

ANTIGEN BINDING PROTEIN

CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority of U.S. Provisional Application No. 63/059,387, filed 31 July
5 2020, which is herein incorporated by reference in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically
in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy,
10 created on July 6, 2021, is named PU66960_SL.txt and is 265,335 bytes in size.

FIELD OF THE INVENTION

The invention relates to antigen binding proteins that specifically bind to BMP1, TLL1 and/or
TLL2, and pharmaceutical compositions and uses thereof. The invention also relates to
15 pharmaceutical compositions containing the antigen binding proteins and uses thereof.

BACKGROUND OF THE INVENTION

Fibrous collagens are integral parts of the extracellular matrix that support tissue integrity and
maintain the cellular microenvironment for normal physiological functions. Collagens I-III, the
20 major isoforms of the fibrous collagen protein family, are synthesized as procollagen
precursors containing N-terminal and C-terminal propeptides. The procollagens are post-
translationally modified by proline hydroxylation, and secreted into the peri-vascular space for
further processing. N-terminal propeptides of the collagens are subsequently cleaved by
proteinases of the ADAMTS (A Disintegrin And Metalloproteinase with ThromboSpondin
25 repeats) family, while the C-terminal propeptides are processed by the Tolloid family of
metalloproteases, which include BMP1 (bone morphogenetic protein 1), TLL1 (tolloid-like 1)
and TLL2 (tolloid-like 2) (Hopkins, D.R. *et al.*, Matrix Biology, 2007, 26, 508-523). The
cleavage of both N- terminal and C-terminal propeptides allows further maturation of the
collagen, leading to cross-linking at lysine residues and formation of insoluble fibrillar
30 structures (Shoulders, M.D. *et al.*, Annual Review of Biochemistry, 2009, 78, 929-958).

Whereas the BMP1, TLL1 and TLL2 proteins are encoded by separate genes, this family also
includes isoforms of BMP1, including multiple isoforms of BMP1 that result from alternative
splicing of the same gene product (see e.g., Takahara, K., *et al.*, The Journal of Biological
35 Chemistry, 1994, 269, 32572-32578; and Cvetjetcanin, B. *et al.*, Medical Hypotheses, 2014,
83, 656-658). The originally discovered form of BMP1 is designated BMP-1-1 or BMP1-1.
Other BMP1 isoforms encoded by splice variant RNA transcripts have been described at the

transcriptional level and designated with sequential suffixes, e.g., as BMP-1-2, BMP-1-3, BMP-1-4, BMP-1-5, BMP-1-6, and BMP-1-7 (see, e.g., Wozney *et al.*, Science (1988), 242: 1528-1534; Kessler *et al.*, Science, (1996) 271 : 360-362; Li *et al.*, Proc. Natl. Acad. Sci. USA (1996), 93: 5127-5130; Janitz *et al.*, J. Mol. Med. (1998), 76: 141-146; Takahara *et al.*, J. Biol. Chem. (1994), 269: 32572- 32578; and Ge and Greenspan, Birth Defect Res. (2006), 78: 47-68).

A number of BMP1 isoforms have also been confirmed at the protein level as circulating in the blood of patients with various diseases and in healthy humans (see, e.g., International Patent publication Nos. WO 2008/011193 and WO 2013/163479, and Grgurevic *et al.*, J. Am. Soc. Nephrol. (2011), 21 :681-692). In addition, the role of BMP1 in processing procollagen leading to fibrosis and scar tissue in a variety of diseases as well as the discovery of blood profiles comprising individual BMP1 isoforms in patients with various diseases has made BMP1 an attractive target for developing new therapies (see, e.g. WO 2008/011193; WO 2013/163479; Grgurevic *et al.*, J. Am. Soc. Nephrol. (2011), 21 :681-692, Cvetjeticanin, B. *et al.*, Medical Hypotheses, 2014, 83, 656- 658; and Turtle *et al.*, Expert Opin. Ther. Patents (2004), 14(8): 1185-1197).

Excessive production of extracellular matrix (ECM) proteins, including collagen, can lead to fibrotic pathologies in various organs or tissues that may be associated with increased tissue rigidity, parenchymal replacement, aberrant electrical conductance, sclerotic wound healing (e.g. infarction and burns), and/or abnormal cell-cell interactions. For example, increased fibrosis and collagen production are consistently observed in patients with acute and chronic cardiac diseases, e.g., heart failure, arrhythmias, hypertrophic cardiomyopathy, and myocardial infarction (Lopez, B. *et al.*, Circulation, 2010, 121, 1645-1654; Ho, C.Y., *et al.*, New England Journal of Medicine, 2010, 363, 552-563; Kostin, S. *et al.*, Cardiovascular Research, 2002, 54, 361-379; See, F. *et al.*, Current Pharmaceutical Design, 2005, 11, 477-487; Cvetjeticanin, B. *et al.* Medical Hypotheses, 2014, 83, 656-658), chronic obstructive pulmonary disease ("COPD") (Salazar, L.M., *et al.*, Lung, 2011, 189, 101-109), liver cirrhosis and nonalcoholic steatohepatitis ("NASH") (Bataller, R., *et al.*, Journal of Clinical Investigation, 2005, 115, 209-218), idiopathic pulmonary fibrosis (Chakraborty, S, *et al.*, Expert Opin Investig Drugs, 2014, 23, 893-910), collagen vascular diseases, e.g. systemic lupus erythematosus, rheumatoid arthritis and scleroderma (Eckes, B., *et al.*, J Mol Med, 2014, 92, 913-924), muscular dystrophies (e.g., Serrano, A.C., *et al.*, Experimental Cell Research, 2010, 316, 3050-3058; Klingler, W., *et al.*, Acta Myologica, XXXI, 2012, 184-195), chronic kidney disease (Liu, Y., Nature Reviews Nephrology, 2011, 7, 684-696), acute kidney injury (Molitoris, B., The Journal of clinical Investigation, 2014, 124, 2355- 2363; Venkatachalam, M.A. *et al.*,

Am J Physiol Renal Physiol 298: F1078-F1094, 2010), diabetic nephropathy (Sun, Y.M., *et al.*, Biochemical and Biophysical Research Communications, 2013, 433, 359-361), keloids, wound healing, adhesions, hypertrophic and other scarring associated with, e.g. burns, surgery and other trauma (Meier K., *et al.*, Expert Opinion on Emerging Drugs, 2006, 11, 39-47; Malecaze, F., *et al.*, Investigative Ophthalmology and Visual Science, 2014, 55, 6712-6721; 5 van der Weer, W. *et al.*, Burns, 2009, 35, 15-29), and stroke, multiple sclerosis and spinal cord injury (Fernandez-Klett, F. and Piller, J. Brain Pathology, 2014, 24, 404-13; Rimar, D. *et al.*, Arthritis & Rheumatology, Vol. 66, No. 3, March 2014, 726-730). Therefore, reducing excessive collagen production and maturation by targeting the BMP1, TLL1 and/or TLL2 10 pathway(s) can be an effective therapeutic strategy for treating fibrotic pathologies such as these diseases. This is supported by recent published studies using pharmacological agents that inhibit BMP1, TLL1 and/or TLL2 activity in cardiac and kidney disease models in small animals (Grgurevic, L., *et al.*, Journal of the American Society of Nephrology, 2011, 21, 681-692; He, W., *et al.*, Proceedings of the National Academy of Sciences, 2010, 107, 21110-21115; 15 Cvetjeticanin, B. *et al.*, Medical Hypotheses, 2014, 83, 656-658; International Patent publication nos. WO 2008/011193 and WO 2013/163479).

The Tolloid family of metalloproteases (BMP1, TLL1 and TLL2) has additional substrates beyond collagens that may also contribute to its role in promoting ECM protein production. For 20 example, the pro-form of lysyl oxidase 1 (LOX1) has been shown to be a substrate of BMP1, and cleavage by BMP1 enhances the LOX enzyme activity and thereby induces collagen cross-linking (Uzel, M.I., *et al.*, Journal of Biological Chemistry, 2001, 276, 22537-22543). Thus, BMP1 also has a role in the development of pathological tissue stiffness via this mechanism, for example in glaucoma (Tovar-Vidales, T., *et al.*, Investigative Ophthalmology & Visual Science, 2013, 54, 4741-4748) and in diastolic dysfunction in the heart (Lopez, B., *et al.*, American Journal of Physiology - Heart and Circulatory Physiology, 2010, 299, H1-H9). 25 TGF-beta binding protein (LTBP) has also been shown to be cleaved by BMP1, allowing enhanced TGF-beta action to induce further collagen production (Ge, G., *et al.*, Journal of Cell Biology, 2006, 175, 11-120). Regulation of TGF-beta by BMP1 may also play roles in other 30 pathologies, such as control of cancer cell metastasis and invasion (Wu, X., *et al.* Oncogene, 2014, 33, 1506-1514). Similarly, BMP1, TLL1 and/or TLL2 also activate a broader range of other TGF-beta like molecules, such as BMPs 2 and 4, by proteolytically processing interacting proteins (Hopkins, D.R. *et al.*, Matrix Biology, 2007, 26, 508-523). The combined actions of BMP1 and its various substrates suggest that BMP1, TLL1 and TLL2 are key regulators of 35 tissue ECM production/maturation and that the members of the tolloid family of metalloproteases are particularly effective targets for anti-fibrosis therapeutic intervention.

BMP1, TLL1 and TLL2 may also affect other biological pathways via additional substrate processing. In particular, they may affect muscle biology via promoting activation of myostatin. Myostatin is a hormone that negatively regulates muscle growth (Lee, S. J., 2004, Annual Review of Cell & Developmental Biology, 20, 61-86). BMP1 has been demonstrated to cleave an inhibitory pro-peptide of myostatin and thus enhance myostatin activity (Wolfman N.M., *et al.*, Proceedings of the National Academy of Sciences, 2003, 100, 15842-15846). Knockout of TLL2 in mice demonstrated enhanced muscle mass, thereby providing support for the connection between tolloid metalloprotease and myostatin (Lee, S.J., PLoS one, 2008, 3, e1628). An inhibitor of BMP1, TLL1 and/or TLL2 could therefore be beneficial in diseases where muscle function or muscle mass is diminished, including muscular dystrophy, sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer or old age.

Taken together, the biology of BMP1, TLL1 and TLL2 lends support for their key roles in collagen processing, assembly and cross-linking, leading to the formation of a fibrillar collagen network that maintains tissue integrity and proper cellular microenvironment. This family of proteins may also play important roles in the etiology of fibrotic conditions, for example in the heart, lung, skeletal muscle, kidney, liver, skin, vasculature, nervous system, and eye, and inhibitors of these metalloproteases may provide broad benefits as anti-fibrotic agents for the treatment of diseases associated with fibrosis, such as myocardial infarction, heart failure, cardiac arrhythmias, hypertrophic cardiomyopathy, chronic kidney disease (CKD), post-acute kidney injury, diabetic nephropathy, delayed graft function post-transplantation, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), liver cirrhosis, nonalcoholic steatohepatitis (NASH), muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), glaucoma, corneal scarring, keloids, wound healing, adhesions, hypertrophic scarring, other scarring, e.g. associated with burns, surgery or other trauma, stroke, collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma, spinal cord injury and multiple sclerosis. Furthermore, BMP1, TLL1 and TLL2 inhibitors may have additional therapeutic applications in muscular disease based on their impact on myostatin biology, in particular muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery-Dreifuss), sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer or old age.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a BMP1, TLL1 and/or TLL2 binding protein, which comprises:

(a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NOs: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, and 222 and/or CDRL1, CDRL2, CDRL3 from SEQ ID NOs: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, and 221; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or

(b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, or 222 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, or 221.

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In an embodiment, provided is a BMP1, TLL1 and/or TLL2 binding protein comprising the following 6 CDRs:

- LCDR1 of RASQSVSSYLA (SEQ ID NO: 1);
- LCDR2 of DASNRAT (SEQ ID NO: 2);
- 15 LCDR3 of QQSDSWPPT (SEQ ID NO: 3);
- HCDR1 of GYYMS (SEQ ID NO: 4);
- HCDR2 of WINPLSGETNYAQKFQG (SEQ ID NO: 5); and
- HCDR3 of DTGELDGMNWFYDL (SEQ ID NO: 6).

20 In an embodiment, provided is a BMP1, TLL1 and/or TLL2 binding protein, which comprises a VH region that is 100% identical to SEQ ID NO: 7 and a VL region that is 100% identical to SEQ ID NO: 8.

In an embodiment, provided is a BMP1, TLL1 and/or TLL2 binding protein, which comprises
25 a light chain that is 100% identical to SEQ ID NO: 9 and a heavy chain that is 100% identical to SEQ ID NO: 10.

According to a further aspect of the invention, there is provided a polynucleotide sequence encoding a BMP1, TLL1 and/or TLL2 binding protein as defined herein.

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According to a further aspect of the invention, there is provided an expression vector comprising a polynucleotide sequence as defined herein.

According to a further aspect of the invention, there is provided a recombinant host cell
35 comprising a polynucleotide sequence as defined herein or an expression vector as defined herein.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a BMP1, TLL1 and/or TLL2 binding protein as defined herein and a pharmaceutically acceptable diluent or carrier.

- 5 According to a further aspect of the invention, there is provided a method for the treatment of a fibrotic related disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein.

- 10 According to a further aspect of the invention, there is provided a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein, for use in therapy.

- According to a further aspect of the invention, there is provided a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein, for use in the treatment of a fibrosis related disease or disorder.
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- According to a further aspect of the invention, there is provided use of a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for use in the treatment of a fibrosis related disease or disorder.
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- According to a further aspect of the invention, there is provided a method for promoting muscle growth and/or improving muscle function in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein.
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- According to a further aspect of the invention, there is provided a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein, for use in promoting muscle growth and/or improving muscle function.
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- According to a further aspect of the invention, there is provided use of a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein in the manufacture of a medicament for use in promoting muscle growth and/or improving muscle function.
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BRIEF DESCRIPTION OF THE FIGURES

Figure 1: FRET assay measuring inhibition of 62.5pM human BMP-1 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Antibodies were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 2: FRET assay measuring inhibition of 50pM mouse BMP-1 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 3: FRET assay measuring inhibition of 250pM biotinylated human TLL-1 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 4: FRET assay measuring inhibition of 500pM human TLL-2 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 5: FRET assay measuring inhibition of 800pM biotinylated mouse TLL-1 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 6: FRET assay measuring inhibition of 2.5nM rat TLL-1 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 7: FRET assay measuring inhibition of 2.5nM rat TLL-2 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

Figure 8: FRET assay measuring inhibition of 750pM biotinylated cyno TLL-1

activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, 13Y039-3E07-2944, and 13Y039-8F02-2949. Molecules were tested from a top concentration of 75nM with a 3-fold dilution series across 11-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

5 **Figure 9:** FRET assay measuring inhibition of 8nM biotinylated cyno TLL-2 activity by anti-BMP1/TLL antibody molecules. Dose-response curves were plotted for 13Y039-4B06-4334, which was tested from a top concentration of 600nM with a 3-fold dilution series across 22-points. Figure shows the mean of duplicate data points, with standard deviation as error bars.

10 **Figure 10:** Binding of 13Y039-4B06-4334 (HEK-expressed and CHO-expressed antibody) to human C1q measured by ELISA.

Figure 11: Inhibition by anti-BMP-1/TLL antibody 13Y039-4B06-4334 of cleavage of latent complex – MSD assay to measure released myostatin.

Figure 12: Plasma BMP1 activity from animals studied in mouse AngII/PE model.
15 For reference, plasma BMP1 levels were determined in naïve mice that had neither received an osmotic pump or i.p. injections (white bar on far right). Compounds A-D are antibodies cloned as reverse chimeric mAbs with human variable region on the mouse IgG2a LAGA Fc and mouse Kappa (referred to herein as Compound A for 4B06-4334 and Compound B for 3E07-2944) and human variable region on rat IgG2b LAGA Fc and rat Kappa (referred to
20 herein as Compound C for 4B06-4334 and Compound D for 3E07-2944). (AngII/PE vs. saline compared by unpaired t-test, * $p < 0.05$; AngII/PE vs. mAb groups compared by one-way ANOVA, # $p < 0.05$, #### $p < 0.0001$; RSV controls vs. dose-paired Compound A or E07, #### $p < 0.0001$).

Figure 13: Plasma PICP measurements from selected groups in the mouse
25 AngII/PE model. PICP levels were measured over multiple immunoblots. Each gel contained all AngII/PE+saline samples, and one of the other test groups. On each gel, all band intensities were normalized to the mean of the respective AngII/PE+saline group. The data were then combined into one graph for visualization. (AngII/PE+saline vs. other groups compared by unpaired t-test, **** $p < 0.0001$).

30 **Figure 14:** Effect of Compound A on skeletal muscle mass in the AngII/PE model. Percentages in black above the treatment groups refer to the increase in normalized gastrocnemius weight above AngII/PE group, while the percentages in red refer to the increase above the model window (the difference between the saline-saline group and the AngII/PE-saline group. (AngII/PE vs. saline compared by unpaired t-test, ** $p < 0.01$; AngII/PE
35 vs. mAb groups compared by one-way ANOVA, # $p < 0.05$, #### $p < 0.001$, ##### $p < 0.0001$).

Figure 15: Effect of Compound A on total plasma myostatin (MSTN) levels in the AngII/PE model. Total plasma myostatin was measured by ELISA. Fold changes are

expressed relative to the AngII/PE control. (AngII/PE vs. saline compared by unpaired t-test, $^{**}p<0.01$; AngII/PE vs. mAb groups compared by one-way ANOVA, $^{##}p<0.01$, $^{####}p<0.0001$; RSV controls vs. dose-paired Compound A or Compound B, $^{##}p<0.01$, $^{###}p<0.001$, $^{####}p<0.0001$).

5 **Figure 16:** Left ventricular hydroxyproline (HDXP) content in the mouse AngII/PE study. Percent changes are calculated versus the AngII/PE group. (AngII/PE vs. saline compared by unpaired t-test, $^{****}p<0.0001$; AngII/PE vs. mAb groups compared by one-way ANOVA (one-sided), $^{#}p<0.05$, $^{##}p<0.01$, $^{###}p<0.001$; RSV controls vs. dose-paired Compound A compared by one-way ANOVA (one-sided), $^{#}p<0.05$).

10 **Figures 17A and 17B:** Effect of Compound C on fibrosis (Figure 17A) and skeletal muscle mass (Figure 17B) in the rat Dahl S model. Figure 17A: Left ventricular fibrosis, measured by quantitative assessment of Masson's Trichrome histopathological staining, in the rat Dahl S study. (PBS+0.3% NaCl vs. PBS+8% NaCl compared by unpaired t-test, $^{**}p<0.01$; PBS+8% NaCl vs. Compound C+8% NaCl compared by one-way ANOVA, $^{#}p<0.05$). Figure 17B: The Compound C-treated group exhibits a 9% increase in skeletal muscle mass compared to PBS+8% NaCl and a 10% increase compared to the anti-RSV treated group. (PBS+8% NaCl vs. mAb groups compared by one-way ANOVA, $^{**}p<0.01$).

15 **Figure 18:** Lean mass measurements in the 2-week recovery phase after hindlimb immobilization in aged mice. Data are shown as a time-course of absolute lean mass (left) and as percent change relative to the post-splint measurement (right). (Percent lean mass change compared by one-way ANOVA. Compound A vs. anti-RSV mAb: $^{*}p<0.05$, $^{**}p<0.01$; anti-myostatin mAb vs. anti-RSV mAb: $^{#}p<0.05$).

20 **Figure 19:** Gastrocnemius (left) and soleus (right) wet weights measured at the conclusion of the hindlimb immobilization study in aged mice. Empty squares are the weights of the unsplinted left hindlimb, while filled squares are the weights of the splinted right hindlimb. (Muscle weights compared by 2-way ANOVA. Compound A or anti-myostatin mAb vs. anti-RSV mAb in unsplinted limb, $^{*}p<0.05$, $^{****}p<0.0001$; Compound A or anti-myostatin mAb vs. anti-RSV mAb in splinted limb, $^{*}p<0.05$, $^{***}p<0.001$, $^{****}p<0.0001$; Splinted vs. unsplinted limbs, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$).

25 **Figure 20:** *In vivo* muscle contractility measurements determined longitudinally through the hindlimb immobilization study in aged mice. Muscle contractility values are shown as absolute tetanic force measurements (left panel), tetanic force relative to the post-splint value (middle panel) and normalized to the gastrocnemius wet weight (right panel). (Relative tetanic force compared by one-way ANOVA: Compound A vs. anti-RSV mAb, $^{*}p<0.05$, anti-myostatin mAb vs. anti-RSV mAb, $^{#}p<0.05$. Normalized force compared by one-way ANOVA, $^{**}p<0.01$).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning
5 commonly understood by a person skilled in the art to which this invention belongs. As used
herein, the following terms have the meanings ascribed to them below.

The term “BMP1, TLL1 and/or TLL2 binding protein” as used herein refers to antibodies and
other protein constructs, such as domains, that are capable of binding to BMP1 (bone
10 morphogenetic protein 1), TLL1 (tolloid-like 1) and/or TLL2 (tolloid-like 2). The terms “BMP1,
TLL1 and/or TLL2 binding protein” and “antigen binding protein” are used interchangeably
herein. This does not include the natural cognate ligand or receptor.

The term “antibody” is used herein in the broadest sense to refer to molecules with an
15 immunoglobulin-like domain (for example IgG, IgM, IgA, IgD or IgE) and includes monoclonal,
recombinant, polyclonal, chimeric, human, humanised, multispecific antibodies, including
bispecific antibodies, and heteroconjugate antibodies; a single variable domain (e.g., a domain
antibody (DAB)), antigen binding antibody fragments, Fab, F(ab')₂, Fv, disulphide linked Fv,
single chain Fv, disulphide-linked scFv, diabodies, TANDABS, etc. and modified versions of
20 any of the foregoing (for a summary of alternative “antibody” formats see Holliger and Hudson,
Nature Biotechnology, 2005, Vol 23, No. 9, 1126-1136).

The terms “full”, “whole” or “intact” used in reference to an antibody, which are used
interchangeably herein, refer to a heterotetrameric glycoprotein with an approximate
25 molecular weight of 150,000 daltons. An intact antibody is composed of two identical heavy
chains (HCs) and two identical light chains (LCs) linked by covalent disulphide bonds. This
H2L2 structure folds to form three functional domains comprising two antigen-binding
fragments, known as ‘Fab’ fragments, and a ‘Fc’ crystallisable fragment. The Fab fragment is
composed of the variable domain at the amino-terminus, variable heavy (VH) or variable light
30 (VL), and the constant domain at the carboxyl terminus, CH1 (heavy) and CL (light). The Fc
fragment is composed of two domains formed by dimerization of paired CH2 and CH3 regions.
The Fc may elicit effector functions by binding to receptors on immune cells or by binding C1q,
the first component of the classical complement pathway. The five classes of antibodies IgM,
IgA, IgG, IgE and IgD are defined by distinct heavy chain amino acid sequences, which are
35 called μ , α , γ , ϵ and δ respectively, each heavy chain can pair with either a K or λ light chain.
The majority of antibodies in the serum belong to the IgG class, there are four isotypes of

human IgG (IgG1, IgG2, IgG3 and IgG4), the sequences of which differ mainly in their hinge region.

5 Fully human antibodies can be obtained using a variety of methods, for example using yeast-based libraries or transgenic animals (e.g. mice) that are capable of producing repertoires of human antibodies. Yeast presenting human antibodies on their surface that bind to an antigen of interest can be selected using FACS (Fluorescence-Activated Cell Sorting) based methods or by capture on beads using labelled antigens. Transgenic animals that have been modified to express human immunoglobulin genes can be immunised with an antigen of interest and
10 antigen-specific human antibodies isolated using B-cell sorting techniques. Human antibodies produced using these techniques can then be characterised for desired properties such as affinity, developability and selectivity.

15 Alternative antibody formats include alternative scaffolds in which the one or more CDRs of the antigen binding protein can be arranged onto a suitable non-immunoglobulin protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, an avimer (see, e.g., U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301) or an EGF domain.

20 The term "neutralises" as used throughout the present specification means that the biological activity of BMP1, TLL1 and/or TLL2 is reduced in the presence of an antigen binding protein as described herein in comparison to the activity of BMP1, TLL1 and/or TLL2 in the absence of the antigen binding protein, *in vitro* or *in vivo*. Neutralisation may be due to one or more of blocking BMP1, TLL1, and/or TLL2 binding to its target substrates, and preventing BMP1,
25 TLL1, and/or TLL2 from cleaving its target substrates. For example, the fluorescence resonance energy transfer (FRET) based assays described in the Examples may be used to assess the neutralising capability of a BMP1, TLL1, and/or TLL2 binding protein.

30 "CDRs" are defined as the complementarity determining region amino acid sequences of an antigen binding protein. These are the hypervariable regions of immunoglobulin heavy and light chains. There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, all three light chain CDRs, all heavy and light chain CDRs, or at least two CDRs.

35 Throughout this specification, amino acid residues in variable domain sequences and variable domain regions within full-length antigen binding sequences, e.g. within an antibody heavy chain sequence or antibody light chain sequence, are numbered according to the Kabat

numbering convention. Similarly, the terms “CDR”, “CDRL1”, “CDRL2”, “CDRL3”, “CDRH1”, “CDRH2”, “CDRH3”, “LCDR1”, “LCDR2”, “LCDR3”, “HCDR1”, “HCDR2”, “HCDR3” used in the Examples and set forth in the Sequence Listing follow the Kabat numbering convention. For further information, see Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

It will be apparent to those skilled in the art that there are alternative numbering conventions for amino acid residues in variable domain sequences and full-length antibody sequences. There are also alternative numbering conventions for CDR sequences, for example those set out in Chothia et al. (1989) Nature 342: 877-883. The structure and protein folding of the antigen binding protein may mean that other residues are considered part of the CDR sequence and would be understood to be so by a skilled person.

Other numbering conventions for CDR sequences available to a skilled person include “AbM” (University of Bath) and “contact” (University College London) methods.

Table 1-1 below represents one definition using each numbering convention for each CDR or binding unit. The Kabat numbering scheme is used in Table 1 to number the variable domain amino acid sequence. It should be noted that some of the CDR definitions may vary depending on the individual publication used.

Table 1-1

	Kabat CDR	Chothia CDR	AbM CDR	Contact CDR
H1	31-35/35A/35B	26-32/33/34	26-35/35A/35B	30-35/35A/35B
H2	50-65	52-56	50-58	47-58
H3	95-102	95-102	95-102	93-101
L1	24-34	24-34	24-34	30-36
L2	50-56	50-56	50-56	46-55
L3	89-97	89-97	89-97	89-96

CDRs may be modified by at least one amino acid substitution, deletion or addition, wherein the variant antigen binding protein substantially retains the biological characteristics of the unmodified protein.

- It will be appreciated that each of CDR H1, H2, H3, L1, L2, L3 may be modified alone or in combination with any other CDR, in any permutation or combination. In one embodiment, a CDR is modified by the substitution, deletion or addition of up to 3 amino acids, for example 1 or 2 amino acids, for example 1 amino acid. Typically, the modification is a substitution, particularly a conservative substitution, for example as shown in Table 1-2 below.

Table 1-2:

Side chain	Members
Hydrophobic	Met, Ala, Val, Leu, Ile
Neutral hydrophilic	Cys, Ser, Thr
Acidic	Asp, Glu
Basic	Asn, Gln, His, Lys, Arg
Residues that influence chain orientation	Gly, Pro
Aromatic	Trp, Tyr, Phe

- For example, in a variant CDR, the flanking residues that comprise the CDR as part of alternative definition(s) e.g. Kabat or Chothia, may be substituted with a conservative amino acid residue.

Such antigen binding proteins comprising variant CDRs as described above may be referred to herein as “functional CDR variants”.

- “Antigen binding site” refers to a site on an antigen binding protein that is capable of specifically binding to an antigen, this may be a single variable domain, or it may be paired VH/VL domains as can be found on a standard antibody. Single-chain Fv (ScFv) domains can also provide antigen binding sites.
- In some embodiments, a BMP1, TLL1 and/or TLL2 binding protein is an anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof.

- A fragment of the antibody (which may also be referred to as “antibody fragment”, “immunoglobulin fragment”, “antigen-binding fragment” or “antigen-binding polypeptide”) as used herein refers to a portion of an antibody (or constructs that contain said portion) that specifically binds to the target, namely BMP1, TLL1 and/or TLL2. Examples of binding fragments encompassed within the term antibody fragment include:

(i) a Fab fragment (a monovalent fragment consisting of the VL, VH, CL and CH1 domains);

- (ii) a F(ab')₂ fragment (a bivalent fragment consisting of two Fab fragments linked by a disulphide bridge at the hinge region);
- (iii) a Fd fragment (consisting of the VH and CH1 domains);
- (iv) a Fv fragment (consisting of the VL and VH domains of a single arm of an antibody);
- 5 (v) a single chain variable fragment, scFv (consisting of VL and VH domains joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules);
- (vi) a VH (an immunoglobulin chain variable domain consisting of a VH domain);
- (vii) a VL (an immunoglobulin chain variable domain consisting of a VL domain);
- 10 (viii) a domain antibody (dAb, consisting of either the VH or VL domain);
- (ix) a minibody (consisting of a pair of scFv fragments which are linked via CH3 domains);
- and
- (x) a diabody (consisting of a noncovalent dimer of scFv fragments that consist of a VH domain from one antibody connected by a small peptide linker a VL domain from another
- 15 antibody).

"Human antibody" refers to antibodies having variable and constant regions derived from human germline immunoglobulin sequences. Said human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.* mutations introduced by random or site-specific mutagenesis or by somatic mutation), for example in the CDRs and in particular CDR3. However, the term is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (*e.g.* a mouse) that is transgenic for human immunoglobulin genes or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences, may also be referred to as

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30 "recombinant human antibodies".

Substituting at least one amino acid residue in the framework region of a non-human immunoglobulin variable domain with the corresponding residue from a human variable domain is referred to as "humanisation". Humanisation of a variable domain may reduce immunogenicity in humans.

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In one embodiment, antigen binding proteins of the present disclosure show cross-reactivity between human BMP1, TLL1 and/or TLL2 and BMP1, TLL1 and/or TLL2 from another species, such as murine, rat, and/or cynomolgus BMP1, TLL1 and/or TLL2. In an embodiment, the antigen binding proteins of the invention specifically bind human and murine BMP1, TLL1 and/or TLL2. This is particularly useful, since drug development typically requires testing of lead drug candidates in mouse systems before the drug is tested in humans. The provision of a drug that can bind human and mouse species allows one to test results in these systems and make side-by-side comparisons of data using the same drug. This avoids the complication of needing to find a drug that works against a mouse BMP1, TLL1 and/or TLL2 and a separate drug that works against human BMP1, TLL1 and/or TLL2 and also avoids the need to compare results in humans and mice using non-identical drugs. Cross reactivity between other species used in disease models such as dog or monkey, such as cynomolgus monkey, is also envisaged.

“Specificity” refers to the number of different types of antigens or antigenic determinants to which a particular antibody or fragment thereof can bind. The specificity of an antibody is the ability of the antibody to recognise a particular antigen as a unique molecular entity and distinguish it from another. An antibody that “specifically binds” to an antigen or an epitope is a term well understood in the art. A molecule is said to exhibit “specific binding” if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen or epitope, than it does with alternative targets. An antibody “specifically binds” to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances.

“Affinity”, represented by the equilibrium constant for the dissociation of an antigen with an antigen-binding polypeptide (KD), is a measure of the binding strength between an antigenic determinant and an antigen-binding site on the antibody (or fragment thereof): the lesser the value of the KD, the stronger the binding strength between an antigenic determinant and the antigen-binding polypeptide. Alternatively, the affinity can also be expressed as the affinity constant (KA), which is 1/KD. Affinity can be determined by known methods, depending on the specific antigen of interest, such as equilibrium methods (e.g. enzyme-linked immunoabsorbent assay (ELISA) or radioimmunoassay (RIA)), or kinetics (e.g. BIACORE analysis). For example, the BIACORE methods described in the Examples may be used to measure binding affinity.

Avidity, also referred to as functional affinity, is the cumulative strength of binding at multiple interaction sites, e.g. the sum total of the strength of binding of two molecules (or more, e.g.

in the case of a bispecific or multispecific molecule) to one another at multiple sites, e.g. taking into account the valency of the interaction.

5 The term "epitope" as used herein refers to that portion of the antigen that makes contact with a particular binding domain of the antigen binding protein, also known as the paratope. An epitope may be linear or conformational/discontinuous. A conformational or discontinuous epitope comprises amino acid residues that are separated by other sequences, i.e. not in a continuous sequence in the antigen's primary sequence assembled by tertiary folding of the polypeptide chain. Although the residues may be from different regions of the polypeptide chain, they are in close proximity in the three-dimensional structure of the antigen. In the case of multimeric antigens, a conformational or discontinuous epitope may include residues from different peptide chains. Particular residues comprised within an epitope can be determined through computer modelling programs or via three-dimensional structures obtained through methods known in the art, such as X-ray crystallography. Epitope mapping can be carried out using various techniques known to persons skilled in the art as described in publications such as *Methods in Molecular Biology 'Epitope Mapping Protocols'*, Mike Schutkowski and Ulrich Reineke (volume 524, 2009) and Johan Rockberg and Johan Nilvebrant (volume 1785, 2018). Exemplary methods include peptide-based approaches such as pepscan whereby a series of overlapping peptides are screened for binding using techniques such as ELISA or by *in vitro* display of large libraries of peptides or protein mutants, e.g. on phage. Detailed epitope information can be determined by structural techniques including X-ray crystallography, solution nuclear magnetic resonance (NMR) spectroscopy and cryogenic-electron microscopy (cryo-EM). Mutagenesis, such as alanine scanning, is an effective approach whereby loss of binding analysis is used for epitope mapping. Another method is hydrogen/deuterium exchange (HDX) combined with proteolysis and liquid-chromatography mass spectrometry (LC-MS) analysis to characterize discontinuous or conformational epitopes.

30 Competition between the BMP1/TLL1/TLL2 binding protein of the invention and a reference BMP1/TLL1/TLL2 binding protein, e.g. a reference antibody, may be determined by one or more techniques known to the skilled person such as ELISA, FMAT, Surface Plasmon Resonance (SPR) or FORTEBIO OCTET Bio-Layer Interferometry (BLI). Such techniques may also be referred to as epitope binning. There are several possible reasons for this competition: the two proteins may bind to the same or overlapping epitopes, there may be steric inhibition of binding, or binding of the first protein may induce a conformational change in the antigen that prevents or reduces binding of the second protein.

The reduction or inhibition in biological activity may be partial or total. A neutralising antigen binding protein may neutralise the activity of BMP1, TLL1 and/or TLL2 by at least 20%, 30% 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 82%, 84%, 86%, 88%, 90%, 92%, 94%, 95%, 96%, 97%, 98%, 99% or 100% relative to BMP1, TLL1 and/or TLL2 activity in the absence of the antigen binding protein.

In some embodiments, the antigen binding protein (*i.e.* polypeptide) of the invention is isolated. An "isolated" antigen binding protein is one that is removed from its original environment. The term "isolated" may be used to refer to an antigen binding protein that is substantially free of other antigen binding proteins having different antigenic specificities (*e.g.* an isolated antigen binding protein that specifically binds BMP1, TLL1 and/or TLL2, or a fragment thereof, is substantially free of antigen binding proteins that specifically bind antigens other than BMP1, TLL1 and/or TLL2). The term "isolated" may also be used to refer to preparations where the isolated antigen binding protein is sufficiently pure to be administered therapeutically when formulated as an active ingredient of a pharmaceutical composition, or at least 70-80% (w/w) pure, more preferably, at least 80-90% (w/w) pure, even more preferably, 90-95% (w/w) pure; and, most preferably, at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

In some embodiments, the polynucleotides used in the present invention are isolated. An "isolated" polynucleotide is one that is removed from its original environment. For example, a naturally-occurring polynucleotide is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of its natural environment or if it is comprised within cDNA.

For the purposes of comparing two closely related polypeptide sequences, the "% sequence identity" between a first polypeptide sequence and a second polypeptide sequence may be calculated using NCBI BLAST v2.0, using standard settings for polypeptide sequences (BLASTP). For the purposes of comparing two closely related polynucleotide sequences, the "% sequence identity" between a first nucleotide sequence and a second nucleotide sequence may be calculated using NCBI BLAST v2.0, using standard settings for nucleotide sequences (BLASTN).

Polypeptide or polynucleotide sequences are said to be the same as or "identical" to other polypeptide or polynucleotide sequences, if they share 100% sequence identity over their entire length. Residues in sequences are numbered from left to right, *i.e.* from N- to C-terminus for polypeptides; from 5' to 3' terminus for polynucleotides.

A “difference” between sequences refers to an insertion, deletion or substitution of a single amino acid residue in a position of the second sequence, compared to the first sequence. Two polypeptide sequences can contain one, two or more such amino acid differences. Insertions, deletions or substitutions in a second sequence which is otherwise identical (100% sequence identity) to a first sequence result in reduced % sequence identity. For example, if the identical sequences are 9 amino acid residues long, one substitution in the second sequence results in a sequence identity of 88.9%. If first and second polypeptide sequences are 9 amino acid residues long and share 6 identical residues, the first and second polypeptide sequences share greater than 66% identity (the first and second polypeptide sequences share 66.7% identity).

Alternatively, for the purposes of comparing a first, reference polypeptide sequence to a second, comparison polypeptide sequence, the number of additions, substitutions and/or deletions made to the first sequence to produce the second sequence may be ascertained. An “addition” is the addition of one amino acid residue into the sequence of the first polypeptide (including addition at either terminus of the first polypeptide). A “substitution” is the substitution of one amino acid residue in the sequence of the first polypeptide with one different amino acid residue. Said substitution may be conservative or non-conservative. A “deletion” is the deletion of one amino acid residue from the sequence of the first polypeptide (including deletion at either terminus of the first polypeptide).

The term “vector”, as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.* bacterial vectors having a bacterial origin of replication and episomal mammalian and yeast vectors). Other vectors (*e.g.* non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.* replication defective

retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions, and also bacteriophage and phagemid systems. The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. Such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell.

References to "subject", "patient" or "individual" refer to a subject, in particular a mammalian subject, to be treated. Mammalian subjects include humans, non-human primates, farm animals (such as cows), sports animals, or pet animals, such as dogs, cats, guinea pigs, rabbits, rats or mice. In some embodiments, the subject is a human. In alternative embodiments, the subject is a non-human mammal, such as a mouse.

The term "sufficient amount" means an amount sufficient to produce a desired effect. The term "therapeutically effective amount" is an amount that is effective to ameliorate a symptom of a disease or disorder. A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy.

As used herein, the term "about" when used herein includes up to and including 10% greater and up to and including 10% lower than the value specified, particularly up to and including 5% greater and up to and including 5% lower than the value specified. The term "between", includes the values of the specified boundaries.

The skilled person will appreciate that, upon production of an antigen binding protein, such as an antibody in a host cell, post-translational modifications may occur. For example, this may include the cleavage of certain leader sequences, the addition of various sugar moieties in various glycosylation patterns, non-enzymatic glycation, deamidation, oxidation, disulfide bond scrambling and other cysteine variants such as free sulfhydryls, racemized disulfides, thioethers and trisulfide bonds, isomerisation, C-terminal lysine clipping, and N-terminal glutamine cyclisation. The invention encompasses the use of antigen binding proteins that have been subjected to, or have undergone, one or more post-translational modifications. Thus an "antigen binding protein" or "antibody" of the invention includes an "antigen binding protein" or "antibody", respectively, as defined earlier that has undergone a post-translational modification such as described herein.

Glycation is a post-translational non-enzymatic chemical reaction between a reducing sugar, such as glucose, and a free amine group in the protein, and is typically observed at the epsilon

amine of lysine side chains or at the N-Terminus of the protein. Glycation can occur during production and storage only in the presence of reducing sugars.

5 Deamidation, which can occur during production and storage, is an enzymatic reaction primarily converting asparagine (N) to iso-aspartic acid (iso-aspartate) and aspartic acid (aspartate) (D) at approximately 3:1 ratio. This deamidation reaction is therefore related to isomerization of aspartate (D) to iso-aspartate. The deamidation of asparagine and the isomerisation of aspartate, both involve the intermediate succinimide. To a much lesser degree, deamidation can occur with glutamine residues in a similar manner. Deamidation can
10 occur in a CDR, in a Fab (non-CDR region), or in the Fc region.

Oxidation can occur during production and storage (i.e. in the presence of oxidizing conditions) and results in a covalent modification of a protein, induced either directly by reactive oxygen species or indirectly by reaction with secondary by-products of oxidative stress. Oxidation
15 happens primarily with methionine residues, but may occur at tryptophan and free cysteine residues. Oxidation can occur in a CDR, in a Fab (non-CDR) region, or in the Fc region.

Disulfide bond scrambling can occur during production and basic storage conditions. Under certain circumstances, disulfide bonds can break or form incorrectly, resulting in unpaired cysteine residues (-SH). These free (unpaired) sulfhydryls (-SH) can promote shuffling.
20 The formation of a thioether and racemization of a disulphide bond can occur under basic conditions, in production or storage, through a beta elimination of disulphide bridges back to cysteine residues via a dehydroalanine and persulfide intermediate. Subsequent crosslinking of dehydroalanine and cysteine results in the formation of a thioether bond or the free cysteine residues can reform a disulphide bond with a mixture of *D*- and *L*-cysteine.

25 Trisulfides result from insertion of a sulfur atom into a disulphide bond (Cys-S-S-S-Cys) and are formed due to the presence of hydrogen sulphide in production cell culture.

30 N-terminal glutamine (Q) and glutamate (glutamic acid) (E) in the heavy chain and/or light chain is likely to form pyroglutamate (pGlu) via cyclization. Most pGlu formation happens in the production bioreactor, but it can be formed non-enzymatically, depending on pH and temperature of processing and storage conditions. Cyclization of N-terminal Q or E is commonly observed in natural human antibodies.

35 C-terminal lysine clipping is an enzymatic reaction catalyzed by carboxypeptidases, and is commonly observed in recombinant and natural human antibodies. Variants of this process include removal of lysine from one or both heavy chains due to cellular enzymes from the

recombinant host cell. Upon administration to the human subject/patient is likely to result in the removal of any remaining C-terminal lysines.

5 Fc engineering methods can be applied to modify the functional or pharmacokinetics properties of an antibody. Effector function may be altered by making mutations in the Fc region that increase or decrease binding to C1q or Fcγ receptors and modify CDC or ADCC activity respectively. Modifications to the glycosylation pattern of an antibody can also be made to change the effector function. The *in vivo* half-life of an antibody can be altered by making mutations that affect binding of the Fc to the FcRn (Neonatal Fc Receptor).

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The term "effector function" as used herein refers to one or more of antibody-mediated effects including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-mediated complement activation including complement-dependent cytotoxicity (CDC), complement-dependent cell-mediated phagocytosis (CDCP), antibody dependent complement-mediated
15 cell lysis (ADCML), and Fc-mediated phagocytosis or antibody-dependent cellular phagocytosis (ADCP).

The interaction between the Fc region of an antigen binding protein or antibody and various Fc receptors (FcR), including FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), FcRn, C1q, and
20 type II Fc receptors is believed to mediate the effector functions of the antigen binding protein or antibody. Significant biological effects can be a consequence of effector functionality. Usually, the ability to mediate effector function requires binding of the antigen binding protein or antibody to an antigen and not all antigen binding proteins or antibodies will mediate every effector function.

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Effector function can be assessed in a number of ways including, for example, evaluating ADCC effector function of antibody coated to target cells mediated by Natural Killer (NK) cells via FcγRIII, or monocytes/macrophages via FcγRI, or evaluating CDC effector function of antibody coated to target cells mediated by complement cascade via C1q. For example, an
30 antigen binding protein of the present invention can be assessed for ADCC effector function in a Natural Killer cell assay. Examples of such assays can be found in Shields et al, 2001, The Journal of Biological Chemistry, Vol. 276, p. 6591-6604; Chappel et al, 1993, The Journal of Biological Chemistry, Vol 268, p. 25124-25131; Lazar et al, 2006, PNAS, 103; 4005-4010. Examples of assays to determine CDC function include those described in J Imm Meth, 1995,
35 184: 29-38.

The effects of mutations on effector functions (e.g., FcRn binding, FcγRs and C1q binding, CDC, ADCML, ADCC, ADGP) can be assessed, e.g., as described in Grevys et al., *J Immunol.* 2015 Jun 1; 194(11): 5497–5508, or Tam et al., *Antibodies* 2017, 6(3); Monnet et al., 2014 *mAbs*, 6:2, 422-436.

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Throughout this specification, amino acid residues in Fc regions, in antibody sequences or full-length antigen binding protein sequences, are numbered according to the EU index numbering convention.

- 10 Some isotypes of human constant regions, in particular IgG4 and IgG2 isotypes, essentially lack the functions of a) activation of complement by the classical pathway; and b) ADCC. Various modifications to the heavy chain constant region of antigen binding proteins may be carried out to alter effector function depending on the desired effector property. IgG1 constant regions containing specific mutations that reduce binding to Fc receptors and reduce an
- 15 effector function, such as ADCC and CDC, have been described (Duncan et al. *Nature* 1988, 332; 563-564; Lund et al. *J. Immunol.* 1991, 147; 2657-2662; Chappel et al. *PNAS* 1991, 88; 9036-9040; Burton and Woof, *Adv. Immunol.* 1992, 51;1-84; Morgan et al., *Immunology* 1995, 86; 319-324; Hezareh et al., *J. Virol.* 2001, 75 (24); 12161-12168).
- 20 In one embodiment, there is provided a BMP1, TLL1 and/or TLL2 binding protein comprising a constant region such that the antigen binding protein has reduced effector function, such as reduced ADCC and/or CDC. In one such embodiment, the heavy chain constant region may comprise a naturally disabled constant region of an IgG2 or IgG4 isotype or a mutated IgG1 constant region. Examples of suitable modifications are described in EP0307434. One
- 25 example comprises substitution with alanine at positions 235 and 237 (EU index numbering), i.e. L235A and G237A (commonly referred to as "LAGA" mutations). Another example comprises substitution with alanine at positions 234 and 235 (EU index numbering), i.e. L234A and L235A (commonly referred to as "LALA" mutations). Further examples, described in EP2691417 and US8969526, comprise P329G or P329R, in combination with the LALA
- 30 mutations (EU index numbering) for IgG1 Fcs and P329G or P329R in combination with S228P and L235E for IgG4 Fcs (EU index numbering).

- Additional alterations and mutations to decrease effector function include: (with reference to IgG1 unless otherwise noted): aglycosylated N297A or N297Q or N297G; L235E;
- 35 IgG4:F234A/L235A; and chimeric IgG2/IgG4. IgG2: H268Q/V309L/A330S/P331S, and IgG2: V234A/G237A/P238S/H268A/V309L/A330S/P331S can reduce FcγR and C1q binding (Wang et al. 2018 and US8961967).

Other mutations that decrease effector function include L234F/L235E/P331S; a chimeric antibody created using the CH1 and hinge region from human IgG2 and the CH2 and CH3 regions from human IgG4; IgG2m4, based on the IgG2 isotype with four key amino acid residue changes derived from IgG4 (H268Q, V309L, A330S and P331S); IgG2 σ that contains V234A/G237A /P238S/H268A/V309L/A330S/P331S substitutions to eliminate affinity for Fc γ receptors and C1q complement protein; IgG2m4 (H268Q/V309L/A330S/P331S, changes to IgG4); IgG4 (S228P/L234A/L235A); hulgG1 L234A/L235A (AA); hulgG4 S228P/L234A/L235A; IgG1 σ (L234A/L235A/G237A/P238S/H268A/A330S/P331S); IgG4 σ 1 (S228P/F234A/L235A/G237A/P238S); and IgG4 σ 2 (S228P/F234A/L235A/ Δ G236/G237A/P238S, wherein Δ denotes a deletion) (Tam et al., Antibodies 2017, 6(3)).

Antigen Binding Proteins

Provided herein are antigen binding proteins capable of specifically binding to BMP1, TLL1 and/or TLL2. In some embodiments, such an antigen binding protein is an anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof.

The antigen binding proteins described herein neutralize the activity of BMP1, TLL1 and/or TLL2 through binding to the catalytic domain of BMP1, TLL1 and/or TLL2. Without being bound by any theory, it is believed that the antigen binding proteins of the invention limit fibrosis and slow organ dysfunction through BMP1, TLL1 and/or TLL2 neutralisation. For example, BMP1/TLL convert soluble procollagen I into insoluble collagen fibrils leading to fibrosis and the antigen binding proteins described herein can neutralize cleavage of procollagen I. It is believed that fibrosis occurs in response to tissue injury across many, if not all, organ systems. While initial fibrosis is beneficial to maintenance of tissue integrity, excessive fibrosis leads to scarring and inhibition of normal organ function. Reducing this pathological fibrosis thus has the potential to delay disease progression. Additionally, BMP1 inhibition can also promote muscle growth and has been shown to increase muscle function, and thus may also reduce frailty.

In one embodiment, the antigen binding protein is an antibody or fragment thereof, wherein the antibody or fragment thereof is an scFv, Fab, Fab', F(ab')₂, Fv, variable domain (e.g. VH or VL), diabody, minibody or monoclonal antibody. In a further embodiment, the antibody or fragment thereof is a monoclonal antibody.

Antibodies of the invention can be of any class, e.g. IgG, IgA, IgM, IgE, IgD, or isotypes thereof, and can comprise a kappa or lambda light chain. In one embodiment, the antibody is an IgG antibody, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. In a further embodiment, the antibody is in a format, such as an IgG format, that has been modified to confer desired properties, such as having the Fc mutated to reduce effector function, extend half-life, alter ADCC, or improve hinge stability. Such modifications are described above.

In one embodiment, the antibody or fragment thereof is human. Thus, the antibody or fragment thereof may be derived from a human immunoglobulin (Ig) sequence. The CDR, framework and/or constant region of the antibody (or fragment thereof) can be derived from a human Ig sequence, in particular a human IgG sequence. The CDR, framework and/or constant region can be substantially identical to a human Ig sequence, in particular a human IgG sequence. An advantage of using human antibodies is that they are low or non-immunogenic in humans.

An antibody or fragment thereof can also be chimeric, for example a mouse-human antibody chimera.

Alternatively, the antibody or fragment thereof is derived from a non-human species, such as a mouse. Such non-human antibodies can be modified to increase their similarity to antibody variants produced naturally in humans, thus the antibody or fragment thereof can be partially or fully humanised. Therefore, in one embodiment, the antibody or fragment thereof is humanised.

In one embodiment, a BMP1, TLL1 and/or TLL2 binding protein is an IgG antibody.

In some embodiments, a BMP1, TLL1 and/or TLL2 binding protein is an IgG antibody comprising at least one mutation to reduce Fc-mediated effector function, such as reduced ADCC.

In some embodiments, a BMP1, TLL1 and/or TLL2 binding protein is an IgG antibody comprising mutations L235A and G237A (also referred to herein as "LAGA" mutations) to reduce Fc-mediated effector function, such as reduced ADCC.

In some embodiments, a BMP1, TLL1 and/or TLL2 binding protein is a fully human monoclonal antibody. In some embodiments, a BMP1, TLL1 and/or TLL2 binding protein is a fully human monoclonal IgG1 antibody comprising mutations L235A and G237A to reduce Fc-mediated effector function, such as reduced ADCC.

Antigen Binding Protein Sequences

BMP1, TLL1 and/or TLL2 antigen binding proteins, such as anti-BMP1, TLL1 and/or TLL2 antibodies or fragments, of the invention can be described with reference to their CDR sequences.

According to a first aspect of the invention, there is provided a BMP1, TLL1 and/or TLL2 antigen binding protein, such as an anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, which comprises:

- 10 (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NOs: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, and 222 and/or CDRL1, CDRL2, CDRL3 from SEQ ID NOs: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, and 221; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- 15 (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, or 222 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, or 221.
- 20 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
 - (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 7, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 8; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
 - 25 (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 7 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 8.

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
 - 30 (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 22, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 21; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
 - (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 22 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 21.
 - 35

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 40, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 39; or (ii) a CDR variant of
- 5 (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 40 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 39.

- 10 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 54, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 53; or (ii) a CDR variant of
- (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- 15 (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 54 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 53.

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
- 20

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 67, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 68; or (ii) a CDR variant of
- (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ
- 25 ID NO: 67 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 68.

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
- 30

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 82, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 81; or (ii) a CDR variant of
- (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ
- ID NO: 82 and/or a VL region comprising a sequence at least 80% identical to the sequence
- 35 of SEQ ID NO: 81.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 96, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 95; or (ii) a CDR variant of
- 5 (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 96 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 95.

- 10 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 110, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 109; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- 15 (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 110 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 109.

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
- 20

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 124, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 123; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ
- 25 ID NO: 124 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 123.

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
- 30

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 138, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 137; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ
- ID NO: 138 and/or a VL region comprising a sequence at least 80% identical to the sequence
- 35 of SEQ ID NO: 137.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- 5 (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 152, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 151; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 152 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 151.

- 10 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 166, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 165; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- 15 (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 166 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 165.

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
- 20

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 180, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 179; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 180 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 179.
- 25

- In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:
- 30

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 194, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 193; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 194 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 193.
- 35

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 207, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 208; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or

(b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 207 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 208.

- 10 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

(a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 222, and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 221; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or

- 15 (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 222 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 221.

- 20 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises one or more of:

a LCDR1 comprising a sequence having at least 80% sequence identity with RASQSVSSYLA (SEQ ID NO: 1); and/or

a LCDR2 comprising a sequence having at least 80% sequence identity with DASNRAT (SEQ ID NO: 2); and/or

- 25 a LCDR3 comprising a sequence having at least 80% sequence identity with QQSDSWPPT (SEQ ID NO: 3); and/or

a HCDR1 comprising a sequence having at least 80% sequence identity with GYYMS (SEQ ID NO: 4); and/or

- 30 a HCDR2 comprising a sequence having at least 80% sequence identity with WINPLSGETNYAQKFQG (SEQ ID NO: 5); and/or

a HCDR3 comprising a sequence having at least 80% sequence identity with DTGELDGMNWFYDL (SEQ ID NO: 6).

- 35 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region comprising a CDR1 comprising a sequence having at least 80% sequence identity with GYYMS (SEQ ID NO: 4).

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region comprising a CDR2 comprising a sequence having at least 80% sequence identity with WINPLSGETNYAQKFQG (SEQ ID NO: 5).

5

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region comprising a CDR3 comprising a sequence having at least 80% sequence identity with DTGELDGMNWFYDL (SEQ ID NO: 6).

10

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region comprising a CDR1 comprising a sequence of GYYMS (SEQ ID NO: 4), a CDR2 comprising a sequence of WINPLSGETNYAQKFQG (SEQ ID NO: 5) and a CDR3 comprising a sequence of DTGELDGMNWFYDL (SEQ ID NO: 6).

15

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region comprising a CDR1 comprising a sequence having at least 80% sequence identity with RASQSVSSYLA (SEQ ID NO: 1).

20

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region comprising a CDR2 comprising a sequence having at least 80% sequence identity with DASNRAT (SEQ ID NO: 2).

25

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region comprising a CDR3 comprising a sequence having at least 80% sequence identity with QQSDSWPPT (SEQ ID NO: 3).

30

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region comprising a CDR1 comprising a sequence of RASQSVSSYLA (SEQ ID NO: 1), a CDR2 comprising a sequence of DASNRAT (SEQ ID NO: 2) and a CDR3 comprising a sequence of QQSDSWPPT (SEQ ID NO: 3).

35

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises the following 6 CDRs: LCDR1 of RASQSVSSYLA (SEQ ID NO: 1); LCDR2 of DASNRAT (SEQ ID NO: 2); LCDR3 of QQSDSWPPT (SEQ ID NO: 3); HCDR1 of GYYMS (SEQ ID NO: 4); HCDR2 of
5 WINPLSGETNYAQKFQG (SEQ ID NO: 5); and HCDR3 of DTGELDGMNWFYDL (SEQ ID NO: 6).

According to a further aspect of the invention, there is provided a BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof,
10 which comprises a VH region comprising CDR1, CDR2 and CDR3 sequences as defined herein and a VL region comprising CDR1, CDR2 and CDR3 sequences as defined herein.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region which comprises
15 LCDR1 of RASQSVSSYLA (SEQ ID NO: 1); LCDR2 of DASNRAT (SEQ ID NO: 2); and LCDR3 of QQSDSWPPT (SEQ ID NO: 3); and a VH region which comprises HCDR1 of GYYMS (SEQ ID NO: 4); HCDR2 of WINPLSGETNYAQKFQG (SEQ ID NO: 5); and HCDR3 of DTGELDGMNWFYDL (SEQ ID NO: 6).

20 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region which comprises an amino acid sequence having at least 80% sequence identity with SEQ ID NO: 7.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1,
25 TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region which comprises an amino acid sequence having at least 80% sequence identity with SEQ ID NO: 8.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region which comprises an
30 amino acid sequence having 100% sequence identity with SEQ ID NO: 7.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VL region which comprises an
35 amino acid sequence having 100% sequence identity with SEQ ID NO: 8.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a VH region which comprises an

amino acid sequence of SEQ ID NO: 7 and a VL region comprising an amino acid sequence of SEQ ID NO: 8.

5 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a light chain which comprises an amino acid sequence having at least 80% sequence identity with SEQ ID NO: 9.

10 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a heavy chain which comprises an amino acid sequence having at least 80% sequence identity with SEQ ID NO: 10.

15 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a light chain which comprises an amino acid sequence having 100% sequence identity with SEQ ID NO: 9.

In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a heavy chain which comprises an amino acid sequence having 100% sequence identity with SEQ ID NO: 10.

20 In one embodiment, the BMP1, TLL1 and/or TLL2 antigen binding protein, such as anti-BMP1, TLL1 and/or TLL2 antibody or fragment thereof, comprises a light chain comprising an amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising an amino acid sequence of SEQ ID NO: 10.

25 In one aspect of the invention, a BMP1, TLL1 and/or TLL2 binding protein is a fully human Fc-disabled monoclonal antibody that binds BMP-1, TLL1 and/or TLL2 selected from the following and defined according to CDR, VH/VL, and/or HC/LC sequences:

30 13Y039-4B06-4334, as shown in SEQ ID NOS: 1 to 10;
13Y039-3E07-2944, as shown in SEQ ID NOS: 15-24;
13Y039-8F02-2949, as shown in SEQ ID NOS: 33-42;
13Y039-4B06-4376, as shown in SEQ ID NOS: 47-56;
13Y039-4B06-4373, as shown in SEQ ID NOS: 61-70;
13Y039-4B06-4364, as shown in SEQ ID NOS: 75-84;
13Y039-4B06-4351, as shown in SEQ ID NOS: 89-98;
35 13Y039-4B06-4348, as shown in SEQ ID NOS: 103-112;
13Y039-4B06-4328, as shown in SEQ ID NOS: 117-126;
13Y039-4B06-4327, as shown in SEQ ID NOS: 131-140;

- 13Y039-4B06-4325, as shown in SEQ ID NOS: 145-154;
13Y039-4B06-4324, as shown in SEQ ID NOS: 159-168;
13Y039-127G03-2890, as shown in SEQ ID NOS: 173-182;
13Y039-152B02-2948, as shown in SEQ ID NOS: 187-196;
5 13Y039-152B02-2940, as shown in SEQ ID NOS: 201-210; and
13Y039-152B02-2935, as shown in SEQ ID NOS: 215-224.

- In a further embodiment, the anti-BMP-1, TLL1 and/or TLL2 antibody is selected from the following and defined according to CDR, VH/VL, and/or HC/LC sequences:
- 10 13Y039-4B06-4334, as shown in SEQ ID NOS: 1 to 10;
13Y039-3E07-2944, as shown in SEQ ID NOS: 15-24; and
13Y039-8F02-2949, as shown in SEQ ID NOS: 33-42.

- In a further embodiment, the anti-BMP-1, TLL1 and/or TLL2 antibody is selected from the following and defined according to CDR, VH/VL, and/or HC/LC sequences:
- 15 13Y039-4B06-4334, as shown in SEQ ID NOS: 1 to 10; and
13Y039-3E07-2944, as shown in SEQ ID NOS: 15-24.

- In a yet further embodiment, the anti-BMP-1, TLL1 and/or TLL2 antibody:
- 20 13Y039-4B06-4334, as shown in SEQ ID NOS: 1 to 10.

- Embodiments which refer herein to "at least 80%" or "80% or greater", will be understood to include all values equal to or greater than 80%, such as 85%, 90%, 95%, 97%, 98%, 99% or 100% sequence identity. In one embodiment, the antigen binding protein, such as antibody or
- 25 fragment of the invention comprises at least 85%, such as at least 90%, at least 95%, at least 97%, at least 98% or at least 99% sequence identity to the specified sequence.

Binding to Target Antigen

- The antigen binding protein of the invention may bind to the catalytic domain of human BMP1 with a binding affinity (KD) as measured by SPR of less than 100 nM. In a further embodiment, the KD is 50 nM or less, such as 10 nM or less. In a yet further embodiment, the KD is less than 5 nM, such as less than 2 nM. For example, according to one aspect, there is provided a human anti-BMP1 antibody which binds to the catalytic domain of BMP1 with a binding affinity (KD) as measured by SPR of less than 2 nM.

- 35 The antigen binding protein of the invention may bind to the catalytic domain of human TLL1 with a binding affinity (KD) as measured by SPR of less than 100 nM. In a further embodiment,

the KD is 50 nM or less, such as 10 nM or less. In a yet further embodiment, the KD is less than 5 nM, such as less than 2 nM. For example, according to one aspect, there is provided a human anti-TLL1 antibody which binds to the catalytic domain of TLL1 with a binding affinity (KD) as measured by SPR of less than 2 nM.

5

The antigen binding protein of the invention may bind to the catalytic domain of human TLL2 with a binding affinity (KD) as measured by SPR of less than 100 nM. In a further embodiment, the KD is 50 nM or less, such as 10 nM or less. In a yet further embodiment, the KD is less than 5 nM, such as less than 4 nM. For example, according to one aspect, there is provided a human anti-TLL2 antibody which binds to the catalytic domain of TLL2 with a binding affinity (KD) as measured by SPR of less than 4 nM.

10

For example, according to one aspect, there is provided a human anti-BMP1, anti-TLL1, and anti-TLL2 antibody which binds to the catalytic domain of BMP1 with a binding affinity (KD) as measured by SPR of less than 2 nM, which binds to the catalytic domain of TLL2 with a binding affinity (KD) as measured by SPR of less than 2 nM and which binds to the catalytic domain of TLL2 with a binding affinity (KD) as measured by SPR of less than 4 nM.

15

Described herein are other assays which may be used to define antigen binding protein function.

20

Polynucleotides and expression vectors

In one aspect of the invention there is provided a polynucleotide encoding the BMP1, TLL1 and/or TLL2 antigen binding protein described herein.

25

In one embodiment, the polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 antigen binding protein comprises a VL comprising a polynucleotide sequence having at least 70% sequence identity with SEQ ID NO: 11.

30

In one embodiment, the polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 antigen binding protein comprises a VH chain comprising a polynucleotide sequence having at least 70% sequence identity with SEQ ID NO: 12.

35

In one embodiment, the polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 antigen binding protein comprises a heavy chain comprising a polynucleotide sequence having at least 70% sequence identity with SEQ ID NO: 13.

In one embodiment, the polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 antigen binding protein comprises a light chain comprising a polynucleotide sequence having at least 70% sequence identity with SEQ ID NO: 14.

- 5 In one embodiment, the polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 antigen binding protein consists of a sequence of SEQ ID NO: 13 and/or 14.

To express the antigen binding proteins, such as antibodies, or fragments thereof, polynucleotides encoding partial or full-length light and heavy chains, as described herein, are
10 inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. Therefore, in one aspect of the invention there is provided an expression vector comprising the polynucleotide sequence as defined herein.

In one embodiment, the expression vector comprises the heavy chain of SEQ ID NO: 13.
15

In one embodiment, the expression vector comprises the light chain of SEQ ID NO: 14.

In one embodiment, the expression vector comprises the heavy chain of SEQ ID NO: 13 and the light chain of SEQ ID NO: 14.
20

It will be understood that the nucleotide sequences described herein comprise additional sequences encoding amino acid residues to aid with translation, purification and detection, however alternative sequences may be used depending upon the expression system used. These optional sequences can be removed, modified or substituted if alternate design,
25 translation, purification or detection strategies are adopted.

Mutations can be made to the DNA or cDNA that encode polypeptides which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, *e.g.* *E. coli* and
30 *S. cerevisiae*, as well as mammalian, specifically human, are known.

Mutation of polypeptides can be achieved for example by substitutions, additions or deletions to a nucleic acid encoding the polypeptide. The substitutions, additions or deletions to a nucleic acid encoding the polypeptide can be introduced by many methods, including for
35 example error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, gene

- reassembly, artificial gene synthesis, Gene Site Saturation Mutagenesis (GSSM), synthetic ligation reassembly (SLR) or a combination of these methods. The modifications, additions or deletions to a nucleic acid can also be introduced by a method comprising recombination, recursive sequence recombination, phosphothioate-modified DNA mutagenesis, uracil-containing template mutagenesis, gapped duplex mutagenesis, point mismatch repair mutagenesis, repair-deficient host strain mutagenesis, chemical mutagenesis, radiogenic mutagenesis, deletion mutagenesis, restriction-selection mutagenesis, restriction-purification mutagenesis, ensemble mutagenesis, chimeric nucleic acid multimer creation, or a combination thereof.
- 10 In particular, artificial gene synthesis may be used. A gene encoding a polypeptide of the invention can be synthetically produced by, for example, solid-phase DNA synthesis. Entire genes may be synthesized *de novo*, without the need for precursor template DNA. To obtain the desired oligonucleotide, the building blocks are sequentially coupled to the growing
- 15 oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, deprotected, and collected. Products can be isolated by high-performance liquid chromatography (HPLC) to obtain the desired oligonucleotides in high purity.
- 20 Expression vectors include, for example, plasmids, retroviruses, cosmids, yeast artificial chromosomes (YACs) and Epstein-Barr virus (EBV) derived episomes. The polynucleotide is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the polynucleotide. Expression and/or control sequences can include promoters, enhancers,
- 25 transcription terminators, a start codon (*i.e.* ATG) 5' to the coding sequence, splicing signals for introns and stop codons. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. SEQ ID NO: 11-12 comprise the nucleotide sequences encoding single chain variable fragments of the invention, comprising a VH region and a VL region. It will be understood that polynucleotides or expression vectors
- 30 of the invention may encode the VH region, the VL region or both; or encode the heavy chain, light chain, or both. Therefore, polynucleotides encoding the VH and VL regions (or heavy chain and light chain) can be inserted into separate vectors, alternatively sequences encoding both regions or chains are inserted into the same expression vector. The polynucleotide(s) are inserted into the expression vector by standard methods (*e.g.* ligation of complementary
- 35 restriction sites on the polynucleotide and vector, or blunt end ligation if no restriction sites are present).

A convenient vector is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, as described herein. The expression vector can also encode a signal peptide that facilitates secretion of the antigen binding protein, such as antibody (or fragment thereof) from a host cell. The polynucleotide may be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antigen binding protein. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (*i.e.* a signal peptide from a non-immunoglobulin protein).

In one aspect of the invention there is provided a cell (*e.g.* a host cell or recombinant host cell) comprising the polynucleotide or expression vector as defined herein. It will be understood that the cell may comprise a first vector encoding the light chain of the antibody or fragment thereof, and a second vector encoding the heavy chain of the antibody or fragment thereof. Alternatively, the heavy and light chains both encoded on the same expression vector may be introduced into the cell.

In one embodiment, the polynucleotide or expression vector encodes a membrane anchor or transmembrane domain fused to the antibody or fragment thereof, wherein the antibody or fragment thereof is presented on an extracellular surface of the cell.

Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors.

Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, *inter alia*, Chinese hamster ovary (CHO) cells, human embryonic kidney (HEK) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.* Hep G2), A549 cells, 3T3 cells, and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and

fungal cells. Antigen-binding fragments of antibodies such as the scFv and Fv fragments can be isolated and expressed in *E. coli* using methods known in the art.

5 The antigen binding proteins are produced by culturing the host cells for a period of time sufficient to allow for expression of the antigen binding proteins in the host cells or, more preferably, secretion of the antigen binding proteins into the culture medium in which the host cells are grown. Antigen binding proteins can be recovered from the culture medium using standard protein purification methods.

10 Antibodies (or fragments) of the invention can be obtained and manipulated using the techniques disclosed for example in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (2012) 4th Edition Cold Spring Harbour Laboratory Press.

15 Monoclonal antibodies in particular can be produced using hybridoma technology, by fusing a specific antibody-producing B cell with a myeloma (B cell cancer) cell that is selected for its ability to grow in tissue culture and for an absence of antibody chain synthesis.

A monoclonal antibody directed against a determined antigen can, for example, be obtained by:

- 20 a) immortalizing lymphocytes obtained from the peripheral blood of an animal previously immunized with a determined antigen, with an immortal cell and preferably with myeloma cells, in order to form a hybridoma,
- b) culturing the immortalized cells (hybridoma) formed and recovering the cells producing the antibodies having the desired specificity.

25

Alternatively, the use of a hybridoma cell is not required. Antigen binding proteins capable of binding to the target antigens as described herein may be isolated from a suitable antibody library via routine practice, for example, using the phage display, yeast display, ribosomal display, or mammalian display technology known in the art. Accordingly, monoclonal

30 antibodies in particular can be obtained, for example, by a process comprising the steps of:

- a) cloning into vectors, especially into phages and more particularly filamentous bacteriophages, DNA or cDNA sequences obtained from lymphocytes especially peripheral blood lymphocytes of an animal (suitably previously immunized with determined antigens),
- b) transforming prokaryotic cells with the above vectors in conditions allowing the
- 35 production of the antibodies,
- c) selecting the antibodies by subjecting them to antigen-affinity selection, and
- d) recovering the antibodies having the desired specificity.

Pharmaceutical compositions

According to a further aspect, there is provided a composition comprising the BMP1, TLL1 and/or TLL2 binding protein as defined herein. In such embodiments, the composition may
5 comprise the antigen binding protein, optionally in combination with other excipients. Also included are compositions comprising one or more additional active agents (e.g. active agents suitable for treating the diseases mentioned herein).

According to a further aspect, there is provided a pharmaceutical composition comprising the
10 BMP1, TLL1 and/or TLL2 binding protein as defined herein, together with a pharmaceutically acceptable diluent or carrier. The antigen binding proteins described herein can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antigen binding protein described herein and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically
15 acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, salts, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for
20 example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable substances such as wetting or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or fragment thereof may also be included in pharmaceutical compositions.

25 The compositions described herein may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g. injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic
30 application. Typical preferred compositions are in the form of injectable or infusible solutions to be administered by injection or continuous infusion (examples include, but are not limited to, intravenous, intraperitoneal, intradermal, subcutaneous, intramuscular, intraocular, and intraportal).

35 The preferred mode of administration is parenteral (e.g. intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antigen binding protein is administered by intravenous infusion or injection. In another preferred embodiment, the

antigen binding protein is administered by intramuscular or subcutaneous injection. In another preferred embodiment, the antigen binding protein is administered by subcutaneous injection, typically once per month.

- 5 Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration.

- 10 It is within the scope of the invention to use the pharmaceutical composition of the invention in therapeutic methods for the treatment of diseases as described herein as an adjunct to, or in conjunction with, other established therapies normally used in the treatment of such diseases.

- 15 In a further aspect of the invention, the antigen binding protein, composition or pharmaceutical composition is administered sequentially, simultaneously or separately with at least one active agent.

- 20 The pharmaceutical composition may be included in a kit containing the antigen binding protein together with other medicaments, and/or with instructions for use. For convenience, the kit may comprise the reagents in predetermined amounts with instructions for use. The kit may also include devices used for administration of the pharmaceutical composition.

- 25 The antigen binding protein described herein may also be used in methods of treatment. It will be appreciated by those skilled in the art that references herein to treatment refer to the treatment of established conditions. However, compounds of the invention may, depending on the condition, also be useful in the prevention of certain diseases. The antigen binding protein described herein is used in an effective amount for therapeutic, prophylactic or preventative treatment. A therapeutically effective amount of the antigen binding protein described herein is an amount effective to ameliorate or reduce one or more symptoms of, or
30 to prevent or cure, the disease.

Treatment methods

- According to a further aspect of the invention, there is provided the BMP1, TLL1 and/or TLL2 binding protein as defined herein or the pharmaceutical composition as defined herein, for use
35 as a medicament or for use in therapy.

The antigen binding proteins of the invention neutralize the activity of BMP1, TLL1 and/or TLL2, and may be particularly useful for treatment of diseases associated with BMP1, TLL1 and/or TLL2 activity, including for example treatment of diseases where inhibition of BMP1, TLL1 and/or TLL2 is of therapeutic benefit. For example, the antigen binding proteins of the invention may be particularly useful for treatment of diseases where inhibition of tissue ECM (extracellular matrix) production and/or maturation would be beneficial, or where inhibition of myostatin activity would be beneficial, or where inhibition of fibrosis would be beneficial.

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from a fibrosis related disease or disorder, for example diseases associated with pathological fibrotic conditions or diseases (e.g. prevention and regression of fibrosis) in body organs or tissues, e.g., such conditions of the:

heart (e.g., myocardial infarction ("MI"), prevention of heart failure post-MI, heart failure (e.g., heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction), cardiac arrhythmias (e.g., atrial fibrillation), cardiac fibrosis (e.g., hypertrophic cardiomyopathy), acute decompensated heart failure, atrial fibrillation);

lung (e.g. chronic obstructive pulmonary disease ("COPD"), pulmonary/lung fibrosis (e.g., idiopathic pulmonary fibrosis ("IPF"), pulmonary arterial hypertension (PAH));

kidney (e.g. diabetic nephropathy, post-acute kidney injury, chronic kidney disease ("CKD"), delayed graft function post- transplantation, renal fibrosis, peritoneal fibrosis and prevention of peritoneal fibrosis in peritoneal dialysis patients (e.g., in end-stage renal patients to delay the time to transition to hemodialysis), focal segmental glomerulosclerosis (FSGS));

liver (e.g. liver cirrhosis, non-alcoholic steatohepatitis ("NASH"), hepatic fibrosis (e.g., post-HCV liver fibrosis));

eye (e.g. glaucoma, corneal scarring);

skeletal muscle (e.g. muscular dystrophies, including Duchenne, Becker, limb- girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery- Dreifuss, repetitive muscle injury);

skin (e.g. keloids, wound healing, adhesions, hypertrophic scarring and other scarring, e.g.,

associated with burns, surgery or other trauma, Dupuytren's contracture, lymphedema, scleroderma);

5 the vasculature (e.g. stroke, and collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma); and

the nervous system (e.g. spinal cord injury, multiple sclerosis).

10 In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from cancer and cancer cell metastasis.

In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from:

15 idiopathic pulmonary fibrosis;
hypertrophic cardiomyopathy; and
prevention of peritoneal fibrosis in peritoneal dialysis patients.

20 In one particular embodiment, the disease associated with BMP1, TLL1 and/or TLL2 activity is NASH (Nonalcoholic steatohepatitis). NASH is a subtype of non-alcoholic fatty liver disease characterized by hepatic inflammation and a substantial risk of progression to cirrhosis with more advanced stages of the disease being characterized by inflammation.

25 In some embodiments, the disease associated with BMP1, TLL1 and/or TLL2 activity is selected from muscular diseases characterized by reduced muscle function and/or mass, e.g., muscular dystrophy (e.g., Duchenne, Becker, limb-girdle, congenital, facioscapulohumeral, myotonic, oculopharyngeal, distal, and Emery- Dreifuss), sarcopenia, and cachexia associated with, e.g., heart failure, CKD, COPD, cancer, or old age.

30 Accordingly, provided is a BMP1, TLL1 and/or TLL2 binding protein as defined herein or a pharmaceutical composition as defined herein for use in the treatment of a fibrosis related disease or disorder as defined herein.

35 According to a further aspect, provided is a method for the treatment of a fibrosis related disease or disorder as defined herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a BMP1, TLL1 and/or TLL2 antigen binding protein as defined herein or a pharmaceutical composition as defined herein.

According to a further aspect, provided is use of a BMP1, TLL1 and/or TLL2 binding protein as defined herein, or a pharmaceutical composition as defined herein in the manufacture of a medicament for use in the treatment of a fibrosis related disease or disorder as defined herein.

- 5 A BMP1, TLL1 and/or TLL2 binding protein as defined herein can also be used to promote muscle growth and/or improve muscle function, for example in cachectic patient populations to reduce frailty (e.g., for muscle wasting).

Thus, according to a further aspect, provided is a method for promoting muscle growth and/or
10 improving muscle function in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a BMP1, TLL1 and/or TLL2 binding protein as defined herein, or a pharmaceutical composition as defined herein.

According to a further aspect, provided is a BMP1, TLL1 and/or TLL2 binding protein as
15 defined herein, or a pharmaceutical composition as defined herein for use in promoting muscle growth and/or improving muscle function.

According to a further aspect, provided is use of a BMP1, TLL1 and/or TLL2 binding protein as defined herein, or a pharmaceutical composition as defined herein in the manufacture of a
20 medicament for promoting muscle growth and/or improving muscle function.

Other features and advantages of the present invention will be apparent from the description provided herein. It should be understood, however, that the description and the specific examples while indicating preferred embodiments of the invention are given by way of
25 illustration only, since various changes and modifications will become apparent to those skilled in the art. The invention will now be described using the following, non-limiting examples:

EXAMPLES

30 Antibody Generation and Characterization

An *in vitro* antibody discovery platform was used to identify and affinity mature a fully human antibody specific for human BMP1/TLL.

Clones from the selection outputs were screened in a series of experiments to understand
35 binding kinetics, potency, and biophysical properties following which a lead panel of 16 monoclonal antibodies with the desired functional properties were selected. The lead panel of 16 antibodies were expressed and purified from HEK293-6E cells for further

functionalization and characterization studies. Functional characterization was carried out against recombinant human and ortholog species, as well as human serum & rat plasma (endogenous expression).

- 5 Because no effector function is required for the desired mechanism of action, residues L235 and G237 within the CH2 domain of the heavy chain constant region were mutated to alanine residues (LAGA mutations). These mutations have previously been shown to remove the ability of IgG1 antibodies to lyse target cells via ADCC or CDC [Bartholomew *et al.* (1995). Immunology 85, 41-48; Bret *et al.* (1997) Immunology 91, 346-353]
- 10 13Y039-4B06-4334 and 13Y039-3E07-2944 were selected for *in vivo* characterisation. These antibodies were cloned as reverse chimeric mAbs with human variable region on the mouse IgG2a LAGA Fc and mouse Kappa (referred to herein as Compound A for 4B06-4334 and Compound B for 3E07-2944) and human variable region on rat IgG2b LAGA Fc
- 15 and rat Kappa (referred to herein as Compound C for 4B06-4334 and Compound D for 3E07-2944). These reverse chimeras were tested in the AngII/PE efficacy studies described below.

Binding characterisation of mammalian expressed anti-BMP1/TLL antibodies

- 20 Binding characterisation of mammalian expressed anti-BMP1/TLL antibodies by surface plasmon resonance (SPR).

Binding of HEK expressed full lead panel to human BMP1 CD+CUB1 by Surface Plasmon Resonance (SPR)

- 25 The 16 lead panel antibodies expressed in HEK cells were evaluated for binding to a truncated version of human BMP containing the catalytic domain and truncated domain (Human BMP1 CD+CUB1 truncated antigen) by SPR using BIACORE T200. HBS-EP+ buffer was used and the experiment run at 25°C. Protein A was immobilised to a CM5 sensor chip via amine coupling. The lead panel antibodies were captured onto protein A surface. Human BMP1
- 30 CD+CUB1 was then passed over the captured antibodies at various concentrations. The results are shown in Table 1 below.

**Table 1: Human antibodies binding to human BMP1 CD+CUB1 truncated antigen.
KD values determined via SPR.**

Antibody Clone Name	KD (nM)	Buffer ¹
13Y039-3E07-2944	4.3	HBS-EP
	4.25	HBS-EP
	0.09	Enzyme Dilution Buffer
	3.66	HBS-EP
	0.05	Enzyme Dilution Buffer
	0.02	Enzyme Dilution Buffer
	0.03	Enzyme Dilution Buffer
13Y039-8F02-2949	1.6	HBS-EP
13Y039-4B06-4376	3.7	HBS-EP
13Y039-4B06-4373	3.3	HBS-EP
13Y039-4B06-4364	2.4	HBS-EP
13Y039-4B06-4351	1.9	HBS-EP
13Y039-4B06-4348	1.5	HBS-EP
13Y039-4B06-4334	0.009	Enzyme Dilution Buffer
	0.01	Enzyme Dilution Buffer
	2.5	HBS-EP
	1.73	HBS-EP
	0.04	Enzyme Dilution Buffer
13Y039-4B06-4328	2.8	HBS-EP
13Y039-4B06-4327	1.5	HBS-EP
13Y039-4B06-4325	2.8	HBS-EP

Antibody Clone Name	KD (nM)	Buffer ¹
13Y039-4B06-4324	3.9	HBS-EP
13Y039-127G03-2890	0.3	HBS-EP
13Y039-152B02-2948	1.4	HBS-EP
13Y039-152B02-2940	1.9	HBS-EP
13Y039-152B02-2935	0.8	HBS-EP

¹ Enzyme dilution buffer = HEPES (25mM), CaCl₂ (5mM), ZnCl₂ solution (1μM) and Brij35 (0.01%); HBS-EP buffer= HEPES (0.2 M), NaCl (3 M), EDTA (60 mM), polysorbate 20 (1.0%), pH 7.6, supplied as 20X (Teknova); HBS-N buffer= HEPES (0.1 M), NaCl (1.5 M), supplied as 10X (Cytiva Life Sciences)

The results in Table 1 demonstrate that all 16 antibodies showed binding to human BMP1 CD+CUB1 and demonstrated affinities in the single digit nM range of 0.3- 4.3 nM. 13Y039-4B06-4334 and 13Y039-3E07-2944 were further evaluated.

Binding of HEK expressed antibodies 13Y039-4B06-4334 and 13Y039-3E07-2944 and reverse chimeras to human TLL2 CD+CUB1 and mouse BMP1 CD+CUB1 by SPR

Both antibodies 13Y039-4B06-4334 and 13Y039-3E07-2944 and the reverse chimeric antibodies were evaluated for binding to human TLL2 CD+CUB1 and mouse BMP1 CD+CUB1 truncated antigens by SPR on a BIACORE T200. Protein A/G was immobilised to a CM5 sensor chip via amine coupling and the antibodies were captured to the protein A/G surface. The antigens were passed over the captured antibody at various concentrations. The measured affinities to human TLL2 CD+CUB1 are shown in Table 2 and the measured affinities to mouse BMP1 CD+CUB1 are shown in Table 3.

Table 2: Antibody binding to human TLL2 CD+CUB1 truncated antigen. KD values determined via SPR.

Ab Clone Name	KD (nM)	Buffer
13Y039-3E07-2944	Non-binder	HBS-EP
	Non-binder	HBS-EP
13Y039-4B06-4334	3.08	HBS-EP

The results in Table 2 demonstrate that 13Y039-4B06-4334 in HBS-EP+ buffer has an affinity of 3.08nM for human TLL2 CD+CUB1 and that 13Y039-3E07-2944 is a non-binder of human TLL2 CD+CUB1.

5 **Table 3: Antibodies binding to mouse BMP1 CD+CUB1 truncated antigen. KD values determined via SPR.**

Ab Clone Name	KD (nM)	Buffer
13Y039-3E07-2944	6.1	HBS-EP
	5.23	HBS-EP
13Y039-4B06-4334	1.7	HBS-EP

The results in Table 3 demonstrate that affinities of both antibodies for mouse BMP1 CD+CUB1 are within the single digit nM range (1.7 – 6.1nM).

10

Reverse chimeric antibodies with a human variable region on a mouse IgG2a LAGA Fc and mouse constant Kappa region were also evaluated for binding to all CD+CUB1 truncates. These experiments included negative antibody controls of anti RSV mouse IgG2a LAGA Fc with a human variable region and mouse constant Kappa region and anti MOPC21 mouse
15 IgG2a. Both negative controls were non binders to all antigens (see Tables 4, 5 and 6).

Affinities of the reverse chimeras to human BMP1 CD+CUB1 are shown in Table 4. When run in HBS-EP+ the affinities for both antibodies are single digit nM (2.33 – 5.31nM). When run in enzyme dilution buffer the affinity is stronger, at double digit pM (40 – 70pM). These results
20 are comparable to the human antibody affinities reported in Table 1

Affinities of the reverse chimeras to human TLL2 CD+CUB1 are shown in Table 5. The affinity measured for 13Y039-4B06-4334 was 3.54nM. 13Y039-3E07-2944 did not bind to human TLL2 CD+CUB1. These results are comparable to the affinities of the human antibodies
25 reported in Table 2

Affinities for the reverse chimeras to mouse BMP1 CD+CUB1 are shown in Table 6. The affinities are in the single digit nM range (0.82 – 6.2nM). These results are comparable to the affinities of the human antibodies reported in Table 3.

30

Both antibody 13Y039-4B06-4334 and its reverse chimera had similar affinity to human BMP1 CD-CUB1, mouse BMP1 CD-CUB1, and human TLL2 CD-CUB1, further supporting the use of the reverse chimera in murine preclinical efficacy studies as a surrogate for 13Y039-4B06-4334.

5

Table 4: Reverse chimeric antibodies with a human variable region on a mouse IgG2a LAGA Fc and mouse constant Kappa region binding to human BMP1 CD+CUB1 truncated antigen. KD values determined via SPR.

Ab Clone Name	KD (nM)	Buffer
13Y039-4B06-4334 human variable region on mouse IgG2a LAGA Fc, mouse cKappa (compound A)	2.33	HBS-EP
	0.04	Enzyme Dilution Buffer
13Y039-3E07-2944 human variable region on mouse IgG2a LAGA Fc, mouse cKappa (Compound B)	0.07	Enzyme Dilution Buffer
	5.31	HBS-EP
Anti RSV human variable region on mouse IgG2a LAGA Fc, mouse cKappa (negative control)	Non-binder	HBS-EP
	Non-binder	Enzyme Dilution Buffer
Anti MOPC21 mouse IgG2a (negative control)	Non-binder	HBS-EP
	Non-binder	Enzyme Dilution Buffer

10

Table 5: Reverse chimeric antibodies with a human variable region on mouse IgG2a LAGA Fc and mouse constant Kappa region, binding to Human TLL2 CD+CUB1 truncated antigen. KD values determined via SPR.

Ab Clone Name	KD (nM)	Buffer
13Y039-4B06-4334 human variable region on mouse IgG2a LAGA Fc, mouse cKappa (Compound A)	3.55	HBS-EP
13Y039-3E07-2944 human variable region on mouse IgG2a LAGA Fc, mouse cKappa (Compound B)	Non binder	HBS-EP
Anti RSV human variable region on mouse IgG2a LAGA Fc, mouse cKappa (negative control)	Non-binder	HBS-EP
Anti MOPC21 mouse IgG2a (negative control)	Non-binder	HBS-EP

Table 6: Reverse chimeric antibodies with a human variable region on mouse IgG2a LAGA Fc and mouse constant Kappa region, binding to mouse BMP1 CD+CUB1 truncated antigen. KD values determined via SPR.

Ab Clone Name	KD (nM)	Buffer
13Y039-4B06-4334 human variable region on mouse IgG2a LAGA Fc, mouse cKappa (Compound A)	0.82	HBS-EP
	1.98	HBS-EP
13Y039-3E07-2944 human variable region on mouse IgG2a LAGA Fc, mouse cKappa (Compound B)	2.66	HBS-EP
	6.2	HBS-EP
Anti RSV human variable region on mouse IgG2a LAGA Fc, mouse cKappa (negative control)	Non-binder	HBS-EP
	Non-binder	HBS-EP
Anti MOPC21 mouse IgG2a (negative control)	Non-binder	HBS-EP
	Non-binder	HBS-EP

- 5 Table 7 is a summary of all kinetic and affinity data for the antibody 13Y039-4B06-4334 expressed in HEK cells binding to all CD+CUB1 antigens. This shows that the antibody has single digit nM affinity for all truncated CD+CUB1 targets when run in HBS-EP+ and the affinity is stronger (40pM) to human BMP1 CD+CUB1 when in enzyme dilution buffer.

Table 7: Affinities and kinetics of the human antibody 13Y039-4B06-4334 binding to human BMP1 CD+CUB1, human TLL2 CD+CUB1 and mouse BMP1 CD+CUB1.

Antigens screened against	Ka (1/Ms)	Kd (1/s)	KD (nM)	Buffer
Human BMP1 CD+CUB1	2.75E+05	6.84E-04	2.5	HBS-EP
	3.67E+05	6.37E-04	1.73	HBS-EP
	6.95E+06	2.49E-04	0.04	Enzyme Dilution Buffer
Human TLL2 CD+CUB1	3.50E+05	10.77E-04	3.08	HBS-EP
Mouse BMP1 CD+CUB1	4.40E+05	7.47E-04	1.7	HBS-EP

- Binding of anti BMP1/TLL antibody 13Y039-4B06-4334 to full length human and orthologue species of BMP1/TLL antigens by Surface Plasmon Resonance (SPR)*
- 13Y039-4B06-4334 was expressed in CHO cells and tested for binding to all full length BMP1 and TLL antigens across human and all orthologue species (cyno, rat and mouse). The proteins used in this assay were recombinant versions of naturally occurring proteins, as compared to the truncated antigens used in the selection assays described above. Results were generated in two buffers: HBS-EP+ and HBS-N + 5mM CaCl₂ and 1μM ZnCl₂. Protein A was immobilised to a CM5 sensor chip via amine coupling and the antibodies were captured to the protein A surface. The antigens were diluted in both buffers and passed over the captured antibody at various concentrations.
- 13Y039-4B06-4334 bound recombinant human BMP1 with an affinity of 23.6 pM, TLL1 with an affinity of 880 pM, and TLL2 with an affinity of 4270 pM. High affinity binding was dependent upon the addition of Zn²⁺ and Ca²⁺, consistent with the importance of these cations in enzyme structure and function.
- The results are shown in Table 8.

Table 8: Binding of anti BMP1/TLL antibody 13Y039-4B06-4334 to full length human and orthologue species of BMP1/TLL antigens.

Antigen	KD in HBS-EP (M)	Average KD in HBS-EP (M)	KD in HBS-N + CaCl ₂ and ZnCl ₂ (M)	Average KD in HBS-N + CaCl ₂ and ZnCl ₂ (M)
Human BMP1-1	3.37E-09	2.87E-09	3.25E-11	2.36E-11
	2.38E-09		1.46E-11	
Mouse BMP1-3: 126-707*	9.77E-09	1.22E-08	3.80E-10	2.65E-10
	1.46E-08		1.50E-10	
Human TLL1	1.15E-08	1.44E-08	7.10E-10	8.80E-10
	1.73E-08		1.05E-09	
Cyno TLL1	1.13E-08	2.02E-08	5.00E-13	6.40E-13
	2.91E-08		7.80E-13	
Mouse TLL1	4.56E+09	4.74E-09	1.08E-09	1.15E-09
	4.93E-09		1.22E-09	
Rat TLL1	6.37E-09	7.73E-09	8.00E-10	1.19E-09
	9.09E-09		1.58E-09	
Human TLL2	NA ¹	NA	4.45E-09	4.27E-09
	NA		4.10E-09	
Cyno TLL2	2.80E-08	3.25E-08	6.86E-09	6.44E-09
	3.69E-08		6.01E-09	
Rat TLL2	9.47E-09	8.71E-09	2.90E-10	2.80E-10
	7.95E-09		2.70E-10	

¹NA= binding data not generated for this enzyme

***In vitro* target engagement potency**

Screening of mammalian expressed lead panel of 16 anti-BMP-1/TLL monoclonal antibodies (mAbs), using FRET based assays, for activity against recombinant human BMP-1-1, human
5 *TLL-1, mouse BMP-1-3 (707 truncate), mouse TLL-1, rat TLL-1, rat TLL-2 and cynomolgus TLL-1 enzymes*

Activity of BMP-1/TLL enzymes was detected using assays based on fluorescence resonance energy transfer (FRET). A peptide substrate spanning the BMP1/TLL cleavage site of
10 physiological protein substrate prolyl oxidase was labeled with two fluorophores, specifically a donor and quencher (acceptor) molecule (hereafter referred to as the "prolyl oxidase FRET peptide"). When the donor fluorophore is excited by light at its excitation wavelength, a transient higher wavelength light emission is usually produced as the molecule returns to its ground state. However, in the FRET peptide, the close proximity of the acceptor fluorophore
15 results in transfer of this energy versus emission of fluorescence signal and effectively quenches fluorescence. Cleavage of the peptide substrate by an enzyme (in this case BMP-1, TLL-1 or TLL-2 of the relevant species) results in separation of the fluorophores which permits fluorescence emission from the donor fluorophore. Antibody inhibition of BMP1/TLL enzyme mediated breakdown of the peptide was determined by measuring the donor
20 emission.

A serial dilution of antibody samples was prepared in enzyme dilution buffer. The antibody samples were pre-incubated with enzyme (diluted in enzyme dilution buffer) with gentle agitation. Following this pre-incubation, the prolyl oxidase FRET peptide was added and
25 incubated. After incubation, the enzyme reaction was stopped with EDTA. Fluorescence was measured using an excitation wavelength of 485 nm and an emission wavelength of 535 nm. Screening was performed on the lead panel of 16 antibodies produced in HEK cells. IC₅₀ values were calculated and compared (Table 9). In this initial screen the 4B06 family showed effective inhibition of human BMP-1 with IC₅₀ values between 0.01nM and 0.09nM; which were
30 typically lower than other families tested. Initial 13Y039-4B06-4334 IC₅₀ values demonstrated effective inhibition across all enzymes: huBMP-1 (IC₅₀), 0.03nM; huTLL-1, 0.02nM; huTLL-2, 0.03nM; mTLL-1, 0.06nM; cynoTLL1, 0.05nM.

Table 9: Summary of initial screening of lead panel of antibodies against huBMP-1, huTLL-1, mTLL-1, cynoTLL-1, and huTLL-2.¹

Antibody Clone	62.5 pM huBMP1	250pM Biotinylated huTLL-1	800pM Biotinylated mTLL-1	750pM Biotinylated cynoTLL-1	500pM huTLL-2
	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)	IC ₅₀ (nM)
13Y039-127G03-2890	0.40	18.20	0.88	0.22 (AL)	0.15 (AL)
13Y039-152B02-2935	0.25	0.09 (AL)	0.07 (AL)	0.11 (AL)	0.20 (AL)
13Y039-152B02-2948	0.31	0.08 (AL)	0.11 (AL)	0.07 (AL)	0.86
13Y039-152B02-2940	0.13	0.05 (AL)	0.10 (AL)	0.06 (AL)	0.28
13Y039-3E07-2944	0.40	0.14	0.14 (AL)	0.10 (AL)	≥398.11
13Y039-4B06-4324	0.02 (AL)	0.03 (AL)	0.10 (AL)	0.07 (AL)	0.04 (AL)
13Y039-4B06-4325	0.03 (AL)	0.02 (AL)	0.07 (AL)	0.05 (AL)	0.05 (AL)
13Y039-4B06-4327	0.01 (AL)	0.01 (AL)	0.04 (AL)	0.02 (AL)	0.03 (AL)
13Y039-4B06-4328	0.03 (AL)	0.04 (AL)	0.07 (AL)	0.07 (AL)	0.02 (AL)
13Y039-4B06-4334	0.03 (AL)	0.02 (AL)	0.06 (AL)	0.05 (AL)	0.03 (AL)
13Y039-4B06-4348	0.02 (AL)	0.04 (AL)	0.12 (AL)	0.18 (AL)	0.04 (AL)
13Y039-4B06-4351	0.03 (AL)	0.05 (AL)	0.14 (AL)	0.13 (AL)	0.03 (AL)
13Y039-4B06-4364	0.02 (AL)	0.06 (AL)	0.13 (AL)	0.11 (AL)	0.05 (AL)
13Y039-4B06-4373	0.09	0.04 (AL)	0.13 (AL)	0.08 (AL)	0.10 (AL)
13Y039-4B06-4376	0.05	0.07 (AL)	0.16 (AL)	0.15 (AL)	0.09 (AL)
13Y039-8F02-2949	0.06	FAIL	0.56	0.02 (AL)	FAIL

¹ "(AL)" indicates that the measured IC₅₀ value was below the assay limit, meaning that any difference in these values may not be significantly different from one another as the assay is not sensitive enough to separate the molecules

Three antibodies were further characterized: 13Y039-3E07-2944, 13Y039-8F02-2949, and 13Y039-4B06-4334. They were tested to investigate inhibition of huBMP-1, mBMP-1, huTLL-1, huTLL-2, mTLL-1, ratTLL-1, ratTLL-2 cynoTLL-1, and cynoTLL-2 activity. Full dose-response curves were plotted for each enzyme, with a representative graph for each enzyme shown in Figures1-9 (Figure 1, huBMP-1; Figure 2, mBMP-1; Figure 3, huTLL-1; Figure 4,

huTLL-2; Figure 5, mTLL-1; Figure 6, ratTLL-1; Figure 7, rat TLL-2; Figure 8, cynoTLL-1; Figure 9, cynoTLL-2).

Antibody 13Y039-4B06-4334 inhibited all enzymes tested. IC₅₀ values across all experiments are shown in Table 10, with mean and standard deviation calculated. The mean IC₅₀ values for each enzyme were: huBMP-1, 0.04nM; huTLL-1, 0.05nM; huTLL-2, 0.05nM; mBMP-1, 0.02nM; mTLL-1, 0.23nM; ratTLL-1, 0.50nM; ratTLL-2, 0.67nM; cynoTLL-1, 0.10nM; cynoTLL-2, 0.31nM.

Table 10: Summary data table of Antibody 13Y039-4B06-4334 IC₅₀ values across all experiments.

	62.5pM Human BMP-1 IC ₅₀ (nM)	250pM BT Human TLL-1 IC ₅₀ (nM)	500pM Human TLL-2 IC ₅₀ (nM)	50pM Mouse BMP-1 IC ₅₀ (nM)	800pM BT Mouse TLL-1 IC ₅₀ (nM)	2.5nM Rat TLL-1 IC ₅₀ (nM)	2.5nM Rat TLL-2 IC ₅₀ (nM)	750pM BT Cyno TLL-1 IC ₅₀ (nM)	8nM BT Cyno TLL-2 IC ₅₀ (nM)
13Y039-4B06-4334 - Mean IC₅₀ (Standard Deviation)	0.04 (0.03)	0.05 (0.03)	0.05 (0.01)	0.02 (0.00)	0.23 (0.12)	0.50 (0.09)	0.67 (0.21)	0.10 (0.04)	0.31 (0.12)

13Y039-4B06-4334 was expressed in HEK and CHO cells and inhibition of recombinant human BMP1, human TLL1, and human TLL2 activity by the HEK- and CHO-expressed protein batches was measured by FRET generally as described above. Potencies were comparable between HEK293-expressed and polyclonal CHO-expressed protein batches (Table 11) when profiled against recombinant human BMP1, human TLL1, human TLL2, and human serum.

Table 11: Inhibition of recombinant human BMP1, TLL1 and TLL2 and inhibition of human serum BMP1/TLL activity by 13Y039-4B06-4334

	Human BMP1 pK_{i,app}	Human TLL1 pIC₅₀	Human TLL2 pIC₅₀	Human serum pIC₅₀
HEK-expressed 13Y039-4B06- 4334	11.09 ± 0.01	10.8 ± 0.5	10.6 ± 0.1	9.5 ± 0.5
HEK-expressed 13Y039-4B06- 4334	11.08 ± 0.02	10.2 ± 0.2	10.3 ± 0.1	
CHO-expressed 13Y039-4B06- 4334	11.07 ± 0.11	10.4 ± 0.2	10.5 ± 0.1	9.4 ± 0.2

- In order to test the biological efficacy of 13Y039-4B06-4334 in preclinical rodent species, reverse chimeras consisting of the variable domain of 13Y039-4B06-4334 fused to the mouse or rat IgG2a Fc-disabled were generated. These constructs were profiled for activity against recombinant human BMP1 and mouse BMP1, as well as human serum, mouse plasma, and rat plasma using the prolyl oxidase FRET peptide as described above.
- 10 The reverse chimeric antibodies and the antibody 13Y039-4B06-4334 had similar pK_i, app values in both the recombinant human BMP1 and mouse BMP1 assays, supporting their use in preclinical efficacy studies as a surrogate for 13Y039-4B06-4334. Activity in human serum and mouse or rat plasma was confirmed for 13Y039-4B06-4334 and the reverse chimeric antibodies (Table 12).

Table 12: Inhibition of recombinant human BMP1 and BMP1/TLL activity in human serum, mouse plasma, and rat plasma by the reverse chimeras of 13Y039-4B06-4334

	Human BMP1 pK _{i,app}	Mouse BMP1 pK _{i,app}	Human serum pIC ₅₀	Mouse plasma pIC ₅₀	Rat plasma pIC ₅₀
13Y039-4B06-4334	11.7	11.1	9.5 ± 0.5 (n=7)		9.8 ± 1.1 (n=2)
13Y039-4B06-4334 reverse chimera mouse IgG2a LAGA (Compound A)	12.3	11.4	10.1 (n=1)	7.5 (n=1)	
13Y039-4B06-4334 reverse chimera rat IgG2a LAGA (Compound C)	11.8	11.3	8.7 (n=1)		9.1 ± 0.5 (n=2)

5 Binding to Fcγ receptors, FcRN and C1q

Binding of anti-BMP1/TLL antibodies including 13Y039-4B06-4334 on an hIgG1 LAGA backbone to soluble recombinant Fcγ receptors, FcRn and C1q was determined by surface plasmon resonance (SPR).

- 10 The HEK expressed antibodies 13Y039-4B06-4334 and 13Y039-3E07-2944, and the CHO expressed antibody 13Y039-4B06-4334 were assessed for binding to recombinant soluble human Fc gamma receptors (FcγR). Antibodies were analysed against a positive control antibody containing a wild type human IgG1 Fc region (Fix Fc+) and a negative control antibody containing two point mutations (L235A/G237A) in the Fc region which reduce the
- 15 interaction with Fc gamma receptors (Fix Fc-). Binding of HEK-expressed 13Y039-4B06-4334, CHO-expressed 13Y039-4B06-4334, and HEK-expressed 13Y039-3E07-2944 to human Fcγ receptors, mouse Fcγ receptors, and cynomolgus macaque Fcγ receptors was assessed by SPR with the Fcγ receptor captured on the surface and the antibody to be tested flowed over the receptor at the desired concentration.

20

As expected with the Fc-disabling mutations, all antibodies having an hIgG1 LAGA backbone did not bind human Fcγ receptors (FcγRI, FcγRIIaH, FcγRIIaR, FcγRIIb, FcγRIIIaV, and FcγRIIIaF), mouse Fcγ receptors (FcγRI, FcγRIIb, FcγRIIIa/b, and FcγRIV),

or cynomolgus macaque Fcγ receptors (FcγRIIIa, FcγRIIb, and FcγRIII), therefore reducing the potential to induce antibody-dependent cytotoxicity (ADCC).

Binding of anti-BMP1/TLL antibodies to the human, cyno, and mouse neonatal Fc receptor FcRn was assessed by SPR. 13Y039-4B06-4334, 13Y039-3E07-2944 and human IgG1 WT control Fix Fc+ were assessed for binding to recombinant soluble human and cyno FcRn. Compound A (13Y039-4B06-4334, mIgG2a LAGA), Compound B (13Y039-3E07-2944, mIgG2a LAGA), anti-RSV mouse IgG2a LAGA, Anti-RSV rat IgG2b LAGA, Compound C (13Y039-4B06-4334 rat IgG2b LAGA), and Compound D (13Y039-3E07-2944 rat IgG2b) were assessed for binding to recombinant soluble mouse FcRn. Fix Fc+, rat IgG2b wild type control and mouse IgG2a control (anti-MOPC) were included. Human and cyno FcRn were tested with hIgG1, and mouse FcRn was tested with rat IgG2b and mIgG2a

13Y039-4B06-4334 and 13Y039-3E07-2944 showed binding to human and cyno FcRn at pH 6 but not at pH 7.4, indicating that the LAGA mutations have not affected binding to human or cyno FcRn. The relative binding affinity of CHO-expressed 13Y039-4B06-4334 for human FcRn was comparable to that of the IgG1 (Fix Fc+) control antibody. Compound A, Compound B and Compound D showed binding to mouse FcRn at pH 6 but not at pH 7.4. Capture of Compound C on the Protein A surface was very unstable, so there was insufficient antibody on the surface to assess binding to mouse FcRn.

Binding of 13Y039-4B06-4334 to human C1q was assessed by SPR with Fix Fc+ and Fix Fc- used as controls. Antibodies were diluted and immobilised via amine coupling to the sensor chip. Human C1q was diluted in HBS-N + 10mM CaCl₂ and injected over the immobilized constructs. Fix Fc+ showed binding as expected to C1q (K_D = 36.3 nM), and Fix Fc- showed no binding to C1q, as is expected for an Fc disabled antibody. 13Y039-4B06-4334 showed binding comparable to the Fix Fc+ control antibody (K_D=36.3 nM).

Binding of 13Y039-4B06-4334 to human C1q was also assessed in an ELISA. Human C1q protein was added to antibody and binding was detected using anti-C1q biotin detection reagent and streptavidin-HRP. The colorimetric signal was detected using SureBlue TMB and the colorimetric reaction was allowed to develop and then measured at 450nm. The positive control test mAb (anti-RSV IgG1) showed a dose-response effect as expected, while the negative control test mAb (anti-RSV LAGA) showed minimal binding to C1q which was as expected. ELISA confirmed that CHO-expressed 13Y039-4B06-4334 binds to C1q with a similar affinity to the hIgG1 WT control.

13Y039-4B06-4334 expressed in both HEK and CHO cells binds to human C1q at a higher level than the positive binding control antibody, anti-RSV IgG1 with a wildtype Fc. Each data point in Figure 10 is representative of n=3 experiments with the exception of 13Y039-4B06-4334 expressed in CHO cells which was only repeated once, but data showed that the molecule behaved comparably to the other CHO material, and anti-RSV WT which represents n=2 because of its known binding activity.

Taken together, these results demonstrate that 13Y039-4B06-4334 is Fc disabled with respect to binding to human and cyno Fcγ receptors, although binding is still seen to human C1q. The Fc disabling mutations have not affected binding to human FcRn.

***In vitro* cellular activity**

13Y039-4B06-4334 also inhibits BMP1-catalyzed cleavage of its native substrate, procollagen I, in a fibroblast-based collagen formation assay ("scar-in-a-jar", SIJ). In this assay, stimulation of human primary cardiac fibroblasts with FicolI induces procollagen formation and cleavage by endogenous BMP1, as measured by the release of procollagen type I C-terminal peptide (PICP). 13Y039-4B06-4334 inhibited PICP formation in a dose-dependent manner, demonstrating that the antibody blocks cleavage of this endogenous protein substrate and attenuates a key element of the fibrosis mechanism in a disease-relevant cell type. Across multiple studies, the average pIC50 value for 13Y039-4B06-4334 in normal human cardiac fibroblasts (NHCFs) was 9.6 ($\pm$ 0.2, n=3).

The mouse reverse chimera for 13Y039-4B06-4334 (compound A) showed activity in the SIJ assay with a pIC50 of 9.8 ($\pm$ 0.6, n=2), comparable to that observed for 13Y039-4B06-4334.

Myostatin latent complex cleavage assay

Anti-BMP1/TLL antibodies were profiled for inhibition of human BMP-1 in cleaving the myostatin latent complex. Recombinant human BMP-1 was pre-treated with a concentration range of anti-BMP1/TLL antibodies before addition to recombinant human myostatin latent complex. BMP-1 alone cleaved the myostatin latent complex, releasing active myostatin which was measured to indicate the activity of BMP-1. When BMP-1 was pre-incubated with anti BMP1/TLL antibodies, overall its enzymatic activity decreased with an increase in antibody concentration. The levels of myostatin released from the complex were measured in a meso scale discovery (MSD) assay which used an anti-myostatin antibody for capture and detection of the myostatin homodimer. The MSD measurements of the myostatin levels were used to calculate the % inhibition of the anti-BMP1/TLL antibodies.

The data in Figure 11 shows that the anti-BMP1/TLL antibody 13Y039-4B06-4334 inhibited BMP1 cleavage of the myostatin latent complex in a dose responsive manner. These results confirm that 13Y039-4B06-4334, inhibits BMP1 enzymatic activity as BMP-1 is prevented from cleaving the myostatin latent complex to release myostatin.

5

***In vivo* Target Engagement, Pharmacodynamic Markers, Antifibrotic and Anabolic Activity**

Pharmacodynamic Markers in the Mouse AngII/PE Model

- 10 Mice administered angiotensin-II (AngII) and phenylephrine (PE) by subcutaneous osmotic pump develop cardiac fibrosis over a two-week treatment period (hereafter referred to as the AngII/PE model). This AngII/PE model was used to evaluate the effect of Compound A, a reverse chimeric construct combining the variable region of 13Y039-4B06-4334 with a murine IgG2a LAGA Fc domain, on pharmacodynamic markers of BMP1 inhibition and cardiac
- 15 fibrosis. Starting at the time of osmotic pump implantation, mice were dosed once-weekly for two weeks. The anti-RSV (mouse IgG2a LAGA/mouse cK) and MOPC-21 (mouse variable and constant region mouse IgG2a/mouse cK) antibodies were used as controls. 13Y039-152B02-1 ("B02") is the mouse reverse chimera (human variable region on a mouse IgG2a/mouse cK) tool anti-BMP1/TLL mAb, while Compound B is the mouse reverse chimera
- 20 (mouse IgG2a LAGA/mouse cK) of another antibody, 13Y039-3E07-2944. In this study, both Compound A/B02 and Compound B inhibited *ex vivo* BMP1 activity from harvested plasma in a dose-dependent manner (Figure 12).

- Using a western blot assay, a significant reduction in circulating procollagen type I C-terminal
- 25 peptide (PICP) levels in AngII/PE mice treated with 5 mg/kg Compound A was also detected (Figure 13).

- An additional effect of Compound A in the mouse AngII/PE model was a significant increase in skeletal muscle mass at high levels of BMP1 inhibition. AngII/PE infusion resulted in a
- 30 significant reduction in left gastrocnemius weight, normalized to total body weight (6.24 ± 0.10 mg/g vs. 5.89 ± 0.08 mg/g, $p < 0.01$, by unpaired t-test). Treatment with Compound A at both 0.5 mg/kg and 5 mg/kg resulted in a restoration of muscle mass to a level greater than the saline osmotic pump control (Figure 14). Accompanying this observation was an accumulation of total myostatin in the plasma of these animals, as determined using a commercial ELISA
- 35 assay that detects total (i.e. free and bound) myostatin species (Figure 15).

Circulating myostatin has been shown to be mostly bound in a latent complex, MSTN-LC, by its inhibitory prodomain fragment (>70% in mouse, with the remainder as other inhibitory complexes; Hill, 2002). Cleavage of the prodomain by BMP1/TLL liberates active myostatin, which signals as a negative growth factor. Thus, the increase in muscle mass and total plasma myostatin levels with Compound A dosing may arise from decreased degradation by BMP1/TLL of the prodomain, and subsequent relief of negative growth regulation that would otherwise accompany release of mature myostatin at local tissue sites in skeletal muscle.

Antifibrotic effects of the mouse reverse chimera (Compound A) in the murine AngII/PE model

Two-week infusion of AngII/PE in mice leads to a significant increase in collagen production in cardiac tissue, as measured by left ventricular hydroxyproline (HDXP) content (compare the two first bars in Figure 16), as measured by liquid chromatography/mass spectrometry (LC/MS).

In this model, treatment with Compound A yielded a reduction (47% at 0.5 mg/kg and 58% at 5 mg/kg) in HDXP content that was statistically significant when compared to either the AngII/PE control or the dose-paired anti-RSV mAb controls. Despite the reduction in this fibrosis biomarker, however, no significant change in fibrosis by histopathological analyses was observed.

Effects of the rat reverse chimera (Compound C) in the Dahl salt-sensitive rat model

When fed high-salt chow (8% NaCl), the Dahl salt-sensitive (Dahl S) rat strain rapidly develops hypertension and associated comorbidities, such as renal dysfunction, hyperlipidemia, and insulin resistance. In previous studies, it was shown that this strain also develops cardiac and renal fibrosis.

To assess the cardiac antifibrotic effects of BMP1 inhibition in this model, Dahl S rats were fed 0.3% NaCl chow (normal salt content) until 4-5 weeks of age; this was increased on Day 0 to 1% NaCl chow and then on Day 7 to 8% NaCl chow. 5 mg/kg anti-RSV mAb control, or 5 mg/kg Compound C (the rat reverse chimera of 13Y039-4B06-4334, n=12 for each group) was dosed subcutaneously on a weekly basis from Day 0 to Day 28 and rats were sacrificed on Day 35. The study included a control group (n=12) that received a 0.3% diet and vehicle injections throughout. For both Compound C and the anti-RSV control, exposures at both peak and trough were within the anticipated target range between the rat plasma assay (Table 12) IC90 and IC95 values of 1,180 and 11,800 ng/mL.

At the end of the study, sections of the left ventricles were stained with Masson's Trichrome to identify fibrotic areas, which were quantified by image analysis. Vehicle-injected rats on 8% NaCl chow exhibited a significant increase in LV fibrosis (~24%) as compared to the normal salt controls, indicating a model effect. Treatment with Compound C, but not the anti-RSV control mAb, yielded a significant reduction (~88%) in LV fibrosis compared to vehicle-treated controls (Figure 17A).

To assess the muscle effects of BMP1 inhibition in this model, the gastrocnemius muscle was isolated and weighed at the end of the study. As had been observed in the AngII/PE model (Figure 14), treatment with the anti-BMP1 antibody yielded a significant increase (e.g., 9% vs. PBS+8% NaCl) in skeletal muscle mass, when compared to the vehicle or control animals (Figure 17B).

Anabolic effects of the mouse reverse chimera (Compound A) in the murine hindlimb immobilization model

To assess the effect of BMP1 inhibition on skeletal muscle growth and function, the reverse chimera Compound A was tested in the murine hindlimb immobilization model. In the first study, designed to test muscle recovery after immobilization, aged mice (males, 22 months old) received a splint to immobilize their right hindlimb for 2 weeks. After removal of the splint, the mice were placed in one of three treatment groups and dosed for 2 weeks with either (i) anti-RSV control mAb, 5mg/kg/week, s.c; (ii) Compound A, 5mg/kg/week, s.c; or (iii) anti-myostatin mAb (positive control), 30mg/kg, 3 doses over 2 weeks, s.c (n=10 per group). Body composition, as measured by quantitative NMR (qNMR), skeletal muscle function, and muscle wet weights were determined after this two-week recovery period. Pharmacodynamic markers associated with BMP1 inhibition were all significantly impacted in the Compound A-treated group, including a 92% reduction in plasma BMP1 activity, a 77% reduction in plasma PICP, and 7.9-fold increase in total myostatin levels. Two-week treatment with Compound A resulted in an ~5% increase in lean mass, significantly greater than that observed with the control anti-RSV mAb (Figure 18).

In addition, treatment with Compound A resulted in an increase in gastrocnemius and soleus wet weights in both the control and splinted limbs, as measured at the completion of the 2-week recovery period. This increase was significantly greater than that observed for the control-treated mice (Figure 19).

Along with the observed increases in muscle mass, which had been previously noted in the AngII/PE model, treatment with Compound A also yielded a significant improvement in muscle

function. The increase in muscle mass was not proportional to the increase in force, resulting in a decrease in force:muscle weight ratio (far right panel of Figure 20), a phenomenon which has been observed in previously generated myostatin knockout mouse strains (Amthor, 2007).

- 5 The results from this study demonstrate that inhibition of BMP1/TLL by Compound A not only promotes skeletal muscle growth in recovery from disuse atrophy in aged mice, but also yields an improvement in muscle function. These results suggest that inhibition of BMP1/TLL by 13Y039-4B06-4334 in the clinical setting would have a benefit in patient populations where frailty and skeletal muscle loss accompany ongoing fibrotic processes.

10

Pharmacokinetics of 13Y039-4B06-4334

The pharmacokinetics of 13Y039-4B06-4334 were determined following both single and repeat dosing in Wistar Han rats.

15 *Single dose pharmacokinetics in rat*

The pharmacokinetics of 13Y039-4B06-4334 were determined following a single intravenous (bolus) or single subcutaneous administration at a nominal dose of 1 mg/kg in Wistar Han rats (n=3).

- 20 The individual and mean pharmacokinetic parameters following a single intravenous or subcutaneous administration at 1 mg/kg are presented in Table 13. 13Y039-4B06-4334 is cleared slowly with a mean terminal half-life of approximately 5 days, excluding animal 1, which had a notably faster clearance. The mean volume of distribution, 94 mL/kg, is close to blood volume suggesting the antibody is mainly confined to the systemic circulation.

Table 13: The pharmacokinetic parameters of 13Y039-4B06-4334 in Wistar Han rats following a single intravenous or subcutaneous administration at a nominal dose of 1mg/kg.

5

Animal	C _{max} (µg/mL)	T _{max} (hr)	AUC (hr*µg/mL)	AUC _{inf} (hr*µg/mL)	Half-life (hr)	MRT (hr)	Cl/ Cl_F* (mL/hr/kg)	V _{ss} / V _{z_F} * (mL/kg)
Intravenous Data								
4	27.2	3	1870	1920	129	138	0.521	81.7
5	20.9	0.25	1830	2310	117	173	0.433	134
6	24.1	0.25	1390	1410	121	120	0.707	94.2
Mean	24.1	0.25**	1700	1880	122	144	0.554	103
Subcutaneous Data								
1	8.19	72	1480	n/a	n/a	n/a	n/a	n/a
2	9.32	72	1940	1990	116	182	0.502	83.9
3	7.77	72	1890	1930	103	191	0.519	76.8
Mean	8.43	72	1770	1960	110	187	0.511	80.4

*CL_F and V_{z_F} are calculated for subcutaneous administration. ** Median reported

Repeat dose pharmacokinetics in rat

- 10 Following weekly subcutaneous dosing at 1 mg/kg for 4 weeks, two of the three animals maintained expected exposure (C_{max} and AUC₆₋₁₆₈). The level of accumulation (2.9-fold increase in AUC₆₋₁₆₈) was as expected for a monoclonal antibody with a 5 day half-life (Table 14). The reduced exposure seen in the third animal could be due to an ADA response, but this could not be confirmed.

15

Table 14: The pharmacokinetic parameters of 13Y039-4B06-4334 in Wistar Han rats following 4 weekly subcutaneous doses of 1 mg/kg.

Parameter		Animal 16	Animal 17	Animal 18	Mean
Week 1	C _{max} (µg/mL)	6.92	5.94	5.62	6.16
	AUC (hr*µg/mL)	741	708	746	732
Week 4	C _{max} (µg/mL)	2.61	15.7	13.3	14.5*
	AUC (hr*µg/mL)	176	2320	1990	2160*

20

*Excludes one animal

EMBODIMENTS

Embodiment 1 is a BMP1, TLL1 and/or TLL2 binding protein, which comprises:

- (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from
 5 SEQ ID NO: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, and 222 and/or
 CDRL1, CDRL2, CDRL3 from SEQ ID NO: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165,
 179, 193, 208, and 221; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino
 acid modifications; or
- (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ
 10 ID NO: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, or 222 and/or a VL
 region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 8, 21,
 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, or 221.

- Embodiment 2 is the BMP1, TLL1 and/or TLL2 binding protein according to embodiment 1,
 15 wherein the CDR of (a)(i) is: CDRL1 of SEQ ID NO: 1; CDRL2 of SEQ ID NO: 2; CDRL3 of
 SEQ ID NO: 3; CDRH1 of SEQ ID NO: 4; CDRH2 of SEQ ID NO: 5; and/or CDRH3 of SEQ
 ID NO: 6.

- Embodiment 3 is the BMP1, TLL1 and/or TLL2 binding protein according to embodiment 1 or
 20 2, comprising one or more of:

- a LCDR1 comprising a sequence having at least 80% sequence identity with
 RASQSVSSYLA (SEQ ID NO: 1); and/or
- a LCDR2 comprising a sequence having at least 80% sequence identity with
 DASNRAT (SEQ ID NO: 2); and/or
- 25 a LCDR3 comprising a sequence having at least 80% sequence identity with
 QQSDSWPPT (SEQ ID NO: 3); and/or
- a HCDR1 comprising a sequence having at least 80% sequence identity with GYYMS
 (SEQ ID NO: 4); and/or
- a HCDR2 comprising a sequence having at least 80% sequence identity with
 30 WINPLSGETNYAQKFQG (SEQ ID NO: 5); and/or
- a HCDR3 comprising a sequence having at least 80% sequence identity with
 DTGELDGMNWFYFDL (SEQ ID NO: 6).

- Embodiment 4 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of
 35 embodiments 1 to 3, which comprises a VH region comprising a CDR1 comprising a sequence
 having at least 80% sequence identity with GYYMS (SEQ ID NO: 4); a CDR2 comprising a
 sequence having at least 80% sequence identity with WINPLSGETNYAQKFQG (SEQ ID NO:

5); and/or a CDR3 comprising a sequence having at least 80% sequence identity with DTGELDGMNWFYDL (SEQ ID NO: 6).

5 Embodiment 5 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of embodiments 1 to 4, which comprises a VH region comprising a CDR1 comprising a sequence of GYYMS (SEQ ID NO: 4), a CDR2 comprising a sequence of WINPLSGETNYAQKFQG (SEQ ID NO: 5) and/or a CDR3 comprising a sequence of DTGELDGMNWFYDL (SEQ ID NO: 6).

10 Embodiment 6 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of embodiments 1 to 5, which comprises a VL region comprising a CDR1 comprising a sequence having at least 80% sequence identity with RASQSVSSYLA (SEQ ID NO: 1); a CDR2 comprising a sequence having at least 80% sequence identity with DASNRAT (SEQ ID NO: 2); and/or a CDR3 comprising a sequence having at least 80% sequence identity with
15 QQSDSWPPT (SEQ ID NO: 3).

Embodiment 7 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of embodiments 1 to 6, which comprises a VL region comprising a CDR1 comprising a sequence of RASQSVSSYLA (SEQ ID NO: 1); a CDR2 comprising a sequence of DASNRAT (SEQ ID
20 NO: 2); and/or a CDR3 comprising a sequence of QQSDSWPPT (SEQ ID NO: 3).

Embodiment 8 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of embodiments 1 to 7, which comprises a LCDR1 comprising a sequence of RASQSVSSYLA (SEQ ID NO: 1), a LCDR2 comprising a sequence of DASNRAT (SEQ ID NO: 2); a LCDR3
25 comprising a sequence of QQSDSWPPT (SEQ ID NO: 3); a HCDR1 comprising a sequence of GYYMS (SEQ ID NO: 4); a HCDR2 comprising a sequence of WINPLSGETNYAQKFQG (SEQ ID NO: 5); and/or a HCDR3 comprising a sequence of DTGELDGMNWFYDL (SEQ ID NO: 6).

30 Embodiment 9 the BMP1, TLL1 and/or TLL2 binding protein according to any one of embodiments 1 to 8, wherein all 6 CDRs are present in the binding protein.

Embodiment 10 is a BMP1, TLL1 and/or TLL2 binding protein comprising the following 6 CDRs:

35 LCDR1 of RASQSVSSYLA (SEQ ID NO: 1);
LCDR2 of DASNRAT (SEQ ID NO: 2);
LCDR3 of QQSDSWPPT (SEQ ID NO: 3);

HCDR1 of GYYMS (SEQ ID NO: 4);
HCDR2 of WINPLSGETNYAQKFQG (SEQ ID NO: 5); and
HCDR3 of DTGELDGMNWFYDL (SEQ ID NO: 6).

- 5 Embodiment 11 is the BMP1, TLL1 and/or TLL2 binding protein according to embodiment 10, wherein the binding protein comprises a VH region that is 80% identical to SEQ ID NO: 7 and/or a VL region that is 80% identical to SEQ ID NO: 8.

- Embodiment 12 is the BMP1, TLL1 and/or TLL2 binding protein according to embodiment 10
10 or embodiment 11, wherein the binding protein comprises a VH region that is 100% identical to SEQ ID NO: 7 and/or a VL region that is 100% identical to SEQ ID NO: 8.

- Embodiment 13 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of
embodiments 10 to 12, wherein the binding protein comprises a heavy chain (HC) sequence
15 at least 80% identical to SEQ ID NO: 10; and/or a light chain (LC) sequence at least 80% identical to SEQ ID NO: 9.

- Embodiment 14 is the BMP1, TLL1 and/or TLL2 binding protein according to any one of
embodiments 10 to 13, wherein the binding protein comprises a heavy chain (HC) sequence
20 that is 100% identical to SEQ ID NO: 10; and/or a light chain (LC) sequence that is 100% identical to SEQ ID NO: 9.

- Embodiment 15 is a BMP1, TLL1 and/or TLL2 binding protein, which comprises a VH region
that is 100% identical to SEQ ID NO: 7 and a VL region that is 100% identical to SEQ ID NO:
25 8.

- Embodiment 16 is the BMP1, TLL1 and/or TLL2 binding protein according to embodiment 15,
which comprises a light chain that is 100% identical to SEQ ID NO: 9 and a heavy chain that
is 100% identical to SEQ ID NO: 10.

- 30 Embodiment 17 is a polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 binding protein according to any one of embodiments 1 to 16.

- Embodiment 18 is the polynucleotide sequence according to embodiment 17, which
35 comprises SEQ ID NO: 13 encoding the heavy chain; and/or SEQ ID NO: 14 encoding the light chain.

Embodiment 19 is an expression vector comprising the polynucleotide sequence as defined in embodiment 17 or embodiment 18.

5 Embodiment 20 is a recombinant host cell comprising the polynucleotide sequence as defined in embodiment 17 or embodiment 18, or the expression vector as defined in embodiment 19.

Embodiment 21 is a method for the production of a BMP1, TLL1 and/or TLL2 binding protein, which method comprises culturing the recombinant host cell of embodiment 20 under conditions suitable for expression of the polynucleotide sequence or expression vector,
10 whereby a polypeptide comprising the BMP1, TLL1 and/or TLL2 binding protein is produced.

Embodiment 22 is the BMP1, TLL1 and/or TLL2 binding protein produced by the method of embodiment 21.

15 Embodiment 23 is a pharmaceutical composition comprising the BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments 1 to 16 or embodiment 22, and a pharmaceutically acceptable diluent or carrier.

Embodiment 24 is a pharmaceutical composition according to embodiment 23, comprising the
20 BMP1, TLL1 and/or TLL2 binding protein as defined in embodiment 15 or embodiment 16.

Embodiment 25 is a method for the treatment of a fibrosis related disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments
25 1 to 16 or embodiment 22, or the pharmaceutical composition as defined in embodiment 23 or embodiment 24 to the subject.

Embodiment 26 is the method according to embodiment 25, wherein the subject is a human.

30 Embodiment 27 is a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments 1 to 16 or embodiment 22, or a pharmaceutical composition as defined in embodiment 23 or embodiment 24 for use in therapy.

Embodiment 28 is a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of
35 embodiments 1 to 16 or embodiment 22, or a pharmaceutical composition as defined in embodiment 23 or embodiment 24 for use in the treatment of a fibrosis related disease or disorder.

Embodiment 29 is use of a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments 1 to 16 or claim 22, or a pharmaceutical composition as defined in embodiment 23 or 24 in the manufacture of a medicament for use in the treatment of a fibrosis related disease or disorder.

Embodiment 30 is the method or use as defined in any one of the preceding claims, wherein the fibrosis related disease or disorder is cardiac fibrosis, pulmonary or lung fibrosis, hepatic fibrosis, renal fibrosis, peritoneal fibrosis, or non-alcoholic steatohepatitis (NASH).

Embodiment 31 is the method or use as defined in embodiment 30, wherein the cardiac fibrosis is hypertrophic cardiomyopathy; and the pulmonary or lung fibrosis is idiopathic pulmonary fibrosis.

Embodiment 32 is a method for promoting muscle growth and/or improving muscle function in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments 1 to 16 or embodiment 22, or the pharmaceutical composition as defined in embodiment 23 or embodiment 24 to the subject.

Embodiment 33 is the method according to embodiment 32, wherein the subject is a human.

Embodiment 34 is a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments 1 to 16 or embodiment 22, or a pharmaceutical composition as defined in embodiment 23 or embodiment 24 for use in promoting muscle growth and/or improving muscle function.

Embodiment 35 is use of a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of embodiments 1 to 16 or embodiment 22, or a pharmaceutical composition as defined in embodiment 23 or 24 in the manufacture of a medicament for promoting muscle growth and/or improving muscle function.

SEQUENCE LISTING

SEQ ID NO.	Description	Sequence
1	13Y039-4B06-4334_LCDR1	RASQSVSSYLA
2	13Y039-4B06-4334_LCDR2	DASNRAT
3	13Y039-4B06-4334_LCDR3	QQSDSWPPT
4	13Y039-4B06-4334_HCDR1	GYYS
5	13Y039-4B06-4334_HCDR2	WINPLSGETNYAQKFQG
6	13Y039-4B06-4334_HCDR3	DTGELDGMNWFYDL
7	13Y039-4B06-4334_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFLGYYMSWVRQAPG QGLEWMGWINPLSGETNYAQKFQGRVTMTRDTSISTAYMELS RLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS
8	13Y039-4B06-4334_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYC QQSDSWPPTFGGGTKVEIK
9	13Y039-4B06-4334-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
10	13Y039-4B06-4334-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFLGYYMSWVRQAPG QGLEWMGWINPLSGETNYAQKFQGRVTMTRDTSISTAYMELS RLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE

		QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
11	13Y039-4B06- 4334_VL	GAGATCGTGCTGACCCAGAGCCCTGCAACCCTGTCCCTGAG CCCTGGCGAAAGGGCCACTCTGAGCTGCAGGGCCAGCCAG AGCGTGAGCAGCTACCTCGCCTGGTACCAGCAGAAGCCCGG CCAGGCCCCTAGGCTGCTGATCTACGACGCCAGCAACAGGG CCACCGGCATTCCCACAAGGTTACGCGGCAGCGGCAGCGG CACCGACTTCACCCTGACCATCAGCAGCCTGGAGCCCGAAG ACTTCGCAGTCTACTACTGCCAGCAGAGCGACAGCTGGCCC CCCACCTTCGGGGGCGGCACCAAGGTGGAGATCAAG
12	13Y039-4B06- 4334_VH	CAGGTGCAGCTCGTGACAGCGGCGCCGAGGTGAAAAAGC CCGGCGCCTCTGTCAAGGTGAGCTGCAAGGCCAGCGGCTA CACCTTCCTGGGCTACTACATGAGCTGGGTGAGGCAGGCTC CCGGACAGGGCCTGGAGTGGATGGGCTGGATCAACCCCT GAGCGGCGAGACCAACTACGCCCAGAAGTTCCAGGGCAGG GTGACCATGACCAGGGACACCAGCATCAGCACCGCCTACAT GGAAGTGAAGCAGGCTGAGGAGCGACGACACCGCCGTGTATT ACTGCGCCAGGGACACCGGCGAGCTGGACGGCATGAACTG GTACTTCGACCTGTGGGGCAGGGGCACCCTGGTGACAGTGA GCAGC
13	13Y039-4B06- 4334_HC	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGC CACCGGTGTGCACAGCCAGGTGCAGCTCGTGACAGCGGC GCCGAGGTGAAAAAGCCCGGCGCCTCTGTCAAGGTGAGCTG CAAGGCCAGCGGCTACACCTTCCTGGGCTACTACATGAGCT GGGTGAGGCAGGCTCCCGACAGGGCCTGGAGTGGATGGG CTGGATCAACCCCTGAGCGGCGAGACCAACTACGCCCAGA AGTTCCAGGGCAGGGTGACCATGACCAGGGACACCAGCATC AGCACCGCCTACATGGAAGTGAAGCAGGCTGAGGAGCGACGA CACCGCCGTGTATTACTGCGCCAGGGACACCGGCGAGCTG GACGGCATGAACTGGTACTTCGACCTGTGGGGCAGGGGCAC CCTGGTGACAGTGAGCAGCGCCAGCACCAAGGGCCCCAGC GTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCG GCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC GAGCCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCA

		GCGGCGTGACACCTTCCCCGCCGTGCTGCAGAGCAGCGG CCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGCA GCCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAG CCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAG CTGTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCCCG AGCTGGCCGAGCCCCAGCGTGTTCTGTTCCCCCCAAG CCTAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGAC CTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGA AGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCC AAGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACCG GGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGA ACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTG CCTGCCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCA GCCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAG ATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTG AAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAG CAACGGCCAGCCCGAGAACAACTACAAGACCACCCCCCTG TGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTG ACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTGAG CTGCTCCGTGATGCACGAGGCCCTGCACAATCACTACACCC AGAAGAGCCTGAGCCTGTCCCCTGGCAAG
14	13Y039-4B06- 4334_LC	ATGGGCTGGTCTGTCATCATCCTGTTTCTGGTGGCCACCGC CACCGGTGTGCACAGCGAGATCGTGCTGACCCAGAGCCCTG CAACCCTGTCCCTGAGCCCTGGCGAAAGGGCCACTCTGAGC TGCAGGGCCAGCCAGAGCGTGAGCAGCTACCTCGCCTGGTA CCAGCAGAAGCCCGGCCAGGCCCTAGGCTGCTGATCTACG ACGCCAGCAACAGGGCCACCGGCATTCCCGCAAGGTTGAGC GGCAGCGGCAGCGGCACCGACTTCACCTGACCATCAGCA GCCTGGAGCCCGAAGACTTCGCAGTCTACTACTGCCAGCAG AGCGACAGCTGGCCCCCACCTTCGGGGGCGGCACCAAGG TGGAGATCAAGCGTACGGTGGCCGCCCCCAGCGTGTTGATC TTCCCCCCCAGCGATGAGCAGCTGAAGAGCGGCACCGCCA GCGTGGTGTGTCTGCTGAACAATTCTACCCCCGGGAGGCC AAGGTGCAGTGGAAGGTGGACAATGCCCTGCAGAGCGGCAA CAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCC ACCTACAGCCTGAGCAGCACCCCTGACCCTGAGCAAGGCCGA

		CTACGAGAAGCACAAGGTGTACGCCTGTGAGGTGACCCACC AGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGG CGAGTGC
15	13Y039-3E07- 2944_LCDR1	QASQDIANYLN
16	13Y039-3E07- 2944_LCDR2	DASNLET
17	13Y039-3E07- 2944_LCDR3	QQADTLPFT
18	13Y039-3E07- 2944_HCDR1	GDYWS
19	13Y039-3E07- 2944_HCDR2	EIDWSGATNYPNPSLKS
20	13Y039-3E07- 2944_HCDR3	GGSKELSFDI
21	13Y039-3E07- 2944_VL	DIQMTQSPSSLSASVGDRVITTCQASQDIANYLNWYQQKPGKA PKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQADTLPFTFGGGTKVEIK
22	13Y039-3E07- 2944_VH	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGDYWSWIRQPPG KGLEWIGEIDWSGATNYPNPSLKSRTISVDTSKNQFSLKLSSVT AADTAVYYCARGGSKELSFDIWGQGTMTVTVSS
23	13Y039-3E07- 2944- mAb light_chain 	DIQMTQSPSSLSASVGDRVITTCQASQDIANYLNWYQQKPGKA PKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQADTLPFTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDESTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
24	13Y039-3E07- 2944- mAb heavy_chain 	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGDYWSWIRQPPG KGLEWIGEIDWSGATNYPNPSLKSRTISVDTSKNQFSLKLSSVT AADTAVYYCARGGSKELSFDIWGQGTMTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKHTHTCPPCPAELAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVELTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE

		NNYKTTTPVLDSGSSFFLYSKLTVDKSRWQQGNVFCSSVMHE ALHNHYTQKSLSLSPGK
25	13Y039-3E07- 2944 VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTGCCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAAC AGGGGTCCCATCAAGGTTCAAGTGAAGTGGATCTGGGACAG ATTTTACTTTACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGCCGATACCCTCCCTTTCACTT TTGGCGGAGGGACCAAGGTTGAGATCAAA
26	13Y039-3E07- 2944 VH	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCT TCAGAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCAT TTTTTGGTGATTACTGGAGTTGGATTTCGTCAACCACCAGGCA AAGGATTGGAGTGGATCGGTGAGATAGACTGGTCAGGCGCG ACTAACTACAATCCAAGTTTAAAATCCAGGGTTACTATCTCCG TAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTG TGACCGCCGCAGACACGGCGGTGTACTACTGCGCCAGAGG CGGTTCTAAAGAATTGTCATTTCGACATATGGGGTCAGGGTAC AATGGTCACCGTCTCCTCA
27	13Y039-3E07- 2944-HC	CAAGTACAATTACAACAGTGGGGAGCTGGTTTATTAAAGCCT TCAGAACTTTAAGTTTGACCTGTGCTGTTTACGGTGGATCAT TTTTTGGTGATTACTGGAGTTGGATTTCGTCAACCACCAGGCA AAGGATTGGAGTGGATCGGTGAGATAGACTGGTCAGGCGCG ACTAACTACAATCCAAGTTTAAAATCCAGGGTTACTATCTCCG TAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGTTCTG TGACCGCCGCAGACACGGCGGTGTACTACTGCGCCAGAGG CGGTTCTAAAGAATTGTCATTTCGACATATGGGGTCAGGGTAC AATGGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCAGCG TGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGG CACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCG AGCCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAG CGGCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGC CTGTACAGCCTGAGCAGCTGGTGACCGTGCCAGCAGCAGC CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCC CAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCT GTGACAAGA

		CCCACACCTGCCCCCCTGCCCTGCCCCGAGCTGGCCGG AGCCCCCAGC GTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGATGATC AGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGAG CCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTGGACG GCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGA GCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACCG TGCTGCACCAGGATT GGCTGAACGGCAAGGAGTACAAGTGTAAAGGTGTCCAACAAG GCCCTGCCTGCCCTATCGAGAAAACCATCAGCAAGGCCAA GGGCCAGCCCAGAGAGCCCCAGGTGTAC ACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGAACCAGGT GTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGCGACA TCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCAGAGAACAA CTACAAGACCACCCCCCTGTGCTGGACAGCGATGGCAGCT TCTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGATGG CAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACGAGGC CCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTGTCCC CTGGCAAG
28	13Y039-3E07- 2944_LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTGCCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAAC AGGGGTCCCATCAAGGTTCAAGTGAAGTGGATCTGGGACAG ATTTTACTTTACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGCCGATACCCTCCCTTTCACTT TTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCC GCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAAC TCTACCCCCGGGAGGCCAAGGTGCAGTGAAGGTGGACAAT GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACCGGGGCGAGTGC

33	13Y039-8F02-2949_LCDR1	RASQGISSWLA
34	13Y039-8F02-2949_LCDR2	AASSLQS
35	13Y039-8F02-2949_LCDR3	QQALSLPYT
36	13Y039-8F02-2949_HCDR1	EWAIS
37	13Y039-8F02-2949_HCDR2	AIPKFGTAEYAQKFQG
38	13Y039-8F02-2949_HCDR3	GAKYYYAEDYMDV
39	13Y039-8F02-2949_VL	DIQMTQSPSSVSASVGDRTITCRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQALSLPYTFGGGKVEIK
40	13Y039-8F02-2949_VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFSEWAIWVRQAPG QGLEWMGAIIPKFGTAEYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCARGAKYYYAEDYMDVWGKGT TVTVSS
41	13Y039-8F02-2949-mAb light_chain	DIQMTQSPSSVSASVGDRTITCRASQGISSWLAWYQQKPGKA PKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQALSLPYTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDSKSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
42	13Y039-8F02-2949-mAb heavy_chain	QVQLVQSGAEVKKPGSSVKVSKASGGTFSEWAIWVRQAPG QGLEWMGAIIPKFGTAEYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCARGAKYYYAEDYMDVWGKGT TVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFC SVMHEALHNHYTQKSLSLSPGK
43	13Y039-8F02-2949 VL	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGTCGGGCGAGTCAGGG

		TATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAG TGGGGTCCCATCAAGGTTTACGCGGCAGTGGATCTGGGACAG ATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG CAACTTATTACTGTCAGCAGGCACTCAGTCTCCCTTACACTTT TGGCGGAGGGACCAAGGTTGAGATCAAA
44	13Y039-8F02- 2949 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCGAGTGGGCTATCAGCTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGCTATCATCCCTAAGT TTGGTACAGCAGAGTACGCACAGAAGTTCCAGGGCAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGGTGCTAAGTACTACTACGCTGAGGACTACATG GACGTATGGGGCAAGGGTACAACGTGTCACCGTCTCCTCA
45	13Y039-8F02- 2949_LC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCGAGTGGGCTATCAGCTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGCTATCATCCCTAAGT TTGGTACAGCAGAGTACGCACAGAAGTTCCAGGGCAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGGTGCTAAGTACTACTACGCTGAGGACTACATG GACGTATGGGGCAAGGGTACAACGTGTCACCGTCTCCTCAGC CAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGC AGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCC TGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTCTGG AACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCCCG CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGT GGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTAC ATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGA CAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACACCT GCCCCCCTGCCCTGCCCCGAGCTGGCCGGAGCCCCCAG CGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGATGAT CAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATGTGA GCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTGGAC

		GGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGG AGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGACC GTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAAGTG TAAGGTGTCCAACAAGGCCCTGCCTGCCCCCTATCGAGAAAA CCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGT GTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGAACC AGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCAGC GACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCCGAGA ACAACTACAAGACCACCCCCCTGTGCTGGACAGCGATGGC AGCTTCTTCCTGTACAGCAAGCTGACCGTGACAAAGAGCAG ATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGCACG AGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGCCTG TCCCCTGGCAAG
46	13Y039-8F02- 2949_LC	GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGGG TATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAG TGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAG ATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTG CAACTTATTACTGTCAGCAGGCACTCAGTCTCCCTTACACTTT TGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCC GCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACT TCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAT GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC CTGTGAGGTGACCCACCGAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACCGGGGCGAGTGC
47	13Y039-4B06- 4376_LCDR1	RASQSVSSYLA
48	13Y039-4B06- 4376_LCDR2	DASNRAT
49	13Y039-4B06- 4376_LCDR3	QQSDSWPPT

50	13Y039-4B06-4376_HCDR1	GYVMN
51	13Y039-4B06-4376_HCDR2	WINPSSGETNYAQKFQG
52	13Y039-4B06-4376_HCDR3	DTGELDGMNWFYDL
53	13Y039-4B06-4376_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYC QQSDSWPPTFGGGTKVEIK
54	13Y039-4B06-4376_VH	QVQLVQSGAEVKKPGASVKVCKASGYTFMGYYMNWVRQAP GQGLEWMGWINPSSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS
55	13Y039-4B06-4376-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
56	13Y039-4B06-4376-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVCKASGYTFMGYYMNWVRQAP GQGLEWMGWINPSSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKD TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
57	13Y039-4B06-4376 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA

58	13Y039-4B06-4376 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCATGGGCTACTATATGAATTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGATGGATCAACCCCTTAG TGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA
59	13Y039-4B06-4376_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCATGGGCTACTATATGAATTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGATGGATCAACCCCTTAG TGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA GCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCA GCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTCT GGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCTGAGGTGAAGTTCACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA

		ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
60	13Y039-4B06- 4376_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
61	13Y039-4B06- 4373_LCDR1	RASQSVSSYLA
62	13Y039-4B06- 4373_LCDR2	DASNRAT
63	13Y039-4B06- 4373_LCDR3	QQSDSWPPT
64	13Y039-4B06- 4373_HCDR1	SYVMN
65	13Y039-4B06- 4373_HCDR2	IINPSSGETSYAQKFQG
66	13Y039-4B06- 4373_HCDR3	DTGELDGMNWYFDL

67	13Y039-4B06-4373_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFRSYIMNWVRQAP GQGLEWMGIINPSSGETSYAQKFQGRVTMTRDTSTSTVYMELS SLRSED TAVYYCARTDGE L DGMN WYFDLWGRGTLTVSS
68	13Y039-4B06-4373_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASN RATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIK
69	13Y039-4B06-4373- mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASN RATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
70	13Y039-4B06-4373- mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFRSYIMNWVRQAP GQGLEWMGIINPSSGETSYAQKFQGRVTMTRDTSTSTVYMELS SLRSED TAVYYCARTDGE L DGMN WYFDLWGRGTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKDTL MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
71	13Y039-4B06-4373 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCA GTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
72	13Y039-4B06-4373 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATAC ACCTTCAGGAGCTACTATATGAATTGGGTGCGACAGGCCCTT GGACAAGGGCTTGAGTGGATGGGAATAATCAACCCTAGTTC GGGTGAGACAAGCTACGCACAGAAGTTCAGGGCAGAGTCA CCATGACCAGGGACACGTCCACGAGCACAGTCTACATGGAG

		CTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA
73	13Y039-4B06- 4373_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATAC ACCTTCAGGAGCTACTATATGAATTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGAATAATCAACCCTAGTTC GGGTGAGACAAGCTACGCACAGAAGTTCAGGGCAGAGTCA CCATGACCAGGGACACGTCCACGAGCACAGTCTACATGGAG CTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA GCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCA GCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCT GGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCCCTGCCCTGCCCCCGAGCTGGCCCGAGCCCCC AGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACCTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTCACTGCTCCGTGATGC

		ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
74	13Y039-4B06- 4373_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
75	13Y039-4B06- 4364_LCDR1	RASQSVSSYLA
76	13Y039-4B06- 4364_LCDR2	DASNRAT
77	13Y039-4B06- 4364_LCDR3	QQSDSWPPT
78	13Y039-4B06- 4364_HCDR1	GYYS
79	13Y039-4B06- 4364_HCDR2	WINPNSGETIYAQKFQG
80	13Y039-4B06- 4364_HCDR3	DTGELDGMNWFYDL
81	13Y039-4B06- 4364_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIK
82	13Y039-4B06- 4364_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFRGYYMSWVRQAP GQGLEWMGWINPNSGETIYAQKFQGRVTMTTRDTSISTAYMELS RLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS

83	13Y039-4B06-4364-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
84	13Y039-4B06-4364-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFRGYYMSWVRQAP GQGLEWMGWINPNSGETIYAQKFQGRVTMTRDTSISTAYMELS RLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKDTL MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
85	13Y039-4B06-4364 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
86	13Y039-4B06-4364 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTCCGGGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACA GTGGTGAGACAATTTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC A
87	13Y039-4B06-4364 HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC

		ACCTTCCGGGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACA GTGGTGAGACAATTTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC AGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCC AGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCC TGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACCTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTAGCTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
88	13Y039-4B06-4364_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC

		ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
89	13Y039-4B06-4351_LCDR1	RASQSVSSYLA
90	13Y039-4B06-4351_LCDR2	DASNRAT
91	13Y039-4B06-4351_LCDR3	QQSDSWPPT
92	13Y039-4B06-4351_HCDR1	GYYS
93	13Y039-4B06-4351_HCDR2	WINPNSGETFYAQKFQG
94	13Y039-4B06-4351_HCDR3	DTGELDGMNWFYDL
95	13Y039-4B06-4351_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIK
96	13Y039-4B06-4351_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFSGYYMSWVRQAP GQGLEWMGWINPNSGETFYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS
97	13Y039-4B06-4351-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

98	13Y039-4B06-4351-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFSGYYMSWVRQAP GQGLEWMGWINPNSGETFYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWYFDLWGRGTLTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKHTHTCPPCPAPELAGAPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
99	13Y039-4B06-4351 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
100	13Y039-4B06-4351 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCTCGGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACA GTGGTGAGACATTTTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTAATACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA
101	13Y039-4B06-4351_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCTCGGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACA GTGGTGAGACATTTTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTAATACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT

		TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA GCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCA GCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCT GGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCCGAGCTGGCCGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACCTACAAGACCACCCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTCACTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
102	13Y039-4B06-4351_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA

		CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
103	13Y039-4B06- 4348_LCDR1	RASQSVSSYLA
104	13Y039-4B06- 4348_LCDR2	DASNRAT
105	13Y039-4B06- 4348_LCDR3	QQSDSWPPT
106	13Y039-4B06- 4348_HCDR1	GYYMS
107	13Y039-4B06- 4348_HCDR2	WINPNSGETYYAQKFQG
108	13Y039-4B06- 4348_HCDR3	DTGELDGMNWFYDL
109	13Y039-4B06- 4348_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYC QQSDSWPPTFGGGTKVEIK
110	13Y039-4B06- 4348_VH	QVQLVQSGAEVKKPGASVKVSCASGYTFGGYYMSWVRQAP GQGLEWMGWINPNSGETYYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLVTVSS
111	13Y039-4B06- 4348- mAb light_chain 	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISLEPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
112	13Y039-4B06- 4348- mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCASGYTFGGYYMSWVRQAP GQGLEWMGWINPNSGETYYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKD TLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR

		EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
113	13Y039-4B06-4348 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
114	13Y039-4B06-4348 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCGGGGGCTACTATATGTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACA GTGGTGAGACATATTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC A
115	13Y039-4B06-4348_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCGGGGGCTACTATATGTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTAACA GTGGTGAGACATATTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC AGCCAGCACCAAGGGCCCCAGCGTGTTCCTCCTGGCCCCC AGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCC TGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC

		GTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTGTTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCT GCCCCATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCC CAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGATG AGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAG GGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA CGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGC TGGACAGCGATGGCAGCTTCTTCTGTACAGCAAGCTGACC GTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTACAGCTG CTCCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGA AGAGCCTGAGCCTGTCCCCTGGCAAG
116	13Y039-4B06-4348_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC

117	13Y039-4B06-4328_LCDR1	RASQSVSSYLA
118	13Y039-4B06-4328_LCDR2	DASNRAT
119	13Y039-4B06-4328_LCDR3	QQSDSWPPT
120	13Y039-4B06-4328_HCDR1	GYVMN
121	13Y039-4B06-4328_HCDR2	WINPLSGETNYAQKFQG
122	13Y039-4B06-4328_HCDR3	DTGELDGMNWFYDL
123	13Y039-4B06-4328_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIK
124	13Y039-4B06-4328_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFHGYVMNWVRQAP GQGLEWMGWINPLSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS
125	13Y039-4B06-4328-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDSKSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
126	13Y039-4B06-4328-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFHGYVMNWVRQAP GQGLEWMGWINPLSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
127	13Y039-4B06-4328 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA

		GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCA GTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
128	13Y039-4B06- 4328 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCCATGGCTACTATATGAATTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTCTGAG TGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTA CTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA
129	13Y039-4B06- 4328_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCCATGGCTACTATATGAATTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTCTGAG TGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTA CTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA GCCAGCACCAAGGGCCCCAGCGTGTCCCCCTGGCCCCCA GCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCT GGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCCCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTG

		GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAAC TACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTCACTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
130	13Y039-4B06-4328_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
131	13Y039-4B06-4327_LCDR1	RASQSVSSYLA
132	13Y039-4B06-4327_LCDR2	DASNRAT
133	13Y039-4B06-4327_LCDR3	QQSDSWPPT

134	13Y039-4B06-4327_HCDR1	GYMT
135	13Y039-4B06-4327_HCDR2	NINPNSGWTNYAQKFQG
136	13Y039-4B06-4327_HCDR3	DTGELDGMNWFYDL
137	13Y039-4B06-4327_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIK
138	13Y039-4B06-4327_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFPGYYMTWVRQAPG QGLEWMGNINPNSGWTNYAQKFQGRVTMTRDTSISTAYMELS RLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS
139	13Y039-4B06-4327-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
140	13Y039-4B06-4327-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFPGYYMTWVRQAPG QGLEWMGNINPNSGWTNYAQKFQGRVTMTRDTSISTAYMELS RLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
141	13Y039-4B06-4327 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA

142	13Y039-4B06-4327 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCCCTGGCTACTATATGACTTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGAAATATCAACCCTAACAG TGGTTGGACAACTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA
143	13Y039-4B06-4327_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCCCTGGCTACTATATGACTTGGGTGCGACAGGCCCT GGACAAGGGCTTGAGTGGATGGGAAATATCAACCCTAACAG TGGTTGGACAACTATGCACAGAAGTTTCAGGGCAGGGTCA CCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGAG CTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACTG CGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTACT TCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTCA GCCAGCACCAAGGGCCCCAGCGTGTCCCCCTGGCCCCCA GCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCTCT GGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCGAGCTGGCCGAGCCCCC AGCGTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCTGAGGTGAAGTTCACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA

		ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
144	13Y039-4B06- 4327_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
145	13Y039-4B06- 4325_LCDR1	RASQSVSSYLA
146	13Y039-4B06- 4325_LCDR2	DASNRAT
147	13Y039-4B06- 4325_LCDR3	QQSDSWPPT
148	13Y039-4B06- 4325_HCDR1	GYYS
149	13Y039-4B06- 4325_HCDR2	WINPQSGETNYAQKFQG
150	13Y039-4B06- 4325_HCDR3	DTGELDGMNWFYDL

151	13Y039-4B06-4325_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYC QQSDSWPPTFGGGTKVEIK
152	13Y039-4B06-4325_VH	QVQLVQSGAEVKKPGASVKVCKASGYTFWGYMSWVRQAP GQGLEWMGWINPQSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVVSS
153	13Y039-4B06-4325-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
154	13Y039-4B06-4325-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVCKASGYTFWGYMSWVRQAP GQGLEWMGWINPQSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCVMHEALHNHYTQKSLSLSPGK
155	13Y039-4B06-4325 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
156	13Y039-4B06-4325 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCTGGGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTCAGA GTGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA

		GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC A
157	13Y039-4B06- 4325_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCTGGGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTCAGA GTGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC AGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCC AGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCC TGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCCCTGCCCTGCCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACCTACAAGACCACCCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTCACTGCTCCGTGATGC

		ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
158	13Y039-4B06- 4325_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
159	13Y039-4B06- 4324_LCDR1	RASQSVSSYLA
160	13Y039-4B06- 4324_LCDR2	DASNRAT
161	13Y039-4B06- 4324_LCDR3	QQSDSWPPT
162	13Y039-4B06- 4324_HCDR1	GYYS
163	13Y039-4B06- 4324_HCDR2	WINPMSGETNYAQKFQG
164	13Y039-4B06- 4324_HCDR3	DTGELDGMNWFYDL
165	13Y039-4B06- 4324_VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIK
166	13Y039-4B06- 4324_VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFRGYYMSWVRQAP GQGLEWMGWINPMSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLTVSS

167	13Y039-4B06-4324-mAb light_chain	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLLIYDASNRATGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQSDSWPPTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
168	13Y039-4B06-4324-mAb heavy_chain	QVQLVQSGAEVKKPGASVKVSCKASGYTFRGYYMSWVRQAP GQGLEWMGWINPMSGETNYAQKFQGRVTMTRDTSISTAYMEL SRLRSDDTAVYYCARDTGELDGMNWFYDLWGRGTLVTSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK
169	13Y039-4B06-4324 VL	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC ACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAA
170	13Y039-4B06-4324 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC ACCTTCCGTGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTATGA GTGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC A
171	13Y039-4B06-4324_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATAC

		ACCTTCCGTGGCTACTATATGAGTTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTATGA GTGGTGAGACAACTATGCACAGAAGTTTCAGGGCAGGGTC ACCATGACCAGGGACACGTCCATCAGCACAGCCTACATGGA GCTGAGCAGGCTGAGATCTGACGACACGGCGGTGTACTACT GCGCCAGAGACACGGGAGAACTTGACGGAATGAACTGGTAC TTCGACCTATGGGGGAGAGGTACCTTGGTCACCGTCTCCTC AGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCC AGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCC TGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACACTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTCACTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
172	13Y039-4B06-4324_LC	GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCT CCAGGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGA GTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCC AGGCTCCCAGGCTCCTCATCTATGATGCATCCAACAGGGCC

		ACTGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGAC AGACTTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTT TGCAGTTTATTACTGTCAGCAGTCCGACTCCTGGCCTCCTAC TTTTGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGG CCGCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAG CTGAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAA CTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACA ATGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGA GCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTAC GCCTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGA CCAAGAGCTTCAACCGGGGCGAGTGC
173	13Y039- 127G03- 2890_LCDR1	QASQDISNYLN
174	13Y039- 127G03- 2890_LCDR2	DASNLET
175	13Y039- 127G03- 2890_LCDR3	QQADIFPLT
176	13Y039- 127G03- 2890_HCDR1	SYAIS
177	13Y039- 127G03- 2890_HCDR2	GIIPVFGSAYYAQKFQG
178	13Y039- 127G03- 2890_HCDR3	EGRAYYGSESYDDSDYMDV
179	13Y039- 127G03- 2890_VL	DIQMTQSPSSLSASVGDRVITTCQASQDISNYLNWYQQKPGKA PKLLIYDASNLETGVPSRFGSGSGTDFTFITISLQPEDATYYC QQADIFPLTFGGGTKVEIK
180	13Y039- 127G03- 2890_VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAISWVRQAPG QGLEWMGGIIPVFGSAYYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCAGEGRAYYGSESYDDSDYMDVWGKGTITVTVSS

181	13Y039- 127G03-2890- mAb light_chain 	DIQMTQSPSSLSASVGDRTITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLQPEDIATYYC QQADIFPLTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDYSLSSLTLSKADYEEKHKVYACEVTHQGLSSPVT KSFNRGEC
182	13Y039- 127G03-2890- mAb heavy_cha in	QVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAISWVRQAPG QGLEWMGGIIPVFGSAYYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCAGEGRAYGSESYDDSDYMDVWGKGTITVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKP KDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMEALHNHYTQKSLSLSPGK
183	13Y039- 127G03- 2890 VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAAC AGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGCCGATATCTTCCCTCTCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAA
184	13Y039- 127G03- 2890 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCTCGTACGCGATCTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCCGTCT TTGGCTCGGCGTACTACGCGCAGAAGTTCCAGGGCAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCGGAGAAGGCCGGGCGTATTATGGGTGCGAGTCGTA CGATGACTCTGACTATATGGACGTCTGGGGCAAGGGTACAA CTGTCACCGTCTCCTCA

185	13Y039- 127G03- 2890_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCTCGTACGCGATCTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCCGTCT TTGGCTCGGCGTACTACGCGCAGAAGTTCCAGGGCAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCGGAGAAGGCCGGCGTATTATGGGTGCGAGTCGTA CGATGACTCTGACTATATGGACGTCTGGGGCAAGGGTACAA CTGTCACCGTCTCCTCAGCCAGCACCAAGGGCCCCAGCGTG TTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCA CAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG CCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCAGCG GCGTGCACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCT GTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGC CTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCC CAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGAGCT GTGACAAGACCCACACCTGCCCCCCTGCCCTGCCCCGAG CTGGCCGGAGCCCCCAGCGTGTTCTGTTCCCCCACAAGCC TAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCT GTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAATGCCA AGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACCGG GTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAA CGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGC CTGCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCAG CCCAGAGAGCCCCAGGTGTACACCCTGCCCCCTAGCAGAGA TGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGA AGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAG CAACGGCCAGCCCGAGAACAACCTACAAGACCACCCCCCTG TGCTGGACAGCGATGGCAGCTTCTCCTGTACAGCAAGCTG ACCGTGGACAAGAGCAGATGGCAGCAGGGCAACGTGTTGAG CTGCTCCGTGATGCACGAGGCCCTGCACAATCACTACACCC AGAAGAGCCTGAGCCTGTCCCCTGGCAAG
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186	13Y039- 127G03- 2890_LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAAC AGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTGTCAGCAGGCCGATATCTTCCCTCTCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCC GCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACT TCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAT GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACCGGGGCGAGTGC
187	13Y039- 152B02- 2948_LCDR1	QASQDISNYLN
188	13Y039- 152B02- 2948_LCDR2	DASNLAT
189	13Y039- 152B02- 2948_LCDR3	QQDDYLPIT
190	13Y039- 152B02- 2948_HCDR1	DFAIS
191	13Y039- 152B02- 2948_HCDR2	GIPIYGTASYAQKFLG
192	13Y039- 152B02- 2948_HCDR3	DVGVLVYHGAFDI

193	13Y039- 152B02- 2948_VL	DIQMTQSPSSLSASVGDRVITITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLQPEDIATYYC QQDDYLPITFGGGTKVEIK
194	13Y039- 152B02- 2948_VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFSDFAISWVRQAPG QGLEWMGGIPIYGTASYAQKFLGRVTITADESTSTAYMELSSLR SEDNAVYYCARDVGVQLVYHGAFDIWGQGTMTVTSS
195	13Y039- 152B02-2948- mAb light_chain 	DIQMTQSPSSLSASVGDRVITITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLQPEDIATYYC QQDDYLPITFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
196	13Y039- 152B02-2948- mAb heavy_cha in	QVQLVQSGAEVKKPGSSVKVSKASGGTFSDFAISWVRQAPG QGLEWMGGIPIYGTASYAQKFLGRVTITADESTSTAYMELSSLR SEDNAVYYCARDVGVQLVYHGAFDIWGQGTMTVTSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
197	13Y039- 152B02- 2948 VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGCAAC AGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGACGATTACCTCCCTATCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAA
198	13Y039- 152B02- 2948 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCGACTTTGCCATCTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATTCCCATCT ATGGCACGGCGAGCTACGCGCAGAAGTTCCTAGGCAGAGTC

		ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGATGTGGGCGTCCAACTCGTCTATCACGGGGCG TTCGACATCTGGGGTCAGGGTACAATGGTCACCGTCTCCTCA
199	13Y039- 152B02- 2948_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCGACTTTGCCATCTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATTCCCATCT ATGGCACGGCGAGCTACGCGCAGAAGTTCCTAGGCAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGATGTGGGCGTCCAACTCGTCTATCACGGGGCG TTCGACATCTGGGGTCAGGGTACAATGGTCACCGTCTCCTCA GCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCA GCAGCAAGAGCACACGAGCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCT GGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCCC CGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGC GTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCT ACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCCCTGCCCTGCCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTGTTCCCCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACCTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTTCACTGCTCCGTGATGC

		ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
200	13Y039- 152B02- 2948_LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGCAAC AGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTGAGCAGGACGATTACCTCCCTATCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCC GCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACT TCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAT GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACCGGGGCGAGTGC
201	13Y039- 152B02- 2940_LCDR1	QASQDISNYLN
202	13Y039- 152B02- 2940_LCDR2	DASNLAT
203	13Y039- 152B02- 2940_LCDR3	QQDDYLPIT
204	13Y039- 152B02- 2940_HCDR1	SDAIS
205	13Y039- 152B02- 2940_HCDR2	GIITNFGTATYAQKFQG
206	13Y039- 152B02- 2940_HCDR3	DVGVQLVYHGAFDI

207	13Y039- 152B02- 2940_VH	QVQLVQSGAEVKKPGSSVKVSKASGGTFSSDAISWVRQAPG QGLEWMGGIITNFGTATYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCARDVGVQLVYHGAFDIWGQGTMTVTVSS
208	13Y039- 152B02- 2940_VL	DIQMTQSPSSLSASVGDRTITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQDDYLPITFGGGTKVEIK
209	13Y039- 152B02-2940- mAb light_chain 	DIQMTQSPSSLSASVGDRTITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQDDYLPITFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQES VTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
210	13Y039- 152B02-2940- mAb heavy_cha in	QVQLVQSGAEVKKPGSSVKVSKASGGTFSSDAISWVRQAPG QGLEWMGGIITNFGTATYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCARDVGVQLVYHGAFDIWGQGTMTVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
211	13Y039- 152B02- 2940 VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGCAAC AGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGACGATTACCTCCCTATCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAA
212	13Y039- 152B02- 2940 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCTCCGACGCGATCTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCACCAACT TTGGGACCGCCACCTACGCGCAGAAGTTCCAGGGGAGAGTC

		ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGATGTGGGGTGCAACTGGTCTATCACGGGGC GTTGACATCTGGGGTCAGGGTACAATGGTCACCGTCTCCT CA
213	13Y039- 152B02- 2940_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCTCCGACGCGATCTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCACCAACT TTGGGACCGCCACCTACGCGCAGAAGTTCCAGGGGAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGATGTGGGGTGCAACTGGTCTATCACGGGGC GTTGACATCTGGGGTCAGGGTACAATGGTCACCGTCTCCT CAGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC CAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGC TGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTC CTGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAG CGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACC TACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCGAGCTGGCCGGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCTGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCAGAGAGCCCCA GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAACCTACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAG

		CAGATGGCAGCAGGGCAACGTGTTTCAGCTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
214	13Y039- 152B02- 2940_LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGCAAC AGGGGTCCCATCAAGGTTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTCACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGACGATTACCTCCCTATCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCC GCCCCCAGCGTGTTTCATCTTCCCCCCCAGCGATGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAACT TCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAT GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACCGGGGCGAGTGC
215	13Y039- 152B02- 2935_LCDR1	QASQDISNYLN
216	13Y039- 152B02- 2935_LCDR2	DASNLAT
217	13Y039- 152B02- 2935_LCDR3	QQDDYLPIT
218	13Y039- 152B02- 2935_HCDR1	ESAIS
219	13Y039- 152B02- 2935_HCDR2	GIPTFDTTNYAQKFQG

220	13Y039- 152B02- 2935_HCDR3	DVGVLVYHGAFDI
221	13Y039- 152B02- 2935_VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQDDYLPITFGGGTKVEIK
222	13Y039- 152B02- 2935_VH	QVQLVQSGAEVKKPGSSVKVCKASGGTFSESAISWVRQAPG QGLEWMGGIIPFTDTTNYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCARDVGVQLVYHGAFDIWGQGMVTVSS
223	13Y039- 152B02-2935- mAb light_chain 	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLATGVPSRFSGSGSGTDFTFTISSLPEDIATYYC QQDDYLPITFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVCLLNFPYFREAKVQWKVDNALQSGNSQES VTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSPVT KSFNRGEC
224	13Y039- 152B02-2935- mAb heavy_cha in	QVQLVQSGAEVKKPGSSVKVCKASGGTFSESAISWVRQAPG QGLEWMGGIIPFTDTTNYAQKFQGRVTITADESTSTAYMELSSL RSED TAVYYCARDVGVQLVYHGAFDIWGQGMVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKHTCTPPCPAPELAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
225	13Y039- 152B02- 2935 VL	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGCAAC AGGGGTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAG ATTTTACTTTACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGTCAGCAGGACGATTACCTCCCTATCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAA

226	13Y039- 152B02- 2935 VH	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCGAGTCCGCGATTTTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCGACCT TTGACACCACCAACTACGCGCAGAAGTTCCAGGGGAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGATGTGCGGGTGCAACTGGTCTACCACGGCGC GTTTCGACATCTGGGGTCAGGGTACAATGGTCACCGTCTCCT CA
227	13Y039- 152B02- 2935_HC	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGC CTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGC ACCTTCAGCGAGTCCGCGATTTTCGTGGGTGCGACAGGCCCC TGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCGACCT TTGACACCACCAACTACGCGCAGAAGTTCCAGGGGAGAGTC ACGATTACCGCGGACGAATCCACGAGCACAGCCTACATGGA GCTGAGCAGCCTGAGATCTGAGGACACGGCGGTGTACTACT GCGCCAGAGATGTGCGGGTGCAACTGGTCTACCACGGCGC GTTTCGACATCTGGGGTCAGGGTACAATGGTCACCGTCTCCT CAGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCC CAGCAGCAAGAGCACACGCGGCGGCACAGCCGCCCTGGGC TGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTC CTGGAACAGCGGAGCCCTGACCAGCGGCGTGACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAG CGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACC TACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTG GACAAGAAGGTGGAGCCCAAGAGCTGTGACAAGACCCACAC CTGCCCCCCTGCCCTGCCCCGAGCTGGCCGAGCCCCC AGCGTGTTCTGTTCCTCCCCCAAGCCTAAGGACACCCTGAT GATCAGCAGAACCCCCGAGGTGACCTGTGTGGTGGTGGATG TGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTG GACGGCGTGAGGTGCACAATGCCAAGACCAAGCCCAGGG AGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAA GTGTAAGGTGTCCAACAAGGCCCTGCCTGCCCTATCGAGA AAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCA

		GGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGA ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCC AGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCG AGAACAAC TACAAGACCACCCCCCTGTGCTGGACAGCGAT GGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG CAGATGGCAGCAGGGCAACGTGTT CAGCTGCTCCGTGATGC ACGAGGCCCTGCACAATCACTACACCCAGAAGAGCCTGAGC CTGTCCCCTGGCAAG
228	13Y039- 152B02- 2935_LC	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCT GTAGGAGACAGAGTCACCATCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAA AGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGCAAC AGGGGTCCCATCAAGGTT CAGTGGAAGTGGATCTGGGACAG ATTTTACTTT CACCATCAGCAGCCTGCAGCCTGAAGATATTG CAACATATTACTGT CAGCAGGACGATTACCTCCCTATCACTTT TGGCGGAGGGACCAAGGTTGAGATCAAACGTACGGTGGCC GCCCCCAGCGTGTT CATCTTCCCCCCCAGCGATGAGCAGCT GAAGAGCGGCACCGCCAGCGTGGTGTGTCTGCTGAACAAC T TCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAAT GCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGC AGGACAGCAAGGACTCCACCTACAGCCTGAGCAGCACCCCTG ACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGC CTGTGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCA AGAGCTTCAACCGGGGCGAGTGC

**Table 16: SEQUENCES OF REVERSE CHIMERIC SEQUENCES LC AND HC HUMAN VARIABLE REGION
WITH EITHER MOUSE (IGG2A LAGA CK) OR RAT (IGG2B LAGA CK) CONSTANT REGION**

5

SEQ ID NO.	Description	Sequence
229	13Y039 4B06-4344 mouse kappa_LC	GAGATCGTGCTGACCCAGAGCCCTGCAACC CTGTCCCTGAGCCCTGGCGAAAGGGCCACT CTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCTACCTCGCCTGGTACCAGCAGAAGCC CGGCCAGGCCCTAGGCTGCTGATCTACGA CGCCAGCAACAGGGCCACCGGCATTCCCG CAAGGTTTCAGCGGCAGCGGCAGCGGCACC GACTTCACCCTGACCATCAGCAGCCTGGAG CCCGAAGACTTCGCAGTCTACTACTGCCAG CAGAGCGACAGCTGGCCCCCACCTTCGG GGGCGGCACCAAGGTGGAGATCAAGAGGG CTGACGCGGCGGCCACCGTGAGCATCTTCC CCCCCAGCAGCGAGCAGCTGACTAGCGGC GGAGCCTCTGTGGTGTGCTTCTGAACAAC TTCTACCCCAAGGACATCAACGTGAAGTGG AAGATCGACGGCAGCGAGAGGCAGAACGG AGTCCTCAACAGCTGGACCGACCAGGACAG CAAGGATAGCACCTACAGCATGAGCAGCAC CCTGACCCTGACCAAGGACGAGTACGAGAG GCACAACAGCTACACCTGCGAAGCCACCCA CAAAACCTCCACCAGCCCCATCGTGAAGAG CTTCAATAGGAACGAGTGC
230	13Y039 4B06-4344 mouse kappa_LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYL AWYQQKPGQAPRLLIYDASNRAIGIPARFSGS GSGTDFTLTISSLEPEDFAVYYCOQSDSWPPT FGGGTKVEIKRADAAPTVSIFPPSSEQLTSGG ASVVCFLNNFYPKDINVWKIDGSEKONGVLN SWTDQDSKDYMSSTLTLTDEYERHNSY TCEATHKSTSPIVKSFNRNEC

231	13Y039 4B06-4344 mouse IgG2a LAGA_HC	CAGGTGCAGCTCGTGCAGAGCGGCGCCGA GGTGAAAAAGCCCGGCGCCTCTGTCAAGGT GAGCTGCAAGGCCAGCGGCTACACCTTCCT GGGCTACTACATGAGCTGGGTGAGGCAGGC TCCCGGACAGGGCCTGGAGTGGATGGGCT GGATCAACCCCTGAGCGGCGAGACCAACT ACGCCCAGAAAGTTCCAGGGCAGGGTGACCA TGACCAGGGACACCAGCATCAGCACCGCCT ACATGGAACTGAGCAGGCTGAGGAGCGACG ACACCGCCGTGTATTACTGCGCCAGGGACA CCGGCGAGCTGGACGGCATGAACTGGTACT TCGACCTGTGGGGCAGGGGCACCCTGGTG ACAGTGAGCAGCGCTAAAACCACCGCCCCC TCCGTGTACCCCTGGCGCCCGTCTGTGGC GACACCACCGGCAGCAGCGTGACACTGGG CTGCCTGGTGAAGGGCTACTTCCCCGAGCC CGTCACCCTGACCTGGAATAGCGGAAGCCT GTCAAGCGGCGTGCACACTTTCCCCGCCGT GCTGCAGTCTGACCTGTACACCCTGAGCAG CAGCGTGACCGTGACCAGCAGCACCTGGCC CAGCCAGTCTATCACTTGCAACGTGGCCCA CCCTGCCAGCTCCACCAAGGTGGACAAGAA GATCGAGCCTAGGGGACCCACCATTAAACC CTGCCCCCCTGCAAGTGCCCCGCCCCCAA TCTGGCCGGAGCCCCCAGCGTGTTTATCTT CCCCCCAAGATCAAGGACGTGCTGATGAT CAGCCTGAGCCCCATCGTGACCTGCGTGGT GGTGGACGTGAGCGAGGACGACCCAGACG TGCAGATCAGCTGGTTTGTGAACAACGTGG AGGTGCACACCGCCCAGACCCAGACCCACA GGGAGGATTACAACAGCACCCCTGAGGGTGG TGAGCGCCCTGCCCATCCAGCAACCAGGACT GGATGTCCGGCAAGGAGTTCAAGTGCAAGG TGAACAACAAGGACCTGCCCGCCCCCATCG AGAGGACCATCAGCAAGCCTAAGGGCAGCG TGAGGGCACCCCAGGTCTACGTGCTGCCCC
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		CCCCAGAGGAGGAAATGACCAAGAAGCAGG TGACCCTGACCTGCATGGTGACCGACTTCA TGCCCCGAGGACATCTACGTGGAGTGGACCA ACAACGGCAAGACCGAGCTGAACTACAAGA ACACCGAGCCCGTGCTGGACAGCGACGGC AGCTACTTCATGTATAGCAAGCTGCGGGTC GAGAAGAAGAACTGGGTGGAGAGGAACAGC TACAGCTGCAGCGTCGTGCACGAAGGCCTC CACAACCACCACACCACCAAGAGCTTCAGC AGGACCCCCGGAAG
232	13Y039 4B06-4344 mouse IgG2a LAGA_HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFLG YYMSWVRQAPGQGLEWMGWINPLSGETNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDTGELDGMNWFYDLWGRGTLVTVSS AKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGY FPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTL SSSVTVTSSSTWPSQSITCNVAHPASSTKVDDK IEPRGPTIKPCPPCKCPAPNLAGAPSVFIFPPKI KDVLMISLSPIVTCVVVDVSEDDPDVQISWVFN NVEVHTAQTQTHREDYNSTLRVVSALPIQHQQD WMSGKEFKCKVNNKDLPAPIERTISKPKGSSVR APOVYVLPPEEEMTKQVTLTCMVTDFMPE DIYVEWTNNGKTELNYKNTEPVLDSDGSYFM YSKLRVEKKNWVERNSYSCSVVHEGLHNHHT TKSFSRTPGK
233	13Y0394B06-4344 rat IgG2b LAGA_HC	QVQLVQSGAEVKKPGASVKVSCKASGYTFLG YYMSWVRQAPGQGLEWMGWINPLSGETNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDTGELDGMNWFYDLWGRGTLVTVSS AQTAPSVYPLAPGCGDTTSSTVTLGCLVKGY FPEPVTVTWNSGALSSDVHTFPAVLQSGLYTL TSSVTSSSTWPSQVTCNVAHPASSTKVDDKV ERRNGGIGHKCPTCPTCHKCPVPELAGAPSV FIFPPKPKDILLISQNAKVTCVVVDVSEEPDV QFSWVFNNEVHTAQTQPREEQYNSTFRVVS ALPIQHQQDWMSGKEFKCKVNNKALPSPIEKTI

		SKPKGLVRKPQVYVMGPPTEQLTEQTVSLTCL TSGFLPNDIGVEWTSNGHIEKNYKNTEPVMDS DGSFFMYSKLNVERSRWDSRAPFVCSVHIEG LHNHHVEKSISRPPGK
234	13Y0394B06-4344 rat IgG2b LAGA_LC	EIVLTQSPATLSLSPGERATLSCRASQSVSSYL AWYQQKPGQAPRLLIYDASNRATGIPARFSGS GSGTDFTLTISSLEPEDFAVYYCQQSDSWPPT FGGGTKVEIKRADAAPTVSIFPPSTEQLATGG ASVVCLMNNFYPRDISVKWKIDGTERRDGVLD SVTDQDSKDYSTYSMSSTLSLTKADYESHNLYT CEVVHKTSSSPVVKSFNRNEC
235	13Y0394B06-4344 rat IgG2b LAGA_LC	GAGATCGTGCTGACCCAGAGCCCTGCAACC CTGTCCCTGAGCCCTGGCGAAAGGGCCACT CTGAGCTGCAGGGCCAGCCAGAGCGTGAG CAGCTACCTCGCCTGGTACCAGCAGAAGCC CGGCCAGGCCCTAGGCTGCTGATCTACGA CGCCAGCAACAGGGCCACCGGCATTCCCG CAAGGTTGAGCGGCAGCGGCAGCGGCACC GACTTCACCTGACCATCAGCAGCCTGGAG CCCGAAGACTTCGCAGTCTACTACTGCCAG CAGAGCGACAGCTGGCCCCCACCTTCGG GGGCGGCACCAAGGTGGAGATCAAGAGGG CCGACGCGGCGGCCACCGTGTCCATCTTCC CCCCCAGCACCGAACAGCTGGCCACTGGC GGAGCTAGCGTGGTGTGCCTGATGAACAAC TTCTACCCAGGGACATCAGCGTGAAGTGG AAGATCGACGGCACCGAGAGGAGGGACGG CGTCCTGGATTCTGTGACCGACCAGGACAG CAAAGACAGCACCTACAGCATGAGCAGCAC CCTGAGCCTGACCAAGGCCGACTACGAGAG CCACAACCTCTACACCTGCGAGGTGGTGCA CAAGACCAGCAGCAGCCCCGTGGTGAAGAG CTTCAACAGGAACGAGTGC
236	13Y0394B06-4344 rat IgG2b LAGA_HC	CAGGTGCAGCTCGTGCAGAGCGGCGCCGA GGTGAAAAAGCCCGGCGCCTCTGTCAAGGT GAGCTGCAAGGCCAGCGGCTACACCTTCCT

	GGGCTACTACATGAGCTGGGTGAGGCAGGC TCCCGGACAGGGCCTGGAGTGGATGGGCT GGATCAACCCCTGAGCGGCGAGACCAACT ACGCCCAGAAGTTCCAGGGCAGGGTGACCA TGACCAGGGACACCAGCATCAGCACCGCCT ACATGGAACTGAGCAGGCTGAGGAGCGACG ACACCGCCGTGTATTACTGCGCCAGGGACA CCGGCGAGCTGGACGGCATGAACTGGTACT TCGACCTGTGGGGCAGGGGCACCCTGGTG ACAGTGAGCAGCGCCCAGACCACAGCTCCC AGCGTGTATCCCCTGGCGCCCGGCTGTGGC GATACTACCAGCAGCACCGTCACCCTGGGC TGCCTGGTGAAAGGCTACTTCCCCGAACCA GTGACCGTGACCTGGAATAGCGGAGCTCTG TCAAGCGACGTGCACACCTTTCCCGCCGTG CTCCAGAGCGGCCTGTACACCCTCACCAGC AGCGTGACTAGCAGCACCTGGCCCTCTCAG ACCGTGACCTGCAACGTGGCCCCACCCCGCC TCTTCCACCAAGGTGGACAAGAAAGTGAG AGGAGGAACGGCGGAATCGGCCACAAGTG CCCAAACCTGCCCCACCTGCCATAAATGCCC CGTGCCCGAACTGGCCGGAGCCCCCAGCG TGTTTCATCTTCCCCCCCCAAGCCCCAAGGACAT CCTGCTGATCAGCCAGAACGCCAAGGTGAC CTGCGTGGTGGTGGACGTCAGCGAGGAGG AGCCCGACGTGCAGTTCAGCTGGTTTGTGA ACAACGTGGAGGTGCACACCGCCCAGACCC AGCCCAGGGAGGAGCAGTACAACAGCACCT TCCGGGTGGTGAGCGCCCTGCCTATCCAGC ACCAGGACTGGATGAGCGGCAAGGAGTTCA AGTGCAAGGTGAACAACAAGGCCCTGCCCA GCCCCATCGAGAAGACCATTAGCAAGCCCA AGGGCCTCGTGAGGAAGCCCCAGGTCTACG TGATGGGACCACCTACCGAGCAGCTGACCG AACAGACCGTGTCCCTGACCTGCCTGACCA GCGGCTTCCTGCCCAACGACATCGGCGTGG
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		AGTGGACCAGCAACGGCCACATCGAGAAGA ACTACAAGAACACCGAGCCCGTGATGGACA GCGACGGCAGCTTCTTCATGTACAGCAAGC TGAACGTGGAGAGGAGCAGGTGGGACAGC AGAGCCCCCTTCGTGTGCAGCGTCGTCCAC GAGGGGCTGCACAACCACCACGTCGAGAAG AGCATCTCTAGGCCCCCGGCAAG
237	13Y039-3E07-2994 rat IgG2b LAGA_LC	DIQMTQSPSSLSASVGDRTITCOASQDIANYL NWYQQKPGKAPKLLIYDASNLETGVPSRFSG SGSGTDFTFTISSLPEDIATYYCQQADTLPT FGGGTKVEIKRAAAPTVSIFPPSTEQLATGG ASVVCLMNNFYPRDISVKWKIDGTERRDGVLD SVTDQDSKDYSTYSMSSTLSLTADYESHNLYT CEVVKHTSSSPVVKSFNRNEC
238	13Y039-3E07-2994 rat IgG2b LAGA_HC	QVQLQQWGAGLLKPSETLSLTCAVYGGSSFFG DYWSWIROPKGLGLEWIGEIDWSGATNYPNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC ARGGSKELSFDIWGQGTMTVSSAQTTAPSV YPLAPGCGDTSSTVTLGCLVKGYFPEPVTVT WNSGALSSDVHTFPAVLQSGLYTLTSSVTSST WPSQTVTCNVAHPASSTKVDKKVERRNGGIG HKCPTCPTCHKCPVPELAGAPSVFIFPPKPKDI LLISQNAKVTQVVDVSEEEPDVQFSWFVNNV EVHTAQTQPREEQYNSTFRVVSALPIQHGDW MSGKEFKCKVNNKALPSPIEKTISKPKGLVRKP QVYVMGPPTEQLTEQTVSLTCLTSGFLPNDIG VEWTSNGHIEKNYKNTPEVMDSDGSFFMYSK LNVERSRWDSRAPFVCSVVHEGLHNHHVEKS ISRPPGK
239	13Y039-3E07-2994 rat IgG2b LAGA_HC	CAGGTGCAGCTGCAGCAGTGGGGCGCCGG ACTGCTGAAGCCCAGCGAGACCCTGAGCCT GACCTGCGCCGTGTACGGCGGGTCCTTCTT CGGCGACTACTGGAGCTGGATCAGGCAGCC CCCCGGCAAAGGCCTGGAGTGGATCGGCG AGATCGACTGGAGCGGCGCCACCAACTACA ACCCAGCCTCAAGAGCAGGGTGACCATCA

	GCGTGGACACCAGCAAGAACCAGTTCAGCC TGAAGCTGAGCAGCGTGACCGCCGCCGACA CCGCCGTGTACTATTGCGCCAGGGGCGGCA GCAAGGAGCTGAGCTTCGACATCTGGGGCC AGGGCACTATGGTCACCGTGAGCAGCGCCC AGACCACAGCTCCCAGCGTGATCCCCTGG CGCCCGGCTGTGGCGATACTACCAGCAGCA CCGTCAACCCTGGGCTGCCTGGTGAAAGGCT ACTTCCCCGAACCAGTGACCGTGACCTGGA ATAGCGGAGCTCTGTCAAGCGACGTGCACA CCTTTCCCGCCGTGCTCCAGAGCGGCCTGT ACACCCTCACCAGCAGCGTGA CTAGCAGCA CCTGGCCCTCTCAGACCGTGACCTGCAACG TGGCCCACCCCGCCTCTTCCACCAAGGTGG ACAAGAAAGTGGAGAGGAGGAACGGCGGA ATCGGCCACAAGTGCCCAACCTGCCCCACC TGCCATAAATGCCCCGTGCCCGA ACTGGCC GGAGCCCCCAGCGTGTT CATCTTCCCCCCC AAGCCCAAGGACATCCTGCTGATCAGCCAG AACGCCAAGGTGACCTGCGTGGTGGTGGAC GTCAGCGAGGAGGAGGCCGACGTGCAGTT CAGCTGGTTTGTGAACAACGTGGAGGTGCA CACCGCCCAGACCCAGCCCAGGGAGGAGC AGTACAACAGCACCTTCCGGGTGGTGAGCG CCCTGCCTATCCAGCACCAAGGACTGGATGA GCGGCAAGGAGTTCAAGTGCAAGGTGAACA ACAAGGCCCTGCCAGCCCCATCGAGAAGA CCATTAGCAAGCCCAAGGGCCTCGTGAGGA AGCCCCAGGTCTACGTGATGGGACCACCTA CCGAGCAGCTGACCGAACAGACCGTGTCCT TGACCTGCCTGACCAGCGGCTTCCTGCCCA ACGACATCGGCGTGGAGTGGACCAGCAACG GCCACATCGAGAAGAACTACAAGAACACCG AGCCCGTGATGGACAGCGACGGCAGCTTCT TCATGTACAGCAAGCTGAACGTGGAGAGGA GCAGGTGGGACAGCAGAGCCCCCTTCGTGT
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		GCAGCGTCGTCCACGAGGGGCTGCACAAC CACCACGTGCGAGAAGAGCATCTCTAGGCCC CCCGGCAAG
240	13Y039-3E07-2994 rat IgG2b LAGA_LC	GACATCCAGATGACTCAGTCCCCCTCTAGC CTGAGCGCTAGCGTGGGCGACAGGGTGAC C ATCACCTGCCAGGCCAGCCAGGACATCGCC AACTACCTGAACTGGTACCAGCAGAAGCCC GGCAAGGCCCCCAAAGTCTGATCTACGAC GCCTCAAACCTCGAGACCGGCGTGCTAGC AGGTTTAGCGGCAGCGGCAGCGGCACCGA CTTCACCTTCACCATCAGCAGCCTGCAGCC C GAGGATATCGCCACCTACTACTGCCAGCAG GCCGACACCCTGCCCTTCACCTTCGGCGGA GGCACCAAGGTGGAGATTAAGAGGGCCGAC GCGGCGCCACCGTGTCCATCTTCCCCCCC AGCACCGAACAGCTGGCCACTGGCGGAGCT AGCGTGGTGTGCCTGATGAACAACCTTCTAC CCCAGGGACATCAGCGTGAAGTGGAAGATC GACGGCACCGAGAGGAGGGACGGCGTCCT G GATTCTGTGACCGACCGAGGACAGCAAAGAC AGCACCTACAGCATGAGCAGCACCTGAGC CTGACCAAGGCCGACTACGAGAGCCACAAC CTCTACACCTGCGAGGTGGTGCACAAGACC AGCAGCAGCCCCGTGGTGAAGAGCTTCAAC AGGAACGAGTGC
29	13Y039-3E07-2944 mouse cK LC	DIQMTQSPSSLSASVGDRVITTCQASQDIANYL NWYQQKPGKAPKLLIYDASNLETGVPSRFSG SGSGTDFTFTISSLPEDIATYYCQQADTLPT FGGGTKVEIKRADAAPTVSIFPPSSEQLTSGG ASVVCFLNNFYPKDINVKWKIDGSEKONGVLN SWTDQDSKSTYSMSSTLTTLTKDEYERHNSY TCEATHKTSTSPIVKSFNREK

30	13Y039-3E07-2944 mouse cK LC	GACATCCAGATGACTCAGTCCCCCTCTAGC CTGAGCGCTAGCGTGGGCGACAGGGTGAC CATCACCTGCCAGGCCAGCCAGGACATCGC CAACTACCTGAACTGGTACCAGCAGAAGCC CGGCAAGGCCCCCAAAGTGTGATCTACGA CGCCTCAAACCTCGAGACCGGCGTGCCTAG CAGGTTTAGCGGCAGCGGCAGCGGCACCG ACTTCACCTTCACCATCAGCAGCCTGCAGC CCGAGGATATCGCCACCTACTACTGCCAGC AGGCCGACACCCTGCCCTTCACCTTCGGCG GAGGCACCAAGGTGGAGATTAAGAGGGCTG ACGCGGCGCCCAACCGTGAGCATCTTCCCCC CCAGCAGCGAGCAGCTGACTAGCGGCGGA GCCTCTGTGGTGTGCTTCCTGAACAACTTCT ACCCCAAGGACATCAACGTGAAGTGGAAGA TCGACGGCAGCGAGAGGCAGAACGGAGTC CTCAACAGCTGGACCGACCAGGACAGCAAG GATAGCACCTACAGCATGAGCAGCACCTG ACCCTGACCAAGGACGAGTACGAGAGGCAC AACAGCTACACCTGCGAAGCCACCCACAAA ACCTCCAACAGCCCCATCGTGAAGAGCTTC AATAGGAACGAGTGC
31	13Y039-3E07-2944 mouse IgG2a LAGA_HC	QVQLQQWGAGLLKPSETLSLTCVYGGSSFFG DYWSWIRQPPGKGLEWIGEIDWSGATNYP LKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC ARGGSKELSFDIWGQGTMTVSSAKTTAPSV YPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTS STWPSQSITCNVAHPASSTKVDKKIEPRGPTIK PCPPCKCPAPNLAGAPSVFIFPPKIKDVLMSL SPIVTCVVVDVSEDDPDVQISWVFNNEVHTA QTQTHREDYNSTLRVVSALPIQHQQDWMSGKE FKCKVNNKDLPAPIERTISKPKGSVRAPQVYVL PPPEEEMTKQVTLTCMVTDFMPEDIYVEWT NNGKTELNYKNTEPVLDSDGSYFMYSKLRVE

			KKNWVERNSYSCSVVHEGLHNHHTTKSFSRT PGK
32	13Y039-3E07-2944 IgG2a LAGA_HC	mouse	CAGGTGCAGCTGCAGCAGTGGGGCGCCGG ACTGCTGAAGCCCAGCGAGACCCTGAGCCT GACCTGCGCCGTGTACGGCGGGTCCTTCTT CGGCGACTACTGGAGCTGGATCAGGCAGCC CCCCGGCAAAGGCCTGGAGTGGATCGGCG AGATCGACTGGAGCGGCGCCACCAACTACA ACCCAGCCTCAAGAGCAGGGTGACCATCA GCGTGGACACCAGCAAGAACCAGTTCAGCC TGAAGCTGAGCAGCGTGACCGCCGCCGACA CCGCCGTGTACTATTGCCCGAGGGGCGGCA GCAAGGAGCTGAGCTTCGACATCTGGGGCC AGGGCACTATGGTCACCGTGAGCAGCGCTA AAACCACCGCCCCCTCCGTGTACCCCTGG CGCCCGTCTGTGGCGACACCACCGGCAGC AGCGTGACACTGGGCTGCCTGGTGAAGGG CTACTTCCCCGAGCCCGTCACCCTGACCTG GAATAGCGGAAGCCTGTCAAGCGGCGTGCA CACTTCCCCGCCGTGCTGCAGTCTGACCT GTACACCCTGAGCAGCAGCGTGACCGTGAC CAGCAGCACCTGGCCCAGCCAGTCTATCAC TTGCAACGTGGCCCCACCCTGCCAGCTCCAC CAAGGTGGACAAGAAGATCGAGCCTAGGGG ACCCACCATTAAACCCTGCCCCCCTGCAA GTGCCCCGCCCCCAATCTGGCCGGAGCCC CCAGCGTGTTTATCTTCCCCCACAAGATCAA GGACGTGCTGATGATCAGCCTGAGCCCCAT CGTGACCTGCGTGGTGGTGGACGTGAGCG AGGACGACCCAGACGTGCAGATCAGCTGGT TTGTGAACAACGTGGAGGTGCACACCGCCC AGACCCAGACCCACAGGGAGGATTACAACA GCACCCTGAGGGTGGTGAGCGCCCTGCCC ATCCAGCACCCAGGACTGGATGTCCGGCAAG GAGTTCAAGTGAAGGTGAACAACAAGGAC CTGCCCGCCCCCATCGAGAGGACCATCAGC

		AAGCCTAAGGGCAGCGTGAGGGCACCCCA GGTCTACGTGCTGCCCCCCCCAGAGGAGGA AATGACCAAGAAGCAGGTGACCCTGACCTG CATGGTGACCGACTTCATGCCCGAGGACAT CTACGTGGAGTGGACCAACAACGGCAAGAC CGAGCTGAACTACAAGAACACCGAGCCCGT GCTGGACAGCGACGGCAGCTACTTCATGTA TAGCAAGCTGCGGGTCGAGAAGAAGAACTG GGTGGAGAGGAACAGCTACAGCTGCAGCGT CGTGCACGAAGGCCTCCACAACCAACCACAC CACCAAGAGCTTCAGCAGGACCCCCGGGAA G
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CLAIMS

1. A BMP1, TLL1 and/or TLL2 binding protein, which comprises:
 - (a)(i) any one or a combination of CDRs selected from CDRH1, CDRH2, CDRH3 from SEQ ID NO: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, and 222 and/or CDRL1, CDRL2, CDRL3 from SEQ ID NO: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, and 221; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
 - (b) a VH region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 7, 22, 40, 54, 67, 82, 96, 110, 124, 138, 152, 166, 180, 194, 207, or 222 and/or a VL region comprising a sequence at least 80% identical to the sequence of SEQ ID NO: 8, 21, 39, 53, 68, 81, 95, 109, 123, 137, 151, 165, 179, 193, 208, or 221.
2. The BMP1, TLL1 and/or TLL2 binding protein according to claim 1, wherein the CDR of (a)(i) is: CDRL1 of SEQ ID NO: 1; CDRL2 of SEQ ID NO: 2; CDRL3 of SEQ ID NO: 3; CDRH1 of SEQ ID NO: 4; CDRH2 of SEQ ID NO: 5; and/or CDRH3 of SEQ ID NO: 6.
3. The BMP1, TLL1 and/or TLL2 binding protein according to claim 1 or claim 2, which comprises a VH region comprising a CDR1 comprising a sequence of GYYMS (SEQ ID NO: 4), a CDR2 comprising a sequence of WINPLSGETNYAQKFQG (SEQ ID NO: 5) and/or a CDR3 comprising a sequence of DTGELDGMNWFYDL (SEQ ID NO: 6).
4. The BMP1, TLL1 and/or TLL2 binding protein according to any one of claims 1 to 3, which comprises a VL region comprising a CDR1 comprising a sequence of RASQSVSSYLA (SEQ ID NO: 1); a CDR2 comprising a sequence of DASNRAT (SEQ ID NO: 2); and/or a CDR3 comprising a sequence of QQSDSWPPT (SEQ ID NO: 3).
5. The BMP1, TLL1 and/or TLL2 binding protein according to any one of claims 1 to 4, wherein all 6 CDRs are present in the binding protein.
6. A BMP1, TLL1 and/or TLL2 binding protein comprising the following 6 CDRs:
LCDR1 of RASQSVSSYLA (SEQ ID NO: 1);
LCDR2 of DASNRAT (SEQ ID NO: 2);
LCDR3 of QQSDSWPPT (SEQ ID NO: 3);
HCDR1 of GYYMS (SEQ ID NO: 4);
HCDR2 of WINPLSGETNYAQKFQG (SEQ ID NO: 5); and
HCDR3 of DTGELDGMNWFYDL (SEQ ID NO: 6).

7. The BMP1, TLL1 and/or TLL2 binding protein according to claim 6, wherein the binding protein comprises a VH region that is 80% identical to SEQ ID NO: 7 and/or a VL region that is 80% identical to SEQ ID NO: 8.
8. The BMP1, TLL1 and/or TLL2 binding protein according to claim 6 or claim 7, wherein the binding protein comprises a VH region that is 100% identical to SEQ ID NO: 7 and/or a VL region that is 100% identical to SEQ ID NO: 8.
9. The BMP1, TLL1 and/or TLL2 binding protein according to any one of claims 6 to 8, wherein the binding protein comprises a heavy chain (HC) sequence at least 80% identical to SEQ ID NO: 10; and/or a light chain (LC) sequence at least 80% identical to SEQ ID NO: 9.
10. The BMP1, TLL1 and/or TLL2 binding protein according to any one of claims 6 to 9, wherein the binding protein comprises a heavy chain (HC) sequence that is 100% identical to SEQ ID NO: 10; and/or a light chain (LC) sequence that is 100% identical to SEQ ID NO: 9.
11. A BMP1, TLL1 and/or TLL2 binding protein, which comprises a VH region that is 100% identical to SEQ ID NO: 7 and a VL region that is 100% identical to SEQ ID NO: 8.
12. The BMP1, TLL1 and/or TLL2 binding protein according to claim 11, which comprises a light chain that is 100% identical to SEQ ID NO: 9 and a heavy chain that is 100% identical to SEQ ID NO: 10.
13. A polynucleotide sequence encoding the BMP1, TLL1 and/or TLL2 binding protein according to any one of claims 1 to 12.
14. The polynucleotide sequence according to claim 13, which comprises SEQ ID NO: 13 encoding the heavy chain; and/or SEQ ID NO: 14 encoding the light chain.
15. An expression vector comprising the polynucleotide sequence as defined in claim 13 or claim 14.
16. A recombinant host cell comprising the polynucleotide sequence as defined in claim 13 or claim 14, or the expression vector as defined in claim 15.

17. A method for the production of a BMP1, TLL1 and/or TLL2 binding protein, which method comprises culturing the recombinant host cell of claim 16 under conditions suitable for expression of the polynucleotide sequence or expression vector, whereby a polypeptide comprising the BMP1, TLL1 and/or TLL2 binding protein is produced.

18. A pharmaceutical composition comprising the BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, and a pharmaceutically acceptable diluent or carrier.

19. A method for the treatment of a fibrosis related disease or disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, or the pharmaceutical composition as defined in claim 18 to the subject.

20. The method according to claim 19, wherein the subject is a human.

21. A BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12 or a pharmaceutical composition as defined in claim 18 for use in therapy.

22. A BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 18 for use in the treatment of a fibrosis related disease or disorder.

23. Use of a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 18 in the manufacture of a medicament for use in the treatment of a fibrosis related disease or disorder.

24. The method or use as defined in any one of the preceding claims, wherein the fibrosis related disease or disorder is cardiac fibrosis, pulmonary or lung fibrosis, hepatic fibrosis, renal fibrosis, peritoneal fibrosis, or non-alcoholic steatohepatitis (NASH).

25. The method or use as defined in claim 24, wherein the cardiac fibrosis is hypertrophic cardiomyopathy; and the pulmonary or lung fibrosis is idiopathic pulmonary fibrosis.

26. A method for promoting muscle growth and/or improving muscle function in a subject in need thereof comprising administering to the subject a therapeutically effective amount of

the BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, or the pharmaceutical composition as defined in claim 18 to the subject.

27. The method according to claim 26, wherein the subject is a human.

28. A BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 18 for use in promoting muscle growth and/or improving muscle function.

29. Use of a BMP1, TLL1 and/or TLL2 binding protein as defined in any one of claims 1 to 12, or a pharmaceutical composition as defined in claim 18 in the manufacture of a medicament for promoting muscle growth and/or improving muscle function.