SUMMARY

[0005] The present disclosure provides antibodies that bind inhibin βA and dimers containing inhibin βA , *e.g.,* Activin A, Activin AB, etc.. The antibodies of the disclosure are useful, *inter alia*, for inhibiting Activin A-mediated signaling, producing beneficial clinical outcomes through the inhibition of Activin A-mediated signaling, *e.g.*, for treating diseases and disorders caused by or related to Activin A activity and/or signaling. The antibodies of the disclosure also have utility for use in conjunction with inhibitors of other ligands of the ActRIIA and ActRIIB receptors, such as GDF8 inhibitors.

[0006] The antibodies of the disclosure can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, *e.g.*, to eliminate residual effector functions (Reddy *et al*., J Immunol 164:1925-1933 (2000)).

[0006a] In one aspect, the present disclosure refers to an isolated antibody or antigen-binding fragment thereof that specifically binds Activin A with a binding dissociation equilibrium constant (K_D) of less than about 5 pM as measured in a surface plasmon resonance assay at 25ºC, wherein the antibody or antigen-binding fragment comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 66; and (b) the CDRs of a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 74.

[0007] The present disclosure provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind Activin A with a binding association equilibrium constant (K_a) of less than about 500 nM and a dissociation equilibrium constant (K_D) of less than about 5 pM as measured in a surface plasmon resonance assay at 25ºC. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, specifically bind Activin A with a K_D of less than about 4 pM as measured in a surface plasmon resonance assay at 25ºC. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, specifically bind Activin A with a binding association equilibrium constant (K_a) of less than about 500 nM.

[0008] The present disclosure provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind Activin A and block binding of at least one Activin A receptor to Activin A. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, block Activin A binding to an Activin A receptor with an IC_{50} value of less than about 80 pM as measured in an *in vivo* receptor/ligand binding bioassay at 25ºC. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, block Activin A binding to an Activin A receptor with an IC_{50} value of less than about 60 pM as measured in an *in vivo* receptor/ligand binding bioassay at 25ºC. The present disclosure also provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind Activin A and block activation of at least one Activin A receptor by Activin A. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, do not significantly block binding of Activin A to an Activin Type II receptor. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, inhibit binding of Activin A to an Activin A receptor selected from the group consisting of Activin Type IIA receptor (ActRIIA), Activin Type IIB receptor (ActRIIB), and Activin Type I receptor. In some examples of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, inhibit Activin A-mediated activation of SMAD complex signaling.

[0009] The present disclosure provides antibodies, or antigen-binding fragments thereof comprising a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 106, 114, 122, 130, 138, 154, 162, 170, 178, 186, 194, and 202, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0010] The present disclosure also provides an antibody or antigen-binding fragment of an antibody comprising a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 146, and 210, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0011] The present disclosure also provides an antibody or antigen-binding fragment thereof comprising a HCVR and LCVR (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/90, 106/90, 114/90, 122/90, 130/90, 138/146, 154/146, 162/146, 170/146, 178/146, 186/146, 194/146, and 202/210.

[0012] The present disclosure also provides an antibody or antigen-binding fragment of an antibody comprising a heavy chain CDR3 (HCDR3) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 112, 120, 128, 136, 144, 160, 168, 176, 184, 192, 200, and 208, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 152, and 216, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0013] In certain examples, the antibody or antigen-binding portion of an antibody comprises a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NO: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/96, 112/96, 120/96, 128/96, 136/96, 144/152, 160/152, 168/152, 176/152, 184/152, 192/152, 200/152, and 208/216.

[0014] The present disclosure also provides an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 108, 116, 124, 132, 140, 156, 164, 172, 180, 188, 196, and 204, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 110, 118, 126, 134, 142, 158, 166, 174, 182, 190, 198, and 206, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 148, and 212, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98%

or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 150, and 214, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0015] Certain non-limiting, exemplary antibodies and antigen-binding fragments of the disclosure comprise HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 domains, respectively, having the amino acid sequences selected from the group consisting of: SEQ ID NOs: 4-6-8-12-14-16 (*e.g.* H4H10423P); 20-22-24-28-30-32 (*e.g.* H4H10424P); 36-38-40-44-46-48 (*e.g.* H4H10426P); 52-54-56-60-62-64 (*e.g.* H4H10429P); 68-70-72-76-78-80 (*e.g.* H4H10430P); 84-86-88-92-94-96 (*e.g.* H4H10432P2; 100-102-104-92-94-96 (*e.g.* H4H10433P2); 108-110-112-92-94-96 (*e.g.* H4H10436P2); 116-118-120-92-94-96 (*e.g.* H4H10437P2); 124-126-128-92-94-96 (*e.g.* H4H10438P2); 132-134-136-92-94-96 (*e.g.* H4H10440P2); 140-142-144-148-150-152 (*e.g.* H4H10442P2); 156-158-160-148-150-152 (H4H10445P2); 164-166-168-148-150-152 (H4H10446P2); 172-174-176-148-150-152 (H4H10447P2); 180-182-184-148-150-152 (H4H10448P2); 188-190-192-148-150-152 (H4H10452P2); 196-198-200-148-150-152 (H4H10468P2); and 204-206-208-212-214-216 (H2aM10965N).

[0016] In a related example, the disclosure includes an antibody or antigen-binding fragment of an antibody which specifically binds Activin A, wherein the antibody or fragment comprises the heavy and light chain CDR domains contained within heavy and light chain variable region (HCVR/LCVR) sequences selected from the group consisting of SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/90, 106/90, 114/90, 122/90, 130/90, 138/146, 154/146, 162/146,170/146, 178/146, 186/146,194/146, and 202/210. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, J Mol Biol *273*:927-948 (1997); and Martin *et al.*, PNAS (USA) 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0017] The present disclosure also provides nucleic acid molecules encoding anti-Activin A antibodies or portions thereof. For example, the present disclosure provides nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity

thereto.

[0018] The present disclosure also provides nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0019] The present disclosure also provides nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0020] The present disclosure also provides nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0021] The present disclosure also provides nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0022] The present disclosure also provides nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0023] The present disclosure also provides nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0024] The present disclosure also provides nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1; in certain examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0025] The present disclosure also provides nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the

HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-Activin A antibodies listed in Table 1.

[0026] The present disclosure also provides nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary anti-Activin A antibodies listed in Table 1.

[0027] The present disclosure also provides nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain examples, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain examples of the disclosure, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-Activin A antibody listed in Table 1.

[0028] The present disclosure also provides recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-Activin A antibody. For example, the present disclosure includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 1. Also included within the scope of the present disclosure are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments, and recovering the antibodies and antibody fragments so produced.

[0029] The present disclosure includes anti-Activin A antibodies having a modified carbohydrate content. In some applications, modification to remove undesirable glycosylation sites may be useful. In some applications, modification to alter glycosylation patterns may be useful, *e.g.*, modifying an antibody to lack a fucose moiety present on an oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield *et al.* J Biol Chem 277:26733 (2002)). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC). In some applications, antibodies may have modified glycosylation patterns in order to minimize effector function. For example, antibodies may be modified to obtain additionally glycosylated or sialylated antibodies.

[0029a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment as described herein, and a pharmaceutically acceptable carrier or diluent. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment as described herein, a growth and differentiation factor 8 (GDF8) antagonist, and a pharmaceutically acceptable carrier or diluent.

[0030] In another example, the disclosure provides a pharmaceutical composition comprising a

recombinant human antibody or fragment thereof which specifically binds Activin A and a pharmaceutically acceptable carrier. In a related example, the disclosure features a composition which is a combination of an anti-Activin A antibody and a second therapeutic agent. In one example, the second therapeutic agent is any agent that is advantageously combined with an anti-Activin A antibody. Exemplary agents that may be advantageously combined with an anti-Activin A antibody include, without limitation, other agents that inhibit Activin A activity (including other antibodies or antigen-binding fragments thereof, peptide inhibitors, small molecule antagonists, etc.) and/or agents which do not directly bind Activin A but nonetheless interfere with, block or attenuate Activin A-mediated signaling. In one example, the secondary therapeutic agent inhibits, interferes, blocks and/or attenuates the activity of another ligand of the ActRIIA and/or ActRIIB receptor (*e.g.*, GDF8, Activin B, Activin AB, Inhibin A, Inhibin B, GDF3, GDF11, Nodal, BMP2, BMP4, and/or BMP7). In one example, the secondary therapeutic agent is an anti-GDF8 antagonist (*e.g.*, a human anti-GDF8 antibody or antigen-binding fragment thereof). Exemplary anti-GDF8 agents for use with the anti-Activin A antibodies of the disclosure include a human anti-GDF8 antibody (*e.g.*, an anti-GDF8 antibody comprising any of the HCVR/LCVR or CDR amino acid sequences as set forth in US 2011-0293630 A1 (*e.g.*, H4H1657N2, which is an anti-GDF8 antibody with heavy chain complementarity determining regions (HCDRs) of a HCVR comprising SEQ ID NO:217 (*e.g.*, the CDR1, CDR2, and CDR3 sequences set forth in SEQ ID NO:218, 219, and 220, respectively), and the light chain complementarity determining regions (LCDRs) of a LCVR comprising SEQ ID NO:221 (*e.g.*, the CDR1, CDR2, and CDR3 sequences set forth in SEQ ID NO:222, 223, and 224)). Additional combination therapies and co-formulations involving the anti-Activin A antibodies of the present disclosure are disclosed elsewhere herein.

[0031] In an additional example of the disclosure, an antigen-binding molecule is provided comprising an Activin A-specific binding domain and a GDF8-specific binding domain. In one example of the disclosure, the antigen-binding molecule is a bispecific antibody comprising a first variable domain that specifically binds Activin A and a second variable domain that specifically binds GDF8.

[0032] In yet another example, the disclosure provides therapeutic methods for inhibiting Activin A activity using an anti-Activin A antibody or antigen-binding portion of an antibody of the disclosure, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the disclosure. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of Activin A activity or signaling. The anti-Activin A antibodies or antibody fragments of the disclosure may function to block the interaction between Activin A and an Activin Type II receptor (*e.g.*, Activin Type IIA receptor and/or Activin Type IIB receptor); between Activin A and an Activin Type I receptor; between Activin A and both a Type II and a Type I receptor; or otherwise inhibit the

signaling activity of Activin A.

[0033] The present disclosure also includes the use of an anti-Activin A antibody or antigen binding portion of an antibody of the disclosure in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by Activin A activity in a patient. The present disclosure also provides methods for increasing muscle mass or strength in a subject by administering to the subject an Activin A antibody or antigen-binding fragment thereof. The present disclosure also provides methods for increasing muscle mass or strength in a subject by administering to the subject an Activin A-specific binding protein and a GDF8-specific binding protein, or by administering to the subject an antigen-binding molecule comprising an Activin A-specific binding domain and a GDF8-specific binding domain.

[0034] The disclosure also includes methods for treating, preventing and/or ameliorating a disease or disorder characterized by decreased muscle mass or strength by administering to a subject in need thereof an Activin A-specific binding protein (*e.g.*, an anti-Activin A antibody). In one aspect, the present disclosure refers to the use of the pharmaceutical composition as described herein for the manufacture of a medicament for treating, preventing or ameliorating a disease or disorder characterized by decreased muscle mass or strength. In a related example, methods of the disclosure include the treating, preventing and/or ameliorating a disease or disorder characterized by decreased muscle mass or strength by administering to a subject in need thereof an Activin A-specific binding protein and a GDF8-specific binding protein (*e.g.*, an anti-Activin A antibody and an anti GDF8 antibody). Methods of the disclosure also include treating, preventing and/or ameliorating a disease or disorder characterized by decreased muscle mass or strength by administering to a subject in need thereof an antigen-binding molecule comprising an Activin A-specific binding domain and a GDF8-specific binding domain. Diseases or disorders characterized by decreased muscle mass or strength that can be treated, prevented and/or ameliorated using methods of the disclosure include sarcopenia, cachexia (*e.g.*, idiopathic cachexia or cachexia secondary to another condition (*e.g.*, cancer, chronic renal failure, or chronic obstructive pulmonary disease)), muscle injury, muscle wasting and/or atrophy (*e.g.*, caused by or associated with disuse, immobilization, bed rest, injury, medical treatment, surgical intervention (*e.g.*, hip fracture, hip replacement, and knee replacement) and by necessity of mechanical ventilation), cancer, obesity, diabetes, arthritis, multiple sclerosis, muscular dystrophy, amyotrophic lateral sclerosis, Parkinson's disease, osteoporosis, osteoarthritis, osteopenia, and metabolic syndromes (*e.g.*, one or more of diabetes, obesity, nutritional disorders, organ atrophy, chronic obstructive pulmonary disease, and anorexia).

[0035] The disclosure also includes methods for treating, preventing and/or ameliorating diseases or disorders caused by, promoted by, exacerbated by, or aggravated by the activity of a molecule containing inhibin βA (*e.g.*, dimers containing inhibin βA , *e.g.,* Activin A, Activin AB, etc.) by administering to a subject in need thereof a binding protein specific for Activin A (*i.e.*, inhibin βA dimer), *e.g.*, an anti-Activin A antibody or antigen-binding fragment thereof. In one example of the disclosure, methods of the disclosure include methods of treating, preventing, and/or ameliorating renal fibrosis by administering to a subject in need thereof an anti-Activin A

antibody. In particular examples of the disclosure, methods of the disclosure include methods of treating, preventing, and/or ameliorating renal fibrosis caused by chronic kidney disease (*e.g.*, as a consequence of hypertension, diabetes, glomerulonephritis, inherited diseases (such as polycystic kidney disease), malformations of the kidney, autoimmune disease (*e.g.*, lupus), or obstructions (*e.g.*, kidney stones, tumors, enlarged prostate gland), or repeated urinary infections) by administering to a subject in need thereof an anti-Activin A antibody. Additional examples of the disclosure include methods of treating, preventing, and/or ameliorating sepsis, chronic heart failure, chronic obstructive pulmonary disease, benign or malignant pheochromocytoma, uterine fibroids/leiomyomata, preeclampsia, keloids, hypertrophic scars, or pulmonary artery hypertension by administering to a subject in need thereof an anti-Activin A antibody. Additional examples of the disclosure include methods of treating, preventing, and/or ameliorating cachexia caused by, promoted by, exacerbated by,or aggravated by Activin A activity by administering to a subject in need thereof an anti-Activin A antibody. Additional examples of the disclosure include methods of treating, preventing, and/or ameliorating weight loss caused by, promoted by, exacerbated by,or aggravated by Activin A activity by administering to a subject in need thereof an anti-Activin A antibody.

[0036] Other examples will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0037] **Figure 1** is a matrix showing the results of an antibody cross-competition assay in which a first anti-Activin A antibody ("Antibody Sample") was applied to an anti-human FC-coated sensor tip, followed by emersion in a solution of a second anti-Activin A antibody (1 μM) pre-bound to Activin A. Binding responses (numerical values 0.22 to 1.84) for each antibody combination tested are depicted. Binding responses presented in white boxes with black type indicate no competition for binding of Activin A, suggesting distinct binding regions.

[0038] **Figure 2**: Panel A shows the effects of 21 days of anti-GDF8 antibody treatment (H4H1657N2, 10mg/kg or 30 mg/kg) on average peak tetanic force compared to isotype control antibody. Data analyzed using one- way analysis of variance (ANOVA) followed by Tukey's test. *$p<0.05$ significance over isotype control (n=6, unpaired Student t test); n.s. = not statistically significant compared to isotype 30mg/kg. Panel B shows the increase in tibialis anterior (TA) muscle peak tetanic force in H4H1657N2-treated mice (10mg/kg) versus mice treated with isotype control antibodies for three weeks (n=6), when stimulated by electric current over a range of frequencies (40 to 100 Hz). Data are expressed as mean average peak force ± SEM.

[0039] **Figure 3**: Panel A shows the design of an experiment to evaluate the effects of H4H1657N2 during the recovery phase from hind limb suspension-induced muscle atrophy. Panel B shows the percentage change in TA and Gastrocnemius (GA) muscle weights for H4H1657N2-treated and isotyple control antibody-treated mice post-recovery after 7 days of

What is claimed is:

1. An isolated antibody or antigen-binding fragment thereof that specifically binds Activin A with a binding dissociation equilibrium constant (K_D) of less than about 5 pM as measured in a surface plasmon resonance assay at 25ºC, wherein the antibody or antigen-binding fragment comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO: 66; and (b) the CDRs of a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO: 74.

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the isolated antibody or antigen-binding fragment thereof specifically binds Activin A with a K_D of less than 4 pM as measured in a surface plasmon resonance assay at 25ºC.

3. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the isolated antibody or antigen-binding fragment thereof specifically binds Activin A with a binding association equilibrium constant (K_a) of less than 500 nM.

4. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the antibody or antigen-binding fragment thereof blocks binding of at least one Activin A receptor to Activin A.

5. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the antibody or antigen-binding fragment thereof blocks activation of at least one Activin A receptor by Activin A.

6. The isolated antibody or antigen-binding fragment thereof of claim 5, wherein the antibody or antigen-binding fragment thereof does not significantly block binding of Activin A to an Activin Type II receptor.

7. The isolated antibody or antigen-binding fragment thereof of claim 4, wherein the antibody or antigen-binding fragment thereof blocks Activin A binding to an Activin A receptor with an IC_{50} value of less than 80 pM as measured in an *in vivo* receptor/ligand binding bioassay at 25ºC.

8. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the antibody or antigen-binding fragment thereof inhibits binding of Activin A to an Activin A receptor selected from the group consisting of Activin Type IIA receptor (ActRIIA), Activin Type IIB receptor (ActRIIB), and Activin Type I receptor.

9. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the antibody or antigen-binding fragment thereof inhibits Activin A-mediated

activation of SMAD complex signaling.

10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the antibody or antigen-binding fragment thereof competes for binding to Activin A with a reference antibody comprising a heavy chain variable region (HCVR)/light chain variable region (LCVR) sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 50/58, 82/90, 106/90, and 130/90.

11. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the antibody or antigen-binding fragment thereof binds to the same epitope on Activin A as a reference antibody comprising an HCVR/LCVR sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 50/58, 82/90, 106/90, and 130/90.

12. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences, respectively, of: SEQ ID NOs: 68-70-72-76-78-80.

13. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair consisting of: SEQ ID NOs: 66/74.

14. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 13, and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 13, a growth and differentiation factor 8 (GDF8) antagonist, and a pharmaceutically acceptable carrier or diluent.

16. The pharmaceutical composition of claim 15, wherein GDF8 antagonist is selected from the group consisting of a GDF8-inhibiting fusion protein, an anti- GDF8 antibody, and an antigen-binding fragment of an anti-GDF8 antibody.

17. The pharmaceutical composition of claim 16, wherein the anti-GDF8 antibody or antigen-binding fragment comprises the heavy chain complementarity determining regions (HCDRs) of a HCVR comprising SEQ ID NO:217, and the light chain complementarity determining regions (LCDRs) of a LCVR comprising SEQ ID NO:221.

18. The pharmaceutical composition of claim 16, wherein the anti-GDF8 antibody or antigen-binding fragment comprises:

a) three HCDRs comprising SEQ ID NO:218, SEQ ID NO:219, and SEQ ID

NO:220, and

b) three LCDRs comprising SEQ ID NO:222, SEQ ID NO:223, and SEQ ID NO:224.

19. The use of the pharmaceutical composition of any one of claims 14 to 18 for the manufacture of a medicament for treating, preventing or ameliorating a disease or disorder characterized by decreased muscle mass or strength.

20. The use of claim 19, wherein the disease or disorder characterized by decreased muscle mass or strength is selected from the group consisting of sarcopenia, cachexia, muscle injury, muscle wasting/atrophy, cancer, obesity, diabetes, arthritis, multiple sclerosis, muscular dystrophy, amyotrophic lateral sclerosis, Parkinson's disease, osteoporosis, osteoarthritis, osteopenia, and a metabolic syndrome.

21. The use of claim 20, wherein the cachexia is idiopathic or is cachexia secondary to another condition.

22. The use of claim 21, wherein the condition is cancer, chronic renal failure, or chronic obstructive pulmonary disease.

23. The use of claim 20, wherein the muscle wasting/atrophy is caused by or associated with a condition selected from the group consisting of disuse, immobilization, bed rest, injury, medical treatment, surgical intervention and by necessity of mechanical ventilation.

24. The use of claim 23, wherein the surgical intervention is selected from the group consisting of hip fracture, hip replacement, and knee replacement.

25. The use of claim 20, wherein the metabolic syndrome includes a disease or disorder selected from the group consisting of diabetes, obesity, nutritional disorders, organ atrophy, chronic obstructive pulmonary disease, and anorexia.