

ANTI-CD93 CONSTRUCTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. provisional application 63/033,755, filed on June 2, 2020, U.S. provisional application 63/058,359, filed on July 29, 2020, and U.S. provisional application 63/084,474, filed on September 28, 2020, the contents of which are incorporated by reference in their entirety for all purposes.

TECHNICAL FIELD

[0002] The present disclosure relates to anti-CD93 constructs (such as anti-CD93 antibodies) and the uses thereof.

SUBMISSION OF SEQUENCE LISTING ON ASCII TEXT FILE

[0003] The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 193852000240SEQLIST.TXT, date recorded: June 1, 2021, size: 185 KB).

BACKGROUND OF THE APPLICATION

[0004] CD93 (Cluster of Differentiation 93) is a protein that in humans is encoded by the CD93 gene. CD93 is a C-type lectin transmembrane receptor which plays a role not only in cell-cell adhesion processes but also in host defense. CD93 was initially thought to be a receptor for C1q, but now is thought to instead be involved in intercellular adhesion and in the clearance of apoptotic cells. The intracellular cytoplasmic tail of this protein contains two highly conserved domains which may be involved in CD93 function. Indeed, the highly charged juxtamembrane domain has been found to interact with moesin, a protein known to play a role in linking transmembrane proteins to the cytoskeleton and in the remodeling of the cytoskeleton. This process appears crucial for adhesion, migration and phagocytosis.

[0005] The disclosures of all publications, patents, patent applications and published patent applications referred to herein are hereby incorporated herein by reference in their entirety.

BRIEF SUMMARY

[0006] The following summary is illustrative only and is not intended to be limiting in any way. That is, the following summary is provided to introduce highlights, benefits and advantages of the novel molecules and the uses thereof. Thus, the following summary is not

intended to identify essential features of the claimed subject matter, nor is it intended for use in determining the scope of the claimed subject matter.

[0006a] In an aspect of the present disclosure, there is provided an anti-CD93 construct comprising an antibody moiety comprising a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein the antibody moiety competes for a binding epitope of CD93 with an antibody or antibody fragment comprising a second heavy chain variable region (V_{H-2}) and a second light chain variable region (V_{L-2}), wherein:

a) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17 or 304, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18 or 305, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, 301, 302, 303, or 306, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22; or

b) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 177, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 178, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 179, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 180 or 353, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 181 or 354, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 182.

[0006b] In another aspect of the present disclosure, there is provided an anti-CD93 construct comprising an antibody moiety that specifically binds to CD93, comprising:

a) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any of SEQ ID NO: 29 and 307-312, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any SEQ ID NO: 30, and 313-318; or

b) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any of SEQ ID NO: 189 and 347-349, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any of SEQ ID NO: 190, and 350-352.

[0006c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the anti-CD93 construct disclosed herein, and a pharmaceutical acceptable carrier.

[0006d] In another aspect of the present disclosure, there is provided an isolated nucleic acid encoding the anti-CD93 construct disclosed herein or a portion thereof.

[0006e] In a further aspect of the present disclosure, there is provided a vector comprising the isolated nucleic acid disclosed herein.

[0006f] In another aspect of the present disclosure, there is provided an isolated host cell comprising the isolated nucleic acid disclosed herein, or the vector disclosed herein.

[0006g] In a further aspect of the present disclosure, there is provided an immunoconjugate comprising the anti-CD93 construct disclosed herein, linked to a therapeutic agent or a label.

[0006h] In another aspect of the present disclosure, there is provided a use of an anti-CD93 construct disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or condition in an individual.

[0006i] In a further aspect of the present disclosure, there is provided an anti-CD93 construct disclosed herein, or the pharmaceutical composition disclosed herein, for use in treating therapy.

[0007] In one example, the present application provides an anti-CD93 construct comprising an antibody moiety comprising a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein the antibody moiety competes for a binding epitope of CD93 with an antibody or antibody fragment comprising a second heavy chain variable region (V_{H-2}) and a second light chain variable region (V_{L-2}), wherein:

a) the V_{H-2} comprising the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 6;

b) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22;

c) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 33, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 34, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 36, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 37, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 38;

d) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 49, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 50, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 51, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 52, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 53, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 54;

e) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 65, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 66, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 67, and the V_{L-2} comprises the LC-

303, or 306, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO:22.

[0008] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs; and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0009] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17 or 304, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18 or 305, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs; and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, 301, 302, 303, or 306, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0010] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 33, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 34, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs; and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 36, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 37, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0011] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 49, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 50, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 51, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 52, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 53, and iii) the LC-

CDR3 comprising the amino acid sequence of SEQ ID NO: 54, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0012] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 65, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 66, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 67, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 68, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 69, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0013] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 81, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 82, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 84, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 85, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 86, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0014] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 97, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 98, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 100, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 101, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0015] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 113, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 114, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 116, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 117, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 118, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0016] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 129, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 130, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 132, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 133, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 134, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0017] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 145, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 146, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 147, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 148, 355, or 358, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 149 or 356, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 150, 357 or 359, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0018] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 161, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 162, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 163, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 164, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 165, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0019] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 177, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 178, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 179, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 180 or 353, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 181 or 354, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 182, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0020] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 193, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 194, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 196, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 197, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0021] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 209, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 210, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 211, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 212, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 213, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 214, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0022] In some examples, the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 289, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 290, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 291, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs, and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 292, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 293, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 294, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0023] In some examples, the V_H comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17 or 304, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18 or 305, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs; and the V_L comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, 301, 302, 303, or 306, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

[0024] The present application in another example comprises an anti-CD93 construct comprising an antibody moiety that specifically binds to CD93, comprising:

n) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in SEQ ID NO: 221, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in SEQ ID NO: 222;

o) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any of SEQ ID NO: 287 and 319-321, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any of SEQ ID NO: 288, and 322-324;

p) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any one of SEQ ID NOs: 307-312, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any one of SEQ ID NOs: 313-318; or

q) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any one of SEQ ID NOs: 319-321, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any one of SEQ ID NOs: 322-324.

[0025] In some examples according to any of the anti-CD93 constructs described above, wherein the V_H comprises an amino acid sequence of any one of SEQ ID NOs: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 287, 307-312 and 319-321, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and/or wherein the V_L comprises an amino acid sequence of any one of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 288, 313-318 and 322-324 or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 13, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 14, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of any of SEQ ID NO: 29 and 307-312, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of any of SEQ ID NO: 30, and 313-318, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 45, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 46, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 61, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 62, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 77, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 78, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 93, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 94, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 109, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO:

110, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 125, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 126, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 141, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 142, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 157, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 158, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 173, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 174, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of any of SEQ ID NO: 189 and 347-349, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of any of SEQ ID NO: 190, and 350-352, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 205, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 206, or a variant comprising an amino acid sequence having at least

about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of SEQ ID NO: 221, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of SEQ ID NO: 222, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity. In some examples, the V_H comprises an amino acid sequence of any of SEQ ID NO: 287 and 319-321, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity; and the V_L comprises an amino acid sequence of any of SEQ ID NO: 288, and 322-324, or a variant comprising an amino acid sequence having at least about 80% (such as at least about any one of 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%) sequence identity.

[0026] In some examples according to any of the anti-CD93 constructs described above, the antibody moiety is an antibody or antigen-binding fragment thereof selected from the group consisting of a full-length antibody, a bispecific antibody, a single-chain Fv (scFv) fragment, a Fab fragment, a Fab' fragment, a F(ab')₂, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a Fv-Fc fusion, a scFv-Fc fusion, a scFv-Fv fusion, a diabody, a tribody, and a tetrabody. In some examples, the antibody moiety is a full-length antibody.

[0027] In some examples according to any of the anti-CD93 constructs described above, the antibody moiety has an Fc fragment is selected from the group consisting of Fc fragments from IgG, IgA, IgD, IgE, IgM, and combinations and hybrids thereof. In some examples, the Fc fragment is selected from the group consisting of Fc fragments from IgG1, IgG2, IgG3, IgG4, and combinations and hybrids thereof. In some examples, the Fc fragment has a reduced effector function as compared to the corresponding wildtype Fc fragment. In some examples, the Fc fragment has an enhanced effector function as compared to the corresponding wildtype Fc fragment. In some examples the Fc fragment has extended serum half-life. In some examples the Fc fragment has reduced serum half-life.

[0028] In some examples according to any of the anti-CD93 constructs described above, the antibody moiety blocks the binding of CD93 to IGFBP7 (such as human IGFBP7).

[0029] In some examples according to any of the anti-CD93 constructs described above, the antibody moiety blocks the binding of CD93 to MMRN2 (such as human MMRN2).

[0030] In some examples according to any of the anti-CD93 constructs described above, the antibody moiety blocks a) the binding of CD93 to IGFBP7 and/or b) the binding of CD93 to MMRN2.

[0031] In some examples according to any of the anti-CD93 constructs described above, the CD93 is a human CD93.

[0032] The present application in another example provides a pharmaceutical composition comprising any of the anti-CD93 constructs described above, and a pharmaceutical acceptable carrier.

[0033] The present application in another example provides an isolated nucleic acid encoding any of the anti-CD93 constructs described above.

[0034] The present application in another example provides a vector comprising any of the isolated nucleic acids described above.

[0035] The present application in another example provides an isolated host cell comprising any of the isolated nucleic acids or vectors described above.

[0036] The present application in another example provides an immunoconjugate comprising the any of the anti-CD93 constructs described above, linked to a therapeutic agent or a label.

[0037] The present application in another example provides a method of producing an anti-CD93 construct comprising: a) culturing the isolated host cell of claim 25 under conditions effective to express the anti-CD93 construct; and b) obtaining the expressed anti-CD93 construct from the host cell.

[0038] The present application in another example provides a method of treating a disease or condition in an individual, comprising administering to the individual an effective amount of any of the anti-CD93 constructs or pharmaceutical compositions described above. In some examples, the disease or condition is associated with an abnormal vascular structure. In some examples, the disease or condition is a cancer. In some examples, the cancer is a solid tumor. In some examples, the cancer comprises CD93+ endothelial cells. In some examples, the cancer comprises IGFBP7+ blood vessels. In some examples, the cancer is characterized by tumor hypoxia. In some examples, the cancer is a locally advanced or metastatic cancer. In some examples, the cancer is selected from the group consisting of a lymphoma, colon cancer, brain cancer, breast cancer, ovarian cancer, endometrial cancer, esophageal cancer, prostate cancer, cervical cancer, renal cancer, bladder cancer, gastric cancer, non-small cell lung cancer, melanoma, and pancreatic cancer. In some examples, the anti-CD93 construct is administered parenterally into the individual. In some examples, the method further comprises administering a second therapy. In some examples, the second

therapy is selected from the group consisting of surgery, radiation, gene therapy, immunotherapy, bone marrow transplantation, stem cell transplantation, hormone therapy, targeted therapy, cryotherapy, ultrasound therapy, photodynamic therapy, and chemotherapy. In some examples, the second therapy is an immunotherapy. In some examples, the immunotherapy comprises administering an immunomodulatory agent. In some examples, the immunomodulatory agent is an immune checkpoint inhibitor. In some examples, the immune checkpoint inhibitor comprises an anti-PD-L1 antibody or an anti-PD-1 antibody. In some examples, the individual is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0039]** FIG. 1 shows binding affinity of 16E4 and MM01 against human or cynomolgus CD93.
- [0040]** FIG. 2 shows binding of various anti-CD93 antibodies to CD93-expressing CHO cells.
- [0041]** FIGS. 3A-3D show that the inhibition of the interaction between CD93 and IGFBP7 by 16E4 and MM01 as compared to mIgG isotype at various concentrations.
- [0042]** FIGS. 4A-4F show the inhibition of HUVEC tube formation by various anti-CD93 antibodies as compared to control.
- [0043]** FIGS. 5A-5B show results of epitope binning of various anti-CD93 antibodies by Octet competition.
- [0044]** FIGS. 6A-6B show cross-binding activities of various anti-CD93 antibodies against human and cynomolgus CD93 measured by bio-layer interferometry (BLI) assay.
- [0045]** FIGS. 7A-7B show alignment of V_H and V_L CDRs according to Kabat numbering. From top to bottom, sequences in FIG 7A are SEQ ID NO: 393-406, and sequences in FIG 7B are SEQ ID NO: 407-420.
- [0046]** FIGS. 8A-8B show alignment of V_H and V_L CDRs determined by the VBASE2 tool. From top to bottom, sequences in FIG 8A are SEQ ID NO: 393-406, and sequences in FIG 8B are SEQ ID NO: 407-420.
- [0047]** FIG. 9 shows binding affinity of 10B1 and 7F3 to human CD93.
- [0048]** FIG. 10 shows binding of 16E4, 10B1 and 7F3 to human CD93-expressing CHO cells and lack of binding to CHO-K1 cells.
- [0049]** FIGS. 11A-11B show that the inhibition of the interaction between CD93 and MMRN2 by 16E4, 10B1, and 7F3 as compared to mIgG isotype at 50 $\mu\text{g/mL}$.
- [0050]** FIG. 12 shows the inhibition of the interaction between CD93 and MMRN2 by 7F3 at different MMRN2 concentrations as compared to control (IgG2a)

CLAIMS

1. An anti-CD93 construct comprising an antibody moiety comprising a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein the antibody moiety competes for a binding epitope of CD93 with an antibody or antibody fragment comprising a second heavy chain variable region (V_{H-2}) and a second light chain variable region (V_{L-2}), wherein:

a) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17 or 304, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18 or 305, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, 301, 302, 303, or 306, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22; or

b) the V_{H-2} comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 177, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 178, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 179, and the V_{L-2} comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 180 or 353, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 181 or 354, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 182.

2. The anti-CD93 construct of claim 1, wherein:

a) the V_H comprises the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 17 or 304, the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 18 or 305, and the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 19, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs; and the V_L comprises the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 20, 301, 302, 303, or 306, the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 21, and the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs; or

b) the V_H comprises i) the HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 177, ii) the HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 178, and iii) the HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 179, or a variant thereof

comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the HC-CDRs; and the V_L comprises i) the LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 180 or 353, ii) the LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 181 or 354, and iii) the LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 182, or a variant thereof comprising up to 5, 4, 3, 2, or 1 amino acid substitutions in the LC-CDRs.

3. An anti-CD93 construct comprising an antibody moiety that specifically binds to CD93, comprising:

a) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any of SEQ ID NO: 29 and 307-312, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any SEQ ID NO: 30, and 313-318; or

b) a HC-CDR1, a HC-CDR2, and a HC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_H chain region having the sequence set forth in any of SEQ ID NO: 189 and 347-349, and a LC-CDR1, a LC-CDR2, and a LC-CDR3, respectively comprising the amino acid sequences of a CDR1, a CDR2, and a CDR3 within a V_L chain region having the sequence set forth in any of SEQ ID NO: 190, and 350-352.

4. The anti-CD93 construct of any one of claims 1-3, wherein:

a) the V_H comprises an amino acid sequence of any one of SEQ ID NOs: 29 and 307-312 or a variant comprising an amino acid sequence having at least about 80% sequence identity; and/or wherein the V_L comprises an amino acid sequence of any one of SEQ ID NOs: 30 and 313-318, or a variant comprising an amino acid sequence having at least about 80% sequence identity; or

(b) the V_H comprises an amino acid sequence of any of SEQ ID NO: 189 and 347-349, or a variant comprising an amino acid sequence having at least about 80% sequence identity; and the V_L comprises an amino acid sequence of any of SEQ ID NO: 190, and 350-352, or a variant comprising an amino acid sequence having at least about 80% sequence identity.

5. The anti-CD93 construct of any one of claims 1-4, wherein the antibody moiety is an antibody or antigen-binding fragment thereof selected from the group consisting of a full-length antibody, a bispecific antibody, a single-chain Fv (scFv) fragment, a Fab fragment, a Fab' fragment, a F(ab')₂, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a Fv-Fc fusion, a scFv-Fc fusion, a scFv-Fv fusion, a diabody, a tribody, and a tetrabody.
6. The anti-CD93 construct of claim 5, wherein the antibody moiety is a full-length antibody.
7. The anti-CD93 construct of any one of claims 1-6, wherein the antibody moiety has an Fc fragment is selected from the group consisting of Fc fragments from IgG, IgA, IgD, IgE, IgM, and combinations and hybrids thereof.
8. The anti-CD93 construct of claim 7, wherein the Fc fragment is selected from the group consisting of Fc fragments from IgG1, IgG2, IgG3, IgG4, and combinations and hybrids thereof.
9. The anti-CD93 construct of claim 7 or claim 8, wherein the Fc fragment has:
 - a) a reduced effector function as compared to the corresponding wildtype Fc fragment;or
 - b) enhanced effector function as compared to the corresponding wildtype Fc fragment.
10. The anti-CD93 construct of any one of claims 1-9, wherein the antibody moiety blocks the binding of CD93 to IGFBP7 and/or MMRN2.
11. The anti-CD93 construct of any one of claims 1-6, wherein the CD93 is a human CD93.
12. A pharmaceutical composition comprising the anti-CD93 construct of any one of claims 1-11, and a pharmaceutical acceptable carrier.
13. An isolated nucleic acid encoding the anti-CD93 construct of any one of claims 1-11 or a portion thereof.
14. A vector comprising the isolated nucleic acid of claim 13.
15. An isolated host cell comprising the isolated nucleic acid of claim 13, or the vector of claim 14.

16. An immunoconjugate comprising the anti-CD93 construct of any one of claims 1-11, linked to a therapeutic agent or a label.
17. Use of an anti-CD93 construct of any one of claims 1-11, or the pharmaceutical composition of claim 12, in the manufacture of a medicament for treating a disease or condition in an individual.
18. The use of claim 17, wherein the disease or condition is associated with an abnormal vascular structure and/or the disease or condition is a cancer; and/or wherein the anti-CD93 construct is to be used parenterally and/or with a second therapy in treating the disease or condition.
19. The use of claim 18, wherein the cancer is a solid tumor; and/or wherein the cancer comprises CD93+ endothelial cells; and/or wherein the cancer comprises IGFBP7+ blood vessels and/or MMRN2+ blood vessels; and/or wherein the cancer is characterized by tumor hypoxia; and/or wherein the cancer is a locally advanced or metastatic cancer.
20. The use of any one of claims 18-19, wherein the cancer is selected from the group consisting of a lymphoma, colon cancer, brain cancer, breast cancer, ovarian cancer, endometrial cancer, esophageal cancer, prostate cancer, cervical cancer, renal cancer, bladder cancer, gastric cancer, non-small cell lung cancer, melanoma, and pancreatic cancer.
21. An anti-CD93 construct of any one of claims 1-11, or the pharmaceutical composition of claim 12, for use in treating therapy.