SUMMARY OF THE INVENTION

[0004] The present invention addresses and resolves the foregoing shortcomings in the prior art with compositions and methods providing improved discrimination between membrane-bound and cytosolic GPC3, for more accurate diagnostic analyses and treatments. In some embodiments, the invention provides anti-GPC3 antibodies, including fragments thereof, and methods of using the same, *e.g.*, for the diagnosis, prevention, and/or treatment of cancer.

[0004a] In one aspect, provided herein is an isolated monoclonal antibody that binds glypican-3 (GPC3), wherein: the heavy chain of the anti-GPC3 antibody comprises a complementary determining region (CDR) 1 set forth as SEQ ID NO: 6, a CDR2 set forth as SEQ ID NO: 8, and a CDR3 set forth as SEQ ID NO: 10, and the light chain of the antibody comprises a CDR1 set forth as SEQ ID NO: 13, a CDR2 set forth as SEQ ID NO: 15, and a CDR3 set forth as SEQ ID NO: 17.

[0004b] In one aspect, provided herein is a method of detecting GPC3 in a tissue preparation, the method comprising: contacting the tissue preparation with the isolated monoclonal antibody as described herein under conditions sufficient for formation of a complex of the isolated monoclonal antibody as described herein with GPC3 present on the cell membrane of cells of the tissue preparation; and detecting binding of the antibody to the tissue preparation.

[0004c] In one aspect, provided herein is a method for predicting a therapeutic effect of an anti-GPC3 immunotherapy on a cancer, the cancer characterized in that cells of the cancer express GPC3, the method comprising: detecting the presence of said cells in a subject via the method as described herein, wherein when the complex of the anti-GPC3 antibody with GPC3 expressed on the membrane of the cancer cells is detected, the anti-GPC3 immunotherapy is predicted to have a therapeutic effect on the cancer in the subject.

[0004d] In one aspect, provided herein is an isolated nucleic acid molecule encoding the monoclonal antibody as described herein.

[0004e] In one aspect, provided herein is an expression vector comprising the isolated nucleic acid molecule as described herein.

[0004f] In one aspect, provided herein is an isolated host cell transformed with the expression vector as described herein.

[0004g] In one aspect, provided herein is a bispecific antibody, comprising the monoclonal antibody as described herein.

[0004h] In one aspect, provided herein is an antibody-drug conjugate (ADC), comprising the isolated monoclonal antibody as described herein.

[0004i] In one aspect, provided herein is a chimeric antigen receptor (CAR) comprising the antibody fragment as described herein.

[0004j] In one aspect, provided herein is a modified immune cell, comprising a chimeric antigen receptor (CAR), wherein said CAR comprises the CAR as described herein.

[0004k] In one aspect, provided herein is a plurality of modified immune cells as described herein.

[0004l] In one aspect, provided herein is a method of inhibiting the growth of a cell that displays a GPC3 epitope that is specifically recognized by the antibody as described herein, comprising contacting said cell with the isolated monoclonal antibody as described herein, the modified immune cell(s) as described herein, or the ADC as described herein.

[0004m] In one aspect, provided herein is a composition comprising a therapeutically effective amount of the isolated monoclonal antibody as described herein, the modified immune cell(s) as described herein, or the ADC as described herein, and a pharmaceutically acceptable carrier.

[0004n] In one aspect, provided herein is a use of the composition as described herein in the manufacture of a medicament for treating a selected subject having a cancer that expresses GPC3.

[0004o] In one aspect, provided herein is a use of the antibody as described herein in the preparation of a medicament for the treatment of cancer.

[0004p] In one aspect, provided herein is a use of the modified immune cell(s) as described herein in the preparation of a medicament for the treatment of cancer.

[0004q] In one aspect, provided herein is a use of the ADC as described herein in the preparation of a medicament for the treatment of cancer.

[0004r] In one aspect, provided herein is a use of the CAR as described herein in the preparation of a medicament for the treatment of cancer.

[0004s] In one aspect, provided herein is a composition as described herein, the antibody as described herein, the modified immune cell(s) as described herein, the ADC as described herein, or the CAR as described herein for use in therapy.

[0005] In one embodiment, anti-GPC3 antibodies of the invention bind to a GPC3 epitope that is positioned in a C-terminal beta chain of GPC3. In one embodiment, the anti-GPC3 antibody comprises a heavy chain variable region comprising SEQ ID NO: 2 and a light chain variable region comprising SEQ ID NO: 4.

[0006] In one embodiment, the heavy chain of an anti-GPC3 antibody of the present invention comprises a complementary determining region (CDR) 1 set forth as SEQ ID NO: 6, a CDR2 set forth as SEQ ID NO: 8, and a CDR3 set forth as SEQ ID NO: 10.

[0007] In one embodiment, the light chain of an anti-GPC3 antibody of the present invention comprises a CDR1 set forth as SEQ ID NO: 13, a CDR2 set forth as SEQ ID NO: 15, and a CDR3 set forth as SEQ ID NO: 17.

[0008] In one embodiment, the heavy chain of an anti-GPC3 antibody of the present invention comprises a complementary determining region (CDR) 1 set forth as SEQ ID NO: 6, a CDR2 set forth as SEQ ID NO: 8, and a CDR3 set forth as SEQ ID NO: 10, and the light chain of the an anti-GPC3 antibody of the present invention comprises a CDR1 set forth as SEQ ID NO: 13, a CDR2 set forth as SEQ ID NO: 15, and a CDR3 set forth as SEQ ID NO: 17.

[0009] In one embodiment, the heavy chain of an anti-GPC3 antibody comprises a CDR1, a CDR2, and a CDR3, respectively set forth as amino acid residues 31-35, 50-66, and 99-105 of SEQ ID NO: 2, and the light chain of the antibody comprises a CDR1, a CDR2, and a CDR3 respectively set forth as amino acid residues 24-34, 50-56, and 89-97 of SEQ ID NO: 4.

[0010] In one embodiment, the invention provides an anti-GPC3 antibody that competes with an antibody comprising a heavy chain variable region comprising SEQ ID NO:2 and a light chain variable region comprising SEQ ID NO: 4 for binding to GPC3.

[0011] Anti-GPC3 antibodies of the invention include, for example, monoclonal antibodies, antibody fragments, including Fab, Fab', F(ab')2, and Fv fragments, diabodies, single domain antibodies, chimeric antibodies, humanized antibodies, single-chain antibodies and antibodies that competitively inhibit the binding of an antibody comprising a heavy chain variable region comprising SEQ ID NO:2 and a light chain variable region comprising SEQ ID NO:4 to the GPC3.