

CLAIMS

It is claimed:

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy
5 chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain
complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide
sequences of:
- (1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;
 - (2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;
 - 10 (3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;
 - (4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;
 - (5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;
 - (6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or
 - (7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;
- 15 wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably
human GPC3.
2. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy
chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain
complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide
20 sequences of:
- (1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;
 - (2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;
 - (3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;
 - (4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;
 - 25 (5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;
 - (6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or
 - (7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;
- wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably
human GPC3.
- 30 3. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy
chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain
complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide
sequences of:
- (1) SEQ ID NOs: 3, 4, 5, 6, 7, and 8, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

4. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 9, 10, 11, 12, 13, and 14, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-4, comprising a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, 71, or 1, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, 72, or 2.

6. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5, comprising:

- a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;
- b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;
- c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
- d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
- e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;
- f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58;
- g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72;
- or
- h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

7. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof is chimeric and/or human or humanized.
8. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 7,
5 wherein the humanized monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least
10 99% identical to any one of SEQ ID NOs: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.
9. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 8, wherein the humanized monoclonal antibody or antigen-binding fragment thereof comprises:
- (1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a
15 light chain variable region having the polypeptide sequence of SEQ ID NO:103;
 - (2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
 - (3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
 - 20 (4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
 - (5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
 - (6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a
25 light chain variable region having the polypeptide sequence of SEQ ID NO:104;
 - (7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;
 - (8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
 - 30 (9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
 - (10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
 - (11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and
35 a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

- (12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
- (13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
- 5 (14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
- (15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
- 10 (16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
- (17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
- (18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
- 15 (19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
- (20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
- (21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and
20 a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
- (22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and
a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
- (23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
- 25 (24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
- (25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
- (26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147,
30 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
- (27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
- (28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

- (29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
- (30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
- 5 (31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
- (32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161,
10 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- 15 (36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203,
20 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
- 25 (41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
- (43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185,
30 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

- (46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- 5 (48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
- (49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- 10 (50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- 15 (53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- 20 (56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- 25 (58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- 30 (60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

- (63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- 5 (65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195,
10 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- 15 (70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187,
20 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
- 25 (75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.
10. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of
claims 1-9, wherein the antibody or antigen-binding fragment thereof is capable of inducing
effector-mediated tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC),
30 antibody-dependent cellular phagocytosis (ADCP), and/or complement-dependent cytotoxicity
(CDC), and/or mediating the recruitment of conjugated drugs, and/or forming a bispecific
antibody with another mAb or antigen-binding fragment thereof with cancer-killing effect.
11. A bispecific antibody or antigen-binding fragment thereof comprising the monoclonal
antibody or antigen-binding fragment thereof of any one of claims 1-10.

12. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10.
13. An isolated nucleic acid encoding the bispecific antibody or antigen-binding fragment thereof of claim 11.
- 5 14. A vector comprising the isolated nucleic acid of claim 12 or 13.
15. A host cell comprising the vector of claim 14.
16. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10 or the bispecific antibody or antigen-binding fragment thereof of claim 11 and a pharmaceutically acceptable carrier.
- 10 17. A method of targeting a TAA on a cancer cell surface, and/or treating a cancer, and/or treating an inflammatory disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 16, optionally wherein the cancer is selected from the group consisting of a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.
- 15 18. A method of producing the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10 or the bispecific antibody or antigen-binding fragment thereof of claim 11, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof and recovering the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof from the cell or culture.
- 20 19. A method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment of any one of claims 1-10 or the bispecific antibody or antigen-binding fragment thereof of claim 11, comprising combining the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.
- 25 20. A method of determining the level of a TAA in a subject, the method comprising:
- 30 a. obtaining a sample from the subject;

- b. contacting the sample with an isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10; and
 - c. determining the level of a TAA in the subject.
- 21. The method of claim 20, wherein the sample is a tissue sample or a blood sample,
 - 5 optionally wherein the tissue sample is a cancer tissue sample.
- 22. An isolated polynucleotide comprising a nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises:
 - (a) an extracellular domain comprising at least one antigen binding domain that specifically binds GPC3;
 - 10 (b) a hinge region;
 - (c) a transmembrane region; and
 - (d) an intracellular signaling domain.
- 23. The isolated polynucleotide of claim 22, wherein the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide
 - 15 sequences of:
 - (1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;
 - (2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;
 - (3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;
 - 20 (4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;
 - (5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;
 - (6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or
 - (7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;
- wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.
- 25 24. The isolated polynucleotide of claim 22, wherein the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:
 - (1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;
 - 30 (2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;
 - (3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;
 - (4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;
 - (5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively; or
 - (6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively;
 - 35 (7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

25. The isolated polynucleotide of any one of claims 22-24, wherein the antigen binding domain comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, or 71, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, or 72.

26. The isolated polynucleotide of claim 25, wherein the antigen binding domain comprises:

- a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;
- b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;
- c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
- d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
- e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;
- f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58;
- or
- g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72.

27. The isolated polynucleotide of any one of claims 22-24, wherein the antigen binding domain is humanized and comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

28. The isolated polynucleotide of claim 27, wherein the antigen binding domain is humanized and comprises:

- (1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
- (2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

- (3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
- (4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
- 5 (5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
- (6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
- (7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102,
10 and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;
- (8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
- (9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
- 15 (10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
- (11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
- (12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122,
20 and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
- (13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
- (14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
- 25 (15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
- (16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
- (17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140,
30 and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
- (18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
- (19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;

- (20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
- (21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
- 5 (22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154,
and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
- (23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
- (24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144,
10 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
- (25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
- (26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
- 15 (27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
- (28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
- (29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148,
20 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
- (30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
- (31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
- 25 (32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162,
30 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

- (37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- 5 (39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
- (40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
- (41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183,
10 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
- (43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- 15 (44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186,
20 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
- 25 (49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192,
30 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

- (54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- 5 (56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193,
10 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- 15 (61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192,
20 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- 25 (66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195,
30 and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- (70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185,
and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

- (71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
- (72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
- 5 (73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
- (74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
- (75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.
- 10 29. The isolated polynucleotide of any one of claims 22-28, wherein the antigen binding domain is a single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3.
30. The isolated polynucleotide of claim 29, wherein the single chain variable fragment
- 15 (scFv) is humanized.
31. The isolated polynucleotide of claim 29 or 30, wherein the single chain variable fragment (scFv) comprises a polypeptide sequence at least 95% identical to any one of SEQ ID NOs: 167-182.
32. The isolated polynucleotide of any one of claims 22-31, wherein the chimeric antigen
- 20 receptor (CAR) comprises one or more antigen binding domains.
33. The isolated polynucleotide of any one of claims 22-32, wherein the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.
34. A chimeric antigen receptor (CAR) encoded by the isolated polynucleotide of any one of
- 25 claims 22-33.
35. A vector comprising the isolated polynucleotide of any one of claims 22-33.
36. A host cell comprising the vector of claim 35.
37. The host cell of claim 36, wherein the host cell is a T cell, preferably a human T cell.
38. The host cell of claim 36, wherein the host cell is a NK cell, preferably a human NK cell.
- 30 39. A method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a T cell with the vector of claim 35.
40. A method of producing a chimeric antigen receptor (CAR)-T cell, the method comprising culturing T cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of claims 22-33 under conditions to produce the
- 35 CAR-T cell and recovering the CAR-T cell.

41. A method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a NK cell with a vector of claim 35.
42. A method of producing a chimeric antigen receptor (CAR)-NK cell, the method comprising culturing NK cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of claims 22-33 under conditions to produce the CAR-NK cell and recovering the CAR-NK cell.
43. A method of generating a cell comprising a chimeric antigen receptor (CAR), the method comprising contacting a cell with the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of claims 22-33, wherein the isolated polynucleotide is an *in vitro* transcribed RNA or synthetic RNA.
44. A method of treating cancer in a subject in need thereof, comprising administering to the subject in need thereof the host cell of any one of claims 36-38, optionally wherein the cancer is selected from a lung cancer, a gastric cancer, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.
45. The method of claim 44, further comprising administering to the subject in need thereof an agent that increases the efficacy of a cell expressing a CAR.
46. The method of claim 44, further comprising administering to the subject in need thereof an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR.
47. The method of claim 44, further comprising administering to the subject in need thereof an agent that treats the disease associated with GPC3.