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 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.

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 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.