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

[0004] The present disclosure provides antibodies and antigen-binding fragments thereof that bind human prolactin receptor (PRLR). The antibodies disclosed herein are useful, *inter alia*, for targeting tumor cells that express PRLR. The anti-PRLR antibodies 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. The present invention refers to subject matter as defined in the attached set of claims.

[0005] The antibodies 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 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.

and recovering the antibodies and antibody fragments so produced.

[0031] The present disclosure includes anti-PRLR antibodies having a modified glycosylation pattern. In some 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 example, disclosed herein is a pharmaceutical composition comprising a recombinant human antibody or fragment thereof which specifically binds PRLR and a pharmaceutically acceptable carrier. In a related example, the disclosure features a composition which is a combination of an anti-PRLR antibody and a second therapeutic agent. In one example, the second therapeutic agent is any agent that is advantageously combined with an anti-PRLR antibody. 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 disclosure are disclosed elsewhere herein. In one example, also disclosed herein is 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 example, also disclosed herein is 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 example, also disclosed herein is 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 example, disclosed herein are 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 disclosure. The therapeutic methods according to this example comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the 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

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: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 44, SEQ ID NO: 46, and SEQ ID NO: 48;

(v) 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;

(vi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 68, SEQ ID NO: 70, SEQ ID NO: 72, SEQ ID NO: 76, SEQ ID NO: 78, and SEQ ID NO: 80;

(vii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 84, SEQ ID NO: 86, SEQ ID NO: 88, SEQ ID NO: 92, SEQ ID NO: 94, and SEQ ID NO: 96;

(viii) 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;

(ix) 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;

(x) 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;

(xi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 148, SEQ ID NO: 150, SEQ ID NO: 152, SEQ ID NO: 156, SEQ ID NO: 158, and SEQ ID NO: 160;

(xii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 164, SEQ ID NO: 166, SEQ ID NO: 168, SEQ ID NO: 172, SEQ ID NO: 174, and SEQ ID NO: 176;

(xiii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 180, SEQ ID NO: 182, SEQ ID NO: 184, SEQ ID NO: 188, SEQ ID NO: 190, and SEQ ID NO: 192;

(xiv) 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;

(xv) 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;

(xvi) 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;

(xvii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 244, SEQ ID NO: 246, SEQ ID NO: 248, SEQ ID NO: 252, SEQ ID NO: 254, and SEQ ID NO: 256;

(xviii) 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;

(xix) 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;

(xx) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 308, SEQ ID NO: 310, SEQ ID NO: 312, SEQ ID NO: 316, SEQ ID NO: 318, and SEQ ID NO: 320;

(xxi) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 324, SEQ ID NO: 326, SEQ ID NO: 328, SEQ ID NO: 332, SEQ ID NO: 334, and SEQ ID NO: 336;

(xxii) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 340, SEQ ID NO: 342, SEQ ID NO: 344, SEQ ID NO: 348, SEQ ID NO: 350, and SEQ ID NO: 352;

(xxiii) 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;

(xxiv) 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; or

(xxv) the antibody or antigen-binding fragment comprises CDRs having the sequences of SEQ ID NO: 388, SEQ ID NO: 390, SEQ ID NO: 392, SEQ ID NO: 396, SEQ ID NO: 398, and SEQ ID NO: 400.

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, 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: 34 and an LCVR having the sequence of SEQ ID NO: 42;

(v) 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;

(vi) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 66 and an LCVR having the sequence of SEQ ID NO: 74;

(vii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 82 and an LCVR having the sequence of SEQ ID NO: 90;

(viii) 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;

(ix) 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;

(x) 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;

(xi) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 146 and an LCVR having the sequence of SEQ ID NO: 154;

(xii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 162 and an LCVR having the sequence of SEQ ID NO: 170;

(xiii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 178 and an LCVR having the sequence of SEQ ID NO: 186;

(xiv) 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;

(xv) 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;

(xvi) 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;

(xvii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 242 and an LCVR having the sequence of SEQ ID NO: 250;

(xviii) 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;

(xix) 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;

(xx) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 306 and an LCVR having the sequence of SEQ ID NO: 314;

(xxi) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 322 and an LCVR having the sequence of SEQ ID NO: 330;

(xxii) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 338 and an LCVR having the sequence of SEQ ID NO: 346;

(xxiii) 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;

(xxiv) 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; or

(xxv) the antibody or antigen-binding fragment comprises an HCVR having the sequence of SEQ ID NO: 386 and an LCVR having the sequence of SEQ ID NO: 394.

4. An antibody-drug conjugate (ADC) comprising an antibody or antigen-binding fragment thereof of claim 1 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, wherein the maytansinoid is connected to the antibody via a cleavable linker.

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

9. The ADC of claim 4, 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 claim 4 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 claim 14, wherein the tumor cells are breast tumor cells.

18. Use of the antibody-drug conjugate (ADC) of claim 4 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.