and/or by inhibiting prolactin-mediated cell signaling through PRLR. In one aspect, the present invention refers to use of the antibody-drug conjugate (ADC) as disclosed herein in the manufacture of a medicament for killing cells that express low levels of cell-surface expressed PRLR.

[0033a] According to an aspect there is provided an isolated antibody or antigen-binding fragment that binds to cell surface-expressed human prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing human PRLR, wherein the antibody or antigen-binding fragment blocks prolactin-mediated signaling in cells expressing human PRLR with an IC50 of less than about 1.3 nM, wherein:

(i) the antibody or antigen-binding fragment comprises complementarity determining regions (CDRs) having the sequences of SEQ ID NO: 292, SEQ ID NO: 294, SEQ ID NO: 296, SEQ ID NO: 300, SEQ ID NO: 302, and SEQ ID NO: 304;

(ii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 14, and SEQ ID NO: 16;

(iii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 28, SEQ ID NO: 30, and SEQ ID NO: 32;

(iv) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 60, SEQ ID NO: 62, and SEQ ID NO: 64;

(v) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 110, and SEQ ID NO: 112;

(vi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 116, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 126, and SEQ ID NO: 128;

(vii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 140, SEQ ID NO: 142, and SEQ ID NO: 144;

(viii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 196, SEQ ID NO: 198, SEQ ID NO: 200, SEQ ID NO: 204, SEQ ID NO: 206, and SEQ ID NO: 208;

(ix) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 212, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 220, SEQ ID NO: 222, and SEQ ID NO: 224;

(x) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 228, SEQ ID NO: 230, SEQ ID NO: 232, SEQ ID NO: 236, SEQ ID NO: 238, and SEQ ID NO: 240;

(xi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 260, SEQ ID NO: 262, SEQ ID NO: 264, SEQ ID NO: 268, SEQ ID NO: 270, and SEQ ID NO: 272;

(xii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 276, SEQ ID NO: 278, SEQ ID NO: 280, SEQ ID NO: 284, SEQ ID NO: 286, and SEQ ID

NO: 288;

(xiii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NO: 368; or

(xiv) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 372, SEQ ID NO: 374, SEQ ID NO: 376, SEQ ID NO: 380, SEQ ID NO: 382, and SEQ ID NO: 384.

[0033b] According to another aspect there is provided an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof described herein conjugated to a cytotoxic agent.

[0033c] According to another aspect there is provided an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to DM1 via an N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (HCDR) 1 comprising SEQ ID NO:292; an HCDR2 comprising SEQ ID NO:294; an HCDR3 comprising SEQ ID NO:296; a light chain complementarity determining region (LCDR)-1 comprising SEQ ID NO:300; an LCDR2 comprising SEQ ID NO:302; and an LCDR3 comprising SEQ ID NO:304.

[0033d] According to another aspect there is provided use of the antibody-drug conjugate (ADC) described herein in the manufacture of a medicament for killing tumor cells that express PRLR.

[0033e] According to another aspect there is provided use of the antibody-drug conjugate (ADC) described herein in the manufacture of a medicament for inhibiting or attenuating tumor growth.

[0033f] According to another aspect there is provided a pharmaceutical composition comprising the isolated antibody or antigen-binding fragment described herein and a pharmaceutically acceptable excipient.

[0033g] According to another aspect there is provided a pharmaceutical composition comprising the ADC described herein and a pharmaceutically acceptable excipient.

[0033h] According to another aspect there is provided use of the isolated antibody or antigen-binding fragment described herein in the manufacture of a medicament for inhibiting or attenuating tumor growth.

[0034] Other embodiments will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION

[0035] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0036] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention

belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

What is claimed is

1. An isolated antibody or antigen-binding fragment that binds to cell surface-expressed human prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing human PRLR, wherein the antibody or antigen-binding fragment blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM, wherein:

(i) the antibody or antigen-binding fragment comprises complementarity determining regions (CDRs) having the sequences of SEQ ID NO: 292, SEQ ID NO: 294, SEQ ID NO: 296, SEQ ID NO: 300, SEQ ID NO: 302, and SEQ ID NO: 304;

(ii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO: 14, and SEQ ID NO: 16;

(iii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 28, SEQ ID NO: 30, and SEQ ID NO: 32;

(iv) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 60, SEQ ID NO: 62, and SEQ ID NO: 64;

(v) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 100, SEQ ID NO: 102, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 110, and SEQ ID NO: 112;

(vi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 116, SEQ ID NO: 118, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 126, and SEQ ID NO: 128;

(vii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, SEQ ID NO: 140, SEQ ID NO: 142, and SEQ ID NO: 144;

(viii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 196, SEQ ID NO: 198, SEQ ID NO: 200, SEQ ID NO: 204, SEQ ID NO: 206, and SEQ ID NO: 208;

(ix) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 212, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 220, SEQ ID NO: 222, and SEQ ID NO: 224;

(x) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 228, SEQ ID NO: 230, SEQ ID NO: 232, SEQ ID NO: 236, SEQ ID NO: 238, and SEQ ID NO: 240;

(xi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 260, SEQ ID NO: 262, SEQ ID NO: 264, SEQ ID NO: 268, SEQ ID NO: 270, and SEQ ID NO: 272;

(xii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 276, SEQ ID NO: 278, SEQ ID NO: 280, SEQ ID NO: 284, SEQ ID NO: 286, and SEQ ID NO: 288;

(xiii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NO: 368; or

(xiv) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 372, SEQ ID NO: 374, SEQ ID NO: 376, SEQ ID NO: 380, SEQ ID NO: 382, and SEQ ID NO: 384.

2. The isolated antibody or antigen-binding fragment of claim 1 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 400 pM.

3. The antibody or antigen-binding fragment of claim 1 or claim 2, wherein:

(i) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 290 and an LCVR having the sequence of SEQ ID NO: 298;

(ii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 2 and an LCVR having the sequence of SEQ ID NO: 10;

(iii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 18 and an LCVR having the sequence of SEQ ID NO: 26;

(iv) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 50 and an LCVR having the sequence of SEQ ID NO: 58;

(v) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 98 and an LCVR having the sequence of SEQ ID NO: 106;

(vi) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 114 and an LCVR having the sequence of SEQ ID NO: 122;

(vii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 130 and an LCVR having the sequence of SEQ ID NO: 138;

(viii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 194 and an LCVR having the sequence of SEQ ID NO: 202;

(ix) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 210 and an LCVR having the sequence of SEQ ID NO: 218;

(x) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 226 and an LCVR having the sequence of SEQ ID NO: 234;

(xi) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 258 and an LCVR having the sequence of SEQ ID NO: 266;

(xii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 274 and an LCVR having the sequence of SEQ ID NO: 282;

(xiii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 354 and an LCVR having the sequence of SEQ ID NO: 362; or

(xiv) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 370 and an LCVR having the sequence of SEQ ID NO: 378.

4. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof of any one of claims 1 to 3 conjugated to a cytotoxic agent.

5. The ADC of claim 4, wherein the cytotoxic agent is a maytansinoid.

6. The ADC of claim 5, wherein the maytansinoid is DM1 or DM4.

7. The ADC of claim 5 or claim 6, wherein the maytansinoid is connected to the antibody via a cleavable linker.

8. The ADC of claim 5 or claim 6, wherein the maytansinoid is connected to the antibody via a non-cleavable linker.

9. The ADC of any one of claims 4 to 8, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (HCDR)-1 comprising SEQ ID NO:292; an HCDR2 comprising SEQ ID NO:294; an HCDR3 comprising SEQ ID NO:296; a light chain complementarity determining region (LCDR)-1 comprising SEQ ID NO:300; an LCDR2 comprising SEQ ID NO:302; and an LCDR3 comprising SEQ ID NO:304.

10. The ADC of claim 9, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) comprising SEQ ID NO:290 and a light chain variable region (LCVR) comprising SEQ ID NO:298.

11. The ADC of claim 5, wherein the maytansinoid is connected to the antibody via an N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker.

12. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to DM1 via an N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region (HCDR)-1 comprising SEQ ID NO:292; an HCDR2 comprising SEQ ID NO:294; an HCDR3 comprising SEQ ID NO:296; a light chain complementarity determining region (LCDR)-1 comprising SEQ ID NO:300; an LCDR2 comprising SEQ ID NO:302; and an LCDR3 comprising SEQ ID NO:304.

13. The ADC of claim 12, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) comprising SEQ ID NO:290 and a light chain variable region (LCVR) comprising SEQ ID NO:298.

14. Use of the antibody-drug conjugate (ADC) of any one of claims 4 to 12 in the manufacture of a medicament for killing tumor cells that express PRLR.

15. The use of claim 14, wherein the tumor cells express less than 1 million copies of PRLR per cell.

16. The use of claim 14, wherein the tumor cells express between 3,000 and 500,000 copies of PRLR per cell.

17. The use of any one of claims 14 to 16, wherein the tumor cells are breast tumor cells.

18. Use of the antibody-drug conjugate (ADC) of any one of claim 4 to 12 in the manufacture of a medicament for inhibiting or attenuating tumor growth.

19. The use of claim 18, wherein the tumor is selected from the group consisting of a renal tumor, a pancreatic tumor, a head and neck tumor, a breast tumor, a prostate tumor, a colon tumor, a gastric tumor, and ovarian tumor, a lung tumor, and a skin tumor.

20. The use of claim 19, wherein the tumor is a breast tumor.

21. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment of any one of claims 1 to 3 and a pharmaceutically acceptable excipient.

22. A pharmaceutical composition comprising the ADC of any one of claims 4 to 12 and a pharmaceutically acceptable excipient.

23. Use of the isolated antibody or antigen-binding fragment of any one of claims 1 to 3 in the manufacture of a medicament for inhibiting or attenuating tumor growth.

24. The use of claim 23, wherein the tumor is selected from the group consisting of a renal tumor, a pancreatic tumor, a head and neck tumor, a breast tumor, a prostate tumor, a colon tumor, a gastric tumor, and ovarian tumor, a lung tumor, and a skin tumor.

25. The use of claim 24, wherein the tumor is a breast tumor.