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, there is provided an isolated antibody or antigen-binding fragment thereof that specifically binds Activin A with a binding dissociation equilibrium constant (K_D) of less than 5 pM, or optionally, 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 25°C, wherein the antibody or antigen-binding fragment comprises: (a) the complementarity determining regions (CDRs) of a HCVR having an amino acid sequence of SEQ ID NO: 162; and (b) the CDRs of a LCVR having an amino acid sequence of SEQ ID NO: 146.

[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 25°C. In some embodiments 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 25°C. In some embodiments 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 embodiments 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 25°C. In some embodiments 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 25°C. 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 embodiments 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 embodiments 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 embodiments of the disclosure, the isolated antibodies, or antigen-binding fragments thereof, inhibit Activin A-mediated activation of SMAD complex signaling.

signaling activity of Activin A.

[0032a] Disclosed is a use of any one of the antibodies or antigen-binding fragments described herein, or any one of the pharmaceutical compositions described herein, in the manufacture of a medicament for increasing muscle mass or strength in a subject.

[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.

[0033a] In another aspect, there is provided a use of any one of the antibodies or antigen-binding fragments described herein, or any one of the pharmaceutical compositions described herein, in the manufacture of a medicament for treating, preventing or ameliorating a disease or disorder characterized by decreased muscle mass or strength, 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.

[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 a related embodiment, 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 embodiment 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

210 pM, less than about 200 pM, less than about 190 pM, less than about 180 pM, less than about 170 pM, less than about 160 pM, less than about 150 pM, less than about 140 pM, less than about 130 pM, less than about 120 pM, less than about 110 pM, less than about 100 pM, less than about 95 pM, less than about 90 pM, less than about 85 pM, less than about 80 pM, less than about 75 pM, less than about 70 pM, less than about 65 pM, less than about 60 pM, less than about 55 pM, less than about 50 pM, less than about 45 pM, less than about 40 pM, less than about 35 pM, less than about 30 pM, less than about 25 pM, less than about 20 pM, less than about 15 pM, less than about 10 pM, less than about 9 pM, less than about 8 pM, less than about 7 pM, less than about 6 pM, less than about 5 pM, less than about 4 pM, or less than about 3 pM, as measured by surface plasmon resonance, *e.g.*, using the assay format as defined in Example 3 herein, or a substantially similar assay.

[0077] The present invention also includes anti-Activin A antibodies and antigen-binding fragments thereof that inhibit Activin A-mediated cellular signaling. For example, the present invention includes anti-Activin A antibodies that inhibit the activation of the SMAD complex signal transduction pathway via the binding of Activin A to Activin Type I or II receptors with an IC_{50} value of less than about 4 nM, as measured in a cell-based blocking bioassay, *e.g.*, using the assay format as defined in Example 6 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention inhibit the activation of the SMAD complex signal transduction pathway via the binding of Activin A to Activin Type I or II receptors with an IC_{50} value of less than about 3nM, less than about 2 nM, less than about 1 nm, less than about 500 pM, less than about 250 pM, less than about 240 pM, less than about 230 pM, less than about 220 pM, less than about 210 pM, less than about 200 pM, less than about 190 pM, less than about 180 pM, less than about 170 pM, less than about 160 pM, less than about 150 pM, less than about 140 pM, less than about 130 pM, less than about 120 pM, less than about 110 pM, less than about 100 pM, less than about 95 pM, less than about 90 pM, less than about 85 pM, less than about 80 pM, less than about 75 pM, less than 70 pM, less than about 65 pM, less than about 60 pM, less than about 55 pM, less than about 50 pM, less than about 49 pM, less than about 48 pM, less than about 47 pM, less than about 46 pM, less than about 45 pM, less than about 44 pM, less than about 43 pM, less than about 42 pM, less than about 41 pM, less than about 40 pM, or less than about 39 pM, as measured in a cell-based blocking bioassay, *e.g.*, using the assay format as defined in Example 6 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention inhibit the signaling activing of Activin B by interfering with the binding of Activin B to Activin Type I or II receptors with an IC_{50} value of less than about 50 nM, less than about 20 nM, less than about 10 nm, less than about 5 nM, or less than about 1 nM, , as measured in a cell-based blocking bioassay, *e.g.*, using the assay format as defined in Example 6 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention inhibit the activation of the

SMAD complex signal transduction pathway via the binding of Activin AB to Activin Type I or II receptors with an IC_{50} value of less than about 500 pM, less than about 450 pM, less than about 440 pM, less than about 430 pM, less than about 420 pM, less than about 410 pM, less than about 400 pM, less than about 390 pM, less than about 380 pM, less than about 370 pM, less than about 360 pM, less than about 350 pM, less than about 340 pM, less than about 320 pM, less than about 310 pM, less than about 300 pM, less than about 290 pM, less than about 280 pM, less than about 270 pM, less than about 260 pM, less than about 250 pM, less than about 240 pM, less than about 230 pM, less than about 220 pM, less than about 210 pM, less than about 200 pM, less than about 190 pM, less than about 180 pM, less than about 170 pM, less than about 160 pM, less than about 150 pM, or less than about 140 pM, as measured in a cell-based blocking bioassay, *e.g.*, using the assay format as defined in Example 6 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present invention inhibit the activation of the SMAD complex signal transduction pathway via the binding of Activin AC to Activin Type I or II receptors with an IC_{50} value of less than about 1 nM, less than about 900 pM, less than about 800 pM, less than about 750 pM, less than about 700 pM, less than about 650 pM, less than about 600 pM, or less than about 580 pM, as measured in a cell-based blocking bioassay, *e.g.*, using the assay format as defined in Example 6 herein, or a substantially similar assay.

[0078] The antibodies of the present invention may possess one or more of the aforementioned biological characteristics, or any combinations thereof. Other biological characteristics of the antibodies of the present invention will be evident to a person of ordinary skill in the art from a review of the present disclosure including the working Examples herein.

Anti-Activin A Antibodies Comprising Fc Variants

[0079] According to certain embodiments of the present invention, anti-Activin A antibodies are provided comprising an Fc domain comprising one or more mutations which enhance or diminish antibody binding to the FcRn receptor, *e.g.*, at acidic pH as compared to neutral pH. For example, the present invention includes anti-Activin A antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.*, in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, *e.g.*, a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (*e.g.*, A, W, H, F or Y [N434A, N434W, N434H, N434F or N434Y]); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (*e.g.*, 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (*e.g.*, M428L) and 434S (*e.g.*, N434S) modification; a 428L, 259I (*e.g.*, V259I), and 308F (*e.g.*, V308F) modification; a 433K (*e.g.*, H433K) and a 434 (*e.g.*, 434Y)

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 5 pM, or optionally, 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 25°C, wherein the antibody or antigen-binding fragment comprises: (a) the complementarity determining regions (CDRs) of a HCVR having an amino acid sequence of SEQ ID NO: 162; and (b) the CDRs of a LCVR having an amino acid sequence of SEQ ID NO: 146.

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 binding association equilibrium constant (K_a) of less than 500 nM.

3. 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.

4. 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, wherein the Activin A receptor is selected from the group consisting of Activin Type IIA receptor (ActRIIA), Activin Type IIB receptor (ActRIIB), and Activin Type I receptor.

5. The isolated antibody or antigen-binding fragment thereof of claim 4, wherein the antibody or antigen-binding fragment thereof does not block binding of Activin A to an Activin Type II receptor.

6. The isolated antibody or antigen-binding fragment thereof of claim 3, 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, or optionally 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 60 pM, as measured in an *in vivo* receptor/ligand binding bioassay at 25°C.

7. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 6, 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.

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 Activin A-mediated activation of SMAD complex signaling.

9. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 8, 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, 138/146, 162/146, and 194/146.

10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 to 8, 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, 138/146, 162/146, and 194/146.

11. 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 domains, respectively, selected from the group consisting of: SEQ ID NOs: 164-166-168-148-150-152.

12. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 11, and a pharmaceutically acceptable carrier or diluent.

13. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 11, a GDF8 antagonist, and a pharmaceutically acceptable carrier or diluent.

14. The pharmaceutical composition of claim 13, 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.

15. A use of an antibody or antigen-binding fragment of any one of claims 1 to 11, or the pharmaceutical composition of any one of claims 12 to 14, in the manufacture of a medicament for treating, preventing or ameliorating a disease or disorder characterized by decreased muscle mass or strength, 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.