

GLYPICAN 3 ANTIBODIES AND CONJUGATES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Application No. 62/631,353, filed February 15, 2018, which is incorporated by reference in its entirety.

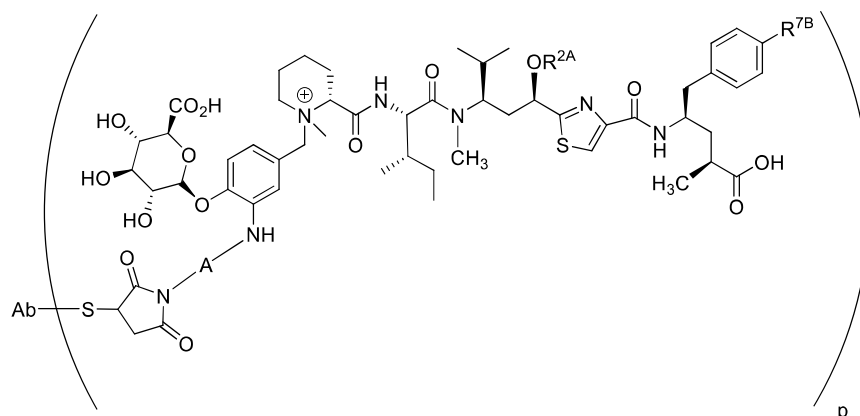
BACKGROUND

[0002] Glypican 3 (GPC3) is a cell surface proteoglycan that is known to be expressed on hepatocellular carcinoma cells and has been reported on a number of malignant cells. The present invention provides GPC3 antibodies and conjugates thereof.

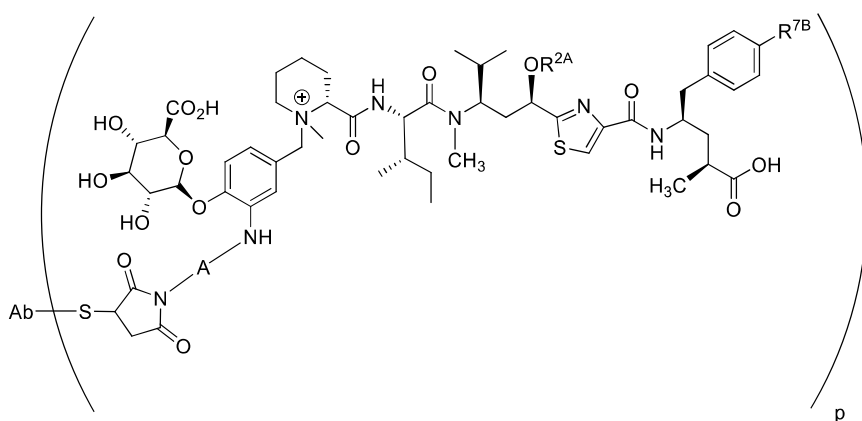
SUMMARY

[0003] Provided herein are anti-GPC3 antibodies and GPC3 directed antibody-drug conjugates. In particular, provided herein are GPC3 directed tubulysin antibody-drug conjugates and methods of using such conjugates to treat GPC3 expressing disorders. Preferred anti-GPC3 antibodies are chimeric or humanized forms of the murine GPC3-1 antibody. The murine GPC3-1 antibody comprises a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO:8 and a light chain variable region having the amino acid sequence set forth in SEQ ID NO:9.

[0003a] In one aspect, the present disclosure refers to an antibody that specifically binds to the human Glypican-3 (GPC3) protein wherein the antibody comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO:1 and the three light chain CDRs of SEQ ID NO:2 wherein the CDRs are as defined by Kabat. In another aspect, the present disclosure refers to an anti-GPC3 antibody-drug conjugate compound having the formula



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein A is a Stretcher Unit; R^{2A} is $-C(=O)R^{2B}$ wherein R^{2B} is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or R^{2A} is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl; R^{7B} is $-H$ or $-OH$; Ab is an antibody as set forth in any of claims 1-14; S is a sulfur atom from the antibody; and subscript p is an integer from 1 to 4. In yet another aspect, the present disclosure refers to use of an antibody-drug conjugate composition in the manufacture of a medicament for treating a patient having a cancer that expresses GPC3, comprising that an effective regimen of the composition is to be administered to the patient, wherein the composition comprises a population of anti-GPC3 antibody-drug conjugate compounds having the formula:



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein A is a Stretcher Unit; R^{2A} is $-C(=O)R^{2B}$ wherein R^{2B} is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or R^{2A} is methyl, ethyl, propyl, iso-

propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl; R^{7B} is $-H$ or $-OH$; Ab is an antibody as set forth in claim 1; S is a sulfur atom from the antibody; and subscript p is an integer from 1 to 4 for each antibody drug conjugate compound; and the average drug loading of the composition is about 2; and the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

BRIEF DESCRIPTION OF THE FIGURES

[0004] Figure 1 shows the sequence of human GPC3.

[0005] Figure 2A shows a sequence alignment of hGPC3-1 heavy chain variants with human vH donor sequence, HV1-18/HJ4.

[0006] Figure 2B shows a sequence alignment of hGPC3-1 heavy chain variants with human vH donor sequence, HV1-69-2/HJ4.

WHAT IS CLAIMED IS:

1. An antibody that specifically binds to the human Glypican-3 (GPC3) protein wherein the antibody comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO:1 and the three light chain CDRs of SEQ ID NO:2 wherein the CDRs are as defined by Kabat.
2. The antibody of claim 1 that is a humanized, chimeric or veneered antibody.
3. The antibody of any one of the preceding claims, which is a humanized antibody comprising a mature heavy chain variable region having at least 90% sequence identity with SEQ ID NO:1 and a mature light chain variable region having at least 90% sequence identity with SEQ ID NO:2.
4. The antibody of any one of the preceding claims, wherein the mature heavy chain variable region has at least 95% sequence identity with SEQ ID NO:1 and the mature light chain variable region has at least 95% sequence identity with SEQ ID NO:2.
5. The antibody of any one of the preceding claims, wherein H24 is occupied by V or A, H38 is occupied by Q, R or K, H48 is occupied by M or I, H66 is occupied by R or K, H67 is occupied by V or A, H69 is occupied by L, H71 is occupied by A, H73 is occupied by K or T, H93 is occupied by G or A, H94 is occupied by R and the following amino acid residues of the light chain are present: L45 is occupied by R or K, L46 is occupied by L or R, L105 is occupied by E or V, L106 is occupied by I or M; numbering is via the Kabat numbering system.
6. The antibody of any one of the preceding claims, wherein the following variable region frameworks positions are occupied as specified: H24 is occupied by V, H38 is occupied by Q, H48 is occupied by M, H66 is occupied by R, H67 is occupied by V, H69 is occupied by L, H71 is occupied by A, H73 is occupied by K, H93 is occupied by G, H94 is occupied by R; numbering is via the Kabat numbering system.
7. The antibody of any one of the preceding claims, wherein the following variable region frameworks positions are occupied as specified: L45 is occupied by R, L46 is occupied by L, L105 is occupied by E, L106 is occupied by I; numbering is via the Kabat numbering system.

8. The antibody of claim 1 that is HALA, HALB, HALC, HBLA, HBLB, HBLC, HBLD, HBLE, HBLB-Q, HBLB-V, HCLA, HCLB, HCLC, HDLA, HDLB and HDLC.

9. The antibody of any one of the preceding claims wherein the mature heavy chain variable region is fused to a heavy chain constant region and the mature light chain variable region is fused to a light chain constant region.

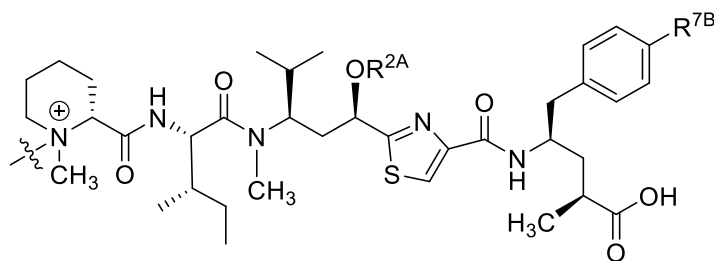
10. The antibody of claim 9, wherein the heavy chain constant region is a mutant form of a natural human constant region which has reduced binding to an Fc gamma receptor relative to the natural human constant region.

11. The antibody of claim 9, wherein the heavy chain constant region is of IgG1 isotype.

12. The antibody of claim 9, wherein the heavy chain constant region has an amino acid sequence comprising SEQ ID NO:5 or SEQ ID NO:6 and the light chain constant region has an amino acid sequence comprising SEQ ID NO:7.

13. The antibody of any one of the preceding claims, wherein the antibody is conjugated to a cytotoxic or cytostatic agent.

14. The antibody of claim 13 wherein the conjugated cytotoxic agent is a conjugated tubulysin having the structure of:

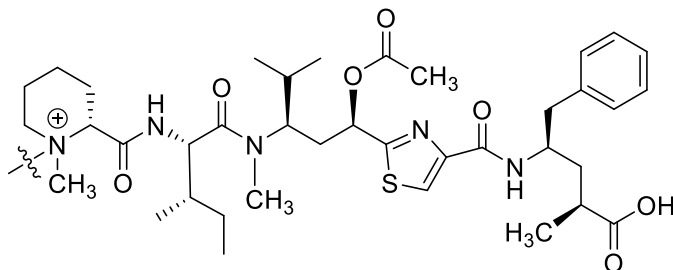


wherein the conjugated tubulysin is in salt form, in particular pharmaceutically acceptable salt form, or a solvate thereof, and wherein the wavy line indicates the site at which the tubulysin is conjugated to the antibody;

R^{2A} is -C(=O)R^{2B} wherein R^{2B} is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or R^{2A} is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl; and

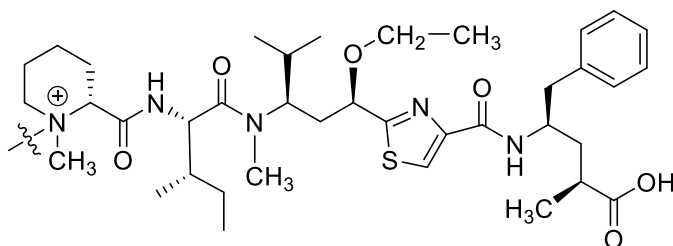
R^{7B} is -H or -OH.

15. The antibody of claim 13 wherein the conjugated cytotoxic agent is a conjugated tubulysin having the structure of:



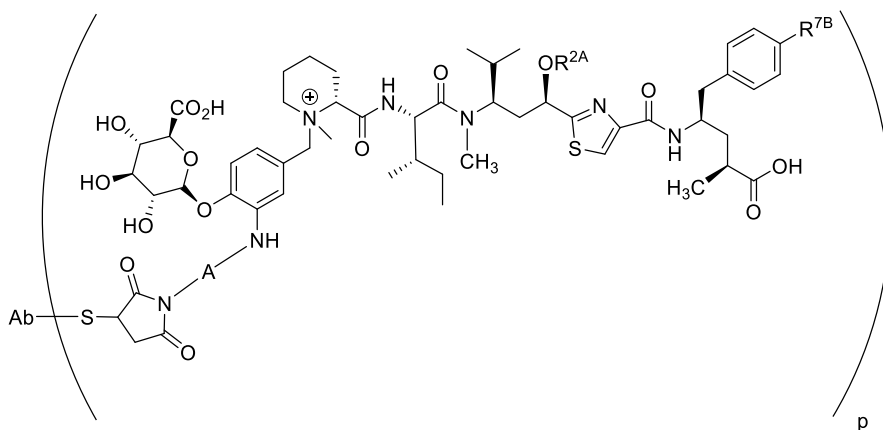
wherein the conjugated tubulysin is in salt form, in particular in pharmaceutically acceptable salt form, or a solvate thereof, and wherein the wavy line indicates the site at which the tubulysin is conjugated to the antibody.

16. The antibody of claim 13 wherein the conjugated cytotoxic agent is a conjugated tubulysin having the structure of:



wherein the conjugated tubulysin is in salt form, in particular in pharmaceutically acceptable salt form, or a solvate thereof, and wherein the wavy line indicates the site at which the tubulysin is conjugated to the antibody.

17. An anti-GPC3 antibody-drug conjugate compound having the formula



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

A is a Stretcher Unit;

R^{2A} is $-C(=O)R^{2B}$ wherein R^{2B} is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or R^{2A} is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl;

R^{7B} is $-H$ or $-OH$;

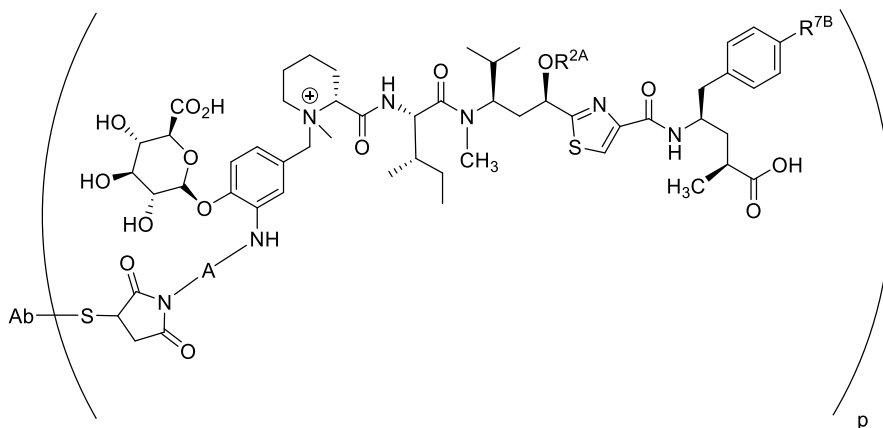
Ab is an antibody as set forth in any of claims 1-14;

S is a sulfur atom from the antibody; and

subscript p is an integer from 1 to 4.

18. Use of an antibody-drug conjugate composition in the manufacture of a medicament for treating a patient having a cancer that expresses GPC3, comprising that an effective regimen of the composition is to be administered to the patient,

wherein the composition comprises a population of anti-GPC3 antibody-drug conjugate compounds having the formula:



in salt form, in particular in pharmaceutically salt form, or solvate thereof, or having the formula above in which the thio-substituted succinimide is in hydrolyzed form; wherein

A is a Stretcher Unit;

R^{2A} is $-C(=O)R^{2B}$ wherein R^{2B} is methyl, ethyl, propyl, iso-propyl, 2-methyl-prop-1-yl, 2,2-dimethyl-prop-1-yl, or vinyl, or R^{2A} is methyl, ethyl, propyl, iso-propyl, prop-2-en-1-yl or 2-methyl-prop-2-en-1-yl;

R^{7B} is $-H$ or $-OH$;

Ab is an antibody as set forth in claim 1;

S is a sulfur atom from the antibody; and

subscript p is an integer from 1 to 4 for each antibody drug conjugate compound; and the average drug loading of the composition is about 2;

and

the subscript p is an integer from 1 to 4; and the average drug load of the composition is about 2.

19. The use of claim 18, wherein the cancer is a hepatocellular carcinoma (HCC), a lung carcinoma, Wilms tumor (nephroblastoma), an ovarian clear cell carcinoma, a colorectal carcinoma, or a sarcoma.

20. The use of claim 18, wherein the cancer is HCC.

21. The antibody of claim 1, wherein the three heavy chain CDRs are as set forth in SEQ ID NOs: 10, 11, and 12, and the three light chain CDRs are as set forth in SEQ ID NOs: 13, 14, and 15.

22. An antibody that specifically binds to the human GPC3 protein wherein the antibody comprises the three heavy chain CDRs as set forth in SEQ ID NOs: 10, 11, and 12, and the three light chain CDRs as set forth in SEQ ID NOs: 13, 14, and 15.