ANTI-ACVR2B ANTIBODIES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to International Patent Application No. PCT/CN2023/110569, filed August 1, 2023, the disclosure of which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] This application contains an electronic Sequence Listing which has been submitted in XML file format with this application, the entire content of which is incorporated by reference herein in its entirety. The Sequence Listing XML file submitted with this application is entitled “14668-03l-228_SEQ_LISTING.xml”, was created on July 29, 2024, and is 242,113 bytes in size.

1. FIELD

[0003] Provided herein are molecules capable of binding to ACVR2B, pharmaceutical compositions comprising same, and uses thereof.

2. BACKGROUND

[0004] Activin receptor type-2B (ACVR2B) is a receptor that mediates the functions of activins among other biological activities. Activins are dimeric growth and differentiation factors which belong to the transforming growth factor-beta (TGF-beta) superfamily of structurally related signaling proteins, playing important role in a multitude of processes during embryonic development, organogenesis and adult homeostasis. Activins signal through a heteromeric complex of receptor serine kinases, including type I and type II receptors, and these receptors are all transmembrane proteins, composed of a ligand-binding extracellular domain with cysteine-rich region, a transmembrane domain, and a cytoplasmic domain with serine/threonine specificity. Type I receptors are essential for signaling; and type II receptors are required for binding ligands and for phosphorylation of type I receptors. Although it has been shown that type II receptors, including ACVR2A and ACVR2B, are involved in various disease conditions, we have developed an ACVR2A specific antibody (see WO 2023/030503), there is a need in the art for improved antibody therapies targeting ACVR2B.

3. SUMMARY

[0005] In one aspect, provided herein is an antibody or antigen binding fragment thereof that binds ACVR2B, wherein the affinity of the antibody or antigen binding fragment to

ACVR2B is greater than to ACVR2A, and wherein the antibody or antigen binding fragment comprises:

(i) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 25, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 26;

(ii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 1, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 2;

(iii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 3, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 4;

(iv) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 5, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 6;

(v) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 8;

(vi) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 9, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 10;

(vii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 12;

(viii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 13, and a LCDR1, a LCDR2, and a

LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 14;

(ix) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 15, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 16;

(x) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 17, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 18;

(xi) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 19, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 20;

(xii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 21, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 22;

(xiii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 23, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 24;

(xiv) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 27, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 28;

(xv) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 29, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 30;

(xvi) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 31, and a LCDR1, a LCDR2, and a

LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 32; or

(xvii) a HCDR1, a HCDR2, and a HCDR3 as set forth in a VH comprising the amino acid sequence of SEQ ID NO: 33, and a LCDR1, a LCDR2, and a LCDR3 as set forth in a VL comprising the amino acid sequence of SEQ ID NO: 34.

[0005a] In one example, provided herein is an antibody or antigen binding fragment thereof that selectively binds ACVR2B. In some examples, the antibodies provided herein bind ACVR2B over ACVR2A. In some examples, the antibody or antigen binding fragment

provided herein binds to ACVR2B with higher affinity than to ACVR2A. The disclosure provides methods of using the ACVR2B-binding proteins. In some examples, the anti-ACVR2B antibody or antigen binding fragment provided herein is capable of inhibiting or blocking the binding to ACVR2B to ACVR2B ligands, such as Activin A, Activin B, Activin AB, GDF8 and GDF11. In some examples, the antibody or antigen binding fragment provided herein does not inhibit or block the binding of ACVR2A to ACVR2A ligands, such as Activin A, Activin B, Activin AB, GDF8 and GDF11. In some examples, the antibody or antigen binding fragment provided herein has greater inhibiting or blocking effect on the binding of ACVR2B to ACVR2B ligands than on the binding of ACVR2A to ACVR2A ligands.

[0006] In some examples, the antibody or antigen binding fragment provided herein comprises:

(i) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 1, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(ii) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 3, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 4;

(iii) a HCDR 1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 5, and a LCDR 1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 6;

(iv) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 8;

(v) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 9, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 10;

(vi) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 12;

(vii) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 13, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 14;

(viii) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 15, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 16;

(ix) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 17, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 18;

(x) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 19, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 20;

(xi) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 21, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 22;

(xii) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 23, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 24;

(xiii) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 25, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 26;

(xiv) a HCDR 1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 27, and a LCDR 1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 28;

(xv) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 29, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 30;

(xvi) a HCDR 1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 31, and a LCDR 1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 32; or

(xvii) a HCDR1, a HCDR2, and a HCDR3 as set forth in SEQ ID NO: 33, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 34.

[0007] In some examples, the antibody or antigen binding fragment provided herein comprises:

(i) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 35, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 36, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 37, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 38, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 39, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 40;

(ii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 41, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 42, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 43, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 45, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 46;

(iii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 47, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 49, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 50, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 51, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 52;

(iv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 53, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 54, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 55, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 56, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 57, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 58;

98, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 99, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 100;

(xii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 101, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 102, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 103, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 104, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 105, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 106;

(xiii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 107, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 108, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 109, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 110, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 111, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 112;

(xiv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 113, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 114, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 115, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 116, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 117, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 118;

(xv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 119, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 120, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 121, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 122, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 123, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 124;

(xvi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 125, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 126, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 127, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 128, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 129, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 130; or

(xvii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 131, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 132, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 133, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 134, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 135, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 136.

[0008] In some examples, the antibody or antigen binding fragment provided herein comprises:

acid sequence of SEQ ID NO: 217, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 218, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 219, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 220;

(xv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 221, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 222, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 223, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 224, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 225, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 226;

(xvi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 227, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 228, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 229, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 230, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 231, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 232;

(xvii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 233, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 234, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 235, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 236, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 237, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 238.

[0009] In some examples, the antibody or antigen binding fragment provided herein comprises:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 1, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 3, and a VL comprising the amino acid sequence of SEQ ID NO: 4;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 5, and a VL comprising the amino acid sequence of SEQ ID NO: 6;

(iv) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 8;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 9, and a VL comprising the amino acid sequence of SEQ ID NO: 10;

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 11, and a VL comprising the amino acid sequence of SEQ ID NO: 12;

(vii) a VH comprising the amino acid sequence of SEQ ID NO: 13, and a VL comprising the amino acid sequence of SEQ ID NO: 14;

(viii) a VH comprising the amino acid sequence of SEQ ID NO: 15, and a VL comprising the amino acid sequence of SEQ ID NO: 16;
(ix) a VH comprising the amino acid sequence of SEQ ID NO: 17, and a VL comprising the amino acid sequence of SEQ ID NO: 18;
(x) a VH comprising the amino acid sequence of SEQ ID NO: 19, and a VL comprising the amino acid sequence of SEQ ID NO: 20;
(xi) a VH comprising the amino acid sequence of SEQ ID NO: 21, and a VL comprising the amino acid sequence of SEQ ID NO: 22;
(xii) a VH comprising the amino acid sequence of SEQ ID NO: 23, and a VL comprising the amino acid sequence of SEQ ID NO: 24;
(xiii) a VH comprising the amino acid sequence of SEQ ID NO: 25, and a VL comprising the amino acid sequence of SEQ ID NO: 26;
(xiv) a VH comprising the amino acid sequence of SEQ ID NO: 27, and a VL comprising the amino acid sequence of SEQ ID NO: 28;
(xv) a VH comprising the amino acid sequence of SEQ ID NO: 29, and a VL comprising the amino acid sequence of SEQ ID NO: 30;
(xvi) a VH comprising the amino acid sequence of SEQ ID NO: 31, and a VL comprising the amino acid sequence of SEQ ID NO: 32; or
(xvii) a VH comprising the amino acid sequence of SEQ ID NO: 33, and a VL comprising the amino acid sequence of SEQ ID NO: 34.

[0010] In some examples, the antibody or antigen binding fragment provided herein is an IgG. In some examples, the antibody or antigen binding fragment provided herein is an IgGl. In some examples, the antibody is a human antibody. In some examples, the antibody or antigen binding fragment provided herein comprises one or more mutations in the Fc region to reduce or eliminate the antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) effect. In some examples, the antibody or antigen binding fragment provided herein comprises one or two mutations of L239A and L240A in the Fc region. In some examples, the antibody or antigen binding fragment provided herein comprises one or two mutations of L234A and L235A in the Fc region (Lund J et al., *J Immunol.* 147:2657-2662 (1991)).

[0011] In some examples, the anti-ACVR2B antibody or antigen binding fragment provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 239. In some examples, the anti-ACVR2B antibody or antigen binding fragment provided herein comprises a light chain comprising the amino acid sequence of SEQ ID NO:

240. In some examples, the anti-ACVR2B antibody or antigen binding fragment provided herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 239, and a light chain comprising the amino acid sequence of SEQ ID NO: 240.

[0012] In some examples, the antibody or antigen binding fragment thereof is genetically fused or chemically conjugated to an agent.

[0013] In another aspect, provided herein is a nucleic acid molecule encoding the antibody or antigen binding fragment provided herein.

[0014] In another aspect, provided herein is a vector comprising the nucleic acid molecule encoding the antibody or antigen binding fragment provided herein.

[0015] In yet another aspect, provided herein is a host cell transformed with the vector encoding the antibody or antigen binding fragment provided herein.

[0016] In yet another aspect, provided herein is a composition comprising a therapeutically effective amount of the antibody or antigen binding fragment, the nucleic acid molecule, or the vector encoding the antibody or antigen binding fragment provided herein, and a pharmaceutically acceptable excipient.

[0017] In yet another example, provided herein is a method of treating a disease or disorder in a subject, comprising administering to the subject the composition provided herein. In some examples, the method further comprises administering to the subject a second agent. In some examples, the disease or disorder is associated with ACVR2B. In some examples, the disease or disorder is associated with ACVR2B ligands, including Activins (such as Activin A, Activin B, Activin AB, Activin C, Activin AC and Activin E), Growth/differentiation factors (GDFs, such as GDF1, GDF3, GDF5, GDF6, GDF7, GDF8, GDF10 and GDF11), bone morphogenetic proteins (BMPs, such as BMP2, BMP4, BMP6, BMP7, BMP8a, BMP8b, BMP9 and BMP 10).

[0018] In some examples of the method of treating a disease or disorder provided herein, the disease or disorder is associated with ACVR2B.

[0019] In another aspect, provided herein is a use of the composition provided herein in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the disease or disorder is associated with ACVR2B; or wherein the disease or disorder is associated with ACVR2B ligands; or wherein the disease or disorder is associated with Activin A, Activin B, Activin AB, GDF8 or GDF11; or wherein the disease or disorder is a

musculoskeletal disease or disorder.

[0019a] In some embodiments, the disease or disorder is a musculoskeletal disease or disorder. In some embodiments, the musculoskeletal disease or disorder is selected from a group consisting of anemia, muscle atrophy, spinal muscular atrophy and cancer cachexia. In some embodiments, the disease or disorder is an age-related condition selected from a group consisting of sarcopenia, skin atrophy, muscle wasting, brain atrophy, atherosclerosis, arteriosclerosis, pulmonary emphysema, osteoporosis, osteoarthritis, immunologic incompetence, high blood pressure, dementia, Huntington's disease, Alzheimer's disease, cataracts, age-related macular degeneration, prostate cancer, stroke, diminished life

expectancy, frailty, memory loss, wrinkles, impaired kidney function, and age-related hearing loss. In some embodiments, the disease or disorder is a metabolic disorder selected from a group consisting of Type II Diabetes, Metabolic Syndrome, hyperglycemia, Nonalcoholic Steatohepatitis (NASH) and obesity. In some embodiments, the disease or disorder is selected from a group consisting of acute and/or chronic renal disease or failure, liver fibrosis or cirrhosis, lung fibrosis, pulmonary hypertension (PH), pulmonary arterial hypertension (PAH), cancer, kidney fibrosis, Parkinson's Disease, Amyotrophic lateral sclerosis (ALS), brain atrophy, dementia and anemia, cachexia, rhabdomyosarcomas, bone-loss. In some embodiments, the disease or disorder is cancer, inducing ovarian cancer, breast cancer, esophageal cancer, head and neck cancer, lung cancer, melanoma, multiple myeloma, colorectal cancer, hepatocellular carcinomas, pancreatic cancer, endometrial cancer and gastrointestinal cancer.

[0020] In another aspect, provided herein is an in vitro method for inhibiting or antagonizing ACVR2B activity in a cell, comprising contacting the cell with the composition provided herein.

[0020a] In another aspect, provided herein is an in vitro method for inhibiting or blocking the binding of an ACVR2B ligand to ACVR2B expressed on a cell or an ACVR2B ligand induced signaling through AC VR2B in a cell, comprising contacting the cell with the composition provided herein, wherein optionally the ACVR2B ligand is Activin A, Activin B, Activin AB, GDF8 or GDF11.

[0020b] In yet another example, provided herein is a method for inhibiting or antagonizing ACVR2B activity in a cell, comprising contacting the cell with the composition provided herein. In yet another example, provided herein is a method for inhibiting or blocking the binding of an ACVR2B ligand to ACVR2B expressed on a cell, comprising contacting the cell with the composition provided herein. In yet another example, provided herein is a method for inhibiting or blocking an ACVR2B ligand induced signaling through ACVR2B in a cell, comprising contacting the cell with the composition provided herein. The ACVR2B ligand includes but not limited to Activin (such as Activin A, Activin B, Activin AB, Activin C, Activin AC and Activin E), Growth/differentiation factor (GDF, such as GDF1, GDF3, GDF5, GDF6, GDF7, GDF8, GDF 10 and GDF11), bone morphogenetic proteins (BMP, such

as BMP2, BMP4, BMP6, BMP7, BMP8a, BMP8b, BMP9 and BMP 10).

4. BRIEF DESCRIPTION OF THE FIGURES

[0021] **FIGs. 1A-1C.** Binding kinetics measurement of the equilibrium dissociation constant (KD) of ACVR2B Hits. The binding kinetics of 3 representative hits antibodies to human ACVR2B protein were analyzed by anti-human Fc capture format at 25°C on a CM5 sensor chip using Biacore 3000. The sensorgrams were fitted by non-linear least squares regression using the 1:1 Langmuir binding model. FIG. 1 A: Binding kinetics measurement of T334 antibody to ACVR2B. FIG. IB: Binding kinetics measurement of T363 antibody to ACVR2B. FIG. IC: Binding kinetics measurement of T377 antibody to ACVR2B.

[0022] **FIGs. 2A-2E.** Activin A Competitive ELISA Assay of ACVR2B Hits. FIGs. 2A-2D: The 23 anti-ACVR2B phage hits from kappa chain shuffling phage-display libraries bind ACVR2B and block interaction between Activin A and ACVR2B. FIG. 2E: Activin A