ANTI-PRLR ANTIBODIES AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to antibodies, and antigen-binding fragments thereof, which specifically bind prolactin receptor (PRLR), as well as antibody-drug conjugates comprising such antibodies, and methods of use thereof.

BACKGROUND

[0002] Prolactin is a polypeptide growth hormone that exerts its activity by interacting with the prolactin receptor (PRLR). PRLR is a single transmembrane receptor belonging to the class 1 cytokine receptor superfamily. The binding of prolactin to PRLR leads to receptor dimerization and intracellular signaling. Signaling through PRLR is associated with various processes such as mammary gland development, lactation, reproduction and immunomodulation. Moreover, high levels of PRLR expression have been detected in breast, prostate and other tumor types.

[0003] Blockade of PRLR signaling has been suggested as a means for treating breast and prostate cancer. (*See, e.g.,* Damiano and Wasserman, Apr. 2013, Clin. Cancer Res. 19(7):1644-1650). Anti-PRLR antibodies are mentioned, *e.g.*, in US Patent Nos. 7,867,493 and 7,422,899. Nonetheless, there is a need in the art for novel PRLR antagonists, such as anti-PRLR antibodies, for the treatment of cancer and other disorders associated with PRLR expression and/or signaling.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0004] The present ~~invention~~ disclosure provides antibodies and antigen-binding fragments thereof that bind human prolactin receptor (PRLR). The antibodies ~~of the invention~~disclosed herein are useful, *inter alia*, for targeting tumor cells that express PRLR. The anti-PRLR antibodies ~~of the invention~~disclosed herein, and antigen-binding portions thereof, may be used alone in unmodified form, or may be included as part of an antibody-drug conjugate or a bispecific antibody.

[0005] The antibodies ~~of the invention~~disclosed herein can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

[0006] Exemplary anti-PRLR antibodies ~~of the present invention~~ are listed in Tables 1 and 2 herein. Table 1 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-PRLR antibodies. Table 2 sets forth the nucleic acid sequence identifiers of the HCVRs, LCVRs, HCDR1, HCDR2 HCDR3, LCDR1, LCDR2 and LCDR3 of the exemplary anti-PRLR antibodies.

[0007] ~~The present invention provides~~Disclosed herein are antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0008] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0009] ~~The present invention also provides~~Also disclosed herein are antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain ~~embodiments~~examples, ~~the present invention provides~~disclosed herein are antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-PRLR antibodies listed in Table 1. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of: 18/26; 66/74; 274/282; 290/298; and 370/378.

[0010] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0011] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0012] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0013] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0014] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0015] Also disclosed herein are~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0016] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino acid sequences listed in Table 1. According to certain ~~embodiment~~examples, ~~the present invention provides~~described herein are antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-PRLR antibodies listed in Table 1. In certain ~~embodiment~~examples, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of: 24/32; 72/80; 280/288; 296/304; and 376/384.

[0017] Also disclosed herein are ~~The present invention also provides~~ antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-PRLR antibodies listed in Table 1. In certain ~~embodiment~~examples, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set is selected from the group consisting of: 20-22-24-28-30-32; 68-70-72-76-78-80; 276-278-280-284-286-288; 292-294-296-300-302-304; and 372-374-376-380-382-384.

[0018] In a related ~~embodiment~~example, disclosed herein are ~~the present invention provides~~ antibodies, or antigen-binding fragments thereof that specifically bind PRLR, comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-PRLR antibodies listed in Table 1. For example, the present ~~invention~~ disclosure includes antibodies or antigen-binding fragments thereof that specifically bind PRLR, comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of: 18/26; 66/74; 274/282; 290/298; and 370/378. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia

definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See, e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol. 273*:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0019] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding anti-PRLR antibodies or portions thereof. For example, ~~the present invention provides~~ disclosed herein are nucleic acid molecules encoding any of the HCVR amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0020] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding any of the LCVR amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0021] Also disclosed herein are~~The present invention also provides~~ nucleic acid molecules encoding any of the HCDR1 amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0022] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding any of the HCDR2 amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0023] Also disclosed herein are~~The present invention also provides~~ nucleic acid molecules encoding any of the HCDR3 amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0024] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding any of the LCDR1 amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR1 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0025] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding any of the LCDR2 amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR2 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0026] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding any of the LCDR3 amino acid sequences listed in Table 1; in certain ~~embodiment~~examples the nucleic acid molecule comprises a polynucleotide sequence selected from any of the LCDR3 nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0027] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding an HCVR, wherein the HCVR comprises a set of three CDRs (*i.e.*, HCDR1-HCDR2-HCDR3), wherein the HCDR1-HCDR2-HCDR3 amino acid sequence set is as defined by any of the exemplary anti-PRLR antibodies listed in Table 1.

[0028] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding an LCVR, wherein the LCVR comprises a set of three CDRs (*i.e.*, LCDR1-LCDR2-LCDR3), wherein the LCDR1-LCDR2-LCDR3 amino acid sequence set is as defined by any of the exemplary anti-PRLR antibodies listed in Table 1.

[0029] Also disclosed herein are ~~The present invention also provides~~ nucleic acid molecules encoding both an HCVR and an LCVR, wherein the HCVR comprises an amino acid sequence of any of the HCVR amino acid sequences listed in Table 1, and wherein the LCVR comprises an amino acid sequence of any of the LCVR amino acid sequences listed in Table 1. In certain ~~embodiment~~examples, the nucleic acid molecule comprises a polynucleotide sequence selected from any of the HCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto, and a polynucleotide sequence selected from any of the LCVR nucleic acid sequences listed in Table 2, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto. In certain ~~embodiment~~examples ~~according to this aspect of the invention~~, the nucleic acid molecule encodes an HCVR and LCVR, wherein the HCVR and LCVR are both derived from the same anti-PRLR antibody listed in Table 1.

[0030] Also disclosed herein are ~~The present invention also provides~~ recombinant expression vectors capable of expressing a polypeptide comprising a heavy or light chain variable region of an anti-PRLR antibody. For example, the present ~~invention~~ disclosure includes recombinant expression vectors comprising any of the nucleic acid molecules mentioned above, *i.e.*, nucleic acid molecules encoding any of the HCVR, LCVR, and/or CDR sequences as set forth in Table 1. Also included within the scope of the present ~~invention~~ disclosure are host cells into which such vectors have been introduced, as well as methods of producing the antibodies or portions thereof by culturing the host cells under conditions permitting production of the antibodies or antibody fragments,

and recovering the antibodies and antibody fragments so produced.

[0031] The present ~~invention~~ disclosure includes anti-PRLR antibodies having a modified glycosylation pattern. In some ~~embodiments~~examples, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0032] In another ~~aspect~~example, disclosed herein is ~~the invention provides~~ a pharmaceutical composition comprising a recombinant human antibody or fragment thereof which specifically binds PRLR and a pharmaceutically acceptable carrier. In a related ~~aspect~~example, the ~~invention~~ disclosure features a composition which is a combination of an anti-PRLR antibody and a second therapeutic agent. In one ~~embodiment~~example, the second therapeutic agent is any agent that is advantageously combined with an anti-PRLR antibody. ~~The present invention also provides~~Disclosed herein are also antibody-drug conjugates (ADCs) comprising an anti-PRLR antibody conjugated to a cytotoxic agent. Exemplary combination therapies, co-formulations, and ADCs involving the anti-PRLR antibodies of the present ~~invention~~ disclosure are disclosed elsewhere herein. In one aspect, the present invention refers to 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 thereof blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM. In another aspect, the present invention refers to an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof that specifically binds cell-surface expressed human prolactin receptor (PRLR), wherein the antibody or fragment is conjugated to a cytotoxic agent, wherein the ADC inhibits the growth of cells expressing PRLR, and wherein the antibody or antigen-binding fragment thereof blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM. In yet another aspect, the present invention refers to an isolated antibody or antigen-binding fragment thereof that binds to cell surface-expressed prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing PRLR, 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.

[0033] In yet another ~~aspect~~example, disclosed herein are ~~the invention provides~~ therapeutic methods for killing tumor cells or for inhibiting or attenuating tumor cell growth using an anti-PRLR antibody or antigen-binding portion of an antibody of the ~~invention~~disclosure. The therapeutic methods according to this ~~aspect~~ example ~~of the invention~~ comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the ~~invention~~ disclosure to a subject in need thereof. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by targeting PRLR

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.

[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 thereof that binds prolactin receptor (PRLR), wherein the antibody or antigen-binding fragment thereof exhibits one or more properties selected from the group consisting of:

(i) binds monomeric human PRLR at 37°C with a K_D of less than about 4.0 nM as measured by surface plasmon resonance;

(ii) binds monomeric human PRLR at 37°C with a t½ of greater than about 5 minutes as measured by surface plasmon resonance;

(iii) binds dimeric human PRLR at 37°C with a K_D of less than about 250 pM as measured by surface plasmon resonance;

(iv) binds dimeric human PRLR at 37°C with a t½ of greater than about 55 minutes as measured by surface plasmon resonance; and

(v) blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM.

2. An isolated antibody or antigen-binding fragment thereof that binds to cell surface-expressed prolactin receptor (PRLR) but does not block prolactin-mediated signaling in cells expressing PRLR.

3. An isolated antibody or antigen-binding fragment thereof that binds to cell surface-expressed prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing PRLR.

4. The isolated antibody or antigen-binding fragment of claim 3, wherein the antibody or antigen-binding fragment thereof blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM.

5. An isolated antibody or antigen-binding fragment thereof that binds prolactin receptor (PRLR), wherein the antibody or antigen-binding fragment comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having an amino acid sequence as set forth in Table 1; and (b) the CDRs of a light chain variable region (LCVR) having an amino acid sequence as set forth in Table 1.

6. The isolated antibody or antigen-binding fragment of claim 5, wherein the antibody or antigen-binding fragment comprises an HCVR having an amino acid sequence as set forth in Table 1 and a LCVR having an amino acid sequence as set forth in Table 1.

7. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof that specifically binds human prolactin receptor (PRLR) conjugated to a

cytotoxic agent, wherein the ADC inhibits the growth of cells expressing PRLR.

8. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof as defined in any one of claims 1 to 7 conjugated to a cytotoxic agent.

9. The ADC of claim 8, wherein the cytotoxic agent is a maytansinoid.

10. The ADC of claim 9, wherein the maytansinoid is DM1, DM4, or a derivative thereof.

11. The ADC of claim 9 or 10, wherein the maytansinoid is connected to the antibody via a cleavable linker.

12. The ADC of claim 9 or 10, wherein the maytansinoid is connected to the antibody via a non-cleavable linker.

13. The ADC of claim 7 or 8, wherein the cytotoxic agent is an auristatin.

14. The ADC of any one of claims 7 to 13, wherein the ADC kills cells that express PRLR at an expression level of less than 30-fold above background, with an IC_{50} of less than 5 nM.

15. The ADC of claim 14, wherein the ADC kills cells that express PRLR at an expression level of less than 20-fold above background, with an IC_{50} of less than 5 nM.

16. The ADC of claim 14, wherein the ADC kills cells that express PRLR at an expression level greater than 12-fold above background but less than 30-fold above background, with an IC_{50} of less than 5 nM.

17. The antibody or antigen-binding fragment of any one of claims 1 to 6, or the ADC of any one of claims 7 to 16, wherein the antibody or antigen-binding fragment thereof competes for binding to PRLR with a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.

18. The antibody or antigen-binding fragment of any one of claims 1 to 6, or the ADC of any one of claims 7 to 16, wherein the antibody or antigen-binding fragment thereof binds to the same epitope on PRLR as a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.

19. A method for killing cells that express low levels of PRLR, the method comprising contacting the cells with an antibody-drug conjugate (ADC) comprising an anti-PRLR antibody

conjugated to a cytotoxic agent.

20. The method of claim 19, wherein the cells are tumor cells.

21. The method of claim 20, wherein the tumor cells express less than 1 million copies of PRLR per cell.

22. The method of claim 21, wherein the tumor cells express between 10,000 and 500,000 copies of PRLR per cell.

23. The method of any one of claims 19 to 22, wherein the cytotoxic agent is a maytansinoid.

24. The method of claim 23, wherein the maytansinoid is DM1 or DM4.

25. The method of claim 23 or 24, wherein the maytansinoid is connected to the antibody via a cleavable linker.

26. The method of claim 23 or 24, wherein the maytansinoid is connected to the antibody via a non-cleavable linker.

27. The method of any one of claims 19 to 22, wherein the cytotoxic agent is an auristatin.

28. The method of any one of claims 19 to 27, wherein the anti-PRLR antibody binds to cell surface-expressed PRLR but does not block prolactin-mediated signaling in cells expressing PRLR.

29. The method of any one of claims 19 to 27, wherein the anti-PRLR antibody binds to cell surface-expressed prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing PRLR.

30. The method of any one of claims 19 to 29, wherein the cells express PRLR at an expression level of less than about 60-fold above background.

31. The method of claim 30, wherein the cells express PRLR at an expression level of less than about 20-fold above background.

32. The method of any one of claims 19 to 31, wherein the anti-PRLR antibody comprises: (a) the complementarity determining regions (CDRs) of a heavy chain variable region (HCVR) having an amino acid sequence as set forth in Table 1; and (b) the CDRs of a light chain variable region (LCVR) having an amino acid sequence as set forth in Table 1.

33. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 6, or the ADC of any one of claims 7 to 16, and a pharmaceutically acceptable carrier or diluent.

34. A method for inhibiting or attenuating tumor growth, the method comprising administering the pharmaceutical composition of claim 33 to a subject afflicted with a tumor.

35. The method of claim 34, 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.

36. A method for inhibiting or attenuating tumor growth in a subject, the method comprising administering to the subject the pharmaceutical composition of claim 33, and a second therapeutic agent, wherein the second therapeutic agent is an antibody or antigen-binding fragment thereof that specifically binds HER2, ErbB3, ErbB4, cMet, IGF1R, Ang2, PDGFR-α or PDGFR-β.

37. A method for inhibiting or attenuating tumor growth in a subject, the method comprising administering to the subject the pharmaceutical composition of claim 33, and a second therapeutic agent, wherein the second therapeutic agent is a VEGF antagonist.

38. A method for inhibiting or attenuating tumor growth in a subject, the method comprising administering to the subject the pharmaceutical composition of claim 33, and a second therapeutic agent, wherein the second therapeutic agent is a chemotherapeutic agent.

39. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof that specifically binds a class I cytokine receptor.

40. A method for killing cells that express low levels of a class I cytokine receptor, the method comprising contacting the cells with an antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof conjugated to a cytotoxic agent, wherein the antibody or antigen-binding fragment specifically binds the class I cytokine receptor.

41. The ADC of claim 39, or the method of claim 40, wherein the class I cytokine receptor is selected from the group consisting of IL-2R, IL-4R, IL-7R, IL-9R, IL-13R, IL-15R, IL-3R, IL-5R, IL-6R, IL-11R, CNTF receptor, LIF receptor, OSM receptor, IL-12R, EPO receptor, G-CSF receptor, leptin receptor and PRLR.

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 thereof blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM.

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 1.2 nM.

3. 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 1.0 nM.

4. 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 900 pM.

5. 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 800 pM.

6. 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 600 pM.

7. 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.

8. 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 200 pM.

9. 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 100 pM.

10. 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 80 pM.

11. 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 60 pM.

12. 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 40 pM.

13. The antibody or antigen-binding fragment of claim 1 that competes for binding to PRLR with a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.

14. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof that specifically binds cell-surface expressed human prolactin receptor (PRLR), wherein the antibody or fragment is conjugated to a cytotoxic agent, wherein the ADC inhibits the growth of cells expressing PRLR, and wherein the antibody or antigen-binding fragment thereof blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.3 nM.

15. The ADC of claim 14, wherein the cytotoxic agent is a maytansinoid.

16. The ADC of claim 15, wherein the maytansinoid is DM1, DM4, or a derivative thereof.

17. The ADC of claim 15, wherein the maytansinoid is connected to the antibody via a cleavable linker.

18. The ADC of claim 15, wherein the maytansinoid is connected to the antibody via a non-cleavable linker.

19. The ADC of claim 14, wherein the ADC kills cells that express PRLR at an expression level of less than 30-fold above background.

20. The ADC of claim 19, wherein the ADC kills cells that express PRLR at an expression level of less than 20-fold above background.

21. The ADC of claim 20, wherein the ADC kills cells that express PRLR at an expression level greater than 12-fold above background but less than 30-fold above background.

22. The ADC of claim 14, wherein the antibody or antigen-binding fragment thereof competes for binding to PRLR with a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.

23. The ADC of claim 14, 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.

24. The ADC of claim 23, 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.

25. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.2 nM.

26. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 1.0 nM.

27. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 900 pM.

28. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 800 pM.

29. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 600 pM.

30. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 400 pM.

31. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 200 pM.

32. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 100 pM.

33. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 80 pM.

34. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 60 pM.

35. The ADC of claim 14 that blocks prolactin-mediated signaling in cells expressing human PRLR with an IC_{50} of less than about 40 pM.

36. The ADC of claim 16, wherein the maytansinoid is connected to the antibody via an N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker.

37. The ADC of claim 36, wherein the maytansinoid is DM1.

38. The ADC of claim 37, 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.

39. The ADC of claim 38, 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.

40. An isolated antibody or antigen-binding fragment thereof that binds to cell surface-expressed prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing PRLR, 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.

41. The isolated antibody or antigen-binding fragment of claim 40, 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

42. Use of the antibody-drug conjugate (ADC) of claim 14 in the manufacture of a medicament for killing cells that express low levels of cell-surface expressed PRLR.

43. The use of claim 42, wherein the cells are tumor cells.

44. The use of claim 43, wherein the tumor cells express less than 1 million copies of PRLR per cell.

45. The use of claim 44, wherein the tumor cells express between 10,000 and 500,000 copies of PRLR per cell.

46. The use of claim 42, wherein the cytotoxic agent is a maytansinoid.

47. The use of claim 46, wherein the maytansinoid is DM1, DM4, or a derivative thereof.

48. The use of claim 46, wherein the maytansinoid is connected to the antibody via a cleavable linker.

49. The use of claim 46, wherein the maytansinoid is connected to the antibody via a non-cleavable linker.

50. The use of claim 42, wherein the anti-PRLR antibody binds to cell surface-expressed

prolactin receptor (PRLR) and blocks prolactin-mediated signaling in cells expressing PRLR.

51. The use of claim 42, wherein the anti-PRLR antibody competes for binding to PRLR with a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.

52. The use of claim 42, wherein the anti-PRLR antibody binds to the same epitope on PRLR as a reference antibody comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 18/26; 66/74; 274/282; 290/298; and 370/378.

53. The use of claim 44, wherein the tumor cells express between 3,000 and 500,000 copies of PRLR per cell.

54. The use of claim 47, wherein the maytansinoid is connected to the antibody via an N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker.

55. The use of claim 54, wherein the maytansinoid is DM1.

56. The use of claim 55, 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.

57. The use of claim 56, 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.