

This application claims priority from GB 2311050.5 filed 19 July 2023, 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.

5 The present disclosure also relates to methods of medical treatment and prophylaxis.

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.

10 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. 15 (2020) 71:263–276 and Fung *et al.*, Cytokine (2022) 149:155750).

Monoclonal antibodies that bind to gp130 and antagonise gp130-mediated signalling have been described previously. Monoclonal mouse anti-human gp130 antibody B-R3 is described *e.g.* in Garbers *et al.*, J Biol Chem. (2013) 288(6): 4346–4354. B-R3 is disclosed in Garbers *et al.* to bind to the cytokine 20 binding module (CBM) of gp130.

WO 2019/126071 A1 describes gp130-binding antibodies mAb16692, mAb16680, mAb16673, mAb16646, mAb16636 and mAb16618, which are disclosed to inhibit signalling mediated by OSM, LIF and CNTF. WO 2019/126071 A1 does not characterise the antibodies for their ability to inhibit signalling 25 mediated by other IL-6 family cytokines. None of the antibodies display binding to mouse gp130 – see Tables 9 and 10 of WO 2019/126071 A1. The antibodies are disclosed to bind to human gp130 with K_D values ranging from 1.66×10^{-7} M to 2.91×10^{-9} M, as determined by surface plasmon resonance analysis by Biacore.

30 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 IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling.

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In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:89.

In some embodiments, the antigen-binding molecule 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:3
- HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:10
- LC-CDR2 having the amino acid sequence of SEQ ID NO:11
- LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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:3
- HC-CDR3 having the amino acid sequence of SEQ ID NO:185; 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:192
- LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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:3
- HC-CDR3 having the amino acid sequence of SEQ ID NO:185; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:10
- LC-CDR2 having the amino acid sequence of SEQ ID NO:11
- LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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: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:192
- LC-CDR3 having the amino acid sequence of SEQ ID NO:12.

In some embodiments, the antigen-binding molecule comprises:

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C,

wherein the VH and VL sequences are selected from the same row of Table C.

In some embodiments, the antigen-binding molecule comprises:

10 (a)

(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:218; and

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

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

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

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

(b)

20 (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:204; and

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

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

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

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

(c)

(i) a heavy chain variable (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; and

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

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

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

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

(d)

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

40 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:195; and

- (ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:26
LC-CDR2 having the amino acid sequence of SEQ ID NO:27
LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- 5 (e)
- (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:214; and
- 10 (ii) a light chain variable (VL) region incorporating the following CDRs:
LC-CDR1 having the amino acid sequence of SEQ ID NO:26
LC-CDR2 having the amino acid sequence of SEQ ID NO:27
LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (f)
- 15 (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:215; and
- (ii) a light chain variable (VL) region incorporating the following CDRs:
- 20 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
LC-CDR2 having the amino acid sequence of SEQ ID NO:27
LC-CDR3 having the amino acid sequence of SEQ ID NO:28.

In some embodiments, the antigen-binding molecule comprises:

- 25 (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 89, 90, 80-88, 74-79 or 2 of Table C, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 89, 90, 80-88, 74-79 or 2 of Table C,
- wherein the VH and VL sequences are selected from the same row of Table C.

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

- 35 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.

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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.

5 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.

10 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.

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.

15 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.

20 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,

5 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,

10 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

15 disease, a viral disease, viral hepatitis, hepatitis B, HIV infection, influenza infection, malaria, tuberculosis, an allergic disease, transplant rejection and graft-versus-host disease.

The present disclosure also provides an *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to the present disclosure bound to gp130.

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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.

25 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.

30 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.

The present disclosure also provides an antigen-binding molecule which binds to gp130 and inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling for use in a method of treatment or prevention of:

35 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

40 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 contacts the region of gp130 shown in SEQ ID NO:89.

The present disclosure also provides the use of an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89 to inhibit IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling.

The present disclosure also provides a method for inhibiting IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling, comprising contacting cells capable of IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-

mediated signalling with an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89.

5 The present disclosure also provides a method for inhibiting IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling in a subject, comprising administering to a subject an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89.

In some embodiments, the antigen-binding molecule comprises:

10 (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:3

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

15 (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

(b)

20 (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:185; and

(ii) a light chain variable (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:192

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

(c)

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

30 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:185; 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

(d)

(i) a heavy chain variable (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: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:192

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

5

In some embodiments, the antigen-binding molecule comprises:

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C, and

10 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C,

wherein the VH and VL sequences are selected from the same row of Table C.

15 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:18

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

20 HC-CDR3 having the amino acid sequence of SEQ ID NO:218; and

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

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

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

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

25 (b)

(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:204; and

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

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

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

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

(c)

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:20; and

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

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

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

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

(d)

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

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

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

HC-CDR3 having the amino acid sequence of SEQ ID NO:195; and

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

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

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

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

(e)

(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

15 HC-CDR3 having the amino acid sequence of SEQ ID NO:214; and

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

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

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

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

20 (f)

(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:215; and

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

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

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

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

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

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 89, 90, 80-88, 74-79 or 2 of Table C, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 89, 90, 80-88, 74-79 or 2 of Table C,

35 wherein the VH and VL sequences 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
40 antigen other than gp130.

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.

- 5 The present disclosure is concerned with gp130-binding antigen-binding molecules that inhibit signalling mediated by cytokine receptor complexes comprising gp130. The antigen-binding molecules of the present disclosure are useful to inhibit signalling mediated by the IL-6 family cytokines.

- 10 In particular, the present disclosure provides gp130-binding antigen-binding molecules that bind to a region of gp130 providing for potent inhibition of all of IL-6-, IL-11-, OSM-, CNTF-, CT-1-, and LIF-mediated signalling. Such antigen-binding molecules may be referred to herein as 'PAN' inhibitors of gp130.

- 15 While the known anti-gp130 antibody B-R3 has previously been described as being a PAN inhibitor of gp130-mediated signalling, this antibody is demonstrated in the present disclosure not to inhibit LIF-mediated signalling in an assay in which A549 cells were stimulated *in vitro* for 15 min with 10 ng/ml recombinant human LIF (see Example 7, Figure 8A).

- 20 Gp130-binding antigen-binding molecules according to the present disclosure moreover display cross-reactive binding to both human gp130 and mouse gp130. By contrast, neither BR-3 (see Example 1, Figure 1B), nor the known anti-gp130 antibodies mAb16692, mAb16680, mAb16673, mAb16646, mAb16636 and mAb16618 (see Tables 9 and 10 of WO 2019/126071 A1) display binding to mouse gp130.

25 **gp130**

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

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

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

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

gp130 is a constituent polypeptide of all receptors in the IL-6 receptor family, providing for signal transduction. Two gp130 polypeptides associate with two IL-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.

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

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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:70, 71 or 72.

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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:70 or 74.

- 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:74.

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

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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:85.

- 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
 10 be triggered by binding of their cognate cytokine(s). That is, in some embodiments, gp130-mediated signalling through a polypeptide complex comprising (i) gp130 and (ii) another polypeptide of the IL-6 receptor family may be triggered by binding of a cytokine to the polypeptide complex formed by protein-protein interaction between (i) and (ii). In some embodiments, gp130-mediated signalling is triggered by binding of IL-6 to a polypeptide complex comprising gp130 and IL-6R α (*i.e.* a gp130:IL-6R α complex). In
 15 some embodiments, gp130-mediated signalling is triggered by binding of IL-11 to a polypeptide complex 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).
 20 In some embodiments, gp130-mediated signalling is triggered by binding of CNTF or CLC to 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 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
 25 gp130:IL-12R β 2 complex).

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
 30 molecule that binds to gp130.

An 'antigen-binding molecule' refers to a molecule that binds to a given target antigen. Antigen-binding molecules include antibodies (*i.e.* immunoglobulins (Igs)) and antigen-binding fragments thereof. As used herein, 'antibodies' include monoclonal antibodies, polyclonal antibodies, monospecific and multispecific
 35 (*e.g.*, bispecific, trispecific, *etc.*) antibodies, and antibody-derived antigen-binding molecules such as scFv, scFab, diabodies, triabodies, scFv-Fc, minibodies, single domain antibodies (*e.g.* VhH), *etc.* Antigen-binding fragments of antibodies include *e.g.* Fv, Fab, F(ab')₂ and F(ab') fragments. In some embodiments, an antigen-binding molecule may be an antibody or an antigen-binding fragment thereof.

40 Antigen-binding molecules according to the present disclosure also include antibody-derived molecules, *e.g.* molecules comprising an antigen-binding region/domain derived from an antibody. Antibody-derived

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

The antigen-binding molecule of the present disclosure comprises a moiety or moieties capable of binding to a target antigen(s). In some embodiments, the moiety capable of binding to a target antigen comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL) of an antibody capable of specific binding to the target antigen. In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an aptamer capable of binding to the target antigen, e.g. a nucleic acid aptamer (reviewed, for example, in Zhou and Rossi *Nat Rev Drug Discov.* 2017 16(3):181-202). In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an antigen-binding peptide/polypeptide, e.g. a peptide aptamer, thioredoxin, monobody, anticalin, Kunitz domain, avimer, knottin, fynomer, atrimer, DARPin, affibody, nanobody (*i.e.* a single-domain antibody (sdAb)), affilin, armadillo repeat protein (ArmRP), OBody or fibronectin – reviewed e.g. in Reverdatto *et al.*, *Curr Top Med Chem.* 2015; 15(12): 1082–1101, which is hereby incorporated by reference in its entirety (see also e.g. Boersma *et al.*, *J Biol Chem* (2011) 286:41273-85 and Emanuel *et al.*, *Mabs* (2011) 3:38-48).

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

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

An antigen-binding molecule may be, or may comprise, an antigen-binding polypeptide, or an antigen-binding polypeptide complex. An antigen-binding molecule may comprise more than one polypeptide

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

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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.

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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.

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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]-
25 [LC-CDR3]-[LC-FR4]-C term.

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

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

embodiments, the antigen-binding molecule comprises the VH region and the VL region of an antigen-binding molecule that binds to gp130.

In some embodiments, the antigen-binding molecule comprises the CDRs, FRs and/or the VH and/or VL regions of an antibody described herein (e.g. an antibody of Table C herein), or CDRs, FRs and/or VH and/or VL regions which are derived from those of an antibody described herein (e.g. an antibody of Table C herein). 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
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In some embodiments, the antigen-binding molecule comprises:

a VH region comprising HC-FR1 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1 are substituted with another amino acid), HC-FR2 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR2 are substituted with another amino acid), HC-FR3 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR3 are substituted with another amino acid) and HC-FR4 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid) as indicated in Column A of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table B, wherein the HC-FR1, HC-FR2, HC-FR3 and HC-FR4 sequences of Column A are selected from the same row of Table B.

By way of illustration, in some embodiments, the antigen-binding molecule comprises a VH region comprising HC-FR1 having the amino acid sequence of SEQ ID NO:5 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:5 are substituted with another amino acid), HC-FR2 having the amino acid sequence of SEQ ID NO:6 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:6 are substituted with another amino acid), HC-FR3 having the amino acid sequence of SEQ ID NO:7 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:7 are substituted with another amino acid) and 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 SEQ ID NO:8 are substituted with another amino acid). It will be appreciated that the HC-FR1, HC-FR2, HC-FR3 and HC-FR4 sequences of the preceding sentence are selected from Column A of the same row (row 1) of Table B.

In some embodiments, the antigen-binding molecule comprises:

a VH region comprising:
 HC-CDR1 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1 are substituted with another amino acid), HC-CDR2 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR2 are substituted with another amino acid) and HC-CDR3 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid) as indicated in Column A of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table A, wherein the HC-CDR1, HC-CDR2 and HC-CDR3 sequences of Column A are selected from the same row of Table A;
 and
 HC-FR1 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1 are substituted with another amino acid), HC-FR2 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR2 are substituted with another amino acid), HC-FR3 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR3 are substituted with another amino acid) and HC-FR4 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid) as indicated in Column A of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table B, wherein the HC-FR1, HC-FR2, HC-FR3 and HC-FR4 sequences of Column A are selected from the same row of Table B.

In some embodiments, the antigen-binding molecule comprises:

a VH region comprising:

HC-CDR1 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR1 are substituted with another amino acid), HC-CDR2 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR2 are substituted with another amino acid) and HC-CDR3 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-CDR3 are substituted with another amino acid) as indicated in Column A of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table A; and

HC-FR1 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR1 are substituted with another amino acid), HC-FR2 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR2 are substituted with another amino acid), HC-FR3 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR3 are substituted with another amino acid) and HC-FR4 (or a variant thereof in which 1 or 2 or 3 amino acids in HC-FR4 are substituted with another amino acid) as indicated in Column A of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table B;

wherein the HC-CDR1, HC-CDR2, HC-CDR3 sequences of Column A of Table A and the HC-FR1, HC-FR2, HC-FR3 and HC-FR4 sequences of Column B of Table B are selected from rows having the same number.

By way of illustration, in some embodiments, the antigen-binding molecule comprises a VH region comprising: HC-CDR1 having the amino acid sequence of SEQ ID NO:2 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:2 are substituted with another amino acid), HC-CDR2 having the amino acid sequence of SEQ ID NO:3 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:3 are substituted with another amino acid) and 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 SEQ ID NO:4 are substituted with another amino acid), HC-FR1 having the amino acid sequence of SEQ ID NO:5 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:5 are substituted with another amino acid), HC-FR2 having the amino acid sequence of SEQ ID NO:6 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:6 are substituted with another amino acid), HC-FR3 having the amino acid sequence of SEQ ID NO:7 (or a variant thereof in which 1 or 2 or 3 amino acids in SEQ ID NO:7 are substituted with another amino acid) and 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 SEQ ID NO:8 are substituted with another amino acid). It will be appreciated that the HC-CDR1, HC-CDR2 and HC-CDR3 sequences of the preceding sentence are selected from Column A of row 1 of Table A, and that the HC-FR1, HC-FR2, HC-FR3 and HC-FR4 sequences are selected from Column A of the row of Table B having the same number (row 1).

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In some embodiments, the antigen-binding molecule comprises a VH region comprising 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 a VH region sequence selected from Column A of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table C.

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In some embodiments, the antigen-binding molecule comprises:

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a VL region comprising LC-CDR1 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1 are substituted with another amino acid), LC-CDR2 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR2 are substituted with another amino acid) and LC-CDR3 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid) as indicated in Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table A, wherein the LC-CDR1, LC-CDR2 and LC-CDR3 sequences of Column B are selected from the same row of Table A.

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In some embodiments, the antigen-binding molecule comprises:

a VL region comprising LC-FR1 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1 are substituted with another amino acid), LC-FR2 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR2 are substituted with another amino acid), LC-FR3 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR3 are substituted with another amino acid) and LC-FR4 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid) as indicated in Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table B, wherein the LC-FR1, LC-FR2, LC-FR3 and LC-FR4 sequences of Column B are selected from the same row of Table B.

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In some embodiments, the antigen-binding molecule comprises:

a VL region comprising:

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

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which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid) as indicated in Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table A, wherein the LC-CDR1, LC-CDR2 and LC-CDR3 sequences of Column B are selected from the same row of Table A; and

LC-FR1 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1 are substituted with another amino acid), LC-FR2 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR2 are substituted with another amino acid), LC-FR3 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR3 are substituted with another amino acid) and LC-FR4 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid) as indicated in Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table B, wherein the LC-FR1, LC-FR2, LC-FR3 and LC-FR4 sequences of Column B are selected from the same row of Table B.

In some embodiments, the antigen-binding molecule comprises:

a VL region comprising:

LC-CDR1 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR1 are substituted with another amino acid), LC-CDR2 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR2 are substituted with another amino acid) and LC-CDR3 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-CDR3 are substituted with another amino acid) as indicated in Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table A; and

LC-FR1 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR1 are substituted with another amino acid), LC-FR2 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR2 are substituted with another amino acid), LC-FR3 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR3 are substituted with another amino acid) and LC-FR4 (or a variant thereof in which 1 or 2 or 3 amino acids in LC-FR4 are substituted with another amino acid) as indicated in Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table B;

wherein the LC-CDR1, LC-CDR2, LC-CDR3 sequences of Column B of Table A and the LC-FR1, LC-FR2, LC-FR3 and LC-FR4 sequences of Column B of Table B are selected from rows having the same number.

In some embodiments, the antigen-binding molecule comprises a VL region comprising 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 a VL region sequence selected from Column B of row 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, or 90 of Table C.

In some embodiments, the antigen-binding molecule comprises a VH region according to any one embodiment as described herein, and a VL region according to any one embodiment as described herein.

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

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

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

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

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

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

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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.

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

In some embodiments, substitution(s) may reduce polyreactivity of the antigen-binding molecule. As used herein, 'polyreactivity' refers to low-affinity interactions via general nonspecific chemistry to molecules other than the target antigen of the antigen-binding molecule. Polyreactivity of an antigen-binding molecule may also be referred to as 'stickiness' of an antigen-binding molecule. High polyreactivity/stickiness of an antigen-binding molecule may result in unacceptably poor PK, potency, bioavailability and/or immunogenicity.

In some embodiments, one or more amino acids are substituted with another amino acid to reduce/prevent polyreactivity of the antigen-binding molecule.

Polyreactivity in therapeutic antibodies is reviewed e.g. in Cunningham et al., MAbs, 2021, 13(1):1999195, which is hereby incorporated by reference in its entirety. The polyreactivity of an antigen-binding molecule may be assessed e.g. by ELISA assays using a range of structurally diverse coating antigens (e.g. E.coli LPS, cardiolipin, insulin, dsDNA, ssDNA, KLH) or by *in silico* methods (e.g. as reviewed in Harvey et al., Nature Communications, 2022, 13:7554, which is hereby incorporated by reference in its entirety).

In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:4, comprising substitution of I at position 8 of SEQ ID NO:4 with another amino acid.

In some embodiments, a VH region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:1, 94, 98, 174, 112 or 117, wherein the VH region comprises substitution of I at position 100 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 104 of SEQ ID NO:1) with another amino acid.

In some embodiments, a VH region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:64, 65, 130, 132, 176, 134, 136, 131, 133, 177, 135 or 137, wherein the VH region comprises substitution of I at position 100 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 104 of SEQ ID NO:64) with another amino acid.

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

In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:4, comprising substitution of V at position 7 of SEQ ID NO:4 with another amino acid.

In some embodiments, a VH region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:1, 94, 98, 174, 112 or 117, wherein the VH region comprises substitution of V at position 99 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 103 of SEQ ID NO:1) with another amino acid.

In some embodiments, a VH region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:64, 65, 130, 132, 176, 134, 136, 131, 133, 177, 135 or 137, wherein the VH region comprises substitution of V at position 99 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 103 of SEQ ID NO:64) with another amino acid.

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

In some embodiments, substitution(s) may prevent/reduce degradation of the antigen-binding molecule. Degradation of an antigen-binding molecule may occur during manufacturing, processing, storage, handling and/or administration. The degradation may be physical and/or chemical. Degradation processes, e.g. chemical degradation processes, include isomerisation, oxidation, fragmentation, deamination, hydrolysis, deglycosylation, racemization, disulphide bond breakage and formation, Maillard reaction, and β -elimination.

Oxidation is a common chemical modifications in monoclonal antibodies and may be induced by reactive oxygen species. Oxidation may occur at cysteine, methionine, tryptophan, tyrosine, lysine and other amino acid residues. Oxidation of amino acid residues may impact protein structure and/or function. In some embodiments, one or more amino acids are substituted with another amino acid to remove an oxidation site. In some embodiments, one or more amino acids susceptible to oxidation are substituted with another amino acid (e.g. an amino acid which is not susceptible to oxidation or is less susceptible to oxidation). In some embodiments, one or more amino acids identified as being oxidised, or identified as being susceptible to oxidation, are substituted with another amino acid (e.g. an amino acid which is not susceptible to oxidation or is less susceptible to oxidation).

Amino acid residues susceptible to oxidation may be identified e.g. by *in silico* methods (e.g. as reviewed in Vatsa S, Mabs, 2022, 14(1):2023938, which is hereby incorporated by reference in its entirety) or by forced oxidation assays (e.g. as reviewed in Nowak C et al, Mabs, 2017, 9(8):1217-1230, and Dyck YFK et al, Bioengineering (Basel), 2019, 6(3):62, which are hereby incorporated by reference in their entirety). Aspartic acid (Asp) isomerization is a spontaneous non-enzymatic post-translation modification causing a change in the structure of the protein backbone, which is commonly observed in therapeutic antibodies during manufacturing and storage. The Asps in Asp–Gly (DG), Asp–Ser (DS), and Asp–Thr (DT) motifs in

the structurally flexible regions, such as complementarity-determining regions (CDRs) in antibodies, are often found to have high rate of isomerization. In some embodiments, one or more amino acids susceptible to isomerisation are substituted with another amino acid (e.g. an amino acid which is not susceptible to isomerisation or is less susceptible to isomerisation). In some embodiments, one or more amino acids present in an amino acid motif susceptible to isomerisation (e.g. Asp–Gly (DG), Asp–Ser (DS), or Asp–Thr (DT)), are substituted with another amino acid (e.g. an amino acid which reduces the susceptibility of an amino acid in the motif to isomerisation).

The susceptibility of an antigen-binding molecule to isomerisation may be assessed in in vitro assays e.g. as described in Lu et al., MAbs, 2019, 11(1):45-57, which is hereby incorporated by reference in its entirety.

In some embodiments, a VL region according to the present disclosure comprises a LC-CDR2 according to SEQ ID NO:11, comprising substitution of D at position 1 of SEQ ID NO:11 with another amino acid. In some embodiments, a VL region according to the present disclosure comprises a LC-CDR2 according to SEQ ID NO:192, comprising substitution of D at position 1 of SEQ ID NO:192 with another amino acid.

In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 186, 187, 188, 189, 190, or 191 wherein the VL region comprises substitution of D at position 50 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 50 of SEQ ID NO:9) with another amino acid.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 245, 246, 247, 248, 249 or 250, wherein the polypeptide comprises substitution of D at position 50 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 50 of SEQ ID NO:66) with another amino acid.

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

In some embodiments, a VL region according to the present disclosure comprises a LC-CDR2 according to SEQ ID NO:11, comprising substitution of G at position 2 of SEQ ID NO:11 with another amino acid. In some embodiments, a VL region according to the present disclosure comprises a LC-CDR2 according to SEQ ID NO:149, comprising substitution of G at position 2 of SEQ ID NO:149 with another amino acid.

In some embodiments, a VL region according to the present disclosure comprises a LC-CDR2 according to SEQ ID NO:162, comprising substitution of G at position 2 of SEQ ID NO:162 with another amino acid.

5 In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 143, 144, 145, 146, 147, 148, 156, 157, 158, 159, 160 or 161, wherein the VL region comprises substitution of G at position 51 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 51 of SEQ ID NO:9) with another
10 amino acid.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 150, 151, 152, 153, 154, 155, 163,
15 164, 165, 166, 167 or 168, wherein the polypeptide comprises substitution of G at position 51 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 51 of SEQ ID NO:66) with another amino acid.

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

In some embodiments, a VL region according to the present disclosure comprises a LC-FR3 according to SEQ ID NO:15, comprising substitution of L at position 2 of SEQ ID NO:15 with another amino acid.
25

In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 143, 144, 145, 146, 147, 148, 156, 157, 158, 159, 160 or 161, wherein the VL region comprises substitution of L at position 54 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 54 of SEQ ID NO:9) with another
30 amino acid.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 150, 151, 152, 153, 154, 155, 163, 164, 165, 166, 167 or 168, wherein the polypeptide comprises substitution of L at position 54 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 54 of SEQ ID NO:66)
35 with another amino acid.
40

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

5 In some embodiments, a VL region according to the present disclosure comprises a LC-FR3 according to SEQ ID NO:108, comprising substitution of V at position 6 of SEQ ID NO:108 with another amino acid. In some embodiments, a VL region according to the present disclosure comprises a LC-FR3 according to SEQ ID NO:111, comprising substitution of V at position 6 of SEQ ID NO:111 with another amino acid.

10 In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 106, 109, 145, 146, 147, 148, 158, 159, 160 or 161, wherein the VL region comprises substitution of V at position 58 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 58 of SEQ ID NO:106) with another amino acid.

15 In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 139, 140, 152, 153, 154, 155, 165, 166, 167 or 168, wherein the polypeptide comprises substitution of V at position 58 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 58 of SEQ ID NO:139) with another amino acid.

20 In some embodiments in accordance with the preceding three paragraphs, V is substituted with G, A, E, N, C, I, D, L, M, F, P, S, T, W, Y, R, K, H or Q. In some embodiments, V is substituted with G. In some embodiments, a VL region according to the present disclosure comprises a LC-FR3 having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or greater amino acid sequence identity to SEQ ID NO:124, 129, 15, 104, 108 or 111, wherein the amino acid at the position corresponding to position 30 of SEQ ID NO:15 is D.

30 In some embodiments, a VL region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 147, 148, 143, 144, 145, 146, 160, 161, 156, 157, 158 or 159 (e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, or 109; e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:147, 148, 143, 144, 145 or 146; e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:160, 161, 156, 157, 158 or 159), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences

of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:9) is D.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%,
5 preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139, 140, 154, 155, 150, 151, 152, 153, 167, 168, 163, 164, 165 or 166 (e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:141, 142, 66, 138, 139 or 140; e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%,
10 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:154, 155, 150, 151, 152 or 153; e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:167, 168, 163, 164, 165 or 166), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of
15 Health, Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:66) is D.

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

In some embodiments, a VL region according to the present disclosure comprises at least 70%,
30 preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, 109, 147, 148, 143, 144, 145, 146, 160, 161, 156, 157, 158 or 159 (e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:121, 126, 9, 102, 106, or 109; e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
35 97%, 98% or greater amino acid sequence identity to SEQ ID NO:147, 148, 143, 144, 145 or 146; e.g. comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:160, 161, 156, 157, 158 or 159), wherein the amino acid at the position corresponding to position 82a (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health,
40 Bethesda, MD, 1991, which corresponds to position 82 of SEQ ID NO:9) is D, and wherein the amino acid sequence comprises one or more (e.g. one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16) amino

acid substitutions relative to the reference amino acid sequence, wherein the one or more amino acid substitutions are provided at the position(s) corresponding to the following positions of the reference sequence: 74, 75, 76, 77, 78, 79, 80, 81, 83, 84, 85, 86, 87, 88, 89, 90 (that is, the one or more amino acid substitutions are provided within the 8 positions immediately N-terminal to (in the context of the amino acid sequence of the VL region) position 82, and/or are provided within the 8 positions immediately C-terminal to position 82).

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

In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:20, comprising substitution of D at position 6 of SEQ ID NO:20 with another amino acid. In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:195, comprising substitution of D at position 6 of SEQ ID NO:195 with another amino acid. In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:204, comprising substitution of D at position 6 of SEQ ID NO:204 with another amino acid.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:17, 193, 194, 202 or 203, wherein the polypeptide comprises substitution of D at position 98 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 101 of SEQ ID NO:17) with another amino acid.

In some embodiments, a VH region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:67, 68, 251, 252, 253, or 254, wherein the VH region comprises substitution of D at position 98 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 101 of SEQ ID NO:67) with another amino acid.

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

10 In some embodiments, D is substituted with G or S. In some embodiments, D is substituted with G.

In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:20, comprising substitution of G at position 7 of SEQ ID NO:20 with another amino acid. In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:195, comprising substitution of G at position 7 of SEQ ID NO:195 with another amino acid. In some embodiments, a VH region according to the present disclosure comprises a HC-CDR3 according to SEQ ID NO:204, comprising substitution of G at position 7 of SEQ ID NO:204 with another amino acid.

In some embodiments, a polypeptide according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or greater amino acid sequence identity to SEQ ID NO:17, 193, 194, 202, 203, 211, 212, 213, 216 or 217 wherein the polypeptide comprises substitution of G at position 99 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 102 of SEQ ID NO:17) with another amino acid.

20 In some embodiments, a VH region according to the present disclosure comprises at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or greater amino acid sequence identity to SEQ ID NO:67, 68, 251, 252, 253, 254, 255, 256, 257, 258 or 259, wherein the VH region comprises substitution of G at position 99 (numbered according to Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991, which corresponds to position 102 of SEQ ID NO:67) with another amino acid.

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

35

The VH and VL region of an antigen-binding region of an antibody together constitute the Fv region. In some embodiments, the antigen-binding molecule according to the present disclosure comprises, or consists of, an Fv region that binds to gp130. In some embodiments, the VH and VL regions of the Fv are provided as single polypeptide joined by a linker sequence, *i.e.* a single chain Fv (scFv). In some embodiments, the VH and VL regions of the Fv are provided as separate polypeptides stabilised by the

introduction of one or more cysteine residues for the formation of an interchain disulfide bond, *i.e.* a disulfide stabilised Fv (dsFv).

5 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).

15 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.

20 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).

30 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.

35 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.

40

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

5 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

10 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:33 or 38. In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%,

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

In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least

20 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:42, 43, 46 or 47. In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%,

25 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:44 or 57.

In some embodiments, the antigen-binding molecule comprises a CH1 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%,

30 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:34 or 39. In some embodiments, the antigen-binding molecule comprises a CH1 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:51.

In some embodiments, the antigen-binding molecule comprises a hinge region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%,

35 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:35. In some embodiments, the antigen-binding molecule

40 comprises a hinge region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

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

5 In some embodiments, the antigen-binding molecule comprises a CH2 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:36 or 45. In some embodiments, the antigen-binding molecule comprises a CH2 region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
10 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:54 or 55.

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

20 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
25 light chain constant sequence is human immunoglobulin kappa constant (IGKC; Cκ). In some embodiments, the immunoglobulin light chain constant sequence is a human immunoglobulin lambda constant (IGLC; Cλ), e.g. IGLC1, IGLC2, IGLC3, IGLC6 or IGLC7.

In some embodiments, the antigen-binding molecule comprises an amino acid sequence having at least
30 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:58, 59, 60, 61, 62 or 63. In preferred embodiments, the antigen-binding molecule comprises an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,
35 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:58.

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

40 In some embodiments, the antigen-binding molecule is or comprises a fully human antibody/antibody fragment. A fully human antibody/antibody fragment may be encoded by human nucleic acid

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

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

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

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

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

Aspects of the present disclosure relate to multispecific antigen-binding molecules. By 'multispecific' it is meant that the antigen-binding molecule displays specific binding to more than one target. In some embodiments, the antigen-binding molecule is a bispecific antigen-binding molecule. In some embodiments, the antigen-binding molecule comprises at least two different antigen-binding domains (*i.e.* at least two antigen-binding domains, *e.g.* comprising non-identical VHs and VLs).

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

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

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

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

In some embodiments, the antigen other than gp130 in a multispecific antigen-binding molecule is an 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 CD3ε)-binding domain, through which the BiTE

recruits T cells. Binding of the BiTE to its target antigen and to the CD3 polypeptide expressed by the T cell results in activation of the T cell, and ultimately directs T cell effector activity against cells expressing the target antigen. Other kinds of immune cell engagers are well known in the art, and include natural killer cell engagers such as bispecific killer engagers (BiKEs), which recruit and activate NK cells.

5

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*; 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-(C α C β) Fab, scFv-HC-IgG, tandem Fab-IgG (orthogonal Fab), Fab-IgG(C α C β Fab), Fab-IgG(CR3), Fab-hinge-IgG(CR3); appended IgGs - LC fusions, e.g. IgG-scFv(LC), scFv(LC)-IgG, dAb-IgG; appended IgGs - HC and LC fusions, e.g. DVD-Ig, TVD-Ig, CODV-Ig, 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.

40 The present disclosure also provides Chimeric Antigen Receptors (CARs). CARs are recombinant receptors that provide both antigen-binding and T cell activating functions. CAR structure and engineering

is reviewed, for example, in Dotti *et al.*, Immunol Rev (2014) 257(1), hereby incorporated by reference in its entirety. CARs comprise an antigen-binding region linked to a cell membrane anchor region and a signalling region. An optional hinge region may provide separation between the antigen-binding region and cell membrane anchor region, and may act as a flexible linker.

5

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

- 10 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.

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

- 20 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
- 25 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.

- 30 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
- 35 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
- 40 (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.

5

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

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

Fc regions

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

25

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

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

40

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

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

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

20 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).

35 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
 5 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.

10 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
 15 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
 20 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
 25 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
 30 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
 35 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
 40 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 Diebold *et al.* Science (2014) 343(6176):1260-3.

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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.

10 In some embodiments, the Fc region comprises a CH2-CH3 region comprising an amino acid difference at one or more of the following positions, relative to the amino acid sequence of a CH2-CH3 region of a reference Fc region: 252, 254 or 256 (according to the EU numbering system). In some embodiments, the Fc region comprises a CH2-CH3 region comprising one or more of the following specified amino acid residues: Y252, T254 or E256 (according to the EU numbering system). In some embodiments, the Fc region comprises a CH2-CH3 region comprising Y252, T254 and E256. In some embodiments, the Fc
15 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).

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

25 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
30 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
35 embodiments, the Fc region comprises modification to reduce/prevent ADCP. In some embodiments, the Fc region comprises modification to reduce/prevent CDC. An antigen-binding molecule comprising an Fc region comprising modification to reduce/prevent an Fc-mediated function (*e.g.* ADCC, ADCP, CDC) induces a reduced level of the relevant effector function as compared to an antigen-binding molecule comprising the corresponding unmodified Fc region.

40 In some embodiments, the Fc region comprises modification to reduce/prevent binding to an Fc receptor. In some embodiments, the Fc region comprises modification to reduce/prevent binding to an Fcγ

- receptor. In some embodiments, the Fc region comprises modification to reduce/prevent binding to one or more of FcγRI, FcγRIIa, FcγRIIb, FcγRIIc, FcγRIIIa and FcγRIIIb. In some embodiments, the Fc region comprises modification to reduce/prevent binding to FcγRIIIa. In some embodiments, the Fc region comprises modification to reduce/prevent binding to FcγRIIa. In some embodiments, the Fc region
- 5 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.
- 10 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).
- 15 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.
- 20 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
- 25 is not able to bind to FcRn. In some embodiments, the Fc region is not able to bind to a complement protein. In some embodiments, the Fc region is not able to bind to C1q. In some embodiments, the Fc region is not glycosylated at the amino acid residue corresponding to N297.
- In some embodiments, the Fc region comprises modification corresponding to N297A or N297Q or N297G as described in Leabman *et al.*, *MAbs*. (2013) 5:896–903. In some embodiments, the Fc region comprises modification corresponding to L235E as described in Alegre *et al.*, *J Immunol.* (1992) 148:3461–3468. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A or F234A/L235A as described in Xu *et al.*, *Cell Immunol.* (2000) 200:16–26. In some embodiments, the Fc region comprises modification corresponding to P329A
- 35 or P329G as described in Schlothauer *et al.*, *Protein Engineering, Design and Selection* (2016), 29(10):457–466. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A/P329G as described in Lo *et al.* *J. Biol. Chem* (2017) 292(9):3900-3908. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions described in Rother *et al.*, *Nat Biotechnol.* (2007) 25:1256–1264. In some
- 40 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–
5 126. In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235E/G237A/A330S/P331S as described in US 2015/0044231 A1.

The combination of substitutions 'L234A/L235A' and corresponding substitutions (such as e.g. F234A/L235A in human IgG4) are known to disrupt binding of Fc to Fcγ receptors and inhibit ADCC, ADCP, and also to reduce C1q binding and thus CDC (Schlothauer *et al.*, Protein Engineering, Design
10 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
15 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
20 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).
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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.
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In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A/P329G.
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In some embodiments, the Fc region comprises modification corresponding to the combination of substitutions L234A/L235A/P329G/N297Q.

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

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

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

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

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

In some embodiments, the antigen-binding molecule does not comprise an Fc region. In some embodiments, the antigen-binding molecule consists essentially of an Fv moiety (e.g. is a scFv or a dsFv). In some embodiments, the antigen-binding molecule consists essentially of a Fab moiety (e.g. is a Fab, CrossFab, scFab, scCrossFab or F(ab')₂).

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

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

5 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

10 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

15 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.

20 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.

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

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

30 a CH3 region of an immunoglobulin (Ig).

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

35 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.

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

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

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

15 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
- 20 (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
- 25 (H) VH-CH1-CH2-CH3 + VL-CL-CH2-CH3
- (I) VH-CL-CH2-CH3 + VL-CH1-CH2-CH3

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

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

- 35 (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
- 40 (O) VL (anti-gp130)-CH1-CH2-CH3 + VH (anti-gp130)-CL
- (P) VL (anti-gp130)-CL-CH2-CH3 + VH (anti-gp130)-CH1

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

Wherein: 'VH(anti-gp130)' refers to the VH of an antigen-binding molecule capable of binding to gp130 as described herein; and 'VL(anti-gp130)' refers to the VL of an antigen-binding molecule capable of binding to gp130 as described herein.

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:183, 184, 112, 117, 179, 1, 180, 94, 181, 98, 182, or 174.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:216, 217, 202, 203, 211, 212, 213, 193, 194, or 17.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:190, 191, 121, 126, 186, 9, 187, 188, 189, 102, 106, 109, 147, 148, 143, 144, 145, 146, 160, 161, 156, 157, 158 or 159. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:190, 191, 121, 126, 186, 9, 187, 188, 189, 102, 106, or 109. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:147, 148, 143, 144, 145 or 146. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:160, 161, 156, 157, 158 or 159.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:230, 231, 25, 219, 220, or 221.

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:243, 244, 135, 137, 134, 136, 239, 65, 240, 131, 241, 133, 242, 177, 130, 132, 176 or 64.

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
5 SEQ ID NO:258, 259, 253, 254, 255, 256, 257, 251, 252, 67 or 68.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to
10 SEQ ID NO:249, 250, 141, 142, 245, 66, 246, 247, 248, 138, 139, 140, 154, 155, 150, 151, 152, 153, 167, 168, 163, 164, 165 or 166. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:249, 250, 141, 142, 245, 66, 246, 247, 248, 138, 139
15 or 140. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:154, 155, 150, 151, 152 or 153. In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid
20 sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:167, 168, 163, 164, 165 or 166.

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide which comprises or consists of an amino acid sequence having at least 70%, preferably one of 80%,
25 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to SEQ ID NO:263, 264, 69, 260, 261, or 262.

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
30 light chain CDRs, of a clone selected from B035-C03-A3, CSP-S-5H8, A3_3.2 VH / A3_3 VL, A3_3.2 VH / A3_4 VL, A3_3.2 VH / A3_5 VL, A3_4.2 VH / A3_3 VL, A3_4.2 VH / A3_4 VL, A3_4.2 VH / A3_5 VL, A3_6.2 VH / A3_3 VL, A3_6.2 VH / A3_4 VL, A3_6.2 VH / A3_5 VL, A3-derived VH CON / A3-derived VL CON, A3-Hum VH CON / A3-Hum VL CON, B035-C03-A3_D50X, A3_3.2 VH / A3_3_D50X VL, A3_3.2 VH / A3_4_D50X VL, A3_3.2 VH / A3_5_D50X VL, A3_4.2 VH / A3_3_D50X VL, A3_4.2 VH /
35 A3_4_D50X VL, A3_4.2 VH / A3_5_D50X VL, A3_6.2 VH / A3_3_D50X VL, A3_6.2 VH / A3_4_D50X VL, A3_6.2 VH / A3_5_D50X VL, A3-derived VH CON / A3-derived VL_D50X CON, A3-Hum VH CON / A3-Hum VL_D50X CON, B035-C03-A3_D50A, A3_3.2 VH / A3_3_D50A VL, A3_3.2 VH / A3_4_D50A VL, A3_3.2 VH / A3_5_D50A VL, A3_4.2 VH / A3_3_D50A VL, A3_4.2 VH / A3_4_D50A VL, A3_4.2 VH / A3_5_D50A VL, A3_6.2 VH / A3_3_D50A VL, A3_6.2 VH / A3_4_D50A VL, A3_6.2 VH / A3_5_D50A VL,
40 A3-derived VH CON / A3-derived VL_D50A CON and A3-Hum VH CON / A3-Hum VL_D50A CON, B035-C03-A3_I100T VH / B035-C03-A3_G51A VL, B035-C03-A3_I100T VH / B035-C03-A3 VL, B035-C03-A3

- VH / B035-C03-A3_G51A VL, A3_3.2_I100T VH / A3_3_G51A VL, A3_3.2_I100T VH / A3_4_G51A VL, A3_3.2_I100T VH / A3_5_G51A VL, A3_3.2_I100T VH / A3_3 VL, A3_3.2_I100T VH / A3_4 VL, A3_3.2_I100T VH / A3_5 VL, A3_3.2 VH / A3_3_G51A VL, A3_3.2 VH / A3_4_G51A VL, A3_3.2 VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3_G51A VL, A3_4.2_I100T VH / A3_4_G51A VL, A3_4.2_I100T VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3 VL, A3_4.2_I100T VH / A3_4 VL, A3_4.2_I100T VH / A3_5 VL, A3_4.2 VH / A3_3_G51A VL, A3_4.2 VH / A3_4_G51A VL, A3_4.2 VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3_G51A VL, A3_6.2_I100T VH / A3_4_G51A VL, A3_6.2_I100T VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3 VL, A3_6.2_I100T VH / A3_4 VL, A3_6.2_I100T VH / A3_5 VL, A3_6.2 VH / A3_3_G51A VL, A3_6.2 VH / A3_4_G51A VL, A3_6.2 VH / A3_5_G51A VL, A3-
- 10 derived_I100T VH CON / A3-derived_G51A VL CON, A3-derived_I100T VH CON / A3-derived VL CON, A3-derived VH CON / A3-derived_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum VL CON, A3-Hum VH CON / A3-Hum_G51A VL CON, 5H8CVH4 VH / 5H8CVL3 VL, 5H8CVH4 VH / 5H8CVL4 VL, 5H8CVH4 VH / 5H8GVL3 VL, 5H8GVH4 VH / 5H8CVL3 VL, 5H8GVH4 VH / 5H8CVL4 VL, 5H8GVH4 VH / 5H8GVL3 VL, 5H8-derived VH CON / 5H8-derived VL
- 15 CON, 5H8-Hum VH CON / 5H8-Hum VL CON, CSP-S-5H8_D98G VH / CSP-S-5H8 VL, 5H8CVH4_D98G VH / 5H8CVL3 VL, 5H8CVH4_D98G VH / 5H8CVL4 VL, 5H8CVH4_D98G VH / 5H8GVL3 VL, 5H8GVH4_D98G VH / 5H8CVL3 VL, 5H8GVH4_D98G VH / 5H8CVL4 VL, 5H8GVH4_D98G VH / 5H8GVL3 VL, 5H8-derived_D98G VH CON / 5H8-derived VL CON or, 5H8-Hum_D98G VH CON / 5H8-Hum VL CON as shown in Table A herein. That is, in some embodiments, the antigen-binding molecule
- 20 comprises a polypeptide or polypeptides comprising: (i) a VH region comprising HC-CDR1, HC-CDR2 and HC-CDR3 as indicated in column A of Table A, and (ii) a VL region comprising LC-CDR1, LC-CDR2 and LC-CDR3 as indicated in column B of Table A, wherein the sequences of columns A and B are selected from the same row of Table A.
- 25 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 a clone selected from B035-C03-A3, CSP-S-5H8, A3_3.2 VH / A3_3 VL, A3_3.2 VH / A3_4 VL, A3_3.2 VH / A3_5 VL, A3_4.2 VH / A3_3 VL, A3_4.2 VH / A3_4 VL, A3_4.2 VH / A3_5 VL, A3_6.2 VH / A3_3 VL, A3_6.2 VH / A3_4 VL, A3_6.2 VH / A3_5 VL, A3-derived VH CON / A3-derived VL
- 30 CON, A3-Hum VH CON / A3-Hum VL CON, B035-C03-A3_D50X, A3_3.2 VH / A3_3_D50X VL, A3_3.2 VH / A3_4_D50X VL, A3_3.2 VH / A3_5_D50X VL, A3_4.2 VH / A3_3_D50X VL, A3_4.2 VH / A3_4_D50X VL, A3_4.2 VH / A3_5_D50X VL, A3_6.2 VH / A3_3_D50X VL, A3_6.2 VH / A3_4_D50X VL, A3_6.2 VH / A3_5_D50X VL, A3-derived VH CON / A3-derived VL_D50X CON, A3-Hum VH CON / A3-Hum VL_D50X CON, B035-C03-A3_D50A, A3_3.2 VH / A3_3_D50A VL, A3_3.2 VH / A3_4_D50A VL, A3_3.2 VH / A3_5_D50A VL, A3_4.2 VH / A3_3_D50A VL, A3_4.2 VH / A3_4_D50A VL, A3_4.2 VH / A3_5_D50A VL, A3_6.2 VH / A3_3_D50A VL, A3_6.2 VH / A3_4_D50A VL, A3_6.2 VH / A3_5_D50A VL, A3-derived VH CON / A3-derived VL_D50A CON and A3-Hum VH CON / A3-Hum VL_D50A CON, B035-C03-A3_I100T VH / B035-C03-A3_G51A VL, B035-C03-A3_I100T VH / B035-C03-A3 VL, B035-C03-A3
- 35 VH / B035-C03-A3_G51A VL, A3_3.2_I100T VH / A3_3_G51A VL, A3_3.2_I100T VH / A3_4_G51A VL, A3_3.2_I100T VH / A3_5_G51A VL, A3_3.2_I100T VH / A3_3 VL, A3_3.2_I100T VH / A3_4 VL, A3_3.2_I100T VH / A3_5 VL, A3_3.2 VH / A3_3_G51A VL, A3_3.2 VH / A3_4_G51A VL, A3_3.2 VH /
- 40

A3_5_G51A VL, A3_4.2_I100T VH / A3_3_G51A VL, A3_4.2_I100T VH / A3_4_G51A VL, A3_4.2_I100T VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3 VL, A3_4.2_I100T VH / A3_4 VL, A3_4.2_I100T VH / A3_5 VL, A3_4.2 VH / A3_3_G51A VL, A3_4.2 VH / A3_4_G51A VL, A3_4.2 VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3_G51A VL, A3_6.2_I100T VH / A3_4_G51A VL, A3_6.2_I100T VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3 VL, A3_6.2_I100T VH / A3_4 VL, A3_6.2_I100T VH / A3_5 VL, A3_6.2 VH / A3_3_G51A VL, A3_6.2 VH / A3_4_G51A VL, A3_6.2 VH / A3_5_G51A VL, A3-derived_I100T VH CON / A3-derived_G51A VL CON, A3-derived_I100T VH CON / A3-derived VL CON, A3-derived VH CON / A3-derived_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum VL CON, A3-Hum VH CON / A3-Hum_G51A VL CON, 5H8CVH4 VH / 5H8CVL3 VL, 5H8CVH4 VH / 5H8CVL4 VL, 5H8CVH4 VH / 5H8GVL3 VL, 5H8GVH4 VH / 5H8CVL3 VL, 5H8GVH4 VH / 5H8CVL4 VL, 5H8GVH4 VH / 5H8GVL3 VL, 5H8-derived VH CON / 5H8-derived VL CON, 5H8-Hum VH CON / 5H8-Hum VL CON, CSP-S-5H8_D98G VH / CSP-S-5H8 VL, 5H8CVH4_D98G VH / 5H8CVL3 VL, 5H8CVH4_D98G VH / 5H8CVL4 VL, 5H8CVH4_D98G VH / 5H8GVL3 VL, 5H8GVH4_D98G VH / 5H8CVL3 VL, 5H8GVH4_D98G VH / 5H8CVL4 VL, 5H8GVH4_D98G VH / 5H8GVL3 VL, 5H8GVH4_D98G VH / 5H8GVL4 VL, 5H8GVH4_D98G VH / 5H8GVL3 VL, 5H8-derived_D98G VH CON / 5H8-derived VL CON or, 5H8-Hum_D98G VH CON / 5H8-Hum VL CON as shown in Table B herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) a VH region comprising HC-FR1, HC-FR2, HC-FR3 and HC-FR4 as indicated in column A of Table B, and (ii) a VL region comprising LC-FR1, LC-FR2, LC-FR3, and LC-FR4 as indicated in column B of Table B, wherein the sequences of columns A and B are selected from the same row of Table B.

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

In some embodiments, the antigen-binding molecule of the present disclosure comprises a polypeptide or polypeptides comprising a VH region and a VL region of a clone selected from B035-C03-A3, CSP-S-5H8, A3_3.2 VH / A3_3 VL, A3_3.2 VH / A3_4 VL, A3_3.2 VH / A3_5 VL, A3_4.2 VH / A3_3 VL, A3_4.2 VH / A3_4 VL, A3_4.2 VH / A3_5 VL, A3_6.2 VH / A3_3 VL, A3_6.2 VH / A3_4 VL, A3_6.2 VH / A3_5 VL, A3-derived VH CON / A3-derived VL CON, A3-Hum VH CON / A3-Hum VL CON, B035-C03-A3_D50X, A3_3.2 VH / A3_3_D50X VL, A3_3.2 VH / A3_4_D50X VL, A3_3.2 VH / A3_5_D50X VL, A3_4.2 VH / A3_3_D50X VL, A3_4.2 VH / A3_4_D50X VL, A3_4.2 VH / A3_5_D50X VL, A3_6.2 VH / A3_3_D50X VL, A3_6.2 VH / A3_4_D50X VL, A3_6.2 VH / A3_5_D50X VL, A3-derived VH CON / A3-derived VL_D50X CON, A3-Hum VH CON / A3-Hum VL_D50X CON, B035-C03-A3_D50A, A3_3.2 VH / A3_3_D50A VL, A3_3.2 VH / A3_4_D50A VL, A3_3.2 VH / A3_5_D50A VL, A3_4.2 VH / A3_3_D50A VL, A3_4.2 VH / A3_4_D50A VL, A3_4.2 VH / A3_5_D50A VL, A3_6.2 VH / A3_3_D50A VL, A3_6.2 VH / A3_4_D50A VL, A3_6.2 VH / A3_5_D50A VL, A3-derived VH CON / A3-derived VL_D50A CON and A3-Hum VH CON /

- A3-Hum VL_D50A CON, B035-C03-A3_I100T VH / B035-C03-A3_G51A VL, B035-C03-A3_I100T VH / B035-C03-A3 VL, B035-C03-A3 VH / B035-C03-A3_G51A VL, A3_3.2_I100T VH / A3_3_G51A VL, A3_3.2_I100T VH / A3_4_G51A VL, A3_3.2_I100T VH / A3_5_G51A VL, A3_3.2_I100T VH / A3_3 VL, A3_3.2_I100T VH / A3_4 VL, A3_3.2_I100T VH / A3_5 VL, A3_3.2 VH / A3_3_G51A VL, A3_3.2 VH / A3_4_G51A VL, A3_3.2 VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3_G51A VL, A3_4.2_I100T VH / A3_4_G51A VL, A3_4.2_I100T VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3 VL, A3_4.2_I100T VH / A3_4 VL, A3_4.2_I100T VH / A3_5 VL, A3_4.2 VH / A3_3_G51A VL, A3_4.2 VH / A3_4_G51A VL, A3_4.2 VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3_G51A VL, A3_6.2_I100T VH / A3_4_G51A VL, A3_6.2_I100T VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3 VL, A3_6.2_I100T VH / A3_4 VL, A3_6.2_I100T VH / A3_5 VL, A3_6.2 VH / A3_3_G51A VL, A3_6.2 VH / A3_4_G51A VL, A3_6.2 VH / A3_5_G51A VL, A3-derived_I100T VH CON / A3-derived_G51A VL CON, A3-derived_I100T VH CON / A3-derived VL CON, A3-derived VH CON / A3-derived_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum VL CON, A3-Hum VH CON / A3-Hum_G51A VL CON, 5H8CVH4 VH / 5H8CVL3 VL, 5H8CVH4 VH / 5H8CVL4 VL, 5H8CVH4 VH / 5H8GVL3 VL, 5H8GVH4 VH / 5H8CVL3 VL, 5H8GVH4 VH / 5H8CVL4 VL, 5H8GVH4 VH / 5H8GVL3 VL, 5H8-derived VH CON / 5H8-derived VL CON, 5H8-Hum VH CON / 5H8-Hum VL CON, CSP-S-5H8_D98G VH / CSP-S-5H8 VL, 5H8CVH4_D98G VH / 5H8CVL3 VL, 5H8CVH4_D98G VH / 5H8CVL4 VL, 5H8CVH4_D98G VH / 5H8GVL3 VL, 5H8GVH4_D98G VH / 5H8CVL3 VL, 5H8GVH4_D98G VH / 5H8CVL4 VL, 5H8GVH4_D98G VH / 5H8GVL3 VL, 5H8-derived_D98G VH CON / 5H8-derived VL CON or, 5H8-Hum_D98G VH CON / 5H8-Hum VL CON as shown in Table C herein. That is, in some embodiments, the antigen-binding molecule comprises a polypeptide or polypeptides comprising: (i) an amino acid sequence indicated in column A of Table C, and (ii) an amino acid sequence indicated in column B of Table C, wherein the sequences of columns A and B are selected from the same row of Table C.
- In some embodiments, the antigen-binding molecule of the present disclosure comprises: (i) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column A of Table D, and (ii) a polypeptide comprising or consisting of an amino acid sequence having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to an amino acid sequence indicated in column B of Table D, wherein the sequences of columns A and B are selected from the same row of Table D.

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

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, rhesus macaque gp130, mouse gp130 and/or rat gp130);
- binds to gp130-expressing cells;
- inhibits signalling mediated by a receptor comprising gp130;
- inhibits signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and/or gp130:IL-12R β 2;
- 10 inhibits signalling mediated by a cytokine that binds to a receptor comprising gp130;
- inhibits IL-6-, IL-11-, OSM-, LIF-, CNTF-, CT-1-, CLC-, IL-27- and/or IL-35-mediated signalling;
- reduces inflammation and/or fibrosis;
- reduces the pathology of a disease/condition characterised by inflammation and/or fibrosis;
- and/or
- 15 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 recited in the preceding paragraph using suitable assays. For example, the assays may be e.g. *in vitro*

20 assays, optionally cell-based assays or cell-free assays. In some embodiments, the assays may be e.g. *in vivo* assays, i.e. performed in non-human animals. In some embodiments, the assays may be e.g. *ex vivo* assays, i.e. performed using cells/tissue/an organ obtained from a subject.

Where assays are cell-based assays, they may comprise treating cells with a given antigen-binding molecule in order to determine whether the antigen-binding molecule displays one or more of the recited properties. Assays may employ species labelled with detectable entities in order to facilitate their detection. Assays may comprise evaluating the recited properties following treatment of cells separately with a range of quantities/concentrations of a given antigen-binding molecule (e.g. a dilution series). It will be appreciated that the cells preferably express the target antigen for the antigen-binding molecule (i.e.

30 gp130).

Analysis of the results of such assays may comprise determining the concentration at which 50% of the maximal level of the relevant activity is attained. The concentration of a given agent at which 50% of the maximal level of the relevant activity is attained may be referred to as the 'half-maximal effective

35 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.

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 macaque gp130. In some embodiments, the antigen-binding molecule binds to canine gp130.

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

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

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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.

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

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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

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(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.

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

In some embodiments, the antigen-binding molecule described herein binds to gp130 with an affinity in the micromolar range, i.e. $K_D = 9.9 \times 10^{-4}$ 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
10 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.
15 $K_D = 9.9 \times 10^{-10}$ 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,
20 ≤ 40 nM, ≤ 30 nM, ≤ 20 nM, ≤ 15 nM, ≤ 12.5 nM, ≤ 10 nM, ≤ 9 nM, ≤ 8 nM, ≤ 7 nM, ≤ 6 nM, ≤ 5 nM, ≤ 4 nM ≤ 3 nM, ≤ 2 nM, ≤ 1 nM, ≤ 500 pM, ≤ 400 pM, ≤ 300 pM, ≤ 200 pM, ≤ 100 pM, ≤ 50 pM, ≤ 40 pM, ≤ 30 pM, ≤ 20 pM, ≤ 10 pM or ≤ 1 pM (e.g. as determined by analysis surface plasmon resonance analysis, e.g. performed as described in Example 2 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,
25 ≤ 20 nM, ≤ 15 nM, ≤ 12.5 nM, ≤ 10 nM, ≤ 9 nM, ≤ 8 nM, ≤ 7 nM, ≤ 6 nM, ≤ 5 nM, ≤ 4 nM ≤ 3 nM, ≤ 2 nM, ≤ 1 nM, ≤ 500 pM, ≤ 400 pM, ≤ 300 pM, ≤ 200 pM, ≤ 100 pM, ≤ 50 pM, ≤ 40 pM, ≤ 30 pM, ≤ 20 pM, ≤ 10 pM or ≤ 1 pM (e.g. as determined by analysis surface plasmon resonance analysis, e.g. performed as described in Example 2 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,
30 ≤ 500 pM, or ≤ 400 pM.

In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of ≤ 200 nM, preferably one of ≤ 190 nM, ≤ 180 nM, ≤ 170 nM, ≤ 160 nM, ≤ 150 nM, ≤ 140 nM, ≤ 130 nM, ≤ 120 nM, ≤ 110 nM, ≤ 100 nM, ≤ 95 nM, ≤ 90 nM, ≤ 85 nM, ≤ 80 nM, ≤ 75 nM, ≤ 60 nM, ≤ 55 nM, ≤ 50 nM,
35 ≤ 45 nM, ≤ 40 nM, ≤ 35 nM, ≤ 30 nM, ≤ 25 nM, ≤ 20 nM, ≤ 15 nM, ≤ 10 nM, ≤ 9 nM, ≤ 8 nM, ≤ 7 nM, ≤ 6 nM, ≤ 5 nM, ≤ 4 nM, ≤ 3 nM, ≤ 2 nM or ≤ 1 nM (e.g. as determined by analysis surface plasmon resonance analysis, e.g. performed as described in Example 2 herein). In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of ≤ 166 nM. In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with a K_D of ≤ 2.91 nM.

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In some embodiments, the antigen-binding molecule described herein binds to human gp130 isoform 1 with an EC₅₀ of 10 µM or less, preferably one of ≤5 µM, ≤2 µM, ≤1 µM, ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM, ≤3 nM, ≤2 nM, ≤1 nM, ≤500 pM, ≤400 pM, ≤300 pM, ≤200 pM, ≤100 pM, ≤50 pM, ≤40 pM, ≤30 pM, ≤20 pM, ≤10 pM or ≤1 pM.

The antigen-binding molecules of the present disclosure may bind to a particular region of interest of gp130. Antigen-binding molecules according to the present disclosure may bind to linear epitope of gp130, consisting of a contiguous sequence of amino acids (*i.e.* an amino acid primary sequence). In some embodiments, an antigen-binding molecules may bind to a conformational epitope of gp130, consisting of a discontinuous sequence of amino acids of the amino acid sequence.

The region of a given target molecule to which an antigen-binding molecule binds can be determined by the skilled person using various methods well known in the art, including X-ray co-crystallography analysis of antibody-antigen complexes, peptide scanning, mutagenesis mapping, hydrogen-deuterium exchange analysis by mass spectrometry, phage display, competition ELISA and proteolysis-based 'protection' methods. Such methods are described, for example, in Gershoni *et al.*, BioDrugs, 2007, 21(3):145-156, which is hereby incorporated by reference in its entirety.

In some embodiments, the antigen-binding molecule of the present disclosure binds to the extracellular domain of gp130. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:75. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:75.

In some embodiments, the antigen-binding molecule of the present disclosure binds to the cytokine binding module of gp130. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:85. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:85.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:89. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:89. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:89. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:89. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:89.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:86. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:86. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:86. In some embodiments, the epitope of the

antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:86. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:87. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:87. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:87. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:87. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:88. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:88. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:88. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:88.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID NOs:86, 87 and 88. In some embodiments, the antigen-binding molecule contacts the regions of gp130 shown in SEQ ID NOs:86, 87 and 88. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:86, 87 and 88. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in SEQ ID NOs:86, 87 and 88.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:93. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:93. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:93. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:93. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:93.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:90. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:90. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:90. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:90. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:91. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:91. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:91. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:91. In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:92. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:92. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of

the region shown in SEQ ID NO:92. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:92.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID
5 NOs:90, 91 and 92. In some embodiments, the antigen-binding molecule contacts the regions of gp130
shown in SEQ ID NOs:90, 91 and 92. In some embodiments, the antigen-binding molecule binds to
gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:90, 91 and 92. In
some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences
shown in SEQ ID NOs:90, 91 and 92.

10 In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID
NO:169. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ
ID NO:169. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or
more amino acids of the region shown in SEQ ID NO:169. In some embodiments, the epitope of the
15 antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:169. In some
embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:170. In
some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID
NO:170. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or
more amino acids of the region shown in SEQ ID NO:170. In some embodiments, the epitope of the
20 antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:170.

In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID
NO:171. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ
ID NO:171. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or
25 more amino acids of the region shown in SEQ ID NO:171. In some embodiments, the epitope of the
antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:171. In some
embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:172. In
some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID
NO:172. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or
30 more amino acids of the region shown in SEQ ID NO:172. In some embodiments, the epitope of the
antigen-binding molecule comprises the amino acid sequence shown in SEQ ID NO:172.

In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID
NOs:169 and 170. In some embodiments, the antigen-binding molecule contacts the regions of gp130
35 shown in SEQ ID NOs:169 and 170. In some embodiments, the antigen-binding molecule binds to gp130
via contact with one or more amino acids of the regions shown in SEQ ID NOs:169 and 170. In some
embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in
SEQ ID NOs:169 and 170.

40 In some embodiments, the antigen-binding molecule binds to the regions of gp130 shown in SEQ ID
NOs:171 and 172. In some embodiments, the antigen-binding molecule contacts the regions of gp130

shown in SEQ ID NOs:171 and 172. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the regions shown in SEQ ID NOs:171 and 172. In some embodiments, the epitope of the antigen-binding molecule comprises the amino acid sequences shown in SEQ ID NOs:171 and 172.

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In some embodiments, the antigen-binding molecule binds to the region of gp130 shown in SEQ ID NO:173. In some embodiments, the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:173. In some embodiments, the antigen-binding molecule binds to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:173. In some embodiments, the epitope of the antigen-binding molecule comprises or consists of the amino acid sequence shown in SEQ ID NO:173. In some embodiments, the antigen-binding molecule binds to a polypeptide comprising or consisting of the amino acid sequence shown in SEQ ID NO:173.

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In some embodiments, the antigen-binding molecule does not bind to the region of gp130 shown in SEQ ID NO:178. In some embodiments, the antigen-binding molecule does not contact the region of gp130 shown in SEQ ID NO:178. In some embodiments, the antigen-binding molecule does not bind to gp130 via contact with one or more amino acids of the region shown in SEQ ID NO:178. In some embodiments, the epitope of the antigen-binding molecule does not consist of the amino acid sequence shown in SEQ ID NO:178. In some embodiments, the antigen-binding molecule does not bind to a polypeptide consisting of the amino acid sequence shown in SEQ ID NO:178.

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The ability of an antigen-binding molecule to bind to a given peptide/polypeptide can be analysed by methods well known to the skilled person, including analysis by ELISA, immunoblot (*e.g.* western blot), immunoprecipitation, SPR and BLI.

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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 selected from B035-C03-A3, CSP-S-5H8, A3_3.2 VH / A3_3 VL, A3_3.2 VH / A3_4 VL, A3_3.2 VH / A3_5 VL, A3_4.2 VH / A3_3 VL, A3_4.2 VH / A3_4 VL, A3_4.2 VH / A3_5 VL, A3_6.2 VH / A3_3 VL, A3_6.2 VH / A3_4 VL, A3_6.2 VH / A3_5 VL, A3-derived VH CON / A3-derived VL CON, A3-Hum VH CON / A3-Hum VL CON, B035-C03-A3_D50X, A3_3.2 VH / A3_3_D50X VL, A3_3.2 VH / A3_4_D50X VL, A3_3.2 VH / A3_5_D50X VL, A3_4.2 VH / A3_3_D50X VL, A3_4.2 VH / A3_4_D50X VL, A3_4.2 VH / A3_5_D50X VL, A3_6.2 VH / A3_3_D50X VL, A3_6.2 VH / A3_4_D50X VL, A3_6.2 VH / A3_5_D50X VL, A3-derived VH CON / A3-derived VL_D50X CON, A3-Hum VH CON / A3-Hum VL_D50X CON, B035-C03-A3_D50A, A3_3.2 VH / A3_3_D50A VL, A3_3.2 VH / A3_4_D50A VL, A3_3.2 VH / A3_5_D50A VL, A3_4.2 VH / A3_3_D50A VL, A3_4.2 VH / A3_4_D50A VL, A3_4.2 VH / A3_5_D50A VL, A3_6.2 VH / A3_3_D50A VL, A3_6.2 VH / A3_4_D50A VL, A3_6.2 VH / A3_5_D50A VL, A3-derived VH CON / A3-derived VL_D50A CON and A3-Hum VH CON / A3-Hum VL_D50A CON, B035-C03-A3_I100T VH / B035-C03-A3_G51A VL, B035-C03-A3_I100T VH / B035-C03-A3 VL, B035-C03-A3 VH / B035-C03-A3_G51A VL, A3_3.2_I100T VH / A3_3_G51A VL, A3_3.2_I100T VH / A3_4_G51A VL, A3_3.2_I100T VH / A3_5_G51A VL, A3_3.2_I100T VH / A3_3 VL, A3_3.2_I100T VH / A3_4 VL,

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A3_3.2_I100T VH / A3_5 VL, A3_3.2 VH / A3_3_G51A VL, A3_3.2 VH / A3_4_G51A VL, A3_3.2 VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3_G51A VL, A3_4.2_I100T VH / A3_4_G51A VL, A3_4.2_I100T VH / A3_5_G51A VL, A3_4.2_I100T VH / A3_3 VL, A3_4.2_I100T VH / A3_4 VL, A3_4.2_I100T VH / A3_5 VL, A3_4.2 VH / A3_3_G51A VL, A3_4.2 VH / A3_4_G51A VL, A3_4.2 VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3_G51A VL, A3_6.2_I100T VH / A3_4_G51A VL, A3_6.2_I100T VH / A3_5_G51A VL, A3_6.2_I100T VH / A3_3 VL, A3_6.2_I100T VH / A3_4 VL, A3_6.2_I100T VH / A3_5 VL, A3_6.2 VH / A3_3_G51A VL, A3_6.2 VH / A3_4_G51A VL, A3_6.2 VH / A3_5_G51A VL, A3-derived_I100T VH CON / A3-derived_G51A VL CON, A3-derived_I100T VH CON / A3-derived VL CON, A3-derived VH CON / A3-derived_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum_G51A VL CON, A3-Hum_I100T VH CON / A3-Hum VL CON, A3-Hum VH CON / A3-Hum_G51A VL CON, 5H8CVH4 VH / 5H8CVL3 VL, 5H8CVH4 VH / 5H8CVL4 VL, 5H8CVH4 VH / 5H8GVL3 VL, 5H8GVH4 VH / 5H8CVL3 VL, 5H8GVH4 VH / 5H8CVL4 VL, 5H8GVH4 VH / 5H8GVL3 VL, 5H8-derived VH CON / 5H8-derived VL CON, 5H8-Hum VH CON / 5H8-Hum VL CON, CSP-S-5H8_D98G VH / CSP-S-5H8 VL, 5H8CVH4_D98G VH / 5H8CVL3 VL, 5H8CVH4_D98G VH / 5H8CVL4 VL, 5H8CVH4_D98G VH / 5H8GVL3 VL, 5H8GVH4_D98G VH / 5H8CVL3 VL, 5H8GVH4_D98G VH / 5H8CVL4 VL, 5H8GVH4_D98G VH / 5H8GVL3 VL, 5H8-derived_D98G VH CON / 5H8-derived VL CON, or 5H8-Hum_D98G VH CON / 5H8-Hum VL CON.

Whether a test antigen-binding molecule binds to the same or an overlapping region of a given target as a reference antigen-binding molecule can be evaluated, for example, by analysis of (i) interaction between the test antigen-binding molecule and the target in the absence of the reference binding molecule, and (ii) interaction between the test antigen-binding molecule in the presence of the reference antigen-binding molecule, or following incubation of the target with the reference antigen-binding molecule. Determination of a reduced level of interaction between the test antigen-binding molecule and the target following analysis according to (ii) as compared to (i) might support an inference that the test and reference antigen-binding molecule bind to the same or an overlapping region of the target. Suitable assays for such analysis include *e.g.* competition ELISA assays and epitope binning assays.

In some embodiments, the antigen-binding molecule of the present disclosure binds to gp130 in a region which is accessible to an antigen-binding molecule (*i.e.*, an extracellular antigen-binding molecule) when gp130 is expressed at the cell surface (*i.e.* in or at the cell membrane). In some embodiments, the antigen-binding molecule binds to gp130 expressed at the cell surface of a cell expressing gp130. In some embodiments, the antigen-binding molecule binds to gp130-expressing cells (*e.g.* fibroblasts). In some embodiments, the antigen-binding molecule does not bind (*i.e.* does not substantially bind) to cells lacking surface expression of gp130.

The ability of an antigen-binding molecule to bind to a given cell type (*e.g.* cells expressing gp130, or cells not expressing gp130) can be analysed by contacting cells with the antigen-binding molecule, and detecting antigen-binding molecule bound to the cells, *e.g.* after a washing step to remove unbound antigen-binding molecule. The ability of an antigen-binding molecule to bind to a given cell type can be analysed by methods such as flow cytometry and immunofluorescence microscopy.

In some embodiments, the antigen-binding molecule of the present disclosure inhibits signalling mediated by a receptor comprising gp130. In some embodiments, the antigen-binding molecule inhibits gp130-mediated signalling (e.g. gp130-mediated signalling as described hereinabove). Signalling mediated by gp130 and/or by receptors comprising gp130 can be analysed using cells expressing gp130/the relevant receptor, e.g. using an assay for detecting and/or quantifying gp130-mediated signalling. Suitable assays include e.g. assays for detecting the phosphorylation/activity/expression of factors which are phosphorylated/activated/expressed as a consequence of signalling 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 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-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 more signal transduction molecules of a signal transduction pathway triggered by signalling through gp130/cytokine receptors comprising gp130 (e.g. the JAK/STAT, MAPK/ERK or PI3K/AKT pathways). For example, the level of gp130-mediated signalling can be analysed by detection and/or quantification of the level of phosphorylation of JAK1, JAK2, STAT1, STAT3, STAT5 and/or ERK (e.g. STAT3 and/or ERK). By way of illustration, in the experimental examples of the present disclosure, gp130-mediated signalling (particularly gp130-mediated signalling in response to stimulation with IL-6, IL-11, OSM, LIF, CT-1 or CNTF) is analysed by evaluating phosphorylation of STAT3 or ERK1/2 by western blot.

The level of gp130-mediated signalling can also be evaluated by analysing one or more correlates of gp130-mediated signalling. For example, gp130-mediated signalling may be investigated by detecting and/or quantifying the expression or activity of a factor whose expression/activity is upregulated or downregulated as a consequence of gp130-mediated signalling. In some embodiments, gp130-mediated signalling may be investigated by detecting and/or quantifying the expression of a factor whose expression is upregulated as a consequence of gp130-mediated signalling, e.g. a proinflammatory/profibrotic/profibroinflammatory factor. By way of illustration, in the experimental examples of the present disclosure, gp130-mediated signalling 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).

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In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130 and/or signalling by a receptor comprising gp130 to less than 1 times, *e.g.* ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, *e.g.* an antigen-binding molecule known not to influence signalling mediated by gp130 and/or signalling by a receptor comprising gp130).

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In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling. In some
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embodiments, the antigen-binding molecule inhibits IL-11-mediated signalling. In some embodiments, the antigen-binding molecule inhibits OSM-mediated signalling. In some embodiments, the antigen-binding molecule inhibits LIF-mediated signalling. In some embodiments, the antigen-binding molecule inhibits CNTF-mediated signalling. In some embodiments, the antigen-binding molecule inhibits CT-1-mediated
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signalling. In some embodiments, the antigen-binding molecule inhibits CLC-mediated signalling. In some
embodiments, the antigen-binding molecule inhibits IL-27-mediated signalling. In some embodiments, the
antigen-binding molecule inhibits IL-35-mediated signalling.

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In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling and inhibits IL-11-mediated signalling and inhibits OSM-mediated signalling and inhibits LIF-mediated signalling and inhibits
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CNTF-mediated signalling and inhibits CT-1-mediated signalling.

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In some embodiments, the antigen-binding molecule inhibits IL-6-mediated signalling and inhibits IL-11-mediated signalling and inhibits OSM-mediated signalling and inhibits LIF-mediated signalling and inhibits CNTF-mediated signalling and inhibits CT-1-mediated signalling and inhibits CLC-mediated signalling and
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inhibits IL-27-mediated signalling and inhibits IL-35-mediated signalling.

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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:OSMR β . In some
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embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:LIFR β . In some
embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:LIFR β :CNTFR α . In
some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-27R α . In some
embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-12R β 2.

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

- 5 In some embodiments, the antigen-binding molecule inhibits signalling mediated by gp130:IL-6R α and inhibits signalling mediated by gp130:IL-11R α and inhibits signalling mediated by gp130:OSMR β and inhibits signalling mediated by gp130:LIFR β and inhibits signalling mediated by gp130:LIFR β :CNTFR α and inhibits signalling mediated by gp130:IL-27R α and inhibits signalling mediated by gp130:IL-12R β 2.
- 10 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 OSM to cells expressing gp130:OSMR β . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of OSM to cells
- 15 expressing gp130:LIFR β . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of LIF to cells expressing gp130:LIFR β . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR α . In some embodiments, the antigen-binding molecule inhibits signalling
- 20 mediated by binding of CLC to cells expressing gp130:LIFR β :CNTFR α . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R α . In some embodiments, the antigen-binding molecule inhibits signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2.
- 25 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 and inhibits signalling mediated by binding of OSM to cells expressing gp130:OSMR β and inhibits signalling mediated by binding of OSM to cells expressing gp130:LIFR β and inhibits signalling mediated by binding of LIF to cells expressing gp130:LIFR β and inhibits signalling mediated by binding of
- 30 CT-1 to cells expressing gp130:LIFR β and inhibits signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR 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
- 35 gp130:IL-11R α and inhibits signalling mediated by binding of OSM to cells expressing gp130:OSMR β and inhibits signalling mediated by binding of OSM to cells expressing gp130:LIFR β and inhibits signalling mediated by binding of LIF to cells expressing gp130:LIFR β and inhibits signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β and inhibits signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR α and inhibits signalling mediated by binding of CLC to cells expressing
- 40 gp130:LIFR β :CNTFR α and inhibits signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R α and inhibits signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2.

In some embodiments, the antigen-binding molecule inhibits 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 inhibits 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). In some embodiments, the antigen-binding molecule inhibits 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 inhibits 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). In some embodiments, the antigen-binding molecule inhibits 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-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). In some embodiments, the antigen-binding molecule inhibits 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.

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In some embodiments, the antigen-binding molecule inhibits OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM to cells expressing gp130:LIFR β to less than 1 times, e.g. ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM to cells expressing gp130:LIFR β). In some embodiments, the antigen-binding molecule inhibits 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 OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM 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 OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM to cells expressing gp130:LIFR β). In some embodiments, the antigen-binding molecule inhibits OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM to cells expressing gp130:LIFR β 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 inhibits LIF-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β to less than 1 times, e.g. ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence LIF-mediated signalling/signalling

mediated by gp130:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β). In some embodiments, the antigen-binding molecule inhibits 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 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). In some embodiments, the antigen-binding molecule inhibits LIF-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of LIF to cells expressing gp130:LIFR β 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 inhibits CT-1-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β to less than 1 times, e.g. ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence CT-1-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β). In some embodiments, the antigen-binding molecule inhibits 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 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). In some embodiments, the antigen-binding molecule inhibits CT-1-mediated signalling/signalling mediated by gp130:LIFR β /signalling mediated by binding of CT-1 to cells expressing gp130:LIFR β 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 inhibits 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 to less than 1 times, e.g. ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times,

- ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence CNTF-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CNTF to cells expressing gp130:LIFR β :CNTFR α). In some embodiments, the antigen-binding molecule inhibits 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 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). In some embodiments, the antigen-binding molecule inhibits 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 with an IC_{50} 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 inhibits CLC-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CLC to cells expressing gp130:LIFR β :CNTFR 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 CLC-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CLC to cells expressing gp130:LIFR β :CNTFR α). In some embodiments, the antigen-binding molecule inhibits 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 CLC-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CLC 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 CLC-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CLC to cells expressing gp130:LIFR β :CNTFR α). In some embodiments, the antigen-binding molecule inhibits CLC-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CLC to cells expressing gp130:LIFR β :CNTFR α with an IC_{50} 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 inhibits IL-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R 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-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R α). In some embodiments, the antigen-binding molecule inhibits 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-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R 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-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R α). In some embodiments, the antigen-binding molecule inhibits IL-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R 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 inhibits IL-35-mediated signalling/signalling mediated by gp130:IL-12R β 2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2 to less than 1 times, e.g. ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level of signalling observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence IL-35-mediated signalling/signalling mediated by gp130:IL-12R β 2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2). In some embodiments, the antigen-binding molecule inhibits 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-35-mediated signalling/signalling mediated by gp130:IL-12R β 2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2 observed in the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence IL-35-mediated signalling/signalling mediated by gp130:IL-12R β 2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-

12R β 2). In some embodiments, the antigen-binding molecule inhibits IL-35-mediated signalling/signalling mediated by gp130:IL-12R β 2/signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R β 2 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: (i) inhibits 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); (ii) inhibits 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-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); (iii) inhibits 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 OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM 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 OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM to cells expressing gp130:LIFR β); (iv) inhibits 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 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); (v) inhibits 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 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); and (vi) inhibits 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 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).
- 10 In some embodiments, the antigen-binding molecule: (i) inhibits 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); (ii) inhibits 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-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); (iii) inhibits 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 OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM 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 OSM-mediated signalling/signalling mediated by gp130:OSMR β /signalling mediated by gp130:LIFR β /signalling mediated by binding of OSM to cells expressing gp130:OSMR β /signalling mediated by binding of OSM to cells expressing gp130:LIFR β); (iv) inhibits 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 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); (v) inhibits 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 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); (vi) inhibits 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 CNTF-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of
- 5 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); (vii) inhibits 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 CLC-
- 10 mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling mediated by binding of CLC 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 CLC-mediated signalling/signalling mediated by gp130:LIFR β :CNTFR α /signalling
- 15 mediated by binding of CLC to cells expressing gp130:LIFR β :CNTFR α); (viii) inhibits 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-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R 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-
- 20 binding molecule known not to influence IL-27-mediated signalling/signalling mediated by gp130:IL-27R α /signalling mediated by binding of IL-27 to cells expressing gp130:IL-27R α); and (ix) inhibits 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-35-mediated signalling/signalling mediated by gp130:IL-12R $\beta 2$ /signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R $\beta 2$ observed in
- 25 the absence of the antigen-binding molecule (or in the presence of an appropriate control antigen-binding molecule, e.g. an antigen-binding molecule known not to influence IL-35-mediated signalling/signalling mediated by gp130:IL-12R $\beta 2$ /signalling mediated by binding of IL-35 to cells expressing gp130:IL-12R $\beta 2$).
- 30 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.
- 35 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 $\beta 1$, etc.) in the presence of the antigen-binding molecule, and subsequently evaluating the cells to determine the level of one or more correlates
- 40 of inflammation/fibrosis. By way of illustration, in the experimental examples of the present disclosure, gp130-specific antigen-binding molecules are evaluated for their ability to reduce fibrosis in *in vitro* assays

in which cells are stimulated with TGF β 1 or IL-11, and in which the fibrotic response is subsequently analysed by evaluating the expression of 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 of more correlates of inflammation and/or fibrosis (*e.g.* in an *in vitro* model of inflammation/fibrosis, or in an *in vivo* model of a disease/condition characterised by inflammation/fibrosis) to less than 1 times, *e.g.* ≤ 0.99 times, ≤ 0.95 times, ≤ 0.9 times, ≤ 0.85 times, ≤ 0.8 times, ≤ 0.75 times, ≤ 0.7 times, ≤ 0.65 times, ≤ 0.6 times, ≤ 0.55 times, ≤ 0.5 times, ≤ 0.45 times, ≤ 0.4 times, ≤ 0.35 times, ≤ 0.3 times, ≤ 0.25 times, ≤ 0.2 times, ≤ 0.15 times, ≤ 0.1 times, ≤ 0.05 times, or ≤ 0.01 times the level observed in the absence of treatment with the antigen-binding molecule (or following treatment with an appropriate control antigen-binding molecule known not to influence the level of the relevant correlate(s)), in a given assay.

Antigen-binding molecules according to the present disclosure may comprise one or more moieties for potentiating cell killing of, or reducing the number/proportion of, cells expressing gp130. For example, an antigen-binding molecule according to the present disclosure may *e.g.* comprise an Fc region and/or a drug moiety.

In some embodiments, an antigen-binding molecule according to the present disclosure may potentiate (*i.e.* upregulate, enhance) cell killing of cells comprising/expressing gp130. In some embodiments, the antigen-binding molecule does not potentiate (*i.e.* does not substantially potentiate) cell killing of cells lacking surface expression of gp130.

Cell killing can be investigated, for example, using any of the methods reviewed in Zaritskaya *et al.*, Expert Rev Vaccines (2011), 9(6):601-616, hereby incorporated by reference in its entirety. Examples of *in vitro* assays of cytotoxicity/cell killing assays include release assays such as the ⁵¹Cr release assay, the lactate dehydrogenase (LDH) release assay, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) release assay, and the calcein-acetoxymethyl (calcein-AM) release assay. These assays measure cell killing based on the detection of factors released from lysed cells. Cell killing of a given test cell type by a given effector immune cell type can be analysed *e.g.* by co-culturing the test cells with the effector immune cells, and measuring the number/proportion of viable/dead (*e.g.* lysed) test cells after a suitable period of time. Other suitable assays include the xCELLigence real-time cytolytic *in vitro* potency assay described in Cerignoli *et al.*, PLoS One. (2018) 13(3): e0193498 (hereby incorporated by reference in its entirety).

In some embodiments an antigen-binding molecule according to the present disclosure is capable of reducing the number/proportion of cells expressing gp130. In some embodiments an antigen-binding molecule according to the present disclosure is capable of reducing the number/proportion of cells expressing gp130. In some embodiments, an antigen-binding molecule according to the present disclosure is capable of depleting/enhancing depletion of such cells.

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

In some embodiments, an antigen-binding molecule according to the present disclosure comprises an Fc region capable of potentiating/directing one or more of ADCC, ADCP, CDC against, and/or potentiating formation of a MAC on or cell degranulation of, a cell expressing gp130 (*e.g.* a cell expressing gp130 at the cell surface).

In some embodiments, an antigen-binding molecule according to the present disclosure is capable of potentiating/directing ADCC against a cell expressing gp130.

The ability of, and extent to which, a given antigen-binding molecule is able to induce ADCC of a given target cell type can be analysed *e.g.* according to the method described in Yamashita *et al.*, Scientific Reports (2016) 6:19772 (hereby incorporated by reference in its entirety), or by ⁵¹Cr release assay as

described *e.g.* in Jedema *et al.*, Blood (2004) 103: 2677–82 (hereby incorporated by reference in its entirety). The ability of, and extent to which, a given antigen-binding molecule is able to induce ADCP can be analysed *e.g.* according to the method described in Kamen *et al.*, J Immunol (2017) 198 (1 Supplement) 157.17 (hereby incorporated by reference in its entirety). The ability of, and extent to which, a given antigen-binding molecule is able to induce CDC can be analysed *e.g.* using a C1q binding assay, *e.g.* as described in Schlothauer *et al.*, Protein Engineering, Design and Selection (2016), 29(10):457–466 (hereby incorporated by reference in its entirety).

In some embodiments, an antigen-binding molecule according to the present disclosure comprises a drug moiety. The antigen-binding molecule may be conjugated to the drug moiety. Antibody-drug conjugates are reviewed *e.g.* in Parslow *et al.*, Biomedicines. 2016 Sep; 4(3):14 (hereby incorporated by reference in its entirety). In some embodiments, the drug moiety is or comprises a cytotoxic agent, such that the antigen-binding molecule displays cytotoxicity to a cell expressing gp130 (*e.g.* a cell expressing gp130 at the cell surface).

15

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.

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).

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.

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,
 5 e.g. as described hereinbelow.

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
 10 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).

15 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.

20 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).

25

Labels and conjugates

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

30 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.

35 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,
 40 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.

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.

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.

- 5 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
10 the genomic DNA of cell into which the vector is introduced.

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.

- 15 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
20 termination codons known in the art may be used to express a peptide or polypeptide from a vector according to the present disclosure.

- 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
25 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).

- 30 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
35 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.

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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.

5

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.

10 **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.

15 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. 20 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, 25 *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 30 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 35 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.

40 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.

In some embodiments polypeptides may be prepared by cell-free-protein synthesis (CFPS), *e.g.*

- 5 according to a system described in Zemella *et al.* *Chembiochem* (2015) 16(17): 2420-2431, which is hereby incorporated by reference in its entirety.

- 10 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 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).

- 15 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, 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
20 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 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
25 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, treatment of the cell pellet with a lysis buffer, and cell disruption *e.g.* by sonification, rapid freeze-thaw or osmotic lysis.

- 30 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 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
35 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
40 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.

5

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.

10

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.

25

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).

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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*.

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

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Compositions

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

5 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.

10

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).

20

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.

30

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.

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40 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 a later stage (*e.g.* a chronic stage or metastasis).

5

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, a gp130-containing complex (*e.g.* selected from a gp130:IL-6R α complex, a gp130:IL-11R α complex, a gp130:OSMR β complex, a gp130:LIFR β complex, a gp130:LIFR β :CNTFR α complex, a gp130:IL-27R α complex and a gp130:IL-12R β 2 complex), or of signalling mediated by a cytokine that signals through a gp130-containing complex (*e.g.* selected from IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 and IL-35).

10

It will also 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 number or activity of cells comprising/expressing gp130 or a gp130-containing complex (*e.g.* selected from a gp130:IL-6R α complex, a gp130:IL-11R α complex, a gp130:OSMR β complex, a gp130:LIFR β complex, a gp130:LIFR β :CNTFR α complex, a gp130:IL-27R α complex and a gp130:IL-12R β 2 complex).

20

For example, the disease/condition may be a disease/condition in which gp130, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex are pathologically-implicated, *e.g.* a disease/condition in which an increased level/activity of gp130, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex 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, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex may be a risk factor for the onset, development or progression of the disease/condition.

25

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, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex, *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, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex, *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).

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Where the disease/condition is a cancer, the level of expression or activity of gp130, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex may be greater than the level

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of expression or activity 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, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex.

5

Treatment in accordance with the methods of the present disclosure may achieve a reduction in the activity of gp130, a gp130-containing complex and/or a cytokine that signals through a gp130-containing complex in a subject (compared to an equivalent untreated subject, or a subject treated with an appropriate control).

10

In some aspects and embodiments, the articles of the present disclosure are provided for the treatment/prevention of disease/condition selected from: a disease/condition in which gp130-mediated signalling is pathologically-implicated, a disease/condition in which signalling through a gp130-containing complex (e.g. a gp130:IL-6R α complex, a gp130:IL-11R α complex, a gp130:OSMR β complex, a gp130:LIFR β complex, a gp130:LIFR β :CNTFR α complex, a gp130:IL-27R α complex or a gp130:IL-12R β 2 complex) is pathologically implicated, a disease/condition in which signalling mediated by a cytokine that signals through a gp130-containing complex (e.g. IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 or IL-35) is pathologically-implicated, pathological inflammation, fibrosis, a disease/condition characterised by inflammation or a disease/condition characterised by fibrosis.

20

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). Inflammation forms part of the innate immune response, and plays an important physiological role in wound healing and the control of infection, and contributes to the restoration of tissue homeostasis.

However, many diseases are associated with an overactive inflammatory response (*i.e.* excessive inflammation and/or aberrantly activated inflammation), and/or chronic (prolonged) inflammation. Herein, excessive and/or chronic inflammation may be referred to as 'pathological inflammation'. Pathological inflammation may refer to inflammation which is implicated in (*i.e.* which positively contributes to) the pathology of a disease.

Inflammation to be treated/prevented in accordance with the present disclosure can be of any tissue/organ of the body. In some embodiments, the inflammation is of the lung (e.g. bronchioles, alveoli), airways (e.g. nasal cavity, oral cavity, pharynx, larynx, trachea, bronchi), heart, kidney, liver, skeletal

muscle, blood vessels, eye, skin, pancreas, bowel, small intestine, large intestine, colon, joints, brain, or bone marrow. Inflammation may also occur in multiple tissues/organs at once.

In some embodiments, inflammation may be of an organ or tissue of the respiratory system, *e.g.* the lung (5 *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. (15

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; (20 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 (25 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 (35 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 (40 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.

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

15 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.

20 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.

25 Damage to tissues can result from various stimuli, including infections, autoimmune reactions, toxins, radiation and mechanical injury. Repair typically involves replacement of injured cells by cells of the same type, and replacement of normal parenchymal tissue with connective tissue. Repair processes become pathologic when they are not controlled properly, resulting in excess deposition of ECM components in which normal parenchymal tissue is replaced with connective tissue. In diseases such as idiopathic pulmonary fibrosis, liver cirrhosis, cardiovascular fibrosis, systemic sclerosis and nephritis, extensive tissue remodelling and fibrosis can ultimately lead to organ failure and death.

30 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 recruit myofibroblasts to the site of injury. Myofibroblasts produce large amounts of extracellular matrix components such as collagen and periostin for wound contracture and closure, and also produce proinflammatory cytokines such as IL-6, and tissue remodelling factors such as MMP2 and TIMP1. Persistent/chronic infection and/or inflammation can result in the generation of too many myofibroblasts, and consequently the over-production of extracellular matrix, resulting in fibrosis. In many diseases and conditions characterised by fibrosis, a persistent inflammatory trigger is crucial to upregulation of

production of growth factors, proteolytic enzymes, angiogenic factors and fibrogenic cytokines, which stimulate the deposition of connective tissue elements that progressively remodel and destroy normal tissue architecture.

- 5 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.

- 15 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.

- 20 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.

- 30 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.

- 35 As used herein, a disease/condition which is 'characterised by inflammation' is a disease/condition in which fibrosis is a symptom of the disease/condition. Diseases/conditions characterised by inflammation include, but are not limited to:

- 40 Diseases/conditions affecting the respiratory system, such as sinusitis, rhinitis, pharyngitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonitis, pleuritis and mediastinitis;
- Diseases/conditions affecting the accessory digestive organs such as hepatitis, ascending cholangitis, cholecystitis, pancreatitis and peritonitis;

- Diseases/conditions affecting the cardiovascular system such as carditis, endocarditis, myocarditis, pericarditis, vasculitis, arteritis, phlebitis, capillaritis and cardiogenic shock;
- Diseases/conditions affecting the urinary system such as nephritis, glomerulonephritis, pyelonephritis, ureteritis, cystitis and urethritis;
- 5 Diseases/conditions affecting the nervous system such as encephalitis, myelitis, meningitis, arachnoiditis and neuritis;
- Diseases/conditions affecting the musculoskeletal system such as arthritis, dermatomyositis, soft tissue, myositis, synovitis/tenosynovitis, bursitis, enthesitis, fasciitis, capsulitis, epicondylitis, tendinitis, panniculitis, osteochondritis: osteitis/osteomyelitis, spondylitis, periostitis and chondritis;
- 10 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;
- 15 Diseases/conditions affecting the skin such as dermatitis, folliculitis, cellulitis and hidradenitis;
- Diseases/conditions affecting the eye such as dacryoadenitis, scleritis, episcleritis, keratitis, retinitis, chorioretinitis, blepharitis, conjunctivitis, uveitis and dry eye syndrome;
- Diseases/conditions affecting the ear such as otitis externa, otitis media, labyrinthitis and mastoiditis;
- 20 Diseases/conditions of the reproductive system such as oophoritis, salpingitis, endometritis, endometriosis, parametritis, cervicitis, vaginitis, vulvitis, mastitis, orchitis, epididymitis, prostatitis, seminal vesiculitis, balanitis, posthitis, balanoposthitis, chorioamnionitis, funisitis and omphalitis;
- Diseases/conditions of the endocrine system such as insulitis, hypophysitis, thyroiditis, parathyroiditis and adrenalitis;
- 25 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.
- 30

It will be appreciated that many of the diseases/conditions listed above are interrelated.

- It will be appreciated that diseases/conditions characterised by inflammation may also exhibit further symptoms/pathologies. For example, a disease/condition characterised by inflammation may further be
- 35 characterised by angiogenesis (e.g. inflammation-induced angiogenesis as described herein) and/or fibrosis (e.g. fibrosis as described herein).

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:

5 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;

10 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);

15 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
20 veins and cerebral infarcts;

Diseases/conditions affecting the kidneys such as tubulointerstitial fibrosis, glomerular fibrosis, renal fibrosis, nephritic syndrome, Alport's syndrome, HIV-associated nephropathy, polycystic kidney disease, Fabry's disease, diabetic nephropathy, chronic glomerulonephritis and nephritis associated with
25 systemic lupus;

Diseases/conditions affecting the pancreas such as pancreatic fibrosis, cystic fibrosis and chronic pancreatitis;

Diseases/conditions affecting the nervous system such as gliosis, Alzheimer's disease and multiple sclerosis;

30 Diseases/conditions affecting the musculoskeletal system such as muscular dystrophy, Duchenne muscular dystrophy (DMD), Becker's muscular dystrophy (BMD) and fibrotic myopathy;

Diseases/conditions affecting the gastrointestinal system such as inflammatory bowel disease (IBD), Crohn's disease, microscopic colitis and primary sclerosing cholangitis (PSC);

35 Diseases/conditions affecting the skin such as scleroderma, nephrogenic systemic fibrosis, Dupuytren's contracture and cutis keloid;

40 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;

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);

- 5 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.

- 10 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
15 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
20 embodiments, the disease/condition to be treated in accordance with the present disclosure is kidney disease sepsis or septic shock. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is hypertrophic cardiomyopathy (HCM). In some embodiments, the
25 disease/condition to be treated in accordance with the present disclosure is dilated cardiomyopathy (DCM). In some embodiments, the disease/condition to be treated in accordance with the present disclosure is cardiogenic shock. In some embodiments, the disease/condition to be treated in accordance with the present disclosure is chronic inflammation, for example, chronic inflammation associated with ageing. In some embodiments, the disease/condition to be treated in accordance with the present
disclosure is cardiovascular disease.

- In some embodiments, the disease/condition to be treated in accordance with the present disclosure is a disease/condition described in WO 2022/090509 A1, which is hereby incorporated by reference in its entirety. In some embodiments, the disease/condition to be treated is an age-related diseases/condition.
30 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.

- 35 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).

As used herein, an "age-related" disease/condition or phenotype may also be referred to as being "aging-related" or "age/aging-associated". In aspects and embodiments of the present disclosure, a disease/condition or phenotype which is described as being "age-related" may arise as a consequence of the age of the subject having the relevant disease/condition or phenotype, rather than another etiological cause. In some aspects and embodiments, a disease/condition or phenotype which is "age-related" may arise as a consequence of cellular senescence. By way of illustration, "age-related" changes in body composition may refer to changes in body composition arising as a consequence of aging of the subject and/or of cellular senescence, rather than the subject's diet.

The accumulation of senescent cells is one of the hallmarks in aging (Hunt *et al.*, Comput Struct Biotechnol J (2019) 17: 1151-1161). Cellular senescence is characterised by reduced replicative capacity and producing senescence-associated secretory phenotype (SASPs) proteins, resulting in a chronic, low-grade inflammatory environment for neighbouring cells (Hunt *et al.*, Comput Struct Biotechnol J (2019) 17: 1151-1161; Borghesan *et al.*, Trends Cell Biol. (2020) 30(10):777-791). Under pathological stress conditions, excessive accumulation of senescence cells in affected tissues adversely affects the tissue's regenerative ability and chronic inflammation that can resemble various age-related disorders such as Alzheimer's disease, cancer, arthritis, cataracts, osteoporosis, atherosclerosis, hypertension, cardiovascular disease, type 2 diabetes, and chronic liver disorders (Baker and Haynes, Trends Biochem Sci (2011) 36(5): 254-261; Kim *et al.*, Curr Opin Gastroenterol (2015) 31(3): 184-191; Hernandez-Segura *et al.*, Trends Cell Biol (2018) 28(6): 436-453; Stahl *et al.* Front Immunol (2018) 9: 2795; Belikov, Ageing Res Rev (2019) 49: 11-26; Campisi *et al.*, Nature (2019) 571(7764): 183-192; Gorgoulis *et al.*, Cell (2019) 179(4): 813-827; Schmeer *et al.*, Cells (2019) 8(11); Papatheodoridi *et al.*, Hepatology (2020) 71(1): 363-374). Cellular senescence is therefore thought to be a key physiological process in the development and progression of age-related diseases (Borghesan *et al.*, Trends Cell Biol. (2020) 30(10):777-791; Pignolo *et al.*, Trends Mol Med (2020) 26(7): 630-638).

In some aspects and embodiments the present disclosure contemplates treatment/prevention of cellular senescence, and diseases/conditions characterised by cellular senescence. In some aspects and embodiments, the methods of the present disclosure comprise inhibiting cellular senescence. In some aspects and embodiments, the methods of the present disclosure comprise inhibiting senescent cells. In some aspects and embodiments, the methods comprise reducing the number of senescent cells and/or inhibiting the activity of senescent cells.

In some embodiments, reducing the number of senescent cells comprises inhibiting the process of cellular senescence. That is, in some embodiments reducing the number of senescent cells comprises inhibiting the development of senescent cells from non-senescent precursor cells. In some embodiments, reducing the number of senescent cells comprises reversing the process of cellular senescence. That is, in some embodiments reducing the number of senescent cells comprises promoting reversion of senescent cells to a non-senescent phenotype. In some embodiments, reducing the number of senescent cells comprises depleting senescent cells.

Cellular senescence is described *e.g.* in Childs *et al.* Nat Med (2015) 21(12):1424-1435 and van Deursen, Nature (2014) 509(7501): 439-446, both of which are hereby incorporated by reference in their entirety. Cellular senescence is characterised by cessation of cell division (associated with activation of 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.

A disease/condition in which cellular senescence is 'pathologically-implicated' may be a disease/condition for which an increase in the number/proportion and/or activity of senescent cells (relative to the non-diseased, healthy state) is positively associated with the onset, development and/or progression of the disease/condition. A disease/condition in which cellular senescence is 'pathologically-implicated' may be a disease/condition for which an increase in the number/proportion and/or activity of senescent cells (relative to the non-diseased, healthy state) is positively associated with the severity of one or more symptoms of the disease/condition. A disease/condition in which cellular senescence is 'pathologically-implicated' may be a disease/condition for which an increase in the number/proportion and/or activity of senescent cells (relative to the non-diseased, healthy state) is a risk factor for the onset, development and/or progression of the disease/condition.

Diseases/conditions (*e.g.* age-related diseases/conditions) contemplated to be treated/presented in accordance with the present disclosure include *e.g.* geriatric syndromes, Alzheimer's disease, cancer,

- hyperlipidaemia, hypertriglyceridemia, hypercholesterolemia, steatosis (e.g. of the liver), non-alcoholic fatty liver disease (NAFLD), non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), cardiovascular disease, hypertension (e.g. systolic, diastolic), heart failure with reduced or preserved ejection fraction, renal disease (e.g. chronic kidney disease), atherosclerosis, hypertension, maculopathy,
- 5 age-related macular degeneration (AMD), cataracts, chronic obstructive pulmonary disease (COPD), arthritis, osteoarthritis, osteopenia, osteoporosis, Parkinson's disease, periodontitis, rheumatoid arthritis, diabetes mellitus, type II diabetes mellitus, chronic liver disease, sarcopenia, constipation, impotence, vaginal dryness, hair loss, skin disease and skin fragility.
- 10 Geriatric syndromes are conditions which are common in elderly patients, and include frailty, cognitive impairment, delirium, dementia, incontinence, hearing impairment, visual impairment, sarcopenia, metabolic syndrome, malnutrition, gait disturbance, falls and pressure ulcers.

- Further exemplary diseases/conditions contemplated to be treated/presented in accordance with the
- 15 present disclosure include frailty, age-related increase in fat mass, sarcopenia, age-related hyperlipidaemia, age-related hypertriglyceridemia, age-related hypercholesterolemia, age-related liver steatosis, age-related non-alcoholic fatty liver disease (NAFLD), age-related non-alcoholic fatty liver (NAFL), age-related non-alcoholic steatohepatitis (NASH), age-related cardiovascular disease, age-related hypertension, age-related renal disease and age-related skin disease.

- 20 Where a disease/condition is described herein as "age-related", reference is made to the disease/condition arising as a consequence of the age of the subject as distinct from other possible etiological causes. For example, "age-related steatosis" refers to the specific subtype of steatosis arising as a consequence of the aging process, which is distinct from steatosis arising e.g. as a consequence of
- 25 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,
- 30 malnutrition, gait disturbance, falls and pressure ulcers.

- In some aspects and embodiments, the present disclosure contemplates the treatment/prevention of frailty.
- 35 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
- 40 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.

- 5 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).

- 25 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).

- 30 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).

- 35 In some embodiments, an age-related change in body composition in accordance with the present disclosure is selected from: age-related reduction in muscle mass, sarcopenia, age-related reduction in bone mass, osteoporosis, and age-related increase in fat mass. In some embodiments, an age-related change in body composition in accordance with the present disclosure is selected from: age-related reduction in muscle mass, sarcopenia and age-related increase in fat mass.

Aging is often associated with increases in serum lipid levels. Older adults display higher serum levels of triglycerides and cholesterol, and in some instances display hyperlipidaemia (e.g. hypertriglyceridemia, hypercholesterolemia or combined hyperlipidaemia (combination of hypertriglyceridemia and hypercholesterolemia). Hyperlipidaemia is in turn commonly associated e.g. with atherosclerosis and cardiovascular disease.

Hypertriglyceridemia is described e.g. in Berglund *et al.*, J. Clin. Endocrinol. Metab. (2012) 97(9):2969-89, and is defined by blood triglyceride level ≥ 150 mg/dL (≥ 1.7 mmol/L). Hypercholesterolemia is described e.g. in Bhatnagar *et al.*, BMJ (2008) 337:a993. The UK NHS defines hypercholesterolemia as blood total cholesterol level of ≥ 5 mmol/L or blood low-density lipoprotein (LDL) level of ≥ 3 mmol/L. The US NIH defines hypercholesterolemia as blood total cholesterol level of ≥ 240 mg/dL.

Aging is often associated with liver steatosis, e.g. as described in Nguyen *et al.*, Cell Rep (2018) Aug 7;24(6):1597-1609. Steatosis refers to the abnormal retention of lipid within a cell/tissue/organ. Steatosis may be macrovesicular or microvesicular, and commonly affects the liver. Age-related steatosis can lead to age-related non-alcoholic fatty liver disease (NAFLD). NAFLD is reviewed e.g. in Benedict and Zhang, World J Hepatol. (2017) 9(16): 715–732 and Albhaisi *et al.*, Version 1. F1000Res. (2018) 7: F1000 Faculty Rev-720, both of which are hereby incorporated by reference in their entirety. NAFLD is characterised by steatosis of the liver, and in particular of hepatocytes. NAFLD includes non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is characterized by steatosis of the liver, involving greater than 5% of parenchyma, with no evidence of hepatocyte injury. NAFL may progress to NASH, which is steatosis combined with inflammation and/or fibrosis (steatohepatitis).

In particular embodiments, a disease/condition to be treated in accordance with the present disclosure may comprise or be characterised by one or more of the following: frailty, a reduction in muscle mass, an increase in fat mass, an increase in serum lipids (e.g. hyperlipidaemia), an increase in serum triglycerides (e.g. hypertriglyceridemia), an increase in serum cholesterol (e.g. hypercholesterolemia), an increase in liver triglycerides (e.g. steatosis of the liver), and a reduction in serum β -hydroxybutyrate. It will be appreciated that a reduction/increase is determined relative to the non-diseased state, or in the absence of the condition.

In some embodiments, a disease/condition to be treated or prevented in accordance with the present disclosure may be, or may be associated with, one or more Hallmark of Ageing. The "Hallmarks of Ageing", as described in López-Otín *et al.* 2013 consist of: telomere attrition, genomic instability, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, loss of proteostasis, deregulated nutrient sensing, epigenetic alterations, and altered intercellular communication. In some embodiments, the disease/condition to be treated or prevented in accordance with the present disclosure is, or is associated with, a Hallmark selected from deregulated nutrient sensing, loss of proteostasis and/or cellular senescence.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition in which gp130-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which signalling mediated by a gp130-containing complex is pathologically-implicated. In some embodiments, 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:OSMR β -mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which gp130:LIFR β -mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which gp130:LIFR β :CNTFR α -mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which gp130:IL-27R α -mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which gp130:IL-12R β 2-mediated signalling is pathologically-implicated.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition in which signalling mediated by a cytokine that signals through a gp130-containing complex is pathologically-implicated. In some embodiments, 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 OSM-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which LIF-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which CNTF-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which CT-1-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which CLC-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which IL-27-mediated signalling is pathologically-implicated. In some embodiments, the disease/condition is a disease/condition in which IL-35-mediated signalling is pathologically-implicated.

A disease/condition in which a given type of signalling is pathologically-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.

In some embodiments, the disease/condition to be treated/prevented 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 signalling mediated by a gp130-containing complex. 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 disease/condition is a disease/condition characterised by an increased level of gp130:OSMR β -mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of gp130:LIFR β -mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of gp130:LIFR β :CNTFR α -mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of gp130:IL-27R α -mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of gp130:IL-12R β 2-mediated signalling.

In some embodiments, the disease/condition to be treated/prevented in accordance with the present disclosure is a disease/condition characterised by an increased level of signalling mediated by a cytokine that signals through a gp130-containing complex. 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 OSM-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of LIF-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of CNTF-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of CT-1-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of CLC-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of IL-27-mediated signalling. In some embodiments, the disease/condition is a disease/condition characterised by an increased level of IL-35-mediated signalling.

The level of gp130-mediated signalling/signalling mediated by a gp130-containing complex/signalling mediated by a cytokine that signals through a gp130-containing complex can be evaluated by means well known to the skilled person, with reference also to the experimental examples of the present disclosure.

An 'increased' level of signalling in accordance with the present disclosure 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, sepsis, septic shock, age-related diseases/conditions, arthritis (e.g. rheumatoid arthritis, juvenile arthritis), lupus, pancreatitis, thyroiditis, Graves' disease, diabetes (e.g. type 1 diabetes and type 2 diabetes), multiple sclerosis, cardiovascular diseases, cardiogenic shock, atherosclerosis, systemic sclerosis, Alzheimer's disease, hippocampal atrophy, pulmonary disease, asthma, cystic fibrosis, hepatitis, inflammatory bowel disease, colitis, stroke, nephropathy, glomerulonephritis and cancers, including hematologic malignancies (e.g. plasmacytoma), lung cancer, colorectal cancer, intestinal cancer, urinary cancer, bladder cancer, vulvar cancer, breast cancer, stomach cancer and liver cancer (e.g. hepatocellular carcinoma). Diseases/conditions in which gp130:IL-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), 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, 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.

- 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 hyperglycemia, systemic sclerosis, keloid, scleroderma, periodontitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, dermatitis, atopic dermatitis, psoriasis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cirrhosis, hepatotoxicity, acetaminophen-induced hepatotoxicity, hepatitis, alcoholic liver disease, pancreatitis,

- steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, kidney injury, acute kidney injury, nephrotoxicity, glomerulonephritis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, Marfan syndrome, Hermansky-Pudlak syndrome, chronic kidney disease,
- 5 Alport syndrome, retinal fibrosis, age-related macular degeneration, wet age-related macular degeneration, breast cancer, stomach cancer, colorectal cancer, endometrial cancer, bone cancer, glioblastoma, liver cancer, leukemia, lung cancer, Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer and skin cancer.
- 10 OSM signalling in health and disease is reviewed *e.g.* in Richards, *ISRN Inflamm.* (2013) 2013:512103 and Dey *et al.*, *J Cell Commun Signal.* (2013) 7(2):103-108, both of which are hereby incorporated by reference in their entirety. OSM/gp130:OSMR β -mediated signalling and/or OSM/gp130:LIFR β -mediated signalling is implicated in the pathology of: autoimmune diseases and inflammatory conditions (*e.g.* rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease (Crohn's disease, ulcerative colitis),
- 15 psoriasis, systemic lupus erythematosus), cancers (breast cancer, lung cancer, ovarian cancer, pancreatic cancer, colorectal cancer, liver cancer), fibrotic diseases (*e.g.* pulmonary fibrosis, liver fibrosis, kidney fibrosis, systemic sclerosis, scleroderma), metabolic disorders (*e.g.* obesity, insulin resistance, type 2 diabetes), neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease), cardiovascular diseases (*e.g.* cardiac hypertrophy, heart failure, atherosclerosis).
- 20 LIF signalling in health and disease is reviewed *e.g.* in Wang *et al.*, *Mol Ther.* (2023) 31(2):331-343, which is hereby incorporated by reference in its entirety. LIF/gp130:LIFR β -mediated signalling is implicated in the pathology of: neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis), autoimmune diseases and inflammatory conditions (*e.g.* rheumatoid
- 25 arthritis, multiple sclerosis, inflammatory bowel disease (Crohn's disease, ulcerative colitis), psoriasis), metabolic disorders (*e.g.* obesity, insulin resistance), cancers (*e.g.* liver cancer, breast cancer, ovarian cancer, leukemia) and cardiovascular diseases (*e.g.* cardiac hypertrophy, heart failure, ischemic heart disease).
- 30 CT-1 signalling in health and disease is reviewed *e.g.* in Asrih, *Mediators Inflamm.* (2013) 2013:370715, which is hereby incorporated by reference in its entirety. CT-1/gp130:LIFR β -mediated signalling is implicated in the pathology of: neurological disorders (*e.g.* Alzheimer's disease, Parkinson's disease, ischemic stroke), metabolic disorders (*e.g.* obesity, insulin resistance, diabetes), skeletal muscle
- 35 disorders (*e.g.* muscular dystrophy, cachexia), inflammatory diseases (*e.g.* rheumatoid arthritis, systemic lupus erythematosus), cardiovascular diseases (*e.g.* heart failure, myocardial infarction, hypertrophic cardiomyopathy), liver diseases (*e.g.* alcoholic liver disease, non-alcoholic fatty liver disease) and renal diseases (*e.g.* renal fibrosis, chronic kidney disease).
- CNTF signalling in health and disease is reviewed *e.g.* in Schuster *et al.*, *J Biol Chem.* (2003) 278(11):9528-35 and Sleeman *et al.*, *Pharm Acta Helv.* (2000) 74(2-3):265-72, both of which are hereby incorporated by reference in their entirety. CNTF/gp130:CNTFR α -mediated signalling is implicated in the

pathology of: neurological disorders (e.g. Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis), retinal disorders (e.g. retinitis pigmentosa, age-related macular degeneration), metabolic disorders (e.g. obesity, insulin resistance), skeletal muscle disorders (e.g. muscular dystrophy, amyotrophy), inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease (Crohn's disease, ulcerative colitis)), cardiovascular diseases (e.g. heart failure, myocardial infarction) and endocrine disorders (e.g. polycystic ovary syndrome).

- CLC/gp130:CNTFR α -mediated signalling is implicated in the pathology of: neurological disorders (e.g. Alzheimer's disease, Parkinson's disease, ischemic stroke), metabolic disorders (e.g. obesity, insulin resistance, diabetes), skeletal muscle disorders (e.g. muscular dystrophy, cachexia), inflammatory diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus), cardiovascular diseases (e.g. heart failure, myocardial infarction, hypertrophic cardiomyopathy), liver diseases (e.g. alcoholic liver disease, non-alcoholic fatty liver disease) and renal diseases (e.g. kidney injury, renal fibrosis).
- IL-27 signalling in health and disease is reviewed e.g. in Meka *et al.*, *Autoimmun Rev.* (2015) 14(12): 1131–1141, Shahi *et al.*, *Int Immunopharmacol.* (2020) 84:106538 and Yoshida and Hunter, *Annu Rev Immunol.* (2015) 33:417–43, all of which are hereby incorporated by reference in their entirety. IL-27/gp130:IL-27R α -mediated signalling is implicated in the pathology of: autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis), inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), infectious disease (e.g. viral hepatitis, hepatitis B, HIV, influenza, malaria, tuberculosis), cancers (e.g. melanoma, lung cancer, breast cancer, hepatocellular carcinoma), allergic diseases (e.g. allergic rhinitis, atopic dermatitis asthma) and neurological disorders (e.g. multiple sclerosis, Alzheimer's disease, stroke).
- IL-35 signalling in health and disease is reviewed e.g. in Ye *et al.*, *J Interferon Cytokine Res.* (2021) 41(11):391–406, which is hereby incorporated by reference in its entirety. IL-35/gp130:IL-12R β 2-mediated signalling is implicated in the pathology of: autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis), inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), infectious disease (e.g. viral disease, malaria, tuberculosis), cancers (e.g. breast cancer, lung cancer, colorectal cancer, hepatocellular carcinoma), transplant rejection and graft-versus-host disease.

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 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 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, 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 embodiments, articles of the present disclosure may be administered topically to the eye or skin. In such embodiments, a micro-dose of the relevant article may be employed.

In some embodiments, articles of the present disclosure may be administered to an immune-privileged site. In some embodiments, administration may be intrathecal or intraocular.

In some aspects and embodiments in accordance with the present disclosure there may be targeted delivery of articles of the present disclosure, *i.e.* wherein the concentration of the relevant agent in the subject is increased in some parts of the body relative to other parts of the body. In some embodiments, the methods comprise intravenous, intra-arterial, intramuscular or subcutaneous administration and wherein the relevant article is formulated in a targeted agent delivery system. Suitable targeted delivery systems include, for example, nanoparticles, liposomes, micelles, beads, polymers, metal particles, dendrimers, antibodies, aptamers, nanotubes or micro-sized silica rods. Such systems may comprise a magnetic element to direct the agent to the desired organ or tissue. Suitable nanocarriers and delivery systems will be apparent to one skilled in the art.

In some cases, the articles of the present disclosure are formulated for targeted delivery to specific cells, a tissue, an organ and/or a tumor.

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.

- 5 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.

- 15 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.

- 25 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.

- 30 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).

- 35 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 , inhibition of signalling mediated by gp130:IL-11R α , inhibition of signalling mediated by gp130:OSMR β , inhibition of signalling mediated by gp130:LIFR β , inhibition of signalling mediated by gp130:LIFR β :CNTFR α , inhibition of signalling mediated by gp130:IL-27R α , inhibition of signalling mediated by gp130:IL-12R β 2, inhibition of

signalling mediated by a cytokine that binds to a receptor comprising gp130, inhibition of IL-6-mediated signalling, inhibition of IL-11-mediated signalling, inhibition of OSM-mediated signalling, inhibition of LIF-mediated signalling, inhibition of CNTF-mediated signalling, inhibition of CT-1-mediated signalling, inhibition of CLC-mediated signalling, inhibition of IL-27-mediated signalling, inhibition of IL-35-mediated signalling, 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 one or more receptors comprising gp130 (e.g. signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and/or gp130:IL-12R β 2; e.g. signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β and/or gp130:LIFR β :CNTFR α), and/or use of an antigen-binding molecule according to the present disclosure to inhibit signalling mediated by one or more cytokines that bind to a receptor comprising gp130 (e.g. signalling mediated by IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 and/or IL-35; e.g. signalling mediated by IL-6, IL-11, OSM, LIF, CNTF and/or CT-1).

The present disclosure further provides methods for inhibiting signalling mediated by one or more receptors comprising gp130 (e.g. signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and/or gp130:IL-12R β 2; e.g. signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β and/or gp130:LIFR β :CNTFR α), and/or methods for inhibiting signalling mediated by one or more cytokines that bind to a receptor comprising gp130 (e.g. signalling mediated by IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 and/or IL-35; e.g. signalling mediated by IL-6, IL-11, OSM, LIF, CNTF and/or CT-1) 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 one or more receptors comprising gp130 (e.g. signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β , gp130:LIFR β :CNTFR α , gp130:IL-27R α and/or gp130:IL-12R β 2; e.g. signalling mediated by gp130:IL-6R α , gp130:IL-11R α , gp130:OSMR β , gp130:LIFR β and/or gp130:LIFR β :CNTFR α) in a subject, and/or methods for inhibiting signalling mediated by one or more cytokines that bind to a receptor comprising gp130 (e.g. signalling mediated by IL-6, IL-11, OSM, LIF, CNTF, CT-1, CLC, IL-27 and/or IL-35; e.g. signalling mediated by IL-6, IL-11, OSM, LIF, CNTF and/or CT-1) in a subject, comprising administering to a subject an antigen-binding molecule according to the present disclosure.

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.

5 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.

10 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.

15 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
20 well known to those of skill in the art and can be selected to correspond with the labelling agent.

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

25 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*.

30 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
35 tests described herein.

Detection in a sample may be used for the purpose of diagnosis of a disease/condition (*e.g.* a cancer), predisposition to a disease/condition, or for providing a prognosis (prognosticating) for a disease/condition, *e.g.* a disease/condition described herein. The diagnosis or prognosis may relate to an
40 existing (previously diagnosed) disease/condition.

A sample may be taken from any tissue or bodily fluid. The sample may comprise or may be derived from: a quantity of blood; a quantity of serum derived from the individual's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a tissue sample or biopsy; pleural fluid; cerebrospinal fluid (CSF); or cells isolated from said individual. In some
5 embodiments, the sample may be obtained or derived from a tissue or tissues which are affected by the disease/condition (e.g. tissue or tissues in which symptoms of the disease manifest, or which are involved in the pathogenesis of the disease/condition).

A subject may be selected for diagnostic/prognostic evaluation based on the presence of symptoms
10 indicative of a disease/condition described herein, or based on the subject being considered to be at risk of developing a disease/condition described herein.

The present disclosure also provides methods for selecting/stratifying a subject for treatment with a gp130-targeted agent. In some embodiments a subject is selected for treatment/prevention in accordance
15 with the methods of the present disclosure, or is identified as a subject which would benefit from such treatment/prevention, based on detection/quantification of gp130, or cells expressing gp130, e.g. in a sample obtained from the individual.

Subjects

20 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).

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
25 preferably mammalian, more preferably human. The subject may be a non-human mammal, but is more preferably human. The subject may be male or female. The subject may be a patient.

A subject may have (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
30 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.

In some embodiments, a subject may be selected for therapeutic or prophylactic intervention as
35 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.

Kits

40 The present disclosure also provides kits of parts.

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.

- 5 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
10 composition further comprising a pharmaceutically-acceptable carrier, diluent, excipient or adjuvant.

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).

- 15 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
20 combined treatment for the specific disease/condition.

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.

25

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
30 between the sequences. Pairwise and multiple sequence alignment for the purposes of determining percent sequence identity between two or more amino acid or nucleic acid sequences can be achieved in various ways known to a person of skill in the art, for instance, using publicly available computer software such as ClustalOmega (Söding, J. 2005, Bioinformatics 21, 951-960), T-coffee (Notredame *et al.* 2000, J. Mol. Biol. (2000) 302, 205-217), Kalign (Lassmann and Sonnhammer 2005, BMC Bioinformatics, 6(298))
35 and MAFFT (Katoh and Standley 2013, Molecular Biology and Evolution, 30(4) 772-780) software. When using such software, the default parameters, *e.g.* for gap penalty and extension penalty, are preferably used.

Numbered statements

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

1. An antigen-binding molecule, optionally isolated, which binds to gp130, wherein the antigen-binding molecule inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling.
- 5
2. The antigen-binding molecule according to para 1, wherein the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:89.
3. The antigen-binding molecule according to para 1 or para 2, wherein the antigen-binding molecule
- 10 comprises:
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
- HC-CDR1 having the amino acid sequence of SEQ ID NO:2
- HC-CDR2 having the amino acid sequence of SEQ ID NO:3
- HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and
- 15 (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.
- 20 4. The antigen-binding molecule according to any one of paras 1 to 3, wherein the antigen-binding molecule comprises:
- (a)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:112, and
- 25 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:121; or
- (b)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:117, and
- 30 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:126; or
- (c)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and
- 35 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or
- (d)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and
- 40 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or

- (e)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:94, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or
- (f)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or
- (g)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or
- (h)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:98, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or
- (i)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:102; or
- (j)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:106; or
- (k)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:174, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:109; or
- (l)
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:1, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:9.

5. The antigen-binding molecule according to para 1 or para 2, wherein the antigen-binding molecule comprises:
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - HC-CDR1 having the amino acid sequence of SEQ ID NO:18
 - HC-CDR2 having the amino acid sequence of SEQ ID NO:19
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:20; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:28.
6. The antigen-binding molecule according to any one of paras 1, 2 or 5, wherein the antigen-binding molecule comprises:
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:17, and
 - (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:25.
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 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.
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 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.
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.

14. An antigen-binding molecule according to any one of paras 1 to 7, a CAR according to para 8, a
 5 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.
15. An antigen-binding molecule according to any one of paras 1 to 7, a CAR according to para 8, a
 10 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 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
 15 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, dermatitis, atopic dermatitis,
 20 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
 25 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
 30 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
 35 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,
 40 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.
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.
20. An antigen-binding molecule which binds to gp130 and inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling 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,

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 contacts the region of gp130 shown in SEQ ID NO:89.

21. Use of an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89 to inhibit IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling.

22. A method for inhibiting IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling, comprising contacting cells capable of IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling with an antigen-

30 binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89.

23. A method for inhibiting IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling in a subject, comprising administering to a subject an antigen-binding molecule that binds to gp130 and that contacts

35 the region of gp130 shown in SEQ ID NO:89.

24. The antigen-binding molecule for use according to para 20, the use according to para 21 or the method according to para 22 or para 23, wherein the antigen-binding molecule comprises:

- (i) a heavy chain variable (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: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.

25. The antigen-binding molecule for use according to para 20 or para 24, the use according to para 21 or para 24, or the method according to any one of paras 22 to 24, wherein the antigen-binding molecule comprises:

10 (a)

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

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

15 (b)

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

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

20 (c)

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

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

25 (d)

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

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

30 (e)

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

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

35 (f)

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

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

40 (g)

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

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

5 (h)

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

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

10 (h)

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

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

15 (i)

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

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

20 (j)

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

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

25 (k)

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

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

30 (l)

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

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

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26. The antigen-binding molecule for use according to para 20, the use according to para 21 or the method according to para 22 or para 23, wherein the antigen-binding molecule comprises:

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

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

40

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

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

- (ii) a light chain variable (VL) region incorporating the following CDRs:
- LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:28.

5

27. The antigen-binding molecule for use according to para 20 or para 26, the use according to para 21 or para 26 or the method according to any one of paras 22, 23 or 26, wherein the antigen-binding molecule comprises:

- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:17, and
- (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to SEQ ID NO:25.

28. The antigen-binding molecule for use according to any one of paras 20 or 24 to 27, the use according to any one of paras 21 or 24 to 27, or the method according to any one of paras 22 to 27, 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.

20 Sequences

SEQ ID NO:	DESCRIPTION	SEQUENCE
1	B035-C03-A3 VH	EVQLVESGGGLVQPGGSLKLSCAASGFTFSNYGIHWIRQAPT KGLEWVALISPSGYSTFYRDSVKGRFTISRDNANSTLYLQMDSLRSEDATYYCATPMMAVITPY YFDYWGQGVMVTVSS
2	B035-C03-A3, A3_3.2, A3_4.2, A3_6.2 HC-CDR1	GFTFSNYG
3	B035-C03-A3, A3_3.2, A3_4.2, A3_6.2 HC-CDR2	ISPSGYST
4	B035-C03-A3, A3_3.2, A3_4.2, A3_6.2 HC-CDR3	ATPMMAVITPY YFDY
5	B035-C03-A3 HC-FR1	EVQLVESGGGLVQPGGSLKLSCAAS
6	B035-C03-A3 HC-FR2	IHWIRQAPT KGLEWVAL
7	B035-C03-A3 HC-FR3	FYRDSVKGRFTISRDNANSTLYLQMDSLRSEDATYYC
8	B035-C03-A3 HC-FR4	WGQGVMVTVSS
9	B035-C03-A3 VL	DVQMTQSPYNLAASPGESVSINCKASKSISKYLA WYQQKPGKANKLLIYDGSTLQSGIPSRFSGSGSGTDFTLTIRSLPEPDFGLYYCQQHNEY PPTFGSGTKLEIK
10	B035-C03-A3, A3_3, A3_4, A3_5 LC-CDR1	KSISKY
11	B035-C03-A3, A3_3, A3_4, A3_5 LC-CDR2	DGS
12	B035-C03-A3, A3_3, A3_4, A3_5 LC-CDR3	QQHNEY PPT
13	B035-C03-A3 LC-FR1	DVQMTQSPYNLAASPGESVSINCKAS

14	B035-C03-A3, A3_3, A3_4 LC-FR2	LAWYQQKPGKANKLLIY
15	B035-C03-A3 LC-FR3	TLQSGIPSRFSGSGSGTDFTLTIRSLEPEDFGLYYC
16	B035-C03-A3 LC-FR4	FGSGTKLEIK
17	CSP-S-5H8 VH	QVQLKESGPGLVQPSQTLSTCTVSGFSLTNNNIHWWRQPPGKGLEWVGAIWSSGGSTDYDSALKS RLTISRDTSKSQVFLKMNSLQAEDTAIFYCTKSFYDGGYYWLGWYWGQGLVTVSS
18	CSP-S-5H8 HC-CDR1	GFSLTNNN
19	CSP-S-5H8 HC-CDR2	IWSGGST
20	CSP-S-5H8 HC-CDR3	TKSFYDGGYYWLGW
21	CSP-S-5H8 HC-FR1	QVQLKESGPGLVQPSQTLSTCTVS
22	CSP-S-5H8 HC-FR2	IHWVRQPPGKGLEWVGA
23	CSP-S-5H8 HC-FR3	DYDSALKSRLTISRDTSKSQVFLKMNSLQAEDTAIFYC
24	CSP-S-5H8, A3_3.2, A3_4.2, A3_6.2 HC-FR4	WGQGLTVTVSS
25	CSP-S-5H8 VL	ETVMTQSPTSMSTSIGERVTLNCKASQSVNDINVDWYQQTPGQSPKLLIYGASNRHTGVPDRFTGSR FGKDFTLTISNVESEDLAVYYCLQYDSIPWTFGGGTKLELK
26	CSP-S-5H8 LC-CDR1	QSVNDIN
27	CSP-S-5H8 LC-CDR2	GAS
28	CSP-S-5H8 LC-CDR3	LQYDSIPWT
29	CSP-S-5H8 LC-FR1	ETVMTQSPTSMSTSIGERVTLNCKAS
30	CSP-S-5H8 LC-FR2	VDWYQQTPGQSPKLLIY
31	CSP-S-5H8 LC-FR3	NRHTGVPDRFTGSRFGKDFTLTISNVESEDLAVYYC
32	CSP-S-5H8 LC-FR4	FGGGTKLELK
33	Human IgG1 constant region (IGHG1; UniProt:P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
34	CH1 IgG1 (positions 1-98 of P01857-1, v1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV
35	Hinge IgG1 (positions 99-110 of P01857-1, v1)	EPKSCDKTHTCP
36	CH2 IgG1 (positions 111-223 of P01857-1, v1)	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
37	CH3 IgG1 (positions 224-330 of P01857-1, v1)	GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
38	Human IgG1 constant region G1m3 allotype (K214R, D356E and L358M (EU numbering) relative to P01857-1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K
39	CH1 IgG1 G1m3 allotype	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
40	CH3 IgG1 G1m3 allotype	GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
41	Human IgG4 constant region (IGHG4; UniProt:P01861-1, v1)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSDQEDPEVKFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
42	Human IgG1 CH2-CH3 region	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK

43	Human IgG1 G1m3 allotype CH2-CH3 region	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG
44	Human IgG4 CH2-CH3 region	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSPG
45	CH2 IgG1 (YTE)	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
46	Human IgG1 CH2-CH3 region (YTE)	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
47	Human IgG1 G1m3 allotype CH2-CH3 region (YTE)	PCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
48	Human IgG1 constant region (YTE)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT LYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVTLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
49	Human IgG1 constant region G1m3 allotype (YTE)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVTLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG K
50	Human IgG4 constant region (S228P, L235E)	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQDWLNGK EYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK
51	Human IgG4 CH1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVDHKPSNTKVDKRV
52	Human IgG4 hinge	ESKYGPPCPPCP
53	Human IgG4 hinge (S228P)	ESKYGPPCPPCP
54	Human IgG4 CH2	APEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
55	Human IgG4 CH2 (L235E)	APEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK
56	Human IgG4 CH3	GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPGK
57	Human IgG4 CH2-CH3 (L235E)	APEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVTLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCS VMHEALHNHYTQKSLSLSPGK
58	Cκ CL (IGKC; UniProt: P01834-1, v2)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
59	Cλ CL1 (IGLC1; UniProt: P0CG04-1, v1)	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNMKY AASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
60	Cλ CL2 (IGLC2; UniProt: P0DOY2-1, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNMKY AASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
61	Cλ CL3 (IGLC3; UniProt: P0DOY3-1, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNMKY AASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
62	Cλ CL6 (IGLC6; UniProt: P0CF74-1, v1)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTGVETTTTPSKQSNMKY AASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPAECS
63	Cλ CL7 (IGLC7; UniProt: A0M8Q6-1, v3)	GQPKAAPSVTFLFPPSSEELQANKATLVCLISDFNPGAVTVAWKADGSPVKVGVETTKPSKQSNMKY AASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVAPAECS

64	B035-C03-A3 hlgG1 HC	EVQLVESGGGLVQPGGSLKLSAASGFTFSNYGIHWIRQAPTQKLEWVALISPSGYSTFYRDSVKGRFTISRDNANSTLYLQMDSLRSEDATYYCATPMMAVITPYFYFDYWGQGVMVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
65	B035-C03-A3 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLKLSAASGFTFSNYGIHWIRQAPTQKLEWVALISPSGYSTFYRDSVKGRFTISRDNANSTLYLQMDSLRSEDATYYCATPMMAVITPYFYFDYWGQGVMVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSL GTKTYTCNVNDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGSPVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSCVMHEALHNHYTQKSLSLSLGK
66	B035-C03-A3 K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGSGS GTDFTLTIRSLPEDFGLYYCQQHNEYPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC L LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
67	CSP-S-5H8 hlgG1 HC	QVQLKESGPGLVQPSQTLSTLTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSGGSTDYDSALKS RLTISRDTSKSQVFLKMNSLQAEDTAIFYCTKSFYDGGYYWLGWYWGQGLTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK
68	CSP-S-5H8 hlgG4(S228P, L235E) HC	QVQLKESGPGLVQPSQTLSTLTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSGGSTDYDSALKS RLTISRDTSKSQVFLKMNSLQAEDTAIFYCTKSFYDGGYYWLGWYWGQGLTVTVSSASTKGPSVFPL APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLG TKTYYTCNVNDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGSPVFLFPPKPKDTLMISRTPEVTCV VVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKG LPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT TTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSCVMHEALHNHYTQKSLSLSLGK
69	CSP-S-5H8 K LC	ETVMTQSPTSMSTSIGERVTLNCKASQSVNDINVDWYQQTPGQSPKLLIYGASNRHTGVPDRFTGSR FGKDFLTISNVEEDLAVYYCLQYDSIPWTFGGGTLKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC L LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC
70	Human gp130 isoform 1 (UniProt: P40189-1, v2)	MLTLQTWLVQALFIFLTTESTGELLDPGCGYISPESPVVQLHSNFTAVCVLKEKCMDFYFHNANYIWW KTNHFTIPKEQYTIINRTASSVTFDTIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEG KKMRCCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENAL GKVTSDHINFDPVYKVKPNPPHNLVINSEELSSILKLTWNTNPSIKSVIILKYNIQYRTKDASTWSQIPP EDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSFYWKIDPSH TQGYRTVQLVWKTLPPEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVG KSDAAVLTPACDFQATHPVMMDLKAFPKDNMLWVEWTPPRESVKKYILEWCVLSDKAPCITDWQQE DGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVTRTKKVGKNEAVLEW DQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLVMDVRMAAYTDEGGKDGPEF TTTTPKFAQGEIEAIVVPVCLAFLLTLLGLVLCFNKRDLIKHIWPNVPDPSKSHIAQWSPHTPPRH NFNKSKDQMYSDGNFTDVSVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRPSIS SSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGD GILPRQQYFKQNCQSHESSPDISHFERSKQVSSVNEEDFVRLKQKQISDHISQSCGSGQMCMFQEV SAADAFGPGTEGQVERFETVGMEAATDEGMPKSYLPQTVRQGGYMPQ
71	Human gp130 isoform 2 (UniProt: P40189-2)	MLTLQTWLVQALFIFLTTESTGELLDPGCGYISPESPVVQLHSNFTAVCVLKEKCMDFYFHNANYIWW KTNHFTIPKEQYTIINRTASSVTFDTIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEG KKMRCCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENAL GKVTSDHINFDPVYKVKPNPPHNLVINSEELSSILKLTWNTNPSIKSVIILKYNIQYRTKDASTWSQIPP EDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDNIAF
72	Human gp130 isoform 3 (UniProt: P40189-3)	MLTLQTWLVQALFIFLTTESTGELLDPGCGYISPESPVVQLHSNFTAVCVLKEKCMDFYFHNANYIWW KTNHFTIPKEQYTIINRTASSVTFDTIASLNIQLTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEG KKMRCCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENAL GKVTSDHINFDPVYKVKPNPPHNLVINSEELSSILKLTWNTNPSIKSVIILKYNIQYRTKDASTWSQIPP EDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKAPSFYWKIDPSH TQGYRTVQLVWKTLPPEANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVG KSDAAVLTPACDFQGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVTRTKKVGKNEA VLEWDQLPVDVQNGFIRNYTIFYRTIIGNETAVNVDSSHTEYTLSSLTSDTLVMDVRMAAYTDEGGK DGEFTTTTPKFAQGEIEAIVVPVCLAFLLTLLGLVLCFNKRDLIKHIWPNVPDPSKSHIAQWSPHTP PRHNFNFKSKDQMYSDGNFTDVSVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSS RPSISSDENESSQNTSSTVQYSTVVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVD GGDGILPRQQYFKQNCQSHESSPDISHFERSKQVSSVNEEDFVRLKQKQISDHISQSCGSGQMCMF QEVSAADAFGPGTEGQVERFETVGMEAATDEGMPKSYLPQTVRQGGYMPQ

73	Human gp130 signal peptide	MLTLQTWLVQALFIFLTTESTG
74	Mature human gp130 isoform 1	ELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNILQTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVPNPPTHNLVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYSWSDWSEEASGITYEDRPSKAPSFYWKIDPSHTQGYRTVQLVWKTLPPEFANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVTRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETA VNV DSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKFAAQGEIAIVVPVCLAFLLTLLGVLCF
75	Human gp130 extracellular domain	ELLDPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNILQTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVPNPPTHNLVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYSWSDWSEEASGITYEDRPSKAPSFYWKIDPSHTQGYRTVQLVWKTLPPEFANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQATHPVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPPSKGPTVTRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETA VNV DSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKFAAQGEIE
76	Human gp130 transmembrane domain	AIVVPVCLAFLLTLLGVLCF
77	Human gp130 cytoplasmic domain	NKRDLIKHIWPNVPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVSVVEIEANDKKPFPEDLKSLDLFKKEKINTEGHSSGIGGSSCMSSSRPSISSSDENESSQNTSSSTVQYSTVVHSGYRHQVPSVQVFSRSESTQPLLDSEERPEDLQLVDHVDGGDGILPRQQYFKQNCQSHESSPDISHFERSKQVSVNEEDFVRLKQKQISDHISQSCGSGQMFMFQEVSAADAFGPGTEGQVERFETVGMEEATDEGMPKSYLPQTVRQGGYMPQ
78	Human gp130 Ig-like C2-type domain	DPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNILQTCNILTFGQLEQNVYGITI
79	Human gp130 FNIII domain 1	PPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDP
80	Human gp130 FNIII domain 2	PPHNLVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYSWSDWSEEASGITYED
81	WSXWS motif	WSDWS
82	Human gp130 FNIII domain 3	APSFYWKIDPSHTQGYRTVQLVWKTLPPEFANGKILDYEVTLTRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTIPACDFQAT
83	Human gp130 FNIII domain 4	PVMDLKAFPKDNMLWVEWTTPRESVKKYILEWCVLSDKAPCITDWQQEDGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQA
84	Human gp130 FNIII domain 5	PPSKGPTVTRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYRTIIGNETA VNV DSSHTEYTLSSLTSDTLYMVRMAAYTDEGGKDGPEFTFTTPKF
85	Human gp130 cytokine-binding module	DPCGYISPESPVVQLHSNFTAVCVLKEKCMDYFHVNANYIVWKTNHFTIPKEQYTIINRTASSVTFTDIASLNILQTCNILTFGQLEQNVYGITIISGLPPEKPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVPNPPTHNLVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMKEDGKGYSWSDWSEEASGITYED
86	CSP-S-5H8 epitope region 1	KPKNLSCIVNEGKKMR
87	CSP-S-5H8 epitope region 2	YRT
88	CSP-S-5H8 epitope region 3	RCMK
89	CSP-S-5H8 epitope region composite	KPKNLSCIVNEGKKMRCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVPNPPTHNLVINSEELSSILKLTWTNPSIKSVIILKYNIQYRTKDASTWSQIPPEDTASTRSSFTVQDLKPFTEYVFRIRCMK
90	B035-C03-A3 epitope region A1	RCEWDGGR
91	B035-C03-A3 epitope region A2	KSEWATHKFADCK
92	B035-C03-A3 epitope region A3	KSVIILKYNIQYR
93	B035-C03-A3 epitope region composite 1	RCEWDGGRETHLETNFTLKSEWATHKFADCKAKRDTPTSTCTVDYSTVYFVNIEVWVEAENALGKVTSDHINFDPVYKVPNPPTHNLVINSEELSSILKLTWTNPSIKSVIILKYNIQYR

94	A3_3.2 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDSVKGRFTISRDN SKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LTVSS
95	A3_3.2 HC-FR1	EVQLLESGGGLVQPGGSLRLSCAAS
96	A3_3.2 HC-FR2	IHWVRQAPGKGLEWVSL
97	A3_3.2 HC-FR3	FYRDSVKGRFTISRDN SKNTLYLQMDSLRAEDTATYYC
98	A3_4.2 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSVKG RFTISRDN AKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LTVSS
99	A3_4.2, A3_6.2 HC-FR1	EVQLVESGGGLVQPGGSLRLSCAAS
100	A3_4.2 HC-FR2	IHWIRQAPGKGLEWVSL
101	A3_4.2, A3_6.2 HC-FR3	FYRDSVKGRFTISRDN AKNTLYLQMDSLRAEDTATYYC
102	A3_3 VL	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQQHNEYPPTFGQGT KLEIK
103	A3_3 LC-FR1	DVQMTQSPSSLSASVGDRVTITCKAS
104	A3_3 LC-FR3	TLQSGIPSRFSGSGSGTDFTLTISSLQPEDFATYYC
105	A3_3, A3_4, A3_5 LC-FR4	FGQGT KLEIK
106	A3_4 VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFGLYYCQQQHNEYPPTFGQGT KLEIK
107	A3_4, A3_5 LC-FR1	DIQMTQSPSSLSASVGDRVTITCKAS
108	A3_4 LC-FR3	TLQSGVPSRFSGSGSGTDFTLTISSLQPEDFGLYYC
109	A3_5 VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYDGSTLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQQHNEYPPTFGQGT KLEIK
110	A3_5 LC-FR2	LAWYQQKPGKAPKLLIY
111	A3_5 LC-FR3	TLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
112	A3-derived VH CON	EVQLX ₁ ESGGGLVQPGGSLX ₂ LSCAASGFTFSNYGIHWX ₃ RQAPX ₄ KGLEWVX ₅ LISPSGYSTFYRDS VKGRFTISRDNX ₆ X ₇ X ₈ TLYLQMDSLRX ₉ EDTATYYCATPMMAVITPYFDYWGQGX ₁₀ X ₁₁ VTVSS wherein X ₁ = V or L, X ₂ = R or K, X ₃ = I or V, X ₄ = G or T, X ₅ = S or A, X ₆ = A or S, X ₇ = K or N, X ₈ = N or S, X ₉ = A or S, X ₁₀ = T or V, X ₁₁ = L or M
113	A3-derived HC-FR1 CON	EVQLX ₁ ESGGGLVQPGGSLX ₂ LSCAAS wherein X ₁ = V or L, X ₂ = R or K
114	A3-derived HC-FR2 CON	IHWX ₁ RQAPX ₂ KGLEWVX ₃ L wherein X ₁ = I or V, X ₂ = G or T, X ₃ = S or A
115	A3-derived HC-FR3 CON	FYRDSVKGRFTISRDNX ₁ X ₂ X ₃ TLYLQMDSLRX ₄ EDTATYYC wherein X ₁ = A or S, X ₂ = K or N, X ₃ = N or S, X ₄ = A or S
116	A3-derived HC-FR4 CON	WGQGX ₁ X ₂ VTVSS wherein X ₁ = T or V, X ₂ = L or M
117	A3-Hum VH CON	EVQLX ₁ ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX ₂ RQAPGKGLEWVX ₃ LISPSGYSTFYRDSV KGRFTISRDNX ₄ KNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LTVSS wherein X ₁ = V or L, X ₂ = I or V, X ₃ = S or A, X ₄ = A or S
118	A3-Hum HC-FR1 CON	EVQLX ₁ ESGGGLVQPGGSLRLSCAAS wherein X ₁ = V or L
119	A3-Hum HC-FR2 CON	IHWX ₁ RQAPGKGLEWVX ₂ L wherein X ₁ = I or V, X ₂ = S or A
120	A3-Hum HC-FR3 CON	FYRDSVKGRFTISRDNX ₁ KNTLYLQMDSLRAEDTATYYC wherein X ₁ = A or S
121	A3-derived VL CON	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ I ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYDGSTLQSGX ₁₁ P SRFSGSGSGTDFTLTIX ₁₂ SLX ₁₃ PEDFX ₁₄ X ₁₅ YYCQQQHNEYPPTFGX ₁₆ GTKLEIK wherein X ₁ = V or I, X ₂ = S or Y, X ₃ = S or N, X ₄ = S or A, X ₅ = V or P, X ₆ = D or E, X ₇ = R or S, X ₈ = T or S, X ₉ = N or T, X ₁₀ = N or P, X ₁₁ = V or I, X ₁₂ = S or R, X ₁₃ = Q or E, X ₁₄ = A or G, X ₁₅ = T or L, X ₁₆ = Q or S
122	A3-derived LC-FR1 CON	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ I ₉ CKAS wherein X ₁ = V or I, X ₂ = S or Y, X ₃ = S or N, X ₄ = S or A, X ₅ = V or P, X ₆ = D or E, X ₇ = R or S, X ₈ = T or S, X ₉ = N or T

123	A3-derived LC-FR2 CON	LAWYQQKPGKAX ₁ KLLIY wherein X ₁ = N or P
124	A3-derived LC-FR3 CON	TLQSGX ₁ PSRFSGSGSGTDFTLIX ₂ SLX ₃ PEDFX ₄ X ₅ YYC wherein X ₁ = V or I, X ₂ = S or R, X ₃ = Q or E, X ₄ = A or G, X ₅ = T or L
125	A3-derived LC-FR4 CON	FGX ₁ GTKLEIK wherein X ₁ = Q or S
126	A3-Hum VL CON	DX ₁ QMTQSPSSLSASVGDRVITICKASKSISKYLAWYQQKPGKAX ₂ KLLIYDGSTLQSGX ₃ PSRFSGSGSGTDFTLTISSLQPEDX ₄ X ₅ LYYCQQHNEYPTFGGQGTKLEIK wherein X ₁ = V or I, X ₂ = N or P, X ₃ = V or I, X ₄ = A or G, X ₅ = T or L
127	A3-Hum LC-FR1 CON	DX ₁ QMTQSPSSLSASVGDRVITICKAS wherein X ₁ = V or I
128	A3-Hum LC-FR2 CON	LAWYQQKPGKAX ₁ KLLIY wherein X ₁ = N or P
129	A3-Hum LC-FR3 CON	TLQSGX ₁ PSRFSGSGSGTDFTLTISSLQPEDX ₂ X ₃ LYYC wherein X ₁ = V or I, X ₂ = A or G, X ₃ = T or L
130	A3_3.2 hlgG1 HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDSVKGRFTISRDN SKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
131	A3_3.2 hlgG4(S228P, L235E) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDSVKGRFTISRDN SKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LVT VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSLGK
132	A3_4.2 hlgG1 HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSVKG RFTISRDN AKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LVT VSSASTKGPSVFLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK
133	A3_4.2 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSVKG RFTISRDN AKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGT LVT VSSASTKGPSVFLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYTCNV DHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSLGK
134	A3-derived CON hlgG1 HC	EVQLX ₁ ESGGGLVQPGGSLX ₂ LSCAASGFTFSNYGIHWX ₃ RQAPX ₄ KGLEWVX ₅ LISPSGYSTFYRDSVKGRFTISRDNX ₆ X ₇ X ₈ TLYLQMDSLRX ₉ EDTATYYCATPMMAVITPYFDYWGQGX ₁₀ X ₁₁ VTVSSASTKGPSVFLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK wherein X ₁ = V or L, X ₂ = R or K, X ₃ = I or V, X ₄ = G or T, X ₅ = S or A, X ₆ = A or S, X ₇ = K or N, X ₈ = N or S, X ₉ = A or S, X ₁₀ = T or V, X ₁₁ = L or M
135	A3-derived hlgG4(S228P, L235E) HC	EVQLX ₁ ESGGGLVQPGGSLX ₂ LSCAASGFTFSNYGIHWX ₃ RQAPX ₄ KGLEWVX ₅ LISPSGYSTFYRDSVKGRFTISRDNX ₆ X ₇ X ₈ TLYLQMDSLRX ₉ EDTATYYCATPMMAVITPYFDYWGQGX ₁₀ X ₁₁ VTVSSASTKGPSVFLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYTCNV DHKPSNTKVDKRVESKYGPCCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQQGNV FSCSV MHEALHNHYTQKSLSLSLGK

		wherein $X_1 = V$ or L , $X_2 = R$ or K , $X_3 = I$ or V , $X_4 = G$ or T , $X_5 = S$ or A , $X_6 = A$ or S , $X_7 = K$ or N , $X_8 = N$ or S , $X_9 = A$ or S , $X_{10} = T$ or V , $X_{11} = L$ or M
136	A3-Hum CON hlgG1 HC	EVQLX ₁ ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX ₂ RQAPGKGLEWVX ₃ LISPSGYSTFYRDSV KGRFTISRDNX ₄ KNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGTLLTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNNKALPAPIEKTKAKAGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK wherein $X_1 = V$ or L , $X_2 = I$ or V , $X_3 = S$ or A , $X_4 = A$ or S
137	A3-Hum hlgG4(S228P, L235E) HC	EVQLX ₁ ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX ₂ RQAPGKGLEWVX ₃ LISPSGYSTFYRDSV KGRFTISRDNX ₄ KNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDYWGQGTLLTVSSASTKGPS VFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS SSLGTQTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKCV SNKGLPSSIEKTKAKAGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFCFSVMHEALHNHYTQKSLSLSPGK wherein $X_1 = V$ or L , $X_2 = I$ or V , $X_3 = S$ or A , $X_4 = A$ or S
138	A3_3 K LC	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGIPSRFSGSGS GTDFTLTISLQPEDFATYYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
139	A3_4 K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDGSTLQSGVPSRFSGSGS GTDFTLTISLQPEDFGLYYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
140	A3_5 K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYDGSTLQSGVPSRFSGSGS GTDFTLTISLQPEDFATYYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
141	A3-derived CON K LC	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ IX ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYDGSTLQSGX ₁₁ P SRFSGSGSGTDFTLTIX ₁₂ SLX ₁₃ PEDFX ₁₄ X ₁₅ YCCQQHNEYPPTFG ₁₆ GTKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC wherein $X_1 = V$ or I , $X_2 = S$ or Y , $X_3 = S$ or N , $X_4 = S$ or A , $X_5 = V$ or P , $X_6 = D$ or E , $X_7 = R$ or S , $X_8 = T$ or S , $X_9 = N$ or T , $X_{10} = N$ or P , $X_{11} = V$ or I , $X_{12} = S$ or R , $X_{13} = Q$ or E , $X_{14} = A$ or G , $X_{15} = T$ or L , $X_{16} = Q$ or S
142	A3-Hum K LC	DX ₁ QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX ₂ KLLIYDGSTLQSGX ₃ PSRFSGS GSGTDFTLTISLQPEDX ₄ SL ₅ LYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC wherein $X_1 = V$ or I , $X_2 = N$ or P , $X_3 = V$ or I , $X_4 = A$ or G , $X_5 = T$ or L
143	B035-C03-A3_D50X VL	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYX ₁ GSTLQSGIPSRFSGSG SGTDFLTIRSLPEDFGLYYCQQHNEYPPTFGSGTKLEIK wherein $X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H$ or Q
144	A3_3_D50X VL	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX ₁ GSTLQSGIPSRFSGSG SGTDFLTISLQPEDFATYYCQQHNEYPPTFGQGTKEIK wherein $X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H$ or Q
145	A3_4_D50X VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX ₁ GSTLQSGVPSRFSGSG SGTDFLTISLQPEDFGLYYCQQHNEYPPTFGQGTKEIK wherein $X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H$ or Q
146	A3_5_D50X VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYX ₁ GSTLQSGVPSRFSGSG SGTDFLTISLQPEDFATYYCQQHNEYPPTFGQGTKEIK wherein $X_1 = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H$ or Q
147	A3-derived_D50X VL CON	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ IX ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYX ₁₁ GSTLQSGX ₁₂ PSRFSGSGSGTDFTLTIX ₁₃ SLX ₁₄ PEDFX ₁₅ X ₁₆ YCCQQHNEYPPTFG ₁₇ GTKLEIK wherein $X_1 = V$ or I , $X_2 = S$ or Y , $X_3 = S$ or N , $X_4 = S$ or A , $X_5 = V$ or P , $X_6 = D$ or E , $X_7 = R$ or S , $X_8 = T$ or S , $X_9 = N$ or T , $X_{10} = N$ or P , $X_{11} = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H$ or Q , $X_{12} = V$ or I , $X_{13} = S$ or R , $X_{14} = Q$ or E , $X_{15} = A$ or G , $X_{16} = T$ or L , $X_{17} = Q$ or S

148	A3-Hum_D50X VL CON	DX ₁ QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX ₂ KLLIYX ₃ GSTLQSGX ₄ PSRFSGSGSGTDFLTITISLQPEDX ₅ X ₆ LYYCQQQHNEYPPTFGQGTKLEIK wherein X ₁ = V or I, X ₂ = N or P, X ₃ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X ₄ = V or I, X ₅ = A or G, X ₆ = T or L
149	B035-C03-A3_D50X, A3_3_D50X, A3_4_D50X, A3_5_D50X LC- CDR2	X ₁ GS wherein X ₁ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
150	B035-C03-A3_D50X K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYX ₁ GSTLQSGIPSRFSGSGSGTDFLTITIRSLPEDFGLYYCQQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC wherein X ₁ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
151	A3_3_D50X K LC	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX ₁ GSTLQSGIPSRFSGSGSGTDFLTITISLQPEDFATYYCQQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC wherein X ₁ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
152	A3_4_D50X K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYX ₁ GSTLQSGVPSRFSGSGSGTDFLTITISLQPEDFGLYYCQQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC wherein X ₁ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
153	A3_5_D50X K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYX ₁ GSTLQSGVPSRFSGSGSGTDFLTITISLQPEDFATYYCQQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC wherein X ₁ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q
154	A3-derived_D50X CON K LC	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ I ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYX ₁₁ GSTLQSGX ₁₂ PSRFSGSGSGTDFLTITIX ₁₃ SLX ₁₄ PEDFX ₁₅ X ₁₆ YYCQQQHNEYPPTFGX ₁₇ GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X ₁ = V or I, X ₂ = S or Y, X ₃ = S or N, X ₄ = S or A, X ₅ = V or P, X ₆ = D or E, X ₇ = R or S, X ₈ = T or S, X ₉ = N or T, X ₁₀ = N or P, X ₁₁ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X ₁₂ = V or I, X ₁₃ = S or R, X ₁₄ = Q or E, X ₁₅ = A or G, X ₁₆ = T or L, X ₁₇ = Q or S
155	A3-Hum_D50X K LC	X ₁ QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX ₂ KLLIYX ₃ GSTLQSGX ₄ PSRFSGSGSGTDFLTITISLQPEDX ₅ X ₆ LYYCQQQHNEYPPTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X ₁ = V or I, X ₂ = N or P, X ₃ = A, E, N, C, G, I, L, M, F, P, S, T, W, Y, V, R, K, H or Q, X ₄ = V or I, X ₅ = A or G, X ₆ = T or L
156	B035-C03-A3_D50A VL	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGSGSGTDFLTITIRSLPEDFGLYYCQQQHNEYPPTFGSGTKLEIK
157	A3_3_D50A VL	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGSGSGTDFLTITISLQPEDFATYYCQQQHNEYPPTFGQGTKLEIK
158	A3_4_D50A VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGVPSRFSGSGSGTDFLTITISLQPEDFGLYYCQQQHNEYPPTFGQGTKLEIK
159	A3_5_D50A VL	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYAGSTLQSGVPSRFSGSGSGTDFLTITISLQPEDFATYYCQQQHNEYPPTFGQGTKLEIK
160	A3-derived_D50A VL CON	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ I ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYAGSTLQSGX ₁₁ PSRFSGSGSGTDFLTITIX ₁₂ SLX ₁₃ PEDFX ₁₄ X ₁₅ YYCQQQHNEYPPTFGX ₁₆ GTKLEIK wherein X ₁ = V or I, X ₂ = S or Y, X ₃ = S or N, X ₄ = S or A, X ₅ = V or P, X ₆ = D or E, X ₇ = R or S, X ₈ = T or S, X ₉ = N or T, X ₁₀ = N or P, X ₁₁ = V or I, X ₁₂ = S or R, X ₁₃ = Q or E, X ₁₄ = A or G, X ₁₅ = T or L, X ₁₆ = Q or S
161	A3-Hum_D50A VL CON	DX ₁ QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX ₂ KLLIYDSTLQSGX ₃ PSRFSGSGSGTDFLTITISLQPEDX ₄ X ₅ LYYCQQQHNEYPPTFGQGTKLEIK wherein X ₁ = V or I, X ₂ = N or P, X ₃ = V or I, X ₄ = A or G, X ₅ = T or L

162	B035-C03-A3_D50A, A3_3_D50A, A3_4_D50A, A3_5_D50A LC- CDR2	AGS
163	B035-C03-A3_D50A K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGSGS GTDFTLTIRSLPEDFGLYYCQQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
164	A3_3_D50A K LC	DVQMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGIPSRFSGSGS GTDFTLTISLQPEDFATYYCQQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
165	A3_4_D50A K LC	DIQMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKANKLLIYAGSTLQSGVPSRFSGSGS GTDFTLTISLQPEDFGLYYCQQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
166	A3_5_D50A K LC	DIQMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKAPKLLIYAGSTLQSGVPSRFSGSGS GTDFTLTISLQPEDFATYYCQQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
167	A3-derived_D50A CON K LC	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ IX ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYAGSTLQSGX ₁₁ P SRFSGSGSGTDFTLTIX ₁₂ SLX ₁₃ PEDFX ₁₄ X ₁₅ YQCQQHNEYPPTFGX ₁₆ GKLEIKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC wherein X ₁ = V or I, X ₂ = S or Y, X ₃ = S or N, X ₄ = S or A, X ₅ = V or P, X ₆ = D or E, X ₇ = R or S, X ₈ = T or S, X ₉ = N or T, X ₁₀ = N or P, X ₁₁ = V or I, X ₁₂ = S or R, X ₁₃ = Q or E, X ₁₄ = A or G, X ₁₅ = T or L, X ₁₆ = Q or S
168	A3-Hum_D50A K LC	DX ₁ QMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKAX ₂ KLLIYDGLTQSGX ₃ PSRFSGS GSGTDFTLTISLQPEDX ₄ X ₅ LYCQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC wherein X ₁ = V or I, X ₂ = N or P, X ₃ = V or I, X ₄ = A or G, X ₅ = T or L
169	B035-C03-A3 epitope B1	CEWDGGRETHL
170	B035-C03-A3 epitope B2	EWATHKFADCKA
171	Residues common to B035-C03-A3 epitope A1 and B1	CEWDGGR
172	Residues common to B035-C03-A3 epitope A2 and B2	EWATHKFADCK
173	B035-C03-A3 epitope region composite 2	CEWDGGRETHLETNFTLKSEWATHKFADCK
174	A3_6.2 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDFYWGQGLTVTVSS
175	A3_6.2 HC-FR2	IHWIRQAPGKGLEWVAL
176	A3_6.2 hlgG1 HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDFYWGQGLTVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSL GTQTYICNVNHKPSNTKVDKKEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVNS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
177	A3_6.2 hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANKNTLYLQMDSLRAEDTATYYCATPMMAVITPYFDFYWGQGLTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSL GKTYTCNVNHKPSNTKVDKRVESKYGPCPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVNSK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPVLDSDGSFFLYSRLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSLGK
178	B-R3 epitope	YSTVYF
179	B035-C03-A3_I100T VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPTKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANSTLYLQMDSLRSEDATATYYCATPMMAVITPYFDFYWGQGMVTVSS

180	A3_3.2_I100T VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSLISPSGYSTFYRDSVKGRFTISRDN SKNTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLT LTVSS
181	A3_4.2_I100T VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVSLISPSGYSTFYRDSVKG RFTISRDN AKNTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLT LTVSS
182	A3_6.2_I100T VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDN AKNTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLT LTVSS
183	A3-derived_I100T VH CON	EVQLX ₁ ESGGGLVQPGGSLX ₂ LSCAASGFTFSNYGIHWX ₃ RQAPX ₄ KGLEWVX ₅ LISPSGYSTFYRDS VKGRFTISRDNX ₆ X ₇ X ₈ TLYLQMDSLRX ₉ EDTATYYCATPMMAVTTPYYFDYWGQGX ₁₀ X ₁₁ VT VSS wherein X ₁ = V or L, X ₂ = R or K, X ₃ = I or V, X ₄ = G or T, X ₅ = S or A, X ₆ = A or S, X ₇ = K or N, X ₈ = N or S, X ₉ = A or S, X ₁₀ = T or V, X ₁₁ = L or M
184	A3-Hum_I100T VH CON	EVQLX ₁ ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX ₂ RQAPGKGLEWVX ₃ LISPSGYSTFYRDSV KGRFTISRDNX ₄ KNTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLT LTVSS wherein X ₁ = V or L, X ₂ = I or V, X ₃ = S or A, X ₄ = A or S
185	B035-C03-A3_I100T HC-CDR3	ATPMMAVTTPYYFDY
186	B035-C03-A3_G51A VL	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYDASTLQSGIPSRFSGSGS GTDFTLTIRSLPEP DFLYYCQQHNEYPPTFGSGTKLEIK
187	A3_3_G51A VL	DVQMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKANKLLIYDASTLQSGIPSRFSGSGS GTDFTLTISLQPEDFATYYCQQHNEYPPTFGQGTKLEIK
188	A3_4_G51A VL	DIQMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKANKLLIYDASTLQSGVPSRFSGSGS GTDFTLTISLQPEDFGLYYCQQHNEYPPTFGQGTKLEIK
189	A3_5_G51A VL	DIQMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKAPKLLIYDASTLQSGVPSRFSGSGS GTDFTLTISLQPEDFATYYCQQHNEYPPTFGQGTKLEIK
190	A3-derived_G51A VL CON	DX ₁ QMTQSPX ₂ X ₃ LX ₄ ASX ₅ GX ₆ X ₇ VX ₈ IX ₉ CKASKSISKYLAWYQQKPGKAX ₁₀ KLLIYDASTLQSGX ₁₁ P SRFSGSGSGTDFTLTIX ₁₂ SLX ₁₃ PEDFX ₁₄ X ₁₅ YYCQQHNEYPPTFGX ₁₆ GTKLEIK wherein X ₁ = V or I, X ₂ = S or Y, X ₃ = S or N, X ₄ = S or A, X ₅ = V or P, X ₆ = D or E, X ₇ = R or S, X ₈ = T or S, X ₉ = N or T, X ₁₀ = N or P, X ₁₁ = V or I, X ₁₂ = S or R, X ₁₃ = Q or E, X ₁₄ = A or G, X ₁₅ = T or L, X ₁₆ = Q or S
191	A3-Hum_G51A VL CON	DX ₁ QMTQSPSSLSASVGDRTITCKASKSISKYLAWYQQKPGKAX ₂ KLLIYDASTLQSGX ₃ PSRFSGS GSGTDFTLTISLQPEDX ₄ X ₅ LYYCQQHNEYPPTFGQGTKLEIK wherein X ₁ = V or I, X ₂ = N or P, X ₃ = V or I, X ₄ = A or G, X ₅ = T or L
192	B035-C03-A3_G51A LC-CDR2	DAS
193	5H8CVH4 VH	QVQLQESGPGLVKPSQTLSTCTVSGFSLTNNNIHWVRQAPGKGLEWVGAIWGGSTDYDSALKS RFTISRDT SKSTVYLQMNSLRAEDTAVYYCTKSFYDGGYYWLG YWGQGLT LTVSS
194	5H8GVH4 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWVRQAPGKGLEWVSAIWGGSTDYDSALKS RFTISRDN SKNTLYLQMDSLRAEDTAVYYCAKSFYDGGYYWLG YWGQGLT LTVSS
195	5H8GVH4 HC-CDR3	AKSFYDGGYYWLG Y
196	5H8CVH4 HC-FR1	QVQLQESGPGLVKPSQTLSTCTVS
197	5H8GVH4 HC-FR1	EVQLLESGGGLVQPGGSLRLSCAAS
198	5H8CVH4 HC-FR2	IHWVRQAPGKGLEWVGA
199	5H8GVH4 HC-FR2	IHWVRQAPGKGLEWVSA
200	5H8CVH4 HC-FR3	DYDSALKSRFTISRDT SKSTVYLQMNSLRAEDTAVYYC
201	5H8GVH4 HC-FR3	DYDSALKSRFTISRDN SKNTLYLQMNSLRAEDTAVYYC
202	5H8-derived VH CON	X ₁ VQLX ₂ ESGX ₃ GLVX ₄ PX ₅ X ₆ X ₇ LX ₈ LX ₉ CX ₁₀ X ₁₁ SGFSLTNNNIHWVRQX ₁₂ PGKGLEWVX ₁₃ AIWGGST DYDSALKSRX ₁₄ TISRDX ₁₅ SKX ₁₆ X ₁₇ X ₁₈ X ₁₉ LX ₂₀ MNSLX ₂₁ AEDTAX ₂₂ YX ₂₃ CX ₂₄ KSFYDGGYYWLG YWGQGLT LTVSS X ₁ = Q or E; X ₂ = K, Q or L; X ₃ = P or G; X ₄ = K or Q; X ₅ = S or G; X ₆ = Q or G; X ₇ = T or S; X ₈ = S or R; X ₉ = T or S; X ₁₀ = T or A; X ₁₁ = V or A; X ₁₂ = P or A; X ₁₃ = G or S; X ₁₄ = L or F; X ₁₅ = T or N; X ₁₆ = S or N; X ₁₇ = Q or T; X ₁₈ = V or L; X ₁₉ = F or Y; X ₂₀ = K or Q; X ₂₁ = Q or R; X ₂₂ = I or V; X ₂₃ = F or Y; X ₂₄ = T or A;
203	5H8-Hum VH CON	X ₁ VQLX ₂ ESGX ₃ GLVX ₄ PX ₅ X ₆ X ₇ LX ₈ LX ₉ CX ₁₀ X ₁₁ SGFSLTNNNIHWVRQAPGKGLEWVX ₁₂ AIWGGST DYDSALKSRFTISRDX ₁₃ SKX ₁₄ TX ₁₅ YLQMNSLRAEDTAVYYCX ₁₆ KSFYDGGYYWLG YWGQGLT LTV SS X ₁ = Q or E; X ₂ = Q or L; X ₃ = P or G; X ₄ = K or Q; X ₅ = S or G; X ₆ = Q or G; X ₇ = T or S; X ₈ = S or R; X ₉ = T or S; X ₁₀ = T or A; X ₁₁ = V or A; X ₁₂ = G or S; X ₁₃ = T or N; X ₁₄ = S or N; X ₁₅ = V or L; X ₁₆ = T or A;
204	5H8-derived CON, 5H8-Hum CON HC-CDR3	XKSFYDGGYYWLG Y X = T or A

205	5H8-derived CON HC-FR1	X ₁ VQLX ₂ ESGX ₃ GLVX ₄ PX ₅ X ₆ X ₇ LX ₈ LX ₉ CX ₁₀ X ₁₁ S X ₁ = Q or E; X ₂ = K, Q or L; X ₃ = P or G; X ₄ = K or Q; X ₅ = S or G; X ₆ = Q or G; X ₇ = T or S; X ₈ = S or R; X ₉ = T or S; X ₁₀ = T or A; X ₁₁ = V or A
206	5H8-derived CON HC-FR2	IHWVRQX ₁ PGKGLEWVX ₂ A X ₁ = P or A; X ₂ = G or S
207	5H8-derived CON HC-FR3	DYDSALKSRX ₁ TISRDX ₂ SKX ₃ X ₄ X ₅ X ₆ LX ₇ MNSLX ₈ AEDTAX ₉ YX ₁₀ C X ₁ = L or F; X ₂ = T or N; X ₃ = S or N; X ₄ = Q or T; X ₅ = V or L; X ₆ = F or Y; X ₇ = K or Q; X ₈ = Q or R; X ₉ = I or V; X ₁₀ = F or Y;
208	5H8-Hum CON HC-FR1	X ₁ VQLX ₂ ESGX ₃ GLVX ₄ PX ₅ X ₆ X ₇ LX ₈ LX ₉ CX ₁₀ X ₁₁ S X ₁ = Q or E; X ₂ = Q or L; X ₃ = P or G; X ₄ = K or Q; X ₅ = S or G; X ₆ = Q or G; X ₇ = T or S; X ₈ = S or R; X ₉ = T or S; X ₁₀ = T or A; X ₁₁ = V or A
209	5H8-Hum CON HC-FR2	IHWVRQAPGKGLEWVXA X = G or S
210	5H8-Hum CON HC-FR3	DYDSALKSRFTISRDX ₁ SKX ₂ TX ₃ YLMNSLRAEDTAVYYC X ₁ = T or N; X ₂ = S or N; X ₃ = V or L
211	CSP-S-5H8_D98G VH	QVQLKESGPGVLVQPSQTLSTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSGGSTDYDSALKS RLTISRDTSKSQVFLKMNSLQAEDTAIFYCTKSFYGGGYWLGWYWGQGLTLTVSS
212	5H8CVH4_D98G VH	QVQLQESGPGVLVKPSQTLSTCTVSGFSLTNNNIHWVRQAPGKGLEWVGAIWSGGSTDYDSALKS RFTISRDTSKSTVYLQMNSLRAEDTAVYYCTKSFYGGGYWLGWYWGQGLTLTVSS
213	5H8GVH4_D98G VH	EVQLLESGGGLVQPGGSLRLSCAASGFSLTNNNIHWVRQAPGKGLEWVSAIWSGGSTDYDSALKS RFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSFYGGGYWLGWYWGQGLTLTVSS
214	CSP-S-5H8_D98G, 5H8CVH4_D98G HC-CDR3	TKSFYGGGYWLGWY
215	5H8GVH4_D98G HC-CDR3	AKSFYGGGYWLGWY
216	5H8-derived_D98G VH CON	X ₁ VQLX ₂ ESGX ₃ GLVX ₄ PX ₅ X ₆ X ₇ LX ₈ LX ₉ CX ₁₀ X ₁₁ SGFSLTNNNIHWVRQX ₁₂ PGKGLEWVX ₁₃ AIWSGGST TDYDSALKSRX ₁₄ TISRDX ₁₅ SKX ₁₆ X ₁₇ X ₁₈ X ₁₉ LX ₂₀ MNSLX ₂₁ AEDTAX ₂₂ YX ₂₃ CX ₂₄ KSFYGGGYWLGWYWGQGLTLTVSS X ₁ = Q or E; X ₂ = K, Q or L; X ₃ = P or G; X ₄ = K or Q; X ₅ = S or G; X ₆ = Q or G; X ₇ = T or S; X ₈ = S or R; X ₉ = T or S; X ₁₀ = T or A; X ₁₁ = V or A; X ₁₂ = P or A; X ₁₃ = G or S; X ₁₄ = L or F; X ₁₅ = T or N; X ₁₆ = S or N; X ₁₇ = Q or T; X ₁₈ = V or L; X ₁₉ = F or Y; X ₂₀ = K or Q; X ₂₁ = Q or R; X ₂₂ = I or V; X ₂₃ = F or Y; X ₂₄ = T or A
217	5H8-Hum_D98G VH CON	X ₁ VQLX ₂ ESGX ₃ GLVX ₄ PX ₅ X ₆ X ₇ LX ₈ LX ₉ CX ₁₀ X ₁₁ SGFSLTNNNIHWVRQAPGKGLEWVX ₁₂ AIWSGGST DYDSALKSRFTISRDX ₁₃ SKX ₁₄ TX ₁₅ YLMNSLRAEDTAVYYCX ₁₆ KSFYGGGYWLGWYWGQGLTLTVSS X ₁ = Q or E; X ₂ = Q or L; X ₃ = P or G; X ₄ = K or Q; X ₅ = S or G; X ₆ = Q or G; X ₇ = T or S; X ₈ = S or R; X ₉ = T or S; X ₁₀ = T or A; X ₁₁ = V or A; X ₁₂ = G or S; X ₁₃ = T or N; X ₁₄ = S or N; X ₁₅ = V or L; X ₁₆ = T or A;
218	5H8-derived_D98G CON, 5H8-Hum_D98G CON HC-CDR3	XKSFYGGGYWLGWY
219	5H8CVL3 VL	ETVMTQSPATLSVSPGERATLSCKASQSVSDINVDWYQQKPGKAPKLLIYGASNRHTGVPDRFSGS RFGKDFTLKISRVEAEDVGVYYCLQYDSIPWTFGQGTKVEIK
220	5H8CVL4 VL	ETVMTQSPATLSVSPGERATLSCKASQSVSDINVDWYQQKPGKAPKLLIYGASNRHTGVPDRFSGS RSGKDFTLKISRVEAEDVGVYYCLQYDSIPWTFGQGTKVEIK
221	5H8GVL3 VL	ETVMTQSPGTLSPGERATLSCKASQSVSDINVDWYQQKPGQAPRLLIYGASNRHTGVPDRFSGS RFGKDFTLTISRLEPEDLAVYYCLQYDSIPWTFGQGTKVEIK
222	5H8CVL3, 5H8CVL4 LC-FR1	ETVMTQSPATLSVSPGERATLSCKAS
223	5H8GVL3 LC-FR1	ETVMTQSPGTLSPGERATLSCKAS
224	5H8CVL3, 5H8CVL4 LC-FR2	VDWYQQKPGKAPKLLIY
225	5H8GVL3 LC-FR2	VDWYQQKPGQAPRLLIY
226	5H8CVL3 LC-FR3	NRHTGVPDRFSGSRFGKDFTLKISRVEAEDVGVYYC
227	5H8CVL4 LC-FR3	NRHTGVPDRFSGSRSGKDFTLKISRVEAEDVGVYYC
228	5H8GVL3 LC-FR3	NRHTGVPDRFSGSRFGKDFTLTISRLEPEDLAVYYC

229	5H8CVL3, 5H8CVL4, 5H8GVL3 LC-FR4	FGQGTKVEIK
230	5H8-derived VL CON	ETVMTQSPX ₁ X ₂ X ₃ SX ₄ SX ₅ GERX ₆ TLX ₇ CKASQSVNDINVDWYQQX ₈ PGX ₉ X ₁₀ PX ₁₁ LLIYGASNRHTGV PDRFX ₁₂ GSRX ₁₃ GKDFTLX ₁₄ ISX ₁₅ X ₁₆ EX ₁₇ EDX ₁₈ X ₁₉ VYYCLQYDSIPWTFGX ₂₀ GTX ₂₁ EX ₂₂ K X ₁ = A or G; X ₂ = T or S; X ₃ = L or M; X ₄ = V, L or T; X ₅ = P or I; X ₆ = A or V; X ₇ = S or N; X ₈ = K or T; X ₉ = K or Q; X ₁₀ = A or S; X ₁₁ = K or R; X ₁₂ = S or T; X ₁₃ = F or S; X ₁₄ = K or T; X ₁₅ = R or N; X ₁₆ = V or L; X ₁₇ = A, P or S; X ₁₈ = V or L; X ₁₉ = G or A; X ₂₀ = Q or G; X ₂₁ = V or L; X ₂₂ = I or L
231	5H8-Hum VL CON	ETVMTQSPX ₁ TLX ₂ SPGERATLSCKASQSVNDINVDWYQQKPGX ₃ APX ₄ LLIYGASNRHTGV PDRFS GSRX ₅ GKDFTLX ₆ SRX ₇ EX ₈ EDX ₉ X ₁₀ VYYCLQYDSIPWTFGQGTKVEIK X ₁ = A or G; X ₂ = V or L; X ₃ = K or Q; X ₄ = K or R; X ₅ = F or S; X ₆ = K or T; X ₇ = V or L; X ₈ = A or P; X ₉ = V or L; X ₁₀ = G or A;
232	5H8-derived CON LC-FR1	ETVMTQSPX ₁ X ₂ X ₃ SX ₄ SX ₅ GERX ₆ TLX ₇ CKAS X ₁ = A or G; X ₂ = T or S; X ₃ = L or M; X ₄ = V, L or T; X ₅ = P or I; X ₆ = A or V; X ₇ = S or N;
233	5H8-derived CON LC-FR2	VDWYQQX ₁ PGX ₂ X ₃ PX ₄ LLIY X ₁ = K or T; X ₂ = K or Q; X ₃ = A or S; X ₄ = K or R;
234	5H8-derived CON LC-FR3	NRHTGVPDRFX ₁ GSRX ₂ GKDFTLX ₃ ISX ₄ X ₅ EX ₆ EDX ₇ X ₈ VYYC X ₁ = S or T; X ₂ = F or S; X ₃ = K or T; X ₄ = R or N; X ₅ = V or L; X ₆ = A, P or S; X ₇ = V or L; X ₈ = G or A
235	5H8-derived CON LC-FR4	FGX ₁ GTX ₂ EX ₃ K X ₁ = Q or G; X ₂ = V or L; X ₃ = I or L
236	5H8-Hum CON LC- FR1	ETVMTQSPX ₁ TLX ₂ SPGERATLSCKAS X ₁ = A or G; X ₂ = V or L;
237	5H8-Hum CON LC- FR2	VDWYQQKPGX ₁ APX ₂ LLIY X ₁ = K or Q; X ₂ = K or R
238	5H8-Hum CON LC- FR3	NRHTGVPDRFSGSRX ₁ GKDFTLX ₂ ISRX ₃ EX ₄ EDX ₅ X ₆ VYYC X ₁ = F or S; X ₂ = K or T; X ₃ = V or L; X ₄ = A or P; X ₅ = V or L; X ₆ = G or A;
239	B035-C03-A3_I100T hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANSTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGMVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS LGTKITYTCNVDHKPSNTKVDKRVEKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK
240	A3_3.2_I100T hlgG4(S228P, L235E) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVK GRFTISRDNANSTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLTVTVSSASTKGPSVF PLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS LGTKITYTCNVDHKPSNTKVDKRVEKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK
241	A3_4.2_I100T hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANSTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS LGTKITYTCNVDHKPSNTKVDKRVEKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCV VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK
242	A3_6.2_I100T hlgG4(S228P, L235E) HC	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGIHWIRQAPGKGLEWVALISPSGYSTFYRDSVKG RFTISRDNANSTLYLQMDSLRAEDTATYYCATPMMAVTTPYYFDYWGQGLTVTVSSASTKGPSVFP LAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS LGTKITYTCNVDHKPSNTKVDKRVEKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCV VVVDVSDQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLSLGK
243	A3-derived_I100T hlgG4(S228P, L235E) HC CON	EVQLX ₁ ESGGGLVQPGGSLX ₂ LSCAASGFTFSNYGIHWX ₃ RQAPX ₄ KGLEWVX ₅ LISPSGYSTFYRDS VKGRFTISRDNX ₆ X ₇ X ₈ TLYLQMDSLRX ₉ EDTATYYCATPMMAVTTPYYFDYWGQGX ₁₀ X ₁₁ VTVSSAS TKGPSVFLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV

		VTVPSSSLGKTYYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK wherein $X_1 = V$ or L, $X_2 = R$ or K, $X_3 = I$ or V, $X_4 = G$ or T, $X_5 = S$ or A, $X_6 = A$ or S, $X_7 = K$ or N, $X_8 = N$ or S, $X_9 = A$ or S, $X_{10} = T$ or V, $X_{11} = L$ or M
244	A3-Hum_I100ThlgG4(S228P, L235E) HC CON	EVQLX₁ESGGGLVQPGGSLRLSCAASGFTFSNYGIHWX₂RQAPGKGLEWVX₃LISPSGYSTFYRDSVKGRFTISRDNX₄KNTLYLQMSDLRAEDTATYYCATPMMAVTTPYYFDYWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK wherein $X_1 = V$ or L, $X_2 = I$ or V, $X_3 = S$ or A, $X_4 = A$ or S
245	B035-C03-A3_G51A K LC	DVQMTQSPYNLAASPGESVSINCKASKSISKYLAWYQQKPGKANKLLIYDASTLQSGIPSRFSGSGSGTDFTLTIRSLPEDFGLYYCQQHNEYPPTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGGLSSPVTKSFNRGEC
246	A3_3_G51A K LC	DVQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDASTLQSGIPSRFSGSGSGTDFTLTISLQPEDFATYYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGGLSSPVTKSFNRGEC
247	A3_4_G51A K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKANKLLIYDASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFGLYYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGGLSSPVTKSFNRGEC
248	A3_5_G51A K LC	DIQMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAPKLLIYDASTLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGGLSSPVTKSFNRGEC
249	A3-derived_G51A K LC CON	DX₁QMTQSPX₂X₃LX₄ASX₅GX₆X₇VX₈I₉CKASKSISKYLAWYQQKPGKAX₁₀KLLIYDASTLQSGX₁₁PSRFSGSGSGTDFTLTIX₁₂SLX₁₃PEDFX₁₄X₁₅YCCQQHNEYPPTFGX₁₆GTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein $X_1 = V$ or I, $X_2 = S$ or Y, $X_3 = S$ or N, $X_4 = S$ or A, $X_5 = V$ or P, $X_6 = D$ or E, $X_7 = R$ or S, $X_8 = T$ or S, $X_9 = N$ or T, $X_{10} = N$ or P, $X_{11} = V$ or I, $X_{12} = S$ or R, $X_{13} = Q$ or E, $X_{14} = A$ or G, $X_{15} = T$ or L, $X_{16} = Q$ or S
250	A3-Hum_G51A K LC CON	DX₁QMTQSPSSLSASVGDRVTITCKASKSISKYLAWYQQKPGKAX₂KLLIYDASTLQSGX₃PSRFSGSGSGTDFTLTISLQPEDX₄SL₅YCCQQHNEYPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC wherein $X_1 = V$ or I, $X_2 = N$ or P, $X_3 = V$ or I, $X_4 = A$ or G, $X_5 = T$ or L
251	5H8CVH4hlgG4(S228P, L235E) HC	QVQLQESGPGLVKPSQTLSTCTVSGFSLTNNNIHWVRQAPGKGLEWVWGAISGGSTDYDSALKSRFTISRDTSKSTYYLQMNSLRAEDTAVYYCTKSFYDGGYYWLGWYWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK
252	5H8GVH4hlgG4(S228P, L235E) HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNTNNNIHWVRQAPGKGLEWVSAISGGSTDYDSALKSRFTISRDNKNTLYLQMNSLRAEDTAVYYCAKSFYDGGYYWLGWYWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK
253	5H8-derivedhlgG4(S228P, L235E) HC CON	X₁VQLX₂ESGX₃GLVX₄PX₅X₆X₇LX₈LX₉CX₁₀X₁₁SGFSLTNNNIHWVRQX₁₂PGKGLEWVX₁₃AIWSGGSTDYDSALKSRX₁₄TISRDX₁₅SKX₁₆X₁₇X₁₈X₁₉LX₂₀MNSLX₂₁AEDTAX₂₂YX₂₃CX₂₄KSFYDGGYYWLGWYWGQGTLLTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLGLGK

		$X_1 = Q$ or E; $X_2 = K$, Q or L; $X_3 = P$ or G; $X_4 = K$ or Q; $X_5 = S$ or G; $X_6 = Q$ or G; $X_7 = T$ or S; $X_8 = S$ or R; $X_9 = T$ or S; $X_{10} = T$ or A; $X_{11} = V$ or A; $X_{12} = P$ or A; $X_{13} = G$ or S; $X_{14} = L$ or F; $X_{15} = T$ or N; $X_{16} = S$ or N; $X_{17} = Q$ or T; $X_{18} = V$ or L; $X_{19} = F$ or Y; $X_{20} = K$ or Q; $X_{21} = Q$ or R; $X_{22} = I$ or V; $X_{23} = F$ or Y; $X_{24} = T$ or A;
254	5H8-Hum hlgG4(S228P, L235E) HC CON	$X_1VQLX_2ESGX_3GLVX_4PX_5X_6X_7LX_8LX_9CX_{10}X_{11}SGFSLTNNNIHWVRQAPGKGLEWVX_{12}AIWSSGGSTDYDSALKSRFTISRDX_{13}SKX_{14}TX_{15}YLMQNSLRAEDTAVYYCX_{16}KSFYDGGYYWLGYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK$ $X_1 = Q$ or E; $X_2 = Q$ or L; $X_3 = P$ or G; $X_4 = K$ or Q; $X_5 = S$ or G; $X_6 = Q$ or G; $X_7 = T$ or S; $X_8 = S$ or R; $X_9 = T$ or S; $X_{10} = T$ or A; $X_{11} = V$ or A; $X_{12} = G$ or S; $X_{13} = T$ or N; $X_{14} = S$ or N; $X_{15} = V$ or L; $X_{16} = T$ or A;
255	CSP-S-5H8_D98G hlgG4(S228P, L235E) HC	$QVQLKESGPGLVQPSQTLSTCTVSGFSLTNNNIHWVRQPPGKGLEWVGAIWSSGGSTDYDSALKSRFTISRDTSKSQVFLKMNLSLAEDTAIYFCTKSFYGGGYWLGWYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK$
256	5H8CVH4_D98G hlgG4(S228P, L235E) HC	$QVQLQESGPGLVKPSQTLSTCTVSGFSLTNNNIHWVRQAPGKGLEWVGAIWSSGGSTDYDSALKSRFTISRDTSKSTVYLMQNSLRAEDTAVYYCTKSFYGGGYWLGWYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK$
257	5H8GVH4_D98G hlgG4(S228P, L235E) HC	$EVQLLESGGGLVQPGGSLRLSCAASGFSLTNNNIHWVRQAPGKGLEWVSAIWSSGGSTDYDSALKSRFTISRDNSTNTLYLQMNSLRAEDTAVYYCAKSFYGGGYWLGWYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK$
258	5H8-derived_D98G hlgG4(S228P, L235E) HC CON	$X_1VQLX_2ESGX_3GLVX_4PX_5X_6X_7LX_8LX_9CX_{10}X_{11}SGFSLTNNNIHWVRQX_{12}PGKGLEWVX_{13}AIWSSGGSTDYDSALKSRX_{14}TISRDX_{15}SKX_{16}X_{17}X_{18}X_{19}LX_{20}MNSLX_{21}AEDTAX_{22}YX_{23}CX_{24}KSFYGGGYWLGWYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK$ $X_1 = Q$ or E; $X_2 = K$, Q or L; $X_3 = P$ or G; $X_4 = K$ or Q; $X_5 = S$ or G; $X_6 = Q$ or G; $X_7 = T$ or S; $X_8 = S$ or R; $X_9 = T$ or S; $X_{10} = T$ or A; $X_{11} = V$ or A; $X_{12} = P$ or A; $X_{13} = G$ or S; $X_{14} = L$ or F; $X_{15} = T$ or N; $X_{16} = S$ or N; $X_{17} = Q$ or T; $X_{18} = V$ or L; $X_{19} = F$ or Y; $X_{20} = K$ or Q; $X_{21} = Q$ or R; $X_{22} = I$ or V; $X_{23} = F$ or Y; $X_{24} = T$ or A;
259	5H8-Hum_D98G hlgG4(S228P, L235E) HC CON	$X_1VQLX_2ESGX_3GLVX_4PX_5X_6X_7LX_8LX_9CX_{10}X_{11}SGFSLTNNNIHWVRQAPGKGLEWVX_{12}AIWSSGGSTDYDSALKSRFTISRDX_{13}SKX_{14}TX_{15}YLMQNSLRAEDTAVYYCX_{16}KSFYGGGYWLGWYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSLSLGLK$ $X_1 = Q$ or E; $X_2 = Q$ or L; $X_3 = P$ or G; $X_4 = K$ or Q; $X_5 = S$ or G; $X_6 = Q$ or G; $X_7 = T$ or S; $X_8 = S$ or R; $X_9 = T$ or S; $X_{10} = T$ or A; $X_{11} = V$ or A; $X_{12} = G$ or S; $X_{13} = T$ or N; $X_{14} = S$ or N; $X_{15} = V$ or L; $X_{16} = T$ or A;
260	5H8CVL3 K LC	$ETVMTQSPATLSVSPGERATLSCASQSVNDINVDWYQQKPGKAPKLLIYGASNRHTGVPDRFSGSRFGKDFTLKISRVEAEDVGVYYCLQYDSIPWTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC$
261	5H8CVL4 K LC	$ETVMTQSPATLSVSPGERATLSCASQSVNDINVDWYQQKPGKAPKLLIYGASNRHTGVPDRFSGSRFGKDFTLKISRVEAEDVGVYYCLQYDSIPWTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASV$

		VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
262	5H8GVL3 K LC	ETVMTQSPGTLSPGERATLSCKASQSVNDINVDWYQQKPGQAPRLLIYGASNRHTGVPDRFSGS RFGKDFLTISRLEPEDLAVYYCLQYDSIPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC
263	5H8-derived K LC CON	ETVMTQSPX ₁ X ₂ X ₃ SX ₄ SX ₅ GERX ₆ TLX ₇ CKASQSVNDINVDWYQQX ₈ PGX ₉ X ₁₀ PX ₁₁ LLIYGASNRHTGV PDRFX ₁₂ GSRX ₁₃ GKDFTLX ₁₄ ISX ₁₅ X ₁₆ EX ₁₇ EDX ₁₈ X ₁₉ VYYCLQYDSIPWTFGX ₂₀ GTKX ₂₁ EX ₂₂ KRTVAA PSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC X ₁ = A or G; X ₂ = T or S; X ₃ = L or M; X ₄ = V, L or T; X ₅ = P or I; X ₆ = A or V; X ₇ = S or N; X ₈ = K or T; X ₉ = K or Q; X ₁₀ = A or S; X ₁₁ = K or R; X ₁₂ = S or T; X ₁₃ = F or S; X ₁₄ = K or T; X ₁₅ = R or N; X ₁₆ = V or L; X ₁₇ = A, P or S; X ₁₈ = V or L; X ₁₉ = G or A; X ₂₀ = Q or G; X ₂₁ = V or L; X ₂₂ = I or L
264	5H8-Hum K LC CON	ETVMTQSPX ₁ TLX ₂ SPGERATLSCKASQSVNDINVDWYQQKPGX ₃ APX ₄ LLIYGASNRHTGVPDRFS GSRX ₅ GKDFTLX ₆ ISRX ₇ EX ₈ EDX ₉ X ₁₀ VYYCLQYDSIPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS GTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC X ₁ = A or G; X ₂ = V or L; X ₃ = K or Q; X ₄ = K or R; X ₅ = F or S; X ₆ = K or T; X ₇ = V or L; X ₈ = A or P; X ₉ = V or L; X ₁₀ = G or A;

Table A

Row	Antibody	Column A			Column B		
		VH			VL		
		HC-CDR1	HC-CDR2	HC-CDR3	LC-CDR1	LC-CDR2	LC-CDR3
1	B035-C03-A3	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
2	CSP-S-5H8	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
3	A3 3.2 VH / A3 3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
4	A3 3.2 VH / A3 4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
5	A3 3.2 VH / A3 5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
6	A3 4.2 VH / A3 3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
7	A3 4.2 VH / A3 4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
8	A3 4.2 VH / A3 5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
9	A3 6.2 VH / A3 3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
10	A3 6.2 VH / A3 4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
11	A3 6.2 VH / A3 5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
12	A3-derived VH CON / A3-derived VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
13	A3-Hum VH CON / A3-Hum VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
14	B035-C03-A3 D50X	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
15	A3 3.2 VH / A3 3 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
16	A3 3.2 VH / A3 4 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
17	A3 3.2 VH / A3 5 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
18	A3 4.2 VH / A3 3 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
19	A3 4.2 VH / A3 4 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
20	A3 4.2 VH / A3 5 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
21	A3 6.2 VH / A3 3 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
22	A3 6.2 VH / A3 4 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
23	A3 6.2 VH / A3 5 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
24	A3-derived VH CON / A3-derived VL D50X CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
25	A3-Hum VH CON / A3-Hum VL D50X CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
26	B035-C03-A3 D50A	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
27	A3 3.2 VH / A3 3 D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
28	A3 3.2 VH / A3 4 D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
29	A3 3.2 VH / A3 5 D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
30	A3 4.2 VH / A3 3 D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
31	A3 4.2 VH / A3 4 D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
32	A3 4.2 VH / A3 5 D50A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
33	A3 6.2 VH / A3 3 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
34	A3 6.2 VH / A3 4 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
35	A3 6.2 VH / A3 5 D50X VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:149	SEQ ID NO:12
36	A3-derived VH CON / A3-derived VL D50A CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12
37	A3-Hum VH CON / A3-Hum VL D50A CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:162	SEQ ID NO:12

38	B035-C03-A3	1100T VH / B035-C03-A3	G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
39	B035-C03-A3	1100T VH / B035-C03-A3	VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
40	B035-C03-A3	VH / B035-C03-A3	G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
41	A3	3.2	1100T VH / A3	3 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
42	A3	3.2	1100T VH / A3	4 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
43	A3	3.2	1100T VH / A3	5 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
44	A3	3.2	1100T VH / A3	3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
45	A3	3.2	1100T VH / A3	4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
46	A3	3.2	1100T VH / A3	5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
47	A3	3.2	VH / A3	3 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
48	A3	3.2	VH / A3	4 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
49	A3	3.2	VH / A3	5 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
50	A3	4.2	1100T VH / A3	3 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
51	A3	4.2	1100T VH / A3	4 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
52	A3	4.2	1100T VH / A3	5 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
53	A3	4.2	1100T VH / A3	3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
54	A3	4.2	1100T VH / A3	4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
55	A3	4.2	1100T VH / A3	5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
56	A3	4.2	VH / A3	3 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
57	A3	4.2	VH / A3	4 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
58	A3	4.2	VH / A3	5 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
59	A3	6.2	1100T VH / A3	3 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
60	A3	6.2	1100T VH / A3	4 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
61	A3	6.2	1100T VH / A3	5 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:192	SEQ ID NO:12
62	A3	6.2	1100T VH / A3	3 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
63	A3	6.2	1100T VH / A3	4 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
64	A3	6.2	1100T VH / A3	5 VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:11	SEQ ID NO:12
65	A3	6.2	VH / A3	3 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
66	A3	6.2	VH / A3	4 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
67	A3	6.2	VH / A3	5 G51A VL	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:192	SEQ ID NO:12
68	A3-derived	1100T VH CON / A3-derived	G51A VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
69	A3-derived	1100T VH CON / A3-derived	VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
70	A3-derived	VH CON / A3-derived	G51A VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
71	A3-Hum	1100T VH CON / A3-Hum	G51A VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
72	A3-Hum	1100T VH CON / A3-Hum	VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:185	SEQ ID NO:10	SEQ ID NO:11	SEQ ID NO:12
73	A3-Hum	VH CON / A3-Hum	G51A VL CON	SEQ ID NO:2	SEQ ID NO:3	SEQ ID NO:4	SEQ ID NO:10	SEQ ID NO:192	SEQ ID NO:12
74	5H8CVH4	VH / 5H8CVL3	VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
75	5H8CVH4	VH / 5H8CVL4	VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
76	5H8CVH4	VH / 5H8GVL3	VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:20	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
77	5H8GVH4	VH / 5H8CVL3	VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:195	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
78	5H8GVH4	VH / 5H8CVL4	VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:195	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28

79	5H8GVH4 VH / 5H8GVL3 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:195	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
80	5H8-derived VH CON / 5H8-derived VL CON	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:204	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
81	5H8-Hum VH CON / 5H8-Hum VL CON	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:204	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
82	CSP-S-5H8_D98G VH / CSP-S-5H8 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:214	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
83	5H8CVH4_D98G VH / 5H8CVL3 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:214	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
84	5H8CVH4_D98G VH / 5H8CVL4 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:214	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
85	5H8CVH4_D98G VH / 5H8GVL3 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:214	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
86	5H8GVH4_D98G VH / 5H8CVL3 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:215	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
87	5H8GVH4_D98G VH / 5H8CVL4 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:215	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
88	5H8GVH4_D98G VH / 5H8GVL3 VL	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:215	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
89	5H8-derived_D98G VH CON / 5H8-derived VL CON	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:218	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28
90	5H8-Hum_D98G VH CON / 5H8-Hum VL CON	SEQ ID NO:18	SEQ ID NO:19	SEQ ID NO:218	SEQ ID NO:26	SEQ ID NO:27	SEQ ID NO:28

Table B

Row	Antibody	Column A						Column B			
		VH						VL			
		HC-FR1	HC-FR2	HC-FR3	HC-FR4	LC-FR1	LC-FR2	LC-FR3	LC-FR4	SEQ ID NO:16	SEQ ID NO:16
1	B035-C03-A3	SEQ ID NO:5	SEQ ID NO:6	SEQ ID NO:7	SEQ ID NO:8	NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16	SEQ ID NO:16	SEQ ID NO:16
2	CSP-S-5H8	SEQ ID NO:21	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:29	SEQ ID NO:30	SEQ ID NO:31	SEQ ID NO:32	SEQ ID NO:32	SEQ ID NO:32
3	A3_3.2 VH / A3_3 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:97	NO:103	SEQ ID NO:104	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105	SEQ ID NO:105
4	A3_3.2 VH / A3_4 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:97	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109
5	A3_3.2 VH / A3_5 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:97	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109
6	A3_4.2 VH / A3_3 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:101	NO:103	SEQ ID NO:104	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105	SEQ ID NO:105
7	A3_4.2 VH / A3_4 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:101	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109
8	A3_4.2 VH / A3_5 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:101	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109
9	A3_6.2 VH / A3_3 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:101	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109
10	A3_6.2 VH / A3_4 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:101	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109
11	A3_6.2 VH / A3_5 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:101	NO:107	SEQ ID NO:108	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:109	SEQ ID NO:109

12	A3-derived VH CON / A3-derived VL CON	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
13	A3-Hum VH CON / A3-Hum VL CON	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:124	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
14	B035-C03-A3_D50X	SEQ ID NO:5	SEQ ID NO:6	SEQ ID NO:7	SEQ ID NO:8	SEQ ID NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16
15	A3_3.2 VH / A3_3_D50X VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
16	A3_3.2 VH / A3_4_D50X VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
17	A3_3.2 VH / A3_5_D50X VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
18	A3_4.2 VH / A3_3_D50X VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
19	A3_4.2 VH / A3_4_D50X VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
20	A3_4.2 VH / A3_5_D50X VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
21	A3_6.2 VH / A3_3_D50X VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
22	A3_6.2 VH / A3_4_D50X VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
23	A3_6.2 VH / A3_5_D50X VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
24	A3-derived VH CON / A3-derived VL_D50X CON	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
25	A3-Hum VH CON / A3-Hum VL_D50X CON	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
26	B035-C03-A3_D50A	SEQ ID NO:5	SEQ ID NO:6	SEQ ID NO:7	SEQ ID NO:8	SEQ ID NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16
27	A3_3.2 VH / A3_3_D50A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
28	A3_3.2 VH / A3_4_D50A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
29	A3_3.2 VH / A3_5_D50A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
30	A3_4.2 VH / A3_3_D50A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
31	A3_4.2 VH / A3_4_D50A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
32	A3_4.2 VH / A3_5_D50A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105

33	A3_6.2 VH / A3_3_D50A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
34	A3_6.2 VH / A3_4_D50A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
35	A3_6.2 VH / A3_5_D50A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
36	A3-derived VH CON / A3-derived VL_D50A CON	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
37	A3-Hum VH CON / A3-Hum VL_D50A CON	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
38	B035-C03-A3_1100T VH / B035-C03-A3_ G51A VL	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
39	B035-C03-A3_1100T VH / B035-C03-A3 VL	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
40	B035-C03-A3 VH / B035-C03-A3_ G51A VL	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
41	A3_3.2_1100T VH / A3_3_ G51A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105
42	A3_3.2_1100T VH / A3_4_ G51A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:110
43	A3_3.2_1100T VH / A3_5_ G51A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
44	A3_3.2_1100T VH / A3_3 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105
45	A3_3.2_1100T VH / A3_4 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:110
46	A3_3.2_1100T VH / A3_5 VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
47	A3_3.2 VH / A3_3_ G51A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105
48	A3_3.2 VH / A3_4_ G51A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:110
49	A3_3.2 VH / A3_5_ G51A VL	SEQ ID NO:95	SEQ ID NO:96	SEQ ID NO:97	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
50	A3_4.2_1100T VH / A3_3_ G51A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105
51	A3_4.2_1100T VH / A3_4_ G51A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:108	SEQ ID NO:109	SEQ ID NO:110
52	A3_4.2_1100T VH / A3_5_ G51A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
53	A3_4.2_1100T VH / A3_3 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:104	SEQ ID NO:105	SEQ ID NO:105

54	A3_4_2_1100T VH / A3_4 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
55	A3_4_2_1100T VH / A3_5 VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
56	A3_4_2 VH / A3_3_G51A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
57	A3_4_2 VH / A3_4_G51A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
58	A3_4_2 VH / A3_5_G51A VL	SEQ ID NO:99	SEQ ID NO:100	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:111	SEQ ID NO:105
59	A3_6.2_1100T VH / A3_3_G51A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
60	A3_6.2_1100T VH / A3_4_G51A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
61	A3_6.2_1100T VH / A3_5_G51A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
62	A3_6.2_1100T VH / A3_3 VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
63	A3_6.2_1100T VH / A3_4 VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
64	A3_6.2_1100T VH / A3_5 VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
65	A3_6.2 VH / A3_3_G51A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:103	SEQ ID NO:14	SEQ ID NO:104	SEQ ID NO:105
66	A3_6.2 VH / A3_4_G51A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:14	SEQ ID NO:108	SEQ ID NO:105
67	A3_6.2 VH / A3_5_G51A VL	SEQ ID NO:99	SEQ ID NO:175	SEQ ID NO:101	SEQ ID NO:24	SEQ ID NO:107	SEQ ID NO:110	SEQ ID NO:111	SEQ ID NO:105
68	A3-derived_1100T VH CON / A3-derived_G51A VL	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
69	A3-derived_1100T VH CON / A3-derived VL	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
70	A3-derived VH CON / A3-derived_G51A VL	SEQ ID NO:113	SEQ ID NO:114	SEQ ID NO:115	SEQ ID NO:116	SEQ ID NO:122	SEQ ID NO:123	SEQ ID NO:124	SEQ ID NO:125
71	A3-Hum_1100T VH CON / A3-Hum_G51A VL	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
72	A3-Hum_1100T VH CON / A3-Hum VL	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
73	A3-Hum VH CON / A3-Hum_G51A VL	SEQ ID NO:118	SEQ ID NO:119	SEQ ID NO:120	SEQ ID NO:24	SEQ ID NO:127	SEQ ID NO:128	SEQ ID NO:129	SEQ ID NO:105
74	5H8CVH4 VH / 5H8CVL3 VL	SEQ ID NO:196	SEQ ID NO:198	SEQ ID NO:200	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:226	SEQ ID NO:229

75	5H8CVH4 VH / 5H8CVL4 VL	SEQ ID NO:196	SEQ ID NO:198	SEQ ID NO:200	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:227	SEQ ID NO:229
76	5H8CVH4 VH / 5H8GVL3 VL	SEQ ID NO:196	SEQ ID NO:198	SEQ ID NO:200	SEQ ID NO:24	SEQ ID NO:223	SEQ ID NO:225	SEQ ID NO:228	SEQ ID NO:229
77	5H8GVH4 VH / 5H8CVL3 VL	SEQ ID NO:197	SEQ ID NO:199	SEQ ID NO:201	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:226	SEQ ID NO:229
78	5H8GVH4 VH / 5H8CVL4 VL	SEQ ID NO:197	SEQ ID NO:199	SEQ ID NO:201	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:227	SEQ ID NO:229
79	5H8GVH4 VH / 5H8GVL3 VL	SEQ ID NO:197	SEQ ID NO:199	SEQ ID NO:201	SEQ ID NO:24	SEQ ID NO:223	SEQ ID NO:225	SEQ ID NO:228	SEQ ID NO:229
80	5H8-derived VH CON / 5H8-derived VL CON	SEQ ID NO:205	SEQ ID NO:206	SEQ ID NO:207	SEQ ID NO:24	SEQ ID NO:232	SEQ ID NO:233	SEQ ID NO:234	SEQ ID NO:235
81	5H8-Hum VH CON / 5H8-Hum VL CON	SEQ ID NO:208	SEQ ID NO:209	SEQ ID NO:210	SEQ ID NO:24	SEQ ID NO:236	SEQ ID NO:237	SEQ ID NO:238	SEQ ID NO:229
82	CSP-S-5H8_D98G VH / CSP-S-5H8 VL	SEQ ID NO:21	SEQ ID NO:22	SEQ ID NO:23	SEQ ID NO:24	SEQ ID NO:13	SEQ ID NO:14	SEQ ID NO:15	SEQ ID NO:16
83	5H8CVH4_D98G VH / 5H8CVL3 VL	SEQ ID NO:196	SEQ ID NO:198	SEQ ID NO:200	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:226	SEQ ID NO:229
84	5H8CVH4_D98G VH / 5H8CVL4 VL	SEQ ID NO:196	SEQ ID NO:198	SEQ ID NO:200	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:227	SEQ ID NO:229
85	5H8CVH4_D98G VH / 5H8GVL3 VL	SEQ ID NO:196	SEQ ID NO:198	SEQ ID NO:200	SEQ ID NO:24	SEQ ID NO:223	SEQ ID NO:225	SEQ ID NO:228	SEQ ID NO:229
86	5H8GVH4_D98G VH / 5H8CVL3 VL	SEQ ID NO:197	SEQ ID NO:199	SEQ ID NO:201	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:226	SEQ ID NO:229
87	5H8GVH4_D98G VH / 5H8CVL4 VL	SEQ ID NO:197	SEQ ID NO:199	SEQ ID NO:201	SEQ ID NO:24	SEQ ID NO:222	SEQ ID NO:224	SEQ ID NO:227	SEQ ID NO:229
88	5H8GVH4_D98G VH / 5H8GVL3 VL	SEQ ID NO:197	SEQ ID NO:199	SEQ ID NO:201	SEQ ID NO:24	SEQ ID NO:223	SEQ ID NO:225	SEQ ID NO:228	SEQ ID NO:229
89	5H8-derived_D98G VH CON / 5H8-derived VL CON	SEQ ID NO:205	SEQ ID NO:206	SEQ ID NO:207	SEQ ID NO:24	SEQ ID NO:232	SEQ ID NO:233	SEQ ID NO:234	SEQ ID NO:235
90	5H8-Hum_D98G VH CON / 5H8-Hum VL CON	SEQ ID NO:208	SEQ ID NO:209	SEQ ID NO:210	SEQ ID NO:24	SEQ ID NO:236	SEQ ID NO:237	SEQ ID NO:238	SEQ ID NO:229

Table C

Row	Antibody	Column A	Column B
		VH	VL
1	B035-C03-A3	SEQ ID NO:1	SEQ ID NO:9
2	CSP-S-5H8	SEQ ID NO:17	SEQ ID NO:25
3	A3 3.2 VH / A3 3 VL	SEQ ID NO:94	SEQ ID NO:102
4	A3 3.2 VH / A3 4 VL	SEQ ID NO:94	SEQ ID NO:106
5	A3 3.2 VH / A3 5 VL	SEQ ID NO:94	SEQ ID NO:109
6	A3 4.2 VH / A3 3 VL	SEQ ID NO:98	SEQ ID NO:102
7	A3 4.2 VH / A3 4 VL	SEQ ID NO:98	SEQ ID NO:106
8	A3 4.2 VH / A3 5 VL	SEQ ID NO:98	SEQ ID NO:109
9	A3 6.2 VH / A3 3 VL	SEQ ID NO:174	SEQ ID NO:102
10	A3 6.2 VH / A3 4 VL	SEQ ID NO:174	SEQ ID NO:106
11	A3 6.2 VH / A3 5 VL	SEQ ID NO:174	SEQ ID NO:109
12	A3-derived VH CON / A3-derived VL CON	SEQ ID NO:112	SEQ ID NO:121
13	A3-Hum VH CON / A3-Hum VL CON	SEQ ID NO:117	SEQ ID NO:126
14	B035-C03-A3 D50X	SEQ ID NO:1	SEQ ID NO:143
15	A3 3.2 VH / A3 3 D50X VL	SEQ ID NO:94	SEQ ID NO:144
16	A3 3.2 VH / A3 4 D50X VL	SEQ ID NO:94	SEQ ID NO:145
17	A3 3.2 VH / A3 5 D50X VL	SEQ ID NO:94	SEQ ID NO:146
18	A3 4.2 VH / A3 3 D50X VL	SEQ ID NO:98	SEQ ID NO:144
19	A3 4.2 VH / A3 4 D50X VL	SEQ ID NO:98	SEQ ID NO:145
20	A3 4.2 VH / A3 5 D50X VL	SEQ ID NO:98	SEQ ID NO:146
21	A3 6.2 VH / A3 3 D50X VL	SEQ ID NO:174	SEQ ID NO:144
22	A3 6.2 VH / A3 4 D50X VL	SEQ ID NO:174	SEQ ID NO:145
23	A3 6.2 VH / A3 5 D50X VL	SEQ ID NO:174	SEQ ID NO:146
24	A3-derived VH CON / A3-derived VL D50X CON	SEQ ID NO:112	SEQ ID NO:147
25	A3-Hum VH CON / A3-Hum VL D50X CON	SEQ ID NO:117	SEQ ID NO:148
26	B035-C03-A3 D50A	SEQ ID NO:1	SEQ ID NO:156
27	A3 3.2 VH / A3 3 D50A VL	SEQ ID NO:94	SEQ ID NO:157
28	A3 3.2 VH / A3 4 D50A VL	SEQ ID NO:94	SEQ ID NO:158
29	A3 3.2 VH / A3 5 D50A VL	SEQ ID NO:94	SEQ ID NO:159
30	A3 4.2 VH / A3 3 D50A VL	SEQ ID NO:98	SEQ ID NO:157
31	A3 4.2 VH / A3 4 D50A VL	SEQ ID NO:98	SEQ ID NO:158
32	A3 4.2 VH / A3 5 D50A VL	SEQ ID NO:98	SEQ ID NO:159
33	A3 6.2 VH / A3 3 D50A VL	SEQ ID NO:174	SEQ ID NO:157
34	A3 6.2 VH / A3 4 D50A VL	SEQ ID NO:174	SEQ ID NO:158
35	A3 6.2 VH / A3 5 D50A VL	SEQ ID NO:174	SEQ ID NO:159
36	A3-derived VH CON / A3-derived VL D50A CON	SEQ ID NO:112	SEQ ID NO:160
37	A3-Hum VH CON / A3-Hum VL D50A CON	SEQ ID NO:117	SEQ ID NO:161
38	B035-C03-A3 I100T VH / B035-C03-A3 G51A VL	SEQ ID NO:179	SEQ ID NO:186
39	B035-C03-A3 I100T VH / B035-C03-A3 VL	SEQ ID NO:179	SEQ ID NO:9
40	B035-C03-A3 VH / B035-C03-A3 G51A VL	SEQ ID NO:1	SEQ ID NO:186
41	A3 3.2 I100T VH / A3 3 G51A VL	SEQ ID NO:180	SEQ ID NO:187
42	A3 3.2 I100T VH / A3 4 G51A VL	SEQ ID NO:180	SEQ ID NO:188
43	A3 3.2 I100T VH / A3 5 G51A VL	SEQ ID NO:180	SEQ ID NO:189
44	A3 3.2 I100T VH / A3 3 VL	SEQ ID NO:180	SEQ ID NO:102
45	A3 3.2 I100T VH / A3 4 VL	SEQ ID NO:180	SEQ ID NO:106
46	A3 3.2 I100T VH / A3 5 VL	SEQ ID NO:180	SEQ ID NO:109
47	A3 3.2 VH / A3 3 G51A VL	SEQ ID NO:94	SEQ ID NO:187
48	A3 3.2 VH / A3 4 G51A VL	SEQ ID NO:94	SEQ ID NO:188
49	A3 3.2 VH / A3 5 G51A VL	SEQ ID NO:94	SEQ ID NO:189
50	A3 4.2 I100T VH / A3 3 G51A VL	SEQ ID NO:181	SEQ ID NO:187
51	A3 4.2 I100T VH / A3 4 G51A VL	SEQ ID NO:181	SEQ ID NO:188
52	A3 4.2 I100T VH / A3 5 G51A VL	SEQ ID NO:181	SEQ ID NO:189
53	A3 4.2 I100T VH / A3 3 VL	SEQ ID NO:181	SEQ ID NO:102
54	A3 4.2 I100T VH / A3 4 VL	SEQ ID NO:181	SEQ ID NO:106
55	A3 4.2 I100T VH / A3 5 VL	SEQ ID NO:181	SEQ ID NO:109
56	A3 4.2 VH / A3 3 G51A VL	SEQ ID NO:98	SEQ ID NO:187
57	A3 4.2 VH / A3 4 G51A VL	SEQ ID NO:98	SEQ ID NO:188
58	A3 4.2 VH / A3 5 G51A VL	SEQ ID NO:98	SEQ ID NO:189
59	A3 6.2 I100T VH / A3 3 G51A VL	SEQ ID NO:182	SEQ ID NO:187
60	A3 6.2 I100T VH / A3 4 G51A VL	SEQ ID NO:182	SEQ ID NO:188

61	A3_6.2_I100T_VH / A3_5_G51A_VL	SEQ ID NO:182	SEQ ID NO:189
62	A3_6.2_I100T_VH / A3_3_VL	SEQ ID NO:182	SEQ ID NO:102
63	A3_6.2_I100T_VH / A3_4_VL	SEQ ID NO:182	SEQ ID NO:106
64	A3_6.2_I100T_VH / A3_5_VL	SEQ ID NO:182	SEQ ID NO:109
65	A3_6.2_VH / A3_3_G51A_VL	SEQ ID NO:174	SEQ ID NO:187
66	A3_6.2_VH / A3_4_G51A_VL	SEQ ID NO:174	SEQ ID NO:188
67	A3_6.2_VH / A3_5_G51A_VL	SEQ ID NO:174	SEQ ID NO:189
68	A3-derived_I100T_VH_CON / A3-derived_G51A_VL_CON	SEQ ID NO:183	SEQ ID NO:190
69	A3-derived_I100T_VH_CON / A3-derived_VL_CON	SEQ ID NO:183	SEQ ID NO:121
70	A3-derived_VH_CON / A3-derived_G51A_VL_CON	SEQ ID NO:112	SEQ ID NO:190
71	A3-Hum_I100T_VH_CON / A3-Hum_G51A_VL_CON	SEQ ID NO:184	SEQ ID NO:191
72	A3-Hum_I100T_VH_CON / A3-Hum_VL_CON	SEQ ID NO:184	SEQ ID NO:126
73	A3-Hum_VH_CON / A3-Hum_G51A_VL_CON	SEQ ID NO:117	SEQ ID NO:191
74	5H8CVH4_VH / 5H8CVL3_VL	SEQ ID NO:193	SEQ ID NO:219
75	5H8CVH4_VH / 5H8CVL4_VL	SEQ ID NO:193	SEQ ID NO:220
76	5H8CVH4_VH / 5H8GVL3_VL	SEQ ID NO:193	SEQ ID NO:221
77	5H8GVH4_VH / 5H8CVL3_VL	SEQ ID NO:194	SEQ ID NO:219
78	5H8GVH4_VH / 5H8CVL4_VL	SEQ ID NO:194	SEQ ID NO:220
79	5H8GVH4_VH / 5H8GVL3_VL	SEQ ID NO:194	SEQ ID NO:221
80	5H8-derived_VH_CON / 5H8-derived_VL_CON	SEQ ID NO:202	SEQ ID NO:230
81	5H8-Hum_VH_CON / 5H8-Hum_VL_CON	SEQ ID NO:203	SEQ ID NO:231
82	CSP-S-5H8_D98G_VH / CSP-S-5H8_VL	SEQ ID NO:211	SEQ ID NO:25
83	5H8CVH4_D98G_VH / 5H8CVL3_VL	SEQ ID NO:212	SEQ ID NO:219
84	5H8CVH4_D98G_VH / 5H8CVL4_VL	SEQ ID NO:212	SEQ ID NO:220
85	5H8CVH4_D98G_VH / 5H8GVL3_VL	SEQ ID NO:212	SEQ ID NO:221
86	5H8GVH4_D98G_VH / 5H8CVL3_VL	SEQ ID NO:213	SEQ ID NO:219
87	5H8GVH4_D98G_VH / 5H8CVL4_VL	SEQ ID NO:213	SEQ ID NO:220
88	5H8GVH4_D98G_VH / 5H8GVL3_VL	SEQ ID NO:213	SEQ ID NO:221
89	5H8-derived_D98G_VH_CON / 5H8-derived_VL_CON	SEQ ID NO:216	SEQ ID NO:230
90	5H8-Hum_D98G_VH_CON / 5H8-Hum_VL_CON	SEQ ID NO:217	SEQ ID NO:231

Table D

Row	Name	Column A	Column B
		Heavy Chain	Light Chain
1	B035-C03-A3 hlgG1	SEQ ID NO:64	SEQ ID NO:66
2	CSP-S-5H8 hlgG1	SEQ ID NO:67	SEQ ID NO:69
3	B035-C03-A3 hlgG4(S228P, L235E)	SEQ ID NO:65	SEQ ID NO:66
4	CSP-S-5H8 hlgG4(S228P, L235E)	SEQ ID NO:68	SEQ ID NO:69
5	A3 3.2 VH / A3 3 VL hlgG1	SEQ ID NO:130	SEQ ID NO:138
6	A3 3.2 VH / A3 4 VL hlgG1	SEQ ID NO:130	SEQ ID NO:139
7	A3 3.2 VH / A3 5 VL hlgG1	SEQ ID NO:130	SEQ ID NO:140
8	A3 4.2 VH / A3 3 VL hlgG1	SEQ ID NO:132	SEQ ID NO:138
9	A3 4.2 VH / A3 4 VL hlgG1	SEQ ID NO:132	SEQ ID NO:139
10	A3 4.2 VH / A3 5 VL hlgG1	SEQ ID NO:132	SEQ ID NO:140
11	A3 6.2 VH / A3 3 VL hlgG1	SEQ ID NO:176	SEQ ID NO:138
12	A3 6.2 VH / A3 4 VL hlgG1	SEQ ID NO:176	SEQ ID NO:139
13	A3 6.2 VH / A3 5 VL hlgG1	SEQ ID NO:176	SEQ ID NO:140
14	A3-derived VH CON / A3-derived VL CON hlgG1	SEQ ID NO:134	SEQ ID NO:141
15	A3-Hum VH CON / A3-Hum VL CON hlgG1	SEQ ID NO:136	SEQ ID NO:142
16	A3 3.2 VH / A3 3 VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:138
17	A3 3.2 VH / A3 4 VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:139
18	A3 3.2 VH / A3 5 VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:140
19	A3 4.2 VH / A3 3 VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:138
20	A3 4.2 VH / A3 4 VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:139
21	A3 4.2 VH / A3 5 VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:140
22	A3 6.2 VH / A3 3 VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:138
23	A3 6.2 VH / A3 4 VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:139
24	A3 6.2 VH / A3 5 VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:140
25	A3-derived VH CON / A3-derived VL CON hlgG4(S228P, L235E)	SEQ ID NO:135	SEQ ID NO:141
26	A3-Hum VH CON / A3-Hum VL CON hlgG4(S228P, L235E)	SEQ ID NO:137	SEQ ID NO:142
27	B035-C03-A3 D50X hlgG1	SEQ ID NO:64	SEQ ID NO:150
28	B035-C03-A3 D50X hlgG4(S228P, L235E)	SEQ ID NO:65	SEQ ID NO:150
29	A3 3.2 VH / A3 3 D50X VL hlgG1	SEQ ID NO:130	SEQ ID NO:151
30	A3 3.2 VH / A3 4 D50X VL hlgG1	SEQ ID NO:130	SEQ ID NO:152
31	A3 3.2 VH / A3 5 D50X VL hlgG1	SEQ ID NO:130	SEQ ID NO:153
32	A3 4.2 VH / A3 3 D50X VL hlgG1	SEQ ID NO:132	SEQ ID NO:151
33	A3 4.2 VH / A3 4 D50X VL hlgG1	SEQ ID NO:132	SEQ ID NO:152
34	A3 4.2 VH / A3 5 D50X VL hlgG1	SEQ ID NO:132	SEQ ID NO:153
35	A3 6.2 VH / A3 3 D50X VL hlgG1	SEQ ID NO:176	SEQ ID NO:151
36	A3 6.2 VH / A3 4 D50X VL hlgG1	SEQ ID NO:176	SEQ ID NO:152
37	A3 6.2 VH / A3 5 D50X VL hlgG1	SEQ ID NO:176	SEQ ID NO:153
38	A3-derived VH CON / A3-derived D50X VL CON hlgG1	SEQ ID NO:134	SEQ ID NO:154
39	A3-Hum VH CON / A3-Hum D50X VL CON hlgG1	SEQ ID NO:136	SEQ ID NO:155
40	A3 3.2 VH / A3 3 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:151
41	A3 3.2 VH / A3 4 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:152
42	A3 3.2 VH / A3 5 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:153
43	A3 4.2 VH / A3 3 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:151
44	A3 4.2 VH / A3 4 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:152
45	A3 4.2 VH / A3 5 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:153
46	A3 6.2 VH / A3 3 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:151
47	A3 6.2 VH / A3 4 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:152
48	A3 6.2 VH / A3 5 D50X VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:153
49	A3-derived VH CON / A3-derived D50X VL hlgG4(S228P, L235E)	SEQ ID NO:135	SEQ ID NO:154
50	A3-Hum VH CON / A3-Hum D50X VL hlgG4(S228P, L235E)	SEQ ID NO:137	SEQ ID NO:155
51	B035-C03-A3 D50A hlgG1	SEQ ID NO:64	SEQ ID NO:163
52	B035-C03-A3 D50A hlgG4(S228P, L235E)	SEQ ID NO:65	SEQ ID NO:163
53	A3 3.2 VH / A3 3 D50A VL hlgG1	SEQ ID NO:130	SEQ ID NO:164
54	A3 3.2 VH / A3 4 D50A VL hlgG1	SEQ ID NO:130	SEQ ID NO:165
55	A3 3.2 VH / A3 5 D50A VL hlgG1	SEQ ID NO:130	SEQ ID NO:166
56	A3 4.2 VH / A3 3 D50A VL hlgG1	SEQ ID NO:132	SEQ ID NO:164
57	A3 4.2 VH / A3 4 D50A VL hlgG1	SEQ ID NO:132	SEQ ID NO:165
58	A3 4.2 VH / A3 5 D50A VL hlgG1	SEQ ID NO:132	SEQ ID NO:166
59	A3 6.2 VH / A3 3 D50A VL hlgG1	SEQ ID NO:176	SEQ ID NO:164
60	A3 6.2 VH / A3 4 D50A VL hlgG1	SEQ ID NO:176	SEQ ID NO:165
61	A3 6.2 VH / A3 5 D50A VL hlgG1	SEQ ID NO:176	SEQ ID NO:166

62	A3-derived VH CON / A3-derived D50A VL CON hlgG1	SEQ ID NO:134	SEQ ID NO:167
63	A3-Hum VH CON / A3-Hum D50A VL CON hlgG1	SEQ ID NO:136	SEQ ID NO:168
64	A3 3.2 VH / A3 3 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:164
65	A3 3.2 VH / A3 4 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:165
66	A3 3.2 VH / A3 5 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:131	SEQ ID NO:166
67	A3 4.2 VH / A3 3 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:164
68	A3 4.2 VH / A3 4 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:165
69	A3 4.2 VH / A3 5 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:133	SEQ ID NO:166
70	A3 6.2 VH / A3 3 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:164
71	A3 6.2 VH / A3 4 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:165
72	A3 6.2 VH / A3 5 D50A VL hlgG4(S228P, L235E)	SEQ ID NO:177	SEQ ID NO:166
73	A3-derived VH CON / A3-derived D50A VL hlgG4(S228P, L235E)	SEQ ID NO:135	SEQ ID NO:167
74	A3-Hum VH CON / A3-Hum D50A VL hlgG4(S228P, L235E)	SEQ ID NO:137	SEQ ID NO:168
75	B035-C03-A3 I100T VH / B035-C03-A3 G51A VL	SEQ ID NO:239	SEQ ID NO:245
76	B035-C03-A3 I100T VH / B035-C03-A3 VL	SEQ ID NO:239	SEQ ID NO:66
77	B035-C03-A3 VH / B035-C03-A3 G51A VL	SEQ ID NO:65	SEQ ID NO:245
78	A3 3.2 I100T VH / A3 3 G51A VL	SEQ ID NO:240	SEQ ID NO:246
79	A3 3.2 I100T VH / A3 4 G51A VL	SEQ ID NO:240	SEQ ID NO:247
80	A3 3.2 I100T VH / A3 5 G51A VL	SEQ ID NO:240	SEQ ID NO:248
81	A3 3.2 I100T VH / A3 3 VL	SEQ ID NO:240	SEQ ID NO:138
82	A3 3.2 I100T VH / A3 4 VL	SEQ ID NO:240	SEQ ID NO:139
83	A3 3.2 I100T VH / A3 5 VL	SEQ ID NO:240	SEQ ID NO:140
84	A3 3.2 VH / A3 3 G51A VL	SEQ ID NO:131	SEQ ID NO:246
85	A3 3.2 VH / A3 4 G51A VL	SEQ ID NO:131	SEQ ID NO:247
86	A3 3.2 VH / A3 5 G51A VL	SEQ ID NO:131	SEQ ID NO:248
87	A3 4.2 I100T VH / A3 3 G51A VL	SEQ ID NO:241	SEQ ID NO:246
88	A3 4.2 I100T VH / A3 4 G51A VL	SEQ ID NO:241	SEQ ID NO:247
89	A3 4.2 I100T VH / A3 5 G51A VL	SEQ ID NO:241	SEQ ID NO:248
90	A3 4.2 I100T VH / A3 3 VL	SEQ ID NO:241	SEQ ID NO:138
91	A3 4.2 I100T VH / A3 4 VL	SEQ ID NO:241	SEQ ID NO:139
92	A3 4.2 I100T VH / A3 5 VL	SEQ ID NO:241	SEQ ID NO:140
93	A3 4.2 VH / A3 3 G51A VL	SEQ ID NO:133	SEQ ID NO:246
94	A3 4.2 VH / A3 4 G51A VL	SEQ ID NO:133	SEQ ID NO:247
95	A3 4.2 VH / A3 5 G51A VL	SEQ ID NO:133	SEQ ID NO:248
96	A3 6.2 I100T VH / A3 3 G51A VL	SEQ ID NO:242	SEQ ID NO:246
97	A3 6.2 I100T VH / A3 4 G51A VL	SEQ ID NO:242	SEQ ID NO:247
98	A3 6.2 I100T VH / A3 5 G51A VL	SEQ ID NO:242	SEQ ID NO:248
99	A3 6.2 I100T VH / A3 3 VL	SEQ ID NO:242	SEQ ID NO:138
100	A3 6.2 I100T VH / A3 4 VL	SEQ ID NO:242	SEQ ID NO:139
101	A3 6.2 I100T VH / A3 5 VL	SEQ ID NO:242	SEQ ID NO:140
102	A3 6.2 VH / A3 3 G51A VL	SEQ ID NO:177	SEQ ID NO:246
103	A3 6.2 VH / A3 4 G51A VL	SEQ ID NO:177	SEQ ID NO:247
104	A3 6.2 VH / A3 5 G51A VL	SEQ ID NO:177	SEQ ID NO:248
105	A3-derived I100T VH CON / A3-derived G51A VL CON	SEQ ID NO:243	SEQ ID NO:249
106	A3-derived I100T VH CON / A3-derived VL CON	SEQ ID NO:243	SEQ ID NO:141
107	A3-derived VH CON / A3-derived G51A VL CON	SEQ ID NO:135	SEQ ID NO:249
108	A3-Hum I100T VH CON / A3-Hum G51A VL CON	SEQ ID NO:244	SEQ ID NO:250
109	A3-Hum I100T VH CON / A3-Hum VL CON	SEQ ID NO:244	SEQ ID NO:142
110	A3-Hum VH CON / A3-Hum G51A VL CON	SEQ ID NO:137	SEQ ID NO:250
111	5H8CVH4 VH / 5H8CVL3 VL	SEQ ID NO:251	SEQ ID NO:260
112	5H8CVH4 VH / 5H8CVL4 VL	SEQ ID NO:251	SEQ ID NO:261
113	5H8CVH4 VH / 5H8GVL3 VL	SEQ ID NO:251	SEQ ID NO:262
114	5H8GVH4 VH / 5H8CVL3 VL	SEQ ID NO:252	SEQ ID NO:260
115	5H8GVH4 VH / 5H8CVL4 VL	SEQ ID NO:252	SEQ ID NO:261
116	5H8GVH4 VH / 5H8GVL3 VL	SEQ ID NO:252	SEQ ID NO:262
117	5H8-derived VH CON / 5H8-derived VL CON	SEQ ID NO:253	SEQ ID NO:263
118	5H8-Hum VH CON / 5H8-Hum VL CON	SEQ ID NO:254	SEQ ID NO:264
119	CSP-S-5H8 D98G VH / CSP-S-5H8 VL	SEQ ID NO:255	SEQ ID NO:69
120	5H8CVH4 D98G VH / 5H8CVL3 VL	SEQ ID NO:256	SEQ ID NO:260
121	5H8CVH4 D98G VH / 5H8CVL4 VL	SEQ ID NO:256	SEQ ID NO:261
122	5H8CVH4 D98G VH / 5H8GVL3 VL	SEQ ID NO:256	SEQ ID NO:262
123	5H8GVH4 D98G VH / 5H8CVL3 VL	SEQ ID NO:257	SEQ ID NO:260
124	5H8GVH4 D98G VH / 5H8CVL4 VL	SEQ ID NO:257	SEQ ID NO:261
125	5H8GVH4 D98G VH / 5H8GVL3 VL	SEQ ID NO:257	SEQ ID NO:262
126	5H8-derived D98G VH CON / 5H8-derived VL CON	SEQ ID NO:258	SEQ ID NO:263

127	5H8-Hum_D98G VH CON / 5H8-Hum VL CON	SEQ ID NO:259	SEQ ID NO:264
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The present disclosure includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

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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.

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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.

15

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).

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25

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.

30

Where a nucleic acid sequence is disclosed herein, the reverse complement thereof is also expressly contemplated.

35

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

Antigen-binding molecules, peptides/polypeptides, peptide/polypeptide complexes, nucleic acids/polynucleotides, vectors, compositions or cells according to the present disclosure may optionally be provided in isolated or purified form. For example, articles according to the present disclosure may be isolated/purified from naturally-occurring biological material.

5

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.

10 **Figures 1A-1B. Evaluation of anti-gp130 clone B-R3 to mouse gp130.** Graphs showing results of ELISA binding assays plotting absorbance (OD) at 450nm upon addition of increasing amounts of B-R3 with (1A) human or (1B) mouse gp130 as the coating protein.

15 **Figure 2. Evaluation of binding of anti-gp130 clone CSP-S-5H8 to human gp130.** Graphs showing results of ELISA binding assays plotting absorbance (OD) at 450nm upon addition of increasing amounts of CSP-S-5H8 with human gp130 as the coating protein.

20 **Figures 3A-3F. STAT3 reporter assay.** Graphs showing % activity of STAT3 in a HEK293-based STAT3 reporter cell line upon stimulation with (3A) 100 ng/ml hIL-6, (3B) 100 ng/ml hIL-11, (3C) 10 ng/ml hOSM, (3D) 10 ng/ml hLIF, (3E) 10 ng/ml hCT-1, or (3F) 10 ng/ml hCNTF, in the presence of increasing concentrations of B035-C03-A3.

25 **Figures 4A-4F. STAT3 reporter assay.** Graphs showing % activity of STAT3 in a HEK293-based STAT3 reporter cell line upon stimulation with (4A) 100 ng/ml hIL-6, (4B) 100 ng/ml hIL-11, (4C) 10 ng/ml hOSM, (4D) 10 ng/ml hLIF, (4E) 10 ng/ml hCT-1, or (4F) 10 ng/ml hCNTF, in the presence of increasing concentrations of CSP-S-5H8.

30 **Figure 5. *In vitro* screening of anti-gp130 mAb clones in primary human cardiac fibroblasts.** Graph showing percentage inhibition of gp130 signalling at increasing concentrations of gp130 mAb clone CSP-S-5H8 as determined by MMP2 concentration in human cardiac fibroblasts following stimulation with 5 ng/ml of recombinant human IL-11 for 24 h in the presence of CSP-S-5H8 (61 pg/ml to 4 µg/ml; 4-fold dilution).

35 **Figure 6A-6D. *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 the presence of 11E10, MAB628, CSP-S-5H8 (5H8), MA5-23817 or PA5-47650 (250 ng/ml or 1.7 nM). (6C and 6D) Immunoblots showing analysis of cell lysates of A549 cells (6C) unstimulated or (6D) stimulated with hIL-11 or hOSM (10 ng/ml) in the absence of antibody or
40 in the presence of antibody clones 11E10, CSP-S-5H8 (5H8), MA5-23817 or PA5-47650 (250 ng/ml or 1.7 nM).

Figures 7A-7B. *In vitro* validation of anti-gp130 clones in primary mouse atrial fibroblasts. (7A)

Immunoblots showing analysis of cell lysates of primary mouse atrial fibroblasts (MAFs) unstimulated (baseline; BL) or stimulated with mL6 or mOSM (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of antibody clones 11E10 or CSP-S-5H8 (5H8) (250 ng/ml). (7B) Graphs showing analysis of % inhibition of gp130-mediated signalling, determined by MMP2 assay, in cells stimulated for 25 h with recombinant mouse IL-11 in the presence of antibody clones 11E10 or CSP-S-5H8 (5H8) (61 pg/ml to 4 µg/ml; 4-fold dilution).

Figures 8A-8B. *In vitro* comparison of B-R3 and CSP-S-5H8 on STAT3 activation in human lung epithelial carcinoma cell line (A549).

Immunoblots showing analysis of (8A) pSTAT3/STAT3 and (8B) pERK/ERK levels in cell lysates of A549 cells unstimulated or 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, B-R3 or CSP-S-5H8 (5H8) (250 ng/ml).

Figure 9. *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 anti-gp130 mAb clone CSP-S-5H8, as determined by MMP2 concentration. Cells were stimulated for 24 h 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).

Figure 10. *In vitro* inhibitory effect of CSP-S-5H8 on STAT3 activation by gp130 ligands in human lung epithelial carcinoma cell line (A549). Immunoblots showing analysis of cell lysates of A549 cells unstimulated (baseline; BL) or stimulated with hCTGF, hCT-1, hIL6, hIL-11, hLIF or hOSM (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of CSP-S-5H8 (5H8) (250 ng/ml).

Figures 11A-11D. *In vitro* inhibitory effects of CSP-S-5H8 on STAT3 or ERK activation by IL-6 or IL-11 in human lung epithelial carcinoma cell line (A549). (11A) Immunoblot showing analysis of cell lysates of A549 cells unstimulated (baseline; BL) or stimulated with recombinant human IL-6 for 15 min in the absence of antibody (-), in the presence of 11E10 (4 µg/ml), or in the presence of CSP-S-5H8 (5H8) (0.06 ng/ml to 4 µg/ml). (11B) Graph showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblot of 11A. (11C) Immunoblot showing analysis of cell lysates of A549 cells unstimulated (baseline; BL) or stimulated with recombinant human IL-11 for 15 min in the absence of antibody (-), in the presence of 11E10 (4 µg/ml), or in the presence of CSP-S-5H8 (5H8) (0.06 ng/ml to 4 µg/ml). (11D) Graphs showing % inhibition of gp130-mediated signalling determined by densitometry analysis of pERK/ERK levels of the immunoblot of 11C.

Figures 12A-12B. *In vitro* inhibitory effects of B-R3 or CSP-S-5H8 on STAT3 activation by LIF in human lung epithelial carcinoma cell line (A549). (12A) Immunoblot showing analysis of cell lysates of A549 cells unstimulated (baseline; BL) or stimulated with recombinant LIF for 15 min in the absence of antibody (-), in the presence of 11E10 (4 µg/ml), or in the presence of CSP-S-5H8 (5H8) or B-R3 (0.06

ng/ml to 4 µg/ml). (12B) Graphs showing % inhibition of LIF-mediated signalling determined by densitometry analysis of pSTAT3/STAT3 levels of the immunoblots of 13A.

Figures 13A-13D. *In vitro* screening of anti-gp130 mAb clones in primary human cardiac

5 **fibroblasts and primary mouse atrial fibroblasts. (13A-13B)** Graphs showing percentage inhibition of gp130 signalling at increasing concentrations of anti-gp130 mAb clone B035-C03-A3 as determined by MMP2 concentration in (13A) primary human cardiac fibroblasts and (13B) primary mouse atrial fibroblasts following stimulation with 5 ng/ml of recombinant, species-matched IL-11 in the presence of B035-C03-A3 (61 pg/ml to 4 µg/ml; 4-fold dilution). (13C-13D) Graphs showing percentage inhibition of
10 gp130 signalling at increasing concentrations of anti-gp130 mAb clone CSP-S-5H8 as determined by MMP2 concentration in (13C) primary human cardiac fibroblasts and (13D) primary mouse atrial fibroblasts, following stimulation with 5 ng/ml of recombinant human IL-11 in the presence of CSP-S-5H8 (61 pg/ml to 4 µg/ml; 4-fold dilution).

15 **Figures 14A-14B. *In vitro* inhibitory effect of B035-C03-A3 and CSP-S-5H8 on STAT3 activation by gp130 ligands in human lung epithelial carcinoma cell line (A549). (14A-14B)** Immunoblots showing analysis of cell lysates of A549 cells unstimulated (baseline; BL) or stimulated with hCTGF, hCT-1, hIL6, hIL-11, hLIF or hOSM (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of negative control 11E10 (250 ng/ml) or CSP-S-5H8 (5H8) or B035-C03-A3 (A3) (250 ng/ml).

20

Figures 15A-15B. *In vitro* inhibitory effects of B035-C03-A3 on STAT3 activation by gp130 ligands in primary mouse atrial fibroblasts. (15A-15B) Immunoblots showing analysis of cell lysates of primary mouse atrial fibroblast cells unstimulated (baseline; BL) or stimulated with mCNTF, mCT-1, mL6, mL-11, mLIF or mOSM (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of negative
25 controls (11E10 or BE0090) or B035-C03-A3 (A3) (250 ng/ml).

Figures 16A-16B. *In vitro* inhibitory effects of B035-C03-A3 and CSP-S-5H8 on STAT3 activation by Hyper IL-6 or Hyper IL-11 in human cardiac fibroblasts (HCFs). Immunoblots showing analysis of cell lysates of HCFs unstimulated (baseline; BL) or stimulated with Hyper IL-6 or Hyper IL-11 (10 ng/ml) in the
30 presence of negative control (BE0090), B035-C03-A3 (A3) (250 ng/ml) or CSP-S-5H8 (5H8) (250 ng/ml).

Figure 17. *In vitro* inhibitory effects of CSP-S-5H8 on STAT3 activation by gp130 ligands in primary mouse atrial fibroblasts. Immunoblots showing analysis of cell lysates of primary mouse atrial fibroblast cells unstimulated (baseline; BL) or stimulated with mCNTF, mCT-1 or mLIF (10 ng/ml) for 15
35 min in the absence of antibody (-) or in the presence of negative control (BE0090) or CSP-S-5H8 (5H8) (250 ng/ml).

Figures 18A-18C. *In vitro* comparison of the inhibitory effects of B035-C03-A3 and B-R3 on LIF activity in human primary cardiac fibroblasts. (18A) Immunoblot showing analysis of cell lysates of
40 human primary cardiac fibroblasts unstimulated (baseline; BL) or stimulated with hLIF (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of negative control (BE0090), B-R3 or B035-C03-A3

(A3). (18B) Graph showing MMP2 levels in cell medium of human primary cardiac fibroblasts unstimulated (baseline; BL) or stimulated with LIF (5 ng/ml) for 24 h in the absence of antibody recombinant mouse LIF in the absence of antibody (-) or in the presence of negative control (BE0090), B-R3 or B035-C03-A3 (A3). (18C) Graph showing % inhibition as measured by MMP2 levels. MMP2 concentrations at baseline were considered maximal inhibition (100%) while MMP2 concentrations after stimulation with LIF in the presence of BE0090 were considered minimum inhibition (0%).

Figure 19. *In vitro* comparison of anti-gp130 clones on IL-11, IL-6 and Hyper IL-6-induced STAT3 activity in mouse primary atrial fibroblasts. Immunoblots showing analysis of cell lysates of primary mouse atrial fibroblast cells unstimulated (baseline; BL) or stimulated with mL-6, mL-11 or mHyper IL-6 (10 ng/ml) for 15 min in the absence of antibody (-) or in the presence of negative control (BE0090), CSP-S-5H8 (5H8) or B035-C03-A3 (A3) (250 ng/ml).

Figures 20A-20D. *In vivo* testing of anti-gp130 clones for immunoblotting and immunohistochemistry. (20A and 20C) 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). (20B and 20D) 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.

Figures 21A-21B. *In vivo* efficacy of CSP-S-5H8 in preventing consequences of acetaminophen-induced liver injury (AILI). Graphs showing (21A) ALT and (21B) AST concentration in mouse serum as measured by colorimetric assay following treatment with acetaminophen (400 mg/kg), with pre-treatment of either CSP-S-5H8 (5H8) or control antibody (11E10).

Figures 22A-22L. *In vivo* efficacy of CSP-S-5H8 in preventing consequences of acute kidney injury (AKI). (22A-22J) Graphs showing (22A) % body weight, (22B) kidney weight (g) (Each data point represents an average weight of right and left kidney from one mouse), (22C) collagen (μg/mg), (22D-22E) kidney function markers, (22F) serum IL-6 levels, (22G) pro-fibrotic markers, (22H) pro-inflammatory markers, and (22I-22J) kidney injury markers, in mice administered vehicle alone (NaHCO₃), or folic acid (200 mg/kg) in the presence of control antibody 11E10 (IgG), anti-IL-11 antibody (anti-IL-11) or CSP-S-5H8 (5H8). (22K-22L) Immunoblots showing analysis of kidney tissue lysates from mice administered vehicle alone (NaHCO₃), or folic acid (200 mg/kg) in the presence of control antibody 11E10 (IgG) or CSP-S-5H8 (5H8).

Figures 23A-23C. Evaluation of the effect of CSP-S-5H8 in a DSS-induced colitis model. (23A) Graph showing serum IL-6 concentration in healthy mice, or mice administered with DSS and treated with 11E10, cyclosporin A, anti-IL-6R antibody BE0047 (which binds to mouse IL-6 receptor) or CSP-S-5H8 (5H8). (23B) Graph showing OSM expression in the colon as determined by qRT-PCR in healthy mice, or mice administered with DSS and treated with 11E10, cyclosporin A or CSP-S-5H8 (5H8). Mean ± SEM.

(23C) Shows colon weight/length (in g/cm) for the colons of healthy mice, or mice administered with DSS and treated with 11E10, cyclosporin A or CSP-S-5H8 (5H8). Mean $\pm$ SEM.

Figures 24A-24D. Epitope mapping of CSP-S-5H8 and B035-C03-A3. (24A and 24C) Schematic representations of the interaction between gp130 and (24A) CSP-S-5H8 and (24B) B035-C03-A3. (24B and 24D) Images showing the epitope site of (24B) CSP-S-5H8 and (24D) B035-C03-A3 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 25A-25F. STAT3 reporter assay. Graphs showing % activity of STAT3 in a HEK293-based STAT3 reporter cell line upon stimulation with (25A) 100 ng/ml hIL-6, for 24 h (25B) 100 ng/ml hIL-11, for 24 h (25C) 10 ng/ml hCT-1, for 24 h (25D) 10 ng/ml hCNTF, for 24 h (25E) 10 ng/ml hOSM, for 48 h, or (25F) 10 ng/ml hLIF, for 48 h, in the presence of the indicated concentrations (in $\mu\text{g/mL}$) of the indicated antibodies.

Figure 26. STAT3 reporter assay. Graphs showing % activity of STAT3 in a HEK293-based STAT3 reporter cell line upon stimulation with 100 ng/ml hIL-6 for 24 h, 100 ng/ml hIL-11 for 24 h, 10 ng/ml hCT-1 for 24 h, 10 ng/ml hCNTF for 24 h, 10 ng/ml hOSM for 48 h, or 10 ng/ml hLIF for 48 h, in the presence of the indicated concentrations (in $\mu\text{g/mL}$) of the indicated antibodies.

Figures 27A-27B. STAT3 reporter assay. Graphs showing % activity of STAT3 in a HEK293-based STAT3 reporter cell line upon stimulation with (27A) 100 ng/ml hIL-6 for 24 h, 100 ng/ml hIL-11 for 24 h, or 10 ng/ml hCT-1 for 24 h; (27B) 10 ng/ml hCNTF for 24 h, 10 ng/ml hOSM for 48 h, or 10 ng/ml hLIF for 48 h, in the presence of the indicated concentrations (in $\mu\text{g/mL}$) of the indicated antibodies.

Figure 28. Ability of mAb16618, mAb16636 and mAb16673 to inhibit IL-6- and CNTF-induced activation of STAT3. Graph showing % STAT3 activity in HEK293 STAT3 reporter cells upon stimulation with rhIL-6 or hCNTF, in the presence of the indicated antibodies.

Figure 29A-29B. Intra-Vitreous Treatment Effects on Laser-Induced CNV in Mice Model. (A) Representative CNV lesions in mouse eyes treated with the vehicle and test compound (B035-C03-A3) were identified through Fluorescein Angiography (FFA). (B) Choroidal vascularity of laser-induced CNV lesions was investigated through FFA. The mean ($\pm$ SEM) CNV lesions from fluorescein angiography were assessed for each timepoint across groups. * $p < 0.05$; $n = 20$ per group.

Figure 30A-30B. Impact of Intra-Vitreous Administration on CNV Volume Area. (A) Representative CNV lesion area scans in mouse eyes treated with the vehicle and test compound (B035-C03-A3) were identified by PS-OCT (Polarization-Sensitive Optical Coherence Tomography). (B) Choroidal vascularity of laser-induced CNV lesion volume area was examined through PS-OCT scans. The mean ($\pm$ SEM)

CNV lesions from optical coherence tomography for the groups were measured. * $p < 0.05$; $n = 20$ per group.

Figure 31A-31B. Retinal Immunostaining of CNV Lesions. (A) Retinal/RPE/Choroid Complex

- 5 immunostaining was performed to validate the size of choroidal neovascularization (CNV) lesions in mouse eyes that was stained with antibodies of IB-4 in purple, Col-1 in green and alpha-SMA in red. DAPI stains nuclei in blue. (B) Provides a quantitative analysis of CNV lesion sizes, visually confirming the efficacy of different treatment modalities.

- 10 **Figure 32. Gene Expression Analysis in Treated Samples.** Gene expression analysis was conducted to assess transcript levels in response to intra-vitreous treatments. Data are expressed as mean $\pm$ SEM. Unpaired, two-tailed t-test was used for statistical analysis; * $p < 0.05$.

Examples

- 15 **General Materials and Methods for Examples 1-18**

Antibodies. Commercially-available antibodies: B-R3 (mouse monoclonal anti-human gp130 antibody IgG_{2A} Clone B-R3; Abcam ab34315), PA5-47650 (goat polyclonal anti-mouse gp130; Life Technologies), , 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).
20 Custom-made gp130 monoclonal antibody clones were obtained: CSP-S-5H8 (also referred to herein as "5H8") and B035-C03-A3 (also referred to herein as "A3"). Negative control 11E10 (mouse monoclonal anti-shigatoxin-2 antibody, IgG₁, Genovac). Neutralising anti-IL-11 antibody (Genovac).

- Cell Culture.** Primary mouse atrial fibroblasts 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 ($\leq P3$).

- 40 A549 cells (ATCC Cat # CCL-185) 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 h to enable cells to adhere to the plates. Cells were then serum-starved for 16 h in DMEM basal medium prior to stimulation. Cells were stimulated as detailed in the example.

- 5 Stimulated cells were compared to unstimulated cells that have been grown for the same duration under the same conditions, but without the stimuli.

Evaluation of MMP2 expression by ELISA. Mouse atrial fibroblasts (MAFs), rat atrial fibroblasts

- 10 (RAFs), human cardiac fibroblasts (HCFs) or canine dermal fibroblasts (CDFs) were seeded in 96-well CellCarrier black plates (6055302, PerkinElmer) at a density of 6×10^3 cells/well, and incubated in growing medium for 24 h to enable cells to adhere to the plates. Cells were serum-starved for 16 h 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
- 15 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

20 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%). In some instances, dose-response curves were plotted, and IC_{50} values for inhibition of MMP2 expression were determined.

- 25 **Immunoblotting.** After stimulations (*i.e.* with the relevant IL-6 family cytokines), 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 h with 3% BSA, and incubated overnight with the relevant primary antibodies (1:1000 in TBST). Protein bands were visualized using the SuperSignal West Femto Maximum Sensitivity substrate with the
- 30 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

35 STAT3/ERK activation levels after stimulation with a given agent, as detailed in the example, in the presence of 11E10 (at the given concentration) constituted minimum inhibition (0%).

Example 1: ELISA development and assessment of monoclonal antibody binding to human and mouse gp130

- 40 Binding of B-R3 to human gp130 and mouse gp130 was evaluated by ELISA.

Briefly, ELISA plates were coated with recombinant human gp130 or mouse gp130 overnight at 4°C and remaining binding sites were blocked with 2 % BSA in PBS. B-R3 or mouse IgG2a isotype control antibodies were applied to wells in a dilution series, and incubated for 2 h at room temperature. Detection of antigen-antibody binding was performed using HRP-conjugated anti-mouse IgG antibody. Following 2 h incubation with the detection antibody, 100 µl of TMB substrate was added for 15 mins and chromogenic reaction stopped with 100 µl of 2 M H₂SO₄. Absorbance reading was measured at 450 nm with reference wavelength correction at 570 nm. Data were fitted with GraphPad Prism software with log transformation of antibody concentrations.

- Figures 1A and 1B show that the isotype control antibody (mIgG_{2A}) exhibited negligible binding to human gp130 and mouse gp130. B-R3 exhibited binding to human gp130, but did not bind to mouse gp130. These results indicate that B-R3 does not display cross-reactive binding to mouse gp130.

- Further ELISA assays were performed to assess the binding of the 5H8 monoclonal antibody (rat isotype) to human gp130 and mouse gp130. Figure 2 shows that CSP-s-5H8 exhibited binding to human gp130.

Overall, these data show that antibodies B-R3 and 5H8 bind to human gp130, but that B-R3 does not bind to mouse gp130.

Example 2: Evaluation of binding affinity of anti-gp130 clones to human gp130 and Rhesus monkey gp130

The affinity with which anti-gp130 antibody clones B035-C03-A3 and CSP-S-5H8 bind to human gp130 (R&D Systems, Cat # 228-GP) or rhesus macaque (Sino Biological, Cat # 9025-C08H) was evaluated by surface plasmon resonance (SPR) analysis using a Biacore T200 instrument.

- Briefly, B035-C03-A3 or CSP-S-5H8 diluted in running buffer comprising HBD-P+ 1mg/mL BSA to a concentration of 2 µg/mL, and were immobilised onto the surface of a Series S Anti-mouse sensor chip to ~110 RU using the Series S Anti-mouse antibody capture kit. For experiments analysing binding to human gp130, a 7 point, 3-fold dilution series (from 60 nM to 0.082 nM) was applied to the chip. For experiments analysing binding to rhesus macaque gp130, an 8 point, 3-fold dilution series (from 180 nM to 0.082 nM) was applied to the chip. Gp130 molecules were applied to the sensor chip in running buffer, at a flow rate of 30 µl/min. The association time used was for 210 s, and the dissociation time was 900 s. Data capture and analysis were performed using Biacore T200 Evaluation Software according to manufacturer's instructions. Responses were reference cell-subtracted, and zero concentration-corrected to normalize for systematic disturbances. The resulting association and dissociation curves were fitted with 1:1 global fitting to obtain values for association rate (k_a), dissociation rate (k_d), and the equilibrium dissociation constant (K_D).

- Kinetic constants for association with and dissociation from human gp130 or rhesus macaque gp130 were determined, and K_D values were calculated (see the table below).

Clone	Analyte	k_a (1/Ms)	k_d (1/s)	K_D (M)	R_{MAX}	χ^2 (RU ²)
B035-C03-A3	Hu GP130	1.14E+05	1.05E-04	9.24E-10	38.9	0.139
B035-C03-A3	Rh GP130	1.01E+05	8.41E-05	8.35E-10	26.5	0.116
CSP-S-5H8	Hu GP130	1.91E+05	2.45E-04	1.28E-09	76.2	0.872
CSP-S-5H8	Rh GP130	1.82E+05	2.55E+04	1.40E-09	68.7	0.751

The results demonstrate that 5H8 and A3 bind to human gp130 with nanomolar affinity, and bind to rhesus macaque gp130 with similar affinity (K_D values are within 2-fold).

5 **Example 3: 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 using the STAT3 Reporter (Luc)-HEK293 cell line (puromycin selection, BPS Bioscience). The cell line encodes a firefly luciferase gene under the control of STAT3 response elements, enabling the level of STAT3 signalling to be monitored.

10

Briefly, were cells seeded at 30,000/well in a 96-well plate, and incubated overnight. The next day, a three-fold serial dilution of B035-C03-A3 or CSP-S-5H8 was added to the cells, and co-incubated for 1 h. After the incubation, the different IL-6 family cytokines were added to the wells at the indicated concentration, and the cells were incubated for 24 h. Cells were subsequently equilibrated to RT for 20 mins, and then the ONE-Step luciferase assay reagent was added to the plates. Luminescence was read in a luminescence plate reader. Background-subtracted (cell free) luminescence of cells stimulated with the relevant cytokine in absence of antibody was set as 100%. Where possible, dose-response curves were fitted and IC_{50} values for the ability of the antibodies to inhibit cytokine-mediated STAT3 signalling were calculated (see table below).

20

B035-C03-A3 displayed dose-dependent inhibition of hIL-6 and hIL-11 activation (Figures 3A and 3B, respectively). In addition, B035-C03-A3 displayed inhibitory activity on cells treated for 24 h with hOSM (Figure 3C), hLIF (Figure 3D), hCT-1 (Figure 3E) and hCNTF (Figure 3F).

25

The anti-gp130 clone CSP-S-5H8 showed dose-dependent inhibition of hIL-6 and hIL-11 activation (Figures 4A and 4B, respectively). Where possible, IC_{50} values were determined (see table below). In addition, CSP-S-5H8 showed inhibitory activity on cells treated for 24 h with hOSM (Figure 4C), hLIF (Figure 4D), hCT-1 (Figure 4E) and hCNTF (Figure 4F).

Clone	hSTAT3 reporter assay IC_{50} μ g/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
B035-C03-A3	5.56	ND*	0.37	3.12	0.49	2.68
CSP-S-5H8	20.62	0.00042	0.5101	12.38	7.163	4.367

30 *ND = IC_{50} not determined as plateau was not achieved

Example 4: In vitro screening of anti-gp130 mAb clones in primary human cardiac fibroblasts (HCF)

CSP-S-5H8 was evaluated for its effect on IL-11R α :gp130-mediated signalling in human cardiac fibroblasts, following stimulation with recombinant human IL-11.

5

Briefly, primary human cardiac fibroblasts were stimulated *in vitro* with 5 ng/ml recombinant human IL-11 for 24 h in the presence of CSP-S-5H8 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 by ELISA as described in “Materials and Methods for Examples 1-18” above.

10

The results are shown in Figure 5. CSP-S-5H8 was found to inhibit IL-11R α :gp130-mediated signalling in human cells. At all concentrations tested, complete/almost complete inhibition (~93-100%) of IL-11 mediated signalling was detected.

Example 5: In vitro comparison of anti-gp130 mAb clones on inhibiting STAT3 activation in human lung epithelial carcinoma cell line (A549)

The effect of CSP-S-5H8 on signalling mediated by receptors comprising human gp130 was examined in A549 cells.

20 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.

25 Human lung epithelial carcinoma (A549) cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 (hIL-6), IL-11 (hIL11), LIF (hLIF), OSM (hOSM) or CTGF (hCTGF) for 15 min in the absence of antibody, in the presence of a negative control antibody clone 11E10, or in the presence of 250 ng/ml of anti-gp130 antibody MAB628, CSP-S-5H8, MA5-23817 or PA5-47650. pSTAT3/STAT3 and pERK/ERK levels were subsequently analysed by immunoblot, as described in “Materials and Methods for Examples 1-18” above.

30

The results are shown in Figures 6A to 6D. Only CSP-S-5H8 was found to inhibit signalling mediated by all of IL-6, IL-11, LIF, OSM and CTGF.

Example 6: In vitro validation of anti-gp130 mAb clones in primary mouse atrial fibroblasts

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

40 Mouse atrial fibroblasts (MAFs) were stimulated *in vitro* with 10 ng/ml recombinant mouse IL-6 (mIL6) or OSM (mOSM) for 15 min in the absence of antibody, or in the presence of 250 ng/ml of antibody 11E10 (negative control) or CSP-S-5H8. pSTAT3/STAT3 and pERK/ERK levels were subsequently analysed by immunoblot, as described in “Materials and Methods for Examples 1-18” above.

Figure 7A demonstrates that CSP-S-5H8 inhibits IL-6-mediated signalling and OSM-mediated signalling.

5 In further experiments, MAFs were stimulated *in vitro* with 5 ng/ml recombinant mouse IL-11 for 24 h in the presence of negative control antibody 11E10, or anti-gp130 antibody clone CSP-S-5H8 in a 4-fold dilution series ranging from 61 pg/ml to 4 µg/ml, and the level of MMP2 in the cell culture medium was subsequently determined by ELISA as described in “Materials and Methods for Examples 1-18” above.

10 The results are shown in Figure 7B. CSP-S-5H8 was found to potently inhibit IL-11-mediated signalling, as determined by inhibition of MMP2 expression.

Example 7: *In vitro* comparison of B-R3 and CSP-S-5H8 on STAT3 activation in human lung epithelial carcinoma cell line (A549)

15 Human lung epithelial carcinoma (A549) cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 (hIL-6), IL-11 (hIL11), LIF (hLIF), OSM (hOSM) or CTGF (hCTGF) for 15 min in the absence of antibody, in the presence of a negative control antibody clone 11E10, or in the presence of 250 ng/ml of anti-gp130 antibody B-R3 or CSP-S-5H8. pSTAT3/STAT3 and pERK/ERK levels were subsequently analysed by immunoblot, as described in “Materials and Methods for Examples 1-18” above.

20 The results are shown in Figures 8A and 8B, and summarised in the table below:

STAT3						
Clone	CNTF	CT1	IL-6	IL-11	LIF	OSM
B-R3	+++	++++	++++	++++	-	++++
CSP-S-5H8	++++	++++	++++	++++	++++	++++
ERK						
Clone	CNTF	CT1	IL-6	IL-11	LIF	OSM
B-R3	+++	++++	N/A	++++	N/A	++++
CSP-S-5H8	++++	++++	N/A	++++	N/A	++++

*Inhibition levels:

- = 0-10%

25 + = >10-25%

++ = >25-50%

+++ = >50-75%

++++ = >75%

N/A = not assessed

30

Importantly, B-R3 was found not to block LIF-mediated signalling in this assay, and is therefore not a ‘pan’ inhibitor of gp130-mediated signalling.

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

CSP-S-5H8 was evaluated for its effect on gp130-mediated signalling in rat atrial fibroblasts stimulated with TGFβ1. TGFβ1 is a profibrotic factor known to upregulate IL-11-mediated signalling (see e.g. Schaefer *et al.*, Nature (2017) 552(7683): 110–115).

5

Briefly, primary rat atrial fibroblasts were stimulated *in vitro* with 5 ng/ml recombinant mouse TGFβ1 for 24 h in the presence of 11E10 or CSP-S-5H8 in a 4-fold dilution series ranging from 61 pg/ml to 4 µg/ml, and the level of MMP2 in the cell culture medium was subsequently determined by ELISA as described in “Materials and Methods for Examples 1-18” above.

10

The results are shown in Figure 9. CSP-S-5H8 was found to potently inhibit TGFβ1-stimulated, IL-6 family cytokine-mediated signalling through gp130, with an IC₅₀ value of 19.72 ng/ml.

Example 9: In vitro inhibitory effects of CSP-S-5H8 on STAT3 activation by gp130 ligands in human epithelial carcinoma cell line (A549)

15

Human lung epithelial carcinoma (A549) cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 (hIL-6), IL-11 (hIL11), LIF (hLIF), OSM (hOSM), CT-1 (hCT1) or CTGF (hCTGF) for 15 min in the absence of antibody, in the presence of 250 ng/ml of anti-gp130 antibody CSP-S-5H8. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in “Materials and Methods for Examples 1-18” above.

20

The results are shown in Figure 10, which demonstrate that CSP-S-5H8 inhibits signalling mediated by all of IL-6, IL-11, CT-1, CNTF, OSM and LIF.

Example 10: In vitro inhibitory effects of CSP-S-5H8 on STAT3 or ERK activation by IL-6 or IL-11 in human lung epithelial carcinoma cell line (A549)

25

The effect of CSP-S-5H8 on signalling mediated by receptors comprising human gp130 was examined in A549 cells.

30

A549 cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 or IL-11 protein for 15 min in the absence of antibody (-), in the presence of 4 µg/ml of negative control antibody clone 11E10, or in the presence of CSP-S-5H8 in a dilution series ranging from 0.06 ng/ml to 4 µg/ml. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in “Materials and Methods for Examples 1-18” above.

35

The results are shown in Figures 11A to 11D. CSP-S-5H8 was found to inhibit IL-6-mediated STAT3 signalling with an IC₅₀ of 16.85 ng/ml (Figure 11B), and to inhibit IL-11-mediated ERK signalling with an IC₅₀ of 54.97 ng/ml (Figure 11D).

40

Together, these results show that clone CSP-S-5H8 strongly inhibits signalling mediated by IL-6/gp130:IL-6Rα and IL-11/gp130:IL-11Rα.

Example 11: *In vitro* inhibitory effects of B-R3 or CSP-S-5H8 on STAT3 activation by LIF in human lung epithelial carcinoma cell line (A549)

The effect of B-R3 and CSP-S-5H8 on LIF-mediated signalling was examined in A549 cells.

A549 cells were stimulated *in vitro* with 10 ng/ml of recombinant human LIF protein for 15 min in the absence of antibody (-), in the presence of 4 µg/ml of negative control antibody clone 11E10, or in the presence of CSP-S-5H8 or B-R3 in a dilution series ranging from 0.06 ng/ml to 4 µg/ml. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in "Materials and Methods for Examples 1-18" above.

The results are shown in Figures 12A and 12B. CSP-S-5H8 was found to inhibit LIF-mediated STAT3 signalling with an IC₅₀ of 31.36 ng/ml, whereas B-R3 did not inhibit LIF-mediated signalling.

Example 12: *In vitro* comparison of CSP-S-5H8 and B035-C03-A3 in primary human cardiac fibroblasts and primary mouse atrial fibroblasts

B035-C03-A3 and CSP-S-5H8 were evaluated for their effects on IL-11Rα:gp130-mediated signalling in human cardiac fibroblasts (HCFs) and mouse atrial fibroblasts (MAFs), following stimulation with recombinant human IL-11.

Briefly, HCFs or MAFs were stimulated *in vitro* with 5 ng/ml recombinant mouse IL-11 for 24 h in the presence of anti-gp130 antibody clones B035-C03-A3 or CSP-S-5H8 in a 4-fold dilution series ranging from 61 pg/ml to 4 µg/ml, and the level of MMP2 in the cell culture medium was subsequently determined by ELISA as described in "Materials and Methods for Examples 1-18" above.

The results are shown in Figures 13A to 13D. B035-C03-A3 was found to potently inhibit IL-11-mediated signalling in HCFs with an IC₅₀ of 1.88 ng/ml (Figure 13A), and in MAFs with an IC₅₀ of 18.35 ng/ml (Figure 13B). CSP-S-5H8 was found to potently inhibit IL-11-mediated signalling in HCFs with an IC₅₀ of 0.73 ng/ml (Figure 13C) and in MAFs with an IC₅₀ of 41.94 ng/ml (Figure 13D).

Example 13: *In vitro* inhibitory effect of B035-C03-A3 and CSP-S-5H8 on STAT3 activation by gp130 ligands in human lung epithelial carcinoma cell line (A549)

Human lung epithelial carcinoma (A549) cells were stimulated *in vitro* with 10 ng/ml of recombinant human IL-6 (hIL-6), IL-11 (hIL11), LIF (hLIF), OSM (hOSM) or CTGF (hCTGF) for 15 min in the absence of antibody, or in the presence of 250 ng/ml of anti-gp130 antibody B035-C03-A3 or CSP-S-5H8. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in "Materials and Methods for Examples 1-18" above.

The results are shown in Figures 14A and 14B, and summarised in the table below. Both B035-C03-A3 (A3) and CSP-S-5H8 (5H8) were found to inhibit signalling mediated by all of IL-6, IL-11, OSM, CNTF, CT-1 and LIF. In general, B035-C03-A3 appeared to be a more potent PAN-inhibitor compared to CSP-S-

5H8, with full inhibition observed at 250 ng/ml for CNTF, CT-1, IL-11 and OSM. CSP-S-5H8 appeared to be slightly more potent at inhibiting IL-6 mediated signalling than B035-C03-A3.

Clones	CNTF	CT1	IL-6	IL-11	LIF	OSM
11E10	-	-	-	-	-	-
B35-C03-A3	++++ (100%)	++++ (99%)	++++ (78%)	++++ (99%)	++++ (93%)	++++ (99%)
CSP-S-5H8	++++ (87%)	++++ (85%)	++++ (90%)	++++ (90%)	++++ (90%)	++++ (86%)

*Inhibition levels:

- 5 - = 0-10%
 + = >10-25%
 ++ = >25-50%
 +++ = >50-75%
 ++++ = >75%

10

Example 14: *In vitro* inhibitory effects of B035-C03-A3 on STAT3 activation by gp130 ligands in primary mouse atrial fibroblasts

The inhibitory effects of B035-C03-A3 on STAT3 activation by gp130 ligands were further validated in primary mouse atrial fibroblasts.

15

Primary mouse atrial fibroblasts were pre-incubated with B035-C03-A3 (A3) (250 ng/ml) for 30 min (or with negative control 11E10 or BE0090), and then stimulated with 10 ng/ml of recombinant human CNTF, CT1, IL-6, IL-11, LIF or OSM for 15 min. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in "Materials and Methods for Examples 1-18" above.

20

The results are shown in Figures 15A and 15B, and summarised in the table below. B035-C03-A3 (A3) was found to inhibit signalling mediated by all of mL-6, mL-11, mLIF, mOSM, mCNTF and mCT1.

Clones	CNTF	CT1	IL-6	IL-11	LIF	OSM
11E10	-	-	-	-	-	-
BE0090	-	-	-	-	-	-
B35-C03-A3	++ (50%)	++++ (78%)	+++ (59%)	++++ (91%)	++++ (78%)	++++ (77%)

*Inhibition levels:

- 25 - = 0-10%
 + = >10-25%
 ++ = >25-50%
 +++ = >50-75%
 ++++ = >75%

30

The results show that the B035-C03-A3 inhibits signalling by binding of IL-6 family cytokines to mgp130 containing receptors, but with lower potency than in humans.

Example 15. *In vitro* comparison of the inhibitory effects of B035-C03-A3 and CSP-S-5H8 on STAT3 activation by Hyper IL-6 and Hyper IL-11 in primary human cardiac fibroblasts

The inhibitory effects of the anti-gp130 clones B035-C03-A3 and CSP-S-5H8 on STAT3 activation by Hyper IL-6 and Hyper IL-11 was investigated in primary human cardiac fibroblasts (HCFs). "Hyper IL-6" refers to an IL-6:IL-6R α fusion protein consisting of the extracellular domain of IL-6 receptor alpha (IL-6R α) 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). Similarly, "Hyper IL-11" refers to an IL-11:IL-11R α fusion protein consisting of the extracellular domain of IL-11 receptor alpha (IL-11R α) 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).

Briefly, HCFs were pre-incubated with either BE0090, B035-C03-A3 or CSP-S-5H8 (250 ng/ml or 1.7nM) for 30 min and then stimulated with 10 ng/ml of recombinant human Hyper IL-6/Hyper IL-11. Immunoblotting and densitometry analysis was performed as described in "Materials and Methods for Examples 1-18" above.

The results are shown in Figures 16A and 16B. B035-C03-A3 and CSP-S-5H8 were both found to strongly inhibit Hyper IL-6- and Hyper IL-11-induced STAT3 signalling in HCFs. The results are summarized in the table below:

20

Clones	Hyper IL-6	Hyper IL-11
BE0090	-	-
CSP-S-5H8	++++ (80%)	+++ (72%)
B35-C03-A3	++++ (87%)	++++ (79%)

*Inhibition levels:

- = 0-10%

+ = >10-25%

++ = >25-50%

25 +++ = >50-75%

++++ = >75%

Example 16. *In vitro* validation of the inhibitory effect of CSP-S-5H8 on STAT3 activation by CNTF, CT1 and LIF in primary mouse atrial fibroblasts

30 The inhibitory effects of CSP-S-5H8 on STAT3 activation by gp130 ligands was validated in primary mouse atrial fibroblasts (MAFs).

Primary mouse atrial fibroblasts were pre-incubated with CSP-S-5H8 (5H8) (250 ng/ml) for 30 min (or with negative control (BE0090) (250 ng/ml) and then stimulated with 10 ng/ml of recombinant human CNTF, CT1 or LIF for 15 min. pSTAT3/STAT3 levels were subsequently analysed by immunoblot, as described in "Materials and Methods for Examples 1-18" above.

35

The results are shown in Figure 17, which demonstrate that CSP-S-5H8 (5H8) inhibits signalling mediated by CNTF, CT1 and LIF. The results are summarised in the table below:

Clones	CNTF	CT1	LIF
BE0090	-	-	-
CSP-S-5H8	+++ (55%)	+++ (71%)	+++ (59%)

*Inhibition levels:

- = 0-10%
- + = >10-25%
- ++ = >25-50%
- +++ = >50-75%
- ++++ = >75%

Example 17: *In vitro* comparison of the inhibitory effects of B035-C03-A3 and B-R3 on LIF activity in human primary cardiac fibroblasts

B-R3 and B035-C03-A3 were evaluated for their inhibitory effects on LIF-mediated signalling in human primary cardiac fibroblasts (HCFs).

Briefly, human primary cardiac fibroblast cells were serum starved for 16 h in basal medium prior to stimulation. Cells were pre-incubated with 250 ng/ml of negative control (BE0090), B-R3 or B035-C03-A3 for 30 min and then stimulated with 10 ng/ml of recombinant human LIF protein for 15 min. Immunoblotting and densitometry analysis was performed as described in "Materials and Methods for Examples 1-18" above.

For the analysis of MMP2 levels, human primary cardiac fibroblast cells were serum starved for 16 h in basal medium prior to stimulation. After starvation, cells were stimulated for 24 h with 5 ng/ml of recombinant mouse LIF in the absence or presence of 250 ng/ml of negative control (BE0090), B-R3 or B035-C03-A3. MMP2 levels in the cell medium were assessed using an ELISA as described in "Materials and Methods for Examples 1-18" above.

The results are shown in Figures 18A to 18C, and summarised in the table below. B035-C03-A3 was found to inhibit LIF-mediated signalling in human primary cardiac fibroblasts, while B-R3 did not.

Assay	B-R3	B035-C03-A3
STAT3	- (3%)	++++ (83%)
MMP2	- (3%)	+++ (73%)

*Inhibition levels:

- = 0-10%
- + = >10-25%
- ++ = >25-50%

+++ = >50-75%
++++ = >75%

Example 18: *In vitro* comparison of anti-gp130 clones on IL-11, IL-6 and Hyper IL-6-induced STAT3 activity in mouse primary atrial fibroblasts

CSP-S-5H8 and B035-C03-A3 were evaluated for their ability to inhibit mL-11, mL-6 and Hyper mL-6-induced STAT3 signalling in mouse primary atrial fibroblasts (MAFs).

Briefly, mouse primary atrial fibroblasts were pre-incubated with each of the antibody clones (250 ng/ml) for 30 min and then stimulated with 10 ng/ml of recombinant mouse IL-6, recombinant mouse IL-11 or recombinant mouse Hyper-IL-6 protein for 15 min. Immunoblotting and densitometry analysis were subsequently performed as described in “Materials and Methods for Examples 1-18” above.

The results are shown in Figure 19, and summarised in the table below. Both CSP-S-5H8 and B035-C03-A3 were found to inhibit mL-11-, mL-6- and Hyper mL-6-induced STAT3 activity in mouse primary atrial fibroblasts.

Clones	mIL-6	mIL-11	mHyper IL-6
BE0090	-	-	-
CSP-S-5H8	++++ (78%)	++++ (98%)	+++ (53%)
B35-C03-A3	++++ (87%)	++++ (100%)	++++ (89%)

*Inhibition levels:

- = 0-10%
+ = >10-25%
++ = >25-50%
+++ = >50-75%
++++ = >75%

Example 19: *In vivo* testing of anti-gp130 clones for immunoblotting and immunohistochemistry

19.1 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^{+/+}-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 h 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 h 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 min then with 2.5% normal goat serum (1 h, 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.

19.2 Results

The ability of CSP-S-5H8 and B035-C03-A3 to bind to gp130 in mouse liver tissue was examined. gp130 conditional knockout mice were generated, and binding of CSP-S-5H8 and B035-C03-A3 was tested in liver tissue by immunoblotting and immunohistochemistry.

Figures 20A to 20D demonstrate that CSP-S-5H8 and B035-C03-A3 bind to gp130 in the WT mouse tissue samples, but do not bind to tissue samples in which gp130 had been knocked-out. Thus, CSP-S-5H8 and B035-C03-A3 bind specifically to gp130, and can be successfully used for the detection of mouse gp130 immunoblotting and immunohistochemistry of tissue samples.

Example 20: In vivo efficacy of CSP-S-5H8 in preventing consequences of acetaminophen-induced liver injury (ALI)

20.1 Materials and Methods

Mouse models of acetaminophen poisoning. Prior to acetaminophen (APAP), 15-week-old male mice were fasted overnight (16 h). Mice were administered 20 mg/kg of either CSP-s-5H8 or control antibody (11E10) by intraperitoneal injection at the start of the fasting period. Following overnight fasting, mice

were given 400 mg/kg dose of APAP (APAP stock: 17.5 mg/ml in saline) by intraperitoneal administration and euthanized at 24 h post APAP.

Colorimetric assays. The concentrations of ALT or AST in mouse serum were measured using ALT or AST Activity Assay Kit according to the manufacturer's protocol. We considered ALT/AST concentrations in the serum of control mice as maximal inhibition (100%), while ALT/AST concentrations in the serum of APAP-injured mice receiving 11E10 (20 mg/kg) constituted minimum inhibition (0%).

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 Dunnett's (with APAP+11E10 designated as the control group). The criterion for statistical significance was $P < 0.05$.

20.2 Results

The ability of CSP-S-5H8 to prevent/protect against the consequences of acetaminophen-induced liver injury (ALI) was examined in a mouse model of ALI.

The concentrations of alanine transaminase (ALT) and aspartate aminotransferase (AST) in mouse serum were measured following treatment with APAP. When liver cells are damaged, they release ALT and AST into the bloodstream; thus, this experiment is a read-out of liver injury induced by acetaminophen. The results are shown in Figures 21A and 21B, which demonstrate that pre-treatment with CSP-S-5H8 (5H8) reduced the concentration of ALT (Figure 21A) and AST (Figure 21B), as compared to mice treated with control antibody.

Overall, these results demonstrate that CSP-A-5H8 is effective at preventing/protecting against/ameliorating the symptoms of APAP-induced liver injury.

Example 21: *In vivo* efficacy of anti-gp130 mAb clones in preventing consequences of acute kidney injury (AKI)

21.1 Methods and Materials

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-5H8 or control antibody (11E10), starting from 6 h before FA administration until the mice were sacrificed (day 21 post-FA). At the end of the study period, each mouse would have 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 IL6 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 h 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).

- 5
- 10 **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.
- 15 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
- 20 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 $P < 0.05$.

21.2 Results

- 25 The effect of CSP-S-5H8 in preventing the consequences of acute kidney injury (AKI) was examined in a folic acid-induced mouse model of nephrotoxicity. The effect was compared with the effect of a neutralising anti-IL-11 antibody.

- Figure 22A demonstrates that treatment with CSP-S-5H8 abolished weight loss in the mouse model of
- 30 acute kidney injury. CSP-S-5H8 also exhibited a stronger treatment effect than the neutralising anti-IL-11 antibody.

- Figure 22B demonstrates that treatment with CSP-S-5H8 significantly reduced the weight loss observed in the kidneys of mice following acute kidney injury, compared to the negative control antibody.

- 35 Figure 22C demonstrates that treatment with CSP-S-5H8 significantly inhibited the increase in renal collagen content observed in mice following acute kidney injury, compared to the negative control antibody. CSP-S-5H8 also exhibited a stronger treatment effect than the neutralising anti-IL-11 antibody.

Figures 22D and 22E demonstrate that treatment with CSP-S-5H8 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 the negative control antibody.

- 5 Figure 22F demonstrates that treatment with CSP-S-5H8 significantly inhibited the increase in serum IL-6 levels observed in mice following acute kidney injury, compared to the negative control antibody. CSP-S-5H8 also exhibited a stronger treatment effect than the neutralising anti-IL-11 antibody.

- 10 Figure 22G demonstrates that treatment with CSP-S-5H8 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. CSP-S-5H8 also exhibited a stronger treatment effect than the neutralising anti-IL-11 antibody.

- 15 Figure 22H demonstrates that treatment with CSP-S-5H8 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 the negative control antibody. CSP-S-5H8 also exhibited a stronger treatment effect than the neutralising anti-IL-11 antibody.

- 20 Figures 22I and 22J demonstrate that treatment with CSP-S-5H8 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 the negative control antibody.

- 25 Figures 22K and 22L demonstrate that treatment with CSP-S-5H8 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.

- 30 Together, these data show that CSP-S-5H8 strongly inhibited gp130-mediated signalling *in vivo* and significantly reduced the pathology of acute kidney injury, as determined by a reduction in the level of correlates of acute kidney injury. They furthermore demonstrate that CSP-S-5H8 is more effective at reducing the pathology of acute kidney injury than a neutralising anti-IL-11 antibody.

Example 22: Evaluation of the effect of CSP-S-5H8 in a DSS-induced colitis model of Inflammatory Bowel Disease (IBD)

22.1 Materials and Methods

- 35 **Materials.** Mice were male C57BL6J and kept at 21-25°C, 40-70% humidity. Antibodies were 11E10, anti-IL-6R (BioXCell BE0047) and CSP-S-5H8. Dextran sulfate sodium (DSS) was supplied by MP Biomedicals, LL, Cyclosporin A (Cs A) was supplied by Selleck. Cyclosporin is known to ameliorate the pathology of IBD, and in particular colitis.

- 40 **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 (Group 1) or water

containing 3% (w/v) DSS (Groups 2 to 5) from Day 1 to Day 7. Treatment or vehicle was administered on day 1 and day 4.

Group	DSS Challenge (3% DSS water)	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-6R (BioXCell BE0047)	20	IP
Group 5	+	CSP-S-5H8	20	IP

5

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.

The significance of the differences among groups and within groups were evaluated by one-way or two-way ANOVA using GraphPad statistic software. A P value < 0.05 is considered statistically significant.

20

22.2 Results

The effects of CSP-S-5H8 were examined *in vivo* in a mouse model of inflammatory bowel disease (DSS-induced colitis model).

Figure 23A demonstrates that treatment with an IL6 receptor blocking antibody (anti-mouse IL-6R BioXCell BE0047) resulted in significant upregulation of serum levels of IL-6, which is a therapeutic challenge (see *e.g.* Nishimoto *et al.*, Blood (2008) 112(10): 3959-64). By contrast, treatment with CSP-S-5H8 did not result in significant upregulation of serum IL-6, and levels of IL-6 were reduced compared to mice treated with the negative control antibody. The results suggest that direct blockade of gp130 is advantageous over blockade of IL6R, as it does not lead to a significant increase in serum IL-6 levels.

Figure 23B demonstrates that treatment with CSP-S-5H8 reduced the level of expression of *Osm* in the colon, as determined by qRT-PCR, restoring the level of expression to the level observed in the absence of DSS challenge.

Increased colon weight-to-length ratio is a pathological correlate of colitis. Figure 23C demonstrates that treatment with CSP-S-5H8 resulted in statistically significant reduction in colon weight/length relative to mice challenged with DSS and treated with the control antibody 11E10.

5

Together, these data show that treatment with CSP-S-5H8 reduced correlates of Inflammatory Bowel Disease pathology *in vivo* in mouse model of colitis, and did not display negative side effects, e.g. a significant increase in serum level of IL-6.

10 **Example 23: Epitope mapping of B035-C03-A3, CSP-S-5H8 and B-R3**

The region(s) of gp130 to which B035-C03-A3, CSP-S-5H8 and known anti-gp130 antibody B-R3 bind were analysed by hydrogen-deuterium exchange mass spectrometry (HDX-MS) and/or cross-linking mass spectrometry (XL-MS).

15 HDX-MS:

Different solutions comprising recombinant human gp130 (rhsgp130) were prepared: rhsgp130 alone (10µM, 150 µl) and rhsgp130 mixed with B35-C03-A3 or B-R3 (Abcam ab34315), at a ratio 1:1, to a final concentration of 10µM and total volume 150 µl. These solutions were subjected to pepsin proteolysis, and subsequently subjected to liquid chromatography and Xevo-G2-XS MSe analysis, in order to determine percent incorporation of deuterium by peptides after 15s, 60s, 180s, 600s, 1800s, and 7200s incubation. Incorporation of deuterium by free recombinant human gp130 was compared to incorporation of deuterium by provided in complex with the different antibodies.

20

XL-MS:

Briefly, mixtures of gp130/CSP-S-5H8 and gp130/B35-C03-A3 were prepared at concentrations of gp130 1.6 µM and antibody 0.85 µM. 20 µL of gp130/antibody mixtures prepared were mixed with 2 µL of disuccinimidyl suberat (DSS) d0/d12 (2mg/mL; DMF) and incubated at room temperature for 180 min. After incubation, the samples were submitted to reduction/alkylation and proteolysis with five different enzymes (trypsin, chymotrypsin, ASP-N, elastase and thermolysin).

30

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.

35

23.2 Results

Amino acid numbering is given in relation to the amino acid sequence of Human gp130 isoform 1 (UniProt: P40189-1, v2; SEQ ID NO:70).

40 In HDX-MS experiments, a significant reduction in deuterium incorporation in human gp130 in complex with B35-C03-A3 was observed at the region formed by positions 144 to 154 of SEQ ID NO:70

(CEWDGGRETHL; SEQ ID NO:169), and at the region formed by positions 163 to 174 of SEQ ID NO:70 (EWATHKFADCKA; SEQ ID NO:170). For human gp130 in complex with B-R3, a significant reduction in deuterium incorporation was observed at the region formed by positions 186 to 191 of SEQ ID NO:70 (YSTVYF; SEQ ID NO:178)

5

The XL-MS analysis indicated that the interaction between CSP-S-5H8 and gp130 includes amino acids corresponding to positions 128, 143, 261, 263, 300 and 303 of SEQ ID NO:70, and the epitope includes amino acids corresponding to positions 128-143 (KPKNLSCIVNEGKKMR; SEQ ID NO:86), 261-263 (YRT; SEQ ID NO:87) and 300-303 (RCMK; SEQ ID NO:88) of SEQ ID NO:70 (Figures 24A and 24B).

10

The XL-MS analysis indicated that the interaction between B35-C03-A3 and gp130 includes amino acids corresponding to positions 143, 150, 161, 166, 173, 250, 256, 261 and 262 of SEQ ID NO:70, and the epitope includes amino acids corresponding to positions 143-150 (RCEWDGGR; SEQ ID NO:90), 161-173 (KSEWATHKFADCK; SEQ ID NO:91) and 250-262 (KSVILKYNIQYR; SEQ ID NO:92) of SEQ ID NO:70 (Figures 24C and 24D).

15

The regions of gp130 identified by analysis by two different methods (XL-MS and HDX-MS) to be important for binding of B35-C03-A3 are positions 144-150 of SEQ ID NO:70 (CEWDGGR; SEQ ID NO:171) and positions 163-173 of SEQ ID NO:70 (EWATHKFADCK; SEQ ID NO:172).

20

While B35-C03-A3, CSP-S-5H8 and B-R3 were all found to bind to gp130 in the cytokine-binding module of human gp130 (SEQ ID NO:85), B-R3 was found to bind to a distinct and non-overlapping region of human gp130 as the region bound by B35-C03-A3 and CSP-S-5H8. The fact that it binds to the cytokine-binding module of human gp130, but to a region distinct from B35-C03-A3, might explain why it displays inhibition of signalling mediated by some but not all of the cytokines whose signalling is inhibited by B35-C03-A3.

25

Furthermore, alignment of the amino acid sequences for human gp130 and mouse gp130 reveals that they share only 33% sequence identity in the region of human gp130 bound by B-R3 (SEQ ID NO:178; *i.e.* 2/6 residues). By contrast, across SEQ ID NOs:171 and 172, human gp130 and mouse gp130 share 72% sequence identity (5/7 and 8/11 residues, respectively). This might explain why B-R3 does not bind to mouse gp130, whereas B35-C03-A3 does bind to mouse gp130.

30

Example 24: Humanized variants of B035-C03-A3

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Multiple humanized antibody variants of B035-C03-A3 were designed based on both composite human antibody (CHAb) and CDR grafting technology.

Two humanized heavy chain variable regions and three humanized light chain variable regions were selected for further development and characterisation:

40

A3_3.2 VH = SEQ ID NO:94

A3_4.2 VH = SEQ ID NO:98
 A3_6.2 VH = SEQ ID NO:174
 A3_3 VL = SEQ ID NO:102
 A3_4 VL = SEQ ID NO:106
 5 A3_5 VL = SEQ ID NO:109

Antibodies comprising Fv regions formed by the following combinations of humanized VH and VL regions were identified as preferred molecules for subsequent evaluation:

10 A3_4.2 VH / A3_3 VL
 A3_4.2 VH / A3_4 VL
 A3_4.2 VH / A3_5 VL
 A3_3.2 VH / A3_3 VL
 A3_3.2 VH / A3_4 VL
 15 A3_6.2 VH / A3_3 VL
 A3_6.2 VH / A3_4 VL

24.1 Functional characterisation of humanized variants of B035-C03-A3

The ability of different humanized ant-gp130 variants of B035-C03-A3 to inhibit signalling mediated by
 20 receptors comprising human gp130 was examined using the STAT3 Reporter (Luc)-HEK293 cell line essentially as described in Example 3.

Briefly, cells were seeded at 30,000/well in a 96-well plate, and incubated overnight. The next day, a nine-
 point, three-fold serial dilution series of different antibodies (beginning at a concentration of 100 µg/mL)
 25 was added to the cells, and co-incubated for 1 h. The following antibodies were evaluated in the experiments:

A3_4.2 VH / A3_3 VL (referred to in Figure 25 as 'CVH4.2/CVL3')
 A3_4.2 VH / A3_4 VL (referred to in Figure 25 as 'CVH4.2/CVL4')
 30 A3_4.2 VH / A3_5 VL (referred to in Figure 25 as 'CVH4.2/CVL5')
 A3_3.2 VH / A3_3 VL (referred to in Figure 25 as 'CVH3.2/CVL3')
 A3_3.2 VH / A3_4 VL (referred to in Figure 25 as 'CVH3.2/CVL4')
 A3_6.2 VH / A3_3 VL (referred to in Figure 25 as 'CVH6.2/CVL3')
 A3_6.2 VH / A3_4 VL (referred to in Figure 25 as 'CVH6.2/CVL4')
 35 Parental B035-C03-A3 (referred to in Figure 25 as 'VH0/VL0').
 B-R3
 Tocilizumab (anti-IL-6 receptor antibody; for IL-6 assay only)
 hlgG4 (isotype-matched negative control)

40 After the incubation, different IL-6 family cytokines were added to the wells at the indicated concentrations, and the cells were incubated for 24 h or 48 h, as indicated below.

rhIL-6: 100 ng/mL, 24 h
 rhIL-11: 100 ng/mL, 24 h
 rhCT-1: 10 ng/mL, 24 h
 rhCNTF: 10 ng/mL, 24 h
 rhOSM: 10 ng/mL, 48 h
 rhLIF: 10 ng/mL, 48 h

- Cells were subsequently equilibrated to RT for 20 mins, and then the ONE-Step luciferase assay reagent was added to the plates. Luminescence was read in a luminescence plate reader. Background-subtracted (cell free) luminescence of cells stimulated with the relevant cytokine in absence of antibody was set as 100%. Dose-response curves were fitted and IC₅₀ values for the ability of the antibodies to inhibit cytokine-mediated STAT3 signalling were calculated (see table below).
- The results are shown in Figures 25A to 25F. All of the humanized variants of B035-C03-A3 retained the ability to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM and LIF, in a dose-dependent manner. The humanized variants moreover inhibited signalling mediated by the various different IL-6 family cytokines with similar (*i.e.* IC₅₀ value within ~2-fold) or improved (lower IC₅₀ value) potency, relative to B035-C03-A3.

20

Antibody	hSTAT3 reporter assay IC ₅₀ µg/ml					
	100 ng/ml hIL-6, 24 h	100 ng/ml hIL-11, 24 h	10 ng/ml hCT-1, 24 h	10 ng/ml hCNTF, 24 h	10 ng/ml hOSM, 48 h	10 ng/ml hLIF, 48 h
B035-C03-A3	1.463	<0.015	0.143	0.094	0.119	0.903
A3_4.2 VH / A3_3 VL	1.483	<0.015	0.116	0.104	0.122	0.857
A3_4.2 VH / A3_4 VL	0.990	<0.015	0.079	0.073	0.054	0.610
A3_4.2 VH / A3_5 VL	2.502	<0.015	0.135	0.096	0.112	1.873
A3_3.2 VH / A3_3 VL	2.066	<0.015	0.118	0.094	0.100	1.033
A3_3.2 VH / A3_4 VL	1.216	<0.015	0.108	0.093	0.099	1.042
A3_6.2 VH / A3_3 VL	1.421	<0.015	0.105	0.076	0.104	0.892
A3_6.2 VH / A3_4 VL	0.963	<0.015	0.100	0.081	0.069	1.067

Example 25: Thermal stability of humanised B035-C03-A3 antibodies comprising VH I100T and VL G51A

- B035-C03-A3, A3_6.2_I100T / A3_3_G51A, and A3_3.2_I100T / A3_4_G51A 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).
- 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).
- The results are shown in the table below.

Antibody (VH/VL)	Ave T_m 1 (°C)	Ave T_{onset} (°C)	T_{agg} (°C)
B035-C03-A3	60.1	54.7	63.9
A3_6.2_I100T / A3_3_G51A	60.2	53.7	66.8
A3_3.2_I100T / A3_4_G51A	63.2	56.0	64.2

Example 26: Binding of humanised B035-C03-A3 antibodies comprising VH I100 variation and VL G51A to human gp130

- The affinity of binding of B035-C03-A3, A3_3.2 / A3_4_G51A, A3_3.2_I100Q / A3_4_G51A, A3_3.2_I100K / A3_4_G51A, A3_3.2_I100T / A3_4_G51A and A3_6.2_I100T / A3_3_G51A to human gp130 was assessed by SPR using Biacore 8K in a multiple cycle kinetics (MCK) analysis, using a range of concentrations of human gp130.

- 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 0.78 nM to 50 nM, 7 point, 2-fold dilution of human gp130). The association and dissociation rates were calculated, and K_D values were determined (see tables below).

Variations at VH I100 were tested in a A3_3.2 / A3_4_G51A background.

Antibody (VH/VL)	k_a (1/Ms)	k_d (1/s)	K_D (M)	Relative K_D	Rmax	Chi2 (RU2)
A3_3.2 / A3_4_G51A	2.74E+05	5.89E-05	2.15E-10	1.00	62.7	0.64
A3_3.2_I100Q / A3_4_G51A	2.84E+05	2.73E-04	9.60E-10	4.47	57.6	1.39
A3_3.2_I100K / A3_4_G51A	2.06E+05	1.62E-04	7.84E-10	3.65	42.3	0.55

A3_3.2_I100T / A3_4_G51A	3.14E+05	2.24E-04	7.15E-10	3.33	77.3	0.58
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A3_6.2_I100T / A3_3_G51A and A3_3.2_I100T / A3_4_G51A were compared to the B035-C03-A3 chimeric antibody.

Antibody (VH/VL)	ka (1/Ms)	kd (1/s)	KD (M)	Relative KD	Rmax	Chi2 (RU2)
B035-C03-A3	4.23E+05	9.81E-05	2.32E-10	1.00	78.0	3.11
A3_6.2_I100T / A3_3_G51A	3.93E+05	2.33E-04	5.92E-10	2.56	73.2	2.53
A3_3.2_I100T / A3_4_G51A	2.95E+05	2.50E-04	8.47E-10	3.65	80.8	1.11

- 5 The variants show good binding to human gp130. A3_6.2_I100T / A3_3_G51A and A3_3.2_I100T / A3_4_G51A retained a K_D within three-fold and four-fold of chimeric antibody respectively.

Example 27: Analysis of the ability of humanised B035-C03-A3 antibodies comprising VH I100T and VL G51A to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM or LIF

- 10 The following antibodies were evaluated in the experiments:

B035-C03-A3 (referred to as 'A A03 VH0/VL0' in Figure 26)

A3_6.2_I100T / A3_3_G51A (referred to as 'B A03 CVH6.2 (I100T)/CVL3 (G51A)' in Figure 26)

A3_3.2_I100T / A3_4_G51A (referred to as 'H A03 GVH3.2 (I100T)/CVL4 (G51A)' in Figure 26)

The antibodies were provided in hlgG4(S228P, L235E) format.

15

The ability of the antibodies to inhibit signalling induced by IL-6, IL-11, CT-1, CNTF, OSM or LIF through gp130 was evaluated using the STAT3 reporter cell line, as described in Example 3.

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/ml), 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. All test conditions were performed in duplicate.

- 25 Figure 26 shows that all of B035-C03-A3, A3_6.2_I100T / A3_3_G51A, and A3_3.2_I100T / A3_4_G51A retained the ability to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM and LIF, in a dose-dependent manner.

The IC_{50} values for inhibition of gp130-mediated signalling induced by the different cytokines determined in these experiments are shown in the table below.

30

Antibody	hSTAT3 reporter assay IC_{50} μ g/ml					
	IL-6	IL-11	CNTF	CT-1	OSM	LIF
B035-C03-A3	2.48*	<0.05	0.83	<0.05	<0.05	2.76*
A3_6.2_I100T / A3_3_G51A	7.13*	<0.05	1.83	<0.05	<0.05	7.64*
A3_3.2_I100T / A3_4_G51A	7.73*	<0.05	2.08	<0.05	<0.05	12.1*

*approximate values as full curve not achieved

These data indicate that the humanised B035-C03-A3 antibodies comprising VH I100T and VL G51A retain the ability to inhibit signalling mediated by all of IL-6, IL-11, LIF, OSM and CTGF and are 'pan'

5 inhibitors of gp130-mediated signalling.

Example 28: Binding of CSP-S-5H8 and humanised CSP-S-5H8 antibodies comprising VH D98 or VH G99 variations to human gp130

The affinity of binding to human gp130 was evaluated by MCK analysis by SPR (Biacore 8K), as described in Example 26. The results are shown below.

10

Variations were introduced at VH D98 or VH G99 of the chimeric antibody CSP-S-5H8.

Antibody (VH/VL)	ka (1/Ms)	kd (1/s)	KD (M)	Relative KD	Rmax	Chi2 (RU2)
CSP-S-5H8	6.47E+05	7.40E-04	1.14E-09	1.00	82.4	1.15
CSP-S-5H8_D98A VH / CSP-S-5H8 VL	5.05E+05	1.58E-03	3.12E-09	2.73	74.0	0.58
CSP-S-5H8_D98E VH / CSP-S-5H8 VL	5.15E+05	1.38E-03	2.68E-09	2.34	80.6	0.36
CSP-S-5H8_D98G VH / CSP-S-5H8 VL	5.39E+05	9.94E-04	1.85E-09	1.61	75.5	0.70
CSP-S-5H8_D98S VH / CSP-S-5H8 VL	5.88E+05	1.00E-03	1.70E-09	1.49	71.9	1.27
CSP-S-5H8_G99A VH / CSP-S-5H8 VL	8.58E+08	4.04E+00	4.71E-09	4.12	46.8	6.66
CSP-S-5H8_G99Y VH / CSP-S-5H8 VL	1.24E+09	4.17E+00	3.36E-09	2.93	23.1	4.86

The variants show good binding to human gp130. All variants retained a K_D within three-fold of the parent chimeric antibody, with the exception of CSP-S-5H8_G99A VH / CSP-S-5H8 VL which retained a K_D just over 4-fold of the parent chimeric antibody.

15

The VH D98G variation was introduced into each of 5H8CVH4 / 5H8CVL3, 5H8CVH4 / 5H8CVL4, 5H8CVH4 / 5H8GVL3, 5H8GVH4 / 5H8CVL4, and 5H8GVH4 / 5H8GVL3.

Antibody (VH/VL)	ka (1/Ms)	kd (1/s)	KD (M)	Relative KD	Rmax	Chi2 (RU2)
CSP-S-5H8	4.51E+05	7.70E-04	1.71E-09	1.00	82.1	1.67
5H8CVH4_D98G / 5H8CVL3	2.59E+05	7.98E-04	3.08E-09	1.80	67.3	0.67
5H8CVH4_D98G / 5H8CVL4	2.51E+05	8.11E-04	3.24E-09	1.90	70.6	0.31
5H8CVH4_D98G / 5H8GVL3	2.98E+05	8.30E-04	2.78E-09	1.63	72.9	0.56
5H8GVH4_D98G / 5H8CVL4	2.24E+05	9.82E-04	4.38E-09	2.56	60.7	0.27
5H8GVH4_D98G / 5H8GVL3	2.53E+05	1.11E-03	4.39E-09	2.57	60.3	0.38

20

The variants show good binding to human gp130. All VH D98G variants retained a K_D within three-fold of the parent chimeric antibody,

The VH D98S variation was introduced into each of 5H8CVH4 / 5H8CVL3, 5H8CVH4 / 5H8CVL4, 5H8CVH4 / 5H8GVL3, 5H8GVH4 / 5H8CVL4, and 5H8GVH4 / 5H8GVL3.

Antibody (VH/VL)	ka (1/Ms)	kd (1/s)	KD (M)	Relative KD	Rmax	Chi2 (RU2)
CSP-S-5H8 (n=1)	5.17E+05	6.94E-04	1.34E-09	0.99	83.9	1.03
CSP-S-5H8 (n=2)	5.02E+05	6.82E-04	1.36E-09	1.01	84.7	1.25
5H8CVH4_D98S / 5H8CVL3	3.97E+05	1.01E-03	2.54E-09	1.88	75.6	0.69
5H8CVH4_D98S / 5H8CVL4	3.19E+05	9.49E-04	2.98E-09	2.20	52.9	0.39
5H8CVH4_D98S / 5H8GVL3	2.92E+05	1.00E-03	3.44E-09	2.54	53.0	0.35
5H8GVH4_D98S / 5H8CVL4	4.13E+05	1.23E-03	2.98E-09	2.21	51.2	0.55
5H8GVH4_D98S / 5H8GVL3	4.20E+05	1.55E-03	3.69E-09	2.74	50.0	0.53

The variants show good binding to human gp130. All VH D98S variants retained a K_D within three-fold and four-fold of chimeric antibody respectively.

Example 29: Analysis of the ability of humanised CSP-S-5H8 antibodies comprising VH D98G to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM or LIF

The following antibodies were evaluated in the experiments:

- 10 CSP-S-5H8 (referred to as '5H8 VH0/VL0' in Figure 27)
- 5H8CVH4_D98G / 5H8CVL3 (referred to as '5H8 CVH4 (D98G)/CVL3' in Figure 27)
- 5H8CVH4_D98G / 5H8CVL4 (referred to as '5H8 CVH4 (D98G)/CVL4' in Figure 27)
- 5H8CVH4_D98G / 5H8GVL3 (referred to as '5H8 CVH4 (D98G)/GVL3' in Figure 27)
- 5H8GVH4_D98G / 5H8CVL4 (referred to as '5H8 GVH4 (D98G)/CVL4' in Figure 27)
- 15 5H8GVH4_D98G / 5H8GVL3 (referred to as '5H8 GVH4 (D98G)/GVL3' in Figure 27)

The antibodies were provided in hlgG4(S228P, L235E) format.

The ability of the antibodies to inhibit signalling induced CSP-S-5H8, 5H8CVH4_D98G / 5H8CVL3, 5H8CVH4_D98G / 5H8CVL4, 5H8CVH4_D98G / 5H8GVL3, 5H8GVH4_D98G / 5H8CVL4 and 5H8GVH4_D98G / 5H8GVL3 provided in hlgG4(S228P, L235E) format to inhibit signalling induced by IL-6, IL-11, CT-1, CNTF, OSM or LIF through gp130 was evaluated using the STAT3 reporter cell line, as described in Example 3.

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/ml), 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. All test conditions were performed in duplicate.

- 30 Figure 27A and Figure 27B show that all of CSP-S-5H8, 5H8CVH4_D98G/5H8CVL3, 5H8CVH4_D98G/5H8CVL4, 5H8CVH4_D98G/5H8GVL3, 5H8GVH4_D98G/5H8CVL4 and 5H8GVH4_D98G/5H8GVL3 retained the ability to inhibit signalling mediated by IL-6, IL-11, CT-1, CNTF, OSM and LIF, in a dose-dependent manner.

These data indicate that the humanised CSP-S-5H8 antibodies retain the ability to inhibit signalling mediated by all of IL-6, IL-11, LIF, OSM and CTGF and are 'pan' inhibitors of gp130-mediated signalling.

5 **Example 30: Analysis of the ability of mAb16618, mAb16636 and mAb16673 to inhibit signalling mediated by IL-6 and CNTF**

Monoclonal antibodies mAb16618, mAb16636 and mAb16673 that bind to gp130 and antagonise gp130-mediated signalling have previously been described in WO 2019/126071 A1.

10 The ability of mAb16618, mAb16636 and mAb16673 to inhibit signalling induced by IL-6 and CNTF was evaluated using the STAT3 reporter cell line, as described in Example 2. IL-6 and CNTF were sourced from Peprotech (recombinant hIL-6 (Cat. No. 200-06, 100 ng/ml; recombinant hCNTF (Cat. No. 450-13, 10 ng/ml).

15 Figure 28 shows that each of mAb16618, mAb16636 and mAb16673 did not inhibit signalling through gp130 induced by IL-6 and CNTF.

The IC₅₀ values for inhibition of gp130-mediated signalling induced by IL-6 and CNTF were determined and showed no inhibition for each of mAb16618, mAb16636 and mAb16673.

20

These data indicate that mAb16618, mAb16636 and mAb16673 do not inhibit signalling mediated by gp130:IL-6R α and gp130:LIFR β :CNTFR α , and are therefore not 'pan' inhibitors of gp130-mediated signalling.

25 **General Materials and Methods for Examples 31-33**

Animals: 20 mice (*Mus musculus*) used in the study were C57BL/6J strain, male, aged 7-9 weeks old, weighing 25-30 g on Day 1 of the study (In-Vivos, Singapore). Mice were purpose-bred and experimentally naïve at the outset of the study.

30 **Experimental Conditions:** Animals were housed in standard cages with free access to food and water under a 12-hour light and 12-hour dark cycle. Mice were housed in groups of five in individually ventilated cages (IVCs, Tecniplast, USA). The holding room temperature and humidity were controlled according to NCLAR guidelines. The temperature in the mice holding room was maintained between 20-26°C, with a relative humidity range of 55-65% and 10-15 air changes per hour, using 100% fresh air.

35

Reagents: B035-C03-A3 used at a concentration of 15 mg/mL. Commercially available Aflibercept (Eylea; Regeneron) used a concentration of 2 mg/0.05 mL

Dose Preparation: The test articles were supplied in terminally sterilized vials with a volume of 2 mL per vial. These formulations were prepared for dosing and required no subsequent dilution. The dosing materials were stored refrigerated (2-8°C) and shielded from light. Documentation of test article usage

was recorded in the raw data. Before administration, the test articles were allowed to reach room temperature for a minimum of 30 minutes. Dosing syringes were filled directly from the provided test article vials using aseptic technique.

5 Study Design:

Animals were allocated to study groups at least one day before the initiation of dosing. Random assignment to groups was performed using a selection method designed to ensure comparable group mean body weights and levels of laser-induced CNV severity.

10 Study design is outlined in Table1 below.

Table 1

Group	Drug Dose (µg/eye/dose)	Drug Dosing Conc. (mg/mL)	Dose Volume (µL/eye/dose)	Number of Animals	
				Dosing Day 3/10/17/24/31	Day 35 Sac
1. PBS	-	-	2 µL	10 (20 eyes)	10
2. B035-C03-A3	30µg	5 mg/mL	2 µL	10 (20 eyes)	10

Anaesthesia: For all experiments, mice were anesthetized using a combination of ketamine (20 mg/kg body weight) and xylazine (2 mg/kg body weight). Pupils were dilated by applying 1 drop of 1% tropicamide followed by 1 drop of 2.5% phenylephrine. The entire procedure took approximately 15-20 minutes per mouse.

Clinical examination: Visual inspection of all eyes for signs of conjunctival irritation, inflammation, or corneal infection was conducted daily after treatment. Additionally, animal behaviour and well-being were closely monitored. Animals were observed twice daily for potential adverse events, and food consumption was qualitatively assessed once daily. Body weights of the animals were recorded on the day of transfer, at the time of animal selection for experiments based on the disease phenotype, and at the end of the study.

Treatment Groups: For this study, 20 male B6J wild-type mice were utilized and randomly assigned to five groups, each consisting of 10 mice, as outlined in Table 1.

Retinal Imaging: Fundus photography and fluorescein fundus angiography (FFA) were captured using a MICRON IV fundus camera from Phoenix Laboratories USA to analyze retinal pathological changes and the extent of leakage. For FFA, animals received intraperitoneal injections of 10% sodium fluorescein at a dosage of 0.01 mL per 5-6 g of body weight.

Real-time monitoring of retinal structure was conducted using posterior-segment Optical Coherence Topography (PS-OCT) to analyze retinal thickness and fibrous area.

The frequency of ophthalmic imaging and dosing is outlined in Table 2.

Table 2

	Day											
Activity	-7	0	3	7	10	14	17	21	24	28	31	35
CFP	X		X	X		X		X		X		
OCT	X		X	X		X		X		X		
FFA		X	X	X		X		X		X		
Induction of CNV												
Treatment			X		X		X		X		X	
Sacrifice												X

OCT: Optical coherence tomography; CFP: color fundus photograph; FFA: fundus fluoresceine

angiography.

Slit lamp Biomicroscopy Examination: Corneal examination was conducted weekly through slit-lamp biomicroscopy before retinal imaging to monitor for any signs of conjunctival irritation, inflammation, or corneal infection.

Mouse model of laser-induced CNV/Retinal Fibrosis: C57BL/6J mice were anesthetized using a combination of Ketamine (20 mg/kg body weight) and Xylazine (2 mg/kg body weight). Pupil dilation was achieved through the topical administration of 1% tropicamide (Alcon Laboratories, Fort Worth, TX, USA) and 2.5% phenylephrine (Bausch and Lomb Pharmaceuticals, Inc., Tampa, FL, USA) ophthalmic solutions.

Laser photocoagulation was performed with the image-guided laser system (Micron IV, Phoenix Research Laboratories, Pleasanton, CA, USA). In each eye, four laser burns were placed at the 3, 6, 9, and 12 o'clock positions, equidistant from the optic disc. A green Argon laser pulse with a wavelength of 532 nm, a fixed diameter of 50 μ m, a duration of 50 ms, and a power of 120 mW was used for the procedure. After laser treatment, mice were kept warm under infrared light until they recovered from anesthesia.

Route of Treatment: Intra-Vitreous (IVT) Injection

Animals received injections in both eyes, with each eye receiving either PBS (vehicle control) or the novel antibody (B035-C03-A3). The injection volume for all groups was 1 μ L, with a single injection at 1 μ g. A 32-gauge needle was utilized to inject all test articles at a volume of 2 μ L into the vitreal space via intravitreal (IVT) injection in both eyes, as specified above.

Clinical Observations: Daily cage-side observations were conducted twice a day during the experimental period. All mice underwent physical restraint for clinical examinations. Slit-lamp

biomicroscopy (qualitative analysis), fundus, and PS-OCT examinations of the eyes were performed one week before and from post-laser treatment day 3 to day 35, as outlined in Table 2, to document the development of neovascularization and retinal fibrosis.

- 5 Visual inspection of all eyes after topical application and assessment for any conjunctival irritation, ocular inflammation, or infection was conducted daily. Clinical observations were made prior to dose administration after laser injury on Day 3, Day 10, Day 17, Day 24, and Day 31. Additional observations were documented as necessary.

- 10 Animals in Groups 1 and 2 were weighed before randomization and assignment to study groups (Day -7 and Day 0, respectively). Animals in Groups 1 and 2 were also weighed at the end of the study.

Full feeder weights and/or feeder weigh-backs were recorded daily throughout the dosing and recovery periods for the determination of food consumption.

15

Readouts: The primary variables under evaluation were the leakage and fibrosis areas. FFA (Fluorescein Fundus Angiography) images and OCT (Optical Coherence Tomography) images were analyzed using ImageJ software to quantify the area of leakage and retinal thickness/area, respectively.

- 20 On day 35 (5 weeks post-treatment), animals were euthanized with an overdose of pentobarbital for the collection of eye tissues.

Immunofluorescent Staining: Retinal cryosections (n = 10 from each group) were fixed in acetone for 10 minutes and subsequently incubated with antibodies against IB-4, α -SMA, and Collagen-I (Abcam,

- 25 Cambridge, United Kingdom) at 4°C overnight. Following three washes with PBS, the retinal sections underwent an additional incubation with DAPI to stain nuclei for 1 hour. Subsequently, the sections were mounted using mounting medium (Vector Laboratories, Burlingame, CA, USA) and captured under a fluorescent microscope (DM2500; Leica Microsystems, Wetzlar, Germany).

- 30 **Molecular biology analysis (RNA Extraction and Quantitative Real-Time PCR):** At the study endpoint, 10 eyes from each group were promptly enucleated and meticulously dissected to extract the retina and RPE/Choroid complex, which were then snap-frozen in liquid nitrogen. Total RNA was extracted from homogenized mouse tissues using the NucleoSpin RNA Mini kit (Macherey-Nagel, Düren, Germany) following the manufacturer's instructions. For cDNA synthesis, the qScript cDNA Supermix
35 (Quanta BioSciences, Beverly, MA, USA) was employed according to the manufacturer's guidelines.

Additionally, total RNA was extracted specifically from retinas using TRIzol Reagent (Invitrogen, Carlsbad, CA, USA), and reverse transcription was performed following the manufacturer's protocol (TaKaRa Bio, Inc., Shiga, Japan). The quantitative RT-PCR procedure was conducted as previously
40 described (Murray AR, *et al.*, IOVS; 2013; 54: 1689–1697).

Gene expression levels of relevant fibrotic genes such as TNF-alpha, VEGF, IL-6, IL-11, TGF-Beta, and Collagen-1a11 were quantified relative to GAPDH, serving as an internal control in the quantitative real-time polymerase chain reaction (RT-qPCR) analysis.

- 5 **Statistical analysis:** Statistical analyses were performed using Prism 10 software (GraphPad, San Diego, CA, USA), employing either a one-way ANOVA or a Student's t-test, as appropriate. All values are presented as mean $\pm$ SEM, with a minimum of three independent measurements conducted for each analysis. A significance threshold of $P < 0.05$ was applied to determine statistical significance.

10 **Example 31: Safety and tolerability of B035-C03-A3 therapy**

Animal Mortality: Each animal in Group 1 and 2 was monitored for signs of death or impending death, following the SEMC SOP. Throughout the study period, all animals remained healthy until the point of sacrifice.

- 15 **Effects of IVT Administration of test article formulations in Body Weight:** Twenty mice were utilized in this experiment, and no significant changes in body weight (25-30g) were observed before and after drug dosing. Throughout the study period, all animals maintained normal eating habits, and there were no noticeable behavioural changes.

- 20 **Clinical observation and Examination for Safety:** The anterior segment was examined to assess the cornea, and any adverse clinical signs in the anterior chamber were noted for the evaluation of inflammation both pre- and post-dosing. The test compound demonstrated safety when delivered via intravitreal (IVT) injection.

- 25 Fundus examination and posterior segment optical coherence tomography (PS-OCT) were conducted to document the visualization of vitreous and retinal layers, capturing any adverse clinical signs in the vitreous body, fundus, and retinal layers. Additionally, these examinations quantified the choroidal neovascularization (CNV) leakage and area.

- 30 All test articles exhibited non-toxicity when administered via IVT, with no observed ocular toxicity or irritation/inflammation in any of the groups.

Example 32: Analysis of the impact of an anti-gp130 therapy on Laser-Induced Choroidal Neovascularization in Mice Model

- 35 To assess the therapeutic potential of test compositions in reducing/preventing angiogenesis, inflammation and/or fibrosis, a mouse model of laser-induced CNV was employed. Test compounds were delivered via the intra-vitreous route.

- 40 On Day 3 post-laser injury, IgG control and B035-C03-A3 were injected intravitreally (IVT) to assess their efficacy in reducing pathological angiogenesis, pathological inflammation and fibrosis in CNV mice. A total of five injections were administered on Day 3, Day 10, Day 17, Day 24, and Day 31 post-laser injury.

Fundus fluorescein angiography (FFA) as described in 'General Materials and Methods for Examples 31-33' was used to examine the extent of choroidal vascularization on post-laser days 3, 7, 14, 21, 28, and 35. Additionally, fibrosis area was examined by posterior-segment optical coherence tomography (PS-OCT) on the same days. Images of CNV lesions were acquired at different time points following fluorescein injection, and the choroidal vascularization area was validated in-vitro at the study endpoint.

Quantification revealed that compared to vehicle-injected eyes, test compound (IVT formulation) eyes exhibited significantly reduced CNV leakage at the study endpoint (Table 2).

The leakage area was significantly reduced from post-day 3 to post-day 35 in the treatment group. Leakage area significantly increased from post-day 3 to post-day 21 in PBS-treated eyes; however, this increase was mitigated after 21 days post-laser, confirming that the leakage area became fibrotic by post-day 28 and post-day 35 after laser injury. The test compound exhibited efficacy with 5 injections (Figure 29A, Figure 29B).

The fibrotic area was significantly reduced from post-day 3 to post-day 35 in the treatment group. Lesion volume area significantly increased from post-day 3 to post-day 35 in PBS-treated eyes compared to the treated group; however, this increase was mitigated after 21 days post-laser as compared to post-day 3, confirming that the lesion area became fibrotic by post-day 28 and post-day 35 after laser injury. The test compound exhibited efficacy with 5 injections (Figure 30A, Figure 30B).

Retinal immunostaining confirmed smaller CNV lesions in eyes treated with test compound (Figure 31A, Figure 31B). The results demonstrate smaller CNV lesions in eyes treated with the test compound.

Example 33: Analysis of the impact of an anti-gp130 antibody therapy on gene expression of fibrosis markers

To assess the therapeutic potential of test compositions in preventing angiogenesis, inflammation and/or fibrosis, a mouse model of laser-induced CNV was employed. Test compounds were delivered via the intra-vitreous route.

On Day 3 post-laser injury, IgG control and B035-C03-A3 were injected intravitreally (IVT) to assess their efficacy in anti-angiogenesis and fibrosis in CNV mice. A total of five injections were administered on Day 3, Day 10, Day 17, Day 24, and Day 31 post-laser injury.

Retinal tissues from five eyes in each group were immunofluorescently stained with Isolectin B4, Collagen-I, and alpha-SMA, as described in 'General Materials and Methods for Examples 31-33'. RNA was extracted for gene expression analysis, focusing on TNF- α , TGF- β , VEGF, IL-6, IL-11, and Col1- α 1, normalized with GAPDH as the internal control.

Gene expression analysis indicated lower transcript levels for each of TNF- α , TGF- β , VEGF, IL-6, IL-11, and Col1-a1 in treated samples compared with control. However, none of the gene expressions were statistically significant compared to vehicle-treated samples (Figure 32).

5 Conclusions

This comprehensive analysis indicates the efficacy of B035-C03-A3 therapy in reducing CNV lesions and fibrosis in the studied mouse model. The results further demonstrate the utility of B035-C03-A3 for treating pathological inflammation and fibrosis.

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Claims:

1. An antigen-binding molecule, optionally isolated, which binds to gp130, wherein the antigen-binding molecule inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling.
2. The antigen-binding molecule according to claim 1, wherein the antigen-binding molecule contacts the region of gp130 shown in SEQ ID NO:89.
3. The antigen-binding molecule according to claim 1 or claim 2, 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:3
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:10
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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:3
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:185; 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:192
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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:3
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:185; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:10
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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: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

5 LC-CDR2 having the amino acid sequence of SEQ ID NO:192

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

4. The antigen-binding molecule according to any one of claims 1 to 3, wherein the antigen-binding molecule comprises:

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(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C, and

15 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C,

wherein the VH and VL sequences are selected from the same row of Table C.

5. The antigen-binding molecule according to claim 1 or claim 2, wherein the antigen-binding molecule comprises:

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(a)

(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

25 HC-CDR3 having the amino acid sequence of SEQ ID NO:218; and

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

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

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

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

30 (b)

(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:204; and

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

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

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

LC-CDR3 having the amino acid sequence of SEQ ID NO:28; 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:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (d)
- (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:195; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (e)
- (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:214; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (f)
- (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:215; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28.
6. The antigen-binding molecule according to any one of claims 1, 2 or 5, wherein the antigen-binding molecule comprises:
- (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 89, 90, 80-88, 74-79 or 2 of Table C, and
 (ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 89, 90, 80-88, 74-79 or 2 of Table C,
 wherein the VH and VL sequences are selected from the same row of Table C.

7. The antigen-binding molecule according to any one of claims 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.
- 5
8. A chimeric antigen receptor (CAR) comprising an antigen-binding molecule according to any one of claims 1 to 7.
9. A nucleic acid, or a plurality of nucleic acids, optionally isolated, encoding an antigen-binding molecule
- 10 according to any one of claims 1 to 7, or a CAR according to claim 8.
10. An expression vector, or a plurality of expression vectors, comprising a nucleic acid or a plurality of nucleic acids according to claim 9.
11. A cell comprising an antigen-binding molecule according to any one of claims 1 to 7, a CAR according to claim 8, a nucleic acid or a plurality of nucleic acids according to claim 9, or an expression vector or a plurality of expression vectors according to claim 10.
12. A method comprising culturing a cell according to claim 11 under conditions suitable for expression of an antigen-binding molecule or CAR by the cell.
13. A composition comprising an antigen-binding molecule according to any one of claims 1 to 7, a CAR according to claim 8, a nucleic acid or a plurality of nucleic acids according to claim 9, an expression vector or a plurality of expression vectors according to claim 10, or a cell according to claim 11, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.
14. An antigen-binding molecule according to any one of claims 1 to 7, a CAR according to claim 8, a nucleic acid or a plurality of nucleic acids according to claim 9, an expression vector or a plurality of expression vectors according to claim 10, a cell according to claim 11, or a composition according to claim 13, for use in a method of medical treatment or prophylaxis.
15. An antigen-binding molecule according to any one of claims 1 to 7, a CAR according to claim 8, a nucleic acid or a plurality of nucleic acids according to claim 9, an expression vector or a plurality of expression vectors according to claim 10, a cell according to claim 11, or a composition according to claim 13, 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.

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16. An *in vitro* complex, optionally isolated, comprising an antigen-binding molecule according to any one of claims 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 claims 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 claims 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 claims 1 to 7 as an *in vitro* or *in vivo* diagnostic or prognostic agent.
- 5 20. An antigen-binding molecule which binds to gp130 and inhibits IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling 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
- 10 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,
- 15 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
- 20 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
- 25 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
- 30 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,
- 35 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
- 40 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 contacts the region of gp130 shown in SEQ ID NO:89.

21. Use of an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89 to inhibit IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling.
22. A method for inhibiting IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling, comprising contacting cells capable of IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and/or LIF-mediated signalling with an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89.
23. A method for inhibiting IL-6-mediated signalling, IL-11-mediated signalling, OSM-mediated signalling, CNTF-mediated signalling, CT-1-mediated signalling, and LIF-mediated signalling in a subject, comprising administering to a subject an antigen-binding molecule that binds to gp130 and that contacts the region of gp130 shown in SEQ ID NO:89.
24. The antigen-binding molecule for use according to claim 20, the use according to claim 21 or the method according to claim 22 or claim 23, wherein the antigen-binding molecule comprises:
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 - HC-CDR1 having the amino acid sequence of SEQ ID NO:2
 - HC-CDR2 having the amino acid sequence of SEQ ID NO:3
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:4; and
 - (ii) a light chain variable (VL) region incorporating the following CDRs:
 - LC-CDR1 having the amino acid sequence of SEQ ID NO:10
 - LC-CDR2 having the amino acid sequence of SEQ ID NO:11
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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:3
 - HC-CDR3 having the amino acid sequence of SEQ ID NO:185; 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:192
 - LC-CDR3 having the amino acid sequence of SEQ ID NO:12; 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:3

HC-CDR3 having the amino acid sequence of SEQ ID NO:185; 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

(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:3

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:192

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

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25. The antigen-binding molecule for use according to claim 20 or claim 24, the use according to claim 21 or claim 24, or the method according to any one of claims 22 to 24, wherein the antigen-binding molecule comprises:

20 (i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 68, 71, 69, 72, 70, 73, 12, 13, 38-67, 3-11 or 1 of Table C,

25 wherein the VH and VL sequences are selected from the same row of Table C.

26. The antigen-binding molecule for use according to claim 20, the use according to claim 21 or the method according to claim 22 or claim 23, wherein the antigen-binding molecule comprises:

30 (a)

(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:218; and

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

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

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

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

(b)

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:204; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (c)
- (i) a heavy chain variable (VH) region incorporating the following CDRs:
 HC-CDR1 having the amino acid sequence of SEQ ID NO:18
 HC-CDR2 having the amino acid sequence of SEQ ID NO:19
 HC-CDR3 having the amino acid sequence of SEQ ID NO:20; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (d)
- (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:195; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (e)
- (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:214; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27
 LC-CDR3 having the amino acid sequence of SEQ ID NO:28; or
- (f)
- (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:215; and
 (ii) a light chain variable (VL) region incorporating the following CDRs:
 LC-CDR1 having the amino acid sequence of SEQ ID NO:26
 LC-CDR2 having the amino acid sequence of SEQ ID NO:27

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

27. The antigen-binding molecule for use according to claim 20 or claim 26, the use according to claim 21 or claim 26 or the method according to any one of claims 22, 23 or 26, wherein the antigen-binding
5 molecule comprises:

(i) a VH region having an amino acid sequence having at least 70% amino acid sequence identity to a VH sequence as indicated in Column A of row 89, 90, 80-88, 74-79 or 2 of Table C, and

(ii) a VL region having an amino acid sequence having at least 70% amino acid sequence identity to a VL sequence as indicated in Column B of row 89, 90, 80-88, 74-79 or 2 of Table C,

10 wherein the VH and VL sequences are selected from the same row of Table C.

28. The antigen-binding molecule for use according to any one of claims 20 or 24 to 27, the use according to any one of claims 21 or 24 to 27, or the method according to any one of claims 22 to 27, wherein the antigen-binding molecule is a multispecific antigen-binding molecule, and wherein the
15 antigen-binding molecule further comprises an antigen-binding domain which binds to an antigen other than gp130.