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, 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.

[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.

[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

ACVR2A over ACVR2B. In some embodiments, the affinity of the antibody or antigen binding fragment provided herein to ACVR2A is at least 10 fold of that to ACVR2B. The disclosure provides methods of using the ACVR2A-binding proteins. In some embodiments,