218388.3 filed 7 December 2022, the contents and elements of which are herein incorporated by reference for all purposes.

Technical Field

The present disclosure relates to the fields of molecular biology, more specifically antibody technology. The present disclosure also relates to methods of medical treatment and prophylaxis.

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Background

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).

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However, because gp130 is important for the signalling mediated by such a range of different cytokines, it has been considered to be an unattractive target for therapeutic intervention for such diseases/conditions. For example, it has been suggested that as a result of its role in promoting resistance to pathogens, therapies targeting gp130 might leave patients vulnerable to opportunistic infections. Moreover, because signalling mediated by some IL-6 family cytokines might be beneficial in certain settings, agents targeting gp130 may cause and/or exacerbate disease (see *e.g.* Silver and Hunter, J Leukoc Biol. (2010) 88(6):1145-1156).

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Monoclonal antibodies that bind to gp130 and antagonise gp130-mediated signalling have previously been described, including mAb16673 which is reported in WO 2019/126071 A1 to inhibit signalling mediated by OSM, LIF and CNTF.

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Summary

In a first aspect, the present disclosure provides an antigen-binding molecule, optionally isolated, which binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , and wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.

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In some embodiments, the antigen-binding inhibits signalling mediated by gp130:IL-6R α and gp130:IL-11R α .

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In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α .

In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:386.

5 In some embodiments, the antigen-binding molecule comprises:

(a)

(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:249

10 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:286; or

15 (b)

(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:246

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

20 (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:281; or

(c)

25 (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:244

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

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

30 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:284; or

(d)

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

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

HC-CDR2 having the amino acid sequence of SEQ ID NO:245

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

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

40 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:281; or

(e)

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:62
 HC-CDR2 having the amino acid sequence of SEQ ID NO:63
 HC-CDR3 having the amino acid sequence of SEQ ID NO:64; and
- 5 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:65
 LC-CDR2 having the amino acid sequence of SEQ ID NO:66
 LC-CDR3 having the amino acid sequence of SEQ ID NO:67; or
- (f)
- 10 (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:
 15 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
- (g)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 20 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:24
 25 LC-CDR2 having the amino acid sequence of SEQ ID NO:25
 LC-CDR3 having the amino acid sequence of SEQ ID NO:26; or
- (h)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:18
 30 HC-CDR2 having the amino acid sequence of SEQ ID NO:19
 HC-CDR3 having the amino acid sequence of SEQ ID NO:32; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
 LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 35 LC-CDR3 having the amino acid sequence of SEQ ID NO:12; or
- (i)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 40 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:45

LC-CDR2 having the amino acid sequence of SEQ ID NO:46

LC-CDR3 having the amino acid sequence of SEQ ID NO:47; or

(i)

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

5 HC-CDR1 having the amino acid sequence of SEQ ID NO:52

HC-CDR2 having the amino acid sequence of SEQ ID NO:53

HC-CDR3 having the amino acid sequence of SEQ ID NO:54; and

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

10 LC-CDR1 having the amino acid sequence of SEQ ID NO:24

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

LC-CDR3 having the amino acid sequence of SEQ ID NO:58.

In some embodiments, the antigen-binding molecule comprises:

15 a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:221, 241, 219, 239, 220, 240, 74, 106, 78, 80, 83, 1, 17, 31, 36, 51, 86 or 87; and

a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:271, 274, 75, 110, 88, 91, 95, 98, 100, 9, 23, 34, 44 or 57.

In some embodiments, the antigen-binding molecule comprises:

20 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 C, 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 C;

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

In some embodiments, the antigen-binding molecule is a multispecific antigen-binding molecule, and wherein the antigen-binding molecule further comprises an antigen-binding domain which binds to an antigen other than gp130.

30 The present disclosure also provides a chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to the present disclosure.

The present disclosure also provides a nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding an antigen-binding molecule or CAR according to the present disclosure.

35 The present disclosure also provides an expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to the present disclosure.

40 The present disclosure also provides a cell comprising an antigen-binding molecule, CAR, nucleic acid or plurality of nucleic acids or expression vector or plurality of expression vectors according to the present disclosure.

The present disclosure also provides a method comprising culturing a cell according to the present disclosure under conditions suitable for expression of an antigen-binding molecule or CAR by the cell.

5 The present disclosure also provides a composition comprising an antigen-binding molecule, CAR, nucleic acid or plurality of nucleic acids, expression vector or plurality of expression vectors or cell according to the present disclosure, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

10 The present disclosure also provides an antigen-binding molecule, CAR, nucleic acid or plurality of nucleic acids, expression vector or plurality of expression vectors, cell or composition according to the present disclosure, for use in a method of medical treatment or prophylaxis.

The present disclosure also provides an antigen-binding molecule, CAR, nucleic acid or plurality of nucleic acids, expression vector or plurality of expression vectors, cell or composition according to the present disclosure, for use in a method of treatment or prevention of: pathological inflammation, fibrosis, a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, a disease/condition in which signalling through a gp130-containing complex is pathologically-implicated, a disease/condition in which a cytokine that signals through a gp130-containing complex is pathologically-implicated, an autoimmune disease, metabolic syndrome, a neurodegenerative disease, a chronic inflammatory disease, arthritis, rheumatoid arthritis, juvenile arthritis, systemic juvenile idiopathic arthritis, lupus, systemic lupus erythematosus, pancreatitis, thyroiditis, periodontitis, rhinitis, allergic rhinitis, dermatitis, atopic dermatitis, psoriasis, Hermansky-Pudlak syndrome, Graves' disease, obesity, insulin resistance, diabetes, type 1 diabetes, type 2 diabetes, pregnancy-associated hyperglycemia, multiple sclerosis, giant cell arteritis, Takayasu arteritis, cardiovascular disease, atherosclerosis, atrial fibrillation, ventricular fibrillation, cardiac hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, cardiogenic shock, heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, ischemic heart disease, myocardial infarction, Marfan syndrome, systemic sclerosis, keloid, scleroderma, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, hippocampal atrophy, pulmonary disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, hepatitis, liver fibrosis, cirrhosis, hepatotoxicity, acetaminophen-induced hepatotoxicity, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, colitis, ulcerative colitis, endometriosis, stroke, ischemic stroke, nephropathy, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, chronic kidney disease, kidney fibrosis, Alport syndrome, adult-onset Still's disease, Castleman's disease, cytokine release syndrome, sepsis, septic shock, a retinal disorder, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, retinitis pigmentosa, dry eye syndrome, COVID-19, Peutz-Jeghers syndrome, a skeletal muscle disorder, muscular dystrophy, amyotrophy, cachexia, an endocrine disorder, polycystic ovary syndrome, a cancer, a hematologic malignancy, leukemia, plasmacytoma, Hodgkin's lymphoma, lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer,

- bone cancer, glioblastoma, breast cancer, stomach cancer, renal cancer, metastatic renal cell cancer, prostate cancer, skin cancer, melanoma, liver cancer, hepatocellular carcinoma, 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, age-related non-alcoholic fatty liver, age-related non-alcoholic steatohepatitis, age-related cardiovascular disease, age-related hypertension, age-related renal disease, age-related skin disease, an infectious disease, a viral disease, viral hepatitis, hepatitis B, HIV infection, influenza infection, malaria, tuberculosis, an allergic disease, transplant rejection and graft-versus-host disease.
- 5
- 10 The present disclosure also provides an *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to the present disclosure bound to gp130.

- The present disclosure also provides a method for detecting gp130 in a sample, comprising contacting a sample containing, or suspected to contain, gp130 with an antigen-binding molecule according to the present disclosure, and detecting the formation of a complex of the antigen-binding molecule with gp130.
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- The present disclosure also provides a method of selecting or stratifying a subject for treatment with a gp130-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to the present disclosure, and detecting the formation of a complex of the antigen-binding molecule with gp130.
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The present disclosure also provides the use of an antigen-binding molecule according to the present disclosure as an *in vitro* or *in vivo* diagnostic or prognostic agent.

- 25 The present disclosure also provides an antigen-binding molecule which binds to gp130 for use in a method of treatment or prevention of: pathological inflammation, fibrosis, a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, a disease/condition in which signalling through a gp130-containing complex is pathologically-implicated, a disease/condition in which a cytokine that signals through a gp130-containing complex is pathologically-implicated, an autoimmune disease, metabolic syndrome, a neurodegenerative disease, a chronic inflammatory disease, arthritis, rheumatoid arthritis, juvenile arthritis, systemic juvenile idiopathic arthritis, lupus, systemic lupus erythematosus, pancreatitis, thyroiditis, periodontitis, rhinitis, allergic rhinitis, dermatitis, atopic dermatitis, psoriasis, Hermansky-Pudlak syndrome, Graves' disease, obesity, insulin resistance, diabetes, type 1 diabetes, type 2 diabetes, pregnancy-associated hyperglycemia, multiple sclerosis, giant cell arteritis, Takayasu arteritis, cardiovascular disease, atherosclerosis, atrial fibrillation, ventricular fibrillation, cardiac hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, cardiogenic shock, heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, ischemic heart disease, myocardial infarction, Marfan syndrome, systemic sclerosis, keloid, scleroderma,
- 30
- 35
- 40 Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, hippocampal atrophy, pulmonary disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, hepatitis, liver fibrosis, cirrhosis, hepatotoxicity,

acetaminophen-induced hepatotoxicity, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, colitis, ulcerative colitis, endometriosis, stroke, ischemic stroke, nephropathy, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis,

5 chronic kidney disease, kidney fibrosis, Alport syndrome, adult-onset Still's disease, Castleman's disease, cytokine release syndrome, sepsis, septic shock, a retinal disorder, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, retinitis pigmentosa, dry eye syndrome, COVID-19, Peutz-Jeghers syndrome, a skeletal muscle disorder, muscular dystrophy, amyotrophy, cachexia, an endocrine disorder, polycystic ovary syndrome, a cancer, a hematologic malignancy, leukemia,

10 plasmacytoma, Hodgkin's lymphoma, lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer, bone cancer, glioblastoma, breast cancer, stomach cancer, renal cancer, metastatic renal cell cancer, prostate cancer, skin cancer, melanoma, liver cancer, hepatocellular carcinoma, frailty, age-related increase in fat mass, sarcopenia, age-related hyperlipidaemia, age-related hypertriglyceridemia, age-

15 related hypercholesterolemia, age-related liver steatosis, age-related non-alcoholic fatty liver disease, age-related non-alcoholic fatty liver, age-related non-alcoholic steatohepatitis, age-related cardiovascular disease, age-related hypertension, age-related renal disease, age-related skin disease, an infectious disease, a viral disease, viral hepatitis, hepatitis B, HIV infection, influenza infection, malaria, tuberculosis, an allergic disease, transplant rejection and graft-versus-host disease, wherein the antigen-

20 binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.

The present disclosure also provides the use of an antigen-binding molecule that binds to gp130 to inhibit

25 IL-6-mediated signalling and/or IL-11-mediated signalling, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.

30 The present disclosure also provides a method for inhibiting IL-6-mediated signalling and/or IL-11-mediated signalling, comprising contacting cells capable of IL-6-mediated signalling and/or IL-11-mediated signalling with an antigen-binding molecule that binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β ,

35 gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.

The present disclosure also provides a method for inhibiting IL-6-mediated signalling and/or IL-11-mediated signalling in a subject, comprising administering to a subject an antigen-binding molecule that binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or

40 gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.

In some embodiments, the antigen-binding molecule, wherein the antigen-binding inhibits signalling mediated by gp130:IL-6R α and gp130:IL-11R α .

In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α .

In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:386.

In some embodiments, the antigen-binding molecule comprises:

(a)

(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:249

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:286; or

(b)

(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:246

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:281; or

(c)

(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:244

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:284; or

(d)

(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:245

- 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
- 5 LC-CDR3 having the amino acid sequence of SEQ ID NO:281; or
- (e)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
- HC-CDR1 having the amino acid sequence of SEQ ID NO:62
- HC-CDR2 having the amino acid sequence of SEQ ID NO:63
- 10 HC-CDR3 having the amino acid sequence of SEQ ID NO:64; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:65
- LC-CDR2 having the amino acid sequence of SEQ ID NO:66
- LC-CDR3 having the amino acid sequence of SEQ ID NO:67; or
- 15 (f)
- (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
- 20 (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; or
- (g)
- 25 (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:
- 30 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
- LC-CDR2 having the amino acid sequence of SEQ ID NO:25
- LC-CDR3 having the amino acid sequence of SEQ ID NO:26; or
- (h)
- 35 (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:32; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:24
- 40 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
- (i)

- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
- 5 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:45
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:47; or
- (j)
- 10 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:52
 HC-CDR2 having the amino acid sequence of SEQ ID NO:53
 HC-CDR3 having the amino acid sequence of SEQ ID NO:54; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- 15 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
 LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 LC-CDR3 having the amino acid sequence of SEQ ID NO:58.

In some embodiments, the antigen-binding molecule comprises:

- 20 a VH region having an amino acid sequence having at least 70% amino acid sequence identity to
 SEQ ID NO:221, 241, 219, 239, 220, 240, 74, 106, 78, 80, 83, 1, 17, 31, 36, 51, 86 or 87; and
 a VL region having an amino acid sequence having at least 70% amino acid sequence identity to
 SEQ ID NO:271, 274, 75, 110, 88, 91, 95, 98, 100, 9, 23, 34, 44 or 57.
- 25 In some embodiments, the antigen-binding molecule 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 C, 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 C;
- 30 wherein the sequences of columns A and B are selected from the same row of Table C.

In some embodiments, the antigen-binding molecule is a multispecific antigen-binding molecule, and
 wherein the antigen-binding molecule further comprises an antigen-binding domain which binds to an
 antigen other than gp130.

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Description

The present disclosure provides antigen-binding molecules that bind to gp130, having novel biophysical
 and/or functional properties as compared to antigen-binding molecules disclosed in the prior art.

- 40 In particular, the present disclosure is concerned with gp130-binding antigen-binding molecules that
 inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α , but which do not inhibit
 signalling mediated by other IL-6 family cytokines or other cytokine receptor complexes comprising

gp130. That is, the present disclosure is concerned in particular with gp130-binding antigen-binding molecules that inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α only.

5 The antigen-binding molecules of the present disclosure are useful to inhibit signalling mediated by the pro-fibroinflammatory IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α signalling axes, without substantial inhibition of signalling mediated by other IL-6 family cytokines.

10 The gp130-containing receptor complexes responsible for transducing IL-11- and IL-6-mediated signalling are formed of a heteromer comprising gp130 and IL-11R α or IL-6R α molecules. By contrast, the gp130-containing receptor complexes responsible for transducing signalling mediated by OSM, LIF, CNTF, CT-1, CLC, IL-27 and IL-35 comprise a single gp130 molecule. Without wishing to be bound by any particular theory, the antigen-binding molecules of the present disclosure may selectively inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α through inhibiting formation of a gp130-containing receptor complex comprising more than one gp130 molecule.

15 The gp130-binding antigen-binding molecules that inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α according to the present disclosure are moreover shown to bind to the membrane-proximal region of gp130.

20 Prior to the present disclosure, it was not appreciated that it would be possible to obtain antigen-binding molecules that are able to inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α (and that do not inhibit signalling mediated by other IL-6 family cytokines or other cytokine receptor complexes comprising gp130). Certainly, it was not clear that it would be possible to selectively inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α through targeting the membrane-proximal
25 region of gp130.

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
30 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:129. Alternative splicing of mRNA encoded by the human *IL6ST* gene yields three main gp130
35 isoforms: isoform 1 (SEQ ID NO:129), isoform 2 (also known as gp130-RAPS; SEQ ID NO:130) and isoform 3 (SEQ ID NO:131). Isoform 2 differs from isoform 1 in that positions 325 to 329 of SEQ ID NO:129 are different, and positions 330-918 are absent. Positions 423 to 483 of SEQ ID NO:129 are absent from isoform 3.

40 The canonical isoform of human gp130 comprises an N-terminal signal peptide (SEQ ID NO:132), followed by an extracellular domain (SEQ ID NO:134), a single-pass transmembrane domain (SEQ ID

NO:135) and a cytoplasmic domain (SEQ ID NO:136) at the C-terminus. The mature form of human gp130 isoform 1 is shown in SEQ ID NO:133.

The extracellular domain comprises an N-terminal Ig-like C2-type domain (SEQ ID NO:137), followed by five fibronectin type III (FNIII) domains (shown in SEQ ID NOs:138, 139, 141, 142 and 143, 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:144). FNIII domain 2 comprises the WSXWS motif shown in SEQ ID NO:140. 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-6R α polypeptides to form the receptor for IL-6, and similarly two gp130 polypeptides associate with two IL-11R α polypeptides to form the receptor for IL-11. gp130 associates with OSMR β to form the type II receptor for OSM, or with LIFR β to form the type I receptor for OSM, which also serves as a receptor for LIF and CT-1. gp130 also associates with LIFR β and CNTFR α to form the receptor for CNTF and CLC. gp130 associates with IL-27R α to form the receptor for IL-27, and associates with IL-12R β 2 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, epitharian, 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 $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 91\%$, $\geq 92\%$, $\geq 93\%$, $\geq 94\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$, $\geq 99\%$ 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).

5

Isoforms, fragments, variants or homologues of a given reference protein may optionally be characterised as having at least 70%, preferably one of $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 91\%$, $\geq 92\%$, $\geq 93\%$, $\geq 94\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$, $\geq 99\%$ 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.

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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.

15

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 association with IL-6R α , IL-11R α , OSMR β , LIFR β and/or CNTFR α .

20

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:129, 130 or 131.

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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:129 or 133.

30

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.

35

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.

40

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:133.

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:134.

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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:144.

- 10 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.

- 15 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.

- 20 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-6R α , IL-11R α , OSMR β , LIFR β , CNTFR α , IL-27R α and IL-12R β 2).

- 25 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.

- 30 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-6R α , IL-11R α , OSMR β , LIFR β , CNTFR α , IL-27R α and IL-12R β 2). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-6R α (*i.e.* a gp130:IL-6R α complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-11R α (*i.e.* a gp130:IL-11R α complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and OSMR β (*i.e.* a gp130:OSMR β complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and LIFR β (*i.e.* a gp130:LIFR β complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130, LIFR β and CNTFR α (*i.e.* a gp130:LIFR β :CNTFR α complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-27R α (*i.e.* a gp130:IL-27R α complex). In some embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising gp130 and IL-12R β 2 (*i.e.* a gp130:IL-12R β 2 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-6R α (*i.e.* a gp130:gp130:IL-6R α complex). In some
5 embodiments, gp130-mediated signalling may be mediated by a polypeptide complex comprising two gp130 polypeptides and IL-11R α (*i.e.* a gp130:gp130:IL-11R α 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
10 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-6R α (*i.e.* a gp130:IL-6R α complex). In some embodiments, gp130-mediated signalling is triggered by binding of IL-11 to a polypeptide complex
15 comprising gp130 and IL-11R α (*i.e.* a gp130:IL-11R α complex). In some embodiments, gp130-mediated signalling is triggered by binding of OSM to a polypeptide complex comprising gp130 and OSMR β (*i.e.* a gp130:OSMR β complex). In some embodiments, gp130-mediated signalling is triggered by binding of OSM, LIF or CT-1 to a polypeptide complex comprising gp130 and LIFR β (*i.e.* a gp130:LIFR β complex). In some embodiments, gp130-mediated signalling is triggered by binding of CNTF or CLC to a
20 polypeptide complex comprising gp130, LIFR β and CNTFR α (*i.e.* a gp130:LIFR β :CNTFR α complex). In some embodiments, gp130-mediated signalling is triggered by binding of IL-27 to a polypeptide complex comprising gp130 and IL-27R α (*i.e.* a gp130:IL-27R α complex). In some embodiments, gp130-mediated signalling is triggered by binding of IL-35 to a polypeptide complex comprising gp130 and IL-12R β 2 (*i.e.* a gp130:IL-12R β 2 complex).

25

Antigen-binding molecules

The present disclosure provides 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.

30

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
35 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,
40 *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 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).

5 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.

10 The antigen-binding molecules of the present disclosure may be designed and prepared using the sequences of monoclonal antibodies (mAbs) capable of binding to gp130. 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.

15 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.

20 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.

25 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
30 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.

35 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
40 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.

5

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:62

HC-CDR2 having the amino acid sequence of SEQ ID NO:63

10 HC-CDR3 having the amino acid sequence of SEQ ID NO:64,

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.

15 (2) 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:249

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

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.

(3) a VH region incorporating the following CDRs:

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

25 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.

30

(4) 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:244

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

35 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.

(5) a VH region incorporating the following CDRs:

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

HC-CDR2 having the amino acid sequence of SEQ ID NO:245

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.

5 (6) 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:246

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

10 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.

(7) a VH region incorporating the following CDRs:

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

15 HC-CDR2 having the amino acid sequence of SEQ ID NO:247

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.

20

(8) 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:248

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

25 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.

(9) a VH region incorporating the following CDRs:

30 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.

35

(10) 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

40 HC-CDR3 having the amino acid sequence of SEQ ID NO:32,

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.

5 (11) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:37

HC-CDR2 having the amino acid sequence of SEQ ID NO:38

HC-CDR3 having the amino acid sequence of SEQ ID NO:39,

10 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.

(12) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:52

15 HC-CDR2 having the amino acid sequence of SEQ ID NO:53

HC-CDR3 having the amino acid sequence of SEQ ID NO:54,

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.

20

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

(13) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:68

HC-FR2 having the amino acid sequence of SEQ ID NO:6

25 HC-FR3 having the amino acid sequence of SEQ ID NO:69

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.

30

(14) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:103

HC-FR2 having the amino acid sequence of SEQ ID NO:104

HC-FR3 having the amino acid sequence of SEQ ID NO:105

35 HC-FR4 having the amino acid sequence of SEQ ID NO:79,

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.

40 (15) a VH region incorporating the following FRs:

HC-FR1 having the amino acid sequence of SEQ ID NO:76

HC-FR2 having the amino acid sequence of SEQ ID NO:6

HC-FR3 having the amino acid sequence of SEQ ID NO:77
HC-FR4 having the amino acid sequence of SEQ ID NO:79,
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.

(16) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:76
HC-FR2 having the amino acid sequence of SEQ ID NO:81
HC-FR3 having the amino acid sequence of SEQ ID NO:82
HC-FR4 having the amino acid sequence of SEQ ID NO:79,
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.

(17) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:84
HC-FR2 having the amino acid sequence of SEQ ID NO:81
HC-FR3 having the amino acid sequence of SEQ ID NO:85
HC-FR4 having the amino acid sequence of SEQ ID NO:79,
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.

(18) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:76
HC-FR2 having the amino acid sequence of SEQ ID NO:81
HC-FR3 having the amino acid sequence of SEQ ID NO:77
HC-FR4 having the amino acid sequence of SEQ ID NO:79,
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.

(19) a VH region incorporating the following FRs:
HC-FR1 having the amino acid sequence of SEQ ID NO:76
HC-FR2 having the amino acid sequence of SEQ ID NO:6
HC-FR3 having the amino acid sequence of SEQ ID NO:82
HC-FR4 having the amino acid sequence of SEQ ID NO:79,
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.

- (20) 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
 - 5 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.
- 10 (21) 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:6
 - HC-FR3 having the amino acid sequence of SEQ ID NO:22
 - HC-FR4 having the amino acid sequence of SEQ ID NO:8,
 - 15 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.
- (22) a VH region incorporating the following FRs:
- 20 HC-FR1 having the amino acid sequence of SEQ ID NO:21
 - HC-FR2 having the amino acid sequence of SEQ ID NO:6
 - HC-FR3 having the amino acid sequence of SEQ ID NO:33
 - 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.
 - 25
- (23) a VH region incorporating the following FRs:
- HC-FR1 having the amino acid sequence of SEQ ID NO:40
 - 30 HC-FR2 having the amino acid sequence of SEQ ID NO:41
 - HC-FR3 having the amino acid sequence of SEQ ID NO:42
 - HC-FR4 having the amino acid sequence of SEQ ID NO:43,
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.
 - 35
- (24) a VH region incorporating the following FRs:
- HC-FR1 having the amino acid sequence of SEQ ID NO:55
 - HC-FR2 having the amino acid sequence of SEQ ID NO:41
 - 40 HC-FR3 having the amino acid sequence of SEQ ID NO:56
 - HC-FR4 having the amino acid sequence of SEQ ID NO:43,

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 In some embodiments, the antigen-binding molecule comprises a VH region comprising the CDRs according to one of (1) to (12) above, and the FRs according to any one of (13) to (24) above.

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

- (25) a VH region comprising the CDRs according to (1) and the FRs according to (7).
10 (26) a VH region comprising the CDRs according to (2) and the FRs according to (7).

(27) a VH region comprising the CDRs according to (3) and the FRs according to (8).

15 (28) a VH region comprising the CDRs according to (3) and the FRs according to (9).

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

(30) a VH region comprising the CDRs according to (3) and the FRs according to (11).
20 (31) a VH region comprising the CDRs according to (3) and the FRs according to (12).

(32) a VH region comprising the CDRs according to (3) and the FRs according to (13).

25 (33) a VH region comprising the CDRs according to (3) and the FRs according to (14).

(34) a VH region comprising the CDRs according to (4) and the FRs according to (8).

(35) a VH region comprising the CDRs according to (4) and the FRs according to (9).
30 (36) a VH region comprising the CDRs according to (4) and the FRs according to (10).

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

35 (38) a VH region comprising the CDRs according to (4) and the FRs according to (12).

(39) a VH region comprising the CDRs according to (4) and the FRs according to (13).

(40) a VH region comprising the CDRs according to (4) and the FRs according to (14).
40 (41) a VH region comprising the CDRs according to (5) and the FRs according to (8).

- (42) a VH region comprising the CDRs according to (5) and the FRs according to (9).
- (43) a VH region comprising the CDRs according to (5) and the FRs according to (10).
- 5 (44) a VH region comprising the CDRs according to (5) and the FRs according to (11).
- (45) a VH region comprising the CDRs according to (5) and the FRs according to (12).
- (46) a VH region comprising the CDRs according to (5) and the FRs according to (13).
- 10 (47) a VH region comprising the CDRs according to (5) and the FRs according to (14).
- (48) a VH region comprising the CDRs according to (6) and the FRs according to (8).
- 15 (49) a VH region comprising the CDRs according to (6) and the FRs according to (9).
- (50) a VH region comprising the CDRs according to (6) and the FRs according to (10).
- (51) a VH region comprising the CDRs according to (6) and the FRs according to (11).
- 20 (52) a VH region comprising the CDRs according to (6) and the FRs according to (12).
- (53) a VH region comprising the CDRs according to (6) and the FRs according to (13).
- 25 (54) a VH region comprising the CDRs according to (6) and the FRs according to (14).
- (55) a VH region comprising the CDRs according to (7) and the FRs according to (8).
- (56) a VH region comprising the CDRs according to (7) and the FRs according to (9).
- 30 (57) a VH region comprising the CDRs according to (7) and the FRs according to (10).
- (58) a VH region comprising the CDRs according to (7) and the FRs according to (11).
- 35 (59) a VH region comprising the CDRs according to (7) and the FRs according to (12).
- (60) a VH region comprising the CDRs according to (7) and the FRs according to (13).
- (61) a VH region comprising the CDRs according to (7) and the FRs according to (14).
- 40 (62) a VH region comprising the CDRs according to (8) and the FRs according to (8).

- (63) a VH region comprising the CDRs according to (8) and the FRs according to (9).
- (64) a VH region comprising the CDRs according to (8) and the FRs according to (10).
- 5 (65) a VH region comprising the CDRs according to (8) and the FRs according to (11).
- (66) a VH region comprising the CDRs according to (8) and the FRs according to (12).
- (67) a VH region comprising the CDRs according to (8) and the FRs according to (13).
- 10 (68) a VH region comprising the CDRs according to (8) and the FRs according to (14).
- (69) a VH region comprising the CDRs according to (9) and the FRs according to (21).
- 15 (70) a VH region comprising the CDRs according to (10) and the FRs according to (22).
- (71) a VH region comprising the CDRs according to (11) and the FRs according to (23).
- (72) a VH region comprising the CDRs according to (12) and the FRs according to (24).
- 20 In some embodiments, the antigen-binding molecule comprises a VH region according to one of:
- (73) 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:74.
- 25 (74) 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:106.
- 30 (75) 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:250.
- (76) 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:78.
- 35 (77) 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:80.
- 40

- (78) 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:83.
- 5 (79) 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.
- (80) 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.
- 10 (81) 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:215.
- 15 (82) 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:216.
- 20 (83) 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:217.
- (84) 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:218.
- 25 (85) 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:219.
- 30 (86) 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:220.
- 35 (87) 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:221.

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- (88) 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:222.
- 5 (89) 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:223.
- (90) 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:224.
- 10 (91) 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:225.
- 15 (92) 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:226.
- 20 (93) 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:227.
- (94) 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:228.
- 25 (95) 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.
- 30 (96) 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:230.
- 35 (97) 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:231.

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- (98) 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:232.
- 5 (99) 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:233.
- (100) 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:234.
- 10 (101) 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:235.
- 15 (102) 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:236.
- 20 (103) 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:237.
- (104) 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:238.
- 25 (105) 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:239.
- 30 (106) 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:240.
- 35 (107) 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:241.

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- (108) 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:242.
- 5 (109) 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:243.
- (110) 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.
- 10 (111) 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:31.
- 15 (112) 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:36.
- 20 (113) 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:51.
- 25 (114) 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:86.
- (115) 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:87.
- 30 In some embodiments, the antigen-binding molecule comprises a VL region according to one of:
- (116) a VL region incorporating the following CDRs:
- 35 LC-CDR1 having the amino acid sequence of SEQ ID NO:65
 LC-CDR2 having the amino acid sequence of SEQ ID NO:66
 LC-CDR3 having the amino acid sequence of SEQ ID NO:67,
 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
 40 another amino acid.
- (117) 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:286,
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
5 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.

(118) a VL region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:10
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.

15 (119) 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:281,
20 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.

(120) a VL region incorporating the following CDRs:
25 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:282,
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
30 another amino acid.

(121) 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
35 LC-CDR3 having the amino acid sequence of SEQ ID NO:283,
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.

40 (122) 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:284,
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.

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(123) 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:285,

10 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.

(124) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:24

15 LC-CDR2 having the amino acid sequence of SEQ ID NO:25

LC-CDR3 having the amino acid sequence of SEQ ID NO:26,

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.

20

(125) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:24

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

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

25 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.

(126) a VL region incorporating the following CDRs:

30 LC-CDR1 having the amino acid sequence of SEQ ID NO:45

LC-CDR2 having the amino acid sequence of SEQ ID NO:46

LC-CDR3 having the amino acid sequence of SEQ ID NO:47,

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.

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(127) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:24

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

40 LC-CDR3 having the amino acid sequence of SEQ ID NO:58,

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.

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

(128) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:70

LC-FR2 having the amino acid sequence of SEQ ID NO:71

LC-FR3 having the amino acid sequence of SEQ ID NO:72

10 LC-FR4 having the amino acid sequence of SEQ ID NO:73,

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.

15 (129) 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:108

LC-FR3 having the amino acid sequence of SEQ ID NO:109

LC-FR4 having the amino acid sequence of SEQ ID NO:90,

20 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.

(130) a VL region incorporating the following FRs:

25 LC-FR1 having the amino acid sequence of SEQ ID NO:89

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:90,

30 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.

(131) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:92

35 LC-FR2 having the amino acid sequence of SEQ ID NO:93

LC-FR3 having the amino acid sequence of SEQ ID NO:15

LC-FR4 having the amino acid sequence of SEQ ID NO:90,

40 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.

(132) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:94

LC-FR2 having the amino acid sequence of SEQ ID NO:93

LC-FR3 having the amino acid sequence of SEQ ID NO:96

LC-FR4 having the amino acid sequence of SEQ ID NO:90,

- 5 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.

(133) a VL region incorporating the following FRs:

- 10 LC-FR1 having the amino acid sequence of SEQ ID NO:97

LC-FR2 having the amino acid sequence of SEQ ID NO:93

LC-FR3 having the amino acid sequence of SEQ ID NO:99

LC-FR4 having the amino acid sequence of SEQ ID NO:90,

- 15 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.

(134) a VL region incorporating the following FRs:

- 20 LC-FR1 having the amino acid sequence of SEQ ID NO:101

LC-FR2 having the amino acid sequence of SEQ ID NO:93

LC-FR3 having the amino acid sequence of SEQ ID NO:102

LC-FR4 having the amino acid sequence of SEQ ID NO:90,

- 25 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.

(135) a VL region incorporating the following FRs:

- 30 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.

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(136) a VL region incorporating the following FRs:

- LC-FR1 having the amino acid sequence of SEQ ID NO:27

LC-FR2 having the amino acid sequence of SEQ ID NO:28

LC-FR3 having the amino acid sequence of SEQ ID NO:29

- 40 LC-FR4 having the amino acid sequence of SEQ ID NO:30,

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.

5 (137) a VL region incorporating the following FRs:

LC-FR1 having the amino acid sequence of SEQ ID NO:27

LC-FR2 having the amino acid sequence of SEQ ID NO:35

LC-FR3 having the amino acid sequence of SEQ ID NO:29

LC-FR4 having the amino acid sequence of SEQ ID NO:30,

10 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.

(138) a VL region incorporating the following FRs:

15 LC-FR1 having the amino acid sequence of SEQ ID NO:48

LC-FR2 having the amino acid sequence of SEQ ID NO:49

LC-FR3 having the amino acid sequence of SEQ ID NO:50

LC-FR4 having the amino acid sequence of SEQ ID NO:30,

20 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.

(139) a VL region incorporating the following FRs:

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

25 LC-FR2 having the amino acid sequence of SEQ ID NO:59

LC-FR3 having the amino acid sequence of SEQ ID NO:60

LC-FR4 having the amino acid sequence of SEQ ID NO:61,

30 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 (116) to (127) above, and the FRs according to any one of (128) to (139) above.

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

(140) a VL region comprising the CDRs according to (116) and the FRs according to (128).

(141) a VL region comprising the CDRs according to (117) and the FRs according to (128).

40 (142) a VL region comprising the CDRs according to (118) and the FRs according to (129).

(143) a VL region comprising the CDRs according to (118) and the FRs according to (130).

- (144) a VL region comprising the CDRs according to (118) and the FRs according to (131).
- (145) a VL region comprising the CDRs according to (118) and the FRs according to (132).
- 5 (146) a VL region comprising the CDRs according to (118) and the FRs according to (133).
- (147) a VL region comprising the CDRs according to (118) and the FRs according to (134).
- 10 (148) a VL region comprising the CDRs according to (118) and the FRs according to (135).
- (149) a VL region comprising the CDRs according to (119) and the FRs according to (129).
- (150) a VL region comprising the CDRs according to (119) and the FRs according to (130).
- 15 (151) a VL region comprising the CDRs according to (119) and the FRs according to (131).
- (152) a VL region comprising the CDRs according to (119) and the FRs according to (132).
- 20 (153) a VL region comprising the CDRs according to (119) and the FRs according to (133).
- (154) a VL region comprising the CDRs according to (119) and the FRs according to (134).
- (155) a VL region comprising the CDRs according to (119) and the FRs according to (135).
- 25 (156) a VL region comprising the CDRs according to (120) and the FRs according to (129).
- (157) a VL region comprising the CDRs according to (120) and the FRs according to (130).
- 30 (158) a VL region comprising the CDRs according to (120) and the FRs according to (131).
- (159) a VL region comprising the CDRs according to (120) and the FRs according to (132).
- (160) a VL region comprising the CDRs according to (120) and the FRs according to (133).
- 35 (161) a VL region comprising the CDRs according to (120) and the FRs according to (134).
- (162) a VL region comprising the CDRs according to (120) and the FRs according to (135).
- 40 (163) a VL region comprising the CDRs according to (121) and the FRs according to (129).
- (164) a VL region comprising the CDRs according to (121) and the FRs according to (130).

- (165) a VL region comprising the CDRs according to (121) and the FRs according to (131).
- (166) a VL region comprising the CDRs according to (121) and the FRs according to (132).
- 5 (167) a VL region comprising the CDRs according to (121) and the FRs according to (133).
- (168) a VL region comprising the CDRs according to (121) and the FRs according to (134).
- 10 (169) a VL region comprising the CDRs according to (121) and the FRs according to (135).
- (170) a VL region comprising the CDRs according to (122) and the FRs according to (129).
- (171) a VL region comprising the CDRs according to (122) and the FRs according to (130).
- 15 (172) a VL region comprising the CDRs according to (122) and the FRs according to (131).
- (173) a VL region comprising the CDRs according to (122) and the FRs according to (132).
- 20 (174) a VL region comprising the CDRs according to (122) and the FRs according to (133).
- (175) a VL region comprising the CDRs according to (122) and the FRs according to (134).
- (176) a VL region comprising the CDRs according to (122) and the FRs according to (135).
- 25 (177) a VL region comprising the CDRs according to (123) and the FRs according to (129).
- (178) a VL region comprising the CDRs according to (123) and the FRs according to (130).
- 30 (179) a VL region comprising the CDRs according to (123) and the FRs according to (131).
- (180) a VL region comprising the CDRs according to (123) and the FRs according to (132).
- (181) a VL region comprising the CDRs according to (123) and the FRs according to (133).
- 35 (182) a VL region comprising the CDRs according to (123) and the FRs according to (134).
- (183) a VL region comprising the CDRs according to (123) and the FRs according to (135).
- 40 (184) a VL region comprising the CDRs according to (124) and the FRs according to (136).
- (185) a VL region comprising the CDRs according to (125) and the FRs according to (137).

(186) a VL region comprising the CDRs according to (126) and the FRs according to (138).

(187) a VL region comprising the CDRs according to (122) and the FRs according to (139).

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

(188) 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:75.

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(189) 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:110.

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(190) 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:88.

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(191) 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:91.

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(192) 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:95.

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(193) 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:98.

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(194) 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:100.

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(195) 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.

(196) 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:251.

- (197) 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:252.
- 5 (198) 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.
- (199) 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:254.
- 10 (200) 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:255.
- 15 (201) 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:256.
- 20 (202) 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:257.
- (203) 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:258.
- 25 (204) 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:259.
- 30 (205) 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:260.
- 35 (206) 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:261.

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- (207) 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:262.
- 5 (208) 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:263.
- (209) 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:264.
- 10 (210) 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:265.
- 15 (211) 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.
- 20 (212) 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:267.
- (213) 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:268.
- 25 (214) 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.
- 30 (215) 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:270.
- 35 (216) 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:271.

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- (217) 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:272.
- 5 (218) 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.
- (219) 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:274.
- 10 (220) 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:275.
- 15 (221) 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.
- 20 (222) 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:277.
- (223) 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.
- 25 (224) 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:279.
- 30 (225) 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:280.
- 35 (226) 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:281.

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(227) 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:34.

- 5 (228) 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:44.

- 10 (229) 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:57.

In some embodiments, the antigen-binding molecule comprises a VH region according to any one of (1) to (115) above, and a VL region according to any one of (116) to (229) above.

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In some embodiments, a VH according according to any one of (73) to (109) comprises an amino acid other than 'D' at the position corresponding to position 54 of SEQ ID NO:1. 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'.

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In some embodiments, a VH according according to any one of (73) to (109) comprises an amino acid other than 'G' at the position corresponding to position 55 of SEQ ID NO:1. 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'.

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In some embodiments, a VL according according to any one of (73) to (109) comprises an amino acid other than 'N' at the position corresponding to position 93 of SEQ ID NO:9. 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'.

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In some embodiments, a VL according according to any one of (73) to (109) comprises an amino acid other than 'G' at the position corresponding to position 94 of SEQ ID NO:9. 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'.

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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),

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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

Amino Acid	Side-chain polarity	Side-chain charge (pH 7.4)
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
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.

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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.

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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).

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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. C κ or C λ). 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).

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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:111 or 116. 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:192 or 193. 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:119 or 194.

5 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:120, 121, 190 or 191. 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:122 or 201.

15 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:112 or 117. 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:195.

20 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:113. 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:196 or 197.

30 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:114 or 189. 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:198 or 199.

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:115 or 118. 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:200.

5 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
10 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%,
15 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:123, 124, 125, 126, 127 or 128. 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%,
20 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:123.

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
25 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
30 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.
35 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
40 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.

- 5 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 humanised antigen-binding molecule (*i.e.* an antigen-binding molecule comprising variable domains derived by humanisation of the variable domains of an antibody from a non-human animal, *e.g.* a mouse) comprising mouse
10 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),
15 in Chapter 8 thereof, in particular section 3 of Chapter 8.

- Humanised antigen-binding molecules can be prepared from mouse antibodies by the process of humanisation, *e.g.* as described in Human Monoclonal Antibodies: Methods and Protocols, Michael
20 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 humanisation are also described *e.g.* in Safdari *et al.*, Biotechnol Genet Eng Rev (2013) 29:175-86.

- 25 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).

- 30 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.

- 35 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.

- 40 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 immune cell surface molecule. In some embodiments, the antigen is a cancer cell antigen. In some embodiments, the antigen is a receptor molecule, e.g. a cell surface receptor. In some embodiments, the antigen is a cell signalling molecule, e.g. a cytokine, chemokine, interferon, interleukin or lymphokine. In some embodiments, the antigen is a growth factor or a hormone.

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 CD3 ϵ)-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 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. IgG₂, F(ab')₂ or CovX-Body; IgG or IgG-like molecules, e.g. IgG, chimeric IgG, $\kappa\lambda$ -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, trivalent dAb.VHH; Non-Ig fusion proteins, e.g. scFv₂-albumin, scDb-albumin, taFv-albumin, taFv-toxin, miniantibody, DNL-Fab₂, DNL-Fab₂-scFv, DNL-Fab₂-IgG-cytokine₂, 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, scFv₄-Ig, scFv₂-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-scFv₂ (tribody), Fab-Fv, Fab-dsFv, Fab-VHH, orthogonal Fab-Fab; non-Ig fusion proteins, e.g. DNL-Fab₃, DNL-Fab₂-scFv, DNL-Fab₂-IgG-cytokine₂; asymmetric IgG or IgG-like molecules, e.g. IgG(kih), IgG(kih) common LC, ZW1 IgG common LC, Biclomics 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*;

10 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),

15 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, scFv₄-IgG, Zyboby; Fc fusions, e.g. Fab-scFv-Fc, scFv₄-Ig; F(ab')₂ fusions, e.g. F(ab')₂-scFv₂; CH1/CL fusion proteins e.g. scFv₂-CH1-hinge/CL; modified IgGs, e.g. DAF (two-in one-IgG), DutaMab, Mab²; and non-Ig fusions, e.g. DNL-Fab₄-IgG. The skilled person is readily able to design and produce multispecific antigen-binding molecules.

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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

25 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

30 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.

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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,

40 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 Fc γ RI 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:113. 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:196 or 197.

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*.

5 **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
10 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.*,
15 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-
20 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
25 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
30 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-
35 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
40 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
 5 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
 10 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
 15 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
 20 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.*
 25 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
 35 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).

40 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 haematopoietic cells, which increases efficient recycling of administered mAb and longer half-life in the plasma.

5 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
10 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
15 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 an reduced level of the relevant effector function as compared to an antigen-binding molecule comprising the corresponding unmodified Fc region.

20 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
25 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.

30 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).

35 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.

40 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
 5 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
 10 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),
 15 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
 20 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–
 25 126. 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,
 30 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
 35 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
 40 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).

- 5 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.

- 10 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.

15

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

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

- 25 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
- 30 CH2 and/or CH3 regions of different polypeptide chains. Suitable modifications are described e.g. in Ha *et al.*, Front. Immunol (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
- 35 formats, as shown in Table 1 of Ha *et al.*, Front. Immunol (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
- 40 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.

5 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.

10 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.

15 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).

20 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.

25 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:

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

40 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

10

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.

15

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

20

25

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 (115); 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 (116) to (229).

30

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:1, 17, 31, 36, 51, 74, 78, 80, 83, 106, 86, 87, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243 or 251.

35

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:221. In some embodiments, the antigen-binding molecule of the present disclosure

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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:219. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence

5 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:241. 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:239. In some

10 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:220. 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

15 of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:240.

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%,

20 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:9, 23, 34, 44, 57, 75, 88, 91, 95, 98, 100, 110, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280 or 287.

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:271. 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%,

30 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:269.

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%,

35 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344,

40 345, 346, 347, 348 or 349.

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:295. In some embodiments, the antigen-binding molecule of the present disclosure

5 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:326. 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%,

10 99% or 100% amino acid sequence identity to SEQ ID NO:315. 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:346. In some

15 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:293. 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

20 identity to SEQ ID NO:324. 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:313. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence

25 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:344. 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:294. In some

30 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:325. 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

35 of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:314. 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:345.

40

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:157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 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, 375, 376, 377, 378, 379 or 380.

5

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

10 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:373.

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

15 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

20 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 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,

25 4D4CVH2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G (as shown in 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 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

30 4D4CVH2.2_D53G/4D4GVL3_N93Q (as shown in 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

35 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

40 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 B). 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
5 from 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G,
4D4CVH2_D53G/4D4GVL3_N93Q and 4D4CVH2.2_D53G/4D4GVL3_N93Q (as shown in 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%,
10 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.

15 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 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
20 (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 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,
25 4D4CVH2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G (as shown in 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 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 C).

30 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
35 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.

40 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.

- 5 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:295, 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%,
10 99% or 100% amino acid sequence identity to SEQ ID NO:370. 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:326, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of
15 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: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of
20 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:315, 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:370. In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an
25 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:346, 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:370.

- 30 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:293, and (ii) a polypeptide comprising or consisting of an amino acid sequence
35 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:373. 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:324, and (ii) a
40 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:373.

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:313, 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:373. 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:344, 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:373.

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:294, 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:370. 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:325, 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:370.

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:314, 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:370. 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:345, 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:370.

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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:

- 5 binds to gp130 (e.g. human gp130, mouse gp130, rat gp130 and/or non-human primate gp130);
- binds to gp130-expressing cells;
- inhibits signalling mediated by a receptor comprising gp130;
- inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α ;
- inhibits signalling mediated by a cytokine that binds to a receptor comprising gp130;
- 10 inhibits IL-6- and/or IL-11-mediated signalling;
- does not inhibit signalling mediated by gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and/or gp130:IL-12R β 2;
- does not inhibit OSM-, LIF-, CNTF-, CT-1-, CLC-, IL-27- and/or IL-35-mediated signalling;
- reduces inflammation and/or fibrosis;
- 15 reduces the pathology of a disease/condition characterised by inflammation and/or fibrosis; and/or
- increases killing of cells expressing gp130.

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

20 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.

25 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

30 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

35 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 'EC₅₀'. By way of illustration, the EC₅₀ 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.

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Depending on the property, the EC₅₀ may also be referred to as the 'half-maximal inhibitory concentration' or 'IC₅₀', this being the concentration of the agent at which 50% of the maximal level of inhibition of a given property is observed.

- 5 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 gp130. In some embodiments, the antigen-binding molecule binds to canine gp130. In some embodiments, the antigen-binding molecule binds to human gp130 and mouse gp130. In some embodiments, the antigen-binding molecule binds to human gp130 and rat gp130. In some embodiments, the antigen-binding molecule binds to human gp130, mouse gp130 and rat gp130.

- 15 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.

- 20 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 radiolabeled 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.

- 30 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.* 0.1×10^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.

- 35 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.

- 40 In some embodiments, the antigen-binding molecule described herein binds to gp130 with an affinity in the micromolar range, *i.e.* $K_D = 9.9 \times 10^{-4}$ to 1×10^{-6} M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with sub-micromolar affinity, *i.e.* $K_D < 1 \times 10^{-6}$ M. In some embodiments, the antigen-binding molecule described herein binds to gp130 with an affinity in the

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

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of 10 μ M or less, preferably one of $\leq 5 \mu$ M, $\leq 2 \mu$ M, $\leq 1 \mu$ M, ≤ 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 as described in Example 4 herein). 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 as described in Example 4 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 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 4 or 25 herein).

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with an EC_{50} of 10 μ M or less, preferably one of $\leq 5 \mu$ M, $\leq 2 \mu$ M, $\leq 1 \mu$ M, ≤ 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:134. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:134.

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In some embodiments, the antigen-binding molecule of the present disclosure does not bind to the cytokine-binding module of gp130. In some embodiments, the antigen-binding molecule does not bind to the region of gp130 shown in SEQ ID NO:144. In some embodiments, the antigen-binding molecule does not contact the region of gp130 shown in SEQ ID NO:144. 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:144. In some embodiments, the antigen-binding molecule does not bind to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:144.

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In some embodiments, the antigen-binding molecule of the present disclosure binds to membrane-proximal region of gp130. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:388. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:388. 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:388. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:388.

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In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:169, SEQ ID NO:170 and/or SEQ ID NO:171. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:169, SEQ ID NO:170 and/or 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:169, SEQ ID NO:170 and/or SEQ ID NO:171. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:169, SEQ ID NO:170 and/or SEQ ID NO:171. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:169, SEQ ID NO:170 and/or 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 or consists of the amino acid sequence shown in SEQ ID NO:172. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:172.

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In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:173 and/or SEQ ID NO:174. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:173 and/or SEQ ID NO:174. 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 and/or SEQ ID NO:174. In some embodiments, the epitope of the antigen-binding molecule comprises or

consists of the amino acid sequence shown in SEQ ID NO:173 and/or SEQ ID NO:174. 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 and/or SEQ ID NO:174. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:175. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:175. 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:175. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:175. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:175.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:176, SEQ ID NO:177 and/or SEQ ID NO:178. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:176, SEQ ID NO:177 and/or SEQ ID NO:178. 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:176, SEQ ID NO:177 and/or SEQ ID NO:178. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:176, SEQ ID NO:177 and/or SEQ ID NO:178. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:176, SEQ ID NO:177 and/or SEQ ID NO:178. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:179. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:179. 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:179. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:179. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:179.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:382 and/or SEQ ID NO:385. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:382 and/or SEQ ID NO:385. 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:180, SEQ ID NO:181, SEQ ID NO:382 and/or SEQ ID NO:385. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:382 and/or SEQ ID NO:385. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:382 and/or SEQ ID NO:385. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:182. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:182. 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:182. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:182. In some embodiments, the antigen-binding molecule

- binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:182. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:386. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:386. 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:386. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:386. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:386.
- 10 In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:381 and/or SEQ ID NO:382. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:381 and/or SEQ ID NO:382. 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:183, SEQ ID NO:184, SEQ ID NO:381 and/or SEQ ID NO:382. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:381 and/or SEQ ID NO:382. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:381 and/or SEQ ID NO:382. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:185. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:185. 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:185. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:185. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:185. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:383. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:383. 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:383. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:383. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:383. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:384. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:384. 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:384. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:384. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:384.
- 40 In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:186 and/or SEQ ID NO:187. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:186 and/or SEQ ID NO:187. 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:186 and/or SEQ ID NO:187. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:186 and/or SEQ ID NO:187. In some
5 embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:186 and/or SEQ ID NO:187. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:188. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:188. 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:188. In some embodiments, the epitope of the antigen-binding molecule comprises
10 or consists of the amino acid sequence shown in SEQ ID NO:188. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:188.

The ability of an antigen-binding molecule to bind to a given peptide/polypeptide can be analysed by
15 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.
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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)
25 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
30 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
35 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.

40 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.

5 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
10 phosphorylated/activated/expressed as a consequence of signalling through 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
15 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-6R α may comprise contacting cells expressing gp130:IL-6R α 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-
20 mediated signalling and/or the ability of an antigen-binding molecule to inhibit signalling mediated by gp130:IL-11R α may comprise contacting cells expressing gp130:IL-11R α 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
25 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
30 (particularly signalling mediated by gp130:IL-6R α in response to stimulation with IL-6, and signalling mediated by gp130:IL-11R α in response to stimulation with IL-11) is analysed by evaluating phosphorylation of STAT3 or ERK1/2 by western blot (see in particular Example 11).

The level of gp130-mediated signalling can also be evaluated by analysing one or more correlates of
35 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/
40 profibrotic/profibroinflammatory factor. By way of illustration, in the experimental examples of the present disclosure, gp130-mediated signalling (particularly signalling mediated by gp130:IL-11R α in response to stimulation with IL-11) is analysed by evaluating the expression of α SMA 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, in the experimental examples of the present disclosure, gp130-mediated signalling is 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 is capable of inhibiting 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 IL-6-mediated signalling and inhibits IL-11-mediated signalling.

In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α . In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-11R α . In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α , and inhibits signalling mediated by gp130:IL-11R α .

In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α , and inhibits signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α .

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α 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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α).

- In some embodiments, the antigen-binding molecule is capable of inhibiting more than 25%, e.g. $\geq 30\%$, $\geq 35\%$, $\geq 40\%$, $\geq 45\%$, $\geq 50\%$, $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$ or $\geq 99\%$ of the IL-6-mediated signalling/signalling mediated by gp130:IL-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α 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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α), e.g. as determined in an assay performed as described in Examples 1 and 11 herein.
- 10 In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α with an IC₅₀ of less than 1 μ M, 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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α with an IC₅₀ 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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α with an IC₅₀ of less than 15 μ g/ml, preferably one of ≤ 11 μ g/ml, ≤ 10 μ g/ml, ≤ 9 μ g/ml, ≤ 8 μ g/ml, ≤ 7 μ g/ml, ≤ 6 μ g/ml, ≤ 5 μ g/ml, ≤ 4 μ g/ml, ≤ 3 μ g/ml, ≤ 2 μ g/ml, ≤ 1 μ g/ml, ≤ 0.9 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.7 μ g/ml, ≤ 0.6 μ g/ml, ≤ 0.5 μ g/ml, ≤ 0.4 μ g/ml, ≤ 0.3 μ g/ml, ≤ 0.2 μ g/ml, ≤ 0.1 μ g/ml, ≤ 0.09 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.07 μ g/ml, ≤ 0.06 μ g/ml, or ≤ 0.05 μ g/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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α with an IC₅₀ of less than 10 μ g/ml, preferably one of ≤ 5 μ g/ml, ≤ 4 μ g/ml, ≤ 3 μ g/ml, ≤ 2 μ g/ml, ≤ 1 μ g/ml, ≤ 0.9 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.7 μ g/ml, ≤ 0.6 μ g/ml or ≤ 0.5 μ g/ml, e.g. as determined by analysis as described in Example 2 or 34 herein.

- In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α 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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α).

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In some embodiments, the antigen-binding molecule is capable of inhibiting more than 50%, *e.g.* $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$ or $\geq 99\%$ of the IL-11-mediated signalling/signalling mediated by gp130:IL-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α 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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α), *e.g.* as determined in an assay performed as described in Examples 1 and 11 herein.

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In some embodiments, the antigen-binding molecule is capable of inhibiting IL-6-mediated signalling/signalling mediated by gp130:IL-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α 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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α 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).

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In some embodiments, the antigen-binding molecule is capable of inhibiting more than 25%, *e.g.* $\geq 30\%$, $\geq 35\%$, $\geq 40\%$, $\geq 45\%$, $\geq 50\%$, $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$ or $\geq 99\%$ of the IL-6-mediated signalling/signalling mediated by gp130:IL-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α 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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α), *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.* $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$ or $\geq 99\%$ of the IL-11-mediated signalling/signalling mediated by gp130:IL-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α 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-11R α /signalling mediated by binding

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of IL-11 to cells expressing gp130:IL-11R α), e.g. as determined in an assay performed as described in Examples 1 and 11 herein.

In some embodiments, the antigen-binding molecule is capable of inhibiting IL-11-mediated signalling/signalling mediated by gp130:IL-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α with an IC₅₀ of less than 1 μ M, 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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α with an IC₅₀ 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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α with an IC₅₀ of less than 1 μ g/ml, preferably one of ≤ 0.9 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.7 μ g/ml, ≤ 0.6 μ g/ml, ≤ 0.5 μ g/ml, ≤ 0.4 μ g/ml, ≤ 0.3 μ g/ml, ≤ 0.2 μ g/ml, ≤ 0.1 μ g/ml, ≤ 0.09 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.07 μ g/ml, ≤ 0.06 μ g/ml, or ≤ 0.05 μ g/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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α with an IC₅₀ of less than 10 μ g/ml, preferably one of ≤ 5 μ g/ml, ≤ 4 μ g/ml, ≤ 3 μ g/ml, ≤ 2 μ g/ml, ≤ 1 μ g/ml, ≤ 0.9 μ g/ml, ≤ 0.8 μ g/ml, ≤ 0.7 μ g/ml, ≤ 0.6 μ g/ml or ≤ 0.5 μ g/ml, e.g. as determined by analysis as described in Example 2 or 34 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 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:OSMR β . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:LIFR β . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:LIFR β :CNTFR α . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:IL-27R α . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:IL-12R β 2. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α , and does not inhibit signalling mediated by gp130:IL-27R α , and does not inhibit signalling mediated by gp130:IL-12R β 2. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by a gp130-containing polypeptide complex other than gp130:IL-6R α or gp130:IL-11R α .

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:OSMR β . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of OSM, LIF or CT-1 to cells expressing gp130:LIFR β . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of CNTF or CLC to cells expressing gp130:LIFR β :CNTFR α . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R α . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2. In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of OSM to cells expressing gp130:OSMR β , and does not inhibit signalling mediated by binding of OSM, LIF or CT-1 to cells expressing gp130:LIFR β , and does not inhibit signalling mediated by binding of CNTF or CLC to cells expressing gp130:LIFR β :CNTFR α . In some embodiments, the antigen-binding molecule does not inhibit signalling mediated by binding of OSM to cells expressing gp130:OSMR β , and does not inhibit signalling mediated by binding of OSM, LIF or CT-1 to cells expressing gp130:LIFR β , and does not inhibit signalling mediated by binding of CNTF or CLC to cells expressing gp130:LIFR β :CNTFR α , and does not inhibit signalling mediated by binding of IL-27 to cells expressing gp130:LIFR β :IL-27R α , and does not inhibit signalling mediated by binding of IL-35 to cells expressing gp130:LIFR β :IL-12R β 2.

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 μ M, preferably one of ≥ 5 μ M, ≥ 10 μ M, ≥ 20 μ M, ≥ 50 μ M, ≥ 100 μ M, ≥ 500 μ M 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. $\leq 15\%$, $\leq 14\%$, $\leq 13\%$, $\leq 12\%$, $\leq 11\%$, $\leq 10\%$, $\leq 9\%$, $\leq 8\%$, $\leq 7\%$, $\leq 6\%$, $\leq 5\%$, $\leq 4\%$, $\leq 3\%$, $\leq 2\%$ or $\leq 1\%$ of the LIF-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β 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:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β), e.g. as determined in an assay performed as described in Examples 1 and 11 herein.

In some embodiments, the antigen-binding molecule inhibits less than 20%, e.g. $\leq 15\%$, $\leq 14\%$, $\leq 13\%$, $\leq 12\%$, $\leq 11\%$, $\leq 10\%$, $\leq 9\%$, $\leq 8\%$, $\leq 7\%$, $\leq 6\%$, $\leq 5\%$, $\leq 4\%$, $\leq 3\%$, $\leq 2\%$ or $\leq 1\%$ of the OSM-mediated signalling/signalling mediated by gp130:OSMR β or gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β or gp130:LIFR β 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:OSMR β or gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β or gp130:LIFR β), e.g. as determined in an assay performed as described in Examples 1 and 11 herein.

In some embodiments, the antigen-binding molecule: (i) is capable of inhibiting more than 25%, e.g. $\geq 30\%$, $\geq 35\%$, $\geq 40\%$, $\geq 45\%$, $\geq 50\%$, $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$,

≥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; (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 1 and 11 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 1 and 11 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 1 and 11 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 1 and 12 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:LIFR β :CNTFR α /signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR α), e.g. as determined in an assay performed as described in Examples 1 and 12 herein.

- 5 In some embodiments, the antigen-binding molecule: (i) is capable of inhibiting more than 25%, e.g. $\geq 30\%$, $\geq 35\%$, $\geq 40\%$, $\geq 45\%$, $\geq 50\%$, $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$ or $\geq 99\%$ of the IL-6-mediated signalling/signalling mediated by gp130:IL-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α 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-6R α /signalling mediated by binding of IL-6 to cells expressing gp130:IL-6R α), e.g. as determined in an assay performed as described in Examples 1 and 11 herein; (ii) is capable of inhibiting more than 50%, e.g. $\geq 55\%$, $\geq 60\%$, $\geq 65\%$, $\geq 70\%$, $\geq 75\%$, $\geq 80\%$, $\geq 85\%$, $\geq 90\%$, $\geq 95\%$, $\geq 96\%$, $\geq 97\%$, $\geq 98\%$ or $\geq 99\%$ of the IL-11-mediated signalling/signalling mediated by gp130:IL-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α 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-11R α /signalling mediated by binding of IL-11 to cells expressing gp130:IL-11R α), e.g. as determined in an assay performed as described in Examples 1 and 11 herein; (iii) inhibits less than 20%, e.g. $\leq 15\%$, $\leq 14\%$, $\leq 13\%$, $\leq 12\%$, $\leq 11\%$, $\leq 10\%$, $\leq 9\%$, $\leq 8\%$, $\leq 7\%$, $\leq 6\%$, $\leq 5\%$, $\leq 4\%$, $\leq 3\%$, $\leq 2\%$ or $\leq 1\%$ of the LIF-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β 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:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β), e.g. as determined in an assay performed as described in Examples 1 and 11 herein; (iv) inhibits less than 20%, e.g. $\leq 15\%$, $\leq 14\%$, $\leq 13\%$, $\leq 12\%$, $\leq 11\%$, $\leq 10\%$, $\leq 9\%$, $\leq 8\%$, $\leq 7\%$, $\leq 6\%$, $\leq 5\%$, $\leq 4\%$, $\leq 3\%$, $\leq 2\%$ or $\leq 1\%$ of the OSM-mediated signalling/signalling mediated by gp130:OSMR β or gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β or gp130:LIFR β 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:OSMR β or gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β or gp130:LIFR β), e.g. as determined in an assay performed as described in Examples 1 and 11 herein; (v) inhibits less than 20%, e.g. $\leq 15\%$, $\leq 14\%$, $\leq 13\%$, $\leq 12\%$, $\leq 11\%$, $\leq 10\%$, $\leq 9\%$, $\leq 8\%$, $\leq 7\%$, $\leq 6\%$, $\leq 5\%$, $\leq 4\%$, $\leq 3\%$, $\leq 2\%$ or $\leq 1\%$ of the CT-1-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β 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:LIFR β /signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β), e.g. as determined in an assay performed as described in Examples 1 and 12 herein, and (vi) inhibits less than 20%, e.g. $\leq 15\%$, $\leq 14\%$, $\leq 13\%$, $\leq 12\%$, $\leq 11\%$, $\leq 10\%$, $\leq 9\%$, $\leq 8\%$, $\leq 7\%$, $\leq 6\%$, $\leq 5\%$, $\leq 4\%$, $\leq 3\%$, $\leq 2\%$ or $\leq 1\%$ of the CNTF-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR α

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:LIFR β :CNTFR α /signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR α), e.g. as determined in an assay performed as described in Examples 1 and 12 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 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, TGF β 1, etc.) in the presence of the antigen-binding molecule, 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 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 α SMA and MMP2.

Analysis *in vivo* of the ability of, and extent to which, a given antigen-binding molecule 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 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*, *Tnfa* and *Il1 β*), 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 or 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 ^{51}Cr 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.

- 5 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).
- 10 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,
- 15 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,
- 20 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).

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Linkers and additional sequences

The antigen-binding molecules and polypeptides of the present disclosure may additionally comprise further amino acids or sequences of amino acids.

- 35 The antigen-binding molecules and polypeptides of the present disclosure may comprise one or more linker sequences between sequences of amino acids. For example, a linker sequence may be provided between a VH sequence and a VL sequence, providing linkage between the VH and VL (e.g. as in an scFv molecule).
- 40 Linker sequences are known to the skilled person, and are described, for example in Chen *et al.*, Adv Drug Deliv Rev (2013) 65(10): 1357-1369, which is hereby incorporated by reference in its entirety. In some embodiments, a linker sequence may be a flexible linker sequence. Flexible linker sequences allow

for relative movement of the amino acid sequences which are linked by the linker sequence. Flexible linkers are known to the skilled person, and several are identified in Chen *et al.*, Adv Drug Deliv Rev (2013) 65(10): 1357-1369. Flexible linker sequences often comprise high proportions of glycine and/or serine residues.

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In some embodiments, the linker sequence comprises at least one glycine residue and/or at least one serine residue. In some embodiments, the linker sequence comprises or consists of glycine and serine residues. In some embodiments, the linker sequence has the structure: (GxS)_n or (GxS)_nG_m; wherein G = glycine, S = serine, x = 3 or 4, n = 2, 3, 4, 5 or 6, and m = 0, 1, 2 or 3. In some embodiments, the linker sequence comprises one or more (e.g. 1, 2, 3, 4, 5 or 6) copies (e.g. in tandem) of the sequence motif G₄S. In some embodiments, the linker sequence comprises or consists of (G₄S)₄ or (G₄S)₆. In some embodiments, the linker sequence has a length of 1-2, 1-3, 1-4, 1-5, 1-10, 1-15, 1-20, 1-25, or 1-30 amino acids.

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The antigen-binding molecules and polypeptides of the present disclosure may comprise amino acid sequence(s) to facilitate expression, folding, trafficking, processing, purification or detection of the antigen-binding molecule/polypeptide. For example, antigen-binding molecules and polypeptides of the present disclosure may additionally comprise a sequence of amino acids forming a detectable moiety, e.g. as described hereinbelow.

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The antigen-binding molecules and polypeptides of the present disclosure may additionally comprise a signal peptide (also known as a leader sequence or signal sequence). Signal peptides normally consist of a sequence of 5-30 hydrophobic amino acids, which form a single alpha helix. Secreted proteins and proteins expressed at the cell surface often comprise signal peptides. Signal peptides are known for many proteins, and are recorded in databases such as GenBank, UniProt and Ensembl, and/or can be identified/predicted e.g. using amino acid sequence analysis tools such as SignalP (Petersen *et al.*, 2011 Nature Methods 8: 785-786) or Signal-BLAST (Frank and Sippl, 2008 Bioinformatics 24: 2172-2176).

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The signal peptide may be present at the N-terminus of the antigen-binding molecule/polypeptide, and may be present in the newly synthesised antigen-binding molecule/polypeptide. The signal peptide provides for efficient trafficking of the antigen-binding molecule/polypeptide. Signal peptides are often removed by cleavage, and thus are not comprised in the mature antigen-binding molecule/polypeptide.

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Signal peptides are known for many proteins, and are recorded in databases such as GenBank, UniProt, Swiss-Prot, TrEMBL, Protein Information Resource, Protein Data Bank, Ensembl, and InterPro, and/or can be identified/predicted e.g. using amino acid sequence analysis tools such as SignalP (Petersen *et al.*, 2011 Nature Methods 8: 785-786) or Signal-BLAST (Frank and Sippl, 2008 Bioinformatics 24: 2172-2176).

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Labels and conjugates

In some embodiments, the antigen-binding molecule or polypeptide of the present disclosure comprises a detectable moiety.

In some embodiments, a detectable moiety is a fluorescent label, phosphorescent label, luminescent label, immuno-detectable label (e.g. an epitope tag), radiolabel, chemical, nucleic acid or enzymatic label. The antigen-binding molecule or polypeptide may be covalently or non-covalently labelled with the detectable moiety.

Fluorescent labels include e.g. fluorescein, rhodamine, allophycocyanin, eosine and NDB, green fluorescent protein (GFP), chelates of rare earths such as europium (Eu), terbium (Tb) and samarium (Sm), tetramethyl rhodamine, Texas Red, 4-methyl umbelliferone, 7-amino-4-methyl coumarin, Cy3, and Cy5. Radiolabels include radioisotopes such as Hydrogen³, Sulfur³⁵, Carbon¹⁴, Phosphorus³², Iodine¹²³, Iodine¹²⁵, Iodine¹²⁶, Iodine¹³¹, Iodine¹³³, Bromine⁷⁷, Technetium^{99m}, Indium¹¹¹, Indium^{113m}, Gallium⁶⁷, Gallium⁶⁸, Ruthenium⁹⁵, Ruthenium⁹⁷, Ruthenium¹⁰³, Ruthenium¹⁰⁵, Mercury²⁰⁷, Mercury²⁰³, Rhenium^{99m}, Rhenium¹⁰¹, Rhenium¹⁰⁵, Scandium⁴⁷, Tellurium^{121m}, Tellurium^{122m}, Tellurium^{125m}, Thulium¹⁶⁵, Thulium¹⁶⁷, Thulium¹⁶⁸, Copper⁶⁷, Fluorine¹⁸, Yttrium⁹⁰, Palladium¹⁰⁰, Bismuth²¹⁷ and Antimony²¹¹. Luminescent labels include as radioluminescent, chemiluminescent (e.g. acridinium ester, luminol, isoluminol) and bioluminescent labels. Immuno-detectable labels include haptens, peptides/polypeptides, antibodies, receptors and ligands such as biotin, avidin, streptavidin or digoxigenin. Nucleic acid labels include aptamers.

In some embodiments, the antigen-binding molecule/polypeptide comprises an epitope tag, e.g. a His, (e.g. 6XHis), FLAG, c-Myc, StrepTag, haemagglutinin, E, calmodulin-binding protein (CBP), glutathione-S-transferase (GST), maltose-binding protein (MBP), thioredoxin, S-peptide, T7 peptide, SH2 domain, avidin, streptavidin, and haptens (e.g. biotin, digoxigenin, dinitrophenol), optionally at the N- or C-terminus of the antigen-binding molecule/polypeptide.

In some embodiments, the antigen-binding molecule/polypeptide comprises a moiety having a detectable activity, e.g. an enzymatic moiety. Enzymatic moieties include e.g. luciferases, glucose oxidases, galactosidases (e.g. beta-galactosidase), glucuronidases, phosphatases (e.g. alkaline phosphatase), peroxidases (e.g. horseradish peroxidase) and cholinesterases.

In some embodiments, the antigen-binding molecule or polypeptide of the present disclosure comprises a chemical moiety. In some embodiments, the antigen-binding molecule/polypeptide of the present disclosure is conjugated to a chemical moiety.

The chemical moiety may be a moiety for providing a therapeutic effect, i.e. a drug moiety. A drug moiety may be a small molecule (e.g. a low molecular weight (< 1000 daltons, typically between ~300-700 daltons) organic compound). Drug moieties are described e.g. in Parslow *et al.*, Biomedicines. 2016 Sep; 4(3):14 (hereby incorporated by reference in its entirety). In some embodiments, a drug moiety may be or comprise a cytotoxic agent. In some embodiments, a drug moiety may be or comprise a chemotherapeutic agent. Drug moieties include e.g. calicheamicin, DM1, DM4, monomethylauristatin E (MMAE), monomethylauristatin F (MMAF), SN-38, doxorubicin, duocarmycin, D6.5 and PBD.

Nucleic acids and vectors

The present disclosure provides a nucleic acid, or a plurality of nucleic acids, encoding an antigen-binding molecule or polypeptide according to the present disclosure. In some embodiments, the nucleic acid(s) comprise or consist of DNA and/or RNA.

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An antigen-binding molecule or polypeptide according to the present disclosure may be produced within a cell by translation of RNA encoding the polypeptide(s). An antigen-binding molecule or polypeptide according to the present disclosure may be produced within a cell by transcription from nucleic acid encoding the polypeptide(s), and subsequent translation of the transcribed RNA.

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In some embodiments, the nucleic acid(s) may be, or may be comprised/contained in, a vector, or a plurality of vectors. A 'vector' as used herein is a nucleic acid molecule used as a vehicle to transfer exogenous nucleic acid into a cell.

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Accordingly, the present disclosure also provides a vector, or plurality of vectors, comprising the nucleic acid or plurality of nucleic acids according to the present disclosure. The vector may facilitate delivery of the nucleic acid(s) encoding a polypeptide according to the present disclosure to a cell. The vector may be an expression vector comprising elements required for expressing a polypeptide according to the present disclosure. The vector may comprise elements facilitating integration of the nucleic acid(s) into the genomic DNA of cell into which the vector is introduced.

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Nucleic acids and vectors according to the present disclosure may be provided in purified or isolated form, *i.e.* from other nucleic acid, or naturally-occurring biological material.

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A vector may be a vector for expression of the nucleic acid in the cell (*i.e.* an expression vector). Such vectors may include a promoter sequence operably linked to a nucleotide sequence encoding an antigen-binding molecule or polypeptide according to the present disclosure. A vector may also include a termination codon (*i.e.* 3' in the nucleotide sequence of the vector to the nucleotide sequence encoding the polypeptide(s)) and expression enhancers. Any suitable vectors, promoters, enhancers and termination codons known in the art may be used to express a peptide or polypeptide from a vector according to the present disclosure.

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The term 'operably linked' may include the situation where nucleic acid encoding a polypeptide according to the present disclosure and regulatory nucleic acid sequence(s) (*e.g.* a promoter and/or enhancers) are covalently linked in such a way as to place the expression of the nucleic acid encoding a polypeptide under the influence or control of the regulatory nucleic acid sequence(s) (thereby forming an expression cassette). Thus, a regulatory sequence is operably linked to the selected nucleic acid sequence if the regulatory sequence is capable of effecting transcription of the nucleic acid sequence. The resulting transcript(s) may then be translated into the desired polypeptide(s).

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Vectors contemplated in connection with the present disclosure include DNA vectors, RNA vectors, plasmids (*e.g.* conjugative plasmids (*e.g.* F plasmids), non-conjugative plasmids, R plasmids, col

plasmids, episomes), viral vectors (e.g. retroviral vectors, e.g. gammaretroviral vectors (e.g. murine Leukemia virus (MLV)-derived vectors, e.g. SFG vector), lentiviral vectors, adenovirus vectors, adeno-associated virus vectors, vaccinia virus vectors and herpesvirus vectors), transposon-based vectors, and artificial chromosomes (e.g. yeast artificial chromosomes), e.g. as described in Maus *et al.*, Annu Rev Immunol (2014) 32:189-225 and Morgan and Boyerinas, Biomedicines (2016) 4:9, which are both hereby incorporated by reference in their entirety. In some embodiments, a vector according to the present disclosure is a lentiviral vector.

In some embodiments, the vector may be a eukaryotic vector, *i.e.* a vector comprising the elements necessary for expression of protein from the vector in a eukaryotic cell. In some embodiments, the vector may be a mammalian vector, e.g. comprising a cytomegalovirus (CMV) or SV40 promoter to drive protein expression.

Constituent polypeptides of an antigen-binding molecule according to the present disclosure may be encoded by different nucleic acids of the plurality of nucleic acids, or by different vectors of the plurality of vectors.

Producing the antigen-binding molecules and polypeptides

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 cases, the antigen-binding molecules of the present disclosure are comprised of more than one polypeptide chain. In such cases, production of the antigen-binding molecule may comprise transcription and translation of more than one polypeptide, and subsequent association of the polypeptide chains to form the antigen-binding molecule.

For recombinant production according to the present disclosure, any cell suitable for the expression of polypeptides may be used. The cell may be a prokaryote or eukaryote. In some embodiments, the cell is

a prokaryotic cell, such as a cell of archaea or bacteria. In some embodiments, the bacteria may be Gram-negative bacteria such as bacteria of the family Enterobacteriaceae, for example *Escherichia coli*. In some embodiments, the cell is a eukaryotic cell such as a yeast cell, a plant cell, insect cell or a mammalian cell, e.g. a cell described hereinabove.

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In some cases, the cell is not a prokaryotic cell because some prokaryotic cells do not allow for the same folding or post-translational modifications as eukaryotic cells. In addition, very high expression levels are possible in eukaryotes and proteins can be easier to purify from eukaryotes using appropriate tags. Specific plasmids may also be utilised which enhance secretion of the protein into the media.

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In some embodiments polypeptides may be prepared by cell-free-protein synthesis (CFPS), e.g. according to a system described in Zemella *et al.* Chembiochem (2015) 16(17): 2420-2431, which is hereby incorporated by reference in its entirety.

15 Production may involve culture or fermentation of a eukaryotic cell modified to express the polypeptide(s) of interest. The culture or fermentation may be performed in a bioreactor provided with an appropriate supply of nutrients, air/oxygen and/or growth factors. Secreted proteins can be collected by partitioning culture media/fermentation broth from the cells, extracting the protein content, and separating individual proteins to isolate secreted polypeptide(s). Culture, fermentation and separation techniques are well
20 known to those of skill in the art, and are described, for example, in Green and Sambrook, Molecular Cloning: A Laboratory Manual (4th Edition; incorporated by reference herein above).

Bioreactors include one or more vessels in which cells may be cultured. Culture in the bioreactor may occur continuously, with a continuous flow of reactants into, and a continuous flow of cultured cells from,
25 the reactor. Alternatively, the culture may occur in batches. The bioreactor monitors and controls environmental conditions such as pH, oxygen, flow rates into and out of, and agitation within the vessel such that optimum conditions are provided for the cells being cultured.

Following culturing the cells that express the polypeptide(s), the polypeptide(s) of interest may be
30 isolated. Any suitable method for separating proteins from cells known in the art may be used. In order to isolate the polypeptide, it may be necessary to separate the cells from nutrient medium. If the polypeptide(s) are secreted from the cells, the cells may be separated by centrifugation from the culture media that contains the secreted polypeptide(s) of interest. If the polypeptide(s) of interest collect within the cell, protein isolation may comprise centrifugation to separate cells from cell culture medium,
35 treatment of the cell pellet with a lysis buffer, and cell disruption e.g. by sonification, rapid freeze-thaw or osmotic lysis.

It may then be desirable to isolate the polypeptide(s) of interest from the supernatant or culture medium, which may contain other protein and non-protein components. A common approach to separating protein
40 components from a supernatant or culture medium is by precipitation. Proteins of different solubilities are precipitated at different concentrations of precipitating agent such as ammonium sulfate. For example, at low concentrations of precipitating agent, water soluble proteins are extracted. Thus, by adding different

increasing concentrations of precipitating agent, proteins of different solubilities may be distinguished. Dialysis may be subsequently used to remove ammonium sulfate from the separated proteins.

Other methods for distinguishing different proteins are known in the art, for example ion exchange chromatography and size chromatography. These may be used as an alternative to precipitation or may be performed subsequently to precipitation.

Once the polypeptide(s) of interest have been isolated from culture it may be desired or necessary to concentrate the polypeptide(s). A number of methods for concentrating proteins are known in the art, such as ultrafiltration or lyophilisation.

Cells comprising/expressing the antigen-binding molecules and polypeptides

The present disclosure also provides a cell comprising or expressing an antigen-binding molecule or polypeptide according to the present disclosure. Also provided is a cell comprising or expressing a nucleic acid, a plurality of nucleic acids, a vector or a plurality of vectors according to the present disclosure.

It will be appreciated that where cells are referred to herein in the singular (*i.e.* 'a/the cell'), pluralities/populations of such cells are also contemplated.

The cell may be a eukaryotic cell, *e.g.* a mammalian cell. The mammal may be a primate (rhesus, cynomolgous, non-human primate or human) or a non-human mammal (*e.g.* rabbit, guinea pig, rat, mouse or other rodent (including any animal in the order Rodentia), cat, dog, pig, sheep, goat, cattle (including cows, *e.g.* dairy cows, or any animal in the order Bos), horse (including any animal in the order Equidae), donkey, and non-human primate).

In some embodiments, the cell is, or is derived from, a cell type commonly used for the expression of polypeptides for use in therapy in humans. Exemplary cells are described *e.g.* in Kunert and Reinhart, Appl Microbiol Biotechnol. (2016) 100:3451–3461 (hereby incorporated by reference in its entirety), and include *e.g.* CHO, HEK 293, PER.C6, NS0 and BHK cells. In preferred embodiments, the cell is, or is derived from, a CHO cell.

The present disclosure also provides a method for producing a cell comprising a nucleic acid(s) or vector(s) according to the present disclosure, comprising introducing a nucleic acid, a plurality of nucleic acids, a vector or a plurality of vectors according to the present disclosure into a cell. In some embodiments, introducing an isolated nucleic acid(s) or vector(s) according to the present disclosure into a cell comprises transformation, transfection, electroporation or transduction (*e.g.* retroviral transduction).

The present disclosure also provides a method for producing a cell expressing/comprising an antigen-binding molecule or polypeptide according to the present disclosure, comprising introducing a nucleic acid, a plurality of nucleic acids, a vector or a plurality of vectors according to the present disclosure in a cell. In some embodiments, the methods additionally comprise culturing the cell under conditions suitable

for expression of the nucleic acid(s) or vector(s) by the cell. In some embodiments, the methods are performed *in vitro*.

The present disclosure also provides cells obtained or obtainable by the methods according to the present disclosure.

Compositions

The present disclosure also provides compositions comprising the antigen-binding molecules, polypeptides, nucleic acids, expression vectors and/or cells described herein.

The antigen-binding molecules, polypeptides, nucleic acids, expression vectors and cells described herein may be formulated as pharmaceutical compositions or medicaments for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant. Thus, the present disclosure also provides a pharmaceutical composition/medicament comprising an antigen-binding molecule, polypeptide, nucleic acid/plurality, expression vector/plurality or cell described herein.

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), stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents or colouring 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, stabiliser, solubiliser, surfactant, masking agent, colouring agent, flavouring 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, stabilisers, solubilisers, surfactants, masking agents, colouring agents, flavouring 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.

Compositions may be formulated for topical, parenteral, systemic, intracavitary, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intraconjunctival, intratumoral, subcutaneous, intradermal, intrathecal, oral or transdermal routes of administration. In some embodiments, a pharmaceutical

composition/medicament may be formulated for administration by injection or infusion, or administration by ingestion.

Suitable formulations may comprise the relevant article in a sterile or isotonic medium. Medicaments and pharmaceutical compositions may be formulated in fluid, including gel, form. Fluid formulations may be formulated for administration by injection or infusion (e.g. via catheter) to a selected region of the human or animal body.

In some embodiments, the composition is formulated for injection or infusion, e.g. into a blood vessel, tissue/organ of interest, or a tumor.

The present disclosure also provides methods for the production of pharmaceutically-useful compositions and medicaments. Such methods may comprise one or more steps selected from: producing an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein; isolating an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein; and/or mixing an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein with a pharmaceutically-acceptable carrier, adjuvant, excipient or diluent.

For example, a further aspect of the present disclosure relates to a method of formulating or producing a medicament or pharmaceutical composition for use in the treatment of a disease/condition (e.g. a disease/condition described herein), the method comprising formulating a pharmaceutical composition or medicament by mixing an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof) or cell described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

Therapeutic and prophylactic applications

The antigen-binding molecules, polypeptides, nucleic acids, expression vectors, cells and compositions described herein find use in therapeutic and prophylactic methods.

The present disclosure provides an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein for use in a method of medical treatment or prophylaxis. Also provided is an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein for use in a method of treating or preventing a disease or condition described herein. Also provided is the use of an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein in the manufacture of a medicament for treating or preventing a disease or condition described herein. Also provided is a method of treating or preventing a disease or condition described herein, comprising administering to a subject a therapeutically or prophylactically effective amount of an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein.

The methods may be effective to reduce the development or progression of a disease/condition, alleviation of the symptoms of a disease/condition or reduction in the pathology of a disease/condition. The methods may be effective to prevent progression of the disease/condition, *e.g.* to prevent worsening of, or to slow the rate of development of, the disease/condition. In some embodiments, the methods may lead to an improvement in the disease/condition, *e.g.* a reduction in the symptoms of the disease/condition or reduction in some other correlate of the severity/activity of the disease/condition. In some embodiments, the methods may prevent development of the disease/condition at a later stage (*e.g.* a chronic stage or metastasis).

It will be appreciated that the articles of the present disclosure may be used for the treatment/prevention of any disease/condition that would derive therapeutic or prophylactic benefit from a reduction in the level/activity of signalling mediated by gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α , or a reduction in the number or activity of cells comprising/expressing gp130, gp130:IL-6R α and/or gp130:IL-11R α .

For example, the disease/condition may be a disease/condition in which gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α , or cells comprising/expressing gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α are pathologically-implicated, *e.g.* a disease/condition in which an increased level/activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α , or an increase in the number/proportion of cells comprising/expressing gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α is positively-associated with the onset, development or progression of the disease/condition, and/or severity of one or more symptoms of the disease/condition. In some embodiments, an increased level/activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α , or an increase in the number/proportion of cells comprising/expressing gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α may be a risk factor for the onset, development or progression of the disease/condition.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition characterised by an increase in the level of expression or activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α , *e.g.* as compared to the level of expression/activity in the absence of the disease/condition. In some embodiments, the disease/condition to be treated/prevented is a disease/condition characterised by an increase in the number/proportion/activity of cells expressing gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α , *e.g.* as compared to the level/number/proportion/activity in the absence of the disease/condition (*e.g.* in a healthy subject, or in equivalent non-diseased tissue).

Where the disease/condition is a cancer, the level of expression or activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α may be greater than the level of expression or activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α in equivalent non-cancerous cells/non-tumor tissue. A cancer/cell thereof may comprise one or more mutations (*e.g.* relative to equivalent non-cancerous cells/non-tumor tissue) causing upregulation of expression or activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α .

Treatment in accordance with the methods of the present disclosure may achieve a reduction in the activity of gp130, IL-6, gp130:IL-6R α , IL-11 and/or gp130:IL-11R α in a subject (compared to an equivalent untreated subject, or a subject treated with an appropriate control).

- 5 In some aspects and embodiments, the articles of the present disclosure are provided for the treatment/prevention of a disease/condition selected from: a disease/condition in which IL-6-mediated signalling is pathologically-implicated, a disease/condition in which gp130:IL-6R α -mediated signalling is pathologically-implicated, a disease/condition in which IL-11-mediated signalling is pathologically-implicated, a disease/condition in which gp130:IL-11R α -mediated signalling is pathologically-implicated, pathological inflammation, fibrosis, a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, or systemic sclerosis.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is systemic sclerosis.

- 15 In some aspects and embodiments, the articles of the present disclosure are provided for the treatment/prevention of inflammation, particularly pathological inflammation.

- Inflammation and its role in health 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).
- 20 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.

- 40 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. 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. a disease/condition characterised by inflammation-induced angiogenesis.

Angiogenesis is known to be dysregulated e.g. in systemic sclerosis, a chronic 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 disposition 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, TGF β 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.

5 In some aspects and embodiments, the articles of the present disclosure are provided for the treatment/prevention of fibrosis.

10 Fibrosis is a form of pathologic tissue remodelling characterised by the formation of excess connective tissue as a consequence of the excess deposition of extracellular matrix (ECM) components (including collagen). 'Excess connective tissue' refers to an amount of connective tissue at a given location (e.g. a given tissue/organ, or part of a given tissue/organ) which is greater than the amount of connective tissue present at that location under normal, non-pathological conditions. Similarly, 'excess deposition of ECM components' refers to a level of deposition of one or more ECM components which is greater than the level of deposition under normal, non-pathological conditions.

15 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, both of which are hereby incorporated by reference in their entirety.

20 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
25 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-fibroinflammatory factors such as TGF β , IL-13 and PDGF, which activate fibroblasts (and other myofibroblast precursor cells) to become α SMA-expressing myofibroblasts, and
30 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
35 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.

40 Fibrosis can be triggered by pathological conditions, e.g. conditions, infections or disease states that lead to production of pro-fibrotic factors (e.g. as TGF β 1). 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) 25(6): 700-706). Environmental injury/stimuli may include exposure to asbestos fibres or silica.

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Fibrosis can be of any tissue/organ of the body. In some embodiments, fibrosis 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. Fibrosis may also occur in multiple tissues/organs at once.

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In some embodiments, fibrosis 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, fibrosis may be of an organ or tissue of the cardiovascular system, e.g. the heart or blood vessels. In some embodiments, fibrosis 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, fibrosis may be of the eye. In some embodiments, fibrosis may be of the skin. In some embodiments, fibrosis may be of an organ or tissue of the nervous system, e.g. the brain. In some embodiments, fibrosis may be of the bone marrow. In some embodiments, fibrosis may be of the joints. In some embodiments, fibrosis may be of an organ or tissue of the urinary system, e.g. the kidneys. In some embodiments, fibrosis may be of an organ or tissue of the musculoskeletal system, e.g. muscle tissue. In some embodiments, fibrosis may be of an organ or tissue of one or more organ systems.

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In some embodiments, the disease/condition to be treated in accordance with the present disclosure is a disease/condition characterised by inflammation. In some embodiments, the disease/condition is a disease/condition characterised by fibrosis. In some embodiments, the disease/condition is a disease/condition characterised by inflammation and fibrosis.

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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:

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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;

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Diseases/conditions affecting the cardiovascular system such as carditis, endocarditis, myocarditis, cardiogenic shock, pericarditis, vasculitis, arteritis, phlebitis and capillaritis;

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;

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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;

5 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;

10 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 and uveitis;

Diseases/conditions affecting the ear such as otitis externa, otitis media, labyrinthitis and mastoiditis;

15 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 insulinitis, hypophysitis, thyroiditis, parathyroiditis and adrenalitis;

20 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.

25 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 and conditions characterised by fibrosis include, but are not limited to:

30 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;

35 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);

40 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;

5 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;

10 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;

15 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;

20 Diseases/conditions affecting the eye such as Grave's ophthalmopathy, epiretinal fibrosis, retinal fibrosis, subretinal fibrosis, subretinal fibrosis associated with macular degeneration (e.g. wet age-related macular degeneration (AMD)), diabetic retinopathy, glaucoma, corneal fibrosis, post-surgical fibrosis (e.g. of the posterior capsule following cataract surgery, or of the bleb following trabeculectomy for glaucoma), conjunctival fibrosis and subconjunctival fibrosis;

Diseases/conditions affecting the joints such as arthrofibrosis, arthritis and adhesive capsulitis;

25 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);

30 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.

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 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 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.

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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.

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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.

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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).

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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.

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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 p16^{INK4a}, p21^{CIP1} 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 p16^{INK4a}, p21^{CIP1} 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.

- 5 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
 10 (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.

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- 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),
 20 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,
 25 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.

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- 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
 35 (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
 40 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).

5 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).

10 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.

15 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
20 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
25 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
30 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
35 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
40 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.

- 5 The therapeutic and prophylactic effects of the present disclosure are achieved through inhibition of IL-11-mediating signalling (i.e. antagonism of IL-11-mediated signalling), e.g. in a cell, tissue/organ/organ system/subject.

10 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
15 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 in accordance with the present disclosure is a disease/condition in which gp130-mediated signalling is pathologically-implicated. In some embodiments,
20 the disease/condition is a disease/condition in which gp130:IL-6R α -mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which gp130:IL-11R α -mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which gp130:IL-6R α -mediated signalling is pathologically-implicated and an increased level of gp130:IL-11R α -mediated signalling is pathologically-implicated. In some embodiments,
25 the disease/condition is a disease/condition in which IL-6-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which IL-11-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which IL-6-mediated signalling is pathologically-implicated and an increased level of IL-11-mediated signalling is pathologically-implicated. A disease/condition in which a given type of signalling is pathologically-
30 implicated may be a disease/condition in which an increased level of the signalling is positively-associated with the onset, development or progression of the disease/condition, and/or severity of one or more symptoms of the disease/condition. In some embodiments, an increased level of the signalling may be a risk factor for the onset, development or progression of the disease/condition.

35 In some embodiments, the disease/condition to be treated in accordance with the present disclosure is a disease/condition characterised by an increased level of gp130-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of gp130:IL-6R α -mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of gp130:IL-11R α -mediated signalling. In some embodiments, the
40 disease/condition is a disease/condition characterised by an increased level of gp130:IL-6R α -mediated signalling and an increased level of gp130:IL-11R α -mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of IL-6-mediated signalling.

In some embodiments, the disease/condition is a disease/condition characterised by an increased level of IL-11-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of IL-6-mediated signalling and an increased level of IL-11-mediated signalling. The level of gp130-mediated signalling, gp130:IL-6R α -mediated signalling, gp130:IL-11R α -mediated signalling, IL-6-mediated signalling and IL-11-mediated signalling can be evaluated by means well known to the skilled person, with reference also to the experimental examples of the present disclosure.

An 'increased' level of signalling in accordance with the preceding two paragraphs may be 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-6R α -mediated signalling is implicated in the pathology of a wide range of diseases/conditions, including metabolic syndrome, neurodegenerative diseases, chronic inflammatory diseases, 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, 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-6R α /IL-6-mediated signalling is pathologically-implicated and/or characterised by an increased level of gp130:IL-6R α /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-6R α -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), sepsis, septic shock, 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-6R α -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-11R α -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-11R α -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, cardiogenic shock, 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-11R α /IL-11-mediated signalling is pathologically-implicated and/or characterised by an increased level of gp130:IL-11R α /IL-11-mediated signalling also include diseases/conditions characterised by pathological inflammation and/or fibrosis, e.g. as described herein.

- 5 Accordingly, in some embodiments, a disease/condition in which IL-11-mediated signalling is pathologically-implicated, or in which gp130:IL-11R α -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
- 10 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
- 15 cholangitis, primary sclerosing cholangitis, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, cardiogenic shock, 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,
- 20 bone cancer, glioblastoma, liver cancer, leukemia, lung cancer, Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer and skin cancer.

- Administration of the articles 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
- 25 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/disorder to be treated, the condition of the individual subject, the site of delivery, the method of administration and other factors known to
- 30 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 topical, parenteral, systemic, intracavitary, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intravitreal, intraconjunctival, subretinal,
- 35 suprachoroidal, subcutaneous, intradermal, intrathecal, oral, nasal or transdermal. Administration may be by injection or infusion. Where the articles of the present disclosure are employed for the treatment of a cancer, administration may be intratumoral.

- In some aspects and embodiments in accordance with the present disclosure there may be targeted
- 40 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.

Administration of the articles of the present disclosure may be alone, or in combination with other treatments, either simultaneously or sequentially dependent upon the disease/condition to be treated. The antigen-binding molecule, cell or composition described herein and another prophylactic/therapeutic agent may be administered simultaneously or sequentially.

In some embodiments, the methods comprise additional therapeutic or prophylactic intervention. In some embodiments, the additional therapeutic or prophylactic intervention is selected from chemotherapy, immunotherapy, radiotherapy, surgery, vaccination and/or hormone therapy. In some embodiments, the additional therapeutic or prophylactic intervention comprises leukapheresis. In some embodiments, the additional therapeutic or prophylactic intervention comprises a stem cell transplant.

Simultaneous administration refers to administration of the antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition and therapeutic agent together, for example as a pharmaceutical composition containing both agents (combined preparation), or immediately after each other 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 antigen-binding molecule/composition or therapeutic agent followed after a given time interval by separate administration of the other agent. It is not required that the two 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, treatment of cancer further comprises chemotherapy and/or radiotherapy. Chemotherapy and radiotherapy respectively refer to treatment of a cancer with a drug or with ionising radiation (e.g. radiotherapy using X-rays or γ -rays). The drug may be a chemical entity, e.g. small molecule pharmaceutical, antibiotic, DNA intercalator, protein inhibitor (e.g. kinase inhibitor), or a biological agent, e.g. antibody, antibody fragment, aptamer, nucleic acid (e.g. DNA, RNA), peptide, polypeptide, or protein. The drug may be formulated as a pharmaceutical composition or medicament. The formulation may comprise one or more drugs (e.g. one or more active agents) together with one or more pharmaceutically acceptable diluents, excipients or carriers.

Chemotherapy may involve administration of more than one drug. A drug may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. The chemotherapy may be administered by one or more routes of administration, e.g. parenteral, intravenous injection, oral, subcutaneous, intradermal or intratumoral. The chemotherapy may

be administered according to a treatment regime. The treatment regime may be a pre-determined timetable, plan, scheme or schedule of chemotherapy administration which may be prepared by a physician or medical practitioner and may be tailored to suit the patient requiring treatment. The treatment regime may indicate one or more of: the type of chemotherapy to administer to the patient; the dose of each drug or radiation; the time interval between administrations; the length of each treatment; the number and nature of any treatment holidays, if any *etc.* For a co-therapy a single treatment regime may be provided which indicates how each drug is to be administered.

Multiple doses of the antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein may be provided. One or more, or each, of the doses may be accompanied by simultaneous or sequential administration of another therapeutic agent.

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 accordance with various aspects of the present disclosure, a method of treating and/or preventing a disease/condition may comprise one or more of the following: inhibition of signalling mediated by a receptor comprising gp130; inhibition of signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α ; inhibition of signalling mediated by a cytokine that binds to a receptor comprising gp130; inhibition of IL-6- and/or IL-11-mediated signalling; does not inhibit signalling mediated by gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and/or gp130:IL-12R β 2; reduction of inflammation and/or fibrosis; reduction of the pathology of a disease/condition characterised by inflammation and/or fibrosis; and/or increased killing of cells expressing gp130.

The present disclosure further provides the use of an antigen-binding molecule according to the present disclosure to inhibit signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , and/or use of an antigen-binding molecule according to the present disclosure to inhibit signalling mediated by IL-6 and/or IL-11.

The present disclosure further provides methods for inhibiting signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , and/or methods for inhibiting signalling mediated by IL-6 and/or IL-11 using an antigen-binding molecule according to the present disclosure.

In some embodiments, the methods comprise contacting cells with an antigen-binding molecule according to the present disclosure. In some embodiments, the cells are cells capable of the relevant signalling which is to be inhibited. In some embodiments, the cells are contacted with the antigen-binding molecule *in vitro* or *ex vivo*. In some embodiments, the cells are contacted with the antigen-binding molecule *in vivo*, e.g. via administration of the antigen-binding molecule to a subject.

Accordingly, the present disclosure provides methods for inhibiting signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α in a subject, and/or methods for inhibiting signalling mediated by IL-6 and/or IL-11 in a subject, comprising administering to a subject an antigen-binding molecule according to the present disclosure.

5

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.

10 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.

15 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.

20

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.

25

Methods comprising detecting gp130, or cells expressing gp130, include methods for diagnosing/prognosing a disease/condition described herein.

30 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*.

35 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.

40

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.

5

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).

10

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.

15

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.

20

Subjects

A subject in accordance with the various aspects of the present disclosure may be any animal or human. Therapeutic and prophylactic applications may be in human or animals (veterinary use).

25

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.

30

A subject may have (e.g. may have been diagnosed with) a disease or condition described herein, may be suspected of having such a disease/condition, or may be at risk of developing/contracting such a disease/condition. In embodiments according to the present disclosure, a subject may be selected for treatment according to the methods based on characterisation for one or more markers of such a disease/condition.

35

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.

40

Kits

The present disclosure also provides kits of parts.

- 5 In some embodiments, the kit may have at least one container having a predetermined quantity of an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein.

- 10 In some embodiments, the kit may comprise materials for producing an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein. In some embodiments, the kit of parts may comprise materials for formulating an antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition described herein to a pharmaceutical composition/medicament, e.g. in a composition further comprising a pharmaceutically-acceptable carrier, diluent, excipient or adjuvant.

- 15 The kit may provide the antigen-binding molecule, polypeptide, nucleic acid (or plurality thereof), expression vector (or plurality thereof), cell or composition together with instructions for administration to a patient in order to treat a specified disease/condition (e.g. a disease/condition described herein).

- 20 In some embodiments the kit may further comprise at least one container having a predetermined quantity of another therapeutic agent (e.g. as described herein). In such embodiments, the kit may also comprise a second medicament or pharmaceutical composition such that the two medicaments or pharmaceutical compositions may be administered simultaneously or separately such that they provide a combined treatment for the specific disease/condition.

- 25 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.

30 **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
- 35 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
- 40 using such software, the default parameters, e.g. for gap penalty and extension penalty, are preferably used.

Numbered statements

The following numbered paragraphs (paras) describe particular aspects and embodiments of the present disclosure:

- 5 1. An antigen-binding molecule, optionally isolated, which binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , and wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.
- 10 2. The antigen-binding molecule according to para 1, wherein the antigen-binding inhibits signalling mediated by gp130:IL-6R α and gp130:IL-11R α .
3. The antigen-binding molecule according to para 1 or para 2, wherein the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α .
- 15 4. The antigen-binding molecule according to any one of paras 1 to 3, wherein the antigen-binding molecule comprises:
 - (a)
 - 20 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - HC-CDR1 having the amino acid sequence of SEQ ID NO:62
 - HC-CDR2 having the amino acid sequence of SEQ ID NO:63
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:64; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - 25 LC-CDR1 having the amino acid sequence of SEQ ID NO:65
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:66
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:67; or
 - (b)
 - 30 (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:
 - 35 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
 - (c)
 - 40 (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:24
 LC-CDR2 having the amino acid sequence of SEQ ID NO:25
 LC-CDR3 having the amino acid sequence of SEQ ID NO:26; or

(d)

- 5 (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:32; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 10 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
 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

(e)

- 15 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:45
 20 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:47; or

(f)

- 25 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:52
 HC-CDR2 having the amino acid sequence of SEQ ID NO:53
 HC-CDR3 having the amino acid sequence of SEQ ID NO:54; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
 LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 30 LC-CDR3 having the amino acid sequence of SEQ ID NO:58.

5. The antigen-binding molecule according to any one of paras 1 to 4, wherein the antigen-binding molecule comprises:

- 35 a VH region having an amino acid sequence having at least 70% amino acid sequence identity to
 SEQ ID NO:74, 106, 78, 80, 83, 1, 17, 31, 36, 51, 86 or 87; and
 a VL region having an amino acid sequence having at least 70% amino acid sequence identity to
 SEQ ID NO:75, 110, 88, 91, 95, 98, 100, 9, 23, 34, 44 or 57.

6. The antigen-binding molecule according to any one of paras 1 to 5, wherein the antigen-binding molecule comprises:

- 40 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 C, 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 C;

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

- 5 7. The antigen-binding molecule according to any one of paras 1 to 6, wherein the antigen-binding molecule is a multispecific antigen-binding molecule, and wherein the antigen-binding molecule further comprises an antigen-binding domain which binds to an antigen other than gp130.
8. A chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to any one of
10 paras 1 to 7.
9. A nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding an antigen-binding molecule according to any one of paras 1 to 7, or a CAR according to para 8.
- 15 10. An expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to para 9.
11. A cell comprising an antigen-binding molecule according to any one of paras 1 to 7, a CAR according to para 8, a nucleic acid or a plurality of nucleic acids according to para 9, or an expression vector or a
20 plurality of expression vectors according to para 10.
12. A method comprising culturing a cell according to para 11 under conditions suitable for expression of an antigen-binding molecule or CAR by the cell.
- 25 13. A composition comprising an antigen-binding molecule according to any one of paras 1 to 7, a CAR according to para 8, a nucleic acid or a plurality of nucleic acids according to para 9, an expression vector or a plurality of expression vectors according to para 10, or a cell according to para 11, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.
- 30 14. An antigen-binding molecule according to any one of paras 1 to 7, a CAR according to para 8, a nucleic acid or a plurality of nucleic acids according to para 9, an expression vector or a plurality of expression vectors according to para 10, a cell according to para 11, or a composition according to para 13, for use in a method of medical treatment or prophylaxis.
- 35 15. An antigen-binding molecule according to any one of paras 1 to 7, a CAR according to para 8, a nucleic acid or a plurality of nucleic acids according to para 9, an expression vector or a plurality of expression vectors according to para 10, a cell according to para 11, or a composition according to para 13, for use in a method of treatment or prevention of: pathological inflammation, fibrosis, a
40 disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, a disease/condition in which IL-6-mediated signalling is pathologically-implicated, a disease/condition in which gp130:IL-6R α -mediated signalling is pathologically-implicated, a disease/condition in which IL-11-mediated signalling is pathologically-

implicated, or a disease/condition in which gp130:IL-11R α -mediated signalling is pathologically-implicated, metabolic syndrome, a neurodegenerative disease, a chronic inflammatory disease, arthritis, rheumatoid arthritis, juvenile arthritis, systemic juvenile idiopathic arthritis, lupus, pancreatitis, thyroiditis, periodontitis, dermatitis, atopic dermatitis, psoriasis, Hermansky-Pudlak syndrome, Graves' disease, diabetes, type 1 diabetes, type 2 diabetes, pregnancy-associated hyperglycemia, multiple sclerosis, giant cell arteritis, Takayasu arteritis, cardiovascular disease, atherosclerosis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, Marfan syndrome, systemic sclerosis, keloid, scleroderma, Alzheimer's disease, hippocampal atrophy, pulmonary disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, hepatitis, cirrhosis, hepatotoxicity, acetaminophen-induced hepatotoxicity, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, colitis, ulcerative colitis, endometriosis, stroke, nephropathy, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, chronic kidney disease, Alport syndrome, adult-onset Still's disease, Castleman's disease, cytokine release syndrome, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, COVID-19, Peutz-Jeghers syndrome, a cancer, a hematologic malignancy, leukemia, plasmacytoma, Hodgkin's lymphoma, lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer, bone cancer, glioblastoma, breast cancer, stomach cancer, renal cancer, metastatic renal cell cancer, prostate cancer, skin cancer, liver cancer, hepatocellular carcinoma, 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.

16. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of paras 1 to 7 bound to gp130.

17. A method for detecting gp130 in a sample, comprising contacting a sample containing, or suspected to contain, gp130 with an antigen-binding molecule according to any one of paras 1 to 7, and detecting the formation of a complex of the antigen-binding molecule with gp130.

18. A method of selecting or stratifying a subject for treatment with a gp130-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to any one of paras 1 to 7, and detecting the formation of a complex of the antigen-binding molecule with gp130.

19. Use of an antigen-binding molecule according to any one of paras 1 to 7 as an *in vitro* or *in vivo* diagnostic or prognostic agent.

Sequences

SEQ ID NO:	DESCRIPTION	SEQUENCE
1	4D4 VH	EVQLVETGGGLVQPGRSLKLSGVSGFTFSNYWMYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNADTVYLQMNSLRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTSS
2	4D4, 4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-CDR1	GFTFSNYW
3	4D4, 4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-CDR2	INADGGST
4	4D4, 4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-CDR3	VKMGLYFGLLPYVMDA
5	4D4 HC-FR1	EVQLVETGGGLVQPGRSLKLSGVSV
6	4D4, 3G9, 4A7/7D8, 4D4CVH2, 4D4CVH2.2 HC-FR2	MYWIRQAPGKGLEWVAS
7	4D4 HC-FR3	YYPDSVKGRFTISRDNADTVYLQMNSLRSEDATYYC
8	4D4, 3G9, 4A7/7D8, HC-FR4	WGQGASVTSS
9	4D4 VL	NIQLTQSPSLLSASVGDVRLTSCCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNLTQTGIPSRFSG SGSDTYTLTISSLQPEDVATYFCYQYTNGYTFGTGKLELK
10	4D4, 4D4C/GVL1, 4D4CVL2, 4D4CVL4, 4D4GVL3, 4D4GVL4, LC-CDR1	QNVNNY
11	4D4, 4A7/7D8, C03-A7, 4D4C/GVL1, 4D4CVL2, 4D4CVL4, 4D4CVL5, 4D4GVL2, 4D4GVL3, 4D4GVL4, LC-CDR2	NTN
12	4D4, 4A7/7D8, 4D4C/GVL1, 4D4CVL2, 4D4CVL4, 4D4GVL3, 4D4GVL4, LC-CDR3	YQYTNGYT
13	4D4, C03-A7 LC-FR1	NIQLTQSPSLLSASVGDVRLTSCCKGS
14	4D4, 4D4C/GVL1 LC- FR2	LAWYQQKLGKTPKLLIY
15	4D4, 4D4C/GVL1, 4D4CVL2, LC-FR3	NLQTGIPSRFSGSGSDTYTLTISSLQPEDVATYFC
16	4D4 LC-FR4	FGTGKLELK
17	3G9 VH	EVQLAETGGGLVQPGRSLKLSGVASGFTFSRYWMYWRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVYLQMNSLRSEDATYYCVKMGVKYGLLLPYVMDAWGQGASVTSS
18	3G9, 4A7/7D8 HC- CDR1	GFTFSRYW
19	3G9, 4A7/7D8 HC- CDR2	INTDGGST
20	3G9 HC-CDR3	VKMGVKYGLLLPYVMDA
21	3G9, 4A7/7D8 HC-FR1	EVQLAETGGGLVQPGRSLKLSGVAS
22	3G9 HC-FR3	YYPDSVQGRFTVSRDNAENTVYLQMNSLRSEDATYYC
23	3G9 VL	NIQLTQSPSLLSTSVGDVRLTSCCKGSQNNINYLAWFQQKLGKTPKLLIYHTNLTQTGIPSRFSGS GSGTDYTLTISSLQPEDVATYFCYQYTSYTFGAGTKLELK
24	3G9, 4A7/7D8, C03-A7 LC-CDR1	QNNINNY
25	3G9 LC-CDR2	HTN
26	3G9 LC-CDR3	YQYTSYTY
27	3G9, 4A7/7D8 LC-FR1	NIQLTQSPSLLSTSVGDVRLTSCCKGS
28	3G9 LC-FR2	LAWFQQKLGKTPKLLIY
29	3G9, 4A7/7D8 LC-FR3	SLQTGIPSRFSGSGSGTDYTLTISSLQPEDVATYFC
30	3G9, 4A7/7D8, 8C6 LC-FR4	FGAGTKLELK
31	4A7/7D8 VH	EVQLAETGGGLVQPGRSLKLSGVASGFTFSRYWMYWRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVFLQMNSLRSEDATYYCVKMGLKYGLLLPYVMDAWGQGASVTSS

32	4A7/7D8 HC-CDR3	VKMGLKYGLLPYVMDA
33	4A7/7D8 HC-FR3	YYPDSVQGRFTVSRDNAENTVFLQMNSLRSEDATYYC
34	4A7/7D8 VL	NIQLTQSPSLLSTSVGDRVTLSCCKGSQNNYLAUWYQKLGEPKLLIYNTNSLQTGIPSRFSGS GSGTDYTLTISSLQPEDVATYFCYQYTNQYTFGAGTKLELK
35	4A7/7D8 LC-FR2	LAWYQQKLGEVPKLLIY
36	8C6 VH	EVQLVESGGGLVQPGSRSLKLSAASGFTFNYYMAWWRQAPTKGLEWVASITKSGGSTNYRD SVRGRFTISRDDAKSTLSLQMDSLRSEDATYYCARGGIYYGLFTGYFDYWGQGMVTVSS
37	8C6 HC-CDR1	GFTFNYY
38	8C6 HC-CDR2	ITKSGGST
39	8C6 HC-CDR3	ARGGIYYGLFTGYFDY
40	8C6 HC-FR1	EVQLVESGGGLVQPGSRSLKLSAAS
41	8C6, C03-A7 HC-FR2	MAWWRQAPTKGLEWVAS
42	8C6 HC-FR3	NYRDSVRGRFTISRDDAKSTLSLQMDSLRSEDATYYC
43	8C6, C03-A7 HC-FR4	WGQGMVTVSS
44	8C6 VL	DTVLTQSPTLAVSPGERVSCRASEGVNSFMHWYQQNPGQPKLLIYKASNLASGVPARFSG SGSGTDFLTIDPVEADDTATYFCQQNWNDPFTFGAGTKLELK
45	8C6 LC-CDR1	EGVNSF
46	8C6 LC-CDR2	KAS
47	8C6 LC-CDR3	QQNWNDPFT
48	8C6 LC-FR1	DTVLTQSPTLAVSPGERVSCRAS
49	8C6 LC-FR2	MHWYQQNPGQPKLLIY
50	8C6 LC-FR3	NLASGVPARFSGSGSGTDFLTIDPVEADDTATYFC
51	C03-A7 VH	EVQLVESGGGLVQPGSRSLKLSVSGSGFTFSNYGMAWWRQAPTKGLEWVASISTGGDNTYYRD SVKGRFTISRDDAKNTQYLQMDSLRSEDATYYCARLGIYYRLLVPYFHYWGQGMVTVSS
52	C03-A7 HC-CDR1	GFTFSNYG
53	C03-A7 HC-CDR2	ISTGGDNT
54	C03-A7 HC-CDR3	ARLGIYYRLLVPYFHY
55	C03-A7 HC-FR1	EVQLVESGGGLVQPGSRSLKLSVGS
56	C03-A7 HC-FR3	YYRDSVKGRFTISRDDAKNTQYLQMDSLRSEDATYYC
57	C03-A7 VL	NIQLTQSPSLLSASVGDRVTLSCCKGSQNNYLAUWYQKLGEPKLLIYNTNSFQTGIPSRFSGS GSGTDYTLTINSLQPEDVATYFCYQYNNGWTFGGGTKLDLK
58	C03-A7 LC-CDR3	YQYNNGWTF
59	C03-A7 LC-FR2	LAWYQQKLGEAPKLLIY
60	C03-A7 LC-FR3	SFQTGIPSRFSGSGSGTDYTLTINSLQPEDVATYFC
61	C03-A7 LC-FR4	FGGGTKLDLK
62	CON'4'9'7/8 HC-CDR1	GFTFSX ₁ YW wherein X ₁ = R or N
63	CON'4'9'7/8 HC-CDR2	INX ₁ DGGST wherein X ₁ = T or A
64	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
65	CON'4'9'7/8 LC-CDR1	QNX ₁ NNY wherein X ₁ = I or V
66	CON'4'9'7/8 LC-CDR2	X ₁ TN wherein X ₁ = N or H
67	CON'4'9'7/8 LC-CDR3	YQYTX ₁ GYT wherein X ₁ = N or S
68	CON'4'9'7/8 HC-FR1	EVQLX ₁ ETGGGLVQPGSRSLKLSVX ₂ S wherein X ₁ = A or V; X ₂ = A or V
69	CON'4'9'7/8 HC-FR3	YYPDSVX ₁ GRFTX ₂ SRDNAEX ₃ TVYLMNSLRSEDATYYC wherein X ₁ = K or Q; X ₂ = I or V; X ₃ = D or N
70	CON'4'9'7/8 LC-FR1	NIQLTQSPSLLSX ₁ SVGDRVTLSCCKGS

		wherein $X_1 = A$ or T
71	CON'4'9'7/8 LC-FR2	LAWX ₁ QQKLGE ₂ PKLLIY
		wherein $X_1 = Y$ or F ; $X_2 = V$ or T
72	CON'4'9'7/8 LC-FR3	X ₁ LQTGIPSRFSGSGSX ₂ TDYTLTISSLQPEDVATYFC
		wherein $X_1 = N$ or S ; $X_2 = D$ or G
73	CON'4'9'7/8 LC-FR4	FGX ₁ GTKLELK
		wherein $X_1 = T$ or A
74	CON'4'9'7/8 VH	EVQLX ₁ ETGGGLVQPGRSLKLSCVX ₂ SGFTFSX ₃ YWMYWRQAPGKGLEWVASINX ₄ DGGSTYY PDSVX ₅ GRFTX ₆ SRDNAEX ₇ TVYLQMNSLRSEDATYYCVKMGX 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
75	CON'4'9'7/8 VL	NIQLTQSPSLLSX ₁ SVGDRVTLSCCKGSQNX ₂ NNYLAWX ₃ QQKLGE ₄ PKLLIYX ₅ TNX ₆ LQTGIPSR FSGSGSX 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
76	4D4CVH2, 4D4CVH3, 4D4CVH2.1, 4D4CVH2.2 HC-FR1	EVQLVESGGGLVQPGRSLRLSCVVS
77	4D4CVH2, 4D4CVH2.1 HC-FR3	YYPDSVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYC
78	4D4CVH2	EVQLVESGGGLVQPGRSLRLSCVVS ₁ SGFTFSNYWMYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYCVKMGLYFGLLPYVMDAWGQGLTVTVSS
79	4D4CVH2, 4D4CVH3, 4D4CVH4, 4D4CVH2.1, 4D4CVH2.2 HC-FR4	WGQGLTVTVSS
80	4D4CVH3	EVQLVESGGGLVQPGRSLRLSCVVS ₁ SGFTFSNYWMYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYCVKMGLYFGLLPYVMDAWGQGLTVTVSS
81	4D4CVH3, 4D4CVH4, 4D4CVH2.1 HC-FR2	MYWWRQAPGKGLEWVAS
82	4D4CVH3, 4D4CVH2.2 HC-FR3	YYPDSVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYC
83	4D4CVH4	EVQLVESGGGLVQPGRSLRLSCAAS ₁ SGFTFSNYWMYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYCVKMGLYFGLLPYVMDAWGQGLTVTVSS
84	4D4CVH4, HC-FR1	EVQLVESGGGLVQPGRSLRLSCAAS
85	4D4CVH4 HC-FR3	YYPDSVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYC
86	4D4CVH2.1	EVQLVESGGGLVQPGRSLRLSCVVS ₁ SGFTFSNYWMYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYCVKMGLYFGLLPYVMDAWGQGLTVTVSS
87	4D4CVH2.2	EVQLVESGGGLVQPGRSLRLSCVVS ₁ SGFTFSNYWMYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNAAEDTVYLQMNSLRAEDATYYCVKMGLYFGLLPYVMDAWGQGLTVTVSS
88	4D4C/GVL1	NIQLTQSPSLLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNQYTFGQGTKLEIK
89	4D4C/GVL1 LC-FR1	NIQLTQSPSLLSASVGDRTITCKGS
90	4D4C/GVL1, 4D4CVL2, 4D4CVL4, , 4D4GVL3, 4D4GVL4, LC-FR4	FGQGTKLEIK
91	4D4CVL2	NIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNQYTFGQGTKLEIK
92	4D4CVL2 LC-FR1	NIQLTQSPSFLSASVGDRTITCKGS
93	4D4CVL2, 4D4CVL4, 4D4GVL3, 4D4GVL4 LC-FR2	LAWYQQKPGKAPKLLIY
94	4D4CVL4, LC-FR1	DIQLTQSPSFLSASVGDRTITCKGS
95	4D4CVL4	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNLTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTNQYTFGQGTKLEIK
96	4D4CVL4 LC-FR3	NLQGTGVPSPSRFSGSGSDTDYTLTISSLQPEDVATYYC
97	4D4GVL3 LC-FR1	DIQLTQSPSFLSASVGDRTITCKGS
98	4D4GVL3	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNLTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTNQYTFGQGTKLEIK
99	4D4GVL3 LC-FR3	NLQGTGVPSPSRFSGSGSDTDYTLTISSLQPEDVATYYC
100	4D4GVL4	DIQMTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNLTGIPSRFSG

		GSQSGTDFTLTISSLQPEDFATYYCYQYTNQYTFGQGTKLEIK
101	4D4GVL4 LC-FR1	DIQMTQSPSSLSASVGDRVTITCKGS
102	4D4GVL4 LC-FR3	NLQGTGPSRFSGSGSGTDFTLTISSLQPEDFATYYC
103	CON4D4P/Hu HC-FR1	EVQLVESGGGLVQPGRSLRLSCX ₁ X ₂ S wherein X ₁ = V or A; X ₂ = V or A
104	CON4D4P/Hu HC-FR2	MYWXX ₁ RQAPGKLEWVAS wherein X ₁ = V or I
105	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
106	CON4D4P/Hu VH	EVQLVESGGGLVQPGRSLRLSCX ₁ X ₂ SGFTFSNYWMYWX ₃ RQAPGKLEWVASINADGGSTYY PDSVKGRFTISRDNX ₄ X ₅ X ₆ TVYLQMNSLRAEDTATYYCVKMGFLYGLLVYVMDAWGQGTGLVT 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
107	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
108	CON4D4P/Hu LC-FR2	LAWYQQKX ₁ GKX ₂ PKLLIY wherein X ₁ = P or L; X ₂ = A or T
109	CON4D4P/Hu LC-FR3	NLQGTGX 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
110	CON4D4P/Hu VL	X ₁ IQX ₂ TQSPSX ₃ LSASVGDRVTITCKGSQNVNNYLAWYQQKX ₄ GKX ₅ PKLLIYNTNQLQTX ₆ PSR FSGSGSX ₇ TDX ₈ TLTISSLQPEDX ₉ ATYX ₁₀ CYQYTNQYTFGQGTKLEIK 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
111	Human IgG1 constant region (IGHG1; UniProt:P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHFFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCTPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALH NHYTQKSLSLSPGK
112	CH1 IgG1 (positions 1-98 of P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHFFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV
113	Hinge IgG1 (positions 99-110 of P01857-1, v1)	EPKSCDKTHTCP
114	CH2 IgG1 (positions 111-223 of P01857-1, v1)	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAK
115	CH3 IgG1 (positions 224-330 of P01857-1, v1)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS FFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK
116	Human IgG1 constant region G1m3 allotype (K214R, D356E and L358M (EU numbering) relative to P01857-1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHFFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV PKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALH NHYTQKSLSLSPGK
117	CH1 IgG1 G1m3 allotype	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHFFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
118	CH3 IgG1 G1m3 allotype	GQPREPQVYTLPPSRDEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS FFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK
119	Human IgG4 constant region (IGHG4; UniProt:P01861-1, v1)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSKVHFFPAVLQSSGLYS LSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPK DTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCVMHEALHNHYT QKSLSLSLGK
120	Human IgG1 CH2-CH3 region	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ QGNVFCSSVMHEALHNHYTQKSLSLSPGK
121	Human IgG1 G1m3	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP

	allotype CH2-CH3 region	REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPG
122	Human IgG4 CH2-CH3 region	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSPG
123	Cκ CL (IGKC; UniProt: P01834-1, v2)	RTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
124	Cλ CL1 (IGLC1; UniProt: P0CG04-1, v1)	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSN KYAASSYLSTLTPQWKSHRSYSQCQVTHEGSTVEKTVAPTECS
125	Cλ CL2 (IGLC2; UniProt: P0DOY2-1, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTSPKQSN KYAASSYLSTLTPQWKSHRSYSQCQVTHEGSTVEKTVAPTECS
126	Cλ CL3 (IGLC3; UniProt: P0DOY3-1, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTTSPKQSN KYAASSYLSTLTPQWKSHRSYSQCQVTHEGSTVEKTVAPTECS
127	Cλ CL6 (IGLC6; UniProt: P0CF74-1, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETTTSPKQSN KYAASSYLSTLTPQWKSHRSYSQCQVTHEGSTVEKTVAPAECS
128	Cλ CL7 (IGLC7; UniProt: A0M8Q6-1, v3)	GQPKAAPSVTFLFPPSSEELQANKATLVCLVDFNPGAVTVAWKADGSPVKGVETTKPSKQSN NKYAASSYLSTLTPQWKSHRSYSQVTHEGSTVEKTVAPAECS
129	Human gp130 isoform 1 (UniProt: P40189-1, v2)	MLTLQTWLVQALFIFLTTTESTGELLDPGGYISPEPVPVQLHSNFTAVCVLKEKCMDYFHVNANYI VWKTNHFTIPKEQYTIINRTASSVTFDIASLNQLTCNLTFGQLEQNVYGITIISGLPPEKPKNLSC IVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCVDTYSTVYFVNIWV VEAENALGKVTSDHINFDVPYKVPNPPHNLVINSEELSSILKLTWTNPSIKSVIILKYNQYRTK DASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITIEDRPS KAPSFWYKIDPSHTQGYRTVQLVWKTLPPEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNL TNDRYLATLTVRNLVGKSDAAVLTPACDFQATHPVMDLKAFKDNMLWVEWTTTPRESVKYIL EWCVLSDKAPCITDWWQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPP SKGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSTHEYTLSSLT DTLYMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTTLGLVFCFNKRDLLKH IWPNVDPDSKSHIAQWSPHTPPRHNFNSKQDQMYSDGNFTDVSVEIEANDKKPFPEDLKSLDLF KKEKINTEGHSSGIGGSSCMSSSRPSISSDENESSQNTSSTVQYSTVHSGYRHHQVPSVQVF SRSESTQPLLDSEERPEDLQLVDHVDGGDGLPRQYFKQNCQHESSPDISHFERSKQVSSV NEEDFVRLKQKQSDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEEATDEGMP KSYLPQTVRQGGYMPQ
130	Human gp130 isoform 2 (UniProt: P40189-2)	MLTLQTWLVQALFIFLTTTESTGELLDPGGYISPEPVPVQLHSNFTAVCVLKEKCMDYFHVNANYI VWKTNHFTIPKEQYTIINRTASSVTFDIASLNQLTCNLTFGQLEQNVYGITIISGLPPEKPKNLSC IVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCVDTYSTVYFVNIWV VEAENALGKVTSDHINFDVPYKVPNPPHNLVINSEELSSILKLTWTNPSIKSVIILKYNQYRTK DASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITIEDNIAS F
131	Human gp130 isoform 3 (UniProt: P40189-3)	MLTLQTWLVQALFIFLTTTESTGELLDPGGYISPEPVPVQLHSNFTAVCVLKEKCMDYFHVNANYI VWKTNHFTIPKEQYTIINRTASSVTFDIASLNQLTCNLTFGQLEQNVYGITIISGLPPEKPKNLSC IVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCVDTYSTVYFVNIWV VEAENALGKVTSDHINFDVPYKVPNPPHNLVINSEELSSILKLTWTNPSIKSVIILKYNQYRTK DASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITIEDRPS KAPSFWYKIDPSHTQGYRTVQLVWKTLPPEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNL TNDRYLATLTVRNLVGKSDAAVLTPACDFQGNLAESKCYLITVTPVYADGPGSPESIKAYLKQA PPSKGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSTHEYTLSSL TSDTYMVRMAAYTDEGGKDGPEFTFTTPKFAQGEIEAIVVPVCLAFLLTTLGLVFCFNKRDLLK KHIWPNVDPDSKSHIAQWSPHTPPRHNFNSKQDQMYSDGNFTDVSVEIEANDKKPFPEDLKSL DLFKKEKINTEGHSSGIGGSSCMSSSRPSISSDENESSQNTSSTVQYSTVHSGYRHHQVPSV QVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGLPRQYFKQNCQHESSPDISHFERSKQV SSVNEEDFVRLKQKQSDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEEATDE GMPKSYLPQTVRQGGYMPQ
132	Human gp130 signal peptide	MLTLQTWLVQALFIFLTTTESTG
133	Mature human gp130 isoform 1	ELLDPGGYISPEPVPVQLHSNFTAVCVLKEKCMDYFHVNANYI VWKTNHFTIPKEQYTIINRTASSVTFDIASLNQLTCNLTFGQLEQNVYGITIISGLPPEKPKNLSC IVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSCVDTYSTVYFVNIWV VEAENALGKVTSDHINFDVPYKVPNPPHNLVINSEELSSILKLTWTNPSIKSVIILKYNQYRTK DASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITIEDRPS KAPSFWYKIDPSHTQGYRTVQLVWKTLPPEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNL TNDRYLATLTVRNLVGKSDAAVLTPACDFQATHPVMDLKAFKDNMLWVEWTTTPRESVKYILEWCVLSDKAPCITDWWQEDG TVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVRTKKVGKNEAVLEW DQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSTHEYTLSSLTSDTYMVRMAAYTDEGGKDG PEFTFTTPKFAQGEIEAIVVPVCLAFLLTTLGLVFCFNKRDLLKH IWPNVDPDSKSHIAQWSPHTPPRHNFNSKQDQMYSDGNFTDVSVEIEANDKKPFPEDLKSLDLF KKEKINTEGHSSGIGGSSCMSSSRPSISSDENESSQNTSSTVQYSTVHSGYRHHQVPSVQVF SRSESTQPLLDSEERPEDLQLVDHVDGGDGLPRQYFKQNCQHESSPDISHFERSKQVSSV NEEDFVRLKQKQSDHISQSCGSGQMKMFQEVSAADAFGPGTEGQVERFETVGMEEATDE GMPKSYLPQTVRQGGYMPQ

		PRHNFNSKDMYSDGNFTDVSVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGSSCMS SSRPSISSDENESSQNTSSSTVQYSTVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQL VDHVDGGDGILPRQQYFKQNCSSQHESSPDISHFERSKQVSSVNEEDFVRLKQKQISDHISQSCG SGQMCMFQEVSAADAFGPGTEGQVERFETVGMEATDEGMPSYLPQTVRQGGYMPQ
134	Human gp130 extracellular domain	ELLDPGYSIPESPVVQLHSNFTAVCVLKEKCMDYFHVNNANYVWKTNHFTIPKEQYTIINRTASS VTFTDIASLNIQLTCNLTFGQLEQNVYGIITISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHL ETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDVPY KVKPNPPHNLSVINSEELSSILKLTWNTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDASTRSSFT VQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSFVYKIDPSHTQGYRTVQ LVWKTLPPEFANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAA VLTIPACDFQATHPVMCLKAFPKDNMLWVEWITPRESVKKYILEWCVLSDKAPCITDWQQEDG TVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPVTRTKKVGNKNEAVLEW DQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDG EFTFTTPKFAQGEIE
135	Human gp130 transmembrane domain	AIVVPVCLAFLLTLLGLVLCF
136	Human gp130 cytoplasmic domain	NKRDLIKHIWPNVPDPSPKSHIAQWSPHTPPRHNFNNSKDMYSDGNFTDVSVEIEANDKKPFP EDLKSLDLFKKEKINTEGHSSGIGSSCMSSSRPSISSDENESSQNTSSSTVQYSTVHSGYRH QVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCSSQHESSPDISHFE RSKQVSSVNEEDFVRLKQKQISDHISQSCGSGQMCMFQEVSAADAFGPGTEGQVERFETVGME AATDEGMPSYLPQTVRQGGYMPQ
137	Human gp130 Ig-like C2-type domain	DPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNNANYVWKTNHFTIPKEQYTIINRTASSVT TDIASLNIQLTCNLTFGQLEQNVYGIITISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHL TVYFVNIEVWVEAENALGKVTSDHINFD
138	Human gp130 FNIII domain 1	PPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYS TVYFVNIEVWVEAENALGKVTSDHINFD
139	Human gp130 FNIII domain 2	PPHNLSVINSEELSSILKLTWNTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDASTRSSFTVQDLK PFTEYVFRIRCMKEDGKGYWSDWSEEASGITYED
140	WSXWS motif	WSDWS
141	Human gp130 FNIII domain 3	APSFVYKIDPSHTQGYRTVQLVWKTLPPEFANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLT NDRYLATLTVRNLVGKSDAAVLTIPACDFQAT
142	Human gp130 FNIII domain 4	PVMDLKAFPKDNMLWVEWITPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAE SKCYLITVTPVYADGPGSPESIKAYLKQA
143	Human gp130 FNIII domain 5	PPSKGPTVTRTKKVGNKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSL TSDTLYMVRMAAYTDEGGKDGPEFTFTTPKF
144	Human gp130 cytokine- binding module	DPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNNANYVWKTNHFTIPKEQYTIINRTASSVT TDIASLNIQLTCNLTFGQLEQNVYGIITISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETN FTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDVPYKVK PNPPHNLSVINSEELSSILKLTWNTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDASTRSSFTVQD LKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYED
145	4D4 hlgG1 HC	EVQLVETGGGLVQPGSRSLKSCVSGFTFSRYWYMWIRQAPGKGLEWVASINADGGSTYYPD SVQGRFTISRDAEDTVYLMNSLRSEDATYYCVKMGVYGLLLPYVMDAWGQASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVTVTPSSSLGTQTYICNVNHPKSNKVDKKVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTKQSLSLSPGK
146	3G9 hlgG1 HC	EVQLAETGGGLVQPGSRSLKSCVSGFTFSRYWYMWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDAEDTVYLMNSLRSEDATYYCVKMGVYGLLLPYVMDAWGQASVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVTVTPSSSLGTQTYICNVNHPKSNKVDKKVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPK PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY FYPDSIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTKQSLSLSPGK
147	4A7/7D8 hlgG1 HC	EVQLAETGGGLVQPGSRSLKSCVSGFTFSRYWYMWIRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDAEDTVYLMNSLRSEDATYYCVKMGVYGLLLPYVMDAWGQASVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVTVTPSSSLGTQTYICNVNHPKSNKVDKKVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPK PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY FYPDSIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTKQSLSLSPGK
148	8C6 hlgG1 HC	EVQLVESGGGLVQPGSRSLKSCAASGFTFNYYMAWVRQAPTGLEWVASITKSGGSTNYRD SVRGRFTISRDDAKSTLSQMDSLRSEDATYYCARGGIYYGLFTGYFDYVWGQGMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SVVTVTPSSSLGTQTYICNVNHPKSNKVDKKVEPKSCDKHTHTCPPCPAPPELLGGPSVFLFPPK KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY

		SDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHY TQKSLSLSPGK
149	C03-A7 hlgG1 HC	EVQLVESGGGLVQPGRSLKLCVSGSFTFSNYGMAWWRQAPTQGLEWVASISTGGDNTYYRD SVKGRFTISRDDAKNTQYLQMDSLRSEDATATYYCARLGIYYRLLVPYFHYWGQGMVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSL SVVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY SDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHY TQKSLSLSPGK
150	CON'4'9'7/8 hlgG1 HC	EVQLX ₁ ETGGGLVQPGRSLKLCVX ₂ SGFTFSX ₃ YWMYWRQAPGKGLEWVASINX ₄ DGGSTYY PDSVX ₅ GRFTX ₆ SRDNAEX ₇ TVYLQMNSLRSEDATATYYCVKMGX ₈ X ₉ X ₁₀ GLLX ₁₁ PYVMDAWGQG ASVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVM HEALHNHYTQKSLSLSPGK 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
151	4D4CVH2 hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRSEDATATYYCVKMGLYFGLLVPYVMDAWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSL SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
152	4D4CVH3 hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNKDTVYLQMNSLRSEDATATYYCVKMGLYFGLLVPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLY SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPGK
153	4D4CVH4 hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNKNTVYLQMNSLRSEDATATYYCVKMGLYFGLLVPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLY SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPGK
154	4D4CVH2.1 hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNKDTVYLQMNSLRSEDATATYYCVKMGLYFGLLVPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLY SLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPGK
155	4D4CVH2.2 hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRSEDATATYYCVKMGLYFGLLVPYVMDAWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSSGLYSL SSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
156	CON4D4P/Hu hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCX ₁ X ₂ SGFTFSNYWYWX ₃ RQAPGKGLEWVASINADGGSTYY PDSVKGRFTISRDNX ₄ X ₅ X ₆ TVYLQMNSLRSEDATATYYCVKMGLYFGLLVPYVMDAWGQGLTV VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSVHTFPAVLQSS GLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHE ALHNHYTQKSLSLSPGK

		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
157	4D4 K LC	NIQLTQSPSLLSASVGDRTVLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGTGKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
158	3G9 K LC	NIQLTQSPSLLSTSVGDRTVLSCKGSQNVNNYLAWYQQKLGKTPKLLIYHTNSLQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGTGKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
159	4A7/7D8 K LC	NIQLTQSPSLLSTSVGDRTVLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNSLQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGTGKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
160	8C6 K LC	DTVLTQSPSLLASVGPGRVVSICRASEGVNSFMHWYQQNPGQKPKLLIYKASNLASGVPARFSGSGSDTDFTLTIDPVEADDTATYFCQQNWDPFTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
161	C03-A7 K LC	NIQLTQSPSLLSASVGDRTVLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNSFQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFCYQYNNGWTFGGGKLDLKRVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
162	CON'4'9'7/8 K LC	NIQLTQSPSLLSX ₁ SVGDRTVLSCKGSQNX ₂ NNYLAWX ₃ QQKLGEX ₄ PKLLIYX ₅ TNX ₆ LQTGIPSRFSGSGSX ₇ TDYTLTISSLQPEDVATYFCYQYTX ₈ GYTFGX ₉ GKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 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
163	4D4C/GVL1 K LC	NIQLTQSPSLLSASVGDRTVITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
164	4D4CVL2 K LC	NIQLTQSPSFLSASVGDRTVITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGIPSRFSGSGSDTDYTLTISSLQPEDVATYFCYQYTNGYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
165	4D4CVL4 K LC	DIQLTQSPSFLSASVGDRTVITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFSGSGSDTDYTLTISSLQPEDVATYCYQYTNGYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
166	4D4GVL3 K LC	DIQLTQSPSFLSASVGDRTVITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFSGSGSDTDYTLTISSLQPEDVATYCYQYTNGYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
167	4D4GVL4 K LC	DIQMTQSPSSLSASVGDRTVITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFSGSGSGSDFTLTISLQPEDVATYCYQYTNGYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
168	CON4D4P/Hu K LC	X_1 IQX ₂ TQSPSX ₃ LSASVGDRTVITCKGSQNVNNYLAWYQQKX ₄ GKX ₅ PKLLIYNTNQLQTGX ₆ PSRFSGSGSX ₇ TDX ₈ TLTISSLQPEDX ₉ ATYX ₁₀ CYQYTNGYTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 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
169	3G9 region a	SKGPTVRTK
170	3G9 region b	RNYTIFY
171	3G9 region c	TDEGGK
172	3G9 region composite	SKGPTVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSTHEYTLSSLTSDTLYMVRMAAYTDEGGK
173	4A7/7D8 region 1a	KEKCMDY
174	4A7/7D8 region 1b	THLETNFT
175	4A7/7D8 region 1 composite	KEKCMDYFHVNNANYIVWKTNHFTIPKEQYTIINRTASSVFTDIASLNIQLTCNILTFGQLEQNVYGITISGLPPEKPKNLSCIVNEGKMRCEWDGGRETHLETNFT
176	4A7/7D8 region 2a	SEELSSILK
177	4A7/7D8 region 2b	YNIQYRT
178	4A7/7D8 region 2c	RYLATLTVR
179	4A7/7D8 region 2	SEELSSILKLTWTNPSIKSVILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIR

	composite	CMKEDGKGYWSDWSEEASGITYEDRPSKAPSFWYKIDPSHTQGYRTVQLVWKTLPPEANGKI LDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVR
180	4D4 region a	YTVNATKLT
181	4D4 region b	KSDAAVLT
182	4D4 region a+b composite	YTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLT
183	8C6 region a	KILDYEVLT
184	8C6 region b	RWKSHLQNY
185	8C6 region a+b composite	KILDYEVTLTRWKSHLQNY
186	C03-A7 region a	RETH
187	C03-A7 region b	KAKRDTPTSCTVDY
188	C03-A7 region a+b composite	RETHLETNFTLKSEWATHKFADCKAKRDTPTSCTVDY
189	CH2 IgG1 (YTE)	PCPAPELLGGPSVFLFPPKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR
190	Human IgG1 CH2-CH3 region (YTE)	PCPAPELLGGPSVFLFPPKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
191	Human IgG1 G1m3 allotype CH2-CH3 region (YTE)	PCPAPELLGGPSVFLFPPKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK
192	Human IgG1 constant region (YTE)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGLVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVESKYGPPCPAPAEFEGGPSVFLFPPKPK PKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALH NHYTQKSLSLSPGK
193	Human IgG1 constant region G1m3 allotype (YTE)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSGLVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVESKYGPPCPAPAEFEGGPSVFLFPPKPK PKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALH NHYTQKSLSLSPGK
194	Human IgG4 constant region (S228P, L235E)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSGLVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVESKYGPPCPAPAEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK
195	Human IgG4 CH1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSGLVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
196	Human IgG4 hinge	ESKYGPPCPSCP
197	Human IgG4 hinge (S228P)	ESKYGPPCPSCP
198	Human IgG4 CH2	APEFEGGPSVFLFPPKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
199	Human IgG4 CH2 (L235E)	APEFEGGPSVFLFPPKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
200	Human IgG4 CH3	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGS FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
201	Human IgG4 CH2-CH3 (L235E)	APEFEGGPSVFLFPPKPKDLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLGK
202	4D4 hlgG4(S228P, L235E) HC	EVQLVETGGGLVQPGSRSLKSCVVSGETFTSNRYWYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSGLVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVESKYGPPCPAPAEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK
203	3G9 hlgG4(S228P, L235E) HC	EVQLAETGGGLVQPGSRSLKSCVVSGETFTSNRYWYWRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDAENTVYLQMNSLRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTWNSGALTSGLVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVESKYGPPCPAPAEFEGGPSVFLFPPKPK

		DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
204	4A7/7D8 hlgG4(S228P, L235E) HC	EVQLAETGGGLVQPGRSLKLSVASGFTFSRYWYWRQAPGKGLEWVASINTDGGSTYYPD SVQGRFTVSRDNAENTVFLQMNSLRSEDATYYCVKMGLEYGLLPYVMDAWGQGASVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
205	8C6 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLKLSCAASGFTFNYYMAWWRQAPTCKGLEWVASITKSGGSTNYRD SVRGRFTISRDDAKSTLSLQMDSLRSEDATYYCARGGIYYGLFTGYFDYWGQGMVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK
206	C03-A7 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLKLSCVSGSFTFSNYGMAWWRQAPTCKGLEWVASISTGGDNTYYRD SVKGRFTISRDDAKNTQYLQMDSLRSEDATYYCARLGIYYRLLVPYFHYWGQGMVTVSSAS TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQ KSLSLSLGK
207	CON'4'9'7/8 hlgG4(S228P, L235E) HC	EVQLX ₁ ETGGGLVQPGRSLKLSVCX ₂ SGFTFSX ₃ YWYWRQAPGKGLEWVASINX ₄ DGGSTYY PDSVX ₅ GRFTX ₆ SRDNAEX ₇ TVYQLQMNSLRSEDATYYCVKMGX ₈ X ₉ X ₁₀ GLLX ₁₁ PYVMDAWGQG ASVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSV FLFPPKPKD TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVME 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
208	4D4CVH2 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDAEDTVYQLQMNSLRAEDATYYCVKMGLEYGLLPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS SSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
209	4D4CVH3 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNKD TVYQLQMNSLRAEDATYYCVKMGLEYGLLPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
210	4D4CVH4 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDNKD TVYQLQMNSLRAEDATYYCVKMGLEYGLLPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSGGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
211	4D4CVH2.1 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINADGGSTYYPD DSVKGRFTISRDAEDTVYQLQMNSLRAEDATYYCVKMGLEYGLLPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS

		DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
212	4D4CVH2.2 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINADGGSTYYPD SVKGRFTISRDN ₃ SKDTVYLQMN ₄ SLRAEDTATYYCV ₅ KMGLYFGLLV ₆ VPYVMDAWGQGT ₇ LVTVSSA STKGP ₈ SVFLAPCSR ₉ STSESTAALGCLVKDYFPEP ₁₀ VT ₁₁ SWNSGALTSGVHTFPAVLQSSGLYSL SSV ₁₂ VTVPSSSLG ₁₃ TKTYCNVDHKPSNTKVDKRVESKYGPPC ₁₄ PPCPAPEFEGG ₁₅ PSVFLRPPKPK DTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHN ₁₆ AKTKPREEQFNSTYRVVSVLT ₁₇ VLH ₁₈ Q DWLNGKEYKCKVSNKGLPSSIEK ₁₉ TISKAKGQPREPQVY ₂₀ TLPPS ₂₁ QEE ₂₂ MTKNQVSL ₂₃ TCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
213	CON4D4P/Hu hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCV ₁ X ₂ SGFTFSNYWMY ₃ W ₄ X ₅ RQAPGKGLEWVASINADGGSTYY PDSVKGRFTISRDN ₆ X ₇ X ₈ TVYLQMN ₉ SLRAEDTATYYCV ₁₀ KMGLYFGLLV ₁₁ VPYVMDAWGQGT ₁₂ LV VSSASTKGP ₁₃ SVFLAPCSR ₁₄ STSESTAALGCLVKDYFPEP ₁₅ VT ₁₆ SWNSGALTSGVHTFPAVLQSS GLYSLSSV ₁₇ VTVPSSSLG ₁₈ TKTYCNVDHKPSNTKVDKRVESKYGPPC ₁₉ PPCPAPEFEGG ₂₀ PSVFLR PKPKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHN ₂₁ AKTKPREEQFNSTYRVVSVLT VLH ₂₂ QDWLNGKEYKCKVSNKGLPSSIEK ₂₃ TISKAKGQPREPQVY ₂₄ TLPPS ₂₅ QEE ₂₆ MTKNQVSL ₂₇ TCLVK GFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEAL HNHYTQKSLSLSLGK
		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
214	4D4_D53G VH	EVQLVETGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRSED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGS ₉ AVTVSS
215	4D4_D53E VH	EVQLVETGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRSED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGS ₉ AVTVSS
216	4D4_D53Q VH	EVQLVETGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRSED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGS ₉ AVTVSS
217	4D4_D53L VH	EVQLVETGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRSED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGS ₉ AVTVSS
218	4D4_G54A VH	EVQLVETGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRSED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGS ₉ AVTVSS
219	4D4CVH2_D53G VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
220	4D4CVH2_D53E VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
221	4D4CVH2_D53Q VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
222	4D4CVH2_D53L VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
223	4D4CVH2_G54A VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
224	4D4CVH3_D53G VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ SKDTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
225	4D4CVH3_D53E VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ SKDTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
226	4D4CVH3_D53Q VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ SKDTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
227	4D4CVH3_D53L VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ SKDTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
228	4D4CVH3_G54A VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ₃ SKDTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
229	4D4CVH4_D53G VH	EVQLVESGGGLVQPGSRSLRLSCAASGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ SKNTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
230	4D4CVH4_D53E VH	EVQLVESGGGLVQPGSRSLRLSCAASGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ SKNTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
231	4D4CVH4_D53Q VH	EVQLVESGGGLVQPGSRSLRLSCAASGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ SKNTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
232	4D4CVH4_D53L VH	EVQLVESGGGLVQPGSRSLRLSCAASGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ SKNTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
233	4D4CVH4_G54A VH	EVQLVESGGGLVQPGSRSLRLSCAASGFTFSNYWMY ₂ WIRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ₃ SKNTVYLQMN ₄ SLRAED ₅ TATYYCV ₆ KMGLYFGLLV ₇ VPYVMDAWGQGT ₈ LVTVSS
234	4D4CVH2.1_D53G VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
235	4D4CVH2.1_D53E VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
236	4D4CVH2.1_D53Q VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS
237	4D4CVH2.1_D53L VH	EVQLVESGGGLVQPGSRSLRLSCVVS ₁ SGFTFSNYWMY ₂ WIRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ₃ AE ₄ DTVYLQMN ₅ SLRAED ₆ TATYYCV ₇ KMGLYFGLLV ₈ VPYVMDAWGQGT ₉ LVTVSS

238	4D4CVH2.1_G54A VH	EVQLVESGGGLVQPGRSLRLSCVVSQFTFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTVTVSS
239	4D4CVH2.2_D53G VH	EVQLVESGGGLVQPGRSLRLSCVVSQFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTVTVSS
240	4D4CVH2.2_D53E VH	EVQLVESGGGLVQPGRSLRLSCVVSQFTFSNYWMYWRQAPGKGLEWVASINAEAGGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTVTVSS
241	4D4CVH2.2_D53Q VH	EVQLVESGGGLVQPGRSLRLSCVVSQFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTVTVSS
242	4D4CVH2.2_D53L VH	EVQLVESGGGLVQPGRSLRLSCVVSQFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTVTVSS
243	4D4CVH2.2_G54A VH	EVQLVESGGGLVQPGRSLRLSCVVSQFTFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNKDTVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTVTVSS
244	4D4_D53G, 4D4CVH2_D53G, 4D4CVH3_D53G, 4D4CVH4_D53G, 4D4CVH2.1_D53G, 4D4CVH2.2_D53G HC- CDR2	INAGGGST
245	4D4_D53E, 4D4CVH2_D53E, 4D4CVH3_D53E, 4D4CVH4_D53E, 4D4CVH2.1_D53E, 4D4CVH2.2_D53E HC- CDR2	INAEAGGST
246	4D4_D53Q, 4D4CVH2_D53Q, 4D4CVH3_D53Q, 4D4CVH4_D53Q, 4D4CVH2.1_D53Q, 4D4CVH2.2_D53Q HC- CDR2	INAGGGST
247	4D4_D53L, 4D4CVH2_D53L, 4D4CVH3_D53L, 4D4CVH4_D53L, 4D4CVH2.1_D53L, 4D4CVH2.2_D53L HC- CDR2	INALGGST
248	4D4_G54A, 4D4CVH2_G54A, 4D4CVH3_G54A, 4D4CVH4_G54A, 4D4CVH2.1_G54A, 4D4CVH2.2_G54A HC- CDR2	INADAGST
249	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
250	CON4D4P/Hu_D53var_ G53var VH	EVQLVESGGGLVQPGRSLRLSCX ₁ X ₂ SGFTFSNYWMYWX ₃ RQAPGKGLEWVASINAX ₄ X ₅ GSTY YPDSVKGRFTISRDNX ₆ X ₇ X ₈ TVYLQMNSLRAEDTATYYCVKMGLYFGLLVIPYVMDAWGQGLTV 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
251	4D4_N93G VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGQYTFGTGKLELK
252	4D4_N93E VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGQYTFGTGKLELK
253	4D4_N93L VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGTGKLELK
254	4D4_N93Q VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGQYTFGTGKLELK
255	4D4_G94A VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGTGKLELK
256	4D4C/GVL1_N93G VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDDTDYTLTISSLQPEDVATYFCYQYTGQYTFGQGTGLEIK
257	4D4C/GVL1_N93E VL	NIQLTQSPSLLSASVGDVRLTSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS

		GSDDTYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIK
258	4D4C/GVL1_N93L VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIK
259	4D4C/GVL1_N93Q VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTGQYTFGQGTKLEIK
260	4D4C/GVL1_G94A VL	NIQLTQSPSLLSASVGDRVTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIK
261	4D4CVL2_N93G VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTGQYTFGQGTKLEIK
262	4D4CVL2_N93E VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIK
263	4D4CVL2_N93L VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIK
264	4D4CVL2_N93Q VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTGQYTFGQGTKLEIK
265	4D4CVL2_G94A VL	NIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGIPSRFSGS GSDDTYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIK
266	4D4CVL4_N93G VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYCYQYTGQYTFGQGTKLEIK
267	4D4CVL4_N93E VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYCYQYTEGYTFGQGTKLEIK
268	4D4CVL4_N93L VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYCYQYTLGYTFGQGTKLEIK
269	4D4CVL4_N93Q VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYCYQYTGQYTFGQGTKLEIK
270	4D4CVL4_G94A VL	DIQLTQSPSFLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDVATYCYQYTNAYTFGQGTKLEIK
271	4D4GVL3_N93G VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYCYQYTGQYTFGQGTKLEIK
272	4D4GVL3_N93E VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYCYQYTEGYTFGQGTKLEIK
273	4D4GVL3_N93L VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYCYQYTLGYTFGQGTKLEIK
274	4D4GVL3_N93Q VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYCYQYTGQYTFGQGTKLEIK
275	4D4GVL3_G94A VL	DIQLTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG SGSDTDYTLTISSLQPEDFATYCYQYTNAYTFGQGTKLEIK
276	4D4GVL4_N93G VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG GSGSGTDFTLTISSLQPEDFATYCYQYTGQYTFGQGTKLEIK
277	4D4GVL4_N93E VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG GSGSGTDFTLTISSLQPEDFATYCYQYTEGYTFGQGTKLEIK
278	4D4GVL4_N93L VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG GSGSGTDFTLTISSLQPEDFATYCYQYTLGYTFGQGTKLEIK
279	4D4GVL4_N93Q VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG GSGSGTDFTLTISSLQPEDFATYCYQYTGQYTFGQGTKLEIK
280	4D4GVL4_G94A VL	DIQMTQSPSSLSASVGDRVTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNNLQTGVPSRFSG GSGSGTDFTLTISSLQPEDFATYCYQYTNAYTFGQGTKLEIK
281	4D4_N93G, 4D4C/GVL1_N93G, 4D4CVL2_N93G, 4D4CVL4_N93G, 4D4GVL3_N93G, 4D4GVL4_N93G LC- CDR3	YQYTGQY
282	4D4_N93E, 4A77D8_N93E, 4D4C/GVL1_N93E, 4D4CVL2_N93E, 4D4CVL4_N93E, 4D4GVL3_N93E, 4D4GVL4_N93E LC- CDR3	YQYTEGYT
283	4D4_N93L, 4A77D8_N93L, 4D4C/GVL1_N93L, 4D4CVL2_N93L, 4D4CVL4_N93L, 4D4GVL3_N93L, 4D4GVL4_N93L LC-	YQYTLGYT

	CDR3	
284	4D4_N93Q, 4D4C/GVL1_N93Q, 4D4CVL2_N93Q, 4D4CVL4_N93Q, 4D4GVL3_N93Q, 4D4GVL4_N93Q LC- CDR3	YQYTQGYT
285	4D4_G94A, 4D4C/GVL1_G94A, 4D4CVL2_G94A, 4D4CVL4_G94A, 4D4GVL3_G94A, 4D4GVL4_G94A LC- CDR3	YQYTNAVY
286	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
287	CON4D4P/Hu_N93var_ G94var VL	X ₁ IQX ₂ TQSPSX ₃ LSASVGDRTITCKGSQNVNNYLAWYQQKX ₄ GKX ₅ PKLLIYNTNNLQTGX ₆ PSR FSGSGSX ₇ TDX ₈ TLTISSLQPEDX ₉ ATYX ₁₀ CYQYTX ₁₁ X ₁₂ YTFGQGTKEIK 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
288	4D4_D53G hlgG1 HC	EVQLVETGGGLVQPGSRSLKLSGVVSGFTFSNYWYWRQAPGKGLEWVASNAGGGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLVPMYMDAWGQGASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPGK
289	4D4_D53E hlgG1 HC	EVQLVETGGGLVQPGSRSLKLSGVVSGFTFSNYWYWRQAPGKGLEWVASNAEGGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLVPMYMDAWGQGASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPGK
290	4D4_D53Q hlgG1 HC	EVQLVETGGGLVQPGSRSLKLSGVVSGFTFSNYWYWRQAPGKGLEWVASNAGGGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLVPMYMDAWGQGASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPGK
291	4D4_D53L hlgG1 HC	EVQLVETGGGLVQPGSRSLKLSGVVSGFTFSNYWYWRQAPGKGLEWVASNALGGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLVPMYMDAWGQGASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPGK
292	4D4_G54A hlgG1 HC	EVQLVETGGGLVQPGSRSLKLSGVVSGFTFSNYWYWRQAPGKGLEWVASNADAGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLVPMYMDAWGQGASVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPGK
293	4D4CVH2_D53G hlgG1 HC	EVQLVESGGGLVQPGSRSLRLSCVVSGFTFSNYWYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDAEDTVYLQMNSLRSEDATYYCVKMGLYFGLLVPMYMDAWGQGGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY

		PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
294	4D4CVH2_D53E hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLYS SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
295	4D4CVH2_D53Q hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLYS SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
296	4D4CVH2_D53L hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLYS SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
297	4D4CVH2_G54A hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLYS SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
298	4D4CVH3_D53G hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINAGGGSTYYP DSVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPGK
299	4D4CVH3_D53E hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINAEGGSTYYP DSVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPGK
300	4D4CVH3_D53Q hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINAQGGSTYYP DSVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALH NHYTQKSLSLSPGK
301	4D4CVH3_D53L hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLYS SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHCTCPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIETISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNH YTQKSLSLSPGK
302	4D4CVH3_G54A hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNADETVYLQMNSLRADETATYYCVKMGLYFGLLVPMYMDAWGQGLTLTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHTFPVAVLQSSGLYS

		SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKLSLSLSPGK
303	4D4CVH4_D53G hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWASINAGGGSTYYPD SVKGRFTISRDN SKNTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YHTQKLSLSLSPGK
304	4D4CVH4_D53E hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWASINAEAGGGSTYYPD SVKGRFTISRDN SKNTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YHTQKLSLSLSPGK
305	4D4CVH4_D53Q hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWASINAGGGSTYYPD SVKGRFTISRDN SKNTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YHTQKLSLSLSPGK
306	4D4CVH4_D53L hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWASINAGGGSTYYPD SVKGRFTISRDN SKNTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKLSLSLSPGK
307	4D4CVH4_G54A hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWASINADAGSTYYPD SVKGRFTISRDN SKNTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSSA STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKLSLSLSPGK
308	4D4CVH2.1_D53G hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS GFTFSNYWMYWRQAPGKGLEWASINAGGGSTYYPD SVKGRFTISRDN AEDTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YHTQKLSLSLSPGK
309	4D4CVH2.1_D53E hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS GFTFSNYWMYWRQAPGKGLEWASINAEAGGGSTYYPD SVKGRFTISRDN AEDTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YHTQKLSLSLSPGK
310	4D4CVH2.1_D53Q hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS GFTFSNYWMYWRQAPGKGLEWASINAGGGSTYYPD SVKGRFTISRDN AEDTVYLQMNSLR AEDTATYYCVKMGLYFGLLV PYVMDAWGQGLTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VHLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YHTQKLSLSLSPGK

311	4D4CVH2.1_D53L hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDN ^{AE} DTVYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
312	4D4CVH2.1_G54A hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ^{AE} DTVYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
313	4D4CVH2.2_D53G hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDN ^{SKDT} VYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
314	4D4CVH2.2_D53E hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINAE ^{GG} STYYPD SVKGRFTISRDN ^{SKDT} VYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
315	4D4CVH2.2_D53Q hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINAE ^{GG} STYYPD SVKGRFTISRDN ^{SKDT} VYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
316	4D4CVH2.2_D53L hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDN ^{SKDT} VYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
317	4D4CVH2.2_G54A hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCVVS ^{SGFTFS} SNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ^{SKDT} VYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTVTVSSA STKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^{ALHNH} YTQKSLSLSPGK
318	CON4D4P/Hu_D53var_ G53var hlgG1 HC	EVQLVESGGGLVQPGRSLRLSCX ₁ X ₂ ^{SGFTFS} SNYWMYWX ₃ RQAPGKGLEWVASINAX ₄ X ₅ GSTY YPDSVKGRFTISRDNX ₆ X ₇ X ₈ TVYLQMNSLRAEDTATYYCVKMGLYFGLLV ^{VPYVMD} AWGQGLTV TVSSASTKGPVSFPLAPSSKSTSGGTAALGCLVKDYFPEPVT ^{SVWNSGALT} SGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLT ^{VL} TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV ^{FSC} SVMH ^E ALHNHYTQKSLSLSPGK 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
319	4D4_D53G hlgG4(S228P, L235E)	EVQLVETGGGLVQPGRSLKLS ^{CVVS} SGFTFS ^{NYWMYWRQAPGKGLEWVASINAGGGSTYYPD} SVKGRFTISRDN ^{AE} DTVYLQMNSL ^{RAEDTATYYCVKMGLYFGLLV} VPYVMD ^{AWGQGS} AVTVSSA

	HC	STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
320	4D4_D53E hlgG4(S228P, L235E) HC	EVQLVETGGGLVQPGSRSLKSCVVSGETFSNYWMYWRQAPGKGLEWVASNAEGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
321	4D4_D53Q hlgG4(S228P, L235E) HC	EVQLVETGGGLVQPGSRSLKSCVVSGETFSNYWMYWRQAPGKGLEWVASNAEGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
322	4D4_D53L hlgG4(S228P, L235E) HC	EVQLVETGGGLVQPGSRSLKSCVVSGETFSNYWMYWRQAPGKGLEWVASNALGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
323	4D4_G54A hlgG4(S228P, L235E) HC	EVQLVETGGGLVQPGSRSLKSCVVSGETFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRSEDATYYCVKMGLYFGLLPYVMDAWGQGASVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
324	4D4CVH2_D53G hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSGETFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRAEDATYYCVKMGLYFGLLPYVMDAWGQGGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
325	4D4CVH2_D53E hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSGETFSNYWMYWRQAPGKGLEWVASINAEGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRAEDATYYCVKMGLYFGLLPYVMDAWGQGGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
326	4D4CVH2_D53Q hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSGETFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRAEDATYYCVKMGLYFGLLPYVMDAWGQGGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT QKSLSLSLGK
327	4D4CVH2_D53L hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSGETFSNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDAEDTVYLQMNLSRAEDATYYCVKMGLYFGLLPYVMDAWGQGGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVNDHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHREALHNNHYT

		QKSLSLSLGK
328	4D4CVH2_G54A hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVS ^G GFTFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ^A EDTVYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
329	4D4CVH3_D53G hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVS ^G GFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYP DSVKGRFTISRDN ^S KD ^T VYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
330	4D4CVH3_D53E hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVS ^G GFTFSNYWMYWRQAPGKGLEWVASINAE ^G GGSTYYP DSVKGRFTISRDN ^S KD ^T VYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
331	4D4CVH3_D53Q hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVS ^G GFTFSNYWMYWRQAPGKGLEWVASINAE ^G GGSTYYP DSVKGRFTISRDN ^S KD ^T VYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
332	4D4CVH3_D53L hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVS ^G GFTFSNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDN ^S KD ^T VYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
333	4D4CVH3_G54A hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVS ^G GFTFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDN ^S KD ^T VYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
334	4D4CVH4_D53G hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAAS ^G GFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYP DSVKGRFTISRDN ^S KNTVYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
335	4D4CVH4_D53E hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAAS ^G GFTFSNYWMYWRQAPGKGLEWVASINAE ^G GGSTYYP DSVKGRFTISRDN ^S KNTVYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTP ^E VT ^C VVDV ^S QEDPEVGFNMYVDGVEVHNAKTKPREEQFNSTYRVVSVLT ^V LHQ DWLNGKEYKCKVSNKGLPSSIEK ^T ISKAKGQPREPQVYTLPPS ^Q EE ^M TKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYK ^T TPPVL ^D SDGSFFLYSRLTVDKSRWQEGNVFSCSV ^M HEALHNHYT QKSLSLSLGK
336	4D4CVH4_D53Q hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAAS ^G GFTFSNYWMYWRQAPGKGLEWVASINAE ^G GGSTYYP DSVKGRFTISRDN ^S KNTVYLQMNSLRAEDTATYYCVKMGLYFGLLPYVMDAWGQGT ^L TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT ^S WNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLG ^T KTYTCNV ^D HKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK

		DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
337	4D4CVH4_D53L hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
338	4D4CVH4_G54A hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
339	4D4CVH2.1_D53G hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
340	4D4CVH2.1_D53E hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINAEAGSTYYPD DSVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
341	4D4CVH2.1_D53Q hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD DSVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
342	4D4CVH2.1_D53L hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
343	4D4CVH2.1_G54A hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
344	4D4CVH2.2_D53G hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINAGGGSTYYPD SVKGRFTISRDNKNTVYLQMNSLRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTkTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
345	4D4CVH2.2_D53E	EVQLVESGGGLVQPGRSLRLSCVVSIGFTFSNYWMYWRQAPGKGLEWVASINAEAGSTYYPD

	hlgG4(S228P, L235E) HC	SVKGRFTISRDNKSDTVYLQMNLSRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
346	4D4CVH2.2_D53Q hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSQGTFTSNYWMYWRQAPGKGLEWVASINAQGGSTYYPD SVKGRFTISRDNKSDTVYLQMNLSRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
347	4D4CVH2.2_D53L hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSQGTFTSNYWMYWRQAPGKGLEWVASINALGGSTYYPD SVKGRFTISRDNKSDTVYLQMNLSRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
348	4D4CVH2.2_G54A hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCVVSQGTFTSNYWMYWRQAPGKGLEWVASINADAGSTYYPD SVKGRFTISRDNKSDTVYLQMNLSRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPK DTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQ DWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT QKSLSLSLGK
349	CON4D4P/Hu_D53var_ G53var hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGSRSLRLSCX ₁ X ₂ SGFTFSNYWMYWX ₃ RQAPGKGLEWVASINAX ₄ X ₅ GSTY YPDSVKGRFTISRDNX ₆ X ₇ X ₈ TVYLQMNLSRAEDTATYYCVKMGLYFGLLVYPYVMDAWGQGLTV TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGKTKYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFP PKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLT VLHQDWLNGKEYCKVSNKGLPSSIEKTSKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEAL HNHYTQKSLSLSLGK 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
350	4D4_N93G K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGYYTFTGTGKLELKRVAAPSVFIFFPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
351	4D4_N93E K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGYYTFTGTGKLELKRVAAPSVFIFFPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
352	4D4_N93L K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGYYTFTGTGKLELKRVAAPSVFIFFPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
353	4D4_N93Q K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTGYYTFTGTGKLELKRVAAPSVFIFFPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
354	4D4_G94A K LC	NIQLTQSPSLLSASVGDRVTLSCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSG SGSDTDYTLTISSLQPEDVATYFCYQYTNAYTFTGTGKLELKRVAAPSVFIFFPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNREGC
355	4D4C/GVL1_N93G K LC	NIQLTQSPSLLSASVGDRVTLITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGYYTFTGQGTKEIKRTVAAPSVFIFFPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNREGC
356	4D4C/GVL1_N93E K LC	NIQLTQSPSLLSASVGDRVTLITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLQTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTGYYTFTGQGTKEIKRTVAAPSVFIFFPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYAC

		EVTHQGLSSPVTKSFNRGEC
357	4D4C/GVL1_N93L K LC	NIQLTQSPSLLSASVGDRTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
358	4D4C/GVL1_N93Q K LC	NIQLTQSPSLLSASVGDRTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
359	4D4C/GVL1_G94A K LC	NIQLTQSPSLLSASVGDRTITCKGSQNVNNYLAWYQQKLGKTPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
360	4D4CVL2_N93G K LC	NIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
361	4D4CVL2_N93E K LC	NIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
362	4D4CVL2_N93L K LC	NIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
363	4D4CVL2_N93Q K LC	NIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
364	4D4CVL2_G94A K LC	NIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGIPSRFSGS GSDTDYTLTISSLQPEDVATYFCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYAC EVTHQGLSSPVTKSFNRGEC
365	4D4CVL4_N93G K LC	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDVATYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
366	4D4CVL4_N93E K LC	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDVATYCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
367	4D4CVL4_N93L K LC	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDVATYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
368	4D4CVL4_N93Q K LC	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDVATYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
369	4D4CVL4_G94A K LC	DIQLTQSPSFLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDVATYCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
370	4D4GVL3_N93G K LC	DIQLTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDFATYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
371	4D4GVL3_N93E K LC	DIQLTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDFATYCYQYTEGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
372	4D4GVL3_N93L K LC	DIQLTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDFATYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC
373	4D4GVL3_N93Q K LC	DIQLTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLTGVP SRFSG SGSDTDYTLTISSLQPEDFATYCYQYTLGYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLKADYEHKHKVYA CEVTHQGLSSPVTKSFNRGEC

374	4D4GVL3_G94A K LC	DIQLTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFS SGSDTDYTLTISSLQPEDFATYYCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
375	4D4GVL4_N93G K LC	DIQMTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCYQYTGQYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
376	4D4GVL4_N93E K LC	DIQMTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCYQYTGQYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
377	4D4GVL4_N93L K LC	DIQMTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCYQYTGQYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
378	4D4GVL4_N93Q K LC	DIQMTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCYQYTGQYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
379	4D4GVL4_G94A K LC	DIQMTQSPSSLSASVGDRTITCKGSQNVNNYLAWYQQKPGKAPKLLIYNTNQLQTGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCYQYTNAYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
380	CON4D4P/Hu_N93var_ G94var K LC	X ₁ IQX ₂ TQSPSX ₃ LSASVGDRTITCKGSQNVNNYLAWYQQKX ₄ GKX ₅ PKLLIYNTNQLQTGX ₆ PSR FSGSGSX ₇ TDX ₈ TLTISSLQPEDX ₉ ATYX ₁₀ CYQYTX ₁₁ X ₁₂ YTFGQGTKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC 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
381	8C6 region c	EVTL
382	8C6 region d, 4D4 region c	LQNYTVNATKLT
383	8C6 region c+d composite	EVTLTRWKSHLQNYTVNATKLT
384	8C6 region a+b+c+d composite	KILDYEVTLTRWKSHLQNYTVNATKLT
385	4D4 region d	LTIPACDFQATHPVM
386	4D4 region a+b+c+d composite	EVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTPACDFQATHPVM
387	Ab343315 region	YSTVYF
388	Human gp130 membrane proximal region	APSFYWKIDPSHTQGYRTVQLVWMTLPPFEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLT NDRYLATLTVRNLVGKSDAAVLTPACDFQATHPVMDLKAFPKDNMLWVEWTPRESVKKYILE WCVLSDKAPCITDQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPS KGPTVTRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAENVNDSSTTEYTLSSLTSD TLYMVRMAAYTDEGGKDGPEFTFTTPKF

Table A

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:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
3G9	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:24	SEQ ID NO:25	SEQ ID NO:26
4A7/7D8	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:32	SEQ ID NO:24	SEQ ID NO:11	SEQ ID NO:12
8C6	SEQ ID NO:37	SEQ ID NO:38	SEQ ID NO:39	SEQ ID NO:45	SEQ ID NO:46	SEQ ID NO:47
C03-A7	SEQ ID NO:52	SEQ ID NO:53	SEQ ID NO:54	SEQ ID NO:24	SEQ ID NO:11	SEQ ID NO:58
CON'4'9'7/8	SEQ ID NO:62	SEQ ID NO:63	SEQ ID NO:64	SEQ ID NO:65	SEQ ID NO:66	SEQ ID NO:67
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:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:281
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, 4D4CVH2/4D4GVL3_N93E, 4D4CVH3/4D4GVL3_N93E, 4D4CVH4/4D4GVL3_N93E,	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:282

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, 4D4CVH2/4D4C/L2_N93L, 4D4CVH3/4D4C/L2_N93L, 4D4CVH4/4D4C/L2_N93L, 4D4CVH2.1/4D4C/L2_N93L, 4D4CVH2.2/4D4C/L2_N93L, 4D4CVH2/4D4C/L4_N93L, 4D4CVH3/4D4C/L4_N93L, 4D4CVH4/4D4C/L4_N93L, 4D4CVH2.1/4D4C/L4_N93L, 4D4CVH2.2/4D4C/L4_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:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:283
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, 4D4CVH2/4D4C/L2_N93Q, 4D4CVH3/4D4C/L2_N93Q, 4D4CVH4/4D4C/L2_N93Q, 4D4CVH2.1/4D4C/L2_N93Q, 4D4CVH2.2/4D4C/L2_N93Q, 4D4CVH2/4D4C/L4_N93Q, 4D4CVH3/4D4C/L4_N93Q, 4D4CVH4/4D4C/L4_N93Q, 4D4CVH2.1/4D4C/L4_N93Q, 4D4CVH2.2/4D4C/L4_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:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:284
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, 4D4CVH2/4D4C/L2_G94A, 4D4CVH3/4D4C/L2_G94A, 4D4CVH4/4D4C/L2_G94A, 4D4CVH2.1/4D4C/L2_G94A, 4D4CVH2.2/4D4C/L2_G94A, 4D4CVH2/4D4C/L4_G94A, 4D4CVH3/4D4C/L4_G94A, 4D4CVH4/4D4C/L4_G94A, 4D4CVH2.1/4D4C/L4_G94A, 4D4CVH2.2/4D4C/L4_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	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:285

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:2	SEQ ID NO:244	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
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:2	SEQ ID NO:245	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
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, 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	SEQ ID NO:2	SEQ ID NO:246	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12

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:2	SEQ ID NO:247	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
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:2	SEQ ID NO:248	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
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, 4D4CVH3_D53G/4D4C/GVL1_N93G, 4D4CVH3_D53G/4D4CVL2_N93G, 4D4CVH3_D53G/4D4CVL4_N93G, 4D4CVH3_D53G/4D4GVL3_N93G,	SEQ ID NO:2	SEQ ID NO:244	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:281

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:2	SEQ ID NO:245	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:281
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:2	SEQ ID NO:246	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:281
4D4_D53L/4D4_N93G, 4D4CVH2_D53L/4D4C/GVL1_N93G, 4D4CVH2_D53L/4D4CVL2_N93G, 4D4CVH2_D53L/4D4CVL4_N93G, 4D4CVH2_D53L/4D4GVL3_N93G, 4D4CVH2_D53L/4D4GVL4_N93G,	SEQ ID NO:2	SEQ ID NO:247	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:281

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:2	SEQ ID NO:248	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:281
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, 4D4CVH2.2_D53G/4D4GVL3_N93E, 4D4CVH2.2_D53G/4D4GVL4_N93E,	SEQ ID NO:2	SEQ ID NO:244	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:282
4D4_D53E/4D4_N93E, 4D4CVH2_D53E/4D4C/GVL1_N93E,	SEQ ID NO:2	SEQ ID NO:245	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:282

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,						
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:2	SEQ ID NO:246	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:282
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, 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,	SEQ ID NO:2	SEQ ID NO:247	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:282

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:2	SEQ ID NO:248	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:282
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:2	SEQ ID NO:244	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:283
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, 4D4CVH2.1_D53E/4D4C/GVL1_N93L, 4D4CVH2.1_D53E/4D4CVL2_N93L, 4D4CVH2.1_D53E/4D4CVL4_N93L, 4D4CVH2.1_D53E/4D4GVL3_N93L,	SEQ ID NO:2	SEQ ID NO:245	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:283

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:2	SEQ ID NO:246	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:283
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:2	SEQ ID NO:247	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:283
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, 4D4CVH4_G54A/4D4CVL2_N93L, 4D4CVH4_G54A/4D4CVL4_N93L, 4D4CVH4_G54A/4D4GVL3_N93L, 4D4CVH4_G54A/4D4GVL4_N93L,	SEQ ID NO:2	SEQ ID NO:248	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:283

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:2	SEQ ID NO:244	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:284
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:2	SEQ ID NO:245	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:284
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, 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,	SEQ ID NO:2	SEQ ID NO:246	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:284

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:2	SEQ ID NO:247	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:284
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:2	SEQ ID NO:248	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:284
4D4_D53G/4D4_G94A, 4D4CVH2_D53G/4D4C/GVL1_G94A, 4D4CVH2_D53G/4D4CVL2_G94A, 4D4CVH2_D53G/4D4CVL4_G94A, 4D4CVH2_D53G/4D4GVL3_G94A, 4D4CVH2_D53G/4D4GVL4_G94A, 4D4CVH3_D53G/4D4C/GVL1_G94A, 4D4CVH3_D53G/4D4CVL2_G94A,	SEQ ID NO:2	SEQ ID NO:244	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:285

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:2	SEQ ID NO:245	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:285
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:2	SEQ ID NO:246	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:285
4D4_D53L/4D4_G94A, 4D4CVH2_D53L/4D4C/GVL1_G94A, 4D4CVH2_D53L/4D4CVL2_G94A, 4D4CVH2_D53L/4D4CVL4_G94A,	SEQ ID NO:2	SEQ ID NO:247	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:285

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,						
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:2	SEQ ID NO:248	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:285
CON4D4P/Hu_D53var_G53var /CON4D4P/Hu_N93var_G94var	SEQ ID NO:2	SEQ ID NO:249	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:286

Table B

Antibody	Column A				Column B			
	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,	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

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								
3G9	SEQ ID NO:21	SEQ ID NO:6	SEQ ID NO:22	SEQ ID NO:8	SEQ ID NO:27	SEQ ID NO:28	SEQ ID NO:29	SEQ ID NO:30
4A7/7D8	SEQ ID NO:21	SEQ ID NO:6	SEQ ID NO:33	SEQ ID NO:8	SEQ ID NO:27	SEQ ID NO:35	SEQ ID NO:29	SEQ ID NO:30
8C6	SEQ ID NO:40	SEQ ID NO:41	SEQ ID NO:42	SEQ ID NO:43	SEQ ID NO:48	SEQ ID NO:49	SEQ ID NO:50	SEQ ID NO:30
C03-A7	SEQ ID NO:55	SEQ ID NO:41	SEQ ID NO:56	SEQ ID NO:43	SEQ ID NO:13	SEQ ID NO:59	SEQ ID NO:60	SEQ ID NO:61
CON'4'9'7/8	SEQ ID NO:68	SEQ ID NO:6	SEQ ID NO:69	SEQ ID NO:8	SEQ ID NO:70	SEQ ID NO:71	SEQ ID NO:72	SEQ ID NO:73
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, 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	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:89	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:90
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,	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:92	SEQ ID NO:93	SEQ ID NO:15	SEQ ID NO:90

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								
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, 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	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:94	SEQ ID NO:93	SEQ ID NO:96	SEQ ID NO:90
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_D53E/4D4GVL3_G94A	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:97	SEQ ID NO:93	SEQ ID NO:99	SEQ ID NO:90

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								
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, 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	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:101	SEQ ID NO:93	SEQ ID NO:102	SEQ ID NO:90
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,	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:89	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:90

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								
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, 4D4CVH3_G54A/4D4CVL2 4D4CVH3_G54A/4D4CVL2_N93G, 4D4CVH3_G54A/4D4CVL2_N93E, 4D4CVH3_G54A/4D4CVL2_N93L, 4D4CVH3_G54A/4D4CVL2_N93Q, 4D4CVH3_G54A/4D4CVL2_G94A	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:92	SEQ ID NO:93	SEQ ID NO:15	SEQ ID NO:90
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,	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:94	SEQ ID NO:93	SEQ ID NO:96	SEQ ID NO:90

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,								
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, 4D4CVH3_G54A/4D4GVL3_N93E, 4D4CVH3_G54A/4D4GVL3_N93L, 4D4CVH3_G54A/4D4GVL3_N93Q, 4D4CVH3_G54A/4D4GVL3_G94A	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:97	SEQ ID NO:93	SEQ ID NO:99	SEQ ID NO:90
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,	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:101	SEQ ID NO:93	SEQ ID NO:102	SEQ ID NO:90

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								
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, 4D4CVH4_G54A/4D4C/GVL1_N93Q, 4D4CVH4_G54A/4D4C/GVL1_G94A	SEQ ID NO:84	SEQ ID NO:81	SEQ ID NO:85	SEQ ID NO:79	SEQ ID NO:89	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:90
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,	SEQ ID NO:84	SEQ ID NO:81	SEQ ID NO:85	SEQ ID NO:79	SEQ ID NO:92	SEQ ID NO:93	SEQ ID NO:15	SEQ ID NO:90

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								
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:84	SEQ ID NO:81	SEQ ID NO:85	SEQ ID NO:79	SEQ ID NO:94	SEQ ID NO:93	SEQ ID NO:96	SEQ ID NO:90
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,	SEQ ID NO:84	SEQ ID NO:81	SEQ ID NO:85	SEQ ID NO:79	SEQ ID NO:97	SEQ ID NO:93	SEQ ID NO:99	SEQ ID NO:90

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								
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:84	SEQ ID NO:81	SEQ ID NO:85	SEQ ID NO:79	SEQ ID NO:101	SEQ ID NO:93	SEQ ID NO:102	SEQ ID NO:90
4D4CVH2.1/4D4C/GVL1, 4D4CVH2.1/4D4C/GVL1_N93G, 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_D53L/4D4C/GVL1_G94A	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:89	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:90

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, 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	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:92	SEQ ID NO:93	SEQ ID NO:15	SEQ ID NO:90
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,	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:94	SEQ ID NO:93	SEQ ID NO:96	SEQ ID NO:90

4D4CVH2.1_G54A/4D4CVL4_N93E, 4D4CVH2.1_G54A/4D4CVL4_N93L, 4D4CVH2.1_G54A/4D4CVL4_N93Q, 4D4CVH2.1_G54A/4D4CVL4_G94A								
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, 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	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:97	SEQ ID NO:93	SEQ ID NO:99	SEQ ID NO:90
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,	SEQ ID NO:76	SEQ ID NO:81	SEQ ID NO:77	SEQ ID NO:79	SEQ ID NO:101	SEQ ID NO:93	SEQ ID NO:102	SEQ ID NO:90

4D4CVH2.1_G54A/4D4GVL4_N93Q, 4D4CVH2.1_G54A/4D4GVL4_G94A								
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, 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	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:89	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:90
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:76	SEQ ID NO:6	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:92	SEQ ID NO:93	SEQ ID NO:15	SEQ ID NO:90

4D4CVH2.2/4D4CVL4, 4D4CVH2.2/4D4CVL4_N93G, 4D4CVH2.2/4D4CVL4_N93E, 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	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:94	SEQ ID NO:93	SEQ ID NO:96	SEQ ID NO:90
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:76	SEQ ID NO:6	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:97	SEQ ID NO:93	SEQ ID NO:99	SEQ ID NO:90
4D4CVH2.2/4D4GVL4, 4D4CVH2.2/4D4GVL4_N93G,	SEQ ID NO:76	SEQ ID NO:6	SEQ ID NO:82	SEQ ID NO:79	SEQ ID NO:101	SEQ ID NO:93	SEQ ID NO:102	SEQ ID NO:90

4D4CVH2.2/4D4GVL4_N93E, 4D4CVH2.2/4D4GVL4_N93L, 4D4CVH2.2/4D4GVL4_N93Q, 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	SEQ ID NO:103	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:79	SEQ ID NO:107	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:90

Table C

Antibody	Column A	Column B
	VH	VL
4D4	SEQ ID NO:1	SEQ ID NO:9
3G9	SEQ ID NO:17	SEQ ID NO:23
4A7/7D8	SEQ ID NO:31	SEQ ID NO:34
8C6	SEQ ID NO:36	SEQ ID NO:44
C03-A7	SEQ ID NO:51	SEQ ID NO:57
CON'4'9'7/8	SEQ ID NO:74	SEQ ID NO:75
4D4CVH2/4D4C/GVL1	SEQ ID NO:78	SEQ ID NO:88
4D4CVH2/4D4C/L2	SEQ ID NO:78	SEQ ID NO:91
4D4CVH2/4D4C/L4	SEQ ID NO:78	SEQ ID NO:95
4D4CVH2/4D4GVL3	SEQ ID NO:78	SEQ ID NO:98
4D4CVH2/4D4GVL4	SEQ ID NO:78	SEQ ID NO:100
4D4CVH3/4D4C/GVL1	SEQ ID NO:80	SEQ ID NO:88
4D4CVH3/4D4C/L2	SEQ ID NO:80	SEQ ID NO:91
4D4CVH3/4D4C/L4	SEQ ID NO:80	SEQ ID NO:95
4D4CVH3/4D4GVL3	SEQ ID NO:80	SEQ ID NO:98
4D4CVH3/4D4GVL4	SEQ ID NO:80	SEQ ID NO:100
4D4CVH4/4D4C/GVL1	SEQ ID NO:83	SEQ ID NO:88
4D4CVH4/4D4C/L2	SEQ ID NO:83	SEQ ID NO:91
4D4CVH4/4D4C/L4	SEQ ID NO:83	SEQ ID NO:95
4D4CVH4/4D4GVL3	SEQ ID NO:83	SEQ ID NO:98
4D4CVH4/4D4GVL4	SEQ ID NO:83	SEQ ID NO:100
4D4CVH2.1/4D4C/GVL1	SEQ ID NO:86	SEQ ID NO:88
4D4CVH2.1/4D4C/L2	SEQ ID NO:86	SEQ ID NO:91
4D4CVH2.1/4D4C/L4	SEQ ID NO:86	SEQ ID NO:95
4D4CVH2.1/4D4GVL3	SEQ ID NO:86	SEQ ID NO:98
4D4CVH2.1/4D4GVL4	SEQ ID NO:86	SEQ ID NO:100
4D4CVH2.2/4D4C/GVL1	SEQ ID NO:87	SEQ ID NO:88
4D4CVH2.2/4D4C/L2	SEQ ID NO:87	SEQ ID NO:91
4D4CVH2.2/4D4C/L4	SEQ ID NO:87	SEQ ID NO:95
4D4CVH2.2/4D4GVL3	SEQ ID NO:87	SEQ ID NO:98
4D4CVH2.2/4D4GVL4	SEQ ID NO:87	SEQ ID NO:100
CON4D4P/Hu	SEQ ID NO:106	SEQ ID NO:110
4D4/4D4_N93G	SEQ ID NO:1	SEQ ID NO:251
4D4/4D4_N93E	SEQ ID NO:1	SEQ ID NO:252
4D4/4D4_N93L	SEQ ID NO:1	SEQ ID NO:253
4D4/4D4_N93Q	SEQ ID NO:1	SEQ ID NO:254
4D4/4D4_G94A	SEQ ID NO:1	SEQ ID NO:255
4D4_D53G/4D4	SEQ ID NO:214	SEQ ID NO:9
4D4_D53E/4D4	SEQ ID NO:215	SEQ ID NO:9
4D4_D53Q/4D4	SEQ ID NO:216	SEQ ID NO:9
4D4_D53L/4D4	SEQ ID NO:217	SEQ ID NO:9
4D4_G54A/4D4	SEQ ID NO:218	SEQ ID NO:9
4D4_D53G/4D4_N93G	SEQ ID NO:214	SEQ ID NO:251
4D4_D53E/4D4_N93G	SEQ ID NO:215	SEQ ID NO:251
4D4_D53Q/4D4_N93G	SEQ ID NO:216	SEQ ID NO:251
4D4_D53L/4D4_N93G	SEQ ID NO:217	SEQ ID NO:251
4D4_G54A/4D4_N93G	SEQ ID NO:218	SEQ ID NO:251
4D4_D53G/4D4_N93E	SEQ ID NO:214	SEQ ID NO:252
4D4_D53E/4D4_N93E	SEQ ID NO:215	SEQ ID NO:252
4D4_D53Q/4D4_N93E	SEQ ID NO:216	SEQ ID NO:252
4D4_D53L/4D4_N93E	SEQ ID NO:217	SEQ ID NO:252
4D4_G54A/4D4_N93E	SEQ ID NO:218	SEQ ID NO:252
4D4_D53G/4D4_N93L	SEQ ID NO:214	SEQ ID NO:253
4D4_D53E/4D4_N93L	SEQ ID NO:215	SEQ ID NO:253
4D4_D53Q/4D4_N93L	SEQ ID NO:216	SEQ ID NO:253
4D4_D53L/4D4_N93L	SEQ ID NO:217	SEQ ID NO:253
4D4_G54A/4D4_N93L	SEQ ID NO:218	SEQ ID NO:253
4D4_D53G/4D4_N93Q	SEQ ID NO:214	SEQ ID NO:254
4D4_D53E/4D4_N93Q	SEQ ID NO:215	SEQ ID NO:254
4D4_D53Q/4D4_N93Q	SEQ ID NO:216	SEQ ID NO:254
4D4_D53L/4D4_N93Q	SEQ ID NO:217	SEQ ID NO:254
4D4_G54A/4D4_N93Q	SEQ ID NO:218	SEQ ID NO:254
4D4_D53G/4D4_G94A	SEQ ID NO:214	SEQ ID NO:255
4D4_D53E/4D4_G94A	SEQ ID NO:215	SEQ ID NO:255
4D4_D53Q/4D4_G94A	SEQ ID NO:216	SEQ ID NO:255

4D4_D53L/4D4_G94A	SEQ ID NO:217	SEQ ID NO:255
4D4_G54A/4D4_G94A	SEQ ID NO:218	SEQ ID NO:255
4D4CVH2/4D4C/GVL1_N93G	SEQ ID NO:78	SEQ ID NO:256
4D4CVH2/4D4C/GVL1_N93E	SEQ ID NO:78	SEQ ID NO:257
4D4CVH2/4D4C/GVL1_N93L	SEQ ID NO:78	SEQ ID NO:258
4D4CVH2/4D4C/GVL1_N93Q	SEQ ID NO:78	SEQ ID NO:259
4D4CVH2/4D4C/GVL1_G94A	SEQ ID NO:78	SEQ ID NO:260
4D4CVH2_D53G/4D4C/GVL1	SEQ ID NO:219	SEQ ID NO:88
4D4CVH2_D53E/4D4C/GVL1	SEQ ID NO:220	SEQ ID NO:88
4D4CVH2_D53Q/4D4C/GVL1	SEQ ID NO:221	SEQ ID NO:88
4D4CVH2_D53L/4D4C/GVL1	SEQ ID NO:222	SEQ ID NO:88
4D4CVH2_G54A/4D4C/GVL1	SEQ ID NO:223	SEQ ID NO:88
4D4CVH2_D53G/4D4C/GVL1_N93G	SEQ ID NO:219	SEQ ID NO:256
4D4CVH2_D53E/4D4C/GVL1_N93G	SEQ ID NO:220	SEQ ID NO:256
4D4CVH2_D53Q/4D4C/GVL1_N93G	SEQ ID NO:221	SEQ ID NO:256
4D4CVH2_D53L/4D4C/GVL1_N93G	SEQ ID NO:222	SEQ ID NO:256
4D4CVH2_G54A/4D4C/GVL1_N93G	SEQ ID NO:223	SEQ ID NO:256
4D4CVH2_D53G/4D4C/GVL1_N93E	SEQ ID NO:219	SEQ ID NO:257
4D4CVH2_D53E/4D4C/GVL1_N93E	SEQ ID NO:220	SEQ ID NO:257
4D4CVH2_D53Q/4D4C/GVL1_N93E	SEQ ID NO:221	SEQ ID NO:257
4D4CVH2_D53L/4D4C/GVL1_N93E	SEQ ID NO:222	SEQ ID NO:257
4D4CVH2_G54A/4D4C/GVL1_N93E	SEQ ID NO:223	SEQ ID NO:257
4D4CVH2_D53G/4D4C/GVL1_N93L	SEQ ID NO:219	SEQ ID NO:258
4D4CVH2_D53E/4D4C/GVL1_N93L	SEQ ID NO:220	SEQ ID NO:258
4D4CVH2_D53Q/4D4C/GVL1_N93L	SEQ ID NO:221	SEQ ID NO:258
4D4CVH2_D53L/4D4C/GVL1_N93L	SEQ ID NO:222	SEQ ID NO:258
4D4CVH2_G54A/4D4C/GVL1_N93L	SEQ ID NO:223	SEQ ID NO:258
4D4CVH2_D53G/4D4C/GVL1_N93Q	SEQ ID NO:219	SEQ ID NO:259
4D4CVH2_D53E/4D4C/GVL1_N93Q	SEQ ID NO:220	SEQ ID NO:259
4D4CVH2_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:221	SEQ ID NO:259
4D4CVH2_D53L/4D4C/GVL1_N93Q	SEQ ID NO:222	SEQ ID NO:259
4D4CVH2_G54A/4D4C/GVL1_N93Q	SEQ ID NO:223	SEQ ID NO:259
4D4CVH2_D53G/4D4C/GVL1_G94A	SEQ ID NO:219	SEQ ID NO:260
4D4CVH2_D53E/4D4C/GVL1_G94A	SEQ ID NO:220	SEQ ID NO:260
4D4CVH2_D53Q/4D4C/GVL1_G94A	SEQ ID NO:221	SEQ ID NO:260
4D4CVH2_D53L/4D4C/GVL1_G94A	SEQ ID NO:222	SEQ ID NO:260
4D4CVH2_G54A/4D4C/GVL1_G94A	SEQ ID NO:223	SEQ ID NO:260
4D4CVH2/4D4C/L2_N93G	SEQ ID NO:78	SEQ ID NO:261
4D4CVH2/4D4C/L2_N93E	SEQ ID NO:78	SEQ ID NO:262
4D4CVH2/4D4C/L2_N93L	SEQ ID NO:78	SEQ ID NO:263
4D4CVH2/4D4C/L2_N93Q	SEQ ID NO:78	SEQ ID NO:264
4D4CVH2/4D4C/L2_G94A	SEQ ID NO:78	SEQ ID NO:265
4D4CVH2_D53G/4D4C/L2	SEQ ID NO:219	SEQ ID NO:91
4D4CVH2_D53E/4D4C/L2	SEQ ID NO:220	SEQ ID NO:91
4D4CVH2_D53Q/4D4C/L2	SEQ ID NO:221	SEQ ID NO:91
4D4CVH2_D53L/4D4C/L2	SEQ ID NO:222	SEQ ID NO:91
4D4CVH2_G54A/4D4C/L2	SEQ ID NO:223	SEQ ID NO:91
4D4CVH2_D53G/4D4C/L2_N93G	SEQ ID NO:219	SEQ ID NO:261
4D4CVH2_D53E/4D4C/L2_N93G	SEQ ID NO:220	SEQ ID NO:261
4D4CVH2_D53Q/4D4C/L2_N93G	SEQ ID NO:221	SEQ ID NO:261
4D4CVH2_D53L/4D4C/L2_N93G	SEQ ID NO:222	SEQ ID NO:261
4D4CVH2_G54A/4D4C/L2_N93G	SEQ ID NO:223	SEQ ID NO:261
4D4CVH2_D53G/4D4C/L2_N93E	SEQ ID NO:219	SEQ ID NO:262
4D4CVH2_D53E/4D4C/L2_N93E	SEQ ID NO:220	SEQ ID NO:262
4D4CVH2_D53Q/4D4C/L2_N93E	SEQ ID NO:221	SEQ ID NO:262
4D4CVH2_D53L/4D4C/L2_N93E	SEQ ID NO:222	SEQ ID NO:262
4D4CVH2_G54A/4D4C/L2_N93E	SEQ ID NO:223	SEQ ID NO:262
4D4CVH2_D53G/4D4C/L2_N93L	SEQ ID NO:219	SEQ ID NO:263
4D4CVH2_D53E/4D4C/L2_N93L	SEQ ID NO:220	SEQ ID NO:263
4D4CVH2_D53Q/4D4C/L2_N93L	SEQ ID NO:221	SEQ ID NO:263
4D4CVH2_D53L/4D4C/L2_N93L	SEQ ID NO:222	SEQ ID NO:263
4D4CVH2_G54A/4D4C/L2_N93L	SEQ ID NO:223	SEQ ID NO:263
4D4CVH2_D53G/4D4C/L2_N93Q	SEQ ID NO:219	SEQ ID NO:264
4D4CVH2_D53E/4D4C/L2_N93Q	SEQ ID NO:220	SEQ ID NO:264
4D4CVH2_D53Q/4D4C/L2_N93Q	SEQ ID NO:221	SEQ ID NO:264
4D4CVH2_D53L/4D4C/L2_N93Q	SEQ ID NO:222	SEQ ID NO:264
4D4CVH2_G54A/4D4C/L2_N93Q	SEQ ID NO:223	SEQ ID NO:264
4D4CVH2_D53G/4D4C/L2_G94A	SEQ ID NO:219	SEQ ID NO:265
4D4CVH2_D53E/4D4C/L2_G94A	SEQ ID NO:220	SEQ ID NO:265
4D4CVH2_D53Q/4D4C/L2_G94A	SEQ ID NO:221	SEQ ID NO:265

4D4CVH2_D53L/4D4CVL2_G94A	SEQ ID NO:222	SEQ ID NO:265
4D4CVH2_G54A/4D4CVL2_G94A	SEQ ID NO:223	SEQ ID NO:265
4D4CVH2/4D4CVL4_N93G	SEQ ID NO:78	SEQ ID NO:266
4D4CVH2/4D4CVL4_N93E	SEQ ID NO:78	SEQ ID NO:267
4D4CVH2/4D4CVL4_N93L	SEQ ID NO:78	SEQ ID NO:268
4D4CVH2/4D4CVL4_N93Q	SEQ ID NO:78	SEQ ID NO:269
4D4CVH2/4D4CVL4_G94A	SEQ ID NO:78	SEQ ID NO:270
4D4CVH2_D53G/4D4CVL4	SEQ ID NO:219	SEQ ID NO:95
4D4CVH2_D53E/4D4CVL4	SEQ ID NO:220	SEQ ID NO:95
4D4CVH2_D53Q/4D4CVL4	SEQ ID NO:221	SEQ ID NO:95
4D4CVH2_D53L/4D4CVL4	SEQ ID NO:222	SEQ ID NO:95
4D4CVH2_G54A/4D4CVL4	SEQ ID NO:223	SEQ ID NO:95
4D4CVH2_D53G/4D4CVL4_N93G	SEQ ID NO:219	SEQ ID NO:266
4D4CVH2_D53E/4D4CVL4_N93G	SEQ ID NO:220	SEQ ID NO:266
4D4CVH2_D53Q/4D4CVL4_N93G	SEQ ID NO:221	SEQ ID NO:266
4D4CVH2_D53L/4D4CVL4_N93G	SEQ ID NO:222	SEQ ID NO:266
4D4CVH2_G54A/4D4CVL4_N93G	SEQ ID NO:223	SEQ ID NO:266
4D4CVH2_D53G/4D4CVL4_N93E	SEQ ID NO:219	SEQ ID NO:267
4D4CVH2_D53E/4D4CVL4_N93E	SEQ ID NO:220	SEQ ID NO:267
4D4CVH2_D53Q/4D4CVL4_N93E	SEQ ID NO:221	SEQ ID NO:267
4D4CVH2_D53L/4D4CVL4_N93E	SEQ ID NO:222	SEQ ID NO:267
4D4CVH2_G54A/4D4CVL4_N93E	SEQ ID NO:223	SEQ ID NO:267
4D4CVH2_D53G/4D4CVL4_N93L	SEQ ID NO:219	SEQ ID NO:268
4D4CVH2_D53E/4D4CVL4_N93L	SEQ ID NO:220	SEQ ID NO:268
4D4CVH2_D53Q/4D4CVL4_N93L	SEQ ID NO:221	SEQ ID NO:268
4D4CVH2_D53L/4D4CVL4_N93L	SEQ ID NO:222	SEQ ID NO:268
4D4CVH2_G54A/4D4CVL4_N93L	SEQ ID NO:223	SEQ ID NO:268
4D4CVH2_D53G/4D4CVL4_N93Q	SEQ ID NO:219	SEQ ID NO:269
4D4CVH2_D53E/4D4CVL4_N93Q	SEQ ID NO:220	SEQ ID NO:269
4D4CVH2_D53Q/4D4CVL4_N93Q	SEQ ID NO:221	SEQ ID NO:269
4D4CVH2_D53L/4D4CVL4_N93Q	SEQ ID NO:222	SEQ ID NO:269
4D4CVH2_G54A/4D4CVL4_N93Q	SEQ ID NO:223	SEQ ID NO:269
4D4CVH2_D53G/4D4CVL4_G94A	SEQ ID NO:219	SEQ ID NO:270
4D4CVH2_D53E/4D4CVL4_G94A	SEQ ID NO:220	SEQ ID NO:270
4D4CVH2_D53Q/4D4CVL4_G94A	SEQ ID NO:221	SEQ ID NO:270
4D4CVH2_D53L/4D4CVL4_G94A	SEQ ID NO:222	SEQ ID NO:270
4D4CVH2_G54A/4D4CVL4_G94A	SEQ ID NO:223	SEQ ID NO:270
4D4CVH2/4D4GVL3_N93G	SEQ ID NO:78	SEQ ID NO:271
4D4CVH2/4D4GVL3_N93E	SEQ ID NO:78	SEQ ID NO:272
4D4CVH2/4D4GVL3_N93L	SEQ ID NO:78	SEQ ID NO:273
4D4CVH2/4D4GVL3_N93Q	SEQ ID NO:78	SEQ ID NO:274
4D4CVH2/4D4GVL3_G94A	SEQ ID NO:78	SEQ ID NO:275
4D4CVH2_D53G/4D4GVL3	SEQ ID NO:219	SEQ ID NO:98
4D4CVH2_D53E/4D4GVL3	SEQ ID NO:220	SEQ ID NO:98
4D4CVH2_D53Q/4D4GVL3	SEQ ID NO:221	SEQ ID NO:98
4D4CVH2_D53L/4D4GVL3	SEQ ID NO:222	SEQ ID NO:98
4D4CVH2_G54A/4D4GVL3	SEQ ID NO:223	SEQ ID NO:98
4D4CVH2_D53G/4D4GVL3_N93G	SEQ ID NO:219	SEQ ID NO:271
4D4CVH2_D53E/4D4GVL3_N93G	SEQ ID NO:220	SEQ ID NO:271
4D4CVH2_D53Q/4D4GVL3_N93G	SEQ ID NO:221	SEQ ID NO:271
4D4CVH2_D53L/4D4GVL3_N93G	SEQ ID NO:222	SEQ ID NO:271
4D4CVH2_G54A/4D4GVL3_N93G	SEQ ID NO:223	SEQ ID NO:271
4D4CVH2_D53G/4D4GVL3_N93E	SEQ ID NO:219	SEQ ID NO:272
4D4CVH2_D53E/4D4GVL3_N93E	SEQ ID NO:220	SEQ ID NO:272
4D4CVH2_D53Q/4D4GVL3_N93E	SEQ ID NO:221	SEQ ID NO:272
4D4CVH2_D53L/4D4GVL3_N93E	SEQ ID NO:222	SEQ ID NO:272
4D4CVH2_G54A/4D4GVL3_N93E	SEQ ID NO:223	SEQ ID NO:272
4D4CVH2_D53G/4D4GVL3_N93L	SEQ ID NO:219	SEQ ID NO:273
4D4CVH2_D53E/4D4GVL3_N93L	SEQ ID NO:220	SEQ ID NO:273
4D4CVH2_D53Q/4D4GVL3_N93L	SEQ ID NO:221	SEQ ID NO:273
4D4CVH2_D53L/4D4GVL3_N93L	SEQ ID NO:222	SEQ ID NO:273
4D4CVH2_G54A/4D4GVL3_N93L	SEQ ID NO:223	SEQ ID NO:273
4D4CVH2_D53G/4D4GVL3_N93Q	SEQ ID NO:219	SEQ ID NO:274
4D4CVH2_D53E/4D4GVL3_N93Q	SEQ ID NO:220	SEQ ID NO:274
4D4CVH2_D53Q/4D4GVL3_N93Q	SEQ ID NO:221	SEQ ID NO:274
4D4CVH2_D53L/4D4GVL3_N93Q	SEQ ID NO:222	SEQ ID NO:274
4D4CVH2_G54A/4D4GVL3_N93Q	SEQ ID NO:223	SEQ ID NO:274
4D4CVH2_D53G/4D4GVL3_G94A	SEQ ID NO:219	SEQ ID NO:275
4D4CVH2_D53E/4D4GVL3_G94A	SEQ ID NO:220	SEQ ID NO:275
4D4CVH2_D53Q/4D4GVL3_G94A	SEQ ID NO:221	SEQ ID NO:275

4D4CVH2_D53L/4D4GVL3_G94A	SEQ ID NO:222	SEQ ID NO:275
4D4CVH2_G54A/4D4GVL3_G94A	SEQ ID NO:223	SEQ ID NO:275
4D4CVH2/4D4GVL4_N93G	SEQ ID NO:78	SEQ ID NO:276
4D4CVH2/4D4GVL4_N93E	SEQ ID NO:78	SEQ ID NO:277
4D4CVH2/4D4GVL4_N93L	SEQ ID NO:78	SEQ ID NO:278
4D4CVH2/4D4GVL4_N93Q	SEQ ID NO:78	SEQ ID NO:279
4D4CVH2/4D4GVL4_G94A	SEQ ID NO:78	SEQ ID NO:280
4D4CVH2_D53G/4D4GVL4	SEQ ID NO:219	SEQ ID NO:100
4D4CVH2_D53E/4D4GVL4	SEQ ID NO:220	SEQ ID NO:100
4D4CVH2_D53Q/4D4GVL4	SEQ ID NO:221	SEQ ID NO:100
4D4CVH2_D53L/4D4GVL4	SEQ ID NO:222	SEQ ID NO:100
4D4CVH2_G54A/4D4GVL4	SEQ ID NO:223	SEQ ID NO:100
4D4CVH2_D53G/4D4GVL4_N93G	SEQ ID NO:219	SEQ ID NO:276
4D4CVH2_D53E/4D4GVL4_N93G	SEQ ID NO:220	SEQ ID NO:276
4D4CVH2_D53Q/4D4GVL4_N93G	SEQ ID NO:221	SEQ ID NO:276
4D4CVH2_D53L/4D4GVL4_N93G	SEQ ID NO:222	SEQ ID NO:276
4D4CVH2_G54A/4D4GVL4_N93G	SEQ ID NO:223	SEQ ID NO:276
4D4CVH2_D53G/4D4GVL4_N93E	SEQ ID NO:219	SEQ ID NO:277
4D4CVH2_D53E/4D4GVL4_N93E	SEQ ID NO:220	SEQ ID NO:277
4D4CVH2_D53Q/4D4GVL4_N93E	SEQ ID NO:221	SEQ ID NO:277
4D4CVH2_D53L/4D4GVL4_N93E	SEQ ID NO:222	SEQ ID NO:277
4D4CVH2_G54A/4D4GVL4_N93E	SEQ ID NO:223	SEQ ID NO:277
4D4CVH2_D53G/4D4GVL4_N93L	SEQ ID NO:219	SEQ ID NO:278
4D4CVH2_D53E/4D4GVL4_N93L	SEQ ID NO:220	SEQ ID NO:278
4D4CVH2_D53Q/4D4GVL4_N93L	SEQ ID NO:221	SEQ ID NO:278
4D4CVH2_D53L/4D4GVL4_N93L	SEQ ID NO:222	SEQ ID NO:278
4D4CVH2_G54A/4D4GVL4_N93L	SEQ ID NO:223	SEQ ID NO:278
4D4CVH2_D53G/4D4GVL4_N93Q	SEQ ID NO:219	SEQ ID NO:279
4D4CVH2_D53E/4D4GVL4_N93Q	SEQ ID NO:220	SEQ ID NO:279
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4D4CVH2_D53L/4D4GVL4_N93Q	SEQ ID NO:222	SEQ ID NO:279
4D4CVH2_G54A/4D4GVL4_N93Q	SEQ ID NO:223	SEQ ID NO:279
4D4CVH2_D53G/4D4GVL4_G94A	SEQ ID NO:219	SEQ ID NO:280
4D4CVH2_D53E/4D4GVL4_G94A	SEQ ID NO:220	SEQ ID NO:280
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4D4CVH2_D53L/4D4GVL4_G94A	SEQ ID NO:222	SEQ ID NO:280
4D4CVH2_G54A/4D4GVL4_G94A	SEQ ID NO:223	SEQ ID NO:280
4D4CVH3/4D4C/GVL1_N93G	SEQ ID NO:80	SEQ ID NO:256
4D4CVH3/4D4C/GVL1_N93E	SEQ ID NO:80	SEQ ID NO:257
4D4CVH3/4D4C/GVL1_N93L	SEQ ID NO:80	SEQ ID NO:258
4D4CVH3/4D4C/GVL1_N93Q	SEQ ID NO:80	SEQ ID NO:259
4D4CVH3/4D4C/GVL1_G94A	SEQ ID NO:80	SEQ ID NO:260
4D4CVH3_D53G/4D4C/GVL1	SEQ ID NO:224	SEQ ID NO:88
4D4CVH3_D53E/4D4C/GVL1	SEQ ID NO:225	SEQ ID NO:88
4D4CVH3_D53Q/4D4C/GVL1	SEQ ID NO:226	SEQ ID NO:88
4D4CVH3_D53L/4D4C/GVL1	SEQ ID NO:227	SEQ ID NO:88
4D4CVH3_G54A/4D4C/GVL1	SEQ ID NO:228	SEQ ID NO:88
4D4CVH3_D53G/4D4C/GVL1_N93G	SEQ ID NO:224	SEQ ID NO:256
4D4CVH3_D53E/4D4C/GVL1_N93G	SEQ ID NO:225	SEQ ID NO:256
4D4CVH3_D53Q/4D4C/GVL1_N93G	SEQ ID NO:226	SEQ ID NO:256
4D4CVH3_D53L/4D4C/GVL1_N93G	SEQ ID NO:227	SEQ ID NO:256
4D4CVH3_G54A/4D4C/GVL1_N93G	SEQ ID NO:228	SEQ ID NO:256
4D4CVH3_D53G/4D4C/GVL1_N93E	SEQ ID NO:224	SEQ ID NO:257
4D4CVH3_D53E/4D4C/GVL1_N93E	SEQ ID NO:225	SEQ ID NO:257
4D4CVH3_D53Q/4D4C/GVL1_N93E	SEQ ID NO:226	SEQ ID NO:257
4D4CVH3_D53L/4D4C/GVL1_N93E	SEQ ID NO:227	SEQ ID NO:257
4D4CVH3_G54A/4D4C/GVL1_N93E	SEQ ID NO:228	SEQ ID NO:257
4D4CVH3_D53G/4D4C/GVL1_N93L	SEQ ID NO:224	SEQ ID NO:258
4D4CVH3_D53E/4D4C/GVL1_N93L	SEQ ID NO:225	SEQ ID NO:258
4D4CVH3_D53Q/4D4C/GVL1_N93L	SEQ ID NO:226	SEQ ID NO:258
4D4CVH3_D53L/4D4C/GVL1_N93L	SEQ ID NO:227	SEQ ID NO:258
4D4CVH3_G54A/4D4C/GVL1_N93L	SEQ ID NO:228	SEQ ID NO:258
4D4CVH3_D53G/4D4C/GVL1_N93Q	SEQ ID NO:224	SEQ ID NO:259
4D4CVH3_D53E/4D4C/GVL1_N93Q	SEQ ID NO:225	SEQ ID NO:259
4D4CVH3_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:226	SEQ ID NO:259
4D4CVH3_D53L/4D4C/GVL1_N93Q	SEQ ID NO:227	SEQ ID NO:259
4D4CVH3_G54A/4D4C/GVL1_N93Q	SEQ ID NO:228	SEQ ID NO:259
4D4CVH3_D53G/4D4C/GVL1_G94A	SEQ ID NO:224	SEQ ID NO:260
4D4CVH3_D53E/4D4C/GVL1_G94A	SEQ ID NO:225	SEQ ID NO:260
4D4CVH3_D53Q/4D4C/GVL1_G94A	SEQ ID NO:226	SEQ ID NO:260

4D4CVH3_D53L/4D4C/GVL1_G94A	SEQ ID NO:227	SEQ ID NO:260
4D4CVH3_G54A/4D4C/GVL1_G94A	SEQ ID NO:228	SEQ ID NO:260
4D4CVH3/4D4CVL2_N93G	SEQ ID NO:80	SEQ ID NO:261
4D4CVH3/4D4CVL2_N93E	SEQ ID NO:80	SEQ ID NO:262
4D4CVH3/4D4CVL2_N93L	SEQ ID NO:80	SEQ ID NO:263
4D4CVH3/4D4CVL2_N93Q	SEQ ID NO:80	SEQ ID NO:264
4D4CVH3/4D4CVL2_G94A	SEQ ID NO:80	SEQ ID NO:265
4D4CVH3_D53G/4D4CVL2	SEQ ID NO:224	SEQ ID NO:91
4D4CVH3_D53E/4D4CVL2	SEQ ID NO:225	SEQ ID NO:91
4D4CVH3_D53Q/4D4CVL2	SEQ ID NO:226	SEQ ID NO:91
4D4CVH3_D53L/4D4CVL2	SEQ ID NO:227	SEQ ID NO:91
4D4CVH3_G54A/4D4CVL2	SEQ ID NO:228	SEQ ID NO:91
4D4CVH3_D53G/4D4CVL2_N93G	SEQ ID NO:224	SEQ ID NO:261
4D4CVH3_D53E/4D4CVL2_N93G	SEQ ID NO:225	SEQ ID NO:261
4D4CVH3_D53Q/4D4CVL2_N93G	SEQ ID NO:226	SEQ ID NO:261
4D4CVH3_D53L/4D4CVL2_N93G	SEQ ID NO:227	SEQ ID NO:261
4D4CVH3_G54A/4D4CVL2_N93G	SEQ ID NO:228	SEQ ID NO:261
4D4CVH3_D53G/4D4CVL2_N93E	SEQ ID NO:224	SEQ ID NO:262
4D4CVH3_D53E/4D4CVL2_N93E	SEQ ID NO:225	SEQ ID NO:262
4D4CVH3_D53Q/4D4CVL2_N93E	SEQ ID NO:226	SEQ ID NO:262
4D4CVH3_D53L/4D4CVL2_N93E	SEQ ID NO:227	SEQ ID NO:262
4D4CVH3_G54A/4D4CVL2_N93E	SEQ ID NO:228	SEQ ID NO:262
4D4CVH3_D53G/4D4CVL2_N93L	SEQ ID NO:224	SEQ ID NO:263
4D4CVH3_D53E/4D4CVL2_N93L	SEQ ID NO:225	SEQ ID NO:263
4D4CVH3_D53Q/4D4CVL2_N93L	SEQ ID NO:226	SEQ ID NO:263
4D4CVH3_D53L/4D4CVL2_N93L	SEQ ID NO:227	SEQ ID NO:263
4D4CVH3_G54A/4D4CVL2_N93L	SEQ ID NO:228	SEQ ID NO:263
4D4CVH3_D53G/4D4CVL2_N93Q	SEQ ID NO:224	SEQ ID NO:264
4D4CVH3_D53E/4D4CVL2_N93Q	SEQ ID NO:225	SEQ ID NO:264
4D4CVH3_D53Q/4D4CVL2_N93Q	SEQ ID NO:226	SEQ ID NO:264
4D4CVH3_D53L/4D4CVL2_N93Q	SEQ ID NO:227	SEQ ID NO:264
4D4CVH3_G54A/4D4CVL2_N93Q	SEQ ID NO:228	SEQ ID NO:264
4D4CVH3_D53G/4D4CVL2_G94A	SEQ ID NO:224	SEQ ID NO:265
4D4CVH3_D53E/4D4CVL2_G94A	SEQ ID NO:225	SEQ ID NO:265
4D4CVH3_D53Q/4D4CVL2_G94A	SEQ ID NO:226	SEQ ID NO:265
4D4CVH3_D53L/4D4CVL2_G94A	SEQ ID NO:227	SEQ ID NO:265
4D4CVH3_G54A/4D4CVL2_G94A	SEQ ID NO:228	SEQ ID NO:265
4D4CVH3/4D4CVL4_N93G	SEQ ID NO:80	SEQ ID NO:266
4D4CVH3/4D4CVL4_N93E	SEQ ID NO:80	SEQ ID NO:267
4D4CVH3/4D4CVL4_N93L	SEQ ID NO:80	SEQ ID NO:268
4D4CVH3/4D4CVL4_N93Q	SEQ ID NO:80	SEQ ID NO:269
4D4CVH3/4D4CVL4_G94A	SEQ ID NO:80	SEQ ID NO:270
4D4CVH3_D53G/4D4CVL4	SEQ ID NO:224	SEQ ID NO:95
4D4CVH3_D53E/4D4CVL4	SEQ ID NO:225	SEQ ID NO:95
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4D4CVH3_D53G/4D4CVL4_N93G	SEQ ID NO:224	SEQ ID NO:266
4D4CVH3_D53E/4D4CVL4_N93G	SEQ ID NO:225	SEQ ID NO:266
4D4CVH3_D53Q/4D4CVL4_N93G	SEQ ID NO:226	SEQ ID NO:266
4D4CVH3_D53L/4D4CVL4_N93G	SEQ ID NO:227	SEQ ID NO:266
4D4CVH3_G54A/4D4CVL4_N93G	SEQ ID NO:228	SEQ ID NO:266
4D4CVH3_D53G/4D4CVL4_N93E	SEQ ID NO:224	SEQ ID NO:267
4D4CVH3_D53E/4D4CVL4_N93E	SEQ ID NO:225	SEQ ID NO:267
4D4CVH3_D53Q/4D4CVL4_N93E	SEQ ID NO:226	SEQ ID NO:267
4D4CVH3_D53L/4D4CVL4_N93E	SEQ ID NO:227	SEQ ID NO:267
4D4CVH3_G54A/4D4CVL4_N93E	SEQ ID NO:228	SEQ ID NO:267
4D4CVH3_D53G/4D4CVL4_N93L	SEQ ID NO:224	SEQ ID NO:268
4D4CVH3_D53E/4D4CVL4_N93L	SEQ ID NO:225	SEQ ID NO:268
4D4CVH3_D53Q/4D4CVL4_N93L	SEQ ID NO:226	SEQ ID NO:268
4D4CVH3_D53L/4D4CVL4_N93L	SEQ ID NO:227	SEQ ID NO:268
4D4CVH3_G54A/4D4CVL4_N93L	SEQ ID NO:228	SEQ ID NO:268
4D4CVH3_D53G/4D4CVL4_N93Q	SEQ ID NO:224	SEQ ID NO:269
4D4CVH3_D53E/4D4CVL4_N93Q	SEQ ID NO:225	SEQ ID NO:269
4D4CVH3_D53Q/4D4CVL4_N93Q	SEQ ID NO:226	SEQ ID NO:269
4D4CVH3_D53L/4D4CVL4_N93Q	SEQ ID NO:227	SEQ ID NO:269
4D4CVH3_G54A/4D4CVL4_N93Q	SEQ ID NO:228	SEQ ID NO:269
4D4CVH3_D53G/4D4CVL4_G94A	SEQ ID NO:224	SEQ ID NO:270
4D4CVH3_D53E/4D4CVL4_G94A	SEQ ID NO:225	SEQ ID NO:270
4D4CVH3_D53Q/4D4CVL4_G94A	SEQ ID NO:226	SEQ ID NO:270

4D4CVH3_D53L/4D4CVL4_G94A	SEQ ID NO:227	SEQ ID NO:270
4D4CVH3_G54A/4D4CVL4_G94A	SEQ ID NO:228	SEQ ID NO:270
4D4CVH3/4D4GVL3_N93G	SEQ ID NO:80	SEQ ID NO:271
4D4CVH3/4D4GVL3_N93E	SEQ ID NO:80	SEQ ID NO:272
4D4CVH3/4D4GVL3_N93L	SEQ ID NO:80	SEQ ID NO:273
4D4CVH3/4D4GVL3_N93Q	SEQ ID NO:80	SEQ ID NO:274
4D4CVH3/4D4GVL3_G94A	SEQ ID NO:80	SEQ ID NO:275
4D4CVH3_D53G/4D4GVL3	SEQ ID NO:224	SEQ ID NO:98
4D4CVH3_D53E/4D4GVL3	SEQ ID NO:225	SEQ ID NO:98
4D4CVH3_D53Q/4D4GVL3	SEQ ID NO:226	SEQ ID NO:98
4D4CVH3_D53L/4D4GVL3	SEQ ID NO:227	SEQ ID NO:98
4D4CVH3_G54A/4D4GVL3	SEQ ID NO:228	SEQ ID NO:98
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4D4CVH3_D53E/4D4GVL3_N93G	SEQ ID NO:225	SEQ ID NO:271
4D4CVH3_D53Q/4D4GVL3_N93G	SEQ ID NO:226	SEQ ID NO:271
4D4CVH3_D53L/4D4GVL3_N93G	SEQ ID NO:227	SEQ ID NO:271
4D4CVH3_G54A/4D4GVL3_N93G	SEQ ID NO:228	SEQ ID NO:271
4D4CVH3_D53G/4D4GVL3_N93E	SEQ ID NO:224	SEQ ID NO:272
4D4CVH3_D53E/4D4GVL3_N93E	SEQ ID NO:225	SEQ ID NO:272
4D4CVH3_D53Q/4D4GVL3_N93E	SEQ ID NO:226	SEQ ID NO:272
4D4CVH3_D53L/4D4GVL3_N93E	SEQ ID NO:227	SEQ ID NO:272
4D4CVH3_G54A/4D4GVL3_N93E	SEQ ID NO:228	SEQ ID NO:272
4D4CVH3_D53G/4D4GVL3_N93L	SEQ ID NO:224	SEQ ID NO:273
4D4CVH3_D53E/4D4GVL3_N93L	SEQ ID NO:225	SEQ ID NO:273
4D4CVH3_D53Q/4D4GVL3_N93L	SEQ ID NO:226	SEQ ID NO:273
4D4CVH3_D53L/4D4GVL3_N93L	SEQ ID NO:227	SEQ ID NO:273
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4D4CVH3_D53G/4D4GVL3_N93Q	SEQ ID NO:224	SEQ ID NO:274
4D4CVH3_D53E/4D4GVL3_N93Q	SEQ ID NO:225	SEQ ID NO:274
4D4CVH3_D53Q/4D4GVL3_N93Q	SEQ ID NO:226	SEQ ID NO:274
4D4CVH3_D53L/4D4GVL3_N93Q	SEQ ID NO:227	SEQ ID NO:274
4D4CVH3_G54A/4D4GVL3_N93Q	SEQ ID NO:228	SEQ ID NO:274
4D4CVH3_D53G/4D4GVL3_G94A	SEQ ID NO:224	SEQ ID NO:275
4D4CVH3_D53E/4D4GVL3_G94A	SEQ ID NO:225	SEQ ID NO:275
4D4CVH3_D53Q/4D4GVL3_G94A	SEQ ID NO:226	SEQ ID NO:275
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4D4CVH3/4D4GVL4_N93L	SEQ ID NO:80	SEQ ID NO:278
4D4CVH3/4D4GVL4_N93Q	SEQ ID NO:80	SEQ ID NO:279
4D4CVH3/4D4GVL4_G94A	SEQ ID NO:80	SEQ ID NO:280
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4D4CVH3_D53E/4D4GVL4	SEQ ID NO:225	SEQ ID NO:100
4D4CVH3_D53Q/4D4GVL4	SEQ ID NO:226	SEQ ID NO:100
4D4CVH3_D53L/4D4GVL4	SEQ ID NO:227	SEQ ID NO:100
4D4CVH3_G54A/4D4GVL4	SEQ ID NO:228	SEQ ID NO:100
4D4CVH3_D53G/4D4GVL4_N93G	SEQ ID NO:224	SEQ ID NO:276
4D4CVH3_D53E/4D4GVL4_N93G	SEQ ID NO:225	SEQ ID NO:276
4D4CVH3_D53Q/4D4GVL4_N93G	SEQ ID NO:226	SEQ ID NO:276
4D4CVH3_D53L/4D4GVL4_N93G	SEQ ID NO:227	SEQ ID NO:276
4D4CVH3_G54A/4D4GVL4_N93G	SEQ ID NO:228	SEQ ID NO:276
4D4CVH3_D53G/4D4GVL4_N93E	SEQ ID NO:224	SEQ ID NO:277
4D4CVH3_D53E/4D4GVL4_N93E	SEQ ID NO:225	SEQ ID NO:277
4D4CVH3_D53Q/4D4GVL4_N93E	SEQ ID NO:226	SEQ ID NO:277
4D4CVH3_D53L/4D4GVL4_N93E	SEQ ID NO:227	SEQ ID NO:277
4D4CVH3_G54A/4D4GVL4_N93E	SEQ ID NO:228	SEQ ID NO:277
4D4CVH3_D53G/4D4GVL4_N93L	SEQ ID NO:224	SEQ ID NO:278
4D4CVH3_D53E/4D4GVL4_N93L	SEQ ID NO:225	SEQ ID NO:278
4D4CVH3_D53Q/4D4GVL4_N93L	SEQ ID NO:226	SEQ ID NO:278
4D4CVH3_D53L/4D4GVL4_N93L	SEQ ID NO:227	SEQ ID NO:278
4D4CVH3_G54A/4D4GVL4_N93L	SEQ ID NO:228	SEQ ID NO:278
4D4CVH3_D53G/4D4GVL4_N93Q	SEQ ID NO:224	SEQ ID NO:279
4D4CVH3_D53E/4D4GVL4_N93Q	SEQ ID NO:225	SEQ ID NO:279
4D4CVH3_D53Q/4D4GVL4_N93Q	SEQ ID NO:226	SEQ ID NO:279
4D4CVH3_D53L/4D4GVL4_N93Q	SEQ ID NO:227	SEQ ID NO:279
4D4CVH3_G54A/4D4GVL4_N93Q	SEQ ID NO:228	SEQ ID NO:279
4D4CVH3_D53G/4D4GVL4_G94A	SEQ ID NO:224	SEQ ID NO:280
4D4CVH3_D53E/4D4GVL4_G94A	SEQ ID NO:225	SEQ ID NO:280
4D4CVH3_D53Q/4D4GVL4_G94A	SEQ ID NO:226	SEQ ID NO:280

4D4CVH3_D53L/4D4GVL4_G94A	SEQ ID NO:227	SEQ ID NO:280
4D4CVH3_G54A/4D4GVL4_G94A	SEQ ID NO:228	SEQ ID NO:280
4D4CVH4/4D4C/GVL1_N93G	SEQ ID NO:83	SEQ ID NO:256
4D4CVH4/4D4C/GVL1_N93E	SEQ ID NO:83	SEQ ID NO:257
4D4CVH4/4D4C/GVL1_N93L	SEQ ID NO:83	SEQ ID NO:258
4D4CVH4/4D4C/GVL1_N93Q	SEQ ID NO:83	SEQ ID NO:259
4D4CVH4/4D4C/GVL1_G94A	SEQ ID NO:83	SEQ ID NO:260
4D4CVH4_D53G/4D4C/GVL1	SEQ ID NO:229	SEQ ID NO:88
4D4CVH4_D53E/4D4C/GVL1	SEQ ID NO:230	SEQ ID NO:88
4D4CVH4_D53Q/4D4C/GVL1	SEQ ID NO:231	SEQ ID NO:88
4D4CVH4_D53L/4D4C/GVL1	SEQ ID NO:232	SEQ ID NO:88
4D4CVH4_G54A/4D4C/GVL1	SEQ ID NO:233	SEQ ID NO:88
4D4CVH4_D53G/4D4C/GVL1_N93G	SEQ ID NO:229	SEQ ID NO:256
4D4CVH4_D53E/4D4C/GVL1_N93G	SEQ ID NO:230	SEQ ID NO:256
4D4CVH4_D53Q/4D4C/GVL1_N93G	SEQ ID NO:231	SEQ ID NO:256
4D4CVH4_D53L/4D4C/GVL1_N93G	SEQ ID NO:232	SEQ ID NO:256
4D4CVH4_G54A/4D4C/GVL1_N93G	SEQ ID NO:233	SEQ ID NO:256
4D4CVH4_D53G/4D4C/GVL1_N93E	SEQ ID NO:229	SEQ ID NO:257
4D4CVH4_D53E/4D4C/GVL1_N93E	SEQ ID NO:230	SEQ ID NO:257
4D4CVH4_D53Q/4D4C/GVL1_N93E	SEQ ID NO:231	SEQ ID NO:257
4D4CVH4_D53L/4D4C/GVL1_N93E	SEQ ID NO:232	SEQ ID NO:257
4D4CVH4_G54A/4D4C/GVL1_N93E	SEQ ID NO:233	SEQ ID NO:257
4D4CVH4_D53G/4D4C/GVL1_N93L	SEQ ID NO:229	SEQ ID NO:258
4D4CVH4_D53E/4D4C/GVL1_N93L	SEQ ID NO:230	SEQ ID NO:258
4D4CVH4_D53Q/4D4C/GVL1_N93L	SEQ ID NO:231	SEQ ID NO:258
4D4CVH4_D53L/4D4C/GVL1_N93L	SEQ ID NO:232	SEQ ID NO:258
4D4CVH4_G54A/4D4C/GVL1_N93L	SEQ ID NO:233	SEQ ID NO:258
4D4CVH4_D53G/4D4C/GVL1_N93Q	SEQ ID NO:229	SEQ ID NO:259
4D4CVH4_D53E/4D4C/GVL1_N93Q	SEQ ID NO:230	SEQ ID NO:259
4D4CVH4_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:231	SEQ ID NO:259
4D4CVH4_D53L/4D4C/GVL1_N93Q	SEQ ID NO:232	SEQ ID NO:259
4D4CVH4_G54A/4D4C/GVL1_N93Q	SEQ ID NO:233	SEQ ID NO:259
4D4CVH4_D53G/4D4C/GVL1_G94A	SEQ ID NO:229	SEQ ID NO:260
4D4CVH4_D53E/4D4C/GVL1_G94A	SEQ ID NO:230	SEQ ID NO:260
4D4CVH4_D53Q/4D4C/GVL1_G94A	SEQ ID NO:231	SEQ ID NO:260
4D4CVH4_D53L/4D4C/GVL1_G94A	SEQ ID NO:232	SEQ ID NO:260
4D4CVH4_G54A/4D4C/GVL1_G94A	SEQ ID NO:233	SEQ ID NO:260
4D4CVH4/4D4C/L2_N93G	SEQ ID NO:83	SEQ ID NO:261
4D4CVH4/4D4C/L2_N93E	SEQ ID NO:83	SEQ ID NO:262
4D4CVH4/4D4C/L2_N93L	SEQ ID NO:83	SEQ ID NO:263
4D4CVH4/4D4C/L2_N93Q	SEQ ID NO:83	SEQ ID NO:264
4D4CVH4/4D4C/L2_G94A	SEQ ID NO:83	SEQ ID NO:265
4D4CVH4_D53G/4D4C/L2	SEQ ID NO:229	SEQ ID NO:91
4D4CVH4_D53E/4D4C/L2	SEQ ID NO:230	SEQ ID NO:91
4D4CVH4_D53Q/4D4C/L2	SEQ ID NO:231	SEQ ID NO:91
4D4CVH4_D53L/4D4C/L2	SEQ ID NO:232	SEQ ID NO:91
4D4CVH4_G54A/4D4C/L2	SEQ ID NO:233	SEQ ID NO:91
4D4CVH4_D53G/4D4C/L2_N93G	SEQ ID NO:229	SEQ ID NO:261
4D4CVH4_D53E/4D4C/L2_N93G	SEQ ID NO:230	SEQ ID NO:261
4D4CVH4_D53Q/4D4C/L2_N93G	SEQ ID NO:231	SEQ ID NO:261
4D4CVH4_D53L/4D4C/L2_N93G	SEQ ID NO:232	SEQ ID NO:261
4D4CVH4_G54A/4D4C/L2_N93G	SEQ ID NO:233	SEQ ID NO:261
4D4CVH4_D53G/4D4C/L2_N93E	SEQ ID NO:229	SEQ ID NO:262
4D4CVH4_D53E/4D4C/L2_N93E	SEQ ID NO:230	SEQ ID NO:262
4D4CVH4_D53Q/4D4C/L2_N93E	SEQ ID NO:231	SEQ ID NO:262
4D4CVH4_D53L/4D4C/L2_N93E	SEQ ID NO:232	SEQ ID NO:262
4D4CVH4_G54A/4D4C/L2_N93E	SEQ ID NO:233	SEQ ID NO:262
4D4CVH4_D53G/4D4C/L2_N93L	SEQ ID NO:229	SEQ ID NO:263
4D4CVH4_D53E/4D4C/L2_N93L	SEQ ID NO:230	SEQ ID NO:263
4D4CVH4_D53Q/4D4C/L2_N93L	SEQ ID NO:231	SEQ ID NO:263
4D4CVH4_D53L/4D4C/L2_N93L	SEQ ID NO:232	SEQ ID NO:263
4D4CVH4_G54A/4D4C/L2_N93L	SEQ ID NO:233	SEQ ID NO:263
4D4CVH4_D53G/4D4C/L2_N93Q	SEQ ID NO:229	SEQ ID NO:264
4D4CVH4_D53E/4D4C/L2_N93Q	SEQ ID NO:230	SEQ ID NO:264
4D4CVH4_D53Q/4D4C/L2_N93Q	SEQ ID NO:231	SEQ ID NO:264
4D4CVH4_D53L/4D4C/L2_N93Q	SEQ ID NO:232	SEQ ID NO:264
4D4CVH4_G54A/4D4C/L2_N93Q	SEQ ID NO:233	SEQ ID NO:264
4D4CVH4_D53G/4D4C/L2_G94A	SEQ ID NO:229	SEQ ID NO:265
4D4CVH4_D53E/4D4C/L2_G94A	SEQ ID NO:230	SEQ ID NO:265
4D4CVH4_D53Q/4D4C/L2_G94A	SEQ ID NO:231	SEQ ID NO:265

4D4CVH4_D53L/4D4CVL2_G94A	SEQ ID NO:232	SEQ ID NO:265
4D4CVH4_G54A/4D4CVL2_G94A	SEQ ID NO:233	SEQ ID NO:265
4D4CVH4/4D4CVL4_N93G	SEQ ID NO:83	SEQ ID NO:266
4D4CVH4/4D4CVL4_N93E	SEQ ID NO:83	SEQ ID NO:267
4D4CVH4/4D4CVL4_N93L	SEQ ID NO:83	SEQ ID NO:268
4D4CVH4/4D4CVL4_N93Q	SEQ ID NO:83	SEQ ID NO:269
4D4CVH4/4D4CVL4_G94A	SEQ ID NO:83	SEQ ID NO:270
4D4CVH4_D53G/4D4CVL4	SEQ ID NO:229	SEQ ID NO:95
4D4CVH4_D53E/4D4CVL4	SEQ ID NO:230	SEQ ID NO:95
4D4CVH4_D53Q/4D4CVL4	SEQ ID NO:231	SEQ ID NO:95
4D4CVH4_D53L/4D4CVL4	SEQ ID NO:232	SEQ ID NO:95
4D4CVH4_G54A/4D4CVL4	SEQ ID NO:233	SEQ ID NO:95
4D4CVH4_D53G/4D4CVL4_N93G	SEQ ID NO:229	SEQ ID NO:266
4D4CVH4_D53E/4D4CVL4_N93G	SEQ ID NO:230	SEQ ID NO:266
4D4CVH4_D53Q/4D4CVL4_N93G	SEQ ID NO:231	SEQ ID NO:266
4D4CVH4_D53L/4D4CVL4_N93G	SEQ ID NO:232	SEQ ID NO:266
4D4CVH4_G54A/4D4CVL4_N93G	SEQ ID NO:233	SEQ ID NO:266
4D4CVH4_D53G/4D4CVL4_N93E	SEQ ID NO:229	SEQ ID NO:267
4D4CVH4_D53E/4D4CVL4_N93E	SEQ ID NO:230	SEQ ID NO:267
4D4CVH4_D53Q/4D4CVL4_N93E	SEQ ID NO:231	SEQ ID NO:267
4D4CVH4_D53L/4D4CVL4_N93E	SEQ ID NO:232	SEQ ID NO:267
4D4CVH4_G54A/4D4CVL4_N93E	SEQ ID NO:233	SEQ ID NO:267
4D4CVH4_D53G/4D4CVL4_N93L	SEQ ID NO:229	SEQ ID NO:268
4D4CVH4_D53E/4D4CVL4_N93L	SEQ ID NO:230	SEQ ID NO:268
4D4CVH4_D53Q/4D4CVL4_N93L	SEQ ID NO:231	SEQ ID NO:268
4D4CVH4_D53L/4D4CVL4_N93L	SEQ ID NO:232	SEQ ID NO:268
4D4CVH4_G54A/4D4CVL4_N93L	SEQ ID NO:233	SEQ ID NO:268
4D4CVH4_D53G/4D4CVL4_N93Q	SEQ ID NO:229	SEQ ID NO:269
4D4CVH4_D53E/4D4CVL4_N93Q	SEQ ID NO:230	SEQ ID NO:269
4D4CVH4_D53Q/4D4CVL4_N93Q	SEQ ID NO:231	SEQ ID NO:269
4D4CVH4_D53L/4D4CVL4_N93Q	SEQ ID NO:232	SEQ ID NO:269
4D4CVH4_G54A/4D4CVL4_N93Q	SEQ ID NO:233	SEQ ID NO:269
4D4CVH4_D53G/4D4CVL4_G94A	SEQ ID NO:229	SEQ ID NO:270
4D4CVH4_D53E/4D4CVL4_G94A	SEQ ID NO:230	SEQ ID NO:270
4D4CVH4_D53Q/4D4CVL4_G94A	SEQ ID NO:231	SEQ ID NO:270
4D4CVH4_D53L/4D4CVL4_G94A	SEQ ID NO:232	SEQ ID NO:270
4D4CVH4_G54A/4D4CVL4_G94A	SEQ ID NO:233	SEQ ID NO:270
4D4CVH4/4D4GVL3_N93G	SEQ ID NO:83	SEQ ID NO:271
4D4CVH4/4D4GVL3_N93E	SEQ ID NO:83	SEQ ID NO:272
4D4CVH4/4D4GVL3_N93L	SEQ ID NO:83	SEQ ID NO:273
4D4CVH4/4D4GVL3_N93Q	SEQ ID NO:83	SEQ ID NO:274
4D4CVH4/4D4GVL3_G94A	SEQ ID NO:83	SEQ ID NO:275
4D4CVH4_D53G/4D4GVL3	SEQ ID NO:229	SEQ ID NO:98
4D4CVH4_D53E/4D4GVL3	SEQ ID NO:230	SEQ ID NO:98
4D4CVH4_D53Q/4D4GVL3	SEQ ID NO:231	SEQ ID NO:98
4D4CVH4_D53L/4D4GVL3	SEQ ID NO:232	SEQ ID NO:98
4D4CVH4_G54A/4D4GVL3	SEQ ID NO:233	SEQ ID NO:98
4D4CVH4_D53G/4D4GVL3_N93G	SEQ ID NO:229	SEQ ID NO:271
4D4CVH4_D53E/4D4GVL3_N93G	SEQ ID NO:230	SEQ ID NO:271
4D4CVH4_D53Q/4D4GVL3_N93G	SEQ ID NO:231	SEQ ID NO:271
4D4CVH4_D53L/4D4GVL3_N93G	SEQ ID NO:232	SEQ ID NO:271
4D4CVH4_G54A/4D4GVL3_N93G	SEQ ID NO:233	SEQ ID NO:271
4D4CVH4_D53G/4D4GVL3_N93E	SEQ ID NO:229	SEQ ID NO:272
4D4CVH4_D53E/4D4GVL3_N93E	SEQ ID NO:230	SEQ ID NO:272
4D4CVH4_D53Q/4D4GVL3_N93E	SEQ ID NO:231	SEQ ID NO:272
4D4CVH4_D53L/4D4GVL3_N93E	SEQ ID NO:232	SEQ ID NO:272
4D4CVH4_G54A/4D4GVL3_N93E	SEQ ID NO:233	SEQ ID NO:272
4D4CVH4_D53G/4D4GVL3_N93L	SEQ ID NO:229	SEQ ID NO:273
4D4CVH4_D53E/4D4GVL3_N93L	SEQ ID NO:230	SEQ ID NO:273
4D4CVH4_D53Q/4D4GVL3_N93L	SEQ ID NO:231	SEQ ID NO:273
4D4CVH4_D53L/4D4GVL3_N93L	SEQ ID NO:232	SEQ ID NO:273
4D4CVH4_G54A/4D4GVL3_N93L	SEQ ID NO:233	SEQ ID NO:273
4D4CVH4_D53G/4D4GVL3_N93Q	SEQ ID NO:229	SEQ ID NO:274
4D4CVH4_D53E/4D4GVL3_N93Q	SEQ ID NO:230	SEQ ID NO:274
4D4CVH4_D53Q/4D4GVL3_N93Q	SEQ ID NO:231	SEQ ID NO:274
4D4CVH4_D53L/4D4GVL3_N93Q	SEQ ID NO:232	SEQ ID NO:274
4D4CVH4_G54A/4D4GVL3_N93Q	SEQ ID NO:233	SEQ ID NO:274
4D4CVH4_D53G/4D4GVL3_G94A	SEQ ID NO:229	SEQ ID NO:275
4D4CVH4_D53E/4D4GVL3_G94A	SEQ ID NO:230	SEQ ID NO:275
4D4CVH4_D53Q/4D4GVL3_G94A	SEQ ID NO:231	SEQ ID NO:275

4D4CVH4_D53L/4D4GVL3_G94A	SEQ ID NO:232	SEQ ID NO:275
4D4CVH4_G54A/4D4GVL3_G94A	SEQ ID NO:233	SEQ ID NO:275
4D4CVH4/4D4GVL4_N93G	SEQ ID NO:83	SEQ ID NO:276
4D4CVH4/4D4GVL4_N93E	SEQ ID NO:83	SEQ ID NO:277
4D4CVH4/4D4GVL4_N93L	SEQ ID NO:83	SEQ ID NO:278
4D4CVH4/4D4GVL4_N93Q	SEQ ID NO:83	SEQ ID NO:279
4D4CVH4/4D4GVL4_G94A	SEQ ID NO:83	SEQ ID NO:280
4D4CVH4_D53G/4D4GVL4	SEQ ID NO:229	SEQ ID NO:100
4D4CVH4_D53E/4D4GVL4	SEQ ID NO:230	SEQ ID NO:100
4D4CVH4_D53Q/4D4GVL4	SEQ ID NO:231	SEQ ID NO:100
4D4CVH4_D53L/4D4GVL4	SEQ ID NO:232	SEQ ID NO:100
4D4CVH4_G54A/4D4GVL4	SEQ ID NO:233	SEQ ID NO:100
4D4CVH4_D53G/4D4GVL4_N93G	SEQ ID NO:229	SEQ ID NO:276
4D4CVH4_D53E/4D4GVL4_N93G	SEQ ID NO:230	SEQ ID NO:276
4D4CVH4_D53Q/4D4GVL4_N93G	SEQ ID NO:231	SEQ ID NO:276
4D4CVH4_D53L/4D4GVL4_N93G	SEQ ID NO:232	SEQ ID NO:276
4D4CVH4_G54A/4D4GVL4_N93G	SEQ ID NO:233	SEQ ID NO:276
4D4CVH4_D53G/4D4GVL4_N93E	SEQ ID NO:229	SEQ ID NO:277
4D4CVH4_D53E/4D4GVL4_N93E	SEQ ID NO:230	SEQ ID NO:277
4D4CVH4_D53Q/4D4GVL4_N93E	SEQ ID NO:231	SEQ ID NO:277
4D4CVH4_D53L/4D4GVL4_N93E	SEQ ID NO:232	SEQ ID NO:277
4D4CVH4_G54A/4D4GVL4_N93E	SEQ ID NO:233	SEQ ID NO:277
4D4CVH4_D53G/4D4GVL4_N93L	SEQ ID NO:229	SEQ ID NO:278
4D4CVH4_D53E/4D4GVL4_N93L	SEQ ID NO:230	SEQ ID NO:278
4D4CVH4_D53Q/4D4GVL4_N93L	SEQ ID NO:231	SEQ ID NO:278
4D4CVH4_D53L/4D4GVL4_N93L	SEQ ID NO:232	SEQ ID NO:278
4D4CVH4_G54A/4D4GVL4_N93L	SEQ ID NO:233	SEQ ID NO:278
4D4CVH4_D53G/4D4GVL4_N93Q	SEQ ID NO:229	SEQ ID NO:279
4D4CVH4_D53E/4D4GVL4_N93Q	SEQ ID NO:230	SEQ ID NO:279
4D4CVH4_D53Q/4D4GVL4_N93Q	SEQ ID NO:231	SEQ ID NO:279
4D4CVH4_D53L/4D4GVL4_N93Q	SEQ ID NO:232	SEQ ID NO:279
4D4CVH4_G54A/4D4GVL4_N93Q	SEQ ID NO:233	SEQ ID NO:279
4D4CVH4_D53G/4D4GVL4_G94A	SEQ ID NO:229	SEQ ID NO:280
4D4CVH4_D53E/4D4GVL4_G94A	SEQ ID NO:230	SEQ ID NO:280
4D4CVH4_D53Q/4D4GVL4_G94A	SEQ ID NO:231	SEQ ID NO:280
4D4CVH4_D53L/4D4GVL4_G94A	SEQ ID NO:232	SEQ ID NO:280
4D4CVH4_G54A/4D4GVL4_G94A	SEQ ID NO:233	SEQ ID NO:280
4D4CVH2.1/4D4C/GVL1_N93G	SEQ ID NO:86	SEQ ID NO:256
4D4CVH2.1/4D4C/GVL1_N93E	SEQ ID NO:86	SEQ ID NO:257
4D4CVH2.1/4D4C/GVL1_N93L	SEQ ID NO:86	SEQ ID NO:258
4D4CVH2.1/4D4C/GVL1_N93Q	SEQ ID NO:86	SEQ ID NO:259
4D4CVH2.1/4D4C/GVL1_G94A	SEQ ID NO:86	SEQ ID NO:260
4D4CVH2.1_D53G/4D4C/GVL1	SEQ ID NO:234	SEQ ID NO:88
4D4CVH2.1_D53E/4D4C/GVL1	SEQ ID NO:235	SEQ ID NO:88
4D4CVH2.1_D53Q/4D4C/GVL1	SEQ ID NO:236	SEQ ID NO:88
4D4CVH2.1_D53L/4D4C/GVL1	SEQ ID NO:237	SEQ ID NO:88
4D4CVH2.1_G54A/4D4C/GVL1	SEQ ID NO:238	SEQ ID NO:88
4D4CVH2.1_D53G/4D4C/GVL1_N93G	SEQ ID NO:234	SEQ ID NO:256
4D4CVH2.1_D53E/4D4C/GVL1_N93G	SEQ ID NO:235	SEQ ID NO:256
4D4CVH2.1_D53Q/4D4C/GVL1_N93G	SEQ ID NO:236	SEQ ID NO:256
4D4CVH2.1_D53L/4D4C/GVL1_N93G	SEQ ID NO:237	SEQ ID NO:256
4D4CVH2.1_G54A/4D4C/GVL1_N93G	SEQ ID NO:238	SEQ ID NO:256
4D4CVH2.1_D53G/4D4C/GVL1_N93E	SEQ ID NO:234	SEQ ID NO:257
4D4CVH2.1_D53E/4D4C/GVL1_N93E	SEQ ID NO:235	SEQ ID NO:257
4D4CVH2.1_D53Q/4D4C/GVL1_N93E	SEQ ID NO:236	SEQ ID NO:257
4D4CVH2.1_D53L/4D4C/GVL1_N93E	SEQ ID NO:237	SEQ ID NO:257
4D4CVH2.1_G54A/4D4C/GVL1_N93E	SEQ ID NO:238	SEQ ID NO:257
4D4CVH2.1_D53G/4D4C/GVL1_N93L	SEQ ID NO:234	SEQ ID NO:258
4D4CVH2.1_D53E/4D4C/GVL1_N93L	SEQ ID NO:235	SEQ ID NO:258
4D4CVH2.1_D53Q/4D4C/GVL1_N93L	SEQ ID NO:236	SEQ ID NO:258
4D4CVH2.1_D53L/4D4C/GVL1_N93L	SEQ ID NO:237	SEQ ID NO:258
4D4CVH2.1_G54A/4D4C/GVL1_N93L	SEQ ID NO:238	SEQ ID NO:258
4D4CVH2.1_D53G/4D4C/GVL1_N93Q	SEQ ID NO:234	SEQ ID NO:259
4D4CVH2.1_D53E/4D4C/GVL1_N93Q	SEQ ID NO:235	SEQ ID NO:259
4D4CVH2.1_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:236	SEQ ID NO:259
4D4CVH2.1_D53L/4D4C/GVL1_N93Q	SEQ ID NO:237	SEQ ID NO:259
4D4CVH2.1_G54A/4D4C/GVL1_N93Q	SEQ ID NO:238	SEQ ID NO:259
4D4CVH2.1_D53G/4D4C/GVL1_G94A	SEQ ID NO:234	SEQ ID NO:260
4D4CVH2.1_D53E/4D4C/GVL1_G94A	SEQ ID NO:235	SEQ ID NO:260
4D4CVH2.1_D53Q/4D4C/GVL1_G94A	SEQ ID NO:236	SEQ ID NO:260

4D4CVH2.1_D53L/4D4C/GVL1_G94A	SEQ ID NO:237	SEQ ID NO:260
4D4CVH2.1_G54A/4D4C/GVL1_G94A	SEQ ID NO:238	SEQ ID NO:260
4D4CVH2.1/4D4CVL2_N93G	SEQ ID NO:86	SEQ ID NO:261
4D4CVH2.1/4D4CVL2_N93E	SEQ ID NO:86	SEQ ID NO:262
4D4CVH2.1/4D4CVL2_N93L	SEQ ID NO:86	SEQ ID NO:263
4D4CVH2.1/4D4CVL2_N93Q	SEQ ID NO:86	SEQ ID NO:264
4D4CVH2.1/4D4CVL2_G94A	SEQ ID NO:86	SEQ ID NO:265
4D4CVH2.1_D53G/4D4CVL2	SEQ ID NO:234	SEQ ID NO:91
4D4CVH2.1_D53E/4D4CVL2	SEQ ID NO:235	SEQ ID NO:91
4D4CVH2.1_D53Q/4D4CVL2	SEQ ID NO:236	SEQ ID NO:91
4D4CVH2.1_D53L/4D4CVL2	SEQ ID NO:237	SEQ ID NO:91
4D4CVH2.1_G54A/4D4CVL2	SEQ ID NO:238	SEQ ID NO:91
4D4CVH2.1_D53G/4D4CVL2_N93G	SEQ ID NO:234	SEQ ID NO:261
4D4CVH2.1_D53E/4D4CVL2_N93G	SEQ ID NO:235	SEQ ID NO:261
4D4CVH2.1_D53Q/4D4CVL2_N93G	SEQ ID NO:236	SEQ ID NO:261
4D4CVH2.1_D53L/4D4CVL2_N93G	SEQ ID NO:237	SEQ ID NO:261
4D4CVH2.1_G54A/4D4CVL2_N93G	SEQ ID NO:238	SEQ ID NO:261
4D4CVH2.1_D53G/4D4CVL2_N93E	SEQ ID NO:234	SEQ ID NO:262
4D4CVH2.1_D53E/4D4CVL2_N93E	SEQ ID NO:235	SEQ ID NO:262
4D4CVH2.1_D53Q/4D4CVL2_N93E	SEQ ID NO:236	SEQ ID NO:262
4D4CVH2.1_D53L/4D4CVL2_N93E	SEQ ID NO:237	SEQ ID NO:262
4D4CVH2.1_G54A/4D4CVL2_N93E	SEQ ID NO:238	SEQ ID NO:262
4D4CVH2.1_D53G/4D4CVL2_N93L	SEQ ID NO:234	SEQ ID NO:263
4D4CVH2.1_D53E/4D4CVL2_N93L	SEQ ID NO:235	SEQ ID NO:263
4D4CVH2.1_D53Q/4D4CVL2_N93L	SEQ ID NO:236	SEQ ID NO:263
4D4CVH2.1_D53L/4D4CVL2_N93L	SEQ ID NO:237	SEQ ID NO:263
4D4CVH2.1_G54A/4D4CVL2_N93L	SEQ ID NO:238	SEQ ID NO:263
4D4CVH2.1_D53G/4D4CVL2_N93Q	SEQ ID NO:234	SEQ ID NO:264
4D4CVH2.1_D53E/4D4CVL2_N93Q	SEQ ID NO:235	SEQ ID NO:264
4D4CVH2.1_D53Q/4D4CVL2_N93Q	SEQ ID NO:236	SEQ ID NO:264
4D4CVH2.1_D53L/4D4CVL2_N93Q	SEQ ID NO:237	SEQ ID NO:264
4D4CVH2.1_G54A/4D4CVL2_N93Q	SEQ ID NO:238	SEQ ID NO:264
4D4CVH2.1_D53G/4D4CVL2_G94A	SEQ ID NO:234	SEQ ID NO:265
4D4CVH2.1_D53E/4D4CVL2_G94A	SEQ ID NO:235	SEQ ID NO:265
4D4CVH2.1_D53Q/4D4CVL2_G94A	SEQ ID NO:236	SEQ ID NO:265
4D4CVH2.1_D53L/4D4CVL2_G94A	SEQ ID NO:237	SEQ ID NO:265
4D4CVH2.1_G54A/4D4CVL2_G94A	SEQ ID NO:238	SEQ ID NO:265
4D4CVH2.1/4D4CVL4_N93G	SEQ ID NO:86	SEQ ID NO:266
4D4CVH2.1/4D4CVL4_N93E	SEQ ID NO:86	SEQ ID NO:267
4D4CVH2.1/4D4CVL4_N93L	SEQ ID NO:86	SEQ ID NO:268
4D4CVH2.1/4D4CVL4_N93Q	SEQ ID NO:86	SEQ ID NO:269
4D4CVH2.1/4D4CVL4_G94A	SEQ ID NO:86	SEQ ID NO:270
4D4CVH2.1_D53G/4D4CVL4	SEQ ID NO:234	SEQ ID NO:95
4D4CVH2.1_D53E/4D4CVL4	SEQ ID NO:235	SEQ ID NO:95
4D4CVH2.1_D53Q/4D4CVL4	SEQ ID NO:236	SEQ ID NO:95
4D4CVH2.1_D53L/4D4CVL4	SEQ ID NO:237	SEQ ID NO:95
4D4CVH2.1_G54A/4D4CVL4	SEQ ID NO:238	SEQ ID NO:95
4D4CVH2.1_D53G/4D4CVL4_N93G	SEQ ID NO:234	SEQ ID NO:266
4D4CVH2.1_D53E/4D4CVL4_N93G	SEQ ID NO:235	SEQ ID NO:266
4D4CVH2.1_D53Q/4D4CVL4_N93G	SEQ ID NO:236	SEQ ID NO:266
4D4CVH2.1_D53L/4D4CVL4_N93G	SEQ ID NO:237	SEQ ID NO:266
4D4CVH2.1_G54A/4D4CVL4_N93G	SEQ ID NO:238	SEQ ID NO:266
4D4CVH2.1_D53G/4D4CVL4_N93E	SEQ ID NO:234	SEQ ID NO:267
4D4CVH2.1_D53E/4D4CVL4_N93E	SEQ ID NO:235	SEQ ID NO:267
4D4CVH2.1_D53Q/4D4CVL4_N93E	SEQ ID NO:236	SEQ ID NO:267
4D4CVH2.1_D53L/4D4CVL4_N93E	SEQ ID NO:237	SEQ ID NO:267
4D4CVH2.1_G54A/4D4CVL4_N93E	SEQ ID NO:238	SEQ ID NO:267
4D4CVH2.1_D53G/4D4CVL4_N93L	SEQ ID NO:234	SEQ ID NO:268
4D4CVH2.1_D53E/4D4CVL4_N93L	SEQ ID NO:235	SEQ ID NO:268
4D4CVH2.1_D53Q/4D4CVL4_N93L	SEQ ID NO:236	SEQ ID NO:268
4D4CVH2.1_D53L/4D4CVL4_N93L	SEQ ID NO:237	SEQ ID NO:268
4D4CVH2.1_G54A/4D4CVL4_N93L	SEQ ID NO:238	SEQ ID NO:268
4D4CVH2.1_D53G/4D4CVL4_N93Q	SEQ ID NO:234	SEQ ID NO:269
4D4CVH2.1_D53E/4D4CVL4_N93Q	SEQ ID NO:235	SEQ ID NO:269
4D4CVH2.1_D53Q/4D4CVL4_N93Q	SEQ ID NO:236	SEQ ID NO:269
4D4CVH2.1_D53L/4D4CVL4_N93Q	SEQ ID NO:237	SEQ ID NO:269
4D4CVH2.1_G54A/4D4CVL4_N93Q	SEQ ID NO:238	SEQ ID NO:269
4D4CVH2.1_D53G/4D4CVL4_G94A	SEQ ID NO:234	SEQ ID NO:270
4D4CVH2.1_D53E/4D4CVL4_G94A	SEQ ID NO:235	SEQ ID NO:270
4D4CVH2.1_D53Q/4D4CVL4_G94A	SEQ ID NO:236	SEQ ID NO:270

4D4CVH2.1_D53L/4D4CVL4_G94A	SEQ ID NO:237	SEQ ID NO:270
4D4CVH2.1_G54A/4D4CVL4_G94A	SEQ ID NO:238	SEQ ID NO:270
4D4CVH2.1/4D4GVL3_N93G	SEQ ID NO:86	SEQ ID NO:271
4D4CVH2.1/4D4GVL3_N93E	SEQ ID NO:86	SEQ ID NO:272
4D4CVH2.1/4D4GVL3_N93L	SEQ ID NO:86	SEQ ID NO:273
4D4CVH2.1/4D4GVL3_N93Q	SEQ ID NO:86	SEQ ID NO:274
4D4CVH2.1/4D4GVL3_G94A	SEQ ID NO:86	SEQ ID NO:275
4D4CVH2.1_D53G/4D4GVL3	SEQ ID NO:234	SEQ ID NO:98
4D4CVH2.1_D53E/4D4GVL3	SEQ ID NO:235	SEQ ID NO:98
4D4CVH2.1_D53Q/4D4GVL3	SEQ ID NO:236	SEQ ID NO:98
4D4CVH2.1_D53L/4D4GVL3	SEQ ID NO:237	SEQ ID NO:98
4D4CVH2.1_G54A/4D4GVL3	SEQ ID NO:238	SEQ ID NO:98
4D4CVH2.1_D53G/4D4GVL3_N93G	SEQ ID NO:234	SEQ ID NO:271
4D4CVH2.1_D53E/4D4GVL3_N93G	SEQ ID NO:235	SEQ ID NO:271
4D4CVH2.1_D53Q/4D4GVL3_N93G	SEQ ID NO:236	SEQ ID NO:271
4D4CVH2.1_D53L/4D4GVL3_N93G	SEQ ID NO:237	SEQ ID NO:271
4D4CVH2.1_G54A/4D4GVL3_N93G	SEQ ID NO:238	SEQ ID NO:271
4D4CVH2.1_D53G/4D4GVL3_N93E	SEQ ID NO:234	SEQ ID NO:272
4D4CVH2.1_D53E/4D4GVL3_N93E	SEQ ID NO:235	SEQ ID NO:272
4D4CVH2.1_D53Q/4D4GVL3_N93E	SEQ ID NO:236	SEQ ID NO:272
4D4CVH2.1_D53L/4D4GVL3_N93E	SEQ ID NO:237	SEQ ID NO:272
4D4CVH2.1_G54A/4D4GVL3_N93E	SEQ ID NO:238	SEQ ID NO:272
4D4CVH2.1_D53G/4D4GVL3_N93L	SEQ ID NO:234	SEQ ID NO:273
4D4CVH2.1_D53E/4D4GVL3_N93L	SEQ ID NO:235	SEQ ID NO:273
4D4CVH2.1_D53Q/4D4GVL3_N93L	SEQ ID NO:236	SEQ ID NO:273
4D4CVH2.1_D53L/4D4GVL3_N93L	SEQ ID NO:237	SEQ ID NO:273
4D4CVH2.1_G54A/4D4GVL3_N93L	SEQ ID NO:238	SEQ ID NO:273
4D4CVH2.1_D53G/4D4GVL3_N93Q	SEQ ID NO:234	SEQ ID NO:274
4D4CVH2.1_D53E/4D4GVL3_N93Q	SEQ ID NO:235	SEQ ID NO:274
4D4CVH2.1_D53Q/4D4GVL3_N93Q	SEQ ID NO:236	SEQ ID NO:274
4D4CVH2.1_D53L/4D4GVL3_N93Q	SEQ ID NO:237	SEQ ID NO:274
4D4CVH2.1_G54A/4D4GVL3_N93Q	SEQ ID NO:238	SEQ ID NO:274
4D4CVH2.1_D53G/4D4GVL3_G94A	SEQ ID NO:234	SEQ ID NO:275
4D4CVH2.1_D53E/4D4GVL3_G94A	SEQ ID NO:235	SEQ ID NO:275
4D4CVH2.1_D53Q/4D4GVL3_G94A	SEQ ID NO:236	SEQ ID NO:275
4D4CVH2.1_D53L/4D4GVL3_G94A	SEQ ID NO:237	SEQ ID NO:275
4D4CVH2.1_G54A/4D4GVL3_G94A	SEQ ID NO:238	SEQ ID NO:275
4D4CVH2.1/4D4GVL4_N93G	SEQ ID NO:86	SEQ ID NO:276
4D4CVH2.1/4D4GVL4_N93E	SEQ ID NO:86	SEQ ID NO:277
4D4CVH2.1/4D4GVL4_N93L	SEQ ID NO:86	SEQ ID NO:278
4D4CVH2.1/4D4GVL4_N93Q	SEQ ID NO:86	SEQ ID NO:279
4D4CVH2.1/4D4GVL4_G94A	SEQ ID NO:86	SEQ ID NO:280
4D4CVH2.1_D53G/4D4GVL4	SEQ ID NO:234	SEQ ID NO:100
4D4CVH2.1_D53E/4D4GVL4	SEQ ID NO:235	SEQ ID NO:100
4D4CVH2.1_D53Q/4D4GVL4	SEQ ID NO:236	SEQ ID NO:100
4D4CVH2.1_D53L/4D4GVL4	SEQ ID NO:237	SEQ ID NO:100
4D4CVH2.1_G54A/4D4GVL4	SEQ ID NO:238	SEQ ID NO:100
4D4CVH2.1_D53G/4D4GVL4_N93G	SEQ ID NO:234	SEQ ID NO:276
4D4CVH2.1_D53E/4D4GVL4_N93G	SEQ ID NO:235	SEQ ID NO:276
4D4CVH2.1_D53Q/4D4GVL4_N93G	SEQ ID NO:236	SEQ ID NO:276
4D4CVH2.1_D53L/4D4GVL4_N93G	SEQ ID NO:237	SEQ ID NO:276
4D4CVH2.1_G54A/4D4GVL4_N93G	SEQ ID NO:238	SEQ ID NO:276
4D4CVH2.1_D53G/4D4GVL4_N93E	SEQ ID NO:234	SEQ ID NO:277
4D4CVH2.1_D53E/4D4GVL4_N93E	SEQ ID NO:235	SEQ ID NO:277
4D4CVH2.1_D53Q/4D4GVL4_N93E	SEQ ID NO:236	SEQ ID NO:277
4D4CVH2.1_D53L/4D4GVL4_N93E	SEQ ID NO:237	SEQ ID NO:277
4D4CVH2.1_G54A/4D4GVL4_N93E	SEQ ID NO:238	SEQ ID NO:277
4D4CVH2.1_D53G/4D4GVL4_N93L	SEQ ID NO:234	SEQ ID NO:278
4D4CVH2.1_D53E/4D4GVL4_N93L	SEQ ID NO:235	SEQ ID NO:278
4D4CVH2.1_D53Q/4D4GVL4_N93L	SEQ ID NO:236	SEQ ID NO:278
4D4CVH2.1_D53L/4D4GVL4_N93L	SEQ ID NO:237	SEQ ID NO:278
4D4CVH2.1_G54A/4D4GVL4_N93L	SEQ ID NO:238	SEQ ID NO:278
4D4CVH2.1_D53G/4D4GVL4_N93Q	SEQ ID NO:234	SEQ ID NO:279
4D4CVH2.1_D53E/4D4GVL4_N93Q	SEQ ID NO:235	SEQ ID NO:279
4D4CVH2.1_D53Q/4D4GVL4_N93Q	SEQ ID NO:236	SEQ ID NO:279
4D4CVH2.1_D53L/4D4GVL4_N93Q	SEQ ID NO:237	SEQ ID NO:279
4D4CVH2.1_G54A/4D4GVL4_N93Q	SEQ ID NO:238	SEQ ID NO:279
4D4CVH2.1_D53G/4D4GVL4_G94A	SEQ ID NO:234	SEQ ID NO:280
4D4CVH2.1_D53E/4D4GVL4_G94A	SEQ ID NO:235	SEQ ID NO:280
4D4CVH2.1_D53Q/4D4GVL4_G94A	SEQ ID NO:236	SEQ ID NO:280

4D4CVH2.1_D53L/4D4GVL4_G94A	SEQ ID NO:237	SEQ ID NO:280
4D4CVH2.1_G54A/4D4GVL4_G94A	SEQ ID NO:238	SEQ ID NO:280
4D4CVH2.2/4D4C/GVL1_N93G	SEQ ID NO:87	SEQ ID NO:256
4D4CVH2.2/4D4C/GVL1_N93E	SEQ ID NO:87	SEQ ID NO:257
4D4CVH2.2/4D4C/GVL1_N93L	SEQ ID NO:87	SEQ ID NO:258
4D4CVH2.2/4D4C/GVL1_N93Q	SEQ ID NO:87	SEQ ID NO:259
4D4CVH2.2/4D4C/GVL1_G94A	SEQ ID NO:87	SEQ ID NO:260
4D4CVH2.2_D53G/4D4C/GVL1	SEQ ID NO:239	SEQ ID NO:88
4D4CVH2.2_D53E/4D4C/GVL1	SEQ ID NO:240	SEQ ID NO:88
4D4CVH2.2_D53Q/4D4C/GVL1	SEQ ID NO:241	SEQ ID NO:88
4D4CVH2.2_D53L/4D4C/GVL1	SEQ ID NO:242	SEQ ID NO:88
4D4CVH2.2_G54A/4D4C/GVL1	SEQ ID NO:243	SEQ ID NO:88
4D4CVH2.2_D53G/4D4C/GVL1_N93G	SEQ ID NO:239	SEQ ID NO:256
4D4CVH2.2_D53E/4D4C/GVL1_N93G	SEQ ID NO:240	SEQ ID NO:256
4D4CVH2.2_D53Q/4D4C/GVL1_N93G	SEQ ID NO:241	SEQ ID NO:256
4D4CVH2.2_D53L/4D4C/GVL1_N93G	SEQ ID NO:242	SEQ ID NO:256
4D4CVH2.2_G54A/4D4C/GVL1_N93G	SEQ ID NO:243	SEQ ID NO:256
4D4CVH2.2_D53G/4D4C/GVL1_N93E	SEQ ID NO:239	SEQ ID NO:257
4D4CVH2.2_D53E/4D4C/GVL1_N93E	SEQ ID NO:240	SEQ ID NO:257
4D4CVH2.2_D53Q/4D4C/GVL1_N93E	SEQ ID NO:241	SEQ ID NO:257
4D4CVH2.2_D53L/4D4C/GVL1_N93E	SEQ ID NO:242	SEQ ID NO:257
4D4CVH2.2_G54A/4D4C/GVL1_N93E	SEQ ID NO:243	SEQ ID NO:257
4D4CVH2.2_D53G/4D4C/GVL1_N93L	SEQ ID NO:239	SEQ ID NO:258
4D4CVH2.2_D53E/4D4C/GVL1_N93L	SEQ ID NO:240	SEQ ID NO:258
4D4CVH2.2_D53Q/4D4C/GVL1_N93L	SEQ ID NO:241	SEQ ID NO:258
4D4CVH2.2_D53L/4D4C/GVL1_N93L	SEQ ID NO:242	SEQ ID NO:258
4D4CVH2.2_G54A/4D4C/GVL1_N93L	SEQ ID NO:243	SEQ ID NO:258
4D4CVH2.2_D53G/4D4C/GVL1_N93Q	SEQ ID NO:239	SEQ ID NO:259
4D4CVH2.2_D53E/4D4C/GVL1_N93Q	SEQ ID NO:240	SEQ ID NO:259
4D4CVH2.2_D53Q/4D4C/GVL1_N93Q	SEQ ID NO:241	SEQ ID NO:259
4D4CVH2.2_D53L/4D4C/GVL1_N93Q	SEQ ID NO:242	SEQ ID NO:259
4D4CVH2.2_G54A/4D4C/GVL1_N93Q	SEQ ID NO:243	SEQ ID NO:259
4D4CVH2.2_D53G/4D4C/GVL1_G94A	SEQ ID NO:239	SEQ ID NO:260
4D4CVH2.2_D53E/4D4C/GVL1_G94A	SEQ ID NO:240	SEQ ID NO:260
4D4CVH2.2_D53Q/4D4C/GVL1_G94A	SEQ ID NO:241	SEQ ID NO:260
4D4CVH2.2_D53L/4D4C/GVL1_G94A	SEQ ID NO:242	SEQ ID NO:260
4D4CVH2.2_G54A/4D4C/GVL1_G94A	SEQ ID NO:243	SEQ ID NO:260
4D4CVH2.2/4D4C/L2_N93G	SEQ ID NO:87	SEQ ID NO:261
4D4CVH2.2/4D4C/L2_N93E	SEQ ID NO:87	SEQ ID NO:262
4D4CVH2.2/4D4C/L2_N93L	SEQ ID NO:87	SEQ ID NO:263
4D4CVH2.2/4D4C/L2_N93Q	SEQ ID NO:87	SEQ ID NO:264
4D4CVH2.2/4D4C/L2_G94A	SEQ ID NO:87	SEQ ID NO:265
4D4CVH2.2_D53G/4D4C/L2	SEQ ID NO:239	SEQ ID NO:91
4D4CVH2.2_D53E/4D4C/L2	SEQ ID NO:240	SEQ ID NO:91
4D4CVH2.2_D53Q/4D4C/L2	SEQ ID NO:241	SEQ ID NO:91
4D4CVH2.2_D53L/4D4C/L2	SEQ ID NO:242	SEQ ID NO:91
4D4CVH2.2_G54A/4D4C/L2	SEQ ID NO:243	SEQ ID NO:91
4D4CVH2.2_D53G/4D4C/L2_N93G	SEQ ID NO:239	SEQ ID NO:261
4D4CVH2.2_D53E/4D4C/L2_N93G	SEQ ID NO:240	SEQ ID NO:261
4D4CVH2.2_D53Q/4D4C/L2_N93G	SEQ ID NO:241	SEQ ID NO:261
4D4CVH2.2_D53L/4D4C/L2_N93G	SEQ ID NO:242	SEQ ID NO:261
4D4CVH2.2_G54A/4D4C/L2_N93G	SEQ ID NO:243	SEQ ID NO:261
4D4CVH2.2_D53G/4D4C/L2_N93E	SEQ ID NO:239	SEQ ID NO:262
4D4CVH2.2_D53E/4D4C/L2_N93E	SEQ ID NO:240	SEQ ID NO:262
4D4CVH2.2_D53Q/4D4C/L2_N93E	SEQ ID NO:241	SEQ ID NO:262
4D4CVH2.2_D53L/4D4C/L2_N93E	SEQ ID NO:242	SEQ ID NO:262
4D4CVH2.2_G54A/4D4C/L2_N93E	SEQ ID NO:243	SEQ ID NO:262
4D4CVH2.2_D53G/4D4C/L2_N93L	SEQ ID NO:239	SEQ ID NO:263
4D4CVH2.2_D53E/4D4C/L2_N93L	SEQ ID NO:240	SEQ ID NO:263
4D4CVH2.2_D53Q/4D4C/L2_N93L	SEQ ID NO:241	SEQ ID NO:263
4D4CVH2.2_D53L/4D4C/L2_N93L	SEQ ID NO:242	SEQ ID NO:263
4D4CVH2.2_G54A/4D4C/L2_N93L	SEQ ID NO:243	SEQ ID NO:263
4D4CVH2.2_D53G/4D4C/L2_N93Q	SEQ ID NO:239	SEQ ID NO:264
4D4CVH2.2_D53E/4D4C/L2_N93Q	SEQ ID NO:240	SEQ ID NO:264
4D4CVH2.2_D53Q/4D4C/L2_N93Q	SEQ ID NO:241	SEQ ID NO:264
4D4CVH2.2_D53L/4D4C/L2_N93Q	SEQ ID NO:242	SEQ ID NO:264
4D4CVH2.2_G54A/4D4C/L2_N93Q	SEQ ID NO:243	SEQ ID NO:264
4D4CVH2.2_D53G/4D4C/L2_G94A	SEQ ID NO:239	SEQ ID NO:265
4D4CVH2.2_D53E/4D4C/L2_G94A	SEQ ID NO:240	SEQ ID NO:265
4D4CVH2.2_D53Q/4D4C/L2_G94A	SEQ ID NO:241	SEQ ID NO:265

4D4CVH2.2_D53L/4D4CVL2_G94A	SEQ ID NO:242	SEQ ID NO:265
4D4CVH2.2_G54A/4D4CVL2_G94A	SEQ ID NO:243	SEQ ID NO:265
4D4CVH2.2/4D4CVL4_N93G	SEQ ID NO:87	SEQ ID NO:266
4D4CVH2.2/4D4CVL4_N93E	SEQ ID NO:87	SEQ ID NO:267
4D4CVH2.2/4D4CVL4_N93L	SEQ ID NO:87	SEQ ID NO:268
4D4CVH2.2/4D4CVL4_N93Q	SEQ ID NO:87	SEQ ID NO:269
4D4CVH2.2/4D4CVL4_G94A	SEQ ID NO:87	SEQ ID NO:270
4D4CVH2.2_D53G/4D4CVL4	SEQ ID NO:239	SEQ ID NO:95
4D4CVH2.2_D53E/4D4CVL4	SEQ ID NO:240	SEQ ID NO:95
4D4CVH2.2_D53Q/4D4CVL4	SEQ ID NO:241	SEQ ID NO:95
4D4CVH2.2_D53L/4D4CVL4	SEQ ID NO:242	SEQ ID NO:95
4D4CVH2.2_G54A/4D4CVL4	SEQ ID NO:243	SEQ ID NO:95
4D4CVH2.2_D53G/4D4CVL4_N93G	SEQ ID NO:239	SEQ ID NO:266
4D4CVH2.2_D53E/4D4CVL4_N93G	SEQ ID NO:240	SEQ ID NO:266
4D4CVH2.2_D53Q/4D4CVL4_N93G	SEQ ID NO:241	SEQ ID NO:266
4D4CVH2.2_D53L/4D4CVL4_N93G	SEQ ID NO:242	SEQ ID NO:266
4D4CVH2.2_G54A/4D4CVL4_N93G	SEQ ID NO:243	SEQ ID NO:266
4D4CVH2.2_D53G/4D4CVL4_N93E	SEQ ID NO:239	SEQ ID NO:267
4D4CVH2.2_D53E/4D4CVL4_N93E	SEQ ID NO:240	SEQ ID NO:267
4D4CVH2.2_D53Q/4D4CVL4_N93E	SEQ ID NO:241	SEQ ID NO:267
4D4CVH2.2_D53L/4D4CVL4_N93E	SEQ ID NO:242	SEQ ID NO:267
4D4CVH2.2_G54A/4D4CVL4_N93E	SEQ ID NO:243	SEQ ID NO:267
4D4CVH2.2_D53G/4D4CVL4_N93L	SEQ ID NO:239	SEQ ID NO:268
4D4CVH2.2_D53E/4D4CVL4_N93L	SEQ ID NO:240	SEQ ID NO:268
4D4CVH2.2_D53Q/4D4CVL4_N93L	SEQ ID NO:241	SEQ ID NO:268
4D4CVH2.2_D53L/4D4CVL4_N93L	SEQ ID NO:242	SEQ ID NO:268
4D4CVH2.2_G54A/4D4CVL4_N93L	SEQ ID NO:243	SEQ ID NO:268
4D4CVH2.2_D53G/4D4CVL4_N93Q	SEQ ID NO:239	SEQ ID NO:269
4D4CVH2.2_D53E/4D4CVL4_N93Q	SEQ ID NO:240	SEQ ID NO:269
4D4CVH2.2_D53Q/4D4CVL4_N93Q	SEQ ID NO:241	SEQ ID NO:269
4D4CVH2.2_D53L/4D4CVL4_N93Q	SEQ ID NO:242	SEQ ID NO:269
4D4CVH2.2_G54A/4D4CVL4_N93Q	SEQ ID NO:243	SEQ ID NO:269
4D4CVH2.2_D53G/4D4CVL4_G94A	SEQ ID NO:239	SEQ ID NO:270
4D4CVH2.2_D53E/4D4CVL4_G94A	SEQ ID NO:240	SEQ ID NO:270
4D4CVH2.2_D53Q/4D4CVL4_G94A	SEQ ID NO:241	SEQ ID NO:270
4D4CVH2.2_D53L/4D4CVL4_G94A	SEQ ID NO:242	SEQ ID NO:270
4D4CVH2.2_G54A/4D4CVL4_G94A	SEQ ID NO:243	SEQ ID NO:270
4D4CVH2.2/4D4GVL3_N93G	SEQ ID NO:87	SEQ ID NO:271
4D4CVH2.2/4D4GVL3_N93E	SEQ ID NO:87	SEQ ID NO:272
4D4CVH2.2/4D4GVL3_N93L	SEQ ID NO:87	SEQ ID NO:273
4D4CVH2.2/4D4GVL3_N93Q	SEQ ID NO:87	SEQ ID NO:274
4D4CVH2.2/4D4GVL3_G94A	SEQ ID NO:87	SEQ ID NO:275
4D4CVH2.2_D53G/4D4GVL3	SEQ ID NO:239	SEQ ID NO:98
4D4CVH2.2_D53E/4D4GVL3	SEQ ID NO:240	SEQ ID NO:98
4D4CVH2.2_D53Q/4D4GVL3	SEQ ID NO:241	SEQ ID NO:98
4D4CVH2.2_D53L/4D4GVL3	SEQ ID NO:242	SEQ ID NO:98
4D4CVH2.2_G54A/4D4GVL3	SEQ ID NO:243	SEQ ID NO:98
4D4CVH2.2_D53G/4D4GVL3_N93G	SEQ ID NO:239	SEQ ID NO:271
4D4CVH2.2_D53E/4D4GVL3_N93G	SEQ ID NO:240	SEQ ID NO:271
4D4CVH2.2_D53Q/4D4GVL3_N93G	SEQ ID NO:241	SEQ ID NO:271
4D4CVH2.2_D53L/4D4GVL3_N93G	SEQ ID NO:242	SEQ ID NO:271
4D4CVH2.2_G54A/4D4GVL3_N93G	SEQ ID NO:243	SEQ ID NO:271
4D4CVH2.2_D53G/4D4GVL3_N93E	SEQ ID NO:239	SEQ ID NO:272
4D4CVH2.2_D53E/4D4GVL3_N93E	SEQ ID NO:240	SEQ ID NO:272
4D4CVH2.2_D53Q/4D4GVL3_N93E	SEQ ID NO:241	SEQ ID NO:272
4D4CVH2.2_D53L/4D4GVL3_N93E	SEQ ID NO:242	SEQ ID NO:272
4D4CVH2.2_G54A/4D4GVL3_N93E	SEQ ID NO:243	SEQ ID NO:272
4D4CVH2.2_D53G/4D4GVL3_N93L	SEQ ID NO:239	SEQ ID NO:273
4D4CVH2.2_D53E/4D4GVL3_N93L	SEQ ID NO:240	SEQ ID NO:273
4D4CVH2.2_D53Q/4D4GVL3_N93L	SEQ ID NO:241	SEQ ID NO:273
4D4CVH2.2_D53L/4D4GVL3_N93L	SEQ ID NO:242	SEQ ID NO:273
4D4CVH2.2_G54A/4D4GVL3_N93L	SEQ ID NO:243	SEQ ID NO:273
4D4CVH2.2_D53G/4D4GVL3_N93Q	SEQ ID NO:239	SEQ ID NO:274
4D4CVH2.2_D53E/4D4GVL3_N93Q	SEQ ID NO:240	SEQ ID NO:274
4D4CVH2.2_D53Q/4D4GVL3_N93Q	SEQ ID NO:241	SEQ ID NO:274
4D4CVH2.2_D53L/4D4GVL3_N93Q	SEQ ID NO:242	SEQ ID NO:274
4D4CVH2.2_G54A/4D4GVL3_N93Q	SEQ ID NO:243	SEQ ID NO:274
4D4CVH2.2_D53G/4D4GVL3_G94A	SEQ ID NO:239	SEQ ID NO:275
4D4CVH2.2_D53E/4D4GVL3_G94A	SEQ ID NO:240	SEQ ID NO:275
4D4CVH2.2_D53Q/4D4GVL3_G94A	SEQ ID NO:241	SEQ ID NO:275

4D4CVH2.2_D53L/4D4GVL3_G94A	SEQ ID NO:242	SEQ ID NO:275
4D4CVH2.2_G54A/4D4GVL3_G94A	SEQ ID NO:243	SEQ ID NO:275
4D4CVH2.2/4D4GVL4_N93G	SEQ ID NO:87	SEQ ID NO:276
4D4CVH2.2/4D4GVL4_N93E	SEQ ID NO:87	SEQ ID NO:277
4D4CVH2.2/4D4GVL4_N93L	SEQ ID NO:87	SEQ ID NO:278
4D4CVH2.2/4D4GVL4_N93Q	SEQ ID NO:87	SEQ ID NO:279
4D4CVH2.2/4D4GVL4_G94A	SEQ ID NO:87	SEQ ID NO:280
4D4CVH2.2_D53G/4D4GVL4	SEQ ID NO:239	SEQ ID NO:100
4D4CVH2.2_D53E/4D4GVL4	SEQ ID NO:240	SEQ ID NO:100
4D4CVH2.2_D53Q/4D4GVL4	SEQ ID NO:241	SEQ ID NO:100
4D4CVH2.2_D53L/4D4GVL4	SEQ ID NO:242	SEQ ID NO:100
4D4CVH2.2_G54A/4D4GVL4	SEQ ID NO:243	SEQ ID NO:100
4D4CVH2.2_D53G/4D4GVL4_N93G	SEQ ID NO:239	SEQ ID NO:276
4D4CVH2.2_D53E/4D4GVL4_N93G	SEQ ID NO:240	SEQ ID NO:276
4D4CVH2.2_D53Q/4D4GVL4_N93G	SEQ ID NO:241	SEQ ID NO:276
4D4CVH2.2_D53L/4D4GVL4_N93G	SEQ ID NO:242	SEQ ID NO:276
4D4CVH2.2_G54A/4D4GVL4_N93G	SEQ ID NO:243	SEQ ID NO:276
4D4CVH2.2_D53G/4D4GVL4_N93E	SEQ ID NO:239	SEQ ID NO:277
4D4CVH2.2_D53E/4D4GVL4_N93E	SEQ ID NO:240	SEQ ID NO:277
4D4CVH2.2_D53Q/4D4GVL4_N93E	SEQ ID NO:241	SEQ ID NO:277
4D4CVH2.2_D53L/4D4GVL4_N93E	SEQ ID NO:242	SEQ ID NO:277
4D4CVH2.2_G54A/4D4GVL4_N93E	SEQ ID NO:243	SEQ ID NO:277
4D4CVH2.2_D53G/4D4GVL4_N93L	SEQ ID NO:239	SEQ ID NO:278
4D4CVH2.2_D53E/4D4GVL4_N93L	SEQ ID NO:240	SEQ ID NO:278
4D4CVH2.2_D53Q/4D4GVL4_N93L	SEQ ID NO:241	SEQ ID NO:278
4D4CVH2.2_D53L/4D4GVL4_N93L	SEQ ID NO:242	SEQ ID NO:278
4D4CVH2.2_G54A/4D4GVL4_N93L	SEQ ID NO:243	SEQ ID NO:278
4D4CVH2.2_D53G/4D4GVL4_N93Q	SEQ ID NO:239	SEQ ID NO:279
4D4CVH2.2_D53E/4D4GVL4_N93Q	SEQ ID NO:240	SEQ ID NO:279
4D4CVH2.2_D53Q/4D4GVL4_N93Q	SEQ ID NO:241	SEQ ID NO:279
4D4CVH2.2_D53L/4D4GVL4_N93Q	SEQ ID NO:242	SEQ ID NO:279
4D4CVH2.2_G54A/4D4GVL4_N93Q	SEQ ID NO:243	SEQ ID NO:279
4D4CVH2.2_D53G/4D4GVL4_G94A	SEQ ID NO:239	SEQ ID NO:280
4D4CVH2.2_D53E/4D4GVL4_G94A	SEQ ID NO:240	SEQ ID NO:280
4D4CVH2.2_D53Q/4D4GVL4_G94A	SEQ ID NO:241	SEQ ID NO:280
4D4CVH2.2_D53L/4D4GVL4_G94A	SEQ ID NO:242	SEQ ID NO:280
4D4CVH2.2_G54A/4D4GVL4_G94A	SEQ ID NO:243	SEQ ID NO:280
CON4D4P/Hu_D53var_G53var	SEQ ID NO:250	SEQ ID NO:287
/CON4D4P/Hu_N93var_G94var		

Table D

Name	Column A	Column B
	Heavy Chain	Light Chain
4D4 hlgG1	SEQ ID NO:145	SEQ ID NO:157
3G9 hlgG1	SEQ ID NO:146	SEQ ID NO:158
4A7/7D8 hlgG1	SEQ ID NO:147	SEQ ID NO:159
8C6 hlgG1	SEQ ID NO:148	SEQ ID NO:160
C03-A7 hlgG1	SEQ ID NO:149	SEQ ID NO:161
CON'4'9'7/8 hlgG1	SEQ ID NO:150	SEQ ID NO:162
4D4CVH2/4D4C/GVL1 hlgG1	SEQ ID NO:151	SEQ ID NO:163
4D4CVH2/4D4CVL2 hlgG1	SEQ ID NO:151	SEQ ID NO:164
4D4CVH2/4D4CVL4 hlgG1	SEQ ID NO:151	SEQ ID NO:165
4D4CVH2/4D4GVL3 hlgG1	SEQ ID NO:151	SEQ ID NO:166
4D4CVH2/4D4GVL4 hlgG1	SEQ ID NO:151	SEQ ID NO:167
4D4CVH3/4D4C/GVL1 hlgG1	SEQ ID NO:152	SEQ ID NO:163
4D4CVH3/4D4CVL2 hlgG1	SEQ ID NO:152	SEQ ID NO:164
4D4CVH3/4D4CVL4 hlgG1	SEQ ID NO:152	SEQ ID NO:165
4D4CVH3/4D4GVL3 hlgG1	SEQ ID NO:152	SEQ ID NO:166
4D4CVH3/4D4GVL4 hlgG1	SEQ ID NO:152	SEQ ID NO:167
4D4CVH4/4D4C/GVL1 hlgG1	SEQ ID NO:153	SEQ ID NO:163
4D4CVH4/4D4CVL2 hlgG1	SEQ ID NO:153	SEQ ID NO:164
4D4CVH4/4D4CVL4 hlgG1	SEQ ID NO:153	SEQ ID NO:165
4D4CVH4/4D4GVL3 hlgG1	SEQ ID NO:153	SEQ ID NO:166
4D4CVH4/4D4GVL4 hlgG1	SEQ ID NO:153	SEQ ID NO:167
4D4CVH2.1/4D4C/GVL1 hlgG1	SEQ ID NO:154	SEQ ID NO:163
4D4CVH2.1/4D4CVL2 hlgG1	SEQ ID NO:154	SEQ ID NO:164
4D4CVH2.1/4D4CVL4 hlgG1	SEQ ID NO:154	SEQ ID NO:165
4D4CVH2.1/4D4GVL3 hlgG1	SEQ ID NO:154	SEQ ID NO:166
4D4CVH2.1/4D4GVL4 hlgG1	SEQ ID NO:154	SEQ ID NO:167

4D4CVH2.2/4D4C/GVL1 hlgG1	SEQ ID NO:155	SEQ ID NO:163
4D4CVH2.2/4D4CVL2 hlgG1	SEQ ID NO:155	SEQ ID NO:164
4D4CVH2.2/4D4CVL4 hlgG1	SEQ ID NO:155	SEQ ID NO:165
4D4CVH2.2/4D4GVL3 hlgG1	SEQ ID NO:155	SEQ ID NO:166
4D4CVH2.2/4D4GVL4 hlgG1	SEQ ID NO:155	SEQ ID NO:167
CON4D4P/Hu hlgG1	SEQ ID NO:156	SEQ ID NO:168
4D4 hlgG4(S228P, L235E)	SEQ ID NO:202	SEQ ID NO:157
3G9 hlgG4(S228P, L235E)	SEQ ID NO:203	SEQ ID NO:158
4A7/7D8 hlgG4(S228P, L235E)	SEQ ID NO:204	SEQ ID NO:159
8C6 hlgG4(S228P, L235E)	SEQ ID NO:205	SEQ ID NO:160
C03-A7 hlgG4(S228P, L235E)	SEQ ID NO:206	SEQ ID NO:161
CON'4 9'7/8 hlgG4(S228P, L235E)	SEQ ID NO:207	SEQ ID NO:162
4D4CVH2/4D4C/GVL1 hlgG4(S228P, L235E)	SEQ ID NO:208	SEQ ID NO:163
4D4CVH2/4D4CVL2 hlgG4(S228P, L235E)	SEQ ID NO:208	SEQ ID NO:164
4D4CVH2/4D4CVL4 hlgG4(S228P, L235E)	SEQ ID NO:208	SEQ ID NO:165
4D4CVH2/4D4GVL3 hlgG4(S228P, L235E)	SEQ ID NO:208	SEQ ID NO:166
4D4CVH2/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:208	SEQ ID NO:167
4D4CVH3/4D4C/GVL1 hlgG4(S228P, L235E)	SEQ ID NO:209	SEQ ID NO:163
4D4CVH3/4D4CVL2 hlgG4(S228P, L235E)	SEQ ID NO:209	SEQ ID NO:164
4D4CVH3/4D4CVL4 hlgG4(S228P, L235E)	SEQ ID NO:209	SEQ ID NO:165
4D4CVH3/4D4GVL3 hlgG4(S228P, L235E)	SEQ ID NO:209	SEQ ID NO:166
4D4CVH3/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:209	SEQ ID NO:167
4D4CVH4/4D4C/GVL1 hlgG4(S228P, L235E)	SEQ ID NO:210	SEQ ID NO:163
4D4CVH4/4D4CVL2 hlgG4(S228P, L235E)	SEQ ID NO:210	SEQ ID NO:164
4D4CVH4/4D4CVL4 hlgG4(S228P, L235E)	SEQ ID NO:210	SEQ ID NO:165
4D4CVH4/4D4GVL3 hlgG4(S228P, L235E)	SEQ ID NO:210	SEQ ID NO:166
4D4CVH4/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:210	SEQ ID NO:167
4D4CVH2.1/4D4C/GVL1 hlgG4(S228P, L235E)	SEQ ID NO:211	SEQ ID NO:163
4D4CVH2.1/4D4CVL2 hlgG4(S228P, L235E)	SEQ ID NO:211	SEQ ID NO:164
4D4CVH2.1/4D4CVL4 hlgG4(S228P, L235E)	SEQ ID NO:211	SEQ ID NO:165
4D4CVH2.1/4D4GVL3 hlgG4(S228P, L235E)	SEQ ID NO:211	SEQ ID NO:166
4D4CVH2.1/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:211	SEQ ID NO:167
4D4CVH2.2/4D4C/GVL1 hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:163
4D4CVH2.2/4D4CVL2 hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:164
4D4CVH2.2/4D4CVL4 hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:165
4D4CVH2.2/4D4GVL3 hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:166
4D4CVH2.2/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:167
CON4D4P/Hu hlgG4(S228P, L235E)	SEQ ID NO:213	SEQ ID NO:168
4D4/4D4_N93G hlgG1	SEQ ID NO:145	SEQ ID NO:350
4D4/4D4_N93E hlgG1	SEQ ID NO:145	SEQ ID NO:351
4D4/4D4_N93L hlgG1	SEQ ID NO:145	SEQ ID NO:352
4D4/4D4_N93Q hlgG1	SEQ ID NO:145	SEQ ID NO:353
4D4/4D4_G94A hlgG1	SEQ ID NO:145	SEQ ID NO:354
4D4_D53G/4D4 hlgG1	SEQ ID NO:288	SEQ ID NO:157
4D4_D53E/4D4 hlgG1	SEQ ID NO:289	SEQ ID NO:157
4D4_D53Q/4D4 hlgG1	SEQ ID NO:290	SEQ ID NO:157
4D4_D53L/4D4 hlgG1	SEQ ID NO:291	SEQ ID NO:157
4D4_G54A/4D4 hlgG1	SEQ ID NO:292	SEQ ID NO:157
4D4_D53G/4D4_N93G hlgG1	SEQ ID NO:288	SEQ ID NO:350
4D4_D53E/4D4_N93G hlgG1	SEQ ID NO:289	SEQ ID NO:350
4D4_D53Q/4D4_N93G hlgG1	SEQ ID NO:290	SEQ ID NO:350
4D4_D53L/4D4_N93G hlgG1	SEQ ID NO:291	SEQ ID NO:350
4D4_G54A/4D4_N93G hlgG1	SEQ ID NO:292	SEQ ID NO:350
4D4_D53G/4D4_N93E hlgG1	SEQ ID NO:288	SEQ ID NO:351
4D4_D53E/4D4_N93E hlgG1	SEQ ID NO:289	SEQ ID NO:351
4D4_D53Q/4D4_N93E hlgG1	SEQ ID NO:290	SEQ ID NO:351
4D4_D53L/4D4_N93E hlgG1	SEQ ID NO:291	SEQ ID NO:351
4D4_G54A/4D4_N93E hlgG1	SEQ ID NO:292	SEQ ID NO:351
4D4_D53G/4D4_N93L hlgG1	SEQ ID NO:288	SEQ ID NO:352
4D4_D53E/4D4_N93L hlgG1	SEQ ID NO:289	SEQ ID NO:352
4D4_D53Q/4D4_N93L hlgG1	SEQ ID NO:290	SEQ ID NO:352
4D4_D53L/4D4_N93L hlgG1	SEQ ID NO:291	SEQ ID NO:352
4D4_G54A/4D4_N93L hlgG1	SEQ ID NO:292	SEQ ID NO:352
4D4_D53G/4D4_N93Q hlgG1	SEQ ID NO:288	SEQ ID NO:353
4D4_D53E/4D4_N93Q hlgG1	SEQ ID NO:289	SEQ ID NO:353
4D4_D53Q/4D4_N93Q hlgG1	SEQ ID NO:290	SEQ ID NO:353
4D4_D53L/4D4_N93Q hlgG1	SEQ ID NO:291	SEQ ID NO:353
4D4_G54A/4D4_N93Q hlgG1	SEQ ID NO:292	SEQ ID NO:353
4D4_D53G/4D4_G94A hlgG1	SEQ ID NO:288	SEQ ID NO:354
4D4_D53E/4D4_G94A hlgG1	SEQ ID NO:289	SEQ ID NO:354

4D4_D53Q/4D4_G94A hlgG1	SEQ ID NO:290	SEQ ID NO:354
4D4_D53L/4D4_G94A hlgG1	SEQ ID NO:291	SEQ ID NO:354
4D4_G54A/4D4_G94A hlgG1	SEQ ID NO:292	SEQ ID NO:354
4D4CVH2/4D4C/GVL1_N93G hlgG1	SEQ ID NO:151	SEQ ID NO:355
4D4CVH2/4D4C/GVL1_N93E hlgG1	SEQ ID NO:151	SEQ ID NO:356
4D4CVH2/4D4C/GVL1_N93L hlgG1	SEQ ID NO:151	SEQ ID NO:357
4D4CVH2/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:151	SEQ ID NO:358
4D4CVH2/4D4C/GVL1_G94A hlgG1	SEQ ID NO:151	SEQ ID NO:359
4D4CVH2_D53G/4D4C/GVL1 hlgG1	SEQ ID NO:293	SEQ ID NO:163
4D4CVH2_D53E/4D4C/GVL1 hlgG1	SEQ ID NO:294	SEQ ID NO:163
4D4CVH2_D53Q/4D4C/GVL1 hlgG1	SEQ ID NO:295	SEQ ID NO:163
4D4CVH2_D53L/4D4C/GVL1 hlgG1	SEQ ID NO:296	SEQ ID NO:163
4D4CVH2_G54A/4D4C/GVL1 hlgG1	SEQ ID NO:297	SEQ ID NO:163
4D4CVH2_D53G/4D4C/GVL1_N93G hlgG1	SEQ ID NO:293	SEQ ID NO:355
4D4CVH2_D53E/4D4C/GVL1_N93G hlgG1	SEQ ID NO:294	SEQ ID NO:355
4D4CVH2_D53Q/4D4C/GVL1_N93G hlgG1	SEQ ID NO:295	SEQ ID NO:355
4D4CVH2_D53L/4D4C/GVL1_N93G hlgG1	SEQ ID NO:296	SEQ ID NO:355
4D4CVH2_G54A/4D4C/GVL1_N93G hlgG1	SEQ ID NO:297	SEQ ID NO:355
4D4CVH2_D53G/4D4C/GVL1_N93E hlgG1	SEQ ID NO:293	SEQ ID NO:356
4D4CVH2_D53E/4D4C/GVL1_N93E hlgG1	SEQ ID NO:294	SEQ ID NO:356
4D4CVH2_D53Q/4D4C/GVL1_N93E hlgG1	SEQ ID NO:295	SEQ ID NO:356
4D4CVH2_D53L/4D4C/GVL1_N93E hlgG1	SEQ ID NO:296	SEQ ID NO:356
4D4CVH2_G54A/4D4C/GVL1_N93E hlgG1	SEQ ID NO:297	SEQ ID NO:356
4D4CVH2_D53G/4D4C/GVL1_N93L hlgG1	SEQ ID NO:293	SEQ ID NO:357
4D4CVH2_D53E/4D4C/GVL1_N93L hlgG1	SEQ ID NO:294	SEQ ID NO:357
4D4CVH2_D53Q/4D4C/GVL1_N93L hlgG1	SEQ ID NO:295	SEQ ID NO:357
4D4CVH2_D53L/4D4C/GVL1_N93L hlgG1	SEQ ID NO:296	SEQ ID NO:357
4D4CVH2_G54A/4D4C/GVL1_N93L hlgG1	SEQ ID NO:297	SEQ ID NO:357
4D4CVH2_D53G/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:293	SEQ ID NO:358
4D4CVH2_D53E/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:294	SEQ ID NO:358
4D4CVH2_D53Q/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:295	SEQ ID NO:358
4D4CVH2_D53L/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:296	SEQ ID NO:358
4D4CVH2_G54A/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:297	SEQ ID NO:358
4D4CVH2_D53G/4D4C/GVL1_G94A hlgG1	SEQ ID NO:293	SEQ ID NO:359
4D4CVH2_D53E/4D4C/GVL1_G94A hlgG1	SEQ ID NO:294	SEQ ID NO:359
4D4CVH2_D53Q/4D4C/GVL1_G94A hlgG1	SEQ ID NO:295	SEQ ID NO:359
4D4CVH2_D53L/4D4C/GVL1_G94A hlgG1	SEQ ID NO:296	SEQ ID NO:359
4D4CVH2_G54A/4D4C/GVL1_G94A hlgG1	SEQ ID NO:297	SEQ ID NO:359
4D4CVH2/4D4CVL2_N93G hlgG1	SEQ ID NO:151	SEQ ID NO:360
4D4CVH2/4D4CVL2_N93E hlgG1	SEQ ID NO:151	SEQ ID NO:361
4D4CVH2/4D4CVL2_N93L hlgG1	SEQ ID NO:151	SEQ ID NO:362
4D4CVH2/4D4CVL2_N93Q hlgG1	SEQ ID NO:151	SEQ ID NO:363
4D4CVH2/4D4CVL2_G94A hlgG1	SEQ ID NO:151	SEQ ID NO:364
4D4CVH2_D53G/4D4CVL2 hlgG1	SEQ ID NO:293	SEQ ID NO:164
4D4CVH2_D53E/4D4CVL2 hlgG1	SEQ ID NO:294	SEQ ID NO:164
4D4CVH2_D53Q/4D4CVL2 hlgG1	SEQ ID NO:295	SEQ ID NO:164
4D4CVH2_D53L/4D4CVL2 hlgG1	SEQ ID NO:296	SEQ ID NO:164
4D4CVH2_G54A/4D4CVL2 hlgG1	SEQ ID NO:297	SEQ ID NO:164
4D4CVH2_D53G/4D4CVL2_N93G hlgG1	SEQ ID NO:293	SEQ ID NO:360
4D4CVH2_D53E/4D4CVL2_N93G hlgG1	SEQ ID NO:294	SEQ ID NO:360
4D4CVH2_D53Q/4D4CVL2_N93G hlgG1	SEQ ID NO:295	SEQ ID NO:360
4D4CVH2_D53L/4D4CVL2_N93G hlgG1	SEQ ID NO:296	SEQ ID NO:360
4D4CVH2_G54A/4D4CVL2_N93G hlgG1	SEQ ID NO:297	SEQ ID NO:360
4D4CVH2_D53G/4D4CVL2_N93E hlgG1	SEQ ID NO:293	SEQ ID NO:361
4D4CVH2_D53E/4D4CVL2_N93E hlgG1	SEQ ID NO:294	SEQ ID NO:361
4D4CVH2_D53Q/4D4CVL2_N93E hlgG1	SEQ ID NO:295	SEQ ID NO:361
4D4CVH2_D53L/4D4CVL2_N93E hlgG1	SEQ ID NO:296	SEQ ID NO:361
4D4CVH2_G54A/4D4CVL2_N93E hlgG1	SEQ ID NO:297	SEQ ID NO:361
4D4CVH2_D53G/4D4CVL2_N93L hlgG1	SEQ ID NO:293	SEQ ID NO:362
4D4CVH2_D53E/4D4CVL2_N93L hlgG1	SEQ ID NO:294	SEQ ID NO:362
4D4CVH2_D53Q/4D4CVL2_N93L hlgG1	SEQ ID NO:295	SEQ ID NO:362
4D4CVH2_D53L/4D4CVL2_N93L hlgG1	SEQ ID NO:296	SEQ ID NO:362
4D4CVH2_G54A/4D4CVL2_N93L hlgG1	SEQ ID NO:297	SEQ ID NO:362
4D4CVH2_D53G/4D4CVL2_N93Q hlgG1	SEQ ID NO:293	SEQ ID NO:363
4D4CVH2_D53E/4D4CVL2_N93Q hlgG1	SEQ ID NO:294	SEQ ID NO:363
4D4CVH2_D53Q/4D4CVL2_N93Q hlgG1	SEQ ID NO:295	SEQ ID NO:363
4D4CVH2_D53L/4D4CVL2_N93Q hlgG1	SEQ ID NO:296	SEQ ID NO:363
4D4CVH2_G54A/4D4CVL2_N93Q hlgG1	SEQ ID NO:297	SEQ ID NO:363
4D4CVH2_D53G/4D4CVL2_G94A hlgG1	SEQ ID NO:293	SEQ ID NO:364
4D4CVH2_D53E/4D4CVL2_G94A hlgG1	SEQ ID NO:294	SEQ ID NO:364

[illegible]

4D4CVH2_D53Q/4D4GVL3_G94A hlgG1	SEQ ID NO:295	SEQ ID NO:374
4D4CVH2_D53L/4D4GVL3_G94A hlgG1	SEQ ID NO:296	SEQ ID NO:374
4D4CVH2_G54A/4D4GVL3_G94A hlgG1	SEQ ID NO:297	SEQ ID NO:374
4D4CVH2/4D4GVL4_N93G hlgG1	SEQ ID NO:151	SEQ ID NO:375
4D4CVH2/4D4GVL4_N93E hlgG1	SEQ ID NO:151	SEQ ID NO:376
4D4CVH2/4D4GVL4_N93L hlgG1	SEQ ID NO:151	SEQ ID NO:377
4D4CVH2/4D4GVL4_N93Q hlgG1	SEQ ID NO:151	SEQ ID NO:378
4D4CVH2/4D4GVL4_G94A hlgG1	SEQ ID NO:151	SEQ ID NO:379
4D4CVH2_D53G/4D4GVL4 hlgG1	SEQ ID NO:293	SEQ ID NO:167
4D4CVH2_D53E/4D4GVL4 hlgG1	SEQ ID NO:294	SEQ ID NO:167
4D4CVH2_D53Q/4D4GVL4 hlgG1	SEQ ID NO:295	SEQ ID NO:167
4D4CVH2_D53L/4D4GVL4 hlgG1	SEQ ID NO:296	SEQ ID NO:167
4D4CVH2_G54A/4D4GVL4 hlgG1	SEQ ID NO:297	SEQ ID NO:167
4D4CVH2_D53G/4D4GVL4_N93G hlgG1	SEQ ID NO:293	SEQ ID NO:375
4D4CVH2_D53E/4D4GVL4_N93G hlgG1	SEQ ID NO:294	SEQ ID NO:375
4D4CVH2_D53Q/4D4GVL4_N93G hlgG1	SEQ ID NO:295	SEQ ID NO:375
4D4CVH2_D53L/4D4GVL4_N93G hlgG1	SEQ ID NO:296	SEQ ID NO:375
4D4CVH2_G54A/4D4GVL4_N93G hlgG1	SEQ ID NO:297	SEQ ID NO:375
4D4CVH2_D53G/4D4GVL4_N93E hlgG1	SEQ ID NO:293	SEQ ID NO:376
4D4CVH2_D53E/4D4GVL4_N93E hlgG1	SEQ ID NO:294	SEQ ID NO:376
4D4CVH2_D53Q/4D4GVL4_N93E hlgG1	SEQ ID NO:295	SEQ ID NO:376
4D4CVH2_D53L/4D4GVL4_N93E hlgG1	SEQ ID NO:296	SEQ ID NO:376
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4D4CVH2_D53L/4D4GVL4_G94A hlgG1	SEQ ID NO:296	SEQ ID NO:379
4D4CVH2_G54A/4D4GVL4_G94A hlgG1	SEQ ID NO:297	SEQ ID NO:379
4D4CVH3/4D4C/GVL1_N93G hlgG1	SEQ ID NO:152	SEQ ID NO:355
4D4CVH3/4D4C/GVL1_N93E hlgG1	SEQ ID NO:152	SEQ ID NO:356
4D4CVH3/4D4C/GVL1_N93L hlgG1	SEQ ID NO:152	SEQ ID NO:357
4D4CVH3/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:152	SEQ ID NO:358
4D4CVH3/4D4C/GVL1_G94A hlgG1	SEQ ID NO:152	SEQ ID NO:359
4D4CVH3_D53G/4D4C/GVL1 hlgG1	SEQ ID NO:298	SEQ ID NO:163
4D4CVH3_D53E/4D4C/GVL1 hlgG1	SEQ ID NO:299	SEQ ID NO:163
4D4CVH3_D53Q/4D4C/GVL1 hlgG1	SEQ ID NO:300	SEQ ID NO:163
4D4CVH3_D53L/4D4C/GVL1 hlgG1	SEQ ID NO:301	SEQ ID NO:163
4D4CVH3_G54A/4D4C/GVL1 hlgG1	SEQ ID NO:302	SEQ ID NO:163
4D4CVH3_D53G/4D4C/GVL1_N93G hlgG1	SEQ ID NO:298	SEQ ID NO:355
4D4CVH3_D53E/4D4C/GVL1_N93G hlgG1	SEQ ID NO:299	SEQ ID NO:355
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4D4CVH3_G54A/4D4C/GVL1_N93L hlgG1	SEQ ID NO:302	SEQ ID NO:357
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4D4CVH3_D53E/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:299	SEQ ID NO:358
4D4CVH3_D53Q/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:300	SEQ ID NO:358
4D4CVH3_D53L/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:301	SEQ ID NO:358
4D4CVH3_G54A/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:302	SEQ ID NO:358
4D4CVH3_D53G/4D4C/GVL1_G94A hlgG1	SEQ ID NO:298	SEQ ID NO:359
4D4CVH3_D53E/4D4C/GVL1_G94A hlgG1	SEQ ID NO:299	SEQ ID NO:359

[illegible]

[illegible]

4D4CVH3_D53Q/4D4GVL4_G94A hlgG1	SEQ ID NO:300	SEQ ID NO:379
4D4CVH3_D53L/4D4GVL4_G94A hlgG1	SEQ ID NO:301	SEQ ID NO:379
4D4CVH3_G54A/4D4GVL4_G94A hlgG1	SEQ ID NO:302	SEQ ID NO:379
4D4CVH4/4D4C/GVL1_N93G hlgG1	SEQ ID NO:153	SEQ ID NO:355
4D4CVH4/4D4C/GVL1_N93E hlgG1	SEQ ID NO:153	SEQ ID NO:356
4D4CVH4/4D4C/GVL1_N93L hlgG1	SEQ ID NO:153	SEQ ID NO:357
4D4CVH4/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:153	SEQ ID NO:358
4D4CVH4/4D4C/GVL1_G94A hlgG1	SEQ ID NO:153	SEQ ID NO:359
4D4CVH4_D53G/4D4C/GVL1 hlgG1	SEQ ID NO:303	SEQ ID NO:163
4D4CVH4_D53E/4D4C/GVL1 hlgG1	SEQ ID NO:304	SEQ ID NO:163
4D4CVH4_D53Q/4D4C/GVL1 hlgG1	SEQ ID NO:305	SEQ ID NO:163
4D4CVH4_D53L/4D4C/GVL1 hlgG1	SEQ ID NO:306	SEQ ID NO:163
4D4CVH4_G54A/4D4C/GVL1 hlgG1	SEQ ID NO:307	SEQ ID NO:163
4D4CVH4_D53G/4D4C/GVL1_N93G hlgG1	SEQ ID NO:303	SEQ ID NO:355
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4D4CVH4_G54A/4D4C/GVL1_N93G hlgG1	SEQ ID NO:307	SEQ ID NO:355
4D4CVH4_D53G/4D4C/GVL1_N93E hlgG1	SEQ ID NO:303	SEQ ID NO:356
4D4CVH4_D53E/4D4C/GVL1_N93E hlgG1	SEQ ID NO:304	SEQ ID NO:356
4D4CVH4_D53Q/4D4C/GVL1_N93E hlgG1	SEQ ID NO:305	SEQ ID NO:356
4D4CVH4_D53L/4D4C/GVL1_N93E hlgG1	SEQ ID NO:306	SEQ ID NO:356
4D4CVH4_G54A/4D4C/GVL1_N93E hlgG1	SEQ ID NO:307	SEQ ID NO:356
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4D4CVH4_D53Q/4D4C/GVL1_N93L hlgG1	SEQ ID NO:305	SEQ ID NO:357
4D4CVH4_D53L/4D4C/GVL1_N93L hlgG1	SEQ ID NO:306	SEQ ID NO:357
4D4CVH4_G54A/4D4C/GVL1_N93L hlgG1	SEQ ID NO:307	SEQ ID NO:357
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4D4CVH4_G54A/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:307	SEQ ID NO:358
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4D4CVH4_G54A/4D4CVL2 hlgG1	SEQ ID NO:307	SEQ ID NO:164
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4D4CVH4_D53Q/4D4CVL2_N93L hlgG1	SEQ ID NO:305	SEQ ID NO:362
4D4CVH4_D53L/4D4CVL2_N93L hlgG1	SEQ ID NO:306	SEQ ID NO:362
4D4CVH4_G54A/4D4CVL2_N93L hlgG1	SEQ ID NO:307	SEQ ID NO:362
4D4CVH4_D53G/4D4CVL2_N93Q hlgG1	SEQ ID NO:303	SEQ ID NO:363
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4D4CVH4_D53Q/4D4CVL2_N93Q hlgG1	SEQ ID NO:305	SEQ ID NO:363
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4D4CVH4_D53G/4D4CVL2_G94A hlgG1	SEQ ID NO:303	SEQ ID NO:364
4D4CVH4_D53E/4D4CVL2_G94A hlgG1	SEQ ID NO:304	SEQ ID NO:364

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4D4CVH4_D53Q/4D4GVL3_G94A hlgG1	SEQ ID NO:305	SEQ ID NO:374
4D4CVH4_D53L/4D4GVL3_G94A hlgG1	SEQ ID NO:306	SEQ ID NO:374
4D4CVH4_G54A/4D4GVL3_G94A hlgG1	SEQ ID NO:307	SEQ ID NO:374
4D4CVH4/4D4GVL4_N93G hlgG1	SEQ ID NO:153	SEQ ID NO:375
4D4CVH4/4D4GVL4_N93E hlgG1	SEQ ID NO:153	SEQ ID NO:376
4D4CVH4/4D4GVL4_N93L hlgG1	SEQ ID NO:153	SEQ ID NO:377
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4D4CVH4/4D4GVL4_G94A hlgG1	SEQ ID NO:153	SEQ ID NO:379
4D4CVH4_D53G/4D4GVL4 hlgG1	SEQ ID NO:303	SEQ ID NO:167
4D4CVH4_D53E/4D4GVL4 hlgG1	SEQ ID NO:304	SEQ ID NO:167
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4D4CVH2.1/4D4C/GVL1_N93E hlgG1	SEQ ID NO:154	SEQ ID NO:356
4D4CVH2.1/4D4C/GVL1_N93L hlgG1	SEQ ID NO:154	SEQ ID NO:357
4D4CVH2.1/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:154	SEQ ID NO:358
4D4CVH2.1/4D4C/GVL1_G94A hlgG1	SEQ ID NO:154	SEQ ID NO:359
4D4CVH2.1_D53G/4D4C/GVL1 hlgG1	SEQ ID NO:308	SEQ ID NO:163
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4D4CVH2.1_D53Q/4D4C/GVL1 hlgG1	SEQ ID NO:310	SEQ ID NO:163
4D4CVH2.1_D53L/4D4C/GVL1 hlgG1	SEQ ID NO:311	SEQ ID NO:163
4D4CVH2.1_G54A/4D4C/GVL1 hlgG1	SEQ ID NO:312	SEQ ID NO:163
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4D4CVH2.1_D53Q/4D4C/GVL1_N93E hlgG1	SEQ ID NO:310	SEQ ID NO:356
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4D4CVH2.1_G54A/4D4C/GVL1_N93E hlgG1	SEQ ID NO:312	SEQ ID NO:356
4D4CVH2.1_D53G/4D4C/GVL1_N93L hlgG1	SEQ ID NO:308	SEQ ID NO:357
4D4CVH2.1_D53E/4D4C/GVL1_N93L hlgG1	SEQ ID NO:309	SEQ ID NO:357
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4D4CVH2.1_G54A/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:312	SEQ ID NO:358
4D4CVH2.1_D53G/4D4C/GVL1_G94A hlgG1	SEQ ID NO:308	SEQ ID NO:359
4D4CVH2.1_D53E/4D4C/GVL1_G94A hlgG1	SEQ ID NO:309	SEQ ID NO:359

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4D4CVH2.1_D53Q/4D4GVL4_G94A hlgG1	SEQ ID NO:310	SEQ ID NO:379
4D4CVH2.1_D53L/4D4GVL4_G94A hlgG1	SEQ ID NO:311	SEQ ID NO:379
4D4CVH2.1_G54A/4D4GVL4_G94A hlgG1	SEQ ID NO:312	SEQ ID NO:379
4D4CVH2.2/4D4C/GVL1_N93G hlgG1	SEQ ID NO:155	SEQ ID NO:355
4D4CVH2.2/4D4C/GVL1_N93E hlgG1	SEQ ID NO:155	SEQ ID NO:356
4D4CVH2.2/4D4C/GVL1_N93L hlgG1	SEQ ID NO:155	SEQ ID NO:357
4D4CVH2.2/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:155	SEQ ID NO:358
4D4CVH2.2/4D4C/GVL1_G94A hlgG1	SEQ ID NO:155	SEQ ID NO:359
4D4CVH2.2_D53G/4D4C/GVL1 hlgG1	SEQ ID NO:313	SEQ ID NO:163
4D4CVH2.2_D53E/4D4C/GVL1 hlgG1	SEQ ID NO:314	SEQ ID NO:163
4D4CVH2.2_D53Q/4D4C/GVL1 hlgG1	SEQ ID NO:315	SEQ ID NO:163
4D4CVH2.2_D53L/4D4C/GVL1 hlgG1	SEQ ID NO:316	SEQ ID NO:163
4D4CVH2.2_G54A/4D4C/GVL1 hlgG1	SEQ ID NO:317	SEQ ID NO:163
4D4CVH2.2_D53G/4D4C/GVL1_N93G hlgG1	SEQ ID NO:313	SEQ ID NO:355
4D4CVH2.2_D53E/4D4C/GVL1_N93G hlgG1	SEQ ID NO:314	SEQ ID NO:355
4D4CVH2.2_D53Q/4D4C/GVL1_N93G hlgG1	SEQ ID NO:315	SEQ ID NO:355
4D4CVH2.2_D53L/4D4C/GVL1_N93G hlgG1	SEQ ID NO:316	SEQ ID NO:355
4D4CVH2.2_G54A/4D4C/GVL1_N93G hlgG1	SEQ ID NO:317	SEQ ID NO:355
4D4CVH2.2_D53G/4D4C/GVL1_N93E hlgG1	SEQ ID NO:313	SEQ ID NO:356
4D4CVH2.2_D53E/4D4C/GVL1_N93E hlgG1	SEQ ID NO:314	SEQ ID NO:356
4D4CVH2.2_D53Q/4D4C/GVL1_N93E hlgG1	SEQ ID NO:315	SEQ ID NO:356
4D4CVH2.2_D53L/4D4C/GVL1_N93E hlgG1	SEQ ID NO:316	SEQ ID NO:356
4D4CVH2.2_G54A/4D4C/GVL1_N93E hlgG1	SEQ ID NO:317	SEQ ID NO:356
4D4CVH2.2_D53G/4D4C/GVL1_N93L hlgG1	SEQ ID NO:313	SEQ ID NO:357
4D4CVH2.2_D53E/4D4C/GVL1_N93L hlgG1	SEQ ID NO:314	SEQ ID NO:357
4D4CVH2.2_D53Q/4D4C/GVL1_N93L hlgG1	SEQ ID NO:315	SEQ ID NO:357
4D4CVH2.2_D53L/4D4C/GVL1_N93L hlgG1	SEQ ID NO:316	SEQ ID NO:357
4D4CVH2.2_G54A/4D4C/GVL1_N93L hlgG1	SEQ ID NO:317	SEQ ID NO:357
4D4CVH2.2_D53G/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:313	SEQ ID NO:358
4D4CVH2.2_D53E/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:314	SEQ ID NO:358
4D4CVH2.2_D53Q/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:315	SEQ ID NO:358
4D4CVH2.2_D53L/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:316	SEQ ID NO:358
4D4CVH2.2_G54A/4D4C/GVL1_N93Q hlgG1	SEQ ID NO:317	SEQ ID NO:358
4D4CVH2.2_D53G/4D4C/GVL1_G94A hlgG1	SEQ ID NO:313	SEQ ID NO:359
4D4CVH2.2_D53E/4D4C/GVL1_G94A hlgG1	SEQ ID NO:314	SEQ ID NO:359
4D4CVH2.2_D53Q/4D4C/GVL1_G94A hlgG1	SEQ ID NO:315	SEQ ID NO:359
4D4CVH2.2_D53L/4D4C/GVL1_G94A hlgG1	SEQ ID NO:316	SEQ ID NO:359
4D4CVH2.2_G54A/4D4C/GVL1_G94A hlgG1	SEQ ID NO:317	SEQ ID NO:359
4D4CVH2.2/4D4CVL2_N93G hlgG1	SEQ ID NO:155	SEQ ID NO:360
4D4CVH2.2/4D4CVL2_N93E hlgG1	SEQ ID NO:155	SEQ ID NO:361
4D4CVH2.2/4D4CVL2_N93L hlgG1	SEQ ID NO:155	SEQ ID NO:362
4D4CVH2.2/4D4CVL2_N93Q hlgG1	SEQ ID NO:155	SEQ ID NO:363
4D4CVH2.2/4D4CVL2_G94A hlgG1	SEQ ID NO:155	SEQ ID NO:364
4D4CVH2.2_D53G/4D4CVL2 hlgG1	SEQ ID NO:313	SEQ ID NO:164
4D4CVH2.2_D53E/4D4CVL2 hlgG1	SEQ ID NO:314	SEQ ID NO:164
4D4CVH2.2_D53Q/4D4CVL2 hlgG1	SEQ ID NO:315	SEQ ID NO:164
4D4CVH2.2_D53L/4D4CVL2 hlgG1	SEQ ID NO:316	SEQ ID NO:164
4D4CVH2.2_G54A/4D4CVL2 hlgG1	SEQ ID NO:317	SEQ ID NO:164
4D4CVH2.2_D53G/4D4CVL2_N93G hlgG1	SEQ ID NO:313	SEQ ID NO:360
4D4CVH2.2_D53E/4D4CVL2_N93G hlgG1	SEQ ID NO:314	SEQ ID NO:360
4D4CVH2.2_D53Q/4D4CVL2_N93G hlgG1	SEQ ID NO:315	SEQ ID NO:360
4D4CVH2.2_D53L/4D4CVL2_N93G hlgG1	SEQ ID NO:316	SEQ ID NO:360
4D4CVH2.2_G54A/4D4CVL2_N93G hlgG1	SEQ ID NO:317	SEQ ID NO:360
4D4CVH2.2_D53G/4D4CVL2_N93E hlgG1	SEQ ID NO:313	SEQ ID NO:361
4D4CVH2.2_D53E/4D4CVL2_N93E hlgG1	SEQ ID NO:314	SEQ ID NO:361
4D4CVH2.2_D53Q/4D4CVL2_N93E hlgG1	SEQ ID NO:315	SEQ ID NO:361
4D4CVH2.2_D53L/4D4CVL2_N93E hlgG1	SEQ ID NO:316	SEQ ID NO:361
4D4CVH2.2_G54A/4D4CVL2_N93E hlgG1	SEQ ID NO:317	SEQ ID NO:361
4D4CVH2.2_D53G/4D4CVL2_N93L hlgG1	SEQ ID NO:313	SEQ ID NO:362
4D4CVH2.2_D53E/4D4CVL2_N93L hlgG1	SEQ ID NO:314	SEQ ID NO:362
4D4CVH2.2_D53Q/4D4CVL2_N93L hlgG1	SEQ ID NO:315	SEQ ID NO:362
4D4CVH2.2_D53L/4D4CVL2_N93L hlgG1	SEQ ID NO:316	SEQ ID NO:362
4D4CVH2.2_G54A/4D4CVL2_N93L hlgG1	SEQ ID NO:317	SEQ ID NO:362
4D4CVH2.2_D53G/4D4CVL2_N93Q hlgG1	SEQ ID NO:313	SEQ ID NO:363
4D4CVH2.2_D53E/4D4CVL2_N93Q hlgG1	SEQ ID NO:314	SEQ ID NO:363
4D4CVH2.2_D53Q/4D4CVL2_N93Q hlgG1	SEQ ID NO:315	SEQ ID NO:363
4D4CVH2.2_D53L/4D4CVL2_N93Q hlgG1	SEQ ID NO:316	SEQ ID NO:363
4D4CVH2.2_G54A/4D4CVL2_N93Q hlgG1	SEQ ID NO:317	SEQ ID NO:363
4D4CVH2.2_D53G/4D4CVL2_G94A hlgG1	SEQ ID NO:313	SEQ ID NO:364
4D4CVH2.2_D53E/4D4CVL2_G94A hlgG1	SEQ ID NO:314	SEQ ID NO:364

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4D4CVH2.2_D53Q/4D4GVL3_G94A hlgG1	SEQ ID NO:315	SEQ ID NO:374
4D4CVH2.2_D53L/4D4GVL3_G94A hlgG1	SEQ ID NO:316	SEQ ID NO:374
4D4CVH2.2_G54A/4D4GVL3_G94A hlgG1	SEQ ID NO:317	SEQ ID NO:374
4D4CVH2.2/4D4GVL4_N93G hlgG1	SEQ ID NO:155	SEQ ID NO:375
4D4CVH2.2/4D4GVL4_N93E hlgG1	SEQ ID NO:155	SEQ ID NO:376
4D4CVH2.2/4D4GVL4_N93L hlgG1	SEQ ID NO:155	SEQ ID NO:377
4D4CVH2.2/4D4GVL4_N93Q hlgG1	SEQ ID NO:155	SEQ ID NO:378
4D4CVH2.2/4D4GVL4_G94A hlgG1	SEQ ID NO:155	SEQ ID NO:379
4D4CVH2.2_D53G/4D4GVL4 hlgG1	SEQ ID NO:313	SEQ ID NO:167
4D4CVH2.2_D53E/4D4GVL4 hlgG1	SEQ ID NO:314	SEQ ID NO:167
4D4CVH2.2_D53Q/4D4GVL4 hlgG1	SEQ ID NO:315	SEQ ID NO:167
4D4CVH2.2_D53L/4D4GVL4 hlgG1	SEQ ID NO:316	SEQ ID NO:167
4D4CVH2.2_G54A/4D4GVL4 hlgG1	SEQ ID NO:317	SEQ ID NO:167
4D4CVH2.2_D53G/4D4GVL4_N93G hlgG1	SEQ ID NO:313	SEQ ID NO:375
4D4CVH2.2_D53E/4D4GVL4_N93G hlgG1	SEQ ID NO:314	SEQ ID NO:375
4D4CVH2.2_D53Q/4D4GVL4_N93G hlgG1	SEQ ID NO:315	SEQ ID NO:375
4D4CVH2.2_D53L/4D4GVL4_N93G hlgG1	SEQ ID NO:316	SEQ ID NO:375
4D4CVH2.2_G54A/4D4GVL4_N93G hlgG1	SEQ ID NO:317	SEQ ID NO:375
4D4CVH2.2_D53G/4D4GVL4_N93E hlgG1	SEQ ID NO:313	SEQ ID NO:376
4D4CVH2.2_D53E/4D4GVL4_N93E hlgG1	SEQ ID NO:314	SEQ ID NO:376
4D4CVH2.2_D53Q/4D4GVL4_N93E hlgG1	SEQ ID NO:315	SEQ ID NO:376
4D4CVH2.2_D53L/4D4GVL4_N93E hlgG1	SEQ ID NO:316	SEQ ID NO:376
4D4CVH2.2_G54A/4D4GVL4_N93E hlgG1	SEQ ID NO:317	SEQ ID NO:376
4D4CVH2.2_D53G/4D4GVL4_N93L hlgG1	SEQ ID NO:313	SEQ ID NO:377
4D4CVH2.2_D53E/4D4GVL4_N93L hlgG1	SEQ ID NO:314	SEQ ID NO:377
4D4CVH2.2_D53Q/4D4GVL4_N93L hlgG1	SEQ ID NO:315	SEQ ID NO:377
4D4CVH2.2_D53L/4D4GVL4_N93L hlgG1	SEQ ID NO:316	SEQ ID NO:377
4D4CVH2.2_G54A/4D4GVL4_N93L hlgG1	SEQ ID NO:317	SEQ ID NO:377
4D4CVH2.2_D53G/4D4GVL4_N93Q hlgG1	SEQ ID NO:313	SEQ ID NO:378
4D4CVH2.2_D53E/4D4GVL4_N93Q hlgG1	SEQ ID NO:314	SEQ ID NO:378
4D4CVH2.2_D53Q/4D4GVL4_N93Q hlgG1	SEQ ID NO:315	SEQ ID NO:378
4D4CVH2.2_D53L/4D4GVL4_N93Q hlgG1	SEQ ID NO:316	SEQ ID NO:378
4D4CVH2.2_G54A/4D4GVL4_N93Q hlgG1	SEQ ID NO:317	SEQ ID NO:378
4D4CVH2.2_D53G/4D4GVL4_G94A hlgG1	SEQ ID NO:313	SEQ ID NO:379
4D4CVH2.2_D53E/4D4GVL4_G94A hlgG1	SEQ ID NO:314	SEQ ID NO:379
4D4CVH2.2_D53Q/4D4GVL4_G94A hlgG1	SEQ ID NO:315	SEQ ID NO:379
4D4CVH2.2_D53L/4D4GVL4_G94A hlgG1	SEQ ID NO:316	SEQ ID NO:379
4D4CVH2.2_G54A/4D4GVL4_G94A hlgG1	SEQ ID NO:317	SEQ ID NO:379
CON4D4P/Hu_D53var_G53var/CON4D4P/Hu_N93var_G94var hlgG1	SEQ ID NO:318	SEQ ID NO:380
4D4/4D4_N93G hlgG4(S228P, L235E)	SEQ ID NO:202	SEQ ID NO:350
4D4/4D4_N93E hlgG4(S228P, L235E)	SEQ ID NO:202	SEQ ID NO:351
4D4/4D4_N93L hlgG4(S228P, L235E)	SEQ ID NO:202	SEQ ID NO:352
4D4/4D4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:202	SEQ ID NO:353
4D4/4D4_G94A hlgG4(S228P, L235E)	SEQ ID NO:202	SEQ ID NO:354
4D4_D53G/4D4 hlgG4(S228P, L235E)	SEQ ID NO:319	SEQ ID NO:157
4D4_D53E/4D4 hlgG4(S228P, L235E)	SEQ ID NO:320	SEQ ID NO:157
4D4_D53Q/4D4 hlgG4(S228P, L235E)	SEQ ID NO:321	SEQ ID NO:157
4D4_D53L/4D4 hlgG4(S228P, L235E)	SEQ ID NO:322	SEQ ID NO:157
4D4_G54A/4D4 hlgG4(S228P, L235E)	SEQ ID NO:323	SEQ ID NO:157
4D4_D53G/4D4_N93G hlgG4(S228P, L235E)	SEQ ID NO:319	SEQ ID NO:350
4D4_D53E/4D4_N93G hlgG4(S228P, L235E)	SEQ ID NO:320	SEQ ID NO:350
4D4_D53Q/4D4_N93G hlgG4(S228P, L235E)	SEQ ID NO:321	SEQ ID NO:350
4D4_D53L/4D4_N93G hlgG4(S228P, L235E)	SEQ ID NO:322	SEQ ID NO:350
4D4_G54A/4D4_N93G hlgG4(S228P, L235E)	SEQ ID NO:323	SEQ ID NO:350
4D4_D53G/4D4_N93E hlgG4(S228P, L235E)	SEQ ID NO:319	SEQ ID NO:351
4D4_D53E/4D4_N93E hlgG4(S228P, L235E)	SEQ ID NO:320	SEQ ID NO:351
4D4_D53Q/4D4_N93E hlgG4(S228P, L235E)	SEQ ID NO:321	SEQ ID NO:351
4D4_D53L/4D4_N93E hlgG4(S228P, L235E)	SEQ ID NO:322	SEQ ID NO:351
4D4_G54A/4D4_N93E hlgG4(S228P, L235E)	SEQ ID NO:323	SEQ ID NO:351
4D4_D53G/4D4_N93L hlgG4(S228P, L235E)	SEQ ID NO:319	SEQ ID NO:352
4D4_D53E/4D4_N93L hlgG4(S228P, L235E)	SEQ ID NO:320	SEQ ID NO:352
4D4_D53Q/4D4_N93L hlgG4(S228P, L235E)	SEQ ID NO:321	SEQ ID NO:352
4D4_D53L/4D4_N93L hlgG4(S228P, L235E)	SEQ ID NO:322	SEQ ID NO:352
4D4_G54A/4D4_N93L hlgG4(S228P, L235E)	SEQ ID NO:323	SEQ ID NO:352
4D4_D53G/4D4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:319	SEQ ID NO:353
4D4_D53E/4D4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:320	SEQ ID NO:353
4D4_D53Q/4D4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:321	SEQ ID NO:353
4D4_D53L/4D4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:322	SEQ ID NO:353
4D4_G54A/4D4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:323	SEQ ID NO:353
4D4_D53G/4D4_G94A hlgG4(S228P, L235E)	SEQ ID NO:319	SEQ ID NO:354

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[illegible]

4D4CVH2.2_D53E/4D4GVL3_G94A hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:374
4D4CVH2.2_D53Q/4D4GVL3_G94A hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:374
4D4CVH2.2_D53L/4D4GVL3_G94A hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:374
4D4CVH2.2_G54A/4D4GVL3_G94A hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:374
4D4CVH2.2/4D4GVL4_N93G hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:375
4D4CVH2.2/4D4GVL4_N93E hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:376
4D4CVH2.2/4D4GVL4_N93L hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:377
4D4CVH2.2/4D4GVL4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:378
4D4CVH2.2/4D4GVL4_G94A hlgG4(S228P, L235E)	SEQ ID NO:212	SEQ ID NO:379
4D4CVH2.2_D53G/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:167
4D4CVH2.2_D53E/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:167
4D4CVH2.2_D53Q/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:167
4D4CVH2.2_D53L/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:167
4D4CVH2.2_G54A/4D4GVL4 hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:167
4D4CVH2.2_D53G/4D4GVL4_N93G hlgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:375
4D4CVH2.2_D53E/4D4GVL4_N93G hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:375
4D4CVH2.2_D53Q/4D4GVL4_N93G hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:375
4D4CVH2.2_D53L/4D4GVL4_N93G hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:375
4D4CVH2.2_G54A/4D4GVL4_N93G hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:375
4D4CVH2.2_D53G/4D4GVL4_N93E hlgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:376
4D4CVH2.2_D53E/4D4GVL4_N93E hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:376
4D4CVH2.2_D53Q/4D4GVL4_N93E hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:376
4D4CVH2.2_D53L/4D4GVL4_N93E hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:376
4D4CVH2.2_G54A/4D4GVL4_N93E hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:376
4D4CVH2.2_D53G/4D4GVL4_N93L hlgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:377
4D4CVH2.2_D53E/4D4GVL4_N93L hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:377
4D4CVH2.2_D53Q/4D4GVL4_N93L hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:377
4D4CVH2.2_D53L/4D4GVL4_N93L hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:377
4D4CVH2.2_G54A/4D4GVL4_N93L hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:377
4D4CVH2.2_D53G/4D4GVL4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:378
4D4CVH2.2_D53E/4D4GVL4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:378
4D4CVH2.2_D53Q/4D4GVL4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:378
4D4CVH2.2_D53L/4D4GVL4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:378
4D4CVH2.2_G54A/4D4GVL4_N93Q hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:378
4D4CVH2.2_D53G/4D4GVL4_G94A hlgG4(S228P, L235E)	SEQ ID NO:344	SEQ ID NO:379
4D4CVH2.2_D53E/4D4GVL4_G94A hlgG4(S228P, L235E)	SEQ ID NO:345	SEQ ID NO:379
4D4CVH2.2_D53Q/4D4GVL4_G94A hlgG4(S228P, L235E)	SEQ ID NO:346	SEQ ID NO:379
4D4CVH2.2_D53L/4D4GVL4_G94A hlgG4(S228P, L235E)	SEQ ID NO:347	SEQ ID NO:379
4D4CVH2.2_G54A/4D4GVL4_G94A hlgG4(S228P, L235E)	SEQ ID NO:348	SEQ ID NO:379
CON4D4P/Hu_D53var_G53var /CON4D4P/Hu_N93var_G94var hlgG4(S228P, L235E)	SEQ ID NO:349	SEQ ID NO:380

The present disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

- 5 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.

40 **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.

Figures 1A and 1B. *In vitro* screening of anti-gp130 mAb clones in mouse atrial fibroblasts.

Tables showing effects of gp130 mAb clones on levels of activated fibroblasts (**1A**) and MMP2 concentration (**1B**) in mouse atrial fibroblasts (MAFs) following stimulation for 24 hours with 5 ng/ml of recombinant mouse IL-11 in the absence or presence of different antibody clones (2 µg/ml).

Figure 2. *In vitro* screening of anti-gp130 mAb clones in primary human cardiac fibroblasts.

Graphs showing percentage inhibition of gp130 signalling at increasing concentrations of gp130 mAb clone as determined by percentage of α SMA⁺ve cells (left) or MMP2 concentration (right) in human cardiac fibroblasts following stimulation with 5 ng/ml of recombinant human IL-11 in the absence or presence of different antibody clones (61 pg/ml to 4 µg/ml; 4-fold dilution).

Figure 3. *In vitro* IC₅₀ screening of anti-gp130 mAb clones in primary mouse atrial

fibroblasts. Graph showing percentage inhibition of gp130 signalling at increasing concentrations of gp130 mAb clone 4D4 as determined by MMP2 concentration.

Figure 4. *In vitro* IC₅₀ screening of anti-gp130 mAb clones in primary rat atrial fibroblasts.

Graphs showing percentage inhibition of gp130 signalling at increasing concentrations of control antibody 11E10, and gp130 mAb clones 8C6 and 4D4, as determined by MMP2 concentration. Cells were stimulated for 24 hours with 5 ng/ml of recombinant mouse TGFβ1 in the absence or presence of different antibody clones (61 pg/ml to 4 µg/ml; 4-fold dilution).

Figures 5A-5C. *In vitro* validation of anti-gp130 clones in primary mouse atrial fibroblasts.

(**5A**) Immunoblots showing analysis of cell lysates of MAFs unstimulated (BL) or stimulated with mL-6 or mOSM (10 ng/ml) for 15 min in the absence of antibody (-), or in the presence of antibody clones 11E10, 4A7 or 8C6 (250 ng/ml). (**5B**) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 or pERK/ERK levels of the immunoblot of **5A**. (**5C**) Graphs showing analysis of % inhibition of gp130-mediated signalling, determined by MMP2 assay, in cells stimulated for 25 hours with recombinant mouse IL-11 in the presence of antibody clones 11E10, MAB4682, MAB628, MA5-23817, PA5-47650, CSP-s-3G9, CSP-s-4A7, CSP-s-7A5, CSP-s-7D8 or CSP-s-8C6 (61 pg/ml to 4 µg/ml; 4-fold dilution).

Figures 6A-6F. *In vitro* comparison of anti-gp130 mAb clones on inhibiting STAT3

activation in human lung epithelial carcinoma cell line (A549). (**6A** and **6B**) Immunoblots showing analysis of cell lysates of A549 cells (**6A**) unstimulated or (**6B**) stimulated with hIL-6, hIL-11, hLIF, hOSM or hCTGF (10 ng/ml) in the absence of antibody or in presence of antibody clones 11E10, MAB628, CSP-s-3G9 (3G9), CSP-s-4A7 (4A7), CSP-s-7D8 (7D8), CSP-s-8C6 (8C6), MA5-23817 or PA5-47650 (250 ng/ml). (**6C**) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblot of **6A**. (**6D** and **6E**) Immunoblots showing analysis of cell lysates of A549 cells (**6D**) unstimulated or (**6E**) stimulated with hIL-11 or hOSM (10 ng/ml) in the absence of antibody or in the presence of antibody clones 11E10, MAB628, CSP-s-3G9 (3G9), CSP-s-

4A7 (4A7), CSP-s-7D8 (7D8), CSP-s-8C6 (8C6), MA5-23817 or PA5-47650 (250 ng/ml). (6F) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pERK/ERK levels of the immunoblot of 6E.

- 5 **Figures 7A-7D. *In vitro* inhibitory effects of CSP-s-4D4 on STAT3 activation by gp130 ligands in human lung epithelial carcinoma cell line (A549).** (7A) Immunoblots showing analysis of cell lysates of A549 cells unstimulated (BL) or stimulated with hCTGF, hCT-1, hIL-6, hIL-11, hLIF or hOSM (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of CSP-s-4D4 (4D4) (250 ng/ml). (7B) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblot of 7A. (7C) Immunoblots showing analysis of cell lysates of A549 cells unstimulated (BL) or stimulated with recombinant human OSM for 15 min in the absence of antibody (-) or in the presence of antibody clone 11E10 (16 µg/ml) or CSP-s-4D4 (3.9 ng/ml to 16 µg/ml). (7D) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblot of 7C.

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- Figures 8A-8F. *In vitro* inhibitory effects of CSP-s-4D4 and CSP-s-8C6 on STAT3 or ERK activation by IL-6 or IL-11 in human lung epithelial carcinoma cell line (A549).** (8A) Immunoblots showing analysis of cell lysates of A549 cells unstimulated (BL) or stimulated with recombinant human IL-6 for 15 min in the absence of antibody (-), in the presence of E11E10 (4 µg/ml), or in the presence of CSP-s-8C6 (8C6) or CSP-s-4D4 (0.06 ng/ml to 4 µg/ml). (8B) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblot of 8A. (8C) Immunoblots showing analysis of cell lysates of A549 cells unstimulated (BL) or stimulated with recombinant human IL-11 for 15 min in the absence of antibody (-), in the presence of E11E10 (4 µg/ml), or in the presence of CSP-s-8C6 (8C6) or CSP-s-4D4 (0.06 ng/ml to 4 µg/ml). (8D) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pERK/ERK levels of the immunoblot of 8C. (8E) Immunoblots showing analysis of cell lysates of A549 cells unstimulated (BL) or stimulated with recombinant human IL-11 for 15 min in the absence of antibody (-), in the presence of E11E10 (4 µg/ml), or in the presence of CSP-s-8C6 (8C6) or CSP-s-4D4 (0.06 ng/ml to 4 µg/ml). (8F) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblot of 8E.

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- Figures 9A and 9B. *In vivo* testing of gp130 clones for Immunoblotting and Immunohistochemistry.** (9A) Immunoblots showing analysis of liver tissue lysate from CAGG^{Cre/+}-gp130^{fl/fl} conditional knock out mouse (gp130 CKO) or CAGG^{+/+}-gp130^{fl/fl} control mouse (WT). (9B) Images showing immunohistochemical staining for livers of CAGG^{Cre/+}-gp130^{fl/fl} conditional knock out mouse (gp130 CKO) or CAGG^{+/+}-gp130^{fl/fl} control mouse (WT). Sections marked with (*) were incubated with DAB for 10 seconds. Remaining sections were incubated with DAB for 1 min.

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- Figures 10A-10J. *In vivo* efficacy of anti-gp130 mAb clones in preventing consequences of acute kidney injury (AKI).** (10A-10H) Graphs showing (10A) % body weight, (10B) kidney weight (g), (10C) collagen (µg/mg), (10D) kidney function markers, (10E) serum IL-6 levels, (10F) pro-fibrotic markers, (10G) pro-inflammatory markers, and (10H) kidney injury markers, in mice administered vehicle

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alone (NaHCO₃), or folic acid (200 mg/kg) in the presence of IgG isotype control 11E10 (IgG), anti-IL-11 antibody (anti-IL-11), CSP-s-8C6 (8C6) or CSP-s-4D4 (4D4). **(10I)** Immunoblots showing analysis of kidney tissue lysates from mice administered vehicle alone (NaHCO₃), or folic acid (200 mg/kg) in the presence of IgG isotype control 11E10 (IgG), anti-IL-11 antibody (anti-IL-11), CSP-s-8C6 (8C6) or CSP-s-4D4 (4D4). **(10J)** Graphs showing p-ERK/ERK, p-STAT3/STAT3, p-NFKB β /NFKB β and α SMA/GAPDH levels determined by densitometry analysis of the immunoblots of **10J**. Each data point represents an average weight of right and left kidney from one mouse (**10B**).

Figures 11A-11C. Evaluation of the effect of CSP-s-8C6 in collagen-induced arthritis (CIA)

model. (11A) Schematic showing timeline of experiment in mouse model of CIA. **(11B and 11C)** Graphs showing **(11B)** body weight and **(11C)** score analysis of naive mice, or mice administered collagen followed by treatment with vehicle + 11E10, dexamethasone, anti-IL-6 or CSP-s-8C6. Mean $\pm$ SEM, n=12/group, * p <0.05, ** p <0.01, *** p <0.001, compared with the vehicle + 11E10 group, a two-way analysis of variance was used with Dunnett's multiple comparison (**11B, 11C**).

Figures 12A-12L. Epitope mapping of gp130 clones. (12A, 12C, 12E, 12G, 12I, 12K) Schematic representation of the interaction between gp130 and **(12A)** CSP-s-3G9, **(12C)** CSP-s-4A7, **(12E)** CSP-s-4D4, **(12G)** CSP-s-7D8, **(12I)** CSP-s-8C6 and **(12K)** C03-A7. **(12B, 12D, 12F, 12H, 12J, 12L)** Images showing the epitope site of **(12B)** CSP-s-3G9, **(12D)** CSP-s-4A7, **(12F)** CSP-s-4D4, **(12H)** CSP-s-7D8, **(12J)** CSP-s-8C6 and **(12L)** C03-A7 on gp130 PDB structure 3L5H. The epitope site is coloured in dark grey. A, B, C, D, E: ribbon/surface representation of front view (A); back view (B), side view 1 (C), side view 2 (D) and top view (E). F, G, H, I, J: ribbon representation of front view (F); back view (G), side view 1 (H), side view 2 (I) and top view (J).

Figures 13A-13L. STAT3 Reporter assay. Graphs showing % activity of STAT3 in a HEK293-based STAT3 reporter cell line upon stimulation with **(13A, 13B)** 100 ng/ml hIL-6, **(13C, 13D)** 100 ng/ml hIL-11, **(13E, 13F)** 10 ng/ml hOSM, **(13G, 13H)** 10ng/ml hLIF, **(13I, 13J)** 10 ng/ml hCT-1, or **(13K, 13L)** 10 ng/ml hCNTF, in the presence of increasing concentrations of CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8, CSP-s-8C6, or B035-C03-A7.

Figures 14A-14E. Evaluation of anti-gp130 clones binding to human and mouse gp130. (14A, 14B) Graphs showing results of ELISA binding assays plotting absorbance (OD) at 450nm upon addition of increasing amounts of CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8 or CSP-s-8C6 with **(14A)** human gp130 or **(14B)** mouse gp130 as the coating protein. **(14C)** Table showing binding of clones CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8 or CSP-s-8C6 to cells transfected with mouse gp130 or human gp130 assessed using flow cytometry. **(14D, 14E)** Graphs showing results of ELISA binding assays plotting absorbance (OD) at 450nm upon addition of increasing amounts of C03-A7 with **(14D)** human gp130 or **(14E)** mouse gp130 as the coating protein.

Figure 15. *In vitro* IC₅₀ screening of anti-gp130 mAb clones in primary adult canine dermal fibroblasts. Graphs showing percentage inhibition of gp130 signalling at increasing concentrations of anti-gp130 mAb clones CSP-s-8C6 and CSP-s-4D4, as determined by MMP2 concentration. Cells were

stimulated for 24 hours with 5 ng/ml of recombinant mouse TGF β 1 in the absence or presence of different antibody clones (61 pg/ml to 4 μ g/ml; 4-fold dilution).

Figures 16A-16C. Evaluation of the effect of CSP-s-4D4 in a DSS-induced colitis model. (16A)

- 5 Graph showing myeloperoxidase MPO concentration of healthy mice, or mice administered DSS and treatment with 11E10, cyclosporin A, or CSP-s-4D4. **(16B)** Graph showing serum IL-6 concentration in healthy mice, or mice administered DSS and treatment with 11E10, cyclosporin A, anti-IL-6 (BioXCell BE0047) or CSP-s-4D4. **(16B)** Graph showing OSM expression in the colon as determined by qRT-PCR in healthy mice, or mice administered DSS and treatment with 11E10, cyclosporin A or CSP-s-4D4. Mean $\pm$ SEM.
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Figures 17A-17D. Evaluation of humanised CSP-s-4D4 antibody variants binding to gp130.

- (17A, 17C)** Graphs showing the response curves of humanised variants binding to gp130 in single cycle kinetic binding experiments. **(17B, 17D)** Table showing the association rate, dissociation rate, K_D , relative K_D , and R_{MAX} for the binding to gp130 of the humanised variants. Highlighted antibodies are the parental control (VH0/VL0) and variants which bind within **(17B)** 2-3-fold affinity or **(17D)** 2-fold affinity of VH0/VL0. K_D values marked with * showed reduced signal/ R_{MAX} .
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Figures 18A-18C. Ability of anti-gp130 clones (A7, 4D4, 7D8, 3G9) to be used for

- immunoblotting and immunohistochemical analysis of gp130 expression. (18A)** Immunoblots showing analysis of liver tissue lysate from CAGG^{Cre/+}-gp130^{fl/fl} conditional knock out mouse (gp130 CKO) or CAGG^{+/+}-gp130^{fl/fl} control mouse (WT). **(18B-18C)** Images showing immunohistochemical staining for livers of CAGG^{Cre/+}-gp130^{fl/fl} conditional knock out mouse (gp130 CKO) or CAGG^{+/+}-gp130^{fl/fl} control mouse (WT).
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Figures 19A-19C. Inhibition of mIL-6- or mIL-11-induced activation of STAT3 in MAFs by 4D4.

- (19A)** Immunoblots showing analysis of STAT3 and p-STAT3 in cell lysates of MAFs unstimulated (BL) or stimulated with mIL-6 or mIL-11 (10 ng/ml) for 15 min in the absence of antibody (-), or in the presence of antibody clones BE0090 (4 μ g/ml) or CSP-s-4D4 at concentrations from 0.06 ng/ml (0.4 fM) to 4 μ g/ml (26.7 nM). **(19B-19C)** Graphs showing analysis of percentage inhibition of STAT3 activation in MAFs stimulated with recombinant mIL-6 (19B) or mIL-11 (19C) in the presence of 4D4 (0.06 ng/ml to 4 μ g/ml; 4-fold dilution).
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Figures 20A-20C. Inhibition of human HyperIL-6- or human HyperIL-11-induced activation of

- STAT3 in HCFs by 4D4. (20A)** Immunoblot showing analysis of HCF cell lysates unstimulated (BL) or stimulated with HyperIL-6 or Hyper IL-11 (10 ng/ml) for 15 min in the presence of antibody clones BE0090 (4 μ g/ml) or CSP-s-4D4 at a concentration of 250 ng/ml (1.7 nM). **(20B-20C)** Graphs showing % inhibition of STAT3 activation in HCFs stimulated with Hyper-IL-6 (20B) or Hyper-IL-11 (20C).
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- Figures 21A and 21B. Inhibition of mouse IL-6-, mouse IL-11 or mouse HyperIL-6-induced activation of STAT3 in MAFs by 4D4, 3G9, 8C6, 4A7, A7. (21A)** Immunoblot showing analysis of MAF cell lysates unstimulated (BL) or stimulated in the presence of mIL-6, mIL-11 or mHyperIL-6 (10 ng/ml) for
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15 min in the absence of antibody (-), or in the presence of antibody clone BE0090, CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-8C6 or B035-C03-A7. Graphs showing % inhibition of STAT3 activation in HCFs stimulated with mL-6, mL-11 or mHyperIL-6.

- 5 **Figures 22A-22B. Inhibition of IL-6-mediated signalling by humanised 4D4 antibodies. (22A-22B)** Graphs showing % STAT3 activity in HEK293 STAT3 reporter cells upon stimulation with human IL-6 (22A) or human IL-11 (22B) in the presence of the indicated antibodies. 4D4 hlgG4(S228P, L235E) = VH0/VL0; 4D4CVH2/4D4GVL3 hlgG4(S228P, L235E) = CVH2/GVL3; 4D4CVH2.2/4D4C/GVL1 hlgG4(S228P, L235E) = CVH2.2/CVL1; 4D4CVH2.2/4D4GVL3 hlgG4(S228P, L235E) = CVH2.2/GVL3; 10 4D4CVH2.2/4D4GVL4 hlgG4(S228P, L235E) = CVH2.2/GVL4; and 4D4CVH3/4D4GVL3 hlgG4(S228P, L235E) = CVH3/GVL3.

- Figure 23. Inhibition of IL-6-mediated signalling by humanised 4D4 antibodies comprising VH D53G/E/Q and/or VL N93G/Q.** Graphs showing % STAT3 activity in HEK293 STAT3 reporter cells upon 15 stimulation with human IL-6 in the presence of the indicated antibodies. 4D4/4D4= VH0VL0; 4D4CVH2/4D4GVL3 = CVH2/GVL3; 4D4CVH2_D53G/4D4GVL3_N93Q = CVH2_D53G/GVL3 (N93Q); 4D4CVH2 (D53Q)/4D4GVL3_N93Q = CVH2 (D53Q)/GVL3 (N93Q); 4D4CVH2_D53E/4D4GVL3_N93Q = CVH2 (D53E)/GVL3 (N93Q); 4D4CVH2_D53G/4D4GVL3_N93G = CVH2 (D53G)/GVL3 (N93G); 4D4CVH2_D53Q/4D4GVL3_N93G = CVH2 (D53Q)/GVL3 (N93G); 4D4CVH2_D53E/4D4GVL3_N93G = 20 CVH2 (D53E)/GVL3 (N93G); 4D4CVH2.2/4D4GVL3 = CVH2.2/GVL3; 4D4CVH2.2_D53G/4D4GVL3_N93Q = CVH2.2 (D53G)/GVL3 (N93Q); 4D4CVH2.2_D53Q/4D4GVL3_N93Q = CVH2.2 (D53Q)/GVL3 (N93Q); 4D4CVH2.2_D53E/4D4GVL3_N93Q = CVH2.2 (D53E)/GVL3 (N93Q); 4D4CVH2.2_D53G/4D4GVL3_N93G = CVH2.2 (D53G)/GVL3 (N93G); 4D4CVH2.2_D53Q/4D4GVL3_N93G = CVH2.2 (D53Q)/GVL3 (N93G); and 25 4D4CVH2.2_D53E/4D4GVL3_N93G = CVH2.2 (D53E)/GVL3 (N93G).

- Figures 24A-24G. Ability of humanised 4D4 antibodies comprising VH D53G/E/Q and/or VL N93G/Q to inhibit IL-6-, IL-11-, CT-1-, CNTF-, OSM- or LIF-induced activation of STAT3.** Graphs 30 showing % STAT3 activity in HEK293 STAT3 reporter cells upon stimulation with rhIL-11 (24A, 24C), 100 rhIL-6 (24B), rhCT1 (24D), rhCNTF (24E), rhOSM (24F) or rhLIF (24G), in the presence of the indicated antibodies. 4D4/4D4= VH0VL0; 4D4CVH2/4D4GVL3 = CVH2/GVL3; 4D4CVH2_D53E/4D4GVL3_N93G = CVH2 (D53E)/GVL3 (N93G); 4D4CVH2_D53Q/4D4GVL3_N93G = CVH2 (D53Q)/GVL3 (N93G); 4D4CVH2_D53G/4D4GVL3_N93Q = CVH2 (D53G)/GVL3 (N93Q); 4D4CVH2.2/4D4GVL3 = 35 CVH2.2/GVL3; 4D4CVH2.2_D53E/4D4GVL3_N93G = CVH2.2 (D53E)/GVL3 (N93G); 4D4CVH2.2_D53G/4D4GVL3_N93Q = CVH2.2 (D53G)/GVL3 (N93Q); and 4D4CVH2.2_D53Q/4D4GVL3_N93G = CVH2.2 (D53Q)/GVL3 (N93G).

Examples

- 40 **Example 1: Materials and Methods (for Examples 1-13)**

Antibodies. Commercially-available antibodies: MAB218 (mouse monoclonal human IL-11 antibody IgG_{2A} Clone # 22626, R&D Systems); MAB628 (mouse monoclonal anti-human gp130 antibody

IgG₁ Clone # 28105, R&D Systems); MA5-23817 (mouse monoclonal anti-human gp130 antibody IgG₁ Clone # 28126, ThermoFisher Scientific). Custom-made gp130 monoclonal antibody clones were obtained: CSP-s-3G9 (also referred to herein as '3G9'), CSP-s-4A7, CSP-s-7D8 (CSP-s-4A7 and CSP-s-7D8 have identical VH and VL sequences, and are also referred to herein as '4A7/7D8'), CSP-s-4D4 (also referred to herein as '4D4'), CSP-s-8C6 (also referred to herein as '8C6'), and B35-C03-A7 (also referred to herein as 'C03-A7' or 'A7'). A neutralising anti-IL-11 monoclonal antibody was obtained from Genovac.

Negative control 11E10 (mouse monoclonal shigatoxin-2 antibody, IgG₁, Genovac). Negative control BE0090 (rat monoclonal anti-keyhole limpet hemocyanin, IgG2b, BioXCell).

Cell Culture. Primary mouse atrial fibroblasts (MAFs) were isolated from heart atria of 6 weeks old C57BL/6J mice. Rat atrial fibroblasts (rat Afs) were isolated from heart atria of 6 month old female Sprague Dawley Taconic rat. Cells were maintained and cultured in complete DMEM supplemented with 10% FBS and 1% P/S at 37°C and 5% CO₂. The growth medium was renewed every 2–3 days and cells were passaged at 80% confluence, using standard trypsinization techniques. All experiments were carried out at low cell passage ($\leq P3$). Stimulated cells were compared to unstimulated cells that have been grown for the same duration under the same conditions, but without the stimuli.

Primary adult human cardiac fibroblasts (HCFs) were isolated from the healthy male heart. Cells were grown and maintained in FM-2 complete medium which contains FM-2 basal medium, Fibroblast growth supplement-2, 5% FBS, and 1% P/S at 37°C and 5% CO₂. Primary adult canine dermal fibroblasts (CDFs) were isolated from Beagle's dermal tissue. Cells were maintained and cultured in fibroblast complete medium at 37°C and 5% CO₂. The growth medium for both HCFs and CDFs was renewed every 2–3 days and cells were passaged at 80% confluence, using standard trypsinization techniques. All experiments were carried out at low cell passage ($\leq P3$).

A549 cells were grown and maintained in DMEM complete medium which contains 10% FBS and 1% P/S at 37°C and 5% CO₂. The growth medium was renewed every 2–3 days and cells were passaged at 80% confluence, using standard trypsinization techniques. A549 were seeded in 6-well cell culture plate (353046, BD FALCON) at a density of 2×10^5 cells/well and incubated in DMEM complete medium for 24 hours to enable cells to adhere to the plates. Cells were then serum-starved for 16 hours in DMEM basal medium prior to stimulation. Cells were stimulated as detailed in the example. Stimulated cells were compared to unstimulated cells that have been grown for the same duration under the same conditions, but without the stimuli.

Operetta phenotype assays. Primary mouse atrial fibroblasts were seeded in 96-well CellCarrier black plate (6055302, PerkinElmer) at a density of 6×10^3 cells/well and incubated in growing medium for 24 hours to enable cells to adhere to the plates. Cells were serum-starved for 16 hours in serum-free DMEM prior to stimulation. Primary HCFs were seeded in 96-well CellCarrier black plate (6055301, PerkinElmer) at a density of 6×10^3 cells/well and incubated in FM-2 complete medium for 24 hours to enable cells to adhere to the plates. Cells were then serum-starved for 16 hours in FM-2 basal medium prior to

stimulation.

Cells were stimulated as detailed in the Examples. After stimulation, culture media were collected for analysis by MMP2 assay, and cells were rinsed twice in PBS and fixed in 4% paraformaldehyde for 15 min. Then cells were washed twice in PBS, permeabilized with 0.1% Triton X-100 in PBS for 5 mins, and then rinsed twice with PBS. Non-specific binding sites were blocked with blocking solution (0.5% BSA and 0.1% Tween -20 in PBS). Cells were incubated overnight (4°C) with α SMA primary antibody (1:500 in blocking solution), followed by 2X rinses with wash buffer (PBS containing 0.25% BSA and 0.1% Tween -20), and incubation with anti-mouse AlexaFluor488 for 1 hour in the dark (1:1000, RT). Cell nuclei were counterstained with DAPI (1 μ g/ml) in blocking solution (15 min, RT). Following a final set of PBS washes, plates were scanned, and images were collected with an Operetta high-content imaging system (PerkinElmer, 1483) at 10X objective lens.

Each condition was assayed in at least duplicate wells and a minimum of 7 fields per well imaged using Operetta high-content imaging system. Cells expressing α SMA were quantified using Harmony v3.5.2 (PerkinElmer) and the percentage of activated fibroblasts (myofibroblasts)/total cell number (α SMA⁺) was determined for each field. Data were processed and analysed using Columbus v2.9.0.

Percentage of α SMA⁺ cells at baseline levels were considered as maximal inhibition (100%), while percentage of α SMA⁺ cells after stimulation with recombinant human IL-11 (5 ng/ml) in the presence of 11E10 (2 μ g/ml) constituted minimum inhibition (0%). Clones with % inhibition values of more than 100% were considered as having maximal inhibition (100%) and clones with % inhibition value of less than 0% were considered as having minimum inhibition (0%).

Enzyme-linked immunosorbent assay (ELISA). Mouse atrial fibroblasts (MAFs), rat AFs, human cardiac fibroblasts (HCFs) or canine dermal fibroblasts (CDFs) were seeded in 96-well CellCarrier black plate (6055302, PerkinElmer) at a density of 6 X 10³ cells/well and incubated in growing medium for 24 hours to enable cells to adhere to the plates. Cells were serum-starved for 16 hours in serum-free DMEM prior to stimulation. After starvation, cells were stimulated as detailed in the experiment. After stimulation, media were collected for MMP2 assay. The levels of MMP2 in equal volumes of cell culture media were quantified using Total MMP-2 Quantikine ELISA kit according to the manufacturer's instructions.

MMP2 concentrations at baseline were considered as maximal inhibition (100%), while MMP2 concentrations after stimulation in the absence of an antibody or in the presence of a negative control antibody [10E10] constituted minimum inhibition (0%). Clones with % inhibition values of more than 100% are considered as having maximal inhibition (100%) and clones with an inhibition value of less than 0% are considered as having minimum inhibition (0%).

Immunoblotting. After stimulation, cells were rinsed twice in cold PBS and lysed in RIPA Lysis and Extraction Buffer containing protease and phosphatase inhibitors. Protein lysates were then separated by SDS-PAGE, transferred to PVDF membranes, blocked for 1 hour with 3% BSA, and incubated overnight

with the primary antibodies (1:1000 in TBST). Protein bands were visualized using the SuperSignal West Femto Maximum Sensitivity substrate with the appropriate HRP secondary antibody (1:5000 in TBST).

Densitometry analysis. Densitometry analysis is performed using ImageJ (version 1.53f51): phospho signals were normalized to their respective total proteins. STAT3/ERK activation levels by MAFs/A549 at baseline (without stimuli or any antibody clone) were considered as maximal inhibition (100%), while STAT3/ERK activation levels after stimulation with a given agent, as detailed in the example, in the presence of 11E10 or BE0090 (at the given concentration) constituted minimum inhibition (0%).

10 **Example 2: Characterisation of anti-gp130 clones in a STAT3 reporter assay**

The effect of different anti-gp130 antibody clones on signalling mediated by receptors comprising human gp130 was examined in a STAT3 reporter cell line. The cell line was a HEK293 background with a firefly luciferase gene driven by STAT3 response elements allowing STAT3 signaling pathway activity to be monitored.

15

Each of the anti-gp130 antibody clones CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8, CSP-s-8C6, and B035-C03-A7 showed dose-dependent inhibition of both hIL-6-induced activation (Figure 13A, Figure 13B) and hIL-11-induced activation (Figure 13C, Figure 13D). Where possible, the IC₅₀ was determined (see table below). Both CSP-s-4D4 and CSP-s-8C6 exhibited excellent IC₅₀ values, at 0.3634 µg/ml and 0.0699 µg/ml for hIL-6 activation respectively, and 0.084 µg/ml and 0.079 µg/ml for hIL-11 activation respectively.

20

In contrast, each of the anti-gp130 antibody clones did not show inhibitory activity on cells treated for 24h with hOSM (Figure 13E, Figure 13F), hLIF (Figure 13G, Figure 13H) hCT-1 (Figure 13I, Figure 13J) or hCNTF (Figure 13K, Figure 13L).

25

Each of CSP-s-3G9, CSP-s-4A7, CSP-s-7D8 and CSP-s-8C6 did not show inhibitory activity on cells treated with hLIF (Figure 13G), Clones CSP-s-4D4 and B035-C03-A7 were not tested in this assay due to low amounts of available antibody, however experiments described hereinbelow demonstrate that CSP-s-4D4 does not show inhibitory activity on hLIF-induced activation (see Example 12 and Figure 7B).

30

Clone	hSTAT3 reporter assay IC ₅₀ µg/ml					
	100 ng/ml hIL-6	100 ng/ml hIL-11	10 ng/ml hOSM	10 ng/ml hLIF	10 ng/ml hCT-1	10 ng/ml hCNTF
CSP-s-3G9	3.777	0.761	*NI	*NI	*NI	*NI
CSP-s-4A7	2.764	0.313	*NI	*NI	*NI	*NI
CSP-s-4D4	0.3634	0.084	*NI	Not tested	*NI	*NI
CSP-s-7D8	3.763	0.486	*NI	*NI	*NI	*NI
CSP-s-8C6	0.0699	0.079	*NI	*NI	*NI	*NI
B035-C03-A7	10.24	ND	*NI	Not tested	*NI	*NI

*NI = not inhibitory

ND = IC₅₀ not determined as plateau was not achieved

Example 3: Characterisation of anti-gp130 clones binding to human and mouse gp130 by ELISA assay

ELISA assays were performed to assess the binding of anti-gp130 clones to human gp130. Figure 14A shows that each of clones CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8 and CSP-s-8C6 exhibit binding to human gp130.

Further ELISA assays were performed to assess the binding of anti-gp130 clones to mouse gp130. Figure 14B shows that each of clones CSP-s-4D4 and CSP-s-8C6 exhibit binding to mouse gp130.

Figure 14C shows that each of clones CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8 and CSP-s-8C6 exhibit binding to BOSC and CHO cells expressing human gp130. Figure 14C also shows that each of clones CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8 and CSP-s-8C6 exhibit binding to CHO cells expressing mouse gp130, although binding of CSP-s-4D4 appears weaker than the other clones in this assay.

Figures 14D and 14E show that C03-A7 displays binding to human gp130, and weak binding to mouse gp130.

Overall these results also show that each of the clones are cross-reactive binders, binding to both human and mouse gp130.

Example 4: Evaluation of binding affinity of gp130 clones to human gp130 and Rhesus monkey gp130

The affinity of binding of gp130 clones CSP-s-3G9, CSP-s-4A7, CSP-s-4D4, CSP-s-7D8 and CSP-s-8C6 to human gp130 was assessed by SPR (Biacore 8K). The assessment of binding of CSP-s-3G9, CSP-s-4A7, and CSP-s-7D8 and was performed using single cycle kinetics (SCK).

Briefly, purified gp130 clones were loaded onto the chip before human gp130 (R&D systems Cat. No. 228-GP) was added to the system. The association and dissociation rates of gp130 were measured and the K_D was determined (see table below).

Clone	Analyte	k_a (1/Ms)	k_d (1/s)	K_D (M)	R_{MAX}	χ^2 (RU ²)
3G9	Hu GP130	1.70E+05	2.68E-04	1.58E-09	23.7	0.0899
4A7	Hu GP130	1.72E+05	2.42E-04	1.40E-09	24	0.14
4D4	Hu GP130	2.92E+05	1.74E-04	5.97E-10	37.06	0.0982
7D8	Hu GP130	1.86E+05	2.09E-04	1.12E-09	29.1	0.161
8C6	Hu GP130	3.56E+05	1.69E-04	4.74E-10	34.84	0.123

The results demonstrate that each of the clones binds to human gp130 with high affinity. CSP-s-4D4 and CSP-s-8C6 showed particularly high affinity with K_D of 5.97E-10 M and 4.74E-10 M respectively.

Further binding assays were run using Biacore to assess the binding of clones CSP-s-4D4 and CSP-s-8C6 to human gp130 and Rhesus gp130 and the K_D was determined (see table below).

Clone	Analyte	k_a (1/Ms)	k_d (1/s)	K_D (M)	R_{MAX}	χ^2 (RU ²)
CSP-s-4D4	Hu GP130	2.09E+05	2.22E-04	1.06E-09	64.8	0.33
CSP-s-4D4	Rh GP130	2.46E+05	2.66E-04	1.08E-09	64.1	0.73
CSP-s-8C6	Hu GP130	2.47E+05	2.29E-04	9.25E-10	41	0.983
CSP-s-8C6	Rh GP130	2.47E+05	2.11E-04	8.53E-10	37.2	0.971

- 5 The results show that both clones bind Rhesus gp130 with similar affinity to human antigen (K_d values are within 2-fold).

Further binding assays were run using Biacore to assess the binding of clone C03-A7 to human gp130 and the K_D was determined (see table below).

Clone	Analyte	k_a (1/Ms)	k_d (1/s)	K_D (M)	R_{MAX}	χ^2 (RU ²)
C03-A7	Hu GP130	1.98E+05	3.96E-04	2.00E-09	50.6	0.31

10

Example 5: *In vitro* screening of anti-gp130 mAb clones in mouse atrial fibroblasts

3G9, 4A7/7D8 and 8C6 were evaluated for their effect on IL-11R α :gp130-mediated signalling in mouse atrial fibroblasts (MAFs), following stimulation with recombinant mouse IL-11.

- 15 Briefly, MAFs were stimulated *in vitro* with 5 ng/ml recombinant mouse IL-11 for 24 hours in the absence of antibody, or in the presence of 2 μ g/ml of CSP-s-3G9, CSP-s-4A7, CSP-s-7D8, CSP-s-8C6 or industry standard, and the proportion of α SMA-expressing, activated fibroblasts and the level of MMP2 in the cell culture medium was subsequently determined.
- 20 The results are shown in Figures 1A and 1B. Each of 3G9, 4A7/7D8 and 8C6 were found to inhibit IL-11R α :gp130-mediated signalling in mouse cells.

Example 6: *In vitro* screening of anti-gp130 mAb clones in primary human cardiac fibroblasts

3G9, 4A7/7D8 and 8C6 were evaluated for their effect on IL-11R α :gp130-mediated signalling in human cardiac fibroblasts, following stimulation with recombinant human IL-11.

25

Briefly, primary human atrial fibroblasts were stimulated *in vitro* with 5 ng/ml recombinant human IL-11 for 24 hours in the presence of CSP-s-3G9, CSP-s-4A7, CSP-s-7D8 or CSP-s-8C6 in a 4-fold dilution series ranging from 61 pg/ml to 4 μ g/ml, and the proportion of α SMA-expressing, activated fibroblasts and the level of MMP2 in the cell culture medium was subsequently determined.

30

The results are shown in Figure 2. 3G9 and 8C6 were found to inhibit IL-11R α :gp130-mediated signalling in human cells.

Example 7: In vitro IC₅₀ screening of anti-gp130 mAb clones in primary mouse atrial fibroblasts

4D4 was evaluated for its effect on IL-11-mediated signalling through IL-11R α :gp130 in mouse atrial fibroblasts, following stimulation with recombinant mouse IL-11.

- 5 Briefly, primary mouse atrial fibroblasts were stimulated *in vitro* with 5 ng/ml recombinant mouse IL-11 for 24 hours in the presence of CSP-s-4D4 in a 4-fold dilution series ranging from 61 pg/ml to 4 μ g/ml, and the level of MMP2 in the cell culture medium was subsequently determined.

The results are shown in Figure 3. 4D4 was found to potently inhibit IL-11-mediated signalling through IL-11R α :gp130, with an IC₅₀ of 14 ng/ml.

Example 8: In vitro IC₅₀ screening of anti-gp130 mAb clones in primary rat atrial fibroblasts

8C6 and 4D4 were evaluated for their effect on gp130-mediated signalling in rat atrial fibroblasts stimulated with TGF β 1. TGF β 1 is a profibrotic factor known to upregulate IL-11-mediated signalling (see e.g. Schaefer *et al.*, Nature (2017) 552(7683): 110–115).

Briefly, primary rat atrial fibroblasts were stimulated *in vitro* with 5 ng/ml recombinant mouse TGF β 1 for 24 hours in the presence of CSP-s-8C6 or CSP-s-4D4 in a 4-fold dilution series ranging from 61 pg/ml to 4 μ g/ml, and the level of MMP2 in the cell culture medium was subsequently determined.

The results are shown in Figure 4. 8C6 and 4D4 were found to potently inhibit TGF β 1-stimulated signalling through gp130, with IC₅₀ values of 46 ng/ml and 18 ng/ml, respectively.

Example 9: In vitro IC₅₀ screening of anti-gp130 mAb clones in primary adult canine dermal fibroblasts

CSP-s-4D4 and CSP-s-8C6 were evaluated for their effect on gp130-mediated signalling in canine dermal fibroblasts stimulated with TGF β 1. TGF β 1 is a profibrotic factor known to upregulate IL-11-mediated signalling (see e.g. Schaefer *et al.*, Nature (2017) 552(7683): 110–115).

Briefly, primary canine dermal fibroblasts were stimulated *in vitro* with 5 ng/ml recombinant human TGF β 1 for 24 hours in the presence of CSP-s-8C6 or CSP-s-4D4 in a 4-fold dilution series ranging from 61 pg/ml to 4 μ g/ml, and the level of MMP2 in the cell culture medium was subsequently determined.

The results are shown in Figure 15. 8C6 and 4D4 were found to potently inhibit TGF β 1-stimulated, IL-11-mediated signalling through gp130, with IC₅₀ values of 22 ng/ml and 19 ng/ml, respectively.

Example 10: In vitro validation of gp130 clones in primary mouse atrial fibroblasts

The effect of different anti-gp130 antibodies on signalling mediated by receptors comprising mouse gp130 was examined in MAFs.

Activation of gp130 triggers downstream signalling through the JAK/STAT and MAPK/ERK signal transduction pathways. Receptor engagement leads to downstream phosphorylation of inter alia STAT3 and ERK. Phosphorylation of STAT3 and ERK was assessed as a measure of gp130 activation.

- 5 Mouse atrial fibroblasts (MAFs) were stimulated *in vitro* with 10 ng/ml recombinant mouse IL-6 (mIL-6) or OSM (mOSM) for 15 minutes in the absence of antibody, or in the presence of 250 ng/ml of antibody 11E10 (negative control), CSP-s-4A7 or CSP-s-8C6. pSTAT3/STAT3 and pERK/ERK levels were subsequently analysed by immunoblot, as described in Example 1.
- 10 Figures 5A and 5B demonstrate that 4A7/7D8 and 8C6 inhibit IL-6-mediated signalling through IL-6R α :gp130, but do not inhibit OSM-mediated signalling through gp130:OSMR β or gp130:LIFR β .

- In further experiments, MAFs were stimulated *in vitro* with 5 ng/ml recombinant mouse IL-11 (mIL-11) for 24 hours in the presence of negative control antibody 11E10, or anti-gp130 antibody clones MAB4682, 15 MAB628, MA5-23817, PA5-47650, CSP-s-3G9, CSP-s-4A7, CSP-s-7D8 or CSP-s-8C6 in a 4-fold dilution series ranging from 61 pg/ml to 4 μ g/ml, and the level of MMP2 in the cell culture medium was subsequently determined.

- The results are shown in Figure 5C. 3G9, 4A7/7D8 and 8C6 were found to potently inhibit IL-11-mediated 20 signalling through IL-11R α :gp130.

Example 11: *In vitro* comparison of anti-gp130 mAb clones on inhibiting STAT3 activation in human lung epithelial carcinoma cell line (A549)

- 25 The effect of different anti-gp130 antibody clones on signalling mediated by receptors comprising human gp130 was examined in A549 cells.

- Human lung epithelial carcinoma (A549) cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 (hIL-6), IL-11 (hIL-11), LIF (hLIF), OSM (hOSM) or CTGF (hCTGF) for 15 minutes in the absence of antibody, in the presence of a negative control antibody clone 11E10, or in the presence of 30 250 ng/ml of anti-gp130 antibody MAB628, CSP-s-3G9 (3G9), CSP-s-4A7 (4A7), CSP-s-7D8 (7D8), CSP-s-8C6 (8C6), MA5-23817 or PA5-47650. pSTAT3/STAT3 and pERK/ERK levels were subsequently analysed by immunoblot, as described in Example 1.

- The results are shown in Figures 6A to 6F. 3G9 inhibited >25%-50% of IL-6-mediated signalling through 35 IL-6R α :gp130, 7D8 inhibited >50%-75% of the signalling, and 4A7 and 8C6 each inhibited >75% of the signalling (Figure 6C). 3G9, 4A7, 7D8 and 8C6 each inhibited >75% (>80%) of IL-11-mediated signalling through IL-11R α :gp130, as determined by analysis of pSTAT3/STAT3 (Figure 6C). By contrast, 3G9, 4A7, 7D8 and 8C6 displayed substantially no inhibition of OSM-mediated signalling, and minimal inhibition (<12.5%) of LIF-mediated signalling (Figure 6C).

- 40 Together, these results show that 3G9, 4A7/7D8 and 8C6 inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α , but do not substantially inhibit signalling mediated by the other IL-6 family

cytokines, OSM and LIF.

Example 12: *In vitro* inhibitory effects of CSP-s-4D4 on STAT3 activation by gp130 ligands in human lung epithelial carcinoma cell line (A549)

5 The effect of 4D4 on signalling mediated by receptors comprising human gp130 was examined in A549 cells.

A549 cells were stimulated with stimulated *in vitro* with 10 ng/ml of recombinant human CNTF, CT-1, IL-6, IL-11, LIF or OSM protein for 15 minutes in the absence of antibody (-) or in the presence of 250 ng/ml of
10 CSP-s-4D4. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in Example 1.

The results are shown in Figures 7A to 7D. 4D4 was found to inhibit of ~100% of IL-6-mediated signalling through IL-6R α :gp130, and of ~100% of IL-11-mediated signalling through IL-11R α :gp130 (Figure 7B). By
15 contrast, 4D4 displayed substantially no inhibition of CNTF- CT-1- LIF- or OSM-mediated signalling (Figure 7B).

Together, these results show that clone 4D4 strongly inhibits signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α , but does not inhibit signalling mediated by the other IL-6 family cytokines,
20 CNTF, CT-1, LIF and OSM.

Example 13: *In vitro* IC₅₀ of the inhibitory effects of CSP-s-4D4 and CSP-s-8C6 on STAT3 or ERK activation by IL-6 or IL-11 in human lung epithelial carcinoma cell line (A549)

The effect of different anti-gp130 antibody clones on signalling mediated by receptors comprising human
25 gp130 was examined in A549 cells.

A549 cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 or IL-11 protein for 15 minutes in the absence of antibody (-), in the presence of 4 μ g/ml of negative control antibody clone 11E10, or in the presence of anti-gp130 antibodies CSP-s-4D4 or CSP-s-8C6 in a dilution series ranging
30 from 0.06 ng/ml to 4 μ g/ml. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in Example 1.

The results are shown in Figures 8A to 8F. 4D4 was found to inhibit IL-6-mediated signalling through IL-6R α :gp130 with an IC₅₀ of 1.94 ng/ml (Figure 8B), and to inhibit IL-11-mediated signalling through IL-11R α :gp130 with an IC₅₀ of 2.21 ng/ml (pERK/ERK; Figure 8D) or 3.68 ng/ml (pSTAT3/STAT3; Figure 8F). 8C6 was found to inhibit IL-6-mediated signalling through IL-6R α :gp130 with an IC₅₀ of 3.77 ng/ml (Figure 8B), and to inhibit IL-11-mediated signalling through IL-11R α :gp130 with an IC₅₀ of 23.65 ng/ml.
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Together, these results show that clones 4D4 and 8C6 strongly inhibit signalling mediated by IL-6/gp130:IL-6R α and IL-11/gp130:IL-11R α .
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Example 14: *In vivo* testing of gp130 clones for Immunoblotting and Immunohistochemistry**14.1 Materials and Methods**

Generation of gp130-floxed mice (*gp130^{fl/fl}*). CRISPR/Cas9 was used to introduce loxP sequences into the mouse *Il6st/gp130* locus (ENSMUSG00000021756) for the conditional deletion of exons 4-5, resulting in a null allele upon Cre recombinase-mediated excision. Cas9, gRNA (with recognition sites on introns 3 and 5), and the targeting construct containing two loxP sequences were co-injected into fertilized eggs for mutant mice production (Cyagen Biosciences Inc). Insertion of loxP sites into the gp130 gene locus was verified by sequencing. Mutant gp130-floxed offspring were generated and maintained on a C57BL/6N background and identified by genotyping to detect the insertion of loxP sites using the following primers: 5'-TGGCTTTTAGGGCTAGAGAGAAGG-3' (forward) and 5'-GATTTCCCTCAGGAAACAGACTGAG-3' (reverse). Wildtype (WT) alleles were identified by a 138 bp PCR product while mutant alleles were identified by a 205 bp PCR product.

Generation of whole body gp130 conditional knockout (*gp130* CKO). To direct global (whole body) gp130 deletion in adult mice, homozygous *gp130*-floxed mice (*gp130^{fl/fl}*) were crossed with hemizygous CAGG-CreERTM transgenic mice (B6.Cg-Tg(CAG-cre/Esr1*)5Amc/J, 004682, The Jackson Laboratory) to generate CAGG^{Cre/+}-*gp130^{fl/fl}* progenies. To globally delete *gp130*, 9-10 week old CAGG^{Cre/+}-*gp130^{fl/fl}* mice received intraperitoneal injections of tamoxifen (50 mg kg⁻¹ body weight; tamoxifen stock (10 mg/ml in corn oil)) per day for 5 consecutive days for the first week followed by biweekly tamoxifen injections for another 5 weeks. CAGG^{Cre/+}-*gp130^{fl/fl}* mice, which were used as controls (WT), received the same dose and duration of tamoxifen. Livers were harvested 6 weeks after the start of tamoxifen administration for immunoblotting and immunohistochemistry.

Immunoblotting. Snap-frozen liver tissues (20-30 mg) were lysed in 1 ml RIPA Lysis and Extraction Buffer containing protease and phosphatase inhibitors. Protein lysates were then separated by SDS-PAGE, transferred to PVDF membranes, blocked for 1 hour with 3% BSA, and incubated overnight in 4°C with primary antibodies (1:1000 in TBST). Protein bands were visualized using the SuperSignal West Femto Maximum Sensitivity substrate with the rat HRP secondary antibody (1:2000 in TBST).

Immunohistochemistry. Livers were fixed for 48 hours at room temperature (RT) in 10% neutral-buffered formalin (NBF), dehydrated, embedded in paraffin blocks and sectioned at 7 µm. Following dewaxing, liver sections were permeabilized with 0.1% PBST, subjected to antigen retrieval process (citric acid, 20 mins, 98°C), and incubated with blocking solution for 10 mins then with 2.5% normal goat serum (1 hour, RT). Liver sections were incubated overnight in 4°C with primary antibodies (1:250 in 0.1% PBST) and visualized using an ImmPRESS HRP goat anti-rat IgG polymer detection kit with ImmPACT DAB Peroxidase Substrate. Hematoxylin was used to stain the nuclei prior to imaging by light microscopy.

14.2 Results

The ability of different anti-gp130 antibody clones to bind to gp130 was examined in mouse liver tissue.

Gp130 conditional knockout mice were generated, and binding of anti-gp130 antibody clones CSP-s-4A7 and CSP-s-8C6 was tested in liver tissue by immunoblotting and immunohistochemistry.

Figures 9A and 9B demonstrate that 4A7/7D8 and 8C6 bind to gp130 in the WT mouse samples, but do not bind to the CKO mouse samples. Thus, these antibodies can be successfully used in immunoblotting and histochemistry of tissue samples.

Example 15: *In vivo* efficacy of anti-gp130 mAb clones in preventing consequences of acute kidney injury (AKI)

15.1 Materials and Methods

Mouse models of folic acid nephrotoxicity. Kidney injury was induced by intraperitoneal injection of folic acid (FA; 200 mg/kg) in vehicle (0.3M NaHCO₃) to 10 to 12-week-old male mice; control mice were administered vehicle alone. Mice were intraperitoneally injected with 5 mg/kg (once a week) of either a neutralising anti-IL-11 antibody, CSP-s-4D4, CSP-s-8C6, or IgG isotype control (11E10) starting from 6 hours before FA administration until the mice were sacrificed (day 21 post-FA). At the end of the study period, each mouse had received a total of 3 antibody treatment injections *i.e.*, on day 0, day 7, and day 14.

ELISA and Colorimetric assays. The concentrations of blood urea nitrogen (BUN), creatinine, and IL-6 in mouse serum were measured using Urea Assay Kit, Creatinine Assay Kit, and Mouse IL-6 Quantikine ELISA kit, respectively. Total hydroxyproline content in mouse kidneys was measured using Quickzyme Total Collagen assay kit (QZBtotco15, Quickzyme Biosciences). All ELISA and colorimetric assays were performed according to the manufacturer's protocol.

Immunoblotting. Snap-frozen kidney tissues (20-30 mg) were lysed in 1 ml RIPA Lysis and Extraction Buffer containing protease and phosphatase inhibitors. Protein lysates were then separated by SDS-PAGE, transferred to PVDF membranes, blocked for 1 hour with 3% BSA, and incubated overnight in 4°C with primary antibodies (1:1000 in TBST). Protein bands were visualized using the SuperSignal West Femto Maximum Sensitivity substrate with the appropriate HRP secondary antibody (1:2000 in TBST).

Quantitative polymerase chain reaction (qPCR). Total RNA was extracted from snap-frozen kidney tissues using Trizol (Invitrogen) followed by Rneasy column (Qiagen) purification. cDNAs were synthesized with iScript™ cDNA synthesis kit (Bio-Rad) according to manufacturer's instructions. Gene expression analysis was performed on duplicate samples with either TaqMan (Applied Biosystems) or fast SYBR green (Qiagen) technology using StepOnePlus™ (Applied Biosystem) over 40 cycles. Expression data were normalized to *GAPDH* mRNA expression and fold change was calculated using 2^{- $\Delta\Delta Ct$} method.

Statistical analysis. Statistical analyses were performed using GraphPad Prism software (version 8). Statistical significance between experimental groups were analysed by one-way ANOVA as indicated and corrected for multiple testing according to Sidak's (with NaHCO₃ designated as the negative control group

and FA+11E10 designated as the positive control group). The criterion for statistical significance was $P < 0.05$.

15.2 Results

- 5 The effects of different anti-gp130 antibodies in preventing the consequences of acute kidney injury (AKI) were examined in a folic acid-induced mouse model of nephrotoxicity.

Figure 10A demonstrates that treatment with 4D4 and 8C6 abolished weight loss in the mouse model of acute kidney injury. 4D4 and 8C6 also exhibited a stronger treatment effect than a neutralising anti-IL-11
10 antibody.

Figure 10B demonstrates that treatment with 4D4 and 8C6 significantly reduced the weight loss observed in the kidneys of mice following acute kidney injury, compared to the negative control antibody.

- 15 Figure 10C demonstrates that treatment with 4D4 and 8C6 significantly inhibited the increase in renal collagen content observed in mice following acute kidney injury, compared to the negative control antibody. 4D4 and 8C6 also exhibited a stronger treatment effect than a neutralising anti-IL-11 antibody.

- Figure 10D demonstrates that treatment with 4D4 and 8C6 significantly inhibited the increase in markers of compromised kidney function (blood urea nitrogen (BUN) and creatine) observed in mice following acute kidney injury, compared to a negative control antibody.
20

- Figure 10E demonstrates that treatment with 4D4 and 8C6 significantly inhibited the increase in serum IL-6 levels observed in mice following acute kidney injury, compared to the negative control antibody. 4D4 and 8C6 also exhibited a stronger treatment effect than a neutralising anti-IL-11 antibody.
25

- Figure 10F demonstrates that treatment with 4D4 and 8C6 significantly inhibited the increase in renal expression of pro-fibrotic markers (*Col1a1*, *Col1a2*, *Col3a1*, *Fn*, *Acta2* and *Il11* RNA) observed in mice following acute kidney injury, compared to the negative control antibody. 4D4 and 8C6 also exhibited a stronger treatment effect than a neutralising anti-IL-11 antibody.
30

- Figure 10G demonstrates that treatment with 4D4 and 8C6 significantly inhibited the increase in renal expression of pro-inflammatory markers (*Ccl2*, *Ccl5*, *Il6*, *Tnfa* and *Il1β* RNA) observed in mice following acute kidney injury, compared to a negative control antibody. 4D4 and 8C6 also exhibited a stronger treatment effect than a neutralising anti-IL-11 antibody.
35

- Figure 10H demonstrates that treatment with clones 4D4 and 8C6 significantly reduced the increase in the expression of markers of kidney injury (*Ngal* and *Kim1* RNA) observed in mice following acute kidney injury, compared to a negative control antibody.
40

Figure 10I and Figure 10J demonstrate that treatment with 4D4 and 8C6 significantly reduced downstream effects of gp130 mediated signalling (phosphorylation of ERK, STAT3 and NFκB, and expression of αSMA) following acute kidney injury, compared to a negative control antibody.

- 5 Together, these data show that 4D4 and 8C6 strongly inhibit gp130-mediated signalling *in vivo* and significantly reduce the pathology of acute kidney injury, as determined by a reduction in the level of correlates of acute kidney injury. They furthermore demonstrate that 4D4 and 8C6 are more effective at reducing the pathology of acute kidney injury than a neutralising anti-IL-11 antibody.

10 **Example 16: Evaluation of the effect of CSP-s-8C6 in collagen-induced arthritis (CIA) model**

16.1 *Materials and Methods*

Materials. Mice were male DBA/1 strain and kept at 20-25°C, 40-70% humidity. Antibodies were 11E10, anti-IL-6, CSP-s-8C6 provided by VVB Bio Pte Ltd. Antibodies were provided in PBS. Weight balance MP5002 and electronic balance SQP SECURA225D-1CN were used.

15

Mouse models of collagen-induced arthritis (CIA). Purified natural collagen was dissolved in 0.1 M acetic acid to make a solution with a concentration of 1 mg/mL and mixed with the same amount of Complete Freund Adjuvant to form a stable emulsion. Emulsion (0.1 mL) was injected into the skin of the tail root of mice at Day 0 and at Day 21.

20

Grouping and dosing. The severity of symptom was assessed by a qualitative clinical score.

Score 0 - Normal

Score 1 – Mild, but definite redness and swelling of the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits

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Score 2 – Moderate redness and swelling of ankle or wrist

Score 3 – Severe redness and swelling of the entire paw including digits

Score 4 – Maximally inflamed limb with involvement of multiple joints

On day 21, the animals were randomly assigned to treatment groups according to the clinical score.

Group	Treatment	Dose (mg/kg)	Route
Group 1	Naive	-	-
Group 2	Vehicle + 11E10	10	IP
Group 3	Dexamethasone (Positive Control)	1	
Group 4	anti-IL-6	10	IP
Group 5	CSP-s-8C6	10	IP

30

Antibodies 11E10, anti-IL-6, and CSP-s-8C6 were administered twice per week for five weeks at 10 mg/kg (Figure 11A).

Analysis. Mice were weighed as described above 3 times per week over the course of the experiment. Plasma samples were collected on day 56 and TNF α , IL-12, IL-6 and INF- γ were analysed using an ELISA kit according to the manufacturer's instructions. Data was analysed by Prism 6.01 (GraphPad software, Inc.)

5

16.2 Results

The effects of anti-gp130 antibody 8C6 were examined in a collagen-induced arthritis (CIA) mouse model.

Figure 11B demonstrates that no significant difference in body weight was observed across the different treatment conditions.

Figure 11C demonstrates that treatment with 8C6 significantly reduced disease score compared to mice treated with a negative control antibody.

These data show that treatment with clone 8C6 reduced the pathology of arthritis, and does not exhibit negative side effects on mouse body weight. Clone 8C6 is therefore an effective treatment in a mouse model of arthritis.

Example 17: Evaluation of the effect of CSP-s-4D4 in a DSS-induced colitis model

17.1 Materials and Methods

Materials. Mice were male C57BL6J and kept at 21-25°C, 40-70% humidity. Antibodies were 11E10, anti-IL-6 (BioXCell BE0047) and CSP-s-4D4. DSS was supplied by MP Biomedicals, LL, Cyclosporin A (Cs A) was supplied by Selleck.

Study Procedure. On Day 0 mice were randomly divided according to their weight with 10 mice in each group. DSS was prepared with drinking water once every two days. Mice drank water or water containing 3% (w/v) DSS from Day 1 to Day 7. Treatment or vehicle was administered on day 1 and day 4.

Group	Treatment	Dose (mg/kg)	Route
Group 1	NIL	-	-
Group 2	11E10	20	IP
Group 3	Cyclosporin A (Positive Control)	20	PO
Group 4	anti-IL-6 (BioXCell BE0047)	20	IP
Group 5	CSP-s-4D4	20	IP

30

Analysis. The body weight, food intake, stool consistency, and intestinal bleeding was recorded daily to calculate the disease activity index (DAI). Clinical signs were observed daily.

On day 8, mice were euthanized with CO₂. Blood was obtained by heart puncture. Plasma was collected for analysis of the level of IL-6. Colon length and weight was measured, and observations on colonic distension, fluid content, hyperemia, and erythema were taken. Colon gross pathology was performed. 2 cm anterior segment of the colon after the cecum was divided into three parts. The first part was placed in 4% paraformaldehyde for histopathological examination (HE staining). The second part was placed in liquid nitrogen immediately and stored at -80°C for subsequent analysis of the expression of OSM. The third part was placed in liquid nitrogen immediately and stored at -80°C, for subsequent analysis of colonic myeloperoxidase (MPO) activity.

- 10 The significances of the differences among groups and within groups were evaluated by one-way or two-way ANOVA using GraphPad statistic software. A p-value of less than 0.05 is considered statistically significant.

17.2 Results

- 15 The effects of CSP-s-4D4 were examined in a mouse model of inflammatory bowel disease (DSS-induced colitis model).

Figure 16A demonstrates that treatment with CSP-s-4D4 reduces the concentration of myeloperoxidase (MPO), a biomarker for assessing IBD disease status, in the colon compared to mice treated with a negative control antibody.

Figure 16B demonstrates that treatment with an IL-6R blocker (anti-IL-6 BioXCell BE0047) results in significant upregulation of serum IL-6, which is a therapeutic challenge (Nishimoto 2008). In contrast, treatment with CSP-s-4D4 does not result in significant upregulation of serum IL-6, and levels of IL-6 are reduced compared to mice treated with a negative control antibody. Therefore, direct blockade of gp130 is advantageous over blockade of IL-6R as it does not lead to a significant increase in serum IL-6 levels.

Figure 16C demonstrates that treatment with CSP-s-4D4 reduces the level of expression of OSM in the colon, as determined by qRT-PCR.

- 30 Together these data show that treatment with CSP-s-4D4 reduces the IBD disease status and does not show negative side effects, e.g. a significant increase in serum IL-6 level. CSP-s-4D4 is therefore an effective treatment in a mouse model of IBD.

35 **Example 18: Epitope mapping of gp130 clones**

18.1 Materials and Methods

Mixtures of gp130/CSP-s-3G9, gp130/CSP-s-4A7, gp130/CSP-s-4D4, gp130/CSP-s-7D8, gp130/CSP-s-8C6, and gp130/B35-003-A7 were prepared at concentrations of gp130 1.6 µM and antibody 0.85 µM.

- 40 20 µL of gp130/antibody mixtures prepared were mixed with 2 µL of DSS d0/d12 (2mg/mL; DMF) and incubated at room temperature for 180 minutes. After incubation, the samples were submitted to

reduction/alkylation and proteolysis with five different enzymes (trypsin, chymotrypsin, ASP-N, elastase and thermolysin).

After proteolysis, 1 µl of each peptide solution generated by proteolysis were loaded onto a nanoliquid chromatography system (Ultimate 3000-RSLC) and assessed by liquid chromatography. Mass spectrometry was performed using a nLC chromatographic system in line with a Q-Exactive Plus Orbitrap mass spectrometer.

18.2 Results

To determine the epitope of anti-gp130 antibodies 3G9, 4A7/7D8, 4D4, 8C6 and C03-A7 on gp130 with high resolution, protein complexes of the antibody and gp130 were incubated with deuterated cross-linkers and subjected to multi-enzymatic cleavage. After enrichment of the cross-linked peptides, the samples were analysed by high resolution mass spectrometry

Using chemical cross-linking, High-Mass MALDI mass spectrometry and nLC-Q-Exactive mass spectrometry the molecular interface between gp130 and the different antibody clones were characterised.

Amino acid numbering is given in relation to the amino acid sequence of Human gp130 isoform 1 (UniProt: P40189-1, v2; SEQ ID NO:129).

The analysis indicates that the interaction between 3G9 and gp130 includes amino acids corresponding to positions 520, 524, 526, 529, 552, 558, 596 and 601 of SEQ ID NO:129, and the epitope site includes amino acids corresponding to positions 520-529 (SKGPTVRTKK; SEQ ID NO:169), 552-558 (RNYTIFY; SEQ ID NO:170) and 596-601 (TDEGGK; SEQ ID NO:171) of SEQ ID NO:129 (Figure 12A and Figure 12B).

The analysis indicates that the interaction between 4A7 and gp130 includes amino acids corresponding to positions 51, 53, 57, 152, 153 and 159 of SEQ ID NO:129, and the epitope site includes amino acids corresponding to positions 51-57 (KEKCMDY; SEQ ID NO:173) and 152-159 (THLETNFT; SEQ ID NO:174) of SEQ ID NO:129 (Figure 12C and Figure 12D).

The analysis indicates that the interaction between CSP-s-7D8 and gp130 includes amino acids corresponding to positions 233, 241, 257, 263, 395, 399, 401 and 403 of SEQ ID NO:129, and the epitope site includes amino acids corresponding to positions 233-241 (SEELSSILK; SEQ ID NO:176), 257-263 (YNIQYRT; SEQ ID NO:177) and 395-403 (RYLATLTVR; SEQ ID NO:178) of SEQ ID NO:129 (Figure 12G and Figure 12H).

The analysis indicates that the interaction between 4D4 and gp130 includes amino acids corresponding to positions 380, 388, 408 and 415 of SEQ ID NO:129, and the epitope site includes amino acids corresponding to positions 380-388 (YTVNATKLT; SEQ ID NO:180) and 408-415 (KSDAAVLT; SEQ ID NO:181) of SEQ ID NO:129 (Figure 12E and Figure 12F).

The analysis indicates that the interaction between 8C6 and gp130 includes amino acids corresponding to positions 362, 369, 372 and 380 of SEQ ID NO:129, and the epitope site includes amino acids corresponding to positions 362-369 (KILDYEVT; SEQ ID NO:183) and 372-380 (RWKSHLQNY; SEQ ID NO:184) of SEQ ID NO:129 (Figure 12I and Figure 12J).

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The analysis indicates that the interaction between C03-A7 and gp130 includes amino acids corresponding to positions 150, 153, 173, 180 and 186 of SEQ ID NO:129, and the epitope site includes amino acids corresponding to positions 150-153 (RETH; SEQ ID NO:186) and 173-186 (KAKRDTPTSTCTVDY; SEQ ID NO:187) of SEQ ID NO:129 (Figure 12K and Figure 12L).

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18.3 HDX-MS analysis

In further experiments, binding of different gp130-binding antibodies to recombinant human gp130 was analysed by hydrogen/deuterium exchange mass spectrometry (HDX-MS) analysis. Briefly, solutions of rhsgp130 alone (10µM, 150 µl) and rhsgp130 mixed with antibody: CSP-s-8C6, CSP-s-4D4, or ab34315 (known anti-gp130 antibody BR-3; Abcam) at a 1:1 ratio.

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Anti-human gp130 antibody B-R3 is described in Garbers *et al.*, J Biol Chem. (2013) 288(6): 4346–4354 to bind to the cytokine binding module of gp130.

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4 µl of each solution was analyzed using a MDX-MS system. 80 µl of the peptide solution generated by proteolysis was loaded onto a liquid chromatography system. Control and exchange experiments were conducted with incubation times of 15s, 60s, 180s, 600s, 1800s and 7200s.

The % incorporation of deuterium was determined for each sample mixture, and deuterium incorporation for each pepsin peptides of rhsgp130 mixed with or without CSP-s-8C6, CSP-s-4D4 or ab34315 for each incubation time allows a deuterium exchange heat map to be obtained, and the epitopes for the antibodies to be inferred.

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The analysis identified the following regions of human gp130 as being regions bound by the indicated antibodies:

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CSP-s-8C6: positions 367-370 (EVTL; SEQ ID NO:381) and positions 377-389 (LQNYTVNATKLTV; SEQ ID NO:382) of SEQ ID NO:129;

CSP-s-4D4: positions 377-389 (LQNYTVNATKLTV; SEQ ID NO:382) and positions 414-428 (LTIPACDFQATHPVM; SEQ ID NO:385) of SEQ ID NO:129;

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Ab343315: positions 186-191 (YSTVYF; SEQ ID NO:387) of SEQ ID NO:129 (which is within the CBM; see SEQ ID NO:144).

18.4 Epitope mapping – conclusions

Interestingly, the gp130-binding molecules described herein 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), and instead bind to the membrane-proximal region of gp130 (shown in SEQ

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ID NO:388). Without wishing to be bound by any particular theory, binding of the antibodies to this region of gp130 may inhibit formation of IL-6:IL-6R α :gp130 and IL-11:IL-11R α :gp130 complexes, thereby inhibiting IL-6- and IL-11-mediated signalling through IL-6R α :gp130 and IL-11R α :gp130, respectively.

5 **Example 19: Characterisation of humanised CSP-s-4D4 antibody variants binding to gp130**

Multiple humanised antibody variants of CSP-s-4D4 were designed based on both composite human antibody (CHAb) and CDR grafting technology. A selection of these designs were expressed in small scale CHO-S cells and screened for binding to human gp130 using single cycle kinetics (Biacore) (Figure 17A). The association and dissociation rates of gp130 were measured and the K_D was determined (Figure 10 17B).

In the initial round of screening two humanised variants (CVH2/CVL1 and CVH2/GVL4) showed binding affinities within ~2-3 fold of the parental CSP-s-4D4 antibody (VH0/VL0) (Figure 17A and Figure 17B).

15 Following these results, additional variants were designed, expressed in small scale CHO-S cells and a second round of screened for binding to human gp130 using single cycle kinetics (Biacore) was performed (Figure 17C). The association and dissociation rates of gp130 were measured and the K_D was determined (Figure 17D). Each of the humanised antibody variants show binding to human gp130 (Figure 17C and Figure 17D). Five of the humanised variants (CVH2/CVL1, CVH2/GVL3, CVH2.2/CVL1, 20 CVH2.2/GVL3, CVH3/GVL3) exhibited particularly good binding, with binding affinities within 2-fold of the parental CSP-s-4D4 antibody (VH0/VL0).

These results show that humanised antibody variants are able to bind to human gp130 with high affinity, with K_D s in the nanomolar range.

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Example 20: Analysis of the ability of anti-gp130 antibody clones to bind to gp130 in tissues

20.1 Materials and Methods

Gp130-floxed mice (*gp130^{fl/fl}*) and whole body gp130 conditional knockout (gp130 CKO) mice were generated as in Example 14. Immunoblotting and immunohistochemistry were conducted as in Example 30 14.

Antibodies and test kit: Rabbit anti-rat IgG H&L (HRP) (ab6734, Abcam), ImmPRESS® HRP Goat Anti-Rabbit IgG Polymer Detection Kit, and Peroxidase (MP-7404-50, Vector Laboratories).

35 **20.2 Results**

The ability of different anti-gp130 antibody clones to bind to gp130 was examined in mouse liver tissue.

Gp130 CKO mice were generated, and binding of parental rat anti-gp130 antibody clones B35-C03-A7, CSP-s-3G9, CSP-s-4D4, CSP-s-7D8 was tested in liver tissue by immunoblotting and 40 immunohistochemistry.

Figure 18A to 18C demonstrate that B35-C03-A7, CSP-s-3G9, CSP-s-4D4, CSP-s-7D8 bind to gp130 in the WT mouse samples, but do not bind to the CKO mouse tissue samples. The lack of binding to gp130 in gp130 knockout mice indicates that the clones specifically bind to gp130 with no off-target binding. Thus, these antibodies can be successfully used to detect gp130 in immunoblotting and immunohistochemical analysis.

Example 21: *In vitro* determination of dose-response inhibitory effects of CSP-s-4D4 on STAT3 activation by IL-6 and IL-11 in mouse atrial fibroblasts

21.1 *Materials and Methods*

Following isolation, MAFs were pre-incubated with either 4 µg/ml of BE0090, or 0.06 ng/ml (0.4 fM) to 4 µg/ml (26.7 nM) of CSP-s-4D4 (4-fold dilution) for 30 minutes, and then stimulated with 10 ng/ml of recombinant mouse IL-6 or IL-11 protein for 15 minutes. Stimulated and unstimulated cells (own for the same duration under the same conditions, but without the stimuli) were compared.

Immunoblotting and densitometry analysis performed as described in Example 1. STAT3 activation levels by MAF at baseline (without stimuli or any antibody clone) was considered maximal inhibition (100%) while STAT3 activation levels after stimulation with the respective recombinant protein (IL-6/IL-11 at 10 ng/ml) in the presence of BE0090 (4 µg/ml) constituted minimum inhibition (0%).

21.2 *Results*

The inhibitory effect of different doses of CSP-s-4D4 on STAT3 activation by IL-6 and IL-11 in mouse atrial fibroblasts (MAFs) was examined.

Figures 19A to 19C demonstrate that 4D4 inhibited IL-6-mediated signalling and IL-11-mediated signalling in a dose-dependent manner through IL-6Rα:gp130 and IL-11Rα:gp130 signalling respectively.

4D4 was found to inhibit IL-6-mediated signalling and IL-11-mediated signalling with an IC₅₀ of 33.0 ng/ml and 18.7 ng/ml respectively.

Example 22: *In vitro* comparison of the inhibitory effects of CSP-s-4D4 and a known neutralising anti-IL-11 antibody on STAT3 activation by HyperIL-6 and HyperIL-11 in human cardiac fibroblasts (HCFs)

22.1 *Materials and Methods*

Following isolation, HCFs were pre-incubated with either BE0090, a known neutralising anti-IL-11 antibody or CSP-s-4D4 (250 ng/ml or 1.7 nM) for 30 minutes and then stimulated with 10 ng/ml of recombinant human HyperIL-6/HyperIL-11. "Hyper IL-6" refers to an IL-6:IL-6Rα fusion protein consisting of the extracellular domain of IL-6 receptor alpha (IL-6Rα) connected via a peptide linker to the amino acid sequence of IL-6 (see e.g. Fischer *et al.*, Nature Biotechnology (1997) 15(2):142–145 and Rose-John Int J Bio Sci (2012) 8(9):1237–1247). Mouse HyperIL-6 (see Example 21) was designed using the corresponding regions of the mouse IL-6 and mouse IL-6Rα. Similarly, "Hyper IL-11" refers to an IL-11:IL-11Rα fusion protein consisting of the extracellular domain of IL-11 receptor alpha (IL-11Rα) connected via

a peptide linker to the amino acid sequence of IL-11 (see e.g. Dams-Kozłowska *et al.*, BMC Biotechnol. (2012) 12:8).

Stimulated cells were compared to unstimulated cells which were grown for the same duration under the same conditions, but without the stimuli. Immunoblotting and densitometry analysis performed as described in Example 1. STAT3 activation levels by HCFs at baseline (without stimuli or any antibody clone) was considered as maximal inhibition (100%) while STAT3 activation levels after stimulation with recombinant human HyperIL-6/HyperIL-11 (10 ng/ml) in the presence of BE0090 constituted minimum inhibition (0%).

22.2 Results

4D4 was evaluated for its ability to inhibit HyperIL-6-induced and Hyper IL-11-induced STAT3 activity in HCFs. A known neutralising anti-IL-11 antibody was included in the analysis as a control.

Figures 20A to 20C and the table below demonstrate that 4D4 inhibited HyperIL-6- or Hyper IL-11-induced gp130-mediated signalling, as determined by inhibition of activation of STAT3 in HCFs.

Clones	HyperIL-6	HyperIL-11
Anti-IL-11	- (0%)	++++ (100%)
CSP-s-4D4	+++ (72%)	++++ (82%)

where '-' corresponds to 0-10% inhibition, '+' corresponds to >10%-25% inhibition, '++' corresponds to >25%-50% inhibition, '+++ corresponds to >50%-75% inhibition, and '++++' corresponds to >75% inhibition.

Example 23: Analysis of the ability of anti-gp130 antibody clones to inhibit IL-6, IL-11 and HyperIL-6-induced STAT3 activation in mouse atrial fibroblasts (MAFs)

23.1 Materials and Methods

Following isolation, MAFs were pre-incubated with each of the antibody clones (250 ng/ml or 1.7 nM) for 30 minutes and then stimulated with 10 ng/ml of recombinant mouse IL-6/IL-11/HyperIL-6 protein for 15 minutes. Stimulated cells were compared to unstimulated cells which were grown for the same duration under the same conditions, but in the absence of stimuli.

Immunoblotting and densitometry analysis performed as described in Example 1. STAT3 activation levels by MAFs at baseline (without stimuli or any antibody clone) constituted maximal inhibition (100%), while STAT3 activation levels after stimulation with recombinant mouse IL-6/IL-11/HyperIL-6 (10 ng/ml) in the presence of BE0090 constituted minimum inhibition (0%).

23.2 Results

A known neutralising anti-IL-11 monoclonal antibody and the anti-gp130 mAb clones 3G9, 4A7, 4D4, 8C6 and C03-A7 were evaluated for their ability to inhibit mL-6-, mL-11- or mHyperIL-6-induced activation of STAT3 in MAFs.

Figures 21A and 21B demonstrate that 3G9, 4A7, 4D4, 8C6 and C03-A7 all inhibit mouse IL-6-induced, mouse IL-11-induced and mouse HyperIL-6-induced, gp130-mediated signalling. The known neutralising anti-IL-11 antibody was included in the analysis as a control, and was found to inhibit mouse IL-11-induced signalling, but not mouse IL-6- or mouse HyperIL-6-induced signalling (Figure 21B).

Example 24: Large scale expression and purification of mouse/human chimeric 4D4 and humanised 4D4 antibodies

4D4 and humanised variants (4D4CVH2/4D4GVL3, 4D4CVH2.2/4D4C/GVL1, 4D4CVH2.2/4D4GVL3, 4D4CVH2.2/GVL4 and 4D4CVH3/GVL3), were expressed recombinantly for further characterisation.

DNA constructs encoding the hlgG4(S228P, L235E) heavy and κ light chains were transiently transfected into CHO cells. CHO supernatants were harvested 12 days post-transfection, filtered and then the supernatants were loaded on 1 mL Hitrap MabSelect Prisma columns (Cytiva, Marlborough, USA). 4D4CVH3/GVL3 required preparative SEC, which was performed on a Superdex 200 16/600 SEC column (Cytiva, Marlborough, USA) due to it being below 90% monomeric character after affinity purification. Samples were quantified by A280 nm using an extinction coefficient ($E_{c(0.1\%)}$) based on the predicted amino acid sequence. Purified antibodies were then analysed by reducing and non-reducing SDS-PAGE and analytical SEC-HPLC.

The concentration, total yield following protein A purification and percentage monomer values are provided in the table below. SDS-PAGE data was as expected for IgG molecules.

Antibody	Conc (mg/ml)	Total yield following protein A purification (per litre of starting culture) (mg)	% monomer
4D4 hlgG4(S228P, L235E)	1.15	74.4	93.15
4D4CVH2/4D4GVL3 hlgG4(S228P, L235E)	1.04	60.0	94.18
4D4CVH2.2/4D4C/GVL1 hlgG4(S228P, L235E)	1.11	97.9	96.31
4D4CVH2.2/4D4GVL3 hlgG4(S228P, L235E)	1.05	75.8	93.94
4D4CVH2.2/GVL4 hlgG4(S228P, L235E)	1.14	90.5	96.48
4D4CVH3/GVL3 hlgG4(S228P, L235E)	1.09	39.9	100.00*

* following preparative SEC purification

Example 25: Binding of humanised anti-gp130 antibodies to human gp130

The affinity of binding of 4D4 and the humanised variants of Example 24 to human gp130 was assessed by SPR using Biacore 8K in a multiple cycle kinetics (MCK) analysis, using concentrations of human gp130 ranging from 0.375 nM to 25 nM.

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Briefly, purified gp130-binding antibodies were immobilised on chips via protein A capture, and human gp130 (Sino Biological Cat. No. 10974-HCCH) was then applied to the Protein A capture Sensor chip. Association and dissociation were measured (association time 210 s, dissociation time 900 s, analysis temperature 25 °C, flow rate 30 µl/min), the chip surface was regenerated using 2x injections with 10 mM glycine-HCl, pH 1.5, and then the procedure was repeated employing a higher concentration of human gp130 (from 0.39 nM to 50 nM, 8 point, 2-fold dilution of human gp130). The association and dissociation rates were calculated, and K_D values were determined (see table below).

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Antibody	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative K_D	R_{MAX}	χ^2 (RU ²)
4D4 hlgG4(S228P, L235E)	1.01E+06	2.78E-04	2.76E-10	1.00	88.8	1.52
4D4CVH2/4D4GVL3 hlgG4(S228P, L235E)	5.56E+05	1.64E-04	2.95E-10	1.07	75.6	0.72
4D4CVH2.2/4D4C/GVL1 hlgG4(S228P, L235E)	4.17E+05	2.08E-04	4.99E-10	1.81	77.3	0.35
4D4CVH2.2/4D4GVL3 hlgG4(S228P, L235E)	4.62E+05	1.54E-04	3.34E-10	1.21	75.3	0.41
4D4CVH2.2/GVL4 hlgG4(S228P, L235E)	4.79E+05	3.85E-04	8.05E-10	2.91	73.0	0.30
4D4CVH3/GVL3 hlgG4(S228P, L235E)	2.39E+05	1.54E-04	6.45E-10	2.33	71.2	0.24

15 The six humanised 4D4 variants show good binding to humanised gp130. Three of the humanised designs retained a K_D within two-fold of the chimeric antibody (4D4CVH2/4D4GVL3, 4D4CVH2.2/4D4C/GVL1 and 4D4CVH2.2/4D4GVL3).

Example 26: Thermal stability of humanised anti-gp130 antibodies20 **26.1 Materials and Methods**

4D4 and the humanised variants of Example 24 were evaluated by UNcle biostability analysis to determine melting and aggregation temperatures. Briefly, a test concentration of 0.5 mg/ml of the relevant antibody was mixed with SyproTM Orange stain, and heated incrementally from 25 to 95 °C at a rate of 0.3 °C/min. As the protein is heated and unfolds, the dye binds to exposed hydrophobic areas and starts to fluoresce. By monitoring the fluorescence, the temperature at which the protein unfolds was determined (n=3).

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In parallel, the measure of the scattering potential of the sample was recorded. As the proteins in the sample unfold and aggregate, the scatter of the wavelength of light used increases, and this can be used

to determine the aggregation temperature (T_{agg}) of the antibody. T_{onset} , T_m and T_{agg} were determined from the Static Light Scattering (SLS) and intrinsic fluorescence measurements throughout the run ($n=3$).

26.2 Results

- 5 The melting and aggregation temperatures (T_{agg}) of the antibodies are shown in the table below. All of the humanised variants had slightly higher melting temperatures and T_{agg} values compared to the mouse/human chimeric antibody.

Antibody	Melting temp (°C)	T_{onset} (°C)	T_{agg} (°C)
4D4 hlgG4(S228P, L235E)	59.0	55.1	61.3
4D4CVH2/4D4GVL3 hlgG4(S228P, L235E)	63.0	56.7	63.7
4D4CVH2.2/4D4C/GVL1 hlgG4(S228P, L235E)	62.9	56.1	62.7
4D4CVH2.2/4D4GVL3 hlgG4(S228P, L235E)	64.9	56.9	65.1
4D4CVH2.2/4D4GVL4 hlgG4(S228P, L235E)	63.8	57.0	63.8
4D4CVH3/4D4GVL3 hlgG4(S228P, L235E)	65.4	57.4	66.1

10 **Example 27: Inhibition of IL-6-mediated signalling by humanised anti-gp130 antibodies**

The ability of 4D4 and the humanised variants of Example 24 to inhibit gp130-mediated signalling was evaluated using the STAT3 reporter cell line described in Example 2.

Each of the 4D4 humanised variants displayed dose-dependent inhibition of hIL-6-induced STAT3

- 15 activation (Figure 22A). The IC_{50} values are shown below. The anti-IL-6R α antibody tocilizumab and the anti-IL-6 antibody ziltivekimab which are known antagonists of IL-6-mediated signalling were included as positive controls.

Sample	IC_{50} value (μ g/ml)
4D4 hlgG4(S228P, L235E)	0.44
4D4CVH2/4D4GVL3 hlgG4(S228P, L235E)	0.57
4D4CVH2.2/4D4C/GVL1 hlgG4(S228P, L235E)	0.63
4D4CVH2.2/4D4GVL3 hlgG4(S228P, L235E)	0.63
4D4CVH2.2/4D4GVL4 hlgG4(S228P, L235E)	1.34
4D4CVH3/4D4GVL3 hlgG4(S228P, L235E)	2.83
Tocilizumab	1.23
Ziltivekimab	0.33

The 4D4 humanised variants were found to inhibit IL-6-mediated signalling through gp130 with similar potency to the parental 4D4 antibody.

Each of the 4D4 humanised variants also displayed dose-dependent inhibition of hIL-11-induced STAT3 activation (Figure 22B).

Example 28: Sequence liability analysis and substitution of residues presenting high risk of post-translational modification

In silico analysis identified the following positions within HC-CDR2 and LC-CDR3 of anti-gp130 antibody

4D4 (and its humanised derivatives) as presenting high risk for potential post-translational modification:

D53-G54 (positions 54 and 55 numbered according to SEQ ID NO:1) of HC-CDR2: potential for isomerisation of D53;

N93-G94 of LC-CDR3: potential for deamidation of N93.

The inventors designed variant VH and VL sequences comprising substitution of D53, G54, N93 or G94 with every other possible amino acid. The variant sequences were analysed to identify the introduction of any new T-cell epitopes, other sequence liabilities or steric clashes. Substitutions having similar chemical properties to the original residue were preferred.

The following substitutions were selected for further characterisation:

D53G, D53E, D53L and D53Q;

G54A;

N93G, N93E, N93L and N93Q;

G94A;

DNA constructs encoding hIgG4(S228P, L235E) heavy and κ light chains comprising 4D4 VH and VL regions comprising these substitutions were transfected into Expi-CHO cells for transient expression, and subsequently purified for further characterisation.

Example 29: Binding of 4D4 comprising substitution at VH D53/G54 and/or VL N93/N94 to human gp130

Binding of antibodies provided in hIgG4(S228P, L235E) format comprising the parental 4D4 VL and 4D4 VH comprising the indicated amino acid substitution, or comprising the parental 4D4 VH and 4D4 VL comprising the indicated amino acid substitution to human gp130 was analysed by SCK analysis, as described in Example 4.

The results are shown in the table below. The antibodies comprising variant VH or VL regions displayed similar binding to human gp130 as parental antibody 4D4, having K_D values within 2-fold of 4D4.

Antibody (VH/VL)	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative K_D	R_{max} (RU)	Kinetics χ^2 (RU ²)
4D4/4D4	7.75E+05	2.73E-04	3.53E-10	1	93.2	1.23

4D4/4D4_N93G	7.46E+05	2.18E-04	2.92E-10	1.21	89.6	1.25
4D4/4D4_N93E	7.29E+05	6.57E-04	9.01E-10	0.39	85.9	0.48
4D4/4D4_N93Q	7.92E+05	3.37E-04	4.26E-10	0.83	90.4	0.95
4D4/4D4_N93L	8.23E+05	3.96E-04	4.81E-10	0.73	82.6	0.65
4D4/4D4_G94A	8.08E+05	5.15E-04	6.38E-10	0.55	90.2	1.03
4D4_D53G/4D4	8.69E+05	2.51E-04	2.88E-10	1.22	5.9	0.03
4D4_D53E/4D4	7.40E+05	3.10E-04	4.19E-10	0.84	90	1.22
4D4_D53L/4D4	7.20E+05	2.71E-04	3.76E-10	0.94	88.6	1.11
4D4_D53Q/4D4	7.62E+05	2.60E-04	3.41E-10	1.03	85.4	1.22
4D4_G54Q/4D4	7.24E+05	2.78E-04	3.84E-10	0.92	87.4	1.2

The inventors next investigated the affinity of binding to human gp130 (by SCK analysis by SPR (Biacore 8K), as described in Example 4) for antibodies comprising different combinations of mutated 4D4 VH and VL domains.

5

The K_D values for binding to human gp130 for the different antibodies are shown below:

Antibody (VH/VL)	K_D (M)
4D4_D53G/4D4_N93G	2.75E-10
4D4_D53E/4D4_N93G	3.45E-10
4D4_D53L/4D4_N93G	3.05E-10
4D4_D53Q/4D4_N93G	2.68E-10
4D4_G54A/4D4_N93G	3.14E-10
4D4_D53G/4D4_N93Q	4.07E-10
4D4_D53E/4D4_N93Q	4.44E-10
4D4_D53L/4D4_N93Q	4.06E-10
4D4_D53Q/4D4_N93Q	3.90E-10
4D4_G54A/4D4_N93Q	4.34E-10
4D4_D53G/4D4_N93L	4.69E-10
4D4_D53E/4D4_N93L	5.41E-10
4D4_D53L/4D4_N93L	4.67E-10
4D4_D53Q/4D4_N93L	4.35E-10
4D4_G54A/4D4_N93L	5.07E-10
4D4_D53G/4D4_G94A	6.22E-10
4D4_D53E/4D4_G94A	7.88E-10
4D4_D53L/4D4_G94A	6.56E-10
4D4_D53Q/4D4_G94A	6.09E-10
4D4_G54A/4D4_G94A	6.63E-10

The results indicate that the VL variants are more important drivers for determining the affinity of binding to gp130 than the VH variants. High expression levels were observed for all of the antibodies.

10

D53G was selected as the most promising VH substitution, as antibodies comprising 4D4_D53G VH displayed high-affinity binding to gp130. D53E and D53Q were also identified as particularly promising VH

substitutions. Of the VL substitutions, N93G was identified as the most promising, as antibodies comprising 4D4_N93G VL displayed high-affinity binding to gp130.

Example 30: Humanised 4D4 antibodies comprising substitution at VH D53 and/or VL N93

- 5 The inventors analysed humanised 4D4 VH sequences 4D4CVH2, 4D4CVH2.2 and 4D4CVH3 to determine whether introduction of D53G, D53E or D53Q into the VH introduced any new T-cell epitopes, other sequence liabilities or steric clashes. Similar analysis was performed for humanised 4D4 VL sequences 4D4C/GVL1, 4D4GVL3 and 4D4GVL4 comprising N93G or N93Q.
- 10 The preferred humanised 4D4 VH sequences selected for further characterisation were 4D4CVH2_D53G, 4D4CVH2_D53E, 4D4CVH2_D53Q, 4D4CVH2.2_D53G, 4D4CVH2.2_D53E and 4D4CVH2.2_D53Q. The preferred humanised 4D4 VL sequences selected for further characterisation were 4D4GVL3_N93G and 4D4GVL3_N93Q.
- 15 DNA constructs encoding hlgG4(S228P, L235E) heavy and κ light chains having humanised 4D4 VH and VL regions comprising these substitutions were transfected into Expi-CHO cells for transient expression.

Example 31: Binding of humanised 4D4 antibodies comprising VH D53G/E/Q and/or VL N93G/Q to human gp130

- 20 The inventors investigated the affinity of binding to human gp130 (by SCK analysis by SPR (Biacore 8K), as described in Example 4) for the antibodies of Example 30.

The results are shown in the table below.

Antibody (VH/VL)	ka (1/Ms)	kd (1/s)	KD (M)
4D4/4D4	8.41E+05	2.57E-04	3.06E-10
4D4CVH2/4D4GVL3	4.41E+05	1.27E-04	2.88E-10
4D4CVH2_D53G/4D4GVL3_N93Q	3.41E+05	1.48E-04	4.35E-10
4D4CVH2_D53Q/4D4GVL3_N93Q	3.25E+05	1.61E-04	4.96E-10
4D4CVH2_D53E/4D4GVL3_N93Q	3.72E+05	1.94E-04	5.21E-10
4D4CVH2_D53G/4D4GVL3_N93G	2.99E+05	9.95E-05	3.32E-10
4D4CVH2_D53Q/4D4GVL3_N93G	2.81E+05	9.18E-05	3.27E-10
4D4CVH2_D53E/4D4GVL3_N93G	3.03E+05	1.39E-04	4.59E-10
4D4CVH2.2/4D4GVL3	3.87E+05	1.24E-04	3.21E-10
4D4CVH2.2_D53G/4D4GVL3_N93Q	3.27E+05	1.39E-04	4.25E-10
4D4CVH2.2_D53Q/4D4GVL3_N93Q	2.99E+05	1.35E-04	4.52E-10
4D4CVH2.2_D53E/4D4GVL3_N93Q	3.31E+05	1.82E-04	5.50E-10
4D4CVH2.2_D53G/4D4GVL3_N93G	2.71E+05	9.50E-05	3.50E-10
4D4CVH2.2_D53Q/4D4GVL3_N93G	2.58E+05	9.19E-05	3.57E-10
4D4CVH2.2_D53E/4D4GVL3_N93G	2.95E+05	1.14E-04	3.88E-10

- 25 In further experiments, the affinity of binding to human gp130 was evaluated by MCK analysis by SPR (Biacore 8K), as described in Example 25. The results are shown below.

Antibody (VH/VL)	ka (1/Ms)	kd (1/s)	KD (M)	Relative KD	Rmax	Chi2 (RU2)
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4D4/4D4	9.22E+05	2.73E-04	2.96E-10		98.7	0.48
4D4CVH2/4D4GVL3	4.80E+05	1.62E-04	3.37E-10	1	86.3	0.43
4D4CVH2_D53E/4D4GVL3_N93G	3.48E+05	1.45E-04	4.16E-10	1.24	85.9	0.25
4D4CVH2_D53G/4D4GVL3_N93G	3.34E+05	1.12E-04	3.34E-10	0.99	76.7	0.34
4D4CVH2_D53Q/4D4GVL3_N93G	2.58E+05	1.26E-04	4.87E-10	1.44	76.5	0.18
4D4CVH2.2_D53E/4D4GVL3_N93Q	3.63E+05	2.21E-04	6.10E-10	1.81	86.3	0.26
4D4CVH2.2_D53G/4D4GVL3_N93Q	3.34E+05	1.79E-04	5.35E-10	1.59	77.7	0.27
4D4CVH2.2_D53Q/4D4GVL3_N93Q	3.61E+05	1.68E-04	4.65E-10	1.38	88.6	0.31
4D4CVH2.2/4D4GVL3	4.21E+05	1.52E-04	3.61E-10	1	84.7	0.31
4D4CVH2.2_D53E/4D4GVL3_N93G	3.13E+05	1.48E-04	4.71E-10	1.31	83.4	0.21
4D4CVH2.2_D53G/4D4GVL3_N93G	2.75E+05	1.13E-04	4.13E-10	1.15	86.3	0.28
4D4CVH2.2_D53Q/4D4GVL3_N93G	2.39E+05	1.23E-04	5.14E-10	1.42	76.6	0.17
4D4CVH2.2_D53E/4D4GVL3_N93Q	3.24E+05	2.09E-04	6.43E-10	1.78	85.3	0.26
4D4CVH2.2_D53G/4D4GVL3_N93Q	2.90E+05	1.73E-04	5.95E-10	1.65	76.3	0.22
4D4CVH2.2_D53Q/4D4GVL3_N93Q	2.91E+05	1.73E-04	5.93E-10	1.64	95.2	0.36

The humanised 4D4 antibodies comprising substitution to remove sequence liabilities at D53 and N93G were found to bind to human gp130 with similar or improved affinity as compared to 4D4.

5 Example 32: Inhibition of IL-6-mediated signalling by humanised 4D4 antibodies comprising VH D53G/E/Q and/or VL N93G/Q

The ability of the antibodies of Example 30 to inhibit IL-6-induced, gp130-mediated signalling was evaluated using the STAT3 reporter cell line described in Example 2. The results are shown in Figure 23, and the IC₅₀ values are shown below. The anti-IL-6R α antibody tocilizumab and the anti-IL-6 antibodies ziltivekimab and siltuximab, which are known antagonists of IL-6-mediated signalling, were included as positive controls.

Antibody (VH/VL)	IC ₅₀ value (μ g/ml)
4D4/4D4	0.87
4D4CVH2/4D4GVL3	0.87
4D4CVH2_D53G/4D4GVL3_N93Q	0.69
4D4CVH2_D53Q/4D4GVL3_N93Q	0.62
4D4CVH2_D53E/4D4GVL3_N93Q	1.53
4D4CVH2_D53G/4D4GVL3_N93G	0.54
4D4CVH2_D53Q/4D4GVL3_N93G	0.35
4D4CVH2_D53E/4D4GVL3_N93G	1.25
4D4CVH2.2/4D4GVL3	0.42
4D4CVH2.2_D53G/4D4GVL3_N93Q	0.77
4D4CVH2.2_D53Q/4D4GVL3_N93Q	0.7
4D4CVH2.2_D53E/4D4GVL3_N93Q	0.64
4D4CVH2.2_D53G/4D4GVL3_N93G	0.36
4D4CVH2.2_D53Q/4D4GVL3_N93G	0.4
4D4CVH2.2_D53E/4D4GVL3_N93G	0.77
Siltuximab	2.42
Ziltivekimab	0.21
Tocilizumab	0.93

Example 33: Thermal stability of humanised anti-gp130 antibodies comprising VH D53G/E/Q and/or VL N93G/Q

- 5 4D4 and the antibodies of Example 30 were evaluated by UNcle biostability analysis to determine melting and aggregation temperatures, as described in Example 26. The results are shown in the table below.

Antibody (VH/VL)	Ave Tm1 (°C)	Ave Tonset (°C)	Tagg (°C)
4D4/4D4	59.1	54.6	60.5
4D4CVH2/4D4GVL3	63.1	57	63.4
4D4CVH2_D53E/4D4GVL3_N93G	59.8	55.4	61.4
4D4CVH2_D53G/4D4GVL3_N93G	58.7	54.5	61
4D4CVH2_D53Q/4D4GVL3_N93G	59.4	55.2	60.7
4D4CVH2_D53E/4D4GVL3_N93Q	62.3	57.3	63.5
4D4CVH2_D53G/4D4GVL3_N93Q	60.9	56.6	62
4D4CVH2_D53Q/4D4GVL3_N93Q	61.3	56.6	61.8
4D4CVH2.2/4D4GVL3	64.8	56.7	64.6
4D4CVH2.2_D53E/4D4GVL3_N93G	62.4	56.3	62.1
4D4CVH2.2_D53G/4D4GVL3_N93G	61.2	56.1	61.3
4D4CVH2.2_D53Q/4D4GVL3_N93G	62.4	56.8	61.4
4D4CVH2.2_D53E/4D4GVL3_N93Q	64.5	57.6	64.1
4D4CVH2.2_D53G/4D4GVL3_N93Q	63.3	57.4	63.1
4D4CVH2.2_D53Q/4D4GVL3_N93Q	63.6	57.4	62.9

10 **Example 34: Analysis of the ability of humanised 4D4 antibodies comprising VH D53G/E/Q and/or VL N93G/Q to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM or LIF**

The ability of 4D4/4D4, 4D4CVH2/4D4GVL3, 4D4CVH2_D53E/4D4GVL3_N93G

4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2.2/4D4GVL3, 4D4CVH2.2_D53E/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G and

- 15 4D4CVH2.2_D53G/4D4GVL3_N93Q provided in hIgG4(S228P, L235E) format to inhibit signalling induced by IL-11, CT-1, CNTF, OSM or LIF through gp130 was evaluated using the STAT3 reporter cell line, as described in Example 2.

- 20 All cytokines were sourced from Peprotech (recombinant hIL-6 (Cat. No. 200-06, 100 ng/ml), recombinant hIL-11 (Cat. No. 200-11, 100 ng/l), recombinant hCT-1 (Cat. No. 300-32, 10 ng/ml), recombinant hCNTF (Cat. No. 450-13, 10 ng/ml), recombinant hOSM (Cat. No. 300-10T, 10 ng/ml), recombinant hLIF (Cat. No. 300-05, 10 ng/ml)). The STAT3 assay was 24 hours for hIL-6, hIL-11, hCT1 and hCNTF cytokines, and 48 hours for hOSM and hLIF cytokines. The anti-IL-6R α antibody tocilizumab and the anti-IL-6 antibodies ziltivekimab and siltuximab, which are known antagonists of IL-6-mediated signalling, were
- 25 included as controls. Antibodies known to inhibit by the relevant cytokines were also employed as controls. All test conditions were performed in duplicate.

Figures 24A and 24C show that all of 4D4/4D4, 4D4CVH2/4D4GVL3, 4D4CVH2_D53E/4D4GVL3_N93G, 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53G/4D4GVL3_N93Q, 4D4CVH2.2/4D4GVL3, 4D4CVH2.2_D53E/4D4GVL3_N93G, 4D4CVH2.2_D53Q/4D4GVL3_N93G and 4D4CVH2.2_D53G/4D4GVL3_N93Q inhibited hIL-11-mediated signalling through gp130 in a dose-dependent fashion.

Figure 24B shows that all of 4D4/4D4, 4D4CVH2_D53E/4D4GVL3_N93G, 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53Q/4D4GVL3_N93G inhibited hIL-6-mediated signalling through gp130 in a dose-dependent fashion.

Figures 24D, 24E, 24F and 24G show that 4D4/4D4, 4D4CVH2_D53E/4D4GVL3_N93G, 4D4CVH2_D53Q/4D4GVL3_N93G, 4D4CVH2.2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53Q/4D4GVL3_N93G did not inhibit signalling through gp130 induced by hCT1 (Figure 24D), hCNTF (Figure 24E), hOSM (Figure 24F) or hLIF (Figure 24G).

The IC₅₀ values for inhibition of gp130-mediated signalling induced by the different cytokines determined in these experiments are shown in the table below (NI = no inhibition).

Antibody (VH/VL)	STAT3 (IC ₅₀ values (µg/ml))					
	IL-6	IL-11	CT-1	CNTF	OSM	LIF
VH0/VL0	1.064	0.63	NI	NI	NI	NI
4D4CVH2_D53Q/4D4GVL3_N93G	0.626	0.646	NI	NI	NI	NI
4D4CVH2.2_D53Q/4D4GVL3_N93G	0.388	0.581	NI	NI	NI	NI
4D4CVH2_D53E/4D4GVL3_N93G	1.039	0.745	NI	NI	NI	NI
4D4CVH2.2_D53E/4D4GVL3_N93G	0.663	0.642	NI	NI	NI	NI

These data indicate that the humanised 4D4 antibodies comprising substitution at VH D53 and/or VL N93 retain the ability to selectively inhibit signalling mediated by gp130:IL-6Rα and gp130:IL-11Rα only.

Example 35: Freeze-thaw stability study of 4D4 designs

All variants were supplied in either PBS/arginine or PBS buffer at concentrations shown below. All samples were tested as received (T0) and subjected to 5 cycles of freeze-thaw: 250 µL of each sample was aliquoted into vials and frozen at -80°C for a minimum of 2 hours, and thawed at room temperature for a minimum of 1 hour.

Samples were analysed at T0 and after cycles 1, 3, and 5 by visual appearance and SE-HPLC.

Antibody (VH/VL)	Concentration (mg/ml)
VH0/VL0	5.2
4D4CVH2_D53G/4D4GVL3_N93Q	2.61

4D4CVH2_D53Q/4D4GVL3_N93G	6.9
4D4CVH2.2_D53G/4D4GVL3_N93Q	5.27
4D4CVH2.2_D53Q/4D4GVL3_N93G	6.4
4D4CVH2_D53E/4D4GVL3_N93G	5.3
4D4CVH2.2_D53E/4D4GVL3_N93G	5.8

Vials were gently swirled and viewed under an off- white light source (10W LED, 2000-3750 Lux) against both black and white backgrounds for clarity/opalescence, any change in colour, and for visible particles.

- 5 All test samples were clear, colourless with no visual particles for T0, cycle 1, cycle 3 and cycle 5. No changes in visual appearance were observed in any of the samples after 1, 3 and 5 freeze-thaw cycles.

Size exclusion chromatography was performed followed by HPLC using an Thermo Dionex Ultimate-3000 UHPLC system with a detection Wavelength of 280 nm.

10

The results of the SE-HPLC freeze-thaw stability study are summarised in the table below.

	Antibody (VH/VL)	T0	Cycle 1	Cycle 3	Cycle 5	Δ from T0
% Monomer	4D4/4D4	98.82	98.79	98.72	98.61	-0.21
	4D4CVH2_D53G/4D4GVL3_N93Q	99.92	99.31	97.95	96.55	-3.37
	4D4CVH2_D53Q/4D4GVL3_N93G	98.47	98.49	98.47	98.43	-0.04
	4D4CVH2.2_D53G/4D4GVL3_N93Q	99.63	98.86	97.33	95.99	-3.64
	4D4CVH2.2_D53Q/4D4GVL3_N93G	97.14	97.08	96.94	96.76	-0.38
	4D4CVH2_D53E/4D4GVL3_N93G	97.55	97.48	97.37	97.37	-0.18
	4D4CVH2.2_D53E/4D4GVL3_N93G	97.3	97.15	96.92	96.84	-0.46
% HMWS	4D4/4D4	1.18	1.21	1.28	1.39	0.21
	4D4CVH2_D53G/4D4GVL3_N93Q	0.08	0.69	2.05	3.45	3.37
	4D4CVH2_D53Q/4D4GVL3_N93G	1.53	1.51	1.53	1.57	0.04
	4D4CVH2.2_D53G/4D4GVL3_N93Q	0.09	0.85	2.3	3.73	3.64
	4D4CVH2.2_D53Q/4D4GVL3_N93G	2.74	2.8	2.94	3.08	0.34
	4D4CVH2_D53E/4D4GVL3_N93G	2.45	2.52	2.63	2.63	0.18
	4D4CVH2.2_D53E/4D4GVL3_N93G	2.31	2.42	2.57	2.62	0.31
% HMWS	4D4/4D4	0	0	0	0	0
	4D4CVH2_D53G/4D4GVL3_N93Q	0	0	0	0	0
	4D4CVH2_D53Q/4D4GVL3_N93G	0	0	0	0	0
	4D4CVH2.2_D53G/4D4GVL3_N93Q	0.28	0.29	0.38	0.28	0
	4D4CVH2.2_D53Q/4D4GVL3_N93G	0.12	0.12	0.12	0.16	0.04
	4D4CVH2_D53E/4D4GVL3_N93G	0	0	0	0	0
	4D4CVH2.2_D53E/4D4GVL3_N93G	0.39	0.43	0.52	0.54	0.14

After 5 cycles of freeze-thaw, 4D4/4D4, 4D4CVH2_D53Q/4D4GVL3_N93G,

- 15 4D4CVH2.2_D53Q/4D4GVL3_N93G, 4D4CVH2_D53E/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G retained high monomeric content, with only slight increases in % High Molecular Weight Species (HMWS). By contrast, 4D4CVH2_D53G/4D4GVL3_N93Q and 4D4CVH2.2_D53G/4D4GVL3_N93Q displayed a marked increase in % HMWS, with ~3.5% increase

- from T0 to cycle 5. Low Molecular Weight Species (LMWS) were only detected for 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53Q/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G. After 5 cycles of freeze-thaw, the % LMWS increased slightly for 4D4CVH2.2_D53G/4D4GVL3_N93Q, 4D4CVH2.2_D53Q/4D4GVL3_N93G and 4D4CVH2.2_D53E/4D4GVL3_N93G. Peak areas for all the samples remained constant, indicating that there was no loss of protein content from T0 to cycle 5. Changes in the % Monomer content are reflected in increase in the amount of HMWS.
- Overall, from T0 to Cycle 5 4D4CVH2_D53G/4D4GVL3_N93Q and 4D4CVH2.2_D53G/4D4GVL3_N93Q displayed the greatest susceptibility to freeze-thaw degradation, via aggregation, and 4D4CVH2_D53Q/4D4GVL3_N93G displayed the least degradation.

Claims:

1. An antigen-binding molecule, optionally isolated, which binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , and wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.
2. The antigen-binding molecule according to claim 1, wherein the antigen-binding inhibits signalling mediated by gp130:IL-6R α and gp130:IL-11R α .
3. The antigen-binding molecule according to claim 1 or claim 2, wherein the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α .
4. The antigen-binding molecule according to any one of claims 1 to 3, wherein the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:386.
5. The antigen-binding molecule according to any one of claims 1 to 4, wherein the antigen-binding molecule comprises:
 - (a)
 - (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:249
 - 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:286; or
 - (b)
 - (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:246
 - 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:281; or
 - (c)
 - (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:244
 - 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:284; or
- 5 (d)
- (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:245
 HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and
- 10 (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:281; or
- (e)
- 15 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:62
 HC-CDR2 having the amino acid sequence of SEQ ID NO:63
 HC-CDR3 having the amino acid sequence of SEQ ID NO:64; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
 20 LC-CDR1 having the amino acid sequence of SEQ ID NO:65
 LC-CDR2 having the amino acid sequence of SEQ ID NO:66
 LC-CDR3 having the amino acid sequence of SEQ ID NO:67; or
- (f)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 25 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
 30 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
- (g)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:18
 35 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:24
 LC-CDR2 having the amino acid sequence of SEQ ID NO:25
 40 LC-CDR3 having the amino acid sequence of SEQ ID NO:26; or
- (h)
- (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:32; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
 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
 (i)
 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:37
 HC-CDR2 having the amino acid sequence of SEQ ID NO:38
 HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:45
 LC-CDR2 having the amino acid sequence of SEQ ID NO:46
 LC-CDR3 having the amino acid sequence of SEQ ID NO:47; or
 (j)
 (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:52
 HC-CDR2 having the amino acid sequence of SEQ ID NO:53
 HC-CDR3 having the amino acid sequence of SEQ ID NO:54; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:24
 LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 LC-CDR3 having the amino acid sequence of SEQ ID NO:58.
6. The antigen-binding molecule according to any one of claims 1 to 5, wherein the antigen-binding molecule comprises:
 a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:221, 241, 219, 239, 220, 240, 74, 106, 78, 80, 83, 1, 17, 31, 36, 51, 86 or 87; and
 a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:271, 274, 75, 110, 88, 91, 95, 98, 100, 9, 23, 34, 44 or 57.
7. The antigen-binding molecule according to any one of claims 1 to 6, wherein the antigen-binding molecule 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 C, 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 C;
 wherein the sequences of columns A and B are selected from the same row of Table C.

8. The antigen-binding molecule according to any one of claims 1 to 7, wherein the antigen-binding molecule is a multispecific antigen-binding molecule, and wherein the antigen-binding molecule further comprises an antigen-binding domain which binds to an antigen other than gp130.
- 5 9. A chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to any one of claims 1 to 8.
- 10 10. A nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding an antigen-binding molecule according to any one of claims 1 to 8, or a CAR according to claim 9.
- 11 11. An expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to claim 9.
- 12 12. A cell comprising an antigen-binding molecule according to any one of claims 1 to 8, a CAR according to claim 9, a nucleic acid or a plurality of nucleic acids according to claim 10, or an expression vector or a plurality of expression vectors according to claim 11.
- 13 13. A method comprising culturing a cell according to claim 12 under conditions suitable for expression of an antigen-binding molecule or CAR by the cell.
- 14 14. A composition comprising an antigen-binding molecule according to any one of claims 1 to 8, a CAR according to claim 9, a nucleic acid or a plurality of nucleic acids according to claim 10, an expression vector or a plurality of expression vectors according to claim 11, or a cell according to claim 12, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.
- 15 15. An antigen-binding molecule according to any one of claims 1 to 8, a CAR according to claim 9, a nucleic acid or a plurality of nucleic acids according to claim 10, an expression vector or a plurality of expression vectors according to claim 11, a cell according to claim 12, or a composition according to claim 14, for use in a method of medical treatment or prophylaxis.
- 16 16. An antigen-binding molecule according to any one of claims 1 to 8, a CAR according to claim 9, a nucleic acid or a plurality of nucleic acids according to claim 10, an expression vector or a plurality of expression vectors according to claim 11, a cell according to claim 12, or a composition according to claim 14, for use in a method of treatment or prevention of: pathological inflammation, fibrosis, a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, a disease/condition in which signalling through a gp130-containing complex is pathologically-implicated, a disease/condition in which a cytokine that signals through a gp130-containing complex is pathologically-implicated, an autoimmune disease, metabolic syndrome, a neurodegenerative disease, a chronic inflammatory disease, arthritis, rheumatoid arthritis, juvenile arthritis, systemic juvenile idiopathic arthritis, lupus, systemic lupus erythematosus, pancreatitis, thyroiditis, periodontitis, rhinitis, allergic rhinitis, dermatitis, atopic dermatitis, psoriasis, Hermansky-Pudlak syndrome, Graves' disease, obesity, insulin resistance, diabetes, type 1

diabetes, type 2 diabetes, pregnancy-associated hyperglycemia, multiple sclerosis, giant cell arteritis, Takayasu arteritis, cardiovascular disease, atherosclerosis, atrial fibrillation, ventricular fibrillation, cardiac hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, cardiogenic shock, heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, ischemic heart disease, myocardial infarction, Marfan syndrome, systemic sclerosis, keloid, scleroderma, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, hippocampal atrophy, pulmonary disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, hepatitis, liver fibrosis, cirrhosis, hepatotoxicity, acetaminophen-induced hepatotoxicity, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, colitis, ulcerative colitis, endometriosis, stroke, ischemic stroke, nephropathy, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, chronic kidney disease, kidney fibrosis, Alport syndrome, adult-onset Still's disease, Castleman's disease, cytokine release syndrome, sepsis, septic shock, a retinal disorder, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, retinitis pigmentosa, dry eye syndrome, COVID-19, Peutz-Jeghers syndrome, a skeletal muscle disorder, muscular dystrophy, amyotrophy, cachexia, an endocrine disorder, polycystic ovary syndrome, a cancer, a hematologic malignancy, leukemia, plasmacytoma, Hodgkin's lymphoma, lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer, bone cancer, glioblastoma, breast cancer, stomach cancer, renal cancer, metastatic renal cell cancer, prostate cancer, skin cancer, melanoma, liver cancer, hepatocellular carcinoma, 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, age-related non-alcoholic fatty liver, age-related non-alcoholic steatohepatitis, age-related cardiovascular disease, age-related hypertension, age-related renal disease, age-related skin disease, an infectious disease, a viral disease, viral hepatitis, hepatitis B, HIV infection, influenza infection, malaria, tuberculosis, an allergic disease, transplant rejection and graft-versus-host disease.

17. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of claims 1 to 8 bound to gp130.

18. A method for detecting gp130 in a sample, comprising contacting a sample containing, or suspected to contain, gp130 with an antigen-binding molecule according to any one of claims 1 to 8, and detecting the formation of a complex of the antigen-binding molecule with gp130.

19. A method of selecting or stratifying a subject for treatment with a gp130-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with an antigen-binding molecule according to any one of claims 1 to 8, and detecting the formation of a complex of the antigen-binding molecule with gp130.

20. Use of an antigen-binding molecule according to any one of claims 1 to 8 as an *in vitro* or *in vivo* diagnostic or prognostic agent.

21. An antigen-binding molecule which binds to gp130 for use in a method of treatment or prevention of: pathological inflammation, fibrosis, a disease/condition characterised by inflammation, a disease/condition characterised by fibrosis, a disease/condition characterised by inflammation and fibrosis, a disease/condition in which signalling through a gp130-containing complex is pathologically-implicated, a disease/condition in which a cytokine that signals through a gp130-containing complex is pathologically-implicated, an autoimmune disease, metabolic syndrome, a neurodegenerative disease, a chronic inflammatory disease, arthritis, rheumatoid arthritis, juvenile arthritis, systemic juvenile idiopathic arthritis, lupus, systemic lupus erythematosus, pancreatitis, thyroiditis, periodontitis, rhinitis, allergic rhinitis, dermatitis, atopic dermatitis, psoriasis, Hermansky-Pudlak syndrome, Graves' disease, obesity, insulin resistance, diabetes, type 1 diabetes, type 2 diabetes, pregnancy-associated hyperglycemia, multiple sclerosis, giant cell arteritis, Takayasu arteritis, cardiovascular disease, atherosclerosis, atrial fibrillation, ventricular fibrillation, cardiac hypertrophy, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, cardiogenic shock, heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, ischemic heart disease, myocardial infarction, Marfan syndrome, systemic sclerosis, keloid, scleroderma, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, hippocampal atrophy, pulmonary disease, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, hepatitis, liver fibrosis, cirrhosis, hepatotoxicity, acetaminophen-induced hepatotoxicity, alcoholic liver disease, pancreatitis, steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, colitis, ulcerative colitis, endometriosis, stroke, ischemic stroke, nephropathy, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, chronic kidney disease, kidney fibrosis, Alport syndrome, adult-onset Still's disease, Castleman's disease, cytokine release syndrome, sepsis, septic shock, a retinal disorder, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, retinitis pigmentosa, dry eye syndrome, COVID-19, Peutz-Jeghers syndrome, a skeletal muscle disorder, muscular dystrophy, amyotrophy, cachexia, an endocrine disorder, polycystic ovary syndrome, a cancer, a hematologic malignancy, leukemia, plasmacytoma, Hodgkin's lymphoma, lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer, bone cancer, glioblastoma, breast cancer, stomach cancer, renal cancer, metastatic renal cell cancer, prostate cancer, skin cancer, melanoma, liver cancer, hepatocellular carcinoma, 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, age-related non-alcoholic fatty liver, age-related non-alcoholic steatohepatitis, age-related cardiovascular disease, age-related hypertension, age-related renal disease, age-related skin disease, an infectious disease, a viral disease, viral hepatitis, hepatitis B, HIV infection, influenza infection, malaria, tuberculosis, an allergic disease, transplant rejection and graft-versus-host disease, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.

22. Use of an antigen-binding molecule that binds to gp130 to inhibit IL-6-mediated signalling and/or IL-11-mediated signalling, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.
23. A method for inhibiting IL-6-mediated signalling and/or IL-11-mediated signalling, comprising contacting cells capable of IL-6-mediated signalling and/or IL-11-mediated signalling with an antigen-binding molecule that binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.
24. A method for inhibiting IL-6-mediated signalling and/or IL-11-mediated signalling in a subject, comprising administering to a subject an antigen-binding molecule that binds to gp130, wherein the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and/or gp130:IL-11R α , wherein the antigen-binding molecule does not inhibit signalling mediated by one or more of: gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and gp130:IL-12R β 2.
25. The antigen-binding molecule for use according to claim 21, the use according to claim 22 or the method according to claim 23 or claim 24, wherein the antigen-binding molecule, wherein the antigen-binding inhibits signalling mediated by gp130:IL-6R α and gp130:IL-11R α .
26. The antigen-binding for use according to claim 21 or claim 25, the use according to claim 22 or claim 25, or the method according to any one of claims 23 to 25, wherein the antigen-binding molecule does not inhibit signalling mediated by gp130:OSMR β , and does not inhibit signalling mediated by gp130:LIFR β , and does not inhibit signalling mediated by gp130:LIFR β :CNTFR α .
27. The antigen-binding for use according to any one of claims 21, 25 or 26, the use according to any one of claims 22, 25 or 26, or the method according to any one of claims 23 to 26, wherein the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:386.
28. The antigen-binding for use according to any one of claims 21 or 25 to 27, the use according to any one of claims 22, 25 to 27, or the method according to any one of claims 23 to 27, wherein the antigen-binding molecule comprises:
- (a)
- (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:249
- 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:286; or

(b)

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

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

HC-CDR2 having the amino acid sequence of SEQ ID NO:246

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

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

10 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:281; or

(c)

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

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

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

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

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

20 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:284; or

(d)

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

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

HC-CDR2 having the amino acid sequence of SEQ ID NO:245

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

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

30 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:281; or

(e)

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

35 HC-CDR1 having the amino acid sequence of SEQ ID NO:62

HC-CDR2 having the amino acid sequence of SEQ ID NO:63

HC-CDR3 having the amino acid sequence of SEQ ID NO:64; and

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

LC-CDR1 having the amino acid sequence of SEQ ID NO:65

LC-CDR2 having the amino acid sequence of SEQ ID NO:66

LC-CDR3 having the amino acid sequence of SEQ ID NO:67; or

(f)

40 (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
- 5 LC-CDR3 having the amino acid sequence of SEQ ID NO:12; or
- (g)
- (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
- 10 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:24
- LC-CDR2 having the amino acid sequence of SEQ ID NO:25
- LC-CDR3 having the amino acid sequence of SEQ ID NO:26; or
- 15 (h)
- (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:32; and
- 20 (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:24
- 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
- (i)
- 25 (i) a heavy chain variable (VH) region incorporating the following CDRs:
- HC-CDR1 having the amino acid sequence of SEQ ID NO:37
- HC-CDR2 having the amino acid sequence of SEQ ID NO:38
- HC-CDR3 having the amino acid sequence of SEQ ID NO:39; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- 30 LC-CDR1 having the amino acid sequence of SEQ ID NO:45
- LC-CDR2 having the amino acid sequence of SEQ ID NO:46
- LC-CDR3 having the amino acid sequence of SEQ ID NO:47; or
- (j)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
- 35 HC-CDR1 having the amino acid sequence of SEQ ID NO:52
- HC-CDR2 having the amino acid sequence of SEQ ID NO:53
- HC-CDR3 having the amino acid sequence of SEQ ID NO:54; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:24
- 40 LC-CDR2 having the amino acid sequence of SEQ ID NO:11
- LC-CDR3 having the amino acid sequence of SEQ ID NO:58.

29. The antigen-binding for use according to any one of claims 21 or 25 to 28, the use according to any one of claims 22, 25 to 28, or the method according to any one of claims 23 to 28, wherein the antigen-binding molecule comprises:
- a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:221, 241, 219, 239, 220, 240, 74, 106, 78, 80, 83, 1, 17, 31, 36, 51, 86 or 87; and
 - a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:271, 274, 75, 110, 88, 91, 95, 98, 100, 9, 23, 34, 44 or 57.
30. The antigen-binding for use according to any one of claims 21 or 25 to 29, the use according to any one of claims 22, 25 to 29, or the method according to any one of claims 23 to 29, wherein the antigen-binding molecule 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 C, 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 C;
- wherein the sequences of columns A and B are selected from the same row of Table C.
31. The antigen-binding for use according to any one of claims 21 or 25 to 30, the use according to any one of claims 22, 25 to 30, or the method according to any one of claims 23 to 30, wherein the antigen-binding molecule is a multispecific antigen-binding molecule, and wherein the antigen-binding molecule further comprises an antigen-binding domain which binds to an antigen other than gp130.