

DEPLETION OF ACTIVATED HEPATIC STELLATE CELLS (HSCS) AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of priority of International Patent Application No. PCT/CN2021/104201 filed on July 2, 2021, the disclosure of which is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] This application incorporates by reference a Sequence Listing submitted with this application as a text file entitled “14668-006-228_SEQ_LISTING.txt,” which was created on June 27, 2022, and is 568,110 bytes in size.

1. FIELD

[0003] Provided herein are molecules capable of binding to activated hepatic stellate cells (HSCs), pharmaceutical compositions comprising same, and uses thereof.

2. BACKGROUND

[0004] Activated hepatic stellate cells (HSC) are the key type of cells mediating fibrogenesis upon liver injury. Therapeutic approach targeting to activated HSCs is highly needed to slow or prevent fibrosis formation and improve quality of life in the patients with liver fibrosis or cirrhosis. The present disclosure addresses this and other needs in the art.

3. SUMMARY

[0004a] In one aspect, provided herein is a binding molecule comprising one binding domain that binds to an antigen expressed on an activated hepatic stellate cell (HSC), and a functional domain that is capable of enhancing an antibody effector function toward the activated HSC, wherein (i) the antigen expressed on the activated HSC is PDGFRb; (ii) the binding domain is an antibody or PDGFRb binding fragment thereof, or a fusion protein comprising said antibody or fragment thereof; and (iii) the functional domain is an Fc region comprising S239D/I332E or S239D/A330L/I332E mutations to enhance ADCC.

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

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

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

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

[0004f] In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for the treatment of a disease or disorder (1) associated with activated HSCs, or (2) liver fibrosis in a subject.

[0004g] In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for depleting activated HSCs in a subject.

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

[0005] In one aspect, provided herein is a binding molecule comprising one or more binding domain(s) that bind(s) to one or more antigen(s) expressed on an activated hepatic stellate cells (HSC), and a functional domain that is capable of enhancing an antibody effector function toward activated HSCs. In some embodiments, the antibody effector function is antibody-dependent cell-mediated cytotoxicity (ADCC). In some embodiments, the functional domain is an Fc region comprising one or more mutation(s) that enhances ADCC. In other embodiments, the functional domain is a domain that activates an immune cell. In some embodiments, the immune cell is a NK cell.

[0006] In some embodiments, the functional domain is the Fc region comprising one or more mutation(s) that enhances ADCC. In some embodiments, the one or more mutation(s) of the Fc region is at the position of 233, 234, 235, 236, 237, 238, 239, 240, 241, 243, 244, 245, 246, 247, 248, 250, 253, 254, 255, 256, 258, 260, 262, 263, 264, 265, 266, 267, 268, 268, 269, 270, 272, 274, 276, 280, 282, 283, 285, 286, 288, 290, 292, 293, 294, 295, 296,

What is claimed:

1. A binding molecule comprising one binding domain that binds to an antigen expressed on an activated hepatic stellate cell (HSC), and a functional domain that is capable of enhancing an antibody effector function toward the activated HSC, wherein
 - (i) the antigen expressed on the activated HSC is PDGFRb;
 - (ii) the binding domain is an antibody or PDGFRb binding fragment thereof, or a fusion protein comprising said antibody or fragment thereof; and
 - (iii) the functional domain is an Fc region comprising S239D/I332E or S239D/A330L/I332E mutations to enhance ADCC.
2. The binding molecule of claim 1, wherein the antibody or fragment thereof comprises a heavy chain complementarity-determining region 1 (HCDR1), a heavy chain complementarity-determining region 2 (HCDR2), and a heavy chain complementarity-determining region 3 (HCDR3) as set forth in SEQ ID NO: 67, and a light chain complementarity-determining region 1 (LCDR1), a light chain complementarity-determining region 2 (LCDR2), and a light chain complementarity-determining region 3 (LCDR3) as set forth in SEQ ID NO: 68.
3. The binding molecule of claim 2, wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 1, the HCDR2 comprises the amino acid sequence of SEQ ID NO: 2, the HCDR3 comprises the amino acid sequence of SEQ ID NO: 3, the LCDR1 comprises the amino acid sequence of SEQ ID NO: 4, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 5, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 6.
4. The binding molecule of claim 2 or claim 3, wherein the antibody or fragment thereof comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 67 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 68.

5. The binding molecule of any one of claims 1 to 4, wherein the binding molecule further comprises:
a domain that activates an immune cell, and wherein optionally the immune cell is a NK cell.
6. The binding molecule of any one of claims 1 to 5, wherein the binding molecule is an IgG antibody or a fusion protein comprising the IgG antibody.
7. The binding molecule of claim 6, wherein the antibody is a humanized antibody.
8. A nucleic acid molecule encoding the binding molecule of any one of claims 1 to 7 or a fragment thereof.
9. A vector comprising the nucleic acid molecule of claim 8.
10. A host cell transformed with the vector of claim 9.
11. A composition comprising a therapeutically effective amount of the binding molecule of any one of claims 1 to 7, the nucleic acid molecule of claim 8, or the vector of claim 9, and a pharmaceutically acceptable excipient.
12. Use of the composition of claim 11 in the manufacture of a medicament for the treatment of a disease or disorder (1) associated with activated HSCs, or (2) liver fibrosis in a subject.
13. The use of claim 12, wherein the disease or disorder is associated with activated HSCs.
14. The use of claim 13, wherein the disease or disorder is liver fibrosis.

15. Use of the composition of claim 11 in the manufacture of a medicament for depleting activated HSCs in a subject.
16. The use of claim 15, wherein the subject has a disease or disorder associated with activated HSCs.
17. The use of claim 15, wherein the disease or disorder is liver fibrosis.
18. The composition of claim 11 for use in therapy.