ANTI-ACVR2A ANTIBODIES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of priority of International Patent Application No. PCT/CN2021/116485 filed on September 03, 2021, the disclosure of which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] This application contains a computer readable 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 "14668-008-228_seqlist.xml", was created on August 27,2022 and is 91,313 bytes in size.

1. FIELD

[0003] Provided herein are molecules capable of binding to ACVR2A, pharmaceutical compositions comprising same, and uses thereof.

2. BACKGROUND

[0004] Activin receptor type-2A (ACVR2A) 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. 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 receptor ACVR2A is involved in various disease conditions, there is a need in the art for improved antibody therapies targeting ACVR2A.

3. SUMMARY

[0004a] In one aspect, provided herein is antibody or antigen binding fragment thereof that binds ACVR2A, wherein the affinity of the antibody or antigen binding fragment to ACVR2A is at least 10 fold of that to ACVR2B, as measured by Enzyme-Linked Immunosorbent Assay (ELISA), radioimmunoassay, biolayer interferometry, or surface plasmon resonance, and wherein optionally the antibody or antigen binding fragment comprises:

(i) an HCDR1, an HCDR2, and an 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;

(xxxv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 35;

(xxxvi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 36;

(xxxvii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 37;

(xxxviii)an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 38;

(xxxix) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 39;

(xxxx) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 40; or

(xxxxi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 9, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 41,

wherein said CDRs are determined according to IMGT, Kabat, AbM, Chothia or Contact numbering.

[0004b] In another aspect, provided herein is a nucleic acid molecule encoding the antibody or antigen binding fragment described herein.

[0004c] In another aspect, provided herein is a vector comprising the nucleic acid molecule described herein.

[0004d] In another aspect, provided herein is a host cell transformed with the vector described herein.

[0004e] In another aspect, provided herein is a composition comprising a therapeutically effective amount of the antibody or antigen binding fragment described herein, the nucleic acid molecule described herein, or the vector described herein, and a pharmaceutically acceptable excipient.

[0004f] In another aspect, provided herein is the use of the composition described herein in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the medicament is to be administered to the subject, , and wherein the disease or disorder is (a) a musculoskeletal disease or disorder, (b) an age-related condition, (c) a metabolic disorder, (d) liver fibrosis or cirrhosis, (e) cancer, or (f) anemia.

[0004g] In another aspect, provided herein is a method for inhibiting or antagonizing ACVR2A in a cell, comprising contacting the cell with the composition described herein.

[0004h] In another aspect, provided herein is the composition described herein for use in therapy.

[0005] In one aspect, provided herein is an antibody or antigen binding fragment thereof that selectively binds ACVR2A. In some embodiments, the antibodies provided herein bind

What is claimed:

1. An antibody or antigen binding fragment thereof that binds ACVR2A, wherein the affinity of the antibody or antigen binding fragment to ACVR2A is at least 10 fold of that to ACVR2B, as measured by Enzyme-Linked Immunosorbent Assay (ELISA), radioimmunoassay, biolayer interferometry, or surface plasmon resonance, and wherein optionally the antibody or antigen binding fragment comprises:

(i) an HCDR1, an HCDR2, and an 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) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 3, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(iii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 4, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(iv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 5, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 6;

(v) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 6;

(vi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 8, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 6;

(vii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 9, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(viii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 10, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(ix) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(x) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(xi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 13, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(xii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 14;

(xiii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 15;

(xiv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 2;

(xv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 16;

(xvi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 17;

(xvii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 18;

(xviii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 19;

(xix) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 20;

(xx) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 21;

(xxi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 22;

(xxii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 23;

(xxiii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 24;

(xxiv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 6;

(xxv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 25;

(xxvi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 26;

(xxvii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 27;

(xxviii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 28;

(xxix) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 29;

(xxx) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 30;

(xxxi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 31;

(xxxii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 32;

(xxxiii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 7, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 33;

(xxxiv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 9, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 34;

(xxxv) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 35;

(xxxvi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 36;

(xxxvii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 11, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 37;

(xxxviii) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 38;

(xxxix) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 39;

(xxxx) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 12, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 40; or

(xxxxi) an HCDR1, an HCDR2, and an HCDR3 as set forth in SEQ ID NO: 9, and a LCDR1, a LCDR2, and a LCDR3 as set forth in SEQ ID NO: 41,

wherein said CDRs are determined according to IMGT, Kabat, AbM, Chothia or Contact numbering.

2. The antibody or antigen binding fragment of claim 1, wherein

(i) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 42, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino

acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(ii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(iii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 49, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(iv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 50, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 52, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 53, or

(v) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 52, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 53, or

(vi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 49, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 52, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 53, or

(vii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 54, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(viii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 55, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(ix) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(x) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 58, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3

comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 59, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xiii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 60, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xiv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 61, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xvi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 62, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xvii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 63, the LCDR2 comprises the amino

acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xviii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 52, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 82, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xix) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 64, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xx) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 65, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 66, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 59, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 67, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxiii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 59, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 68, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxiv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 52, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 46, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 53, or

(xxv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 59, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 69, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxvi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 59, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 70, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxvii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 71, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxviii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3

comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 72, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxix) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 73, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxx) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 74, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 75, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 67, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxiii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 48, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 51, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino

acid sequence of SEQ ID NO: 68, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxiv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 54, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 76, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxv) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 77, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxvi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 78, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxvii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 79, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxviii) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 69, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxix) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 80, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxx) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 57, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 70, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47, or

(xxxxi) the HCDR1 comprises the amino acid sequence of SEQ ID NO: 54, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 43, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 44, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 45, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 81, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 47.

3. The antibody or antigen binding fragment of claim 1 or 2, 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: 2;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 4, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(iv) 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;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 6;

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 8, and a VL comprising the amino acid sequence of SEQ ID NO: 6;

(vii) a VH comprising the amino acid sequence of SEQ ID NO: 9, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(viii) a VH comprising the amino acid sequence of SEQ ID NO: 10, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(ix) a VH comprising the amino acid sequence of SEQ ID NO: 11, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(x) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(xi) a VH comprising the amino acid sequence of SEQ ID NO: 13, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(xii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 14;

(xiii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 15;

(xiv) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 2;

(xv) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 16;

(xvi) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 17;

(xvii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 18;

(xviii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 19;

(xix) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 20;

(xx) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 21;

(xxi) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 22;

(xxii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 23;

(xxiii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 24;

(xxiv) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 6;

(xxv) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 25;

(xxvi) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 26;

(xxvii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 27;

(xxviii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 28;

(xxix) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 29;

(xxx) a VH comprising the amino acid sequence of SEQ ID NO: 11, and a VL comprising the amino acid sequence of SEQ ID NO: 30;

(xxxi) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 31;

(xxxii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 32;

(xxxiii) a VH comprising the amino acid sequence of SEQ ID NO: 7, and a VL comprising the amino acid sequence of SEQ ID NO: 33;

(xxxiv) a VH comprising the amino acid sequence of SEQ ID NO: 9, and a VL comprising the amino acid sequence of SEQ ID NO: 34;

(xxxv) a VH comprising the amino acid sequence of SEQ ID NO: 11, and a VL comprising the amino acid sequence of SEQ ID NO: 35;

(xxxvi) a VH comprising the amino acid sequence of SEQ ID NO: 11, and a VL comprising the amino acid sequence of SEQ ID NO: 36;

(xxxvii) a VH comprising the amino acid sequence of SEQ ID NO: 11, and a VL comprising the amino acid sequence of SEQ ID NO: 37;

(xxxviii) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 38;

(xxxix) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 39;

(xxxx) a VH comprising the amino acid sequence of SEQ ID NO: 12, and a VL comprising the amino acid sequence of SEQ ID NO: 40; or

(xxxxi) a VH comprising the amino acid sequence of SEQ ID NO: 9, and a VL comprising the amino acid sequence of SEQ ID NO: 41.

4. The antibody or antigen binding fragment of any one of claims 1-3, wherein the antibody is an IgG.

5. The antibody of any one of claims 1-4, wherein the antibody is a humanized antibody.

6. The antibody of any one of claims 1-5, wherein the antibody or antigen binding fragment thereof is genetically fused or chemically conjugated to an agent.

7. A nucleic acid molecule encoding the antibody or antigen binding fragment of any one of claims 1-6.

8. A vector comprising the nucleic acid molecule of claim 7.

9. A host cell transformed with the vector of claim 8.

10. A composition comprising a therapeutically effective amount of the antibody or antigen binding fragment of any one of claims 1-6, the nucleic acid molecule of claim 7, or the vector of claim 8, and a pharmaceutically acceptable excipient.

11. Use of the composition of claim 10 in the manufacture of a medicament for treating a disease or disorder in a subject, wherein the medicament is to be administered to the subject, and wherein the disease or disorder is

(a) a musculoskeletal disease or disorder,

(b) an age-related condition,

(c) a metabolic disorder,

(d) liver fibrosis or cirrhosis,

(e) cancer, or

(f) anemia.

12. The use of claim 11, wherein the disease or disorder is associated with ACVR2A.

13. The use of claim 11, wherein the disease or disorder is associated with ACVR2A ligands.

14. The use of claim 11, wherein the disease or disorder is associated with Activin A, GDF8 or GDF11.

15. The use of claim 11-14, wherein the musculoskeletal disease or disorder is selected from a group consisting of muscle atrophy, spinal muscular atrophy and cancer cachexia.

16. The use of any one of claims 11-14, wherein the age- related condition selected from a group consisting of sarcopenia, muscle wasting, osteoporosis, and osteoarthritis.

17. The use of any one of claims 11-14, wherein the metabolic disorder selected from a group consisting of Type II Diabetes, Metabolic Syndrome, hyperglycemia, NASH and obesity.

18. The use of any one of claims 11-14, wherein the cancer selected from a group consisting of sarcoma, ovarian cancers, breast cancer, esophageal cancer, head and neck cancer, lung cancer, melanoma, multiple myeloma, colorectal cancer, hepatocellular carcinomas, pancreatic cancer, endometrial cancer, gastrointestinal cancers, prostate cancer and bone-loss-inducing cancers.

19. The use of any one of claims 11 to 18, wherein a second agent is to be further administered to the subject.

20. The use of claim 19, wherein the second agent is an ACVR2B antagonist, wherein optionally the ACVR2B antagonist is an ACVR2B extracellular domain fusion protein, Luspatercept.

21. The use of claim 19, wherein the second agent is an anti-PD-Ll antibody.

22. The use of claim 19, wherein the second agent is a chemotherapy agent such as carboplatin.

23. A method for inhibiting or antagonizing ACVR2A in a cell, comprising contacting the cell with the composition of claim 10.

24. The composition of claim 10 for use in therapy.