CLAIMS

What is claimed is:

1. An isolated anti-Glypican-3 (anti-GPC3) construct comprising an antibody moiety specifically recognizing GPC3 (anti-GPC3 antibody moiety), wherein the anti-GPC3 antibody moiety comprises:

(1) a heavy chain complementarity determining region (HC-CDR) 1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 54, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 105, a light chain complementarity determining region (LC-CDR) 1 comprising the amino acid sequence of SEQ ID NO: 156, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 207, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 258;

(2) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 21, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 72, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 123, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 174, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 225, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 276;

(3) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 126, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 177, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 228, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 279;

(4) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 52, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 103, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 154, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 205, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 256;

(5) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 11, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 62, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 113, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 164, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 215, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 266; or

(6) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 12, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 63, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 114, an LC-CDR1 comprising the amino acid sequence of SEQ

ID NO: 165, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 216, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 267.

2. The isolated anti-GPC3 construct of claim 1, wherein the anti-GPC3 antibody moiety comprises:

(1) i) a heavy chain variable domain (VH) comprising the amino acid sequence of SEQ ID NO: 309, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 309; and ii) a light chain variable domain (VL) comprising the amino acid sequence of SEQ ID NO: 360, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 360;

(2) i) a VH comprising the amino acid sequence of SEQ ID NO: 327, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 327; and ii) a VL comprising the amino acid sequence of SEQ ID NO: 378, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 378;

(3) i) a VH comprising the amino acid sequence of SEQ ID NO: 330, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 330; and ii) a VL comprising the amino acid sequence of SEQ ID NO: 381, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 381;

(4) i) a VH comprising the amino acid sequence of SEQ ID NO: 307, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 307; and ii) a VL comprising the amino acid sequence of SEQ ID NO: 358, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 358;

or

(5) i) a VH comprising the amino acid sequence of SEQ ID NO: 317, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 317; and ii) a VL comprising the amino acid sequence of SEQ ID NO: 368, or a variant thereof having at least about 95% sequence identity to SEQ ID NO: 368.

3. The isolated anti-GPC3 construct of claim 1, wherein the anti-GPC3 antibody moiety is fused to an Fc fragment optionally via a linker.

4. The isolated anti-GPC3 construct of claim 1, wherein the isolated anti-GPC3 construct is a tandem scFv comprising two scFvs linked by a peptide linker.

5. The isolated anti-GPC3 construct of claim 1, wherein the isolated anti-GPC3 construct is a chimeric antigen receptor (CAR) comprising:

(a) an extracellular domain comprising the anti-GPC3 antibody moiety;

(b) a transmembrane domain; and

(c) an intracellular signaling domain.

6. The isolated anti-GPC3 construct of claim 1, wherein the isolated anti-GPC3 construct is a chimeric antibody-T cell receptor (TCR) construct (caTCR) comprising:

(a) an extracellular domain comprising the anti-GPC3 antibody moiety; and

(b) a TCR module (TCRM) comprising i) a first TCR domain (TCRD) comprising a first TCR transmembrane domain (TCR-TM), and ii) a second TCRD comprising a second TCR-TM, wherein the TCRM facilitates recruitment of at least one TCR-associated signaling molecule.

7. The isolated anti-GPC3 construct of claim 1, wherein the isolated anti-GPC3 construct is an immunoconjugate comprising the anti-GPC3 antibody moiety and an effector molecule.

8. The isolated anti-GPC3 construct of claim 7, wherein the effector molecule is a label.

9. An isolated nucleic acid encoding the polypeptide components of the isolated anti-GPC3 construct of claim 1.

10. An isolated host cell comprising the isolated anti-GPC3 construct of claim 1.

11. An effector cell expressing the isolated anti-GPC3 construct of claim 5.

12. A pharmaceutical composition comprising the isolated anti-GPC3 construct of claim 1, and a pharmaceutically acceptable carrier.

13. A kit comprising the isolated anti-GPC3 construct of claim 1.

14. Use of the isolated anti-GPC3 construct of claim 1, wherein:

i) the isolated anti-GPC3 construct is expressed on the cell surface of an immune effector cell;

ii) the isolated anti-GPC3 construct further comprises a second antigen-binding moiety specifically recognizing a cell surface antigen on an immune effector cell; or

iii) the isolated anti-GPC3 construct further comprises an effector molecule, wherein the effector molecule is a therapeutic agent selected from the group consisting of a drug, a toxin, a radioisotope, a protein, a peptide, and a nucleic acid,

in the manufacture of a medicament for treating an individual having a GPC3-positive cancer.

15. A method of diagnosing an individual having a GPC3-positive disease, comprising determining the level of the label of the isolated anti-GPC3 construct of claim 8 in the individual who has been administered an effective amount of the isolated anti-GPC3 construct of claim 8, wherein a level of the label above a threshold level indicates that the individual has the GPC3-positive disease.

16. A method of diagnosing an individual having a GPC3-positive disease, comprising:

a) contacting a sample derived from the individual with the isolated anti-GPC3 construct of claim 8; and

b) determining the number of cells bound with the isolated anti-GPC3 construct in the sample, wherein a value for the number of cells bound with the isolated anti-GPC3 construct above a threshold level indicates that the individual has the GPC3-positive disease.

17. A method of producing an isolated anti-GPC3 construct, comprising:

(a) culturing a host cell comprising the isolated nucleic acid of claim 9 under a condition effective to express the isolated anti-GPC3 construct; and

(b) obtaining the expressed anti-GPC3 construct from said host cell.

18. The isolated anti-GPC3 construct of claim 1, wherein the isolated anti-GPC3 construct is a chimeric co-stimulatory receptor (CSR) comprising:

(a) an extracellular ligand-binding module comprising the anti-GPC3 antibody moiety;

(b) a transmembrane module; and

(c) an intracellular co-stimulatory immune cell signaling module.

19. The isolated anti-GPC3 construct of claim 1, wherein the anti-GPC3 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 3, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 54, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 105, an LC-CDR1 comprising the amino acid sequence of SEQ

ID NO: 156, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 207, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 258.

20. The isolated anti-GPC3 construct of claim 19, wherein the anti-GPC3 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 309, and a VL comprising the amino acid sequence of SEQ ID NO: 360.

21. The isolated anti-GPC3 construct of claim 1, wherein the anti-GPC3 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 21, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 72, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 123, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 174, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 225, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 276.

22. The isolated anti-GPC3 construct of claim 21, wherein the anti-GPC3 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 327, and a VL comprising the amino acid sequence of SEQ ID NO: 378.

23. The isolated anti-GPC3 construct of claim 1, wherein the anti-GPC3 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 126, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 177, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 228, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 279.

24. The isolated anti-GPC3 construct of claim 23, wherein the anti-GPC3 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 330, and a VL comprising the amino acid sequence of SEQ ID NO: 381.

25. The effector cell of claim 11, wherein the effector cell is a T cell.