PROLACTIN RECEPTOR BINDING PROTEINS AND USES THEREOF

RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application No. 61/745,707, filed December 24, 2012, the entire contents of which is hereby incorporated by reference herein.

FIELD OF THE INVENTION

The present invention relates to prolactin receptor (PRLR) binding proteins and their use in the prevention and/or treatment of various diseases including cancer.

BACKGROUND OF THE INVENTION

The prolactin receptor (PRLR) is a transmembrane receptor that interacts with prolactin (PRL), a peptide hormone. PRLR contains a single transmembrane domain and is homologous to receptors for cytokines, such as IL2, IL3, IL4, IL6, IL7, erythropoietin, and GM-CSF. PRLR is present in mammary glands, ovaries, pituitary glands, heart, lung, thymus, spleen, liver, pancreas, kidney, adrenal gland, uterus, skeletal muscle, skin, and areas of the central nervous system (Mancini, *et al.*, *Endocrinol Metab Clin North Am*, 2008, 37(1):67-99). Upon activation by prolactin, PRLR dimerizes., resulting in activation of Janus kinase 2, a tyrosine kinase that initiates the JAK-STAT pathway and also results in the activation of mitogen-activated protein kinases and Src kinase. Growth hormone also binds to PRLR and activates the receptor.

PRLR is involved in multiple biological functions, including cell growth, differentiation, development, lactation and reproduction. The human PRLR cDNA was originally isolated from hepatoma and breast cancer libraries (Boutin *et al.*, *Molec. Endocr.* 3: 1455-1461, 1989). The nucleotide sequence predicted a mature protein of 598 amino acids with a much longer cytoplasmic domain than the rat liver PRLR. The PRLR gene resides in the same chromosomal region as the growth hormone receptor gene, which has been mapped to 5p13-p14 (Arden, *et al.*, *Cytogenet. Cell Gene* 53: 161-165, 1990).

The genomic organization of the human PRLR gene has been determined (Hu, Z.-Z. *et al., J. Clin. Endocr. Metab.* 84: 1153-1156, 1999). The 5-prime-untranslated region of the PRLR gene contains 2 alternative first exons: E13, the human counterpart of the rat and mouse E13, and a novel human type of alternative first exon termed E1N. The 5-prime-untranslated region also contains a common noncoding exon 2 and part of exon 3, which contains the translation initiation codon. The E13 and E1N exons are within 800 base pairs of each other. These 2 exons are expressed in human breast tissue, breast cancer cells, gonads, and liver. Overall, the transcript containing E13 is prevalent in most tissues. The PRLR gene product is encoded by exons 3-10, of

which exon 10 encodes most of the intracellular domain. The E13 and E1N exons are transcribed from alternative promoters PIII and PN, respectively. The PIII promoter contains Sp1 and C/EBP elements that are identical to those in the rodent promoter and is 81% similar to the region -480/-106 in the rat and mouse. The PN promoter contains putative binding sites for ETS family proteins and a half-site for nuclear receptors.

PRLR exists in a number of different isoforms that differ in the length of their cytoplasmic domains. Four PRLR mRNA isoforms (L, I, S1a, and S1b) have been found in human subcutaneous abdominal adipose tissue and breast adipose tissue (Ling, C. *et al.*, *J. Clin. Endocr. Metab.* 88: 1804-1808, 2003). In addition, expression of both L-PRLR and I-PRLR has been detected in human subcutaneous abdominal adipose tissue and breast adipose tissue using immunoblot analysis. Recent reports have suggested that PRLR is expressed and activated in human breast cancer and prostate cancer tissues (Li *et al., Cancer Res.*, 64:4774-4782, 2004; Gill *et al., J Clin Pathol.*, 54:956-960, 2001; Touraine *et al., J Clin Endocrinol Metab.*, 83:667-674, 1998). It was reported that Stat5 activation and PRLR expression is associated with high histological grade in 54% of prostate cancer specimens (Li *et al., supra*). Other reports have suggested that primary breast cancer specimens are responsive to PRL in colony formation assays and that plasma PRL concentrations correlate with breast cancer risk (Tworoger *et al., Cancer Res.*, 64:6814-6819, 2004; Tworoger *et al., Cancer Res.*, 66:2476-2482, 2006). Another report indicated that PRL transgenic mice develop malignant mammary carcinomas or prostate hyperplasia (Wennbo *et al., J Clin Invest.*, 100:2744-2751, 1997; Wennbo *et al., Endocrinology*, 138:4410-4415, 1997).

A PRLR monoclonal antibody has been shown to diminish the incidence of mammary tumors in mice (Sissom *et al., Am. J. Pathol.* 133:589-595, 1988). In addition, a PRL antagonist (S179D mutant PRL) has been shown to inhibit proliferation of a human prostate carcinoma cell line, DU-145, *in vitro* and DU-145 induced tumors *in vivo* (Xu *et al., Cancer Res.*, 61:6098-6104, 2001).

Accordingly, there remains a need for PRLR binding proteins that can be used for therapeutic purposes for treating cancer.

SUMMARY OF THE INVENTION

This invention pertains to PRLR binding proteins and conjugates thereof. Binding proteins of the inventions include, but are not limited to antibodies, antigen binding portions, and other antigen binding proteins capable of binding the human PRLR. Further, the invention provides methods of making and using PRLR binding proteins and conjugates thereof.

In one aspect, the present invention is directed to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, comprising an antigen binding domain, said binding protein

capable of binding prolactin receptor (PRLR), said antigen binding domain comprising at least one CDR comprising an amino acid sequence selected from the group consisting of SEQ ID Nos:97, 98, 99, 100, 101, 102, 151 and 152. In one embodiment, the at least one CDR comprises an amino acid sequence selected from the group consisting of SEQ ID Nos:40-42, 46, 47, 49-51, 56-58, 62, 63, 65-67, 71-73, 77, 79-81, 85-87, 92-94, 149 and 150. In another embodiment, the binding protein *e.g.*, antibody, or antigen binding fragment thereof, comprises at least 3 CDRs. In yet another embodiment, the 3 CDRs are a heavy chain variable domain CDR set (CDR1, CDR2, and CDR3) selected from the group consisting of SEQ ID NOs: 40, 41, and 42; SEQ ID NOs: 46, 47, and 42; SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 62, 63, and 58; SEQ ID NOs: 71, 72, and 73; SEQ ID NOs: 71, 77, and 73; SEQ ID NOs: 85, 86, and 87; SEQ ID NOs: 149, 150, and 87. Alternatively or in combination, 3 CDRs are a light chain variable domain CDR set (CDR1, CDR2, and CDR3) selected from the group consisting of SEQ ID NOs: 49, 50, and 51; SEQ ID NOs: 65, 66, and 67; SEQ ID NOs: 79, 80, and 81; and SEQ ID NOs: 92, 93, and 94.

In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, comprises at least one heavy chain variable domain CDR set and at least one light chain variable domain CDR set. In some embodiments, the at least two variable domain CDR sets are selected from a group consisting of:

1) either of the heavy chain variable domain CDR sets SEQ ID Nos:40, 41 and 42 or SEQ ID Nos:46, 47 and 42, and the light chain variable domain CDR set SEQ ID Nos:49, 50 and 51;

(2) either of the heavy chain variable domain CDR sets SEQ ID Nos:56, 57 and 58 or SEQ ID Nos: 62, 63 and 58, and the light chain variable domain CDR set SEQ ID Nos 65, 66 and 67;

(3) either of the heavy chain variable domain CDR sets SEQ ID Nos: 71, 72 and 73 or SEQ ID Nos: 71, 77 and 73, and the light chain variable domain CDR set SEQ ID Nos: 79, 80 and 81; and

(4) either of the heavy chain variable domain CDR sets SEQ ID Nos:85, 86 and 87 or SEQ ID Nos: 149, 150 and 87, and the light chain variable domain CDR set SEQ ID Nos: 92, 93 and 94..

In other embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, further comprises a human acceptor framework. In some embodiments, the human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID Nos:14-38. In yet other embodiments, the human acceptor framework comprises at least one Framework Region amino acid substitution, wherein the amino acid sequence of the

framework is at least 65% identical to the sequence of said human acceptor framework and comprises at least 70 amino acid residues identical to said human acceptor framework. Alternatively, the human acceptor framework comprises at least one Framework Region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;

a glycosylation site residue;

a rare residue;

a residue capable of interacting with human PRLR;

a residue capable of interacting with a CDR;

a canonical residue;

a contact residue between heavy chain variable region and light chain variable region;

a residue within a Vernier zone; and

a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

In other embodiments, the key residue is selected from the group consisting of 2L, 43L, 48L, 58L, 64L, 87L, 27H, 48H, 60H, 63H, 64H, 65H, 67H, 69H, 71H, 73H, 75H, 93H. In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, is a consensus human variable domain.

In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, comprises at least one variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60; SEQ ID NO: 61; SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75; SEQ ID NO: 76; SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122 and SEQ ID NO: 123. In some embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of:

(1) one of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 or SEQ ID NO: 45; and one of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 or SEQ ID NO:54;

(2) one of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 or SEQ ID NO: 61; and one of SEQ ID NO:64, SEQ ID NO:68 or SEQ ID NO: 69;

(3) one of SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75 or SEQ ID NO: 76; and one of SEQ ID NO:78, SEQ ID NO:82 or SEQ ID NO: 83; and

(4) one of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122 or SEQ ID NO: 123; and one of SEQ ID NO:91, SEQ ID NO:95 or SEQ ID NO:96.

In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, comprises at least one variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 48; SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 78; SEQ ID NO: 82; SEQ ID NO: 83; SEQ ID NO: 91; SEQ ID NO: 95; and SEQ ID NO: 96.

In a particular embodiment, the binding protein comprises a heavy chain sequence and a light chain sequence selected from the group consisting of: (a) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 125; (b) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 126; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 127; (d) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 128; (e) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 125; (f) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 126; (g) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 127; (h) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 128; (i) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 125; (j) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 126; (k) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 127; (l) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 128; (m) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 132; (n) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 133; (o) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 134; (p) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 132; (q) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO:

133; (r) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 134; (s) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 132; (t) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 133; (u) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 134; (v) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 138; (w) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 139; (x) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 140; (y) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 138; (z) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 139; (aa) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 140; (bb) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 138; (cc) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 139; (dd) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 140; (ee) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 144; (ff) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 145; (gg) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 146; (hh) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 144; (ii) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 145; (jj) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 146; (kk) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 144; (ll) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 145; (mm) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 146; (nn) a heavy chain having the amino acid sequence of SEQ ID NO: 153; and a light chain having the amino acid sequence of SEQ ID NO: 139; (oo) a heavy chain having the amino acid sequence of SEQ ID NO: 154; and a light chain having the amino acid sequence of SEQ ID NO:

139; and (pp) a heavy chain having the amino acid sequence of SEQ ID NO: 155; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, binds PRLR. In some embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, is capable of modulating a biological function of PRLR. In other embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, is capable of neutralizing PRLR. In yet other embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, has an on rate constant (K_{on}) to PRLR selected from the group consisting of: at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; and at least about $10^6 M^{-1}s^{-1}$; as measured by surface plasmon resonance. In other embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, has an off rate constant (K_{off}) to PRLR selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance. In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, has a dissociation constant (K_D) to PRLR selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that competes with an antibody. In one embodiment, a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, competes with an antibody comprising a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(1) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54;

(2) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69;

(3) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96;

(4) the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103;

(5) the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104;

(6) the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105;

(7) the variable heavy chain amino acid sequence set forth in SEQ ID NO:116 and the variable light chain amino acid sequence set forth in SEQ ID NO:107;

(8) the variable heavy chain amino acid sequence set forth in SEQ ID NO:117 and the variable light chain amino acid sequence set forth in SEQ ID NO:108;

(9) the variable heavy chain amino acid sequence set forth in SEQ ID NO:118 and the variable light chain amino acid sequence set forth in SEQ ID NO:109;

(10) the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110; and

(11) the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111.

In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, competes with an antibody comprising a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(1) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54;

(2) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69;

(3) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96;

(4) the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103;

(5) the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104;

(6) the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105; and

(7) the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111.

In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, competes with an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110.

In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, competes with an antibody comprising a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(1) the variable heavy chain amino acid sequence set forth in SEQ ID NO:115 and the variable light chain amino acid sequence set forth in SEQ ID NO:106;

(2) the variable heavy chain amino acid sequence set forth in SEQ ID NO:116 and the variable light chain amino acid sequence set forth in SEQ ID NO:107; and

(3) the variable heavy chain amino acid sequence set forth in SEQ ID NO:117 and the variable light chain amino acid sequence set forth in SEQ ID NO:108.

In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, competes with an antibody comprising a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54. In other embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, competes with an antibody comprising a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96.

In another aspect, the invention is directed to a binding protein capable of binding PRLR that competes with an antibody comprising a heavy chain sequence and a light chain sequence selected from the group consisting of (a) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 125; (b) a heavy

chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 126; (c) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 127; (d) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 128; (e) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 125; (f) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 126; (g) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 127; (h) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 128; (i) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 125; (j) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 126; (k) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 127; (l) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 128; (m) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 132; (n) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 133; (o) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 134; (p) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 132; (q) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 133; (r) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 134; (s) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 132; (t) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 133; (u) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 134; (v) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 138; (w) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 139; (x) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 140; (y) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 138; (z) a heavy chain

having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 139; (aa) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 140; (bb) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 138; (cc) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 139; (dd) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 140; (ee) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 144; (ff) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 145; (gg) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 146; (hh) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 144; (ii) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 145; (jj) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 146; (kk) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 144; (ll) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 145; (mm) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 146; (nn) a heavy chain having the amino acid sequence of SEQ ID NO: 153; and a light chain having the amino acid sequence of SEQ ID NO: 139; (oo) a heavy chain having the amino acid sequence of SEQ ID NO: 154; and a light chain having the amino acid sequence of SEQ ID NO: 139; and (pp) a heavy chain having the amino acid sequence of SEQ ID NO: 155; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising three, four, five, six, seven, eight, nine or all of the amino acid residues E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises at least five of the amino acid residues. In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and

W191 of SEQ ID NO:2. In a particular embodiment, the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab6, chAb6, and Ab14-Ab25.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising three, four, five, six, seven, eight, nine or all of the amino acid residues E8, I9, F10, K11, C12, R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises at least five of the amino acid residues. In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues E8, I9, F10, K11, C12, R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2. In a particular embodiment, the the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab4, Ab7, chAb7, Ab35-Ab43 and Ab53-Ab55.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising 13, 14, 15, 16, 17, 18, 19, 20, 21 or all of the amino acid residues R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161, G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191, and W194 of SEQ ID NO:2. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises at least 15 of the amino acid residues. In some embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161, G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191, and W194 of SEQ ID NO:2. In a particular embodiment, the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab3, Ab8, chAb8 and Ab44-Ab52.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising at least one, two, three, four or all of the amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2. In some embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2. In a particular

embodiment, the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab3, Ab4, Ab6-Ab8, chAb6, chAb7, chAb8, Ab14-Ab25 and Ab35-Ab55.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising amino acids 91-96 of SEQ ID NO:2. In a particular embodiment, the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab4, Ab6, Ab7, chAb6, chAb7, Ab14-Ab25, Ab35-Ab43 and Ab53-Ab55.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope having residues within at least amino acids 8-100, 185-191, 8-143, or 183-194 of SEQ ID NO:2. In a particular embodiment, the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab3, Ab4, Ab6-Ab8, chAb6, chAb7, chAb8, Ab14-Ab25 and Ab35-Ab55.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR and having the same epitopic specificity as an antibody, or antigen-binding portion thereof, selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab9, chAb9, Ab10, chAb10, Ab11, chAb11, Ab12, chAb12, Ab13, chAb13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 and Ab55.

In various embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, is capable of modulating a biological function of PRLR. In other embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, binds the ligand binding D1 domain of PRLR. In other embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, binds an epitope of PRLR which does not inhibit dimerization of PRLR. In further embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, does not bind the D2 domain of PRLR. In further embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, binds the ligand binding region of the D1 domain of PRLR. In additional embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, does not compete with antibody LFA102 for binding of PRLR. In additional embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, blocks binding of prolactin to PRLR.

In particular embodiments of any of the foregoing embodiments of the invention, the binding protein is an antibody, or an antigen binding portion thereof. In particular embodiments of any of the foregoing embodiments of the invention, the binding protein is a human antibody, or an antigen binding portion thereof.

In another aspect, the binding protein of any of the foregoing embodiments of the invention is a crystallized binding protein, *e.g.*, antibody, or antigen binding fragment thereof.

In another aspect, the invention pertains to an antibody construct comprising a binding protein wherein said antibody construct further comprises a linker polypeptide or an immunoglobulin constant domain. In one embodiment, the binding protein of said antibody construct is selected from the group consisting of an immunoglobulin molecule, a disulfide linked Fv, a monoclonal antibody, a scFv, a chimeric antibody, a single domain antibody, a CDR-grafted antibody, a diabody, a humanized antibody, a multispecific antibody, a Fab,a dual specific antibody, a Fab', a bispecific antibody, a F(ab')2, and a Fv,

Alternatively, or in addition, the binding protein of said antibody construct may comprise a heavy chain immunoglobulin constant domain selected from the group consisting of a human IgM constant domain, a human IgG4 constant domain, a human IgG1 constant domain, a human IgE constant domain, a human IgG2 constant domain, and a human IgG3 constant domain, a human IgA constant domain.

In other embodiments, the antibody construct comprises an immunoglobulin constant domain having an amino acid sequence selected from the group consisting of SEQ ID Nos:10-13.

In another aspect, the invention pertains to an antibody conjugate comprising an antibody construct as described previously, wherein said antibody conjugate further comprises an agent selected from the group consisting of: an immunoadhension molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent. In one embodiment, the antibody conjugate comprises an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin. In another embodiment, the antibody conjugate comprises a radiolabel selected from the group consisting of: ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm. In other embodiments, the antibody conjugate comprises a therapeutic or cytotoxic agent selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent. For example, the anti-mitotic agent may be selected from the group consisting of a dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, and a vinca alkaloid. In some embodiments, the binding protein of said antibody construct possesses a human glycosylation pattern.

In certain embodiments, the antibody construct is a crystallized antibody construct. In some embodiments, the crystallized antibody construct is a carrier-free pharmaceutical controlled

release crystallized antibody construct. In another embodiment, the antibody construct has a greater half life *in vivo* than the soluble counterpart of said antibody construct. In some embodiments, the antibody construct retains biological activity.

In another aspect, the invention pertains to an isolated nucleic acid encoding a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, amino acid sequence. In another aspect, the invention pertains to an isolated nucleic acid encoding an antibody construct amino acid sequence, as described herein, wherein said antibody construct further comprises a linker polypeptide or an immunoglobulin constant domain.

In another aspect, the invention provides a vector comprising said isolated nucleic acid. In another embodiment, said vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.

In another aspect, the invention provides a host cell comprising said vector. In another embodiment, said host cell is a prokaryotic cell, while in yet other embodiments, said host cell is *E.Coli*. In other embodiments, said host cell is a eukaryotic cell. In some embodiments, said eukaryotic cell is selected from the group consisting of a protist cell, an animal cell, a plant cell and a fungal cell. In still other embodiments, the eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell, while in other embodiments, the host cell is a CHO cell. In another embodiment, the host cell is COS, while in other embodiments, the host cell is a yeast cell. In some embodiments, said yeast cell is *Saccharomyces cerevisiae*. In other embodiments, the host cell is an insect Sf9 cell.

In another aspect, the invention pertains to a method of producing a protein capable of binding PRLR, comprising culturing a host cell as described above, for example, comprising a vector comprising an isolated nucleic acid encoding an antibody construct amino acid sequence as described above, in culture medium under conditions sufficient to produce a binding protein capable of binding PRLR. In one embodiment, the invention pertains to a protein produced according to said method.

In another aspect, the invention pertains to a composition for the release of a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, said composition comprising: (a) a formulation, wherein said formulation comprises a crystallized binding protein, as described herein, and an ingredient; and (b) at least one polymeric carrier. In one embodiment, the polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutryate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo) phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and

cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polysaccharides, blends and copolymers thereof. In another embodiment, said ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β- cyclodextrin, methoxypolyethylene glycol and polyethylene glycol. In another embodiment, the invention pertains to a method for treating a mammal comprising the step of administering to the mammal an effective amount of said composition.

In another aspect, the invention pertains to a pharmaceutical composition comprising a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, as described herein, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutically acceptable carrier functions as adjuvant useful to increase the absorption, or dispersion of the binding protein, *e.g.*, antibody, or antigen binding fragment thereof. In another embodiment, said adjuvant is hyaluronidase.

In another aspect, the pharmaceutical composition further comprises at least one additional therapeutic agent for treating a disorder in which PRLR activity is detrimental. For example, the additional agent may be selected from the group consisting of: therapeutic agent, imaging agent, cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an anti-rheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an oral steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

In another aspect, the invention provides a method for reducing human PRLR activity by contacting human PRLR with a binding protein of the invention, *e.g.*, antibody, or antigen binding fragment thereof, such that human PRLR activity is reduced.

In another aspect, the invention provides a method for reducing human PRLR activity in a human subject suffering from a disorder in which PRLR activity is detrimental, by administering to the human subject a binding protein of the invention, *e.g.*, antibody, or antigen binding fragment thereof, such that human PRLR activity in the human subject is reduced.

In another aspect, the invention provides a method for treating a subject for a disease or a disorder in which PRLR activity is detrimental by administering to the subject a binding protein of the invention, *e.g.*, antibody, or antigen binding fragment thereof, such that treatment is achieved. In one embodiment, the disorder is a cancer. In another embodiment, the cancer is

selected from the group consisting of melanoma, endometrial cancer, lymphoma, breast cancer, ovarian cancer, renal carcinoma, gastrointestinal cancer, colon cancer, lung cancer, pancreatic cancer, and prostate cancer. In yet another embodiment, the cancer is breast cancer. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, is administered to the subject by at least one mode selected from the group consisting of parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

In another aspect, the invention provides an anti-PRLR antibody, or antigen binding fragment thereof, that specifically competes with an anti-PRLR binding protein as described herein, wherein said competition can be detected in a competitive binding assay using said antibody, the human PRLR polypeptide, and the anti-PRLR binding protein.

In another aspect, the invention pertains to an anti-PRLR Antibody Drug Conjugate (ADC) comprising an anti-PRLR antibody, or antigen-binding fragment thereof, and at least one drug, wherein the antibody, or antigen-binding portion thereof, comprises at least 3 CDRs

For example, the invention provides an anti-PRLR Antibody Drug Conjugate (ADC) wherein the antibody, or antigen-binding portion thereof, comprises at least 3 CDRs selected from a heavy chain variable domain CDR set (CDR1, CDR2, and CDR3) consisting of SEQ ID NOs: 40, 41, and 42; SEQ ID NOs: 46, 47, and 42; SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 62, 63, and 58; SEQ ID NOs: 71, 72, and 73; SEQ ID NOs: 71, 77, and 73; SEQ ID NOs: 85, 86, and 87; SEQ ID NOs: 149, 150, and 87. Alternatively or in combination, the invention provides an anti-PRLR Antibody Drug Conjugate (ADC) wherein the antibody, or antigen-binding portion thereof, comprises at least 3 CDRs selected from a light chain variable domain CDR set (CDR1, CDR2, and CDR3) consisting of SEQ ID NOs: 49, 50, and 51; SEQ ID NOs: 65, 66, and 67; SEQ ID NOs: 79, 80, and 81; and SEQ ID NOs: 92, 93, and 94.

In another embodiment of the ADC set forth above, the drug is selected from the group consisting of a mitotic inhibitor, an antitumor antibiotic, an immunomodulating agent, a vector for gene therapy, an alkylating agent, an antiangiogenic agent, an antimetabolite, a boron-containing agent, a chemoprotective agent, a hormone, an antihormone agent, a corticosteroid, a photoactive therapeutic agent, an oligonucleotide, a radionuclide agent, a topoisomerase inhibitor, a tyrosine kinase inhibitor, and a radiosensitizer. In another embodiment, the invention features an ADC, wherein the drug is selected from the group consisting of Ixempra, dolastatin

10, dolatstin 15, auristatin E, auristatin PE, monomethyl auristatin D (MMAD or auristatin D derivative), monomethyl auristatin E (MMAE or auristatin E derivative), monomethyl auristatin F (MMAF or auristatin F derivative), auristatin F phenylenediamine (AFP), auristatin EB (AEB), auristatin EFP (AEFP), 5-benzoylvaleric acid-AE ester (AEVB), methotrexate, daunorubicin, vincristine, maytansine, maytansinol, C-3 esters of maytansinol, ansamitocin P1, ansamitocin P2, ansamitocin P3, ansamitocin P4, docetaxel, paclitaxel, nanoparticle paclitaxel, vindesine sulfate, vincristine, vinblastine, vinorelbine, actinomycines, pyrrolo[2,1-c][1,4]benzodiazepines, pyrrolobenzodiazepines (PBD) dimers, actinomycin D, anthramycin, chicamycin A, DC-18, DC-81, mazethramycin, neothramycin A, neothramycin B, porothramycin, prothracarcin B, SG2285, sibanomicin, sibiromycin, tomaymycin, anthracyclines, daunorubicin, doxorubicin, epirubicin, idarubicin, calicheamicins, γ_1^I, α_2^I, α_3^I, N-acetyl-γ_1^I, PSAG, θ^I_1, duocarmycins, adozelesin, bizelesin, and carzelesin, bleomycin, mitomycin, plicamycin, bacillus calmette-guerin (BCG), levamisole, cancer vaccines, recombinant bivalent human papillomavirus (HPV) vaccine types 16 and 18 vaccine, recombinant quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 vaccine, sipuleucel-T, cytokines, parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH), hepatic growth factor; fibroblast growth factor, prolactin, placental lactogen, tumor necrosis factor, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, inhibin, activin, vascular endothelial growth factor, integrin, thrombopoietin (TPO), nerve growth factors such as NGF, platelet-growth factor, transforming growth factors (TGFs), insulin-like growth factor-I and -II, erythropoietin (EPO), osteoinductive factors, interferons such as interferon α, β, and γ, colony stimulating factors (CSFs), granulocyte-macrophage-C-SF (GM-CSF), and granulocyte-CSF (G-CSF), interleukins (ILs) such as IL-1, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, tumor necrosis factor and other polypeptide factors including LIF and kit ligand (KL), colony-stimulating factors, erythropoietin (epoetin), filgrastim, sargramostim, promegapoietin, Oprelvekin, immunomodulating gene therapeutics, nucleic acid encoding a functional, therapeutic gene that is used to replace a mutated or otherwise dysfuntional (*e.g.* truncated) gene associated with cancer, nucleic acid that encodes for or otherwise provides for the production of a therapeutic protein to treat cancer, alkyl sulfonates, busulfan, nitrogen mustards, chlorambucil, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, and melphalan, nitrosoureas, carmustine, fotemustine, lomustine, nimustine, streptozocin, triazines and hydrazines, dacarbazine, procarbazine, temozolomide, ethylenimimes, thiopeta, diaziquone, mitomycin C, methylamine derivatives, epoxides, altretamine, dianhydrogalactitol, dibromodulcitol, angiostatin, ABX EFG, C1-1033, PKI-166, EGF vaccine, EKB-569, GW2016, ICR-62, EMD 55900, CP358, PD153035, AG1478, IMC-C225, OSI-774, Erlotinib, angiostatin, arrestin,

endostatin, BAY 12-9566 and w/fluorouracil or doxorubicin, canstatin, carboxyamidotriozole and with paclitaxel, EMD121974, S-24, vitaxin, dimethylxanthenone acetic acid, IM862, Interleukin-12, Interleukin-2, NM-3, HuMV833, PTK787, RhuMab, angiozyme, IMC-1C11, Neovastat, marimstat, prinomastat, BMS-275291, COL-3, MM1270, SU101, SU6668, SU11248, SU5416, with paclitaxel, with gemcitabine and cisplatin, and with irinotecan and cisplatin and with radiation, tecogalan, temozolomide and PEG interferon α2b, tetrathiomolybdate, TNP-470, thalidomide, CC-5013 and with taxotere, tumstatin, 2-methoxyestradiol, VEGF trap, mTOR inhibitors (deforolimus, everolimus, and temsirolimus), tyrosine kinase inhibitors (*e.g.*, imatinib, gefitinib, dasatinib, sunitinib, nilotinib, lapatinib, sorafenib, phosphoinositide 3-kinases (PI3K), folic acid antagonists, methotrexate, 4-amino-folic acid, lometrexol, pemetrexed, trimetrexate, a pyrimidine antagonists, azacitidine, capecitabine, cytarabine, decitabine, 5-fluorouracil, 5-fluoro-2'-deoxyuridine 5'-phosphate, 5-fluorouridine triphosphate, gemcitabine, foxuridine, a purine antagonist azathioprine, cladribine, mercaptopurine, fludarabine, pentostatin, 6-thioguanine, adenosine deaminase inhibitors, Cladribine, Fludarabine, Nelarabine, Pentostatin, borophycin, bortezomib, chemoprotective agents, amifostine, dexrazoxane, mesna, androgens, estrogens, medroxyprogesterone acetate, progestins, aminoglutethimide, anastrozole, bicalutamide, chlorotrianises, cyproterone acetate, degarelix, exemestane, flutamide, fulvestrant, goserelin, letrozole, leuprolide, lupron, medroxyprogesterone acetate, Megestrol acetate, tamoxifen, triptorelin, asparaginase, dacarbazine, hydroxyurea, levamisole, mitotane, procarbazane, tretinoin, glucocorticoids, prednisone, chromagens, dyes, antisense oligonucleotides whether naturally occurring or synthesized using standard and/or non-standard nucleotides (including RNA interference (RNAi)), double-stranded RNA (dsRNA), small interfering RNA (siRNA), microRNA (miRNA), aptamers, CpG oligonucleotides, ribozymes, angiozyme, ^{111}In, ^{177}Lu, ^{212}Bi, ^{213}Bi, ^{211}At, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{90}Y, ^{125}I, ^{131}I, ^{32}P, ^{33}P, ^{47}Sc, ^{111}Ag, ^{67}Ga, ^{142}Pr, ^{153}Sm, ^{161}Tb, ^{166}Dy, ^{166}Ho, ^{186}Re, ^{188}Re, ^{189}Re, ^{212}Pb, ^{223}Ra, ^{225}Ac, ^{59}Fe, ^{75}Se, ^{77}As, ^{89}Sr, ^{99}Mo, ^{105}Rh, ^{109}Pd, ^{143}Pr, ^{149}Pm, ^{169}Er, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}'Pb, Co-58, Ga-67, Br-80m, Tc-99m, Rh-103m, Pt-109, In-111 1, Sb-119, I-125, Ho-161 , Os-189m, Ir-192, Dy-152, At-211 , Bi-212, Ra-223, Rn-219, Po-215, Bi-21 1, Ac-225, Fr-221, At-217, Bi-213, Fm-255, ^{11}C, ^{13}N, ^{15}0, ^{75}Br, ^{198}Au, ^{224}Ac, ^{126}I, ^{133}I, ^{77}Br, ^{113m}In, ^{95}Ru, ^{97}Ru, ^{103}Ru, ^{105}Ru, ^{107}Hg, ^{203}Hg, ^{121m}Te, ^{122m}Te, ^{125m}Te, ^{165}Tm, ^{167}Tm, ^{168}Tm, ^{197}Pt, ^{109}Pd, ^{105}Rh, ^{142}Pr, ^{143}Pr, ^{161}Tb, ^{166}Ho, ^{199}Au, ^{57}Co, ^{58}Co, ^{51}Cr, ^{59}Fe, ^{75}Se, ^{201}Tl, ^{225}Ac, ^{76}Br, ^{169}Yb, taxane, cisplatin, metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, E09, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FUdR), hydroxyurea, hematoporphyrin derivatives, Photofrin(r), benzoporphyrin derivatives, NPe6, tin etioporphyrin (SnET2), pheoborbide a, bacteriochlorophyll a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, camptothecins, irinotecan,

topotecan, amsacrine, daunorubicin, doxotrubicin, epipodophyllotoxins, ellipticines, epirubicin, etoposide, razoxane, teniposide, Axitinib, Bosutinib, Cediranib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sunitinib, Vandetanib, abrin, abrin A chain, alpha toxin, Aleurites fordii proteins, amatoxin, crotin, curcin, dianthin proteins, diptheria toxin, diphtheria A chain, nonbinding active fragments of diphtheria toxin, deoxyribonuclease (Dnase), gelonin, mitogellin, modeccin A chain, momordica charantia inhibitor, neomycin, onconase, phenomycin, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), pokeweed antiviral protein, Pseudomonas endotoxin, Pseudomonas exotoxin, exotoxin A chain from Pseudomonas aeruginosa, restrictocin, ricin, ricin A chain, ribonuclease (Rnase), sapaonaria officinalis inhibitor, saporin, alpha-sarcin, Staphylcoccal enterotoxin-A, tetanus toxin, cisplatin, carboplatin, and oxaliplatin (Eloxatin, Sanofi Aventis), proteasome inhibitors, PS-341, HDAC inhibitors, vorinostat, belinostat, entinostat, mocetinostat, panobinostat, COX-2 inhibitors, substituted ureas, heat shock protein inhibitors, Geldanamycin, adrenocortical suppressants, tricothecenes, A12, 19D12, Cp751-871, H7C10, alphaIR3, ScFV/FC, EM/164, Matuzumab, Erbitux, Vectibix, mAb 806, Nimotuxumab, AVEO, AMG102, 5D5 (OA-5d5), H244G11, Ab #14 (MM 121-14), Herceptin, 1B4C3; 2D1D12, NVP-AEW541-A, BMS-536,924 (1H-benzoimidazol-2-yl)-1H-pyridin-2-one), BMS-554,417, Cycloligan, TAE226, PQ401 , Iressa, CI-1033 (PD 183805), Lapatinib (GW-572016), Tykerb, Tarceva, PKI-166, PD-158780, EKB-569, Tyrphostin AG 1478 (4-(3-Chloroanillino)-6,7-dimethoxyquinazoline), PHA665752, ARQ 197, Capecitabine, 5-Trifluoromethyl-2'-deoxyuridine, Methotrexate sodium, Raltitrexed, Pemetrexed, Tegafur, Cytosine Arabinoside (Cytarabine), 5-azacytidine, 6-mercaptopurine (Mercaptopurine, 6-MP), Azathioprine, 6-thioguanine, Pentostatin, Fludarabine phosphate, Cladribine (2-CdA, 2-chlorodeoxyadenosine), Ribonucleotide Reductase Inhibitor, Cyclophosphamide, Neosar, ifosfamide, Thiotepa, BCNU→ 1,3-bis(2-chloroethyl)-1-nitosourea, CCNU→ 1, -(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (methyl CCNU), Hexamethylmelamine, busulfan, Procarbazine HCL, Dacarbazine (DTIC), chlorambucil, melphalan, carboplatin, oxaliplatin, doxorubicin HCL, daunorubicin citrate, mitoxantrone HCL, actinomycin D, etoposide, topotecan HCl, teniposide, irinotecan HCL(CPT-ll), vincristine, vinblastine sulfate, vinorelbine tartrate, vindesine sulphate, pac1itaxel, docetaxel, abraxane, ixabepilone, imatinib mesylate, sunitinib malate, sorafenib toslate, nilotinib hydrochloride monohydrate, L-asparaginase, alpha interferon, Avastin, IL-2, Aldesleukin, Proleukin, IL-12, Toremifene citrate, Fulvestrant, raloxifene HCL, anastrazole, letrozole, Fadrozole (CGS 16949A), exemestane, leuprolide acetate, Lupron, goserelin acetate, triptorelin pamoate, buserelin, Nafarelin, cetrorelix, bicalutamide, nilutamide, megestrol acetate, somatostatin Analogs, prendinsolone, dexamethasone, ketoconazole, sirolimus, temsirolimus (CCI-779), deforolimus (AP23573), and everolimus (RAD00I).

In another aspect, the invention pertains to a pharmaceutical composition comprising an ADC as described above.

In yet another aspect, the invention pertains to a method of treating cancer in a subject in need thereof, said method comprising administering an ADC as described above, such that the subject is treated.

In another aspect, the invention pertains to a method of treating cancer in a subject in need thereof, said method comprising administering an ADC as described above, such that the subject is treated, wherein the cancer is selected from the group consisting of melanoma, endometrial cancer, lymphoma, breast cancer, ovarian cancer, renal carcinoma, gastrointestinal cancer, colon cancer, lung cancer, pancreatic cancer, and prostate cancer. In other embodiments, the invention pertains to to a method of treating cancer in a subject in need thereof, said method comprising administering an ADC as described above, such that the subject is treated, wherein the cancer is breast cancer. In other embodiments, the invention pertains to to a method of treating cancer in a subject in need thereof, said method comprising administering an ADC as described above, such that the subject is treated, wherein the ADC is administered to the subject by a mode selected from the group consisting of parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Alignment of variable heavy chain sequences for murine antibodies Ab5 (SEQ ID NO:112), Ab6 (SEQ ID NO:113), Ab7 (SEQ ID NO:114), Ab8 (SEQ ID NO:115), Ab9 (SEQ ID NO:116), Ab10 (SEQ ID NO:117), Ab11 (SEQ ID NO:118), Ab12 (SEQ ID NO:119) and Ab13 (SEQ ID NO:120).

Figure 2. Alignment of variable light chain sequences for murine antibodies Ab5 (SEQ ID NO:103), Ab6 (SEQ ID NO:104), Ab7 (SEQ ID NO:105), Ab8 (SEQ ID NO:106), Ab9 (SEQ ID NO:107), Ab10 (SEQ ID NO:108), Ab11 (SEQ ID NO:109), Ab12 (SEQ ID NO:110) and Ab13 (SEQ ID NO:111).

Figure 3. Alignment of variable heavy chain sequences for murine antibodies Ab5 (SEQ ID NO:112), Ab6 (SEQ ID NO:113), Ab7 (SEQ ID NO:114) and Ab8 (SEQ ID NO:115); and humanized variable heavy chain sequences derived therefrom, *i.e.*, Ab1 VH.1z (SEQ ID NO:39), Ab1 VH.1 (SEQ ID NO:43), Ab1 VH.1a (SEQ ID NO:44), Ab1 VH.1b (SEQ ID NO:45), Ab2

VH.1z (SEQ ID NO:55), Ab2 VH.1 (SEQ ID NO:59), Ab2 VH.1a (SEQ ID NO:60), Ab2 VH.1b (SEQ ID NO:61), Ab3 VH.1z (SEQ ID NO:70), Ab3 VH.1 (SEQ ID NO:74), Ab3 VH.1a (SEQ ID NO:75), Ab3 VH.1b (SEQ ID NO:76), Ab4 VH.1z (SEQ ID NO:84), Ab4 VH.1 (SEQ ID NO:88), Ab4 VH.1a (SEQ ID NO:89), Ab4 VH.1a.2 (SEQ ID NO:121), Ab4 VH.1a.3 (SEQ ID NO:122), Ab4 VH.1b (SEQ ID NO:123), and Ab4 VH.1b.2 (SEQ ID NO:90).

Figure 4. Alignment of variable light chain sequences for murine antibodies Ab5 (SEQ ID NO:103), Ab6 (SEQ ID NO:104), Ab7 (SEQ ID NO:105) and Ab8 (SEQ ID NO:106); and humanized variable heavy chain sequences derived therefrom, *i.e.*, Ab1 VL.1 (SEQ ID NO:48), Ab1 VL.1a (SEQ ID NO:52), Ab1 VL.2 (SEQ ID NO:53), Ab1 VL.2a (SEQ ID NO:54), Ab2 VL.1 (SEQ ID NO:64), Ab2 VL.1a (SEQ ID NO:68), Ab2 VL.1b (SEQ ID NO:69), Ab3 VL.1 (SEQ ID NO:78), Ab3 VL.1a (SEQ ID NO:82), Ab3 VL.1b (SEQ ID NO:83), Ab4 VL.1 (SEQ ID NO:91), Ab4 VL.1a (SEQ ID NO:95) and Ab4 VL.1b (SEQ ID NO:96).

Figure 5. Effect of anti-PRLR antibodies on the growth of Nb2-11 cells implanted in SCID-beige mice. Antibodies were dosed on the indicated study day (day 7, 14 and 21). Error bars indicate the standard error of the mean (see Example 3).

Figure 6. PRLR antibody epitope grouping summary for murine antibodies Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11 and Ab12, and for the LFA102 antibody (see Example 4).

Figure 7. Simultaneous binding assay results for chimeric and humanized antibodies chAb7, Ab39, Ab40, chAb5, Ab30, chAb6, Ab19, Ab21, chAb8, Ab48 and Ab49, and for the LFA102 antibody demonstrate that the humanization of chimeric antibodies did not significantly change the core epitope for each root antibody (see Example 4).

Figure 8. PRLR antibody epitope grouping summary for chimeric and humanized antibodies chAb7, Ab39, Ab40, chAb5, Ab30, chAb6, Ab19, Ab21, chAb8, Ab48 and Ab49, and for the LFA102 antibody (see Example 4).

Figure 9. Depiction of epitope surfaces for Ab6 and LFA102 mapped onto the structure of the PRL-PRLR ternary compex (see Example 5).

Figure 10. Comparison of binding of certain anti-PRLR antibodies to huPRLR, cyPRLR and muPRLR as follows (see Example 10).

Figure 11. Comparison of binding of certain anti-PRLR antibodies upon humanization from the chimeric antibody.

DETAILED DESCRIPTION OF THE INVENTION

This invention pertains to human PRLR binding proteins, particularly anti-PRLR antibodies, or antigen-binding portions thereof, that bind PRLR, and uses thereof. Various aspects of the invention relate to antibodies and antibody fragments, conjugates thereof and pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors

and host cells for making such antibodies and fragments. Methods of using the antibodies of the invention to detect human PRLR, to inhibit human PRLR activity, either *in vitro* or *in vivo*; and to prevent or treat disorders such as breast cancer are also encompassed by the invention.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

That the present invention may be more readily understood, select terms are defined below.

The term "polypeptide" as used herein, refers to any polymeric chain of amino acids. The terms "peptide" and "protein" are used interchangeably with the term polypeptide and also refer to a polymeric chain of amino acids. The term "polypeptide" encompasses native or artificial proteins, protein fragments and polypeptide analogs of a protein sequence. A polypeptide may be monomeric or polymeric.

The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide that by virtue of its origin or source of derivation is not associated with naturally associated components that accompany it in its native state; is substantially free of other proteins from the same species;

is expressed by a cell from a different species; or does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

The term "recovering" as used herein, refers to the process of rendering a chemical species such as a polypeptide substantially free of naturally associated components by isolation, *e.g.*, using protein purification techniques well known in the art.

The terms "human PRLR" and "human PRLR wild type" (abbreviated herein as hPRLR, hPRLRwt), as used herein, refers to a single membrane spanning class 1 cytokine receptor. Human PRLR includes an extracellular region that binds prolactin, a transmembrane region, and a cytoplasmic region. The term human PRLR is intended to include recombinant human PRLR (rhPRLR), which can be prepared by standard recombinant expression methods. Table 1 provides the amino acid sequence of human PRLR (*i.e.*, SEQ ID NO. 1), and the extracellular domain thereof (*i.e.*, SEQ ID NO:2), which are known in the art. In addition, various isoforms of hPRLR are known in the art and are set forth in Table 1 below.

TABLE 1: Sequence of human PRLR

Protein	Sequence Identifier	Sequence
		123456789**0**123456789**0**123456789**0**12
Human PRLR	**SEQ ID NO.:1**	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEKGK SEELLSALGCQDFPPTSDYEDLLVEYLEVDDS EDQHLMSVHSKEHPSQGMKPTYLDPDTDSGRG SCDSPSLLSEKCEEPQANPSTFYDPEVIEKPE NPETTHTWDPQCISMEGKIPYFHAGGSKCSTW PLPQPSQHNPRSSYHNITDVCELAVGPAGAPA TLLNEAGKDALKSSQTIKSREEGKATQQREVE SFHSETDQDTPWLLPQEKTPFGSAKPLDYVEI HKVNKDGALSLLPKQRENSGKPKKPGTPENNK EYAKVSGVMDNNILVLVPDPHAKNVACFEESA KEAPPSLEQNQAEKALANFTATSSKCRLQLGG LDYLDPACFTHSFH
Human PRLR Extracellular Domain	**SEQ ID NO:2**	QLPPGKPEIFKCRSPNKETFTCWWRPGTDGGL PTNYSLTYHREGETLMHECPDYITGGPNSCHF GKQYTSMWRTYIMMVNATNQMGSSFSDELYVD VTYIVQPDPPLELAVEVKQPEDRKPYLWIKWS PPTLIDLKTGWFTLLYEIRLKPEKAAEWEIHF AGQQTEFKILSLHPGQKYLVQVRCKPDHGYWS AWSPATFIQIPSDFTMN

Protein	Sequence Identifier	Sequence
		123456789**0**123456789**0**123456789**0**12
Human PRLR Isoform 2	**SEQ ID NO:3**	MKENVASATVFTLLLFLNTCLLNVQPDPPLEL AVEVKQPEDRKPYLWIKWSPPTLIDLKTGWFT LLYEIRLKPEKAAEWEIHFAGQQTEFKILSLH PGQKYLVQVRCKPDHGYWSAWSPATFIQIPSD FTMNDTTVWISVAVLSAVICLIIVWAVALKGY SMVTCIFPPVPGPKIKGFDAHLLEKGKSEELL SALGCQDFPPTSDYEDLLVEYLEVDDSEDQHL MSVHSKEHPSQGMKPTYLDPDTDSGRGSCDSP SLLSEKCEEPQANPSTFYDPEVIEKPENPETT HTWDPQCISMEGKIPYFHAGGSKCSTWPLPQP SQHNPRSSYHNITDVCELAVGPAGAPATLLNE AGKDALKSSQTIKSREEGKATQQREVESFHSE TDQDTPWLLPQEKTPFGSAKPLDYVEIHKVNK DGALSLLPKQRENSGKPKKPGTPENNKEYAKV SGVMDNNILVLVPDPHAKNVACFEESAKEAPP SLEQNQAEKALANFTATSSKCRLQLGGLDYLD PACFTHSFH
Human PRLR Isoform 3	**SEQ ID NO:4**	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSAW
Human PRLR Isoform 4	**SEQ ID NO:5**	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEKGK SEELLSALGCQDFPPTSDYEDLLVEYLEVDDS EDQHLMSVHSKEHPSQGDPLMLGASHYKNLKS YRPRKISSQGRLAVFTKATLTTVQ
Human PRLR Isoform 5	**SEQ ID NO:6**	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEKGK SEELLSALGCQDFPPTSDYEDLLVEYLEVDDS EDQHLMSVHSKEHPSQEREQRQAQEARDS
Human PRLR Isoform 6	**SEQ ID NO:7**	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEVTP

Protein	Sequence Identifier	Sequence
		123456789**0**123456789**0**123456789**0**12
Human PRLR Isoform 7	**SEQ ID NO:8**	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSGDPLMLGASHYKNLKSYRPRKISSQGRL AVFTKATLTTVQ
Human PRLR Isoform 8	**SEQ ID NO:9**	MHECPDYITGGPNSCHFGKQYTSMWRTYIMMV NATNQMGSSFSDELYVDVTYIVQPDPPLELAV EVKQPEDRKPYLWIKWSPPTLIDLKTGWFTLL YEIRLKPEKAAEWEIHFAGQQTEFKILSLHPG QKYLVQVRCKPDHGYWSAWSPATFIQIPSDFT MNDTTVWISVAVLSAVICLIIVWAVALKGYSM VTCIFPPVPGPKIKGFDAHLLEVTP

"Biological activity " as used herein, refers to all inherent biological properties of the prolactin receptor. Biological properties of PRLR include but are not limited to binding prolactin, binding growth hormone, binding placental lactogen, activation of JAK2 kinase activity, activation of transmembrane receptor protein tyrosine kinase activity, anti-apoptotic activity, cell surface receptor signaling, cytokine mediated signaling, involvement in embryo implantation, JAK-STAT cascade activity, JAK STAT cascade activity involved in growth hormone signaling, involvement in lactation, involvement in mammary gland alveolus development, involvement in mammary gland epithelial cell differentiation, involvement in mammary gland epithelium development, involvement in prostate gland growth, regulation of cell adhesion, regulation of epithelial cell differentiation, steroid biosynthetic activity, and T cell activation.

The terms "specific binding" or "specifically binding", as used herein, in reference to the interaction of an antibody, a protein, or a peptide with a second chemical species, mean that the interaction is dependent upon the presence of a particular structure (*e.g.*, an antigenic determinant or epitope) on the chemical species; for example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody is specific for epitope "A", the presence of a molecule containing epitope A (or free, unlabeled A), in a reaction containing labeled "A" and the antibody, will reduce the amount of labeled A bound to the antibody.

The term "antibody", as used herein, broadly refers to any immunoglobulin (Ig) molecule comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment, mutant, variant, or derivation thereof, which retains the essential epitope binding features of an Ig molecule. Such mutant, variant, or derivative antibody formats are known in the art. Non-limiting embodiments of which are discussed below.

In a full-length antibody, each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Immunoglobulin molecules can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG 1, IgG2, IgG 3, IgG4, IgA1 and IgA2) or subclass.

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, hPRLR). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Such antibody embodiments may also be bispecific, dual specific, or multi-specific formats; specifically binding to two or more different antigens. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546, Winter *et al.*, PCT publication WO 90/05144 A1 herein incorporated by reference), which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see *e.g.*, Holliger, P., *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R.J., *et al.* (1994) *Structure* 2:1121-1123). Such antibody binding portions

are known in the art (Kontermann and Dubel eds., Antibody Engineering (2001) Springer-Verlag. New York. 790 pp. (ISBN 3-540-41354-5).

The term "antibody construct" as used herein refers to a polypeptide comprising one or more the antigen binding portions of the invention linked to a linker polypeptide or an immunoglobulin constant domain. Linker polypeptides comprise two or more amino acid residues joined by peptide bonds and are used to link one or more antigen binding portions. Such linker polypeptides are well known in the art (see *e.g.*, Holliger, P., *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R.J., *et al.* (1994) *Structure* 2:1121-1123). An immunoglobulin constant domain refers to a heavy or light chain constant domain. Human IgG heavy chain and light chain constant domain amino acid sequences are known in the art and represented in Table 2.

TABLE 2: Sequence of human IgG heavy chain constant domain and light chain constant domain

Protein	Sequence Identifier	Sequence
		123456789**0**123456789**0**123456789**0**12
Ig gamma-1 constant region	**SEQ ID NO.:10**	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
Ig gamma-1 constant region mutant	**SEQ ID NO.:11**	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
Ig Kappa constant region	**SEQ ID NO.:12**	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
Ig Lambda constant region	**SEQ ID NO.:13**	QPKAAPSVTLFPPSSEELQANKATLVCLISDF YPGAVTVAWKADSSPVKAGVETTTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS

Still further, an antibody or antigen-binding portion thereof may be part of a larger immunoadhesion molecules, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, S.M., *et al.* (1995) *Human Antibodies and Hybridomas* 6:93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov, S.M., *et al.* (1994) *Mol. Immunol.* 31:1047-1058). Antibody portions, such as Fab and $F(ab')_2$ fragments, can be prepared from whole antibodies using conventional techniques, such as papain or pepsin digestion, respectively, of whole antibodies. Moreover, antibodies, antibody portions and immunoadhesion molecules can be obtained using standard recombinant DNA techniques, as described herein.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds hPRLR is substantially free of antibodies that specifically bind antigens other than hPRLR). An isolated antibody that specifically binds hPRLR may, however, have cross-reactivity to other antigens, such as PRLR molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further in Section II C, below), antibodies isolated from a recombinant, combinatorial human antibody library (Hoogenboom H.R., (1997) *TIB Tech.* 15:62-70; Azzazy H., and Highsmith W.E., (2002) *Clin. Biochem.* 35:425-445; Gavilondo J.V., and Larrick J.W. (2002) *BioTechniques* 29:128-145; Hoogenboom H., and Chames P. (2000) *Immunology Today* 21:371-378), antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor, L. D., *et al.* (1992) Nucl. Acids Res. 20:6287-6295; Kellermann S-A., and Green L.L. (2002) *Current Opinion in Biotechnology* 13:593-597; Little M. et al (2000) *Immunology Today* 21:364-370) or antibodies prepared, expressed, created or

isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*. One embodiment provides fully human antibodies capable of binding human PRLR which can be generated using techniques well known in the art, such as, but not limited to, using human Ig phage libraries such as those disclosed in Jermutus *et al.*, PCT publication No. WO 2005/007699 A2.

The term "chimeric antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species and constant region sequences from another species, such as antibodies having murine heavy and light chain variable regions linked to human constant regions.

The term "CDR-grafted antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species but in which the sequences of one or more of the CDR regions of VH and/or VL are replaced with CDR sequences of another species, such as antibodies having murine heavy and light chain variable regions in which one or more of the murine CDRs (*e.g.*, CDR3) has been replaced with human CDR sequences.

The terms "Kabat numbering", "Kabat definitions and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (*i.e.,* hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat *et al.* (1971) *Ann. NY Acad, Sci.* 190:382-391 and , Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3. For the light chain variable region, the hypervariable region ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

As used herein, the terms "acceptor" and "acceptor antibody" refer to the antibody or nucleic acid sequence providing or encoding at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or 100% of the amino acid sequences of one or more of the framework regions. In some embodiments, the term "acceptor" refers to the antibody amino acid or nucleic acid sequence providing or encoding the constant region(s). In yet another embodiment, the term

"acceptor" refers to the antibody amino acid or nucleic acid sequence providing or encoding one or more of the framework regions and the constant region(s). In a specific embodiment, the term "acceptor" refers to a human antibody amino acid or nucleic acid sequence that provides or encodes at least 80%, preferably, at least 85%, at least 90%, at least 95%, at least 98%, or 100% of the amino acid sequences of one or more of the framework regions. In accordance with this embodiment, an acceptor may contain at least 1, at least 2, at least 3, least 4, at least 5, or at least 10 amino acid residues that does (do) not occur at one or more specific positions of a human antibody. An acceptor framework region and/or acceptor constant region(s) may be, *e.g.*, derived or obtained from a germline antibody gene, a mature antibody gene, a functional antibody (*e.g.*, antibodies well-known in the art, antibodies in development, or antibodies commercially available).

As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. There are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" as used herein refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat *et al.*, Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Chothia and coworkers (Chothia *et al.*, *J. Mol. Biol.* 196:901-917 (1987) and Chothia *et al.*, Nature 342:877-883 (1989)) found that certain sub- portions within Kabat CDRs adopt nearly identical peptide backbone conformations, despite having great diversity at the level of amino acid sequence. These sub-portions were designated as L1, L2 and L3 or H1, H2 and H3 where the "L" and the "H" designates the light chain and the heavy chains regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan (FASEB J. 9:133-139 (1995)) and MacCallum (*J Mol Biol* 262(5):732-45 (1996)). Still other CDR boundary definitions may not strictly follow one of the above systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems, although preferred embodiments use Kabat or Chothia defined CDRs.

As used herein, the term "canonical" residue refers to a residue in a CDR or framework that defines a particular canonical CDR structure as defined by Chothia *et al.* (*J. Mol. Biol.* 196:901-907 (1987); Chothia *et al.*, *J. Mol. Biol.* 227:799 (1992), both are incorporated herein by reference). According to Chothia *et al.*, critical portions of the CDRs of many antibodies have nearly identical peptide backbone confirmations despite great diversity at the level of amino acid sequence. Each canonical structure specifies primarily a set of peptide backbone torsion angles for a contiguous segment of amino acid residues forming a loop.

As used herein, the terms "donor" and "donor antibody" refer to an antibody providing one or more CDRs. In a preferred embodiment, the donor antibody is an antibody from a species different from the antibody from which the framework regions are obtained or derived. In the context of a humanized antibody, the term "donor antibody" refers to a non-human antibody providing one or more CDRs.

As used herein, the term "framework" or "framework sequence" refers to the remaining sequences of a variable region minus the CDRs. Because the exact definition of a CDR sequence can be determined by different systems, the meaning of a framework sequence is subject to correspondingly different interpretations. The six CDRs (CDR-L1, CDR-L2, and CDR-L3 of light chain and CDR-H1, CDR-H2, and CDR-H3 of heavy chain) also divide the framework regions on the light chain and the heavy chain into four sub-regions (FR1, FR2, FR3 and FR4) on each chain, in which CDR1 is positioned between FR1 and FR2, CDR2 between FR2 and FR3, and CDR3 between FR3 and FR4. Without specifying the particular sub-regions as FR1, FR2, FR3 or FR4, a framework region, as referred by others, represents the combined FR's within the variable region of a single, naturally occurring immunoglobulin chain. As used herein, a FR represents one of the four sub- regions, and FRs represents two or more of the four sub- regions constituting a framework region.

Human heavy chain and light chain acceptor sequences are known in the art. In one embodiment of the invention the human heavy chain and light chain acceptor sequences are selected from the sequences described in Table 3 and Table 4.

TABLE 3: Heavy Chain Acceptor Sequences

SEQ ID No.	Protein region	Sequence
		123456789**0**123456789**0**123456789**0**12
14	VH1-18&JH6 FR1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT
15	VH1-18&JH6 FR2	WVRQAPGQGLEWMG
16	VH1-18&JH6 FR3	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR
17	VH1-18&JH6 FR4	WGQGTTVTVSS
14	21/28&JH4 FR1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT
18	21/28&JH4 FR2	WVRQAPGQRLEWMG
19	21/28&JH4 FR3	RVTITRDTSASTAYMELSSLRSEDTAVYYCAR

SEQ ID No.	Protein region	Sequence
		123456789**0**123456789**0**123456789**0**12
20	21/28&JH4 FR4	WGQGTLVTVSS
21	VH2-26&JH6 FR1	QVTLKESGPVLVKPTETLTLTCTVSGFSLS
22	VH2-26&JH6 FR2	WIRQPPGKALEWLAH
23	VH2-26&JH6 FR3	RLTISKDTSKSQVVLTMTNMDPVDTATYYCAR
17	VH2-26&JH6 FR4	WGQGTTVTVSS
24	M60&JH4 FR1	QVTLRESGPALVKPTQTLTLTCTLYGFSLS
25	M60&JH4 FR2	WIRQPPGKALEWLA
26	M60&JH4 FR3	RLTISKDTSKNQVVLTMTNMDPVDTATYYCAR
20	M60&JH4 FR4	WGQGTLVTVSS
14	VH1-46&JH6 FR1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT
15	VH1-46&JH6 FR2	WVRQAPGQGLEWMG
27	VH1-46&JH6 FR3	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
17	VH1-46&JH6 FR4	WGQGTTVTVSS

TABLE 4: Light Chain Acceptor Sequences

SEQ ID No.	Protein region	Sequence
		123456789**0**123456789**0**123456789**0**12
28	A20&JK4 FR1	DIQMTQSPSSLSASVGDRVTITC
29	A20&JK4 FR2	WYQQKPGKVPKLLIY
30	A20&JK4 FR3	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC
31	A20&JK4 FR4	FGGGTKVEIKR
28	III-3R&JK4 FR1	DIQMTQSPSSLSASVGDRVTITC
29	III-3R&JK4 FR2	WYQQKPGKAPKLLIY
32	III-3R&JK4 FR3	GVPSRISGSGSGTDFTFTISSLQPEDIATYYC
31	III-3R&JK4 FR4	FGGGTKVEIKR
33	A1&JK4 FR1	DVVMTQSPLSLPVTLGQPASISC
34	A1&JK4 FR2	WFQQRPGQSPRRLIY
35	A1&JK4 FR3	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC
31	A1&JK4 FR4	FGGGTKVEIKR
36	01&JK2 FR1	DIVMTQTPLSLPVTPGEPASISC
37	01&JK2 FR2	WYLQKPGQSPQLLIY
35	01&JK2 FR3	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC
38	01&JK2 FR4	FGQGTKLEIKR

As used herein, the term "germline antibody gene" or "gene fragment" refers to an immunoglobulin sequence encoded by non- lymphoid cells that have not undergone the maturation process that leads to genetic rearrangement and mutation for expression of a particular immunoglobulin. (See, *e.g.*, Shapiro *et al.*, *Crit. Rev. Immunol.* 22(3): 183-200 (2002); Marchalonis *et al.*, *Adv Exp Med Biol.* 484:13-30 (2001)). One of the advantages provided by various embodiments of the present invention stems from the recognition that germline antibody genes are more likely than mature antibody genes to conserve essential amino acid sequence structures characteristic of individuals in the species, hence less likely to be recognized as from a foreign source when used therapeutically in that species.

As used herein, the term "key" residues refer to certain residues within the variable region that have more impact on the binding specificity and/or affinity of an antibody, in particular a humanized antibody. A key residue includes, but is not limited to, one or more of the following: a residue that is adjacent to a CDR, a potential glycosylation site (can be either N- or O-glycosylation site), a rare residue, a residue capable of interacting with the antigen, a residue capable of interacting with a CDR, a canonical residue, a contact residue between heavy chain variable region and light chain variable region, a residue within the Vernier zone, and a residue in the region that overlaps between the Chothia definition of a variable heavy chain CDR1 and the Kabat definition of the first heavy chain framework.

As used herein, the term "humanized antibody" is an antibody or a variant, derivative, analog or fragment thereof which immunospecifically binds to an antigen of interest and which comprises a framework (FR) region having substantially the amino acid sequence of a human antibody and a complementary determining region (CDR) having substantially the amino acid sequence of a non-human antibody. As used herein, the term "substantially" in the context of a CDR refers to a CDR having an amino acid sequence at least 80%, preferably at least 85%, at least 90%, at least 95%, at least 98% or at least 99% identical to the amino acid sequence of a non-human antibody CDR. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', F(ab') 2, FabC, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (*i.e.*, donor antibody) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. Preferably, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. In some embodiments, a humanized antibody contains both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. In some embodiments, a humanized antibody only contains a humanized light chain. In some embodiments, a humanized antibody only contains a humanized heavy chain. In specific embodiments, a humanized antibody only contains a humanized variable domain of a light chain and/or humanized heavy chain.

The humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including without limitation IgG 1, IgG2, IgG3 and IgG4. The humanized antibody may comprise sequences from more than one class or isotype, and particular constant domains may be selected to optimize desired effector functions using techniques well- known in the art.

The framework and CDR regions of a humanized antibody need not correspond precisely to the parental sequences, *e.g.*, the donor antibody CDR or the consensus framework may be mutagenized by substitution, insertion and/or deletion of at least one amino acid residue so that

the CDR or framework residue at that site does not correspond to either the donor antibody or the consensus framework. In a preferred embodiment, such mutations, however, will not be extensive. Usually, at least 80%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% of the humanized antibody residues will correspond to those of the parental FR and CDR sequences. As used herein, the term "consensus framework" refers to the framework region in the consensus immunoglobulin sequence. As used herein, the term "consensus immunoglobulin sequence" refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related immunoglobulin sequences (See *e.g.*, Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of immunoglobulins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence.

As used herein, "Vernier" zone refers to a subset of framework residues that may adjust CDR structure and fine-tune the fit to antigen as described by Foote and Winter (1992, *J. Mol. Biol.* 224:487-499, which is incorporated herein by reference). Vernier zone residues form a layer underlying the CDRs and may impact on the structure of CDRs and the affinity of the antibody.

The term "multivalent binding protein" is used in this specification to denote a binding protein comprising two or more antigen binding sites. The multivalent binding protein is preferably engineered to have the three or more antigen binding sites, and is generally not a naturally occurring antibody. The term "multispecific binding protein" refers to a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins as used herein, are binding proteins that comprise two or more antigen binding sites and are tetravalent or multivalent binding proteins. Such DVDs may be monospecific, *i.e.*, capable of binding one antigen or multispecific, *i.e.* capable of binding two or more antigens. DVD binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to a DVD Ig. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, and a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

As used herein, the term "neutralizing" refers to neutralization of biological activity of a cytokine receptor when a binding protein specifically binds the cytokine receptor. Preferably, a neutralizing binding protein is a neutralizing antibody whose binding to hPRLR results in inhibition of a biological activity of hPRLR. Preferably the neutralizing binding protein binds hPRLR and reduces a biologically activity of hPRLR by at least about 20%, 40%, 60%, 80%, 85% or more. Inhibition of a biological activity of hPRLR by a neutralizing binding protein can be assessed by measuring one or more indicators of hPRLR biological activity well known in the

art. For example, inhibition of phosphorylation of PRLR, pSTAT5 or ERK1/2in a PRLR expressing cell line, *e.g.,* the human breast carcinoma cell line T47D, can be measured. Alternatively, inhibition of proliferation of PRLR expressing cell lines, *e.g.,* Baf3 pro-B lymphoid cells transfected with human PRLR, Nb2-11 rat lymphoma cells, MDA-MB-231-PRLR human breast carcinoma cells transfected with PRLR or BT474 human breast cancer cells, can be measured.

The term "activity" includes activities such as the binding specificity/affinity of an antibody for an antigen, for example, an anti-hPRLR antibody that binds to an hPRLR antigen and/or the neutralizing potency of an antibody, for example, an anti-hPRLR antibody whose binding to hPRLR inhibits the biological activity of hPRLR, *e.g.*, inhibition of phosphorylation of PRLR, pSTAT5 or ERK1/2 in a PRLR expressing cell line, *e.g.,* the human breast carcinoma cell line T47D, or inhibition of proliferation of PRLR expressing cell lines, *e.g.,* Ba/F3 pro-B lymphoid cells transfected with human PRLR, Nb2-11 rat lymphoma cells, MDA-MB-231-PRLR human breast carcinoma cells transfected with PRLR or BT474 human breast cancer cells.

The term "epitope" includes any polypeptide determinant capable of specific binding to a binding protein, *e.g.*, an antibody or antigen binding portion thereof. In certain embodiments, epitope determinants include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl, or sulfonyl, and, in certain embodiments, may have specific three dimensional structural characteristics, and/or specific charge characteristics. In various embodiments, an epitope may be a linear or sequential epitope, *i.e.*, a linear sequence of amino acids, of the primary structure of the antigen, i.e., PRLR. Alternatively, in other embodiments, an epitope may be a conformational epitope having a specific three-dimensional shape when the antigen assumes its secondary structure. For example, the conformational epitope may comprise non-linear, *i.e.*, non-sequential, amino acids of the antigen.

In a particular embodiment, an epitope is a region of an antigen that is bound by a binding protein, *e.g.*, antibody or antigen binding portion thereof. In certain embodiments, a binding protein, *e.g.*, antibody or antigen binding portion thereof, is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In a particular embodiment, an epitope of the antigen, *i.e.*, PRLR, includes those amino acid residues within 4 angstroms (Å) of the binding protein, *e.g.*, antibody or antigen binding portion thereof, when the binding protein is bound to the antigen.

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ). For further descriptions, see Jönsson, U., *et al.* (1993) *Ann. Biol. Clin.* 51:19-26; Jönsson, U., *et al.* (1991) *Biotechniques*

11:620-627; Johnsson, B., *et al.* (1995) *J. Mol. Recognit.* 8:125-131; and Johnnson, B., *et al.* (1991) *Anal. Biochem.* 198:268-277.

The term " k_{on} ", as used herein, is intended to refer to the on rate constant for association of an antibody to the antigen to form the antibody/antigen complex as is known in the art.

The term " k_{off} ", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex as is known in the art.

The term " K_D ", as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction as is known in the art.

The term "labeled binding protein" as used herein, refers to a protein with a label incorporated that provides for the identification of the binding protein. Preferably, the label is a detectable marker, *e.g.*, incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (*e.g.*, streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, or ^{153}Sm); fluorescent labels (*e.g.*, FITC, rhodamine, lanthanide phosphors), enzymatic labels (*e.g.*, horseradish peroxidase, luciferase, alkaline phosphatase); chemiluminescent markers; biotinyl groups; predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags); and magnetic agents, such as gadolinium chelates.

The term "antibody drug conjugate" or "ADC" refers to a binding protein, such as an antibody or antigen binding fragment thereof, chemically linked to one or more chemical agent(s) that may optionally be therapeutic or cytotoxic agents. Examples of agents that may be used in the ADCs of the invention include, but are not limited to, mitotic inhibitors, antitumor antibiotics, immunomodulating agents, vectors for gene therapy, alkylating agents, antiangiogenic agents, antimetabolites, boron-containing agents, chemoprotective agents, hormones, antihormone agents, corticosteroids, photoactive therapeutic agents, oligonucleotides, radionuclide agents, topoisomerase inhibitors, tyrosine kinase inhibitors, and radiosensitizers.

The term "agent" or "drug" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

The term "cytotoxin" or "cytotoxic agent" includes any agent that is detrimental to (*e.g.*, kills) cells. In one embodiment of the invention, an anitbody described herein is conjugated to a cytotoxic agent.

The terms "crystal", and "crystallized" as used herein, refer to an antibody, or antigen binding portion thereof, that exists in the form of a crystal. Crystals are one form of the solid state of matter, which is distinct from other forms such as the amorphous solid state or the

liquid crystalline state. Crystals are composed of regular, repeating, three-dimensional arrays of atoms, ions, molecules (*e.g.*, proteins such as antibodies), or molecular assemblies (*e.g.*, antigen/antibody complexes). These three-dimensional arrays are arranged according to specific mathematical relationships that are well-understood in the field. The fundamental unit, or building block, that is repeated in a crystal is called the asymmetric unit. Repetition of the asymmetric unit in an arrangement that conforms to a given, well-defined crystallographic symmetry provides the "unit cell" of the crystal. Repetition of the unit cell by regular translations in all three dimensions provides the crystal. See Giege, R. and Ducruix, A. Barrett, Crystallization of Nucleic Acids and Proteins, a Practical Approach, 2nd ea., pp. 20 1-16, Oxford University Press, New York, New York, (1999)."

The term "polynucleotide" as used herein refers to a polymeric form of two or more nucleotides, either ribonucleotides or deoxvnucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA but preferably is double-stranded DNA.

The term "isolated polynucleotide" as used herein shall mean a polynucleotide (*e.g.*, of genomic, cDNA, or synthetic origin, or some combination thereof) that, by virtue of its origin , the "isolated polynucleotide": is not associated with all or a portion of a polynucleotide with which the "isolated polynucleotide" is found in nature; is operably linked to a polynucleotide that it is not linked to in nature; or does not occur in nature as part of a larger sequence.

The term "vector", as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term "operably linked" refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences. "Operably linked" sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in *trans* or at a distance to control the gene of interest. The term "expression control sequence" as used herein refers to polynucleotide sequences which are necessary to effect the expression and processing of coding sequences to which they are ligated. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*i.e.*, Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. Protein constructs of the present invention may be expressed, and purified using expression vectors and host cells known in the art, including expression cassettes, vectors, recombinant host cells and methods for the recombinant expression and proteolytic processing of recombinant polyproteins and pre-proteins from a single open reading frame (*e.g.*, WO 2007/014162 incorporated herein by reference).

"Transformation", as defined herein, refers to any process by which exogenous DNA enters a host cell. Transformation may occur under natural or artificial conditions using various methods well known in the art. Transformation may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method is selected based on the host cell being transformed and may include, but is not limited to, viral infection, electroporation, lipofection, and particle bombardment. Such "transformed" cells include stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome. They also include cells which transiently express the inserted DNA or RNA for limited periods of time.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which exogenous DNA has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell, but, to the progeny of such a

cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein. Preferably host cells include prokaryotic and eukaryotic cells selected from any of the Kingdoms of life. Preferred eukaryotic cells include protist, fungal, plant and animal cells. Most preferably host cells include but are not limited to the prokaryotic cell line *E.Coli*; mammalian cell lines CHO, HEK 293 and COS; the insect cell line Sf9; and the fungal cell *Saccharomyces cerevisiae*.

Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.*, electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See *e.g.*, Sambrook *et al.* Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose.

"Transgenic organism", as known in the art and as used herein, refers to an organism having cells that contain a transgene, wherein the transgene introduced into the organism (or an ancestor of the organism) expresses a polypeptide not naturally expressed in the organism. A "transgene" is a DNA construct, which is stably and operably integrated into the genome of a cell from which a transgenic organism develops, directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic organism.

The term "regulate" and "modulate" are used interchangeably, and, as used herein, refers to a change or an alteration in the activity of a molecule of interest (*e.g.*, the biological activity of hPRLR). Modulation may be an increase or a decrease in the magnitude of a certain activity or function of the molecule of interest. Exemplary activities and functions of a molecule include, but are not limited to, binding characteristics, enzymatic activity, cell receptor activation, and signal transduction.

Correspondingly, the term "modulator," as used herein, is a compound capable of changing or altering an activity or function of a molecule of interest (*e.g.*, the biological activity of hPRLR). For example, a modulator may cause an increase or decrease in the magnitude of a certain activity or function of a molecule compared to the magnitude of the activity or function observed in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of at least one activity or function of a molecule. Exemplary inhibitors include, but are not limited to, proteins, peptides, antibodies, peptibodies, carbohydrates or small organic molecules. Peptibodies are described, *e.g.*, in WO01/83525.

The term "agonist", as used herein, refers to a modulator that, when contacted with a molecule of interest, causes an increase in the magnitude of a certain activity or function of the molecule compared to the magnitude of the activity or function observed in the absence of the agonist. Particular agonists of interest may include, but are not limited to, hPRLR polypeptides or polypeptides, nucleic acids, carbohydrates, or any other molecules that bind to hPRLR.

The term "antagonist" or "inhibitor", as used herein, refer to a modulator that, when contacted with a molecule of interest causes a decrease in the magnitude of a certain activity or function of the molecule compared to the magnitude of the activity or function observed in the absence of the antagonist. Particular antagonists of interest include those that block or modulate the biological or immunological activity of hPRLR. Antagonists and inhibitors of hPRLR may include, but are not limited to, proteins, nucleic acids, carbohydrates, or any other molecules, which bind to hPRLR.

The term "inhibit binding to prolactin" refers to the ability of the binding protein to prevent the binding of prolactin ("PRL") to hPRLR. Such inhibition of binding to prolactin would result in diminishing or abolishing the biological activity mediated by binding of prolactin to hPRLR.

As used herein, the term "effective amount" refers to the amount of a therapy which is sufficient to reduce or ameliorate the severity and/or duration of a disorder or one or more symptoms thereof, prevent the advancement of a disorder, cause regression of a disorder, prevent the recurrence, development, onset or progression of one or more symptoms associated with a disorder, detect a disorder, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy (*e.g.* , prophylactic or therapeutic agent).

The term "sample", as used herein, is used in its broadest sense. A "biological sample", as used herein, includes, but is not limited to, any quantity of a substance from a living thing or formerly living thing. Such living things include, but are not limited to, humans, mice, rats, monkeys, dogs, rabbits and other animals. Such substances include, but are not limited to, blood, serum, urine, synovial fluid, cells, organs, tissues, bone marrow, lymph nodes and spleen.

As used herein, the term "LFA102" refers to an anti-PRLR humanized antibody of the IgG1 kappa subtype described in WO 2008022295 A2 (Novartis) and comprising the heavy chain set forth in SEQ ID NO:156 and the light chain set forth in SEQ ID NO:157. LFA102 binds to the putative dimerization region of PRLR in a non-ligand competitive manner and inhibits PRL-induced signaling. LFA102 binds to the membrane proximal D2 domain of PRLR, which is believed to contain the dimerization interface of the receptor. PRLR does not bind to the D1 domain (see, *e.g.*, Damiano *et al.*, 2013, *Molec.Cancer. Therapeuics,* 12:295-305). As such, while LFA102 is capable of inhibiting PRLR dimerization, because LFA102 does not exhibit direct contact with the D1 domain of PRLR which contains the majority of the ligand-binding

pocket, LFA102 appears to allow simulataneous binding of prolactin to PRLR (see, *e.g.*, Damiano *et al.*, 2013, *Molec.Cancer. Therapeuics,* 12:295-305 and van *et al.*, 2010, *J. Mol. Biol.,* 404:112-26).

I. Antibodies that Bind Human hPRLR

One aspect of the present invention provides isolated murine monoclonal antibodies, or antigen-binding portions thereof, that bind to PRLR with high affinity, a slow off rate and high neutralizing capacity. A second aspect of the invention provides chimeric antibodies that bind PRLR. A third aspect of the invention provides humanized antibodies, or antigen-binding portions thereof, that bind PRLR. Preferably, the antibodies, or portions thereof, are isolated antibodies. Preferably, the antibodies of the invention are neutralizing human anti-PRLR antibodies.

A. Method of Making Anti-PRLR Antibodies

Antibodies of the present invention may be made by any of a number of techniques known in the art.

1. Anti-PRLR Monoclonal Antibodies Using Hybridoma Technology

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow *et al.* , Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. In one embodiment, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a

polypeptide of the invention (See Example 1). Briefly, mice can be immunized with a PRLR antigen. In a preferred embodiment, the PRLR antigen is administered with an adjuvant to stimulate the immune response. Such adjuvants include complete or incomplete Freund's adjuvant, RIBI (muramyl dipeptides) or ISCOM (immunostimulating complexes). Such adjuvants may protect the polypeptide from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system. Preferably, if a polypeptide is being administered, the immunization schedule will involve two or more administrations of the polypeptide, spread out over several weeks.

After immunization of an animal with a PRLR antigen, antibodies and/or antibody-producing cells may be obtained from the animal. An anti-PRLR antibody-containing serum is obtained from the animal by bleeding or sacrificing the animal. The serum may be used as it is obtained from the animal, an immunoglobulin fraction may be obtained from the serum, or the anti-PRLR antibodies may be purified from the serum. Serum or immunoglobulins obtained in this manner are polyclonal, thus having a heterogeneous array of properties.

Once an immune response is detected, *e.g.*, antibodies specific for the antigen PRLR are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well-known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding PRLR. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

In another embodiment, antibody-producing immortalized hybridomas may be prepared from the immunized animal. After immunization, the animal is sacrificed and the splenic B cells are fused to immortalized myeloma cells as is well known in the art. See, *e.g.*, Harlow and Lane, *supra.* In a preferred embodiment, the myeloma cells do not secrete immunoglobulin polypeptides (a non-secretory cell line). After fusion and antibiotic selection, the hybridomas are screened using PRLR, or a portion thereof, or a cell expressing PRLR. In a preferred embodiment, the initial screening is performed using an enzyme-linked immunoassay (ELISA) or a radioimmunoassay (RIA), preferably an ELISA. An example of ELISA screening is provided in WO 00/37504, herein incorporated by reference.

Anti- PRLR antibody-producing hybridomas are selected, cloned and further screened for desirable characteristics, including robust hybridoma growth, high antibody production and desirable antibody characteristics, as discussed further below. Hybridomas may be cultured and expanded *in vivo* in syngeneic animals, in animals that lack an immune system, *e.g.*, nude mice, or

in cell culture *in vitro*. Methods of selecting, cloning and expanding hybridomas are well known to those of ordinary skill in the art.

In a preferred embodiment, the hybridomas are mouse hybridomas, as described above. In another preferred embodiment, the hybridomas are produced in a non-human, non-mouse species such as rats, sheep, pigs, goats, cattle or horses. In another embodiment, the hybridomas are human hybridomas, in which a human non-secretory myeloma is fused with a human cell expressing an anti-PRLR antibody.

Antibody fragments that recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CHI domain of the heavy chain.

2. Anti-PRLR Monoclonal Antibodies Using SLAM

In another aspect of the invention, recombinant antibodies are generated from single, isolated lymphocytes using a procedure referred to in the art as the selected lymphocyte antibody method (SLAM), as described in U.S. Patent No. 5,627,052, PCT Publication WO 92/02551 and Babcock, J.S. *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:7843-7848. In this method, single cells secreting antibodies of interest, *e.g.*, lymphocytes derived from any one of the immunized animals described in Section 1, are screened using an antigen-specific hemolytic plaque assay, wherein the antigen PRLR, a subunit of PRLR, or a fragment thereof, is coupled to sheep red blood cells using a linker, such as biotin, and used to identify single cells that secrete antibodies with specificity for PRLR. Following identification of antibody-secreting cells of interest, heavy- and light-chain variable region cDNAs are rescued from the cells by reverse transcriptase-PCR and these variable regions can then be expressed, in the context of appropriate immunoglobulin constant regions (*e.g.*, human constant regions), in mammalian host cells, such as COS or CHO cells. The host cells transfected with the amplified immunoglobulin sequences, derived from *in vivo* selected lymphocytes, can then undergo further analysis and selection *in vitro*, for example by panning the transfected cells to isolate cells expressing antibodies to PRLR. The amplified immunoglobulin sequences further can be manipulated *in vitro*, such as by *in vitro* affinity maturation methods such as those described in PCT Publication WO 97/29131 and PCT Publication WO 00/56772.

3. Anti-PRLR Monoclonal Antibodies Using Transgenic Animals

In another embodiment of the instant invention, antibodies are produced by immunizing a non-human animal comprising some, or all, of the human immunoglobulin locus with a PRLR antigen. In a preferred embodiment, the non-human animal is a XENOMOUSE transgenic mouse, an engineered mouse strain that comprises large fragments of the human immunoglobulin loci and is deficient in mouse antibody production. *See, e.g.,* Green *et al. Nature Genetics* 7:13-21 (1994) and United States Patents 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001, 6,114,598 and 6,130,364. See also WO 91/10741, published July 25,1991, WO 94/02602, published February 3, 1994, WO 96/34096 and WO 96/33735, both published October 31, 1996, WO 98/16654, published April 23, 1998, WO 98/24893, published June 11, 1998, WO 98/50433, published November 12, 1998, WO 99/45031, published September 10, 1999, WO 99/53049, published October 21, 1999, WO 00 09560, published February 24, 2000 and WO 00/037504, published June 29, 2000. The XENOMOUSE transgenic mouse produces an adult-like human repertoire of fully human antibodies, and generates antigen-specific human Mabs. The XENOMOUSE transgenic mouse contains approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and x light chain loci. See Mendez *et al.*, *Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998), the disclosures of which are hereby incorporated by reference.

4. Anti-PRLR Monoclonal Antibodies Using Recombinant Antibody Libraries

In vitro methods also can be used to make the antibodies of the invention, wherein an antibody library is screened to identify an antibody having the desired binding specificity. Methods for such screening of recombinant antibody libraries are well known in the art and include methods described in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* PCT Publication No. WO 92/18619; Dower *et al.* PCT Publication No. WO 91/17271; Winter *et al.* PCT Publication No. WO 92/20791; Markland *et al.* PCT Publication No. WO 92/15679; Breitling *et al.* PCT Publication No. WO 93/01288; McCafferty *et al.* PCT Publication No. WO 92/01047; Garrard *et al.* PCT Publication No. WO 92/09690; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibod Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; McCafferty *et al.*, *Nature* (1990) 348:552-554; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J Mol Biol* 226:889-896; Clackson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; and Barbas *et al.* (1991) *PNAS* 88:7978-7982, US patent application publication 20030186374, and PCT Publication No. WO 97/29131, the contents of each of which are incorporated herein by reference.

The recombinant antibody library may be from a subject immunized with PRLR, or a portion of PRLR, such as the extracellular domain. Alternatively, the recombinant antibody library may be from a naïve subject, *i.e.*, one who has not been immunized with PRLR, such as a human antibody library from a human subject who has not been immunized with human PRLR. Antibodies of the invention are selected by screening the recombinant antibody library with the peptide comprising human PRLR to thereby select those antibodies that recognize PRLR. Methods for conducting such screening and selection are well known in the art, such as described in the references in the preceding paragraph. To select antibodies of the invention having particular binding affinities for hPRLR, such as those that dissociate from human PRLR with a particular k_{off} rate constant, the art-known method of surface plasmon resonance can be used to select antibodies having the desired k_{off} rate constant. To select antibodies of the invention having a particular neutralizing activity for hPRLR, such as those with a particular an $IC_{50,}$ standard methods known in the art for assessing the inhibition of hPRLR activity may be used.

In one aspect, the invention pertains to an isolated antibody, or an antigen-binding portion thereof, that binds human PRLR. Preferably, the antibody is a neutralizing antibody. In various embodiments, the antibody is a recombinant antibody or a monoclonal antibody.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular, such phage can be utilized to display antigen-binding domains expressed from a repertoire or combinatorial antibody library (*e.g.*, human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, *e.g.*, using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman *et al.*, *J. Immunol. Methods* 182:41-50 (1995); Ames *et al.*, *J. Immunol. Methods* 184:177-186 (1995); Kettleborough *et al.*, *Eur. J. Immunol.* 24:952-958 (1994); Persic *et al.*, Gene 187 9-18 (1997); Burton *et al.*, *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780, 225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies including human antibodies or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, *e.g.*, as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax *et al.*, *BioTechniques* 12(6):864-869 (1992); and Sawai *et al.*, *AJRI* 34:26-34 (1995); and Better *et al.*, *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties). Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Pat. 4,946,778 and 5,258,498; Huston *et al.*, *Methods in Enzymology* 203:46-88 (1991); Shu *et al.*, *PNAS* 90:7995-7999 (1993); and Skerra *et al.*, *Science* 240:1038-1040 (1988).

Alternative to screening of recombinant antibody libraries by phage display, other methodologies known in the art for screening large combinatorial libraries can be applied to the identification of dual specificity antibodies of the invention. One type of alternative expression system is one in which the recombinant antibody library is expressed as RNA-protein fusions, as described in PCT Publication No. WO 98/31700 by Szostak and Roberts, and in Roberts, R.W. and Szostak, J.W. (1997) *Proc. Natl. Acad. Sci. USA* 94:12297-12302. In this system, a covalent fusion is created between an mRNA and the peptide or protein that it encodes by *in vitro* translation of synthetic mRNAs that carry puromycin, a peptidyl acceptor antibiotic, at their 3' end. Thus, a specific mRNA can be enriched from a complex mixture of mRNAs (*e.g.*, a combinatorial library) based on the properties of the encoded peptide or protein, *e.g.*, antibody, or portion thereof, such as binding of the antibody, or portion thereof, to the dual specificity antigen. Nucleic acid sequences encoding antibodies, or portions thereof, recovered from screening of such libraries can be expressed by recombinant means as described above (*e.g.*, in mammalian host cells) and, moreover, can be subjected to further affinity maturation by either additional rounds of screening of mRNA-peptide fusions in which mutations have been introduced into the originally selected sequence(s), or by other methods for affinity maturation *in vitro* of recombinant antibodies, as described above.

In another approach the antibodies of the present invention can also be generated using yeast display methods known in the art. In yeast display methods, genetic methods are used to tether antibody domains to the yeast cell wall and display them on the surface of yeast. In particular, such yeast can be utilized to display antigen-binding domains expressed from a repertoire or combinatorial antibody library (*e.g.*, human or murine). Examples of yeast display methods that can be used to make the antibodies of the present invention include those disclosed in Wittrup *et al.* (U.S. Patent No. 6,699,658) incorporated herein by reference.

B. Production of Recombinant PRLR Antibodies

Antibodies of the present invention may be produced by any of a number of techniques known in the art. For example, expression from host cells, wherein expression vector(s) encoding the heavy and light chains is (are) transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, *e.g.*, electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is possible to express the antibodies of the invention in either prokaryotic or eukaryotic host cells, expression of antibodies in eukaryotic cells is preferable, and most preferable in mammalian host cells, because such eukaryotic cells (and in particular mammalian cells) are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active antibody.

Preferred mammalian host cells for expressing the recombinant antibodies of the invention include Chinese Hamster Ovary (CHO cells) (including dhfr- CHO cells, described in Urlaub and Chasin, (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, *e.g.*, as described in R.J. Kaufman and P.A. Sharp (1982) *Mol. Biol.* 159:601-621), NS0 myeloma cells, COS cells and SP2 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Host cells can also be used to produce functional antibody fragments, such as Fab fragments or scFv molecules. It will be understood that variations on the above procedure are within the scope of the present invention. For example, it may be desirable to transfect a host cell with DNA encoding functional fragments of either the light chain and/or the heavy chain of an antibody of this invention. Recombinant DNA technology may also be used to remove some, or all, of the DNA encoding either or both of the light and heavy chains that is not necessary for binding to the antigens of interest. The molecules expressed from such truncated DNA molecules are also encompassed by the antibodies of the invention. In addition, bifunctional antibodies may be produced in which one heavy and one light chain are an antibody of the invention and the other heavy and light chain are specific for an antigen other than the antigens of interest by crosslinking an antibody of the invention to a second antibody by standard chemical crosslinking methods.

In a preferred system for recombinant expression of an antibody, or antigen-binding portion thereof, of the invention, a recombinant expression vector encoding both the antibody heavy chain and the antibody light chain is introduced into dhfr- CHO cells by calcium phosphate-mediated transfection. Within the recombinant expression vector, the antibody heavy and light chain genes are each operatively linked to CMV enhancer/AdMLP promoter regulatory elements to drive high levels of transcription of the genes. The recombinant expression vector also carries a DHFR gene, which allows for selection of CHO cells that have been transfected with the vector using methotrexate selection/amplification. The selected transformant host cells are cultured to allow for expression of the antibody heavy and light chains and intact antibody is recovered from the culture medium. Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recover the antibody from the culture medium. Still further the invention provides a method of synthesizing a recombinant antibody of the invention by culturing a host cell of the invention in a suitable culture medium until a recombinant antibody of the invention is synthesized. The method can further comprise isolating the recombinant antibody from the culture medium.

1. Humanized Anti PRLR Antibodies

Table 5 is a list of amino acid sequences of VH and VL regions of preferred humanized anti-hPRLR antibodies of the invention.

TABLE 5: List of Amino Acid Sequences of VH and VL regions

SEQ ID No.	Protein region		Sequence
			123456789**0**123456789**0**1234567890
39	**VH.1z Ab1**		QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT TYWMH**WVRQAPGQGLEWMG**EIDPSDSYSNY NQKFKD**RVTITADKSTSTAYMELSSLRSED TAVYYCAR**NGGLGPAWFSY**WGQGTLVTVSS
40	VH.1z Ab1 CDR-H1	Residues 26-35 of SEQ ID No.: 39	**GYTFTTYWMH**
41	VH.1z Ab1 CDR-H2	Residues 50-66 of SEQ ID No.: 39	**EIDPSDSYSNYNQKFKD**
42	VH.1z Ab1 CDR-H3	Residues 99-109 of SEQ ID No.: 39	**NGGLGPAWFSY**
			123456789**0**123456789**0**1234567890
43	**VH.1 Ab1**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT TYWMH**WVRQAPGQGLEWMG**EIDPSDSYSNY NQKFKD**RVTITADKSTSTAYMELSSLRSED TAVYYCAR**NGGLGPAWFSY**WGQGTLVTVSS
40	VH.1 Ab1 CDR-H1	Residues 26-35 of SEQ ID No.: 43	**GYTFTTYWMH**
41	VH.1 Ab1 CDR-H2	Residues 50-66 of SEQ ID No.: 43	**EIDPSDSYSNYNQKFKD**
42	VH.1 Ab1 CDR-H3	Residues 99-109 of SEQ ID No.: 43	**NGGLGPAWFSY**

			123456789**0**123456789**0**1234567890
44	**VH.1a Ab1**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT TYWMH**WVRQAPGQGLEWIG**EIDPSDSYSNY NQKFKD**RATLTVDKSTSTAYMELSSLRSED TAVYYCAR**NGGLGPAWFSY**WGQGTLVTVSS
40	VH.1a Ab1 CDR-H1	Residues 26-35 of SEQ ID No.: 44	**GYTFTTYWMH**
41	VH.1a Ab1 CDR-H2	Residues 50-66 of SEQ ID No.: 44	**EIDPSDSYSNYNQKFKD**
42	VH.1a Ab1 CDR-H3	Residues 99-109 of SEQ ID No.: 44	**NGGLGPAWFSY**
			123456789**0**123456789**0**1234567890
45	**VH.1b Ab1**		EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFT TYWMH**WVRQAPGQGLEWIG**EIDPSDSYSNY AQKF**QGRVTITVDKSTSTAYMELSSLRSED TAVYYCAR**NGGLGPAWFSY**WGQGTLVTVSS
46	VH.1b Ab1 CDR-H1	Residues 26-35 of SEQ ID No.: 45	**GGTFTTYWMH**
47	VH.1b Ab1 CDR-H2	Residues 50-64 of SEQ ID No.: 45	**EIDPSDSYSNYAQKF**
42	VH.1b Ab1 CDR-H3	Residues 99-109 of SEQ ID No.: 45	**NGGLGPAWFSY**
			123456789**0**123456789**0**1234567890
48	**VL.1 Ab1**		DIQMTQSPSSVSASVGDRVTITC**KASQYVG TAVA**WYQQKPGKAPKLLIY**SASNRYT**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QQ YSSYPWT**FGGGTKVEIK
49	VL.1 Ab1 CDR-L1	Residues 24-34 of SEQ ID No.: 48	**KASQYVGTAVA**
50	VL.1 Ab1 CDR-L2	Residues 50-56 of SEQ ID No.: 48	**SASNRYT**
51	VL.1 Ab1 CDR-L3	Residues 89-97 of SEQ ID No.: 48	**QQYSSYPWT**
			123456789**0**123456789**0**1234567890
52	**VL.1a Ab1**		DIQMTQSPSSVSASVGDRVTITC**KASQYVG TAVA**WYQQKPGK<u>S</u>PKLLIY**SASNRYT**GVPS RFSDSGSGTDFTLTISSLQPEDFATY<u>F</u>C**QQ YSSYPWT**FGGGTKVEIK
49	VL.1a Ab1 CDR-L1	Residues 24-34 of SEQ ID No.: 52	**KASQYVGTAVA**
50	VL.1a Ab1 CDR-L2	Residues 50-56 of SEQ ID No.: 52	**SASNRYT**
51	VL.1a Ab1 CDR-L3	Residues 89-97 of SEQ ID No.: 52	**QQYSSYPWT**
			123456789**0**123456789**0**1234567890
53	**VL.2 Ab1**		EIVMTQSPATLSVSPGERATLSC**KASQYVG TAVA**WYQQKPGQAPRLLIY**SASNRYT**GIPA RFSGSGSGTEFTLTISSLQSEDFAVYYC**QQ YSSYPWT**FGGGTKVEIK
49	VL.2 Ab1 CDR-L1	Residues 24-34 of SEQ ID No.: 53	**KASQYVGTAVA**
50	VL.2 Ab1 CDR-L2	Residues 50-56 of SEQ ID No.: 53	**SASNRYT**
51	VL.2 Ab1 CDR-L3	Residues 89-97 of SEQ ID No.: 53	**QQYSSYPWT**
			123456789**0**123456789**0**1234567890
54	**VL.2a Ab1**		EIVMTQSPATLSVSPGERATLSC**KASQYVG TAVA**WYQQKPGQ<u>S</u>PRLLIY**SASNRYT**GVPA RFSDSGSGTEFTLTISSLQSEDFAVY<u>F</u>C**QQ YSSYPWT**FGGGTKVEIK
49	VL.2a Ab1 CDR-L1	Residues 24-34 of SEQ ID No.: 54	**KASQYVGTAVA**

50	VL.2a Ab1 CDR-L2	Residues 50-56 of SEQ ID No.: 54	**SASNRYT**
51	VL.2a Ab1 CDR-L3	Residues 89-97 of SEQ ID No.: 54	**QQYSSYPWT**
			123456789**0**123456789**0**1234567890

SEQ ID No.	**Protein region**		**Sequence**
			123456789**0**123456789**0**1234567890
55	**VH.1z Ab2**		QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT SFWMH**WVRQAPGQGLEWMG**VIDPSDTYTNY NQKFKG**RVTITADESTSTAYMELSSLRSED TAVYYCAR**GDYSNWFTY**WGQGTLVTVSS
56	VH.1z Ab2 CDR-H1	Residues 26-35 of SEQ ID No.: 55	**GYTFTSFWMH**
57	VH.1z Ab2 CDR-H2	Residues 50-66 of SEQ ID No.: 55	**VIDPSDTYTNYNQKFKG**
58	VH.1z Ab2 CDR-H3	Residues 99-107 of SEQ ID No.: 55	**GDYSNWFTY**
			123456789**0**123456789**0**1234567890
59	**VH.1 Ab2**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT SFWMH**WVRQAPGQGLEWMG**VIDPSDTYTNY NQKFKG**RVTITADESTSTAYMELSSLRSED TAVYYCAR**GDYSNWFTY**WGQGTLVTVSS
56	VH.1 Ab2 CDR-H1	Residues 26-35 of SEQ ID No.: 59	**GYTFTSFWMH**
57	VH.1 Ab2 CDR-H2	Residues 50-66 of SEQ ID No.: 59	**VIDPSDTYTNYNQKFKG**
58	VH.1 Ab2 CDR-H3	Residues 99-107 of SEQ ID No.: 59	**GDYSNWFTY**
			123456789**0**123456789**0**1234567890
60	**VH.1a Ab2**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT SFWMH**WVRQAPGQGLEWIG**VIDPSDTYTNY NQKFKG**RATLTVDESSSTAYMELSSLRSED TAVYYCAR**GDYSNWFTY**WGQGTLVTVSS
56	VH.1a Ab2 CDR-H1	Residues 26-35 of SEQ ID No.: 60	**GYTFTSFWMH**
57	VH.1a Ab2 CDR-H2	Residues 50-66 of SEQ ID No.: 60	**VIDPSDTYTNYNQKFKG**
58	VH.1a Ab2 CDR-H3	Residues 99-107 of SEQ ID No.: 60	**GDYSNWFTY**
			123456789**0**123456789**0**1234567890
61	**VH.1b Ab2**		EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFT SFWMH**WVRQAPGQGLEWIG**VIDPSDTYTNY AQKFQG**RVTITVDESTSTAYMELSSLRSED TAVYYCAR**GDYSNWFTY**WGQGTLVTVSS
62	VH.1b Ab2 CDR-H1	Residues 26-35 of SEQ ID No.: 61	**GGTFTSFWMH**
63	VH.1b Ab2 CDR-H2	Residues 50-66 of SEQ ID No.: 61	**VIDPSDTYTNYAQKFQG**
58	VH.1b Ab2 CDR-H3	Residues 99-107 of SEQ ID No.: 61	**GDYSNWFTY**
			123456789**0**123456789**0**1234567890
64	**VL.1 Ab2**		DIVMTQTPLSLSVTPGQPASISC**RSSQRLV HSNGNTYLH**WYLQKPGQSPQLLIY**KVSNRF S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**SQSTHVPWT**FGGGTKVEIK
65	VL.1 Ab2 CDR-L1	Residues 24-39 of SEQ ID No.: 64	**RSSQRLVHSNGNTYLH**
66	VL.1 Ab2 CDR-L2	Residues 55-61 of SEQ ID No.: 64	**KVSNRFS**

67	VL.1 Ab2 CDR-L3	Residues 94-102 of SEQ ID No.: 64	**SQSTHVPWT**
			12345678901234567890123456789**0**
68	**VL.1a Ab2**		DVVMTQTPLSLSVTPGQPASISC**RSSQRLV HSNGNTYLH**WYLQKPGQSPQLLIY**KVSNRF S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YFC**SQSTHVPWT**FGGGTKVEIK
65	VL.1a Ab2 CDR-L1	Residues 24-39 of SEQ ID No.: 64	**RSSQRLVHSNGNTYLH**
66	VL.1a Ab2 CDR-L2	Residues 55-61 of SEQ ID No.: 64	**KVSNRFS**
67	VL.1a Ab2 CDR-L3	Residues 94-102 of SEQ ID No.: 64	**SQSTHVPWT**
			12345678901234567890123456789**0**
69	**VL.1b Ab2**		DVVMTQTPLSLSVTPGQPASISC**RSSQRLV HSNGNTYLH**WYLQKPGQSPQLLIY**KVSNRF S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**SQSTHVPWT**FGGGTKVEIK
65	VL.1b Ab2 CDR-L1	Residues 24-39 of SEQ ID No.: 69	**RSSQRLVHSNGNTYLH**
66	VL.1b Ab2 CDR-L2	Residues 55-61 of SEQ ID No.: 69	**KVSNRFS**
67	VL.1b Ab2 CDR-L3	Residues 94-102 of SEQ ID No.: 69	**SQSTHVPWT**
			12345678901234567890123456789**0**

SEQ ID No.	**Protein region**		**Sequence**
			12345678901234567890123456789**0**
70	**VH.1z Ab3**		QVQLVQSGAEVKKPGASVKVSCKAS**GYTFT DYNIH**WVRQAPGQGLEWMG**YIYPNNDGTGY NQKFKS**RVTMTTDTSTSTAYMELRSLRSDD TAVYYCAR**GDGNYVGDMDY**WGQGTTVTVSS
71	VH.1z Ab3 CDR-H1	Residues 26-35 of SEQ ID No.: 70	**GYTFTDYNIH**
72	VH.1z Ab3 CDR-H2	Residues 50-66 of SEQ ID No.: 70	**YIYPNNDGTGYNQKFKS**
73	VH.1z Ab3 CDR-H3	Residues 99-109 of SEQ ID No.: 70	**GDGNYVGDMDY**
			12345678901234567890123456789**0**
74	**VH.1 Ab3**		EVQLVQSGAEVKKPGASVKVSCKAS**GYTFT DYNIH**WVRQAPGQGLEWMG**YIYPNNDGTGY NQKFKS**RVTMTTDTSTSTAYMELRSLRSDD TAVYYCAR**GDGNYVGDMDY**WGQGTTVTVSS
71	VH.1 Ab3 CDR-H1	Residues 26-35 of SEQ ID No.: 74	**GYTFTDYNIH**
72	VH.1 Ab3 CDR-H2	Residues 50-66 of SEQ ID No.: 74	**YIYPNNDGTGYNQKFKS**
73	VH.1 Ab3 CDR-H3	Residues 99-109 of SEQ ID No.: 74	**GDGNYVGDMDY**
			12345678901234567890123456789**0**
75	**VH.1a Ab3**		EVQLVQSGAEVKKPGASVKVSCKAS**GYTFT DYNIH**WVRQAPGQGLEWIG**YIYPNNDGTGY NQKFKS**RATLTVDNSTSTAYMELRSLRSDD TAVYYCAR**GDGNYVGDMDY**WGQGTTVTVSS
71	VH.1a Ab3 CDR-H1	Residues 26-35 of SEQ ID No.: 75	**GYTFTDYNIH**
72	VH.1a Ab3 CDR-H2	Residues 50-66 of SEQ ID No.: 75	**YIYPNNDGTGYNQKFKS**
73	VH.1a Ab3 CDR-H3	Residues 99-109 of SEQ ID No.: 75	**GDGNYVGDMDY**
			12345678901234567890123456789**0**

76	**VH.1b Ab3**		EVQLVQSGAEVKKPGASVKVSCKAS**GYTFT DYNIH**WVRQAPGQGLEWIG**YIYPNNDGTGY AQKLQG**RVTMTVDTSTSTAYMELRSLRSDD TAVYYCAR**GDGNYVGDMDY**WGQGTIVTVSS
71	VH.1b Ab3 CDR-H1	Residues 26-35 of SEQ ID No.: 76	**GYTFTDYNIH**
77	VH.1b Ab3 CDR-H2	Residues 50-66 of SEQ ID No.: 76	**YIYPNNDGTGYAQKLQG**
73	VH.1b Ab3 CDR-H3	Residues 99-109 of SEQ ID No.: 76	**GDGNYVGDMDY**
			123456789**0**123456789**0**1234567890
78	**VL.1 Ab3**		DIQMTQSPSSLSASVGDRVTITC**RASENIY SYLA**WYQQKPGKAPKLLIY**NAKTLAE**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QH HYATPFT**FGQGIKLEIK
79	VL.1 Ab3 CDR-L1	Residues 24-34 of SEQ ID No.: 78	**RASENIYSYLA**
80	VL.1 Ab3 CDR-L2	Residues 50-56 of SEQ ID No.: 78	**NAKTLAE**
81	VL.1 Ab3 CDR-L3	Residues 99-107 of SEQ ID No.: 78	**QHHYATPFT**
			123456789**0**123456789**0**1234567890
82	**VL.1a Ab3**		DIQMTQSPSSLSASVGDRVTITC**RASENIY SYLA**WYQQKPGKPPKLLVY**NAKTLAE**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QH HYATPFT**FGQGIKLEIK
79	VL.1a Ab3 CDR-L1	Residues 24-34 of SEQ ID No.: 82	**RASENIYSYLA**
80	VL.1a Ab3 CDR-L2	Residues 50-56 of SEQ ID No.: 82	**NAKTLAE**
81	VL.1a Ab3 CDR-L3	Residues 99-107 of SEQ ID No.: 82	**QHHYATPFT**
			123456789**0**123456789**0**1234567890
83	**VL.1b Ab3**		DIQMTQSPSSLSASVGDRVTITC**RASENIY SYLA**WYQQKPGKAPKLLVY**NAKTLAE**GVPS RFSGSGSGTDFTLTISSLQPEDFATYYC**QH HYATPFT**FGQGIKLEIK
79	VL.1b Ab3 CDR-L1	Residues 24-34 of SEQ ID No.: 83	**RASENIYSYLA**
80	VL.1b Ab3 CDR-L2	Residues 50-56 of SEQ ID No.: 83	**NAKTLAE**
81	VL.1b Ab3 CDR-L3	Residues 99-107 of SEQ ID No.: 83	**QHHYATPFT**
			123456789**0**123456789**0**1234567890

SEQ ID No.	**Protein region**		**Sequence**
			123456789**0**123456789**0**1234567890
84	**VH.1z Ab4**		QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT SYWIH**WVRQAPGQGLEWMG**EIDPSDSYTNY NQKFKG**RVTIIADKSTSTAYMELSSLRSED TAVYYCAR**SFFTNWFAY**WGQGTLVTVSS
85	VH.1z Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 84	**GYTFTSYWIH**
86	VH.1z Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 84	**EIDPSDSYTNYNQKFKG**
87	VH.1z Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 84	**SFFTNWFAY**
			123456789**0**123456789**0**1234567890

88	**VH.1 Ab4**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT** **SYWIH**WVRQAPGQGLEWMG**EIDPSDSYTNY** **NQKFKG**RVTITADKSTSTAYMELSSLRSED TAVYYCAR**SFFTNWFAY**WGQGTLVTVSS
85	VH.1 Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 88	**GYTFTSYWIH**
86	VH.1 Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 88	**EIDPSDSYTNYNQKFKG**
87	VH.1 Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 88	**SFFTNWFAY**
			12345678901234567890123456789**0**
89	**VH.1a Ab4**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT** **SYWIH**WVRQAPGQGLEWIG**EIDPSDSYTNY** **NQKFKG**RATLTVDKSSSTAYMELSSLRSED TAVYYCAR**SFFTNWFAY**WGQGTLVTVSS
85	VH.1a Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 89	**GYTFTSYWIH**
86	VH.1a Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 89	**EIDPSDSYTNYNQKFKG**
87	VH.1a Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 89	**SFFTNWFAY**
			12345678901234567890123456789**0**
121	**VH.1a.2 Ab4**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT** **SYWIH**WVRQAPGQGLEWIG**EIDPSDSYTNY** **NQKFKG**RATLTVDRSSSTAYMELSSLRSED TAVYYCGR**SFFTNWFAY**WGQGTLVTVSS
85	VH.1a.2 Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 121	**GYTFTSYWIH**
86	VH.1a.2 Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 121	**EIDPSDSYTNYNQKFKG**
87	VH.1a.2 Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 121	**SFFTNWFAY**
			12345678901234567890123456789**0**
122	**VH.1a.3 Ab4**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT** **SYWIH**WVRQAPGQGLEWIG**EIDPSDSYTNY** **NQKFKG**RATLTVDKSSSTAYMELSSLRSED TAVYYCGR**SFFTNWFAY**WGQGTLVTVSS
85	VH.1a.3 Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 122	**GYTFTSYWIH**
86	VH.1a.3 Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 122	**EIDPSDSYTNYNQKFKG**
87	VH.1a.3 Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 122	**SFFTNWFAY**
			12345678901234567890123456789**0**
123	**VH.1b Ab4**		EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFT** **SYWIH**WVRQAPGQGLEWIG**EIDPSDSYTNY** **AQKFQG**RVTITVDKSTSTAYMELSSLRSED TAVYYCAR**SFFTNWFAY**WGQGTLVTVSS
149	VH.1b Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 123	**GGTFTSYWIH**
150	VH.1b Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 123	**EIDPSDSYTNYAQKFQG**
87	VH.1b Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 123	**SFFTNWFAY**
			12345678901234567890123456789**0**
90	**VH.1b.2 Ab4**		EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFT** **SYWIH**WVRQAPGQGLEWIG**EIDPSDSYTNY** **NQKFKG**RVTITVDKSTSTAYMELSSLRSED TAVYYCAR**SFFTNWFAY**WGQGTLVTVSS
85	VH.1b.2 Ab4 CDR-H1	Residues 26-35 of SEQ ID No.: 90	**GYTFTSYWIH**

86	VH.1b.2 Ab4 CDR-H2	Residues 50-66 of SEQ ID No.: 90	**EIDPSDSYTNYNQKFKG**
87	VH.1b.2 Ab4 CDR-H3	Residues 99-107 of SEQ ID No.: 90	**SFFTNWFAY**
			123456789**0**123456789**0**1234567890
91	**VL.1 Ab4**		DIVMTQTPLSLSVTPGQPASISC**RSSQSLV HSNGNTYLH**WYLQKPGQSPQLLIY**KVSNRF S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**SQSTHVPFT**FGGGTKVEIK
92	VL.1 Ab4 CDR-H1	Residues 24-39 of SEQ ID No.: 91	**RSSQSLVHSNGNTYLH**
93	VL.1 Ab4 CDR-H2	Residues 55-61 of SEQ ID No.: 91	**KVSNRFS**
94	VL.1 Ab4 CDR-H3	Residues 94-102 of SEQ ID No.: 91	**SQSTHVPFT**
			123456789**0**123456789**0**1234567890
95	**VL.1a Ab4**		DVVMTQTPLSLSVTPGQPASISC**RSSQSLV HSNGNTYLH**WYLQKPGQSPQLLIY**KVSNRF S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YFC**SQSTHVPFT**FGGGTKVEIK
92	VL.1a Ab4 CDR-H1	Residues 24-39 of SEQ ID No.: 95	**RSSQSLVHSNGNTYLH**
93	VL.1a Ab4 CDR-H2	Residues 55-61 of SEQ ID No.: 95	**KVSNRFS**
94	VL.1a Ab4 CDR-H3	Residues 94-102 of SEQ ID No.: 95	**SQSTHVPFT**
			123456789**0**123456789**0**1234567890
96	**VL.1b Ab4**		DVVMTQTPLSLSVTPGQPASISC**RSSQSLV HSNGNTYLH**WYLQKPGQSPQLLIY**KVSNRF S**GVPDRFSGSGSGTDFTLKISRVEAEDVGV YYC**SQSTHVPFT**FGGGTKVEIK
92	VL.1b Ab4 CDR-H1	Residues 24-39 of SEQ ID No.: 96	**RSSQSLVHSNGNTYLH**
93	VL.1b Ab4 CDR-H2	Residues 55-61 of SEQ ID No.: 96	**KVSNRFS**
94	VL.1b Ab4 CDR-H3	Residues 94-102 of SEQ ID No.: 96	**SQSTHVPFT**
			123456789**0**123456789**0**1234567890

As used herein, the term "Ab1" refers to an antibody comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and (ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54.

As used herein, the term "Ab2" refers to an antibody comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and (ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69.

As used herein, the term "Ab3" refers to an antibody comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75 and SEQ ID NO: 76; and (ii) one variable light chain having an

amino acid sequence selected from the group consisting of SEQ ID NO:78, SEQ ID NO:82 and SEQ ID NO: 83.

As used herein, the term "Ab4" refers to an antibody comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO:121, SEQ ID NO:122 and SEQ ID NO:123; and (ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96.

In particular embodiments, the present invention provides humanized antibodies Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 and Ab55 having heavy chain and light chain sequences as set forth in Table 6 below:

TABLE 6: Humanized PRLR Antibodies and Sequences Thereof

Ab	Heavy Chain Sequence	HC SEQ ID NO:	Light Chain Sequence	LC SEQ ID NO:	Variable Sequences
	123456789**0**123456789**0**1234567890		123456789**0**123456789**0**1234567890		
Ab14	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWMGEIDPSDSYSNY NQKFKDRVTITADKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	124	DIQMTQSPSSVSASVGDRVTITCKASQYVG TAVAWYQQKPGKAPKLLIYSASNRYTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	125	Ab1 HC.1 & Ab1 LC.1
	123456789**0**123456789**0**1234567890		123456789**0**123456789**0**1234567890		
Ab15	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWMGEIDPSDSYSNY NQKFKDRVTITADKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	124	DIQMTQSPSSVSASVGDRVTITCKASQYVG TAVAWYQQKPGKSPKLLIYSASNRYTGVPS RFSDSGSGTDFTLTISSLQPEDFATYFCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	126	Ab1 HC.1 and Ab1 LC.1a
	123456789**0**123456789**0**1234567890		123456789**0**123456789**0**1234567890		

Ab16	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWMGEIDPSDSYSNY NQKFKDRVTITADKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	124	EIVMTQSPATLSVSPGERATLSCKASQYVG TAVAWYQQKPGQAPRLLIYSASNRYTGIPA RFSGSGSGTEFTLTISSLQSEDFAVYYCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	127	Ab1 HC.1 and Ab1 LC.2
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab17	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWMGEIDPSDSYSNY NQKFKDRVTITADKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	124	EIVMTQSPATLSVSPGERATLSCKASQYVG TAVAWYQQKPGQSPRLLIYSASNRYTGVPA RFSDSGSGTEFTLTISSLQSEDFAVYFCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	128	Ab1 HC.1 and Ab1 LC.2a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab18	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY NQKFKDRATLTVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	129	DIQMTQSPSSVSASVGDRVTITCKASQYVG TAVAWYQQKPGKAPKLLIYSASNRYTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	125	Ab1 HC.1a and Ab1 LC.1
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab19	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY NQKFKDRATLTVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	129	DIQMTQSPSSVSASVGDRVTITCKASQYVG TAVAWYQQKPGKSPKLLIYSASNRYTGVPS RFSDSGSGTDFTLTISSLQPEDFATYFCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	126	Ab1 HC.1a and Ab1 LC.1a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		

Ab20	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY NQKFKDRATLTVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	129	EIVMTQSPATLSVSPGERATLSCKASQYVG TAVAWYQQKPGQAPRLLIYSASNRYTGIPA RFSGSGSGTEFTLTISSLQSEDFAVYYCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	127	Ab1 HC.1a and Ab1 LC.2
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab21	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY NQKFKDRATLTVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	129	EIVMTQSPATLSVSPGERATLSCKASQYVG TAVAWYQQKPGQSPRLLIYSASNRYTGVPA RFSDSGSGTEFTLTISSLQSEDFAVYFCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	128	Ab1 HC.1a and Ab1 LC.2a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab22	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	130	DIQMTQSPSSVSASVGDRVTITCKASQYVG TAVAWYQQKPGKAPKLLIYSASNRYTGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	125	Ab1 HC.1b and Ab1 LC.1
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab23	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	130	DIQMTQSPSSVSASVGDRVTITCKASQYVG TAVAWYQQKPGKSPKLLIYSASNRYTGVPS RFSDSGSGTDFTLTISSLQPEDFATYFCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	126	Ab1 HC.1b and Ab1 LC.1a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		

Ab24	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	130	EIVMTQSPATLSVSPGERATLSCKASQYVG TAVAWYQQKPGQAPRLLIYSASNRYTGIPA RFSGSGSGTEFTLTISSLQSEDFAVYYCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	127	Ab1 HC.1b and Ab1 LC.2
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab25	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT TYWMHWVRQAPGQGLEWIGEIDPSDSYSNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARNGGLGPAWFSYWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	130	EIVMTQSPATLSVSPGERATLSCKASQYVG TAVAWYQQKPGQSPRLLIYSASNRYTGVPA RFSDSGSGTEFTLTISSLQSEDFAVYFCQQ YSSYPWTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	128	Ab1 HC.1b and Ab1 LC.2a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab26	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SFWMHWVRQAPGQGLEWMGVIDPSDTYTNY NQKFKGRVTITADESTSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	131	DIVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	132	Ab2 HC.1 and Ab2 LC.1
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab27	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SFWMHWVRQAPGQGLEWMGVIDPSDTYTNY NQKFKGRVTITADESTSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	131	DVVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	133	Ab2 HC.1 and Ab2 LC.1a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		

Ab28	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SFWMHWVRQAPGQGLEWMGVIDPSDTYTNY NQKFKGRVTITADESTSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	131	DVVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	134	Ab2 HC.1 and Ab2 LC.1b
	123456789**0**123456789**0**1234567890		123456789**0**123456789**0**1234567890		
Ab29	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SFWMHWVRQAPGQGLEWIGVIDPSDTYTNY NQKFKGRATLTVDESSSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	135	DIVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	132	Ab2 HC.1a and Ab2 LC.1
	123456789**0**123456789**0**1234567890		123456789**0**123456789**0**1234567890		
Ab30	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SFWMHWVRQAPGQGLEWIGVIDPSDTYTNY NQKFKGRATLTVDESSSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	135	DVVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	133	Ab2 HC.1a and Ab2 LC.1a
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Ab31	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SFWMHWVRQAPGQGLEWIGVIDPSDTYTNY NQKFKGRATLTVDESSSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	135	DVVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	134	Ab2 HC.1a and Ab2 LC.1b
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Ab32	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT SFWMHWVRQAPGQGLEWIGVIDPSDTYTNY AQKFQGRVTITVDESTSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	136	DIVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	132	Ab2 HC.1b and Ab2 LC.1
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Ab33	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT SFWMHWVRQAPGQGLEWIGVIDPSDTYTNY AQKFQGRVTITVDESTSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	136	DVVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	133	Ab2 HC.1b and Ab2 LC.1a
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Ab34	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT SFWMHWVRQAPGQGLEWIGVIDPSDTYTNY AQKFQGRVTITVDESTSTAYMELSSLRSED TAVYYCARGDYSNWFTYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	136	DVVMTQTPLSLSVTPGQPASISCRSSQRLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPWTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	134	Ab2 HC.1b and Ab2 LC.1b
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Ab35	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWMGEIDPSDSYTNY NQKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	137	DIVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	138	Ab4 HC.1 and Ab4 LC.1
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Ab36	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWMGEIDPSDSYTNY NQKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	137	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	139	Ab4 HC.1 and Ab4 LC.1a
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Ab37	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWMGEIDPSDSYTNY NQKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	137	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	140	Ab4 HC.1 and Ab4 LC.1b
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Ab38	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY NQKFKGRATLTVDKSSSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	141	DIVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	138	Ab4 HC.1a and Ab4 LC.1
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Ab39	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY NQKFKGRATLTVDKSSSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	141	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	139	Ab4 HC.1a and Ab4 LC.1a
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Ab40	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY NQKFKGRATLTVDKSSSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	141	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	140	Ab4 HC.1a and Ab4 LC.1b
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Ab41	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	142	DIVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	138	Ab4 HC.1b and Ab4 LC.1
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Ab42	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	142	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	139	Ab4 HC.1b and Ab4 LC.1a
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Ab43	EVQLVQSGAEVKKPGSSVKVSCKASGGTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY AQKFQGRVTITVDKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	142	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	140	Ab4 HC.1b and Ab4 LC.1b
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Ab44	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWMGYIYPNNDGTGY NQKFKSRVTMTTDTSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	143	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKAPKLLIYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	144	Ab3 HC.1 and Ab3 LC.1
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab45	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWMGYIYPNNDGTGY NQKFKSRVTMTTDTSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	143	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKPPKLLVYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	145	Ab3 HC.1 and Ab3 LC.1a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab46	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWMGYIYPNNDGTGY NQKFKSRVTMTTDTSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	143	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKAPKLLVYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	146	Ab3 HC.1 and Ab3 LC.1b
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab47	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWIGYIYPNNDGTGY NQKFKSRATLTVDNSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	147	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKAPKLLIYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	144	Ab3 HC.1a and Ab3 LC.1
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		

Ab48	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWIGYIYPNNDGTGY NQKFKSRATLTVDNSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	147	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKPPKLLVYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	145	Ab3 HC.1a and Ab3 LC.1a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab49	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWIGYIYPNNDGTGY NQKFKSRATLTVDNSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	147	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKAPKLLVYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	146	Ab3 HC.1a and Ab3 LC.1b
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab50	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWIGYIYPNNDGTGY AQKLQGRVTMTVDTSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	148	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKAPKLLIYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	144	Ab3 HC.1b and Ab3 LC.1
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		
Ab51	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWIGYIYPNNDGTGY AQKLQGRVTMTVDTSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	148	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKPPKLLVYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	145	Ab3 HC.1b and Ab3 LC.1a
	12345678901234567890123456789**0**		12345678901234567890123456789**0**		

Ab52	EVQLVQSGAEVKKPGASVKVSCKASGYTFT DYNIHWVRQAPGQGLEWIGYIYPNNDGTGY AQKLQGRVTMTVDTSTSTAYMELRSLRSDD TAVYYCARGDGNYVGDMDYWGQGTTVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	148	DIQMTQSPSSLSASVGDRVTITCRASENIY SYLAWYQQKPGKAPKLLVYNAKTLAEGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQH HYATPFTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC	146	Ab3 HC.1b and Ab3 LC.1b
Ab53	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY NQKFKGRVTITVDKSTSTAYMELSSLRSED TAVYYCARSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	153	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	139	Ab4 HC.1b.2 and Ab4 LC.1a
Ab54	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY NQKFKGRATLTVDKSSSTAYMELSSLRSED TAVYYCGRSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	154	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	139	Ab4 HC.1a.3 and Ab4 LC.1a
Ab55	EVQLVQSGAEVKKPGSSVKVSCKASGYTFT SYWIHWVRQAPGQGLEWIGEIDPSDSYTNY NQKFKGRATLTVDRSSSTAYMELSSLRSED TAVYYCGRSFFTNWFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	155	DVVMTQTPLSLSVTPGQPASISCRSSQSLV HSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGV YFCSQSTHVPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC	139	Ab4 HC.1a.2 and Ab4 LC.1a

In one embodiment, the present invention is directed to antibody Ab14 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 125.

In one embodiment, the present invention is directed to antibody Ab15 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 126.

In one embodiment, the present invention is directed to antibody Ab16 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 127.

In one embodiment, the present invention is directed to antibody Ab17 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 128.

In one embodiment, the present invention is directed to antibody Ab18 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 125.

In one embodiment, the present invention is directed to antibody Ab19 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 126.

In one embodiment, the present invention is directed to antibody Ab20 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 127.

In one embodiment, the present invention is directed to antibody Ab21 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 128.

In one embodiment, the present invention is directed to antibody Ab22 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 125.

In one embodiment, the present invention is directed to antibody Ab23 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 126.

In one embodiment, the present invention is directed to antibody Ab24 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 127.

In one embodiment, the present invention is directed to antibody Ab25 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 128.

In one embodiment, the present invention is directed to antibody Ab26 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 132.

In one embodiment, the present invention is directed to antibody Ab27 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 133.

In one embodiment, the present invention is directed to antibody Ab28 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 134.

In one embodiment, the present invention is directed to antibody Ab29 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 132.

In one embodiment, the present invention is directed to antibody Ab30 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 133.

In one embodiment, the present invention is directed to antibody Ab31 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 134.

In one embodiment, the present invention is directed to antibody Ab32 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 132.

In one embodiment, the present invention is directed to antibody Ab33 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 133.

In one embodiment, the present invention is directed to antibody Ab34 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 134.

In one embodiment, the present invention is directed to antibody Ab35 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 138.

In one embodiment, the present invention is directed to antibody Ab36 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the present invention is directed to antibody Ab37 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 140.

In one embodiment, the present invention is directed to antibody Ab38 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 138.

In one embodiment, the present invention is directed to antibody Ab39 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the present invention is directed to antibody Ab40 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 140.

In one embodiment, the present invention is directed to antibody Ab41 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 138.

In one embodiment, the present invention is directed to antibody Ab42 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the present invention is directed to antibody Ab43 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 140.

In one embodiment, the present invention is directed to antibody Ab44 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 144.

In one embodiment, the present invention is directed to antibody Ab45 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 145.

In one embodiment, the present invention is directed to antibody Ab46 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 146.

In one embodiment, the present invention is directed to antibody Ab47 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 144.

In one embodiment, the present invention is directed to antibody Ab48 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 145.

In one embodiment, the present invention is directed to antibody Ab49 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 146.

In one embodiment, the present invention is directed to antibody Ab50 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 144.

In one embodiment, the present invention is directed to antibody Ab51 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 145.

In one embodiment, the present invention is directed to antibody Ab52 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 146.

In one embodiment, the present invention is directed to antibody Ab53 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 153; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the present invention is directed to antibody Ab54 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 154; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In one embodiment, the present invention is directed to antibody Ab55 comprising a heavy chain having the amino acid sequence of SEQ ID NO: 155; and a light chain having the amino acid sequence of SEQ ID NO: 139.

The foregoing isolated anti-PRLR antibody CDR sequences establish a novel family of PRLR binding proteins, isolated in accordance with this invention, and comprising polypeptides that include the CDR sequences listed in Table 7a or 7b below. To generate and to select CDRs of the invention having preferred PRLR binding and/or neutralizing activity with respect to hPRLR, standard methods known in the art for generating binding proteins of the present invention and assessing the PRLR binding and/or neutralizing characteristics of those binding protein may be used, including but not limited to those specifically described herein.

TABLE 7a: Consensus PRLR CDR affinity ligands based on murine antibodies (alternative residues are listed below each amino acid position; - indicates residue may be absent).

CDR region	Sequence Identifier	Consensus Sequence
CDR-H1	SEQ ID NO.:97	26 27 28 29 30 31 32 33 34 35 35a X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} G Y T F T S Y W M H - F S I S D F N I F N T D Y A W
CDR-H2	SEQ ID NO.:98	50 51 52 52a 53 54 55 56 57 58 59 60 61 62 63 64 65 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} X_{17} Y I D P S D G Y T N Y N Q K F K G V F Y N Y N S G S G F P D E L S E S - N G D H A Y P T V D G G S T S S N R

CDR region	Sequence Identifier	Consensus Sequence
CDR-H3	SEQ ID NO.:99	95 96 97 98 99 100 100a 100b 100c 100d 100e 101 102 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} G D G S Y W F – – – – D Y S F F N N V G D M A M T N G Y T G P A W F A S Q L W L I G Y A G S G M Y R Y – – A
CDR-L1	SEQ ID NO.:100	24 25 26 27 27a 27b 27c 27d 27e 28 29 30 31 32 33 34 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} R A S Q – – – – – N G N T Y L H K S E S L V H S Y I Y S A V A S S R I – V G M T S V G E V
CDR-L2	SEQ ID NO.:101	50 51 52 53 54 55 56 X_1 X_2 X_3 X_4 X_5 X_6 X_7 K A S N R F S N V K T L A E S T Y T L S
CDR-L3	SEQ ID NO.:102	89 90 91 92 93 94 95 95a 96 97 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} Q Q S S H V P – F T S H H T S T P W F G Y A Y L Y G W V
Note: Except for CDR-H1, the CDR and residue position are defined by Kabat et al (1991) Sequences of Proteins of Immunological Interest, Fifth Edition. NIH Publication No. 91-3242. For CDR-H1 residues 26 to 30 are included.		

TABLE 7b: Consensus PRLR CDR affinity ligands based on murine and humanized antibodies (alternative residues are listed below each amino acid position; - indicates residue may be absent).

CDR region	Sequence Identifier	Consensus Sequence
CDR-H1	SEQ ID NO.: 151	26 27 28 29 30 31 32 33 34 35 35a X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} G Y T F T S Y W M H – F S I S D F N I F N G T D Y A W
CDR-H2	SEQ ID NO.: 152	50 51 52 52a 53 54 55 56 57 58 59 60 61 62 63 64 65 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} X_{17} Y I D P S D G Y T N Y N Q K F K G V F Y N Y N S G S G F P D E L Q S E S – N G D H A Y A P T V D G G S T S R S T N S

CDR region	Sequence Identifier	Consensus Sequence
CDR-H3	SEQ ID NO.: 99	95 96 97 98 99 100 100a 100b 100c 100d 100e 101 102 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} G D G S Y W F – – – – D Y S F F N N V G D M A M T N G Y T G P A W F A S Q L W L I G Y A G S G M Y S R Y – – A
CDR-L1	SEQ ID NO.: 100	24 25 26 27 27a 27b 27c 27d 27e 28 29 30 31 32 33 34 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} R A S Q – – – – – N G N T Y L H K S E S L V H S Y I Y S A V A S S R I – V G M T S V E
CDR-L2	SEQ ID NO.: 101	50 51 52 53 54 55 56 X_1 X_2 X_3 X_4 X_5 X_6 X_7 K A S N R F S N V K T L A E S T Y T L S
CDR-L3	SEQ ID NO.: 102	89 90 91 92 93 94 95 95a 96 97 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} Q Q S S H V P – F T S H H T S T P W F G Y A Y L Y G W V
Note: Except for CDR-H1, the CDR and residue position are defined by Kabat et al (1991) Sequences of Proteins of Immunological Interest, Fifth Edition. NIH Publication No. 91-3242. For CDR-H1 residues 26 to 30 are included.		

2. Anti PRLR Chimeric Antibodies

A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See *e.g.*, Morrison, *Science* 229:1202 (1985); Oi *et al.*, *BioTechniques* 4:214 (1986); Gillies *et al.*, (1989) *J. Immunol. Methods* 125:191-202; U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entireties. In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, *Proc. Natl. Acad. Sci.* 81:851-855; Neuberger *et al.*, 1984, *Nature* 312:604-608; Takeda *et al.*, 1985, *Nature* 314:452-454, each of which are incorporated herein by reference in their entireties) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used.

In a specific embodiment, the chimeric antibody of the invention comprises a heavy chain variable region (V_H) comprising the amino acid sequence of SEQ ID NO: 112; SEQ ID NO: 113; SEQ ID NO: 114; SEQ ID NO: 115; SEQ ID NO: 116; SEQ ID NO: 117; SEQ ID NO: 118; SEQ ID NO:119 or SEQ ID NO:120 and a light chain variable region (V_L) comprising the amino acid sequence of SEQ ID NO: 103; SEQ ID NO: 104; SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107; SEQ ID NO: 108; SEQ ID NO: 109; SEQ ID NO: 110 or SEQ ID NO: 111 set forth in Table 8 below.

TABLE 8: Murine Anti-PRLR Antibody Variable Chain Sequences

Protein Region	Sequence Identifier	Variable Sequence
Ab5 Variable Light Chain	SEQ ID NO.:103	DVVMTQTPLSLPVSLGDQASISCRSSQRLVHSNGNTYLHWYLQKPGQS PKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQS THVPWTFGGGTKLEIK
Ab6 Variable Light Chain	SEQ ID NO.:104	DIVMTQSQKFMSTTVGDRVSITCKASQYVGTAVAWYQQKPGQSPKLLI YSASNRYTGVPDRFTDSGSGTDFTLTISNLQSEDLADYFCQQYSSYPW TFGGGTKLEIK
Ab7 Variable Light Chain	SEQ ID NO.:105	DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQS PKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKINRVEAEDLGVYFCSQS THVPFTFGSGTKLEIK
Ab8 Variable Light Chain	SEQ ID NO.:106	DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQGKPPQLLV YNAKTLAEGVPSRFSGGGSGTQFSLKINSLQPEDFGSYYCQHHYATPF TFGSGTKLEIK
Ab9 Variable Light Chain	SEQ ID NO.:107	DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQGKSPQLLV YNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPEDFGSYYCQHHSGTPF TFGSGTKLEIK
Ab10 Variable Light Chain	SEQ ID NO.:108	DIQMTQSPASLSASVGETVTITCRASENIYSYLTWYQQKQGKSPQLLV YNAKTLAEGVPSRFSGSGSGTQFSLKINSLQPEDFGSYHCQHHSVTPL TFGAGTKLELK
Ab11 Variable Light Chain	SEQ ID NO.:109	DVLMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQS PKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQG SHVPFTFGSGTKLEIK
Ab12 Variable Light Chain	SEQ ID NO.:110	QIVLTQSPGIMSASPGEKVTMTCSASSSVTYMYWYQQKPRSSPKPWIY LTSNLASGVPARFSGSGSGTSYSLTISSMEAEDGATYYCQQWSSTPPL TFGGGTKLELN
Ab13 Variable Light Chain	SEQ ID NO.:111	DVVMTQTPFSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQS PKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLELYFCSQS THVPWTFGGGTKLEIK
Ab5 Variable Heavy Chain	SEQ ID NO.:112	QVQLQQPGAELVRPGTSVKLSCKASGYTFTSFWMHWVKQRPGQGLEWI GVIDPSDTYTNYNQKFKGKATLTVDTSSSTAYMQLSSLTSEDSAVYYC ARGDYSNWFTYWGQGTLVTVSA

Protein Region	Sequence Identifier	Variable Sequence
Ab6 Variable Heavy Chain	SEQ ID NO.:113	QVQLQQPGAELVMPGSSVKLSCKASGYTFTTYWMHWVKQRPGQGLEWI GEIDPSDSYSNYNQKFKDKATLTVDKSSSTAYMQLSSLTSEDSAVYYC ARNGGLGPAWFSYWGQGTLVTVSA
Ab7 Variable Heavy Chain	SEQ ID NO.:114	QVQLQQPGAELVMPGTSVKLSCKASGYTFTSYWIHWVKQRPGQGLEWI GEIDPSDSYTNYNQKFKGKATLTVDRSSSTAYMQLSSLTSEDSAVYYC GRSFFTNWFAYWGQGTLVTVSA
Ab8 Variable Heavy Chain	SEQ ID NO.:115	EVQLQQSGPELVKPGASVKISCKASGYTFTDYNIHWVKQSHGKSLEWI GYIYPNNDGTGYNQKFKSKATLTVDNSSSTAYMEVRSLTSEDSAVYYC ARGDGNYVGDMDYWGQGTSVTVSS
Ab9 Variable Heavy Chain	SEQ ID NO.:116	EVQLQQSGPELVRPGASVKISCKASGYSFTDYNMHWVKQSHGKSLEWI GYIYPYNGGAGYNQKFKSKATMNVGISSSTAYMELRSLTSEDSAVYYC ARGDGNYVGDMDYWGQGTSVTVSS
Ab10 Variable Heavy Chain	SEQ ID NO.:117	EVQLHQSGPELVKPGASVKISCKASGYTFTDYNMHWMKQSHGKSLEWI GYFYPYNGGTGYNQEFKNKATLTVDISSSTAYMELRRLTSEDSAVYYC ARGGWGIYYAMDYWGQGTSVTVSS
Ab11 Variable Heavy Chain	SEQ ID NO.:118	EVKLVESGGGLVQPGGSLKLSCAASGFTFSDYYMFWVRQTPEKSLEWV AYISNGGGSTYYPDTVKGRFTISRDNAKNTLYLQMSRLKSEDTAMYYC SRQLFYYGSRGAMGYWGQGTSVTVSS
Ab12 Variable Heavy Chain	SEQ ID NO.:119	DVQLQESGPGLVKPSQSLSLTCTVTGYSITSDYAWNWIRQFPGNKLEW MGYIGYSGRTSFNPSLKSRISITRDTSKNQFFLQLNSVTTEDTATYYC ARGGFAMDYWGQGTSVTVSS
Ab13 Variable Heavy Chain	SEQ ID NO.:120	QVQLQQPGAELVRPGTSVKLSCKASGYTFTSFWMHWVKQRPGQGLEWI GVIDPSDSHTNYNQKFKGKATLTVNTSSSTAYMHLSSLTSEDSAVYYC ARGDYSNWFTYWGQGTLVTVSA

An alignment of the variable heavy chain amino acid sequences for murine antibodies Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, and Ab13 is shown in Figures 1 and 3. An alignment of the variable light chain amino acid sequences for murine antibodies Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11, Ab12, and Ab13 is shown in Figures 2 and 4.

As used herein, the term "Ab5" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103. As used herein, the term "chAb5" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:112, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:103 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab6" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104. As used herein, the term "chAb6" refers to a chimeric

antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:113, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:104 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab7" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105. As used herein, the term "chAb7" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:114, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:105 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab8" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:115 and the variable light chain amino acid sequence set forth in SEQ ID NO:106. As used herein, the term "chAb8" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:115, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:106 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab9" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:116 and the variable light chain amino acid sequence set forth in SEQ ID NO:107. As used herein, the term "chAb9" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:116, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:107 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab10" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:117 and the variable light chain amino acid sequence set forth in SEQ ID NO:108. As used herein, the term "chAb10" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:117, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:108 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab11" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:118 and the variable light chain amino acid sequence set forth in SEQ ID NO:109. As used herein, the term "chAb11" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:118,

the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:109 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab12" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110. As used herein, the term "chAb12" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:119, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:110 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

As used herein, the term "Ab13" refers to an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111. As used herein, the term "chAb13" refers to a chimeric antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:120, the constant heavy chain amino acid sequence set forth in SEQ ID NO: 10, the variable light chain amino acid sequence set forth in SEQ ID NO:111 and the constant light chain amino acid sequence set forth in SEQ ID NO: 12.

3. Generation of Anti-PRLR Humanized Antibodies

Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and framework regions from a human immunoglobulin molecule. Known human Ig sequences are disclosed, *e.g.*, www.ncbi.nlm.nih.gov/entrez- /query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/; www.abcam.com/; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/.about.pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH- 05/kuby05.htm; www.library.thinkquest.org/12429/Immune/Antibody.html; www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/.about.mrc7/m- ikeimages.html; www.antibodyresource.com/; mcb.harvard.edu/BioLinks/Immuno-logy.html.www.immunologylink.com/; pathbox.wustl.edu/.about.hcenter/index.- html; www.biotech.ufl.edu/.about.hcl/; www.pebio.com/pa/340913/340913.html- ; www.nal.usda.gov/awic/pubs/antibody/; www.m.ehime-u.acjp/.about.yasuhito- /Elisa.html; www.biodesign.com/table.asp; www.icnet.uk/axp/facs/davies/lin- ks.html; www.biotech.ufl.edu/.about.fccl/protocol.html; www.isac-net.org/sites_geo.html; aximtl.imt.uni-marburg.de/.about.rek/AEP- Start.html; baserv.uci.kun.nl/.about.jraats/linksl.html;

www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html; imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/.about.martin/abs/index.html; antibody.bath.ac.uk/; abgen.cvm.tamu.edu/lab/wwwabgen.html; www.unizh.ch/.about.honegger/AHOseminar/Slide01.html; www.cryst.bbk.ac.uk/.about.ubcg07s/; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm; www.path.cam.ac.uk/.about.mrc7/humanisation/TAHHP.html; www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html; www.cryst.bioc.cam.ac.uk/.abo- ut.fmolina/Webpages/Pept/spottech.html; www.jerini.de/fr roducts.htm; www.patents.ibm.com/ibm.html.Kabat *et al.*, Sequences of Proteins of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference. Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art.

Framework residues in the human framework regions may be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, *e.g.*, Queen *et al.*, U.S. Pat. No. 5,585,089; Riechmann *et al.*, Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, *i.e.*, the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Antibodies can be humanized using a variety of techniques known in the art, such as but not limited to those described in Jones *et al.*, Nature 321:522 (1986); Verhoeyen *et al.*, Science 239:1534 (1988)), Sims *et al.*, J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987), Carter *et al.*, Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta *et al.*, J. Immunol. 151:2623 (1993), Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka *et al.*, Protein Engineering 7(6):805-814 (1994); Roguska. *et al.* , PNAS 91:969-973 (1994); PCT publication WO 91/09967, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755;

WO90/14443, WO90/14424, WO90/14430, EP 229246, EP 592,106; EP 519,596, EP 239,400, U.S. Pat. Nos. 5,565,332, 5,723,323, 5,976,862, 5,824,514, 5,817,483, 5814476, 5763192, 5723323, 5,766886, 5,714,352, 6,204,023, 6,180,370, 5,693,762, 5,530,101, 5,585,089, 5,225,539; 4,816,567, each entirely incorporated herein by reference, included references cited therein.

Examples of anti-PRLR humanized antibodies are provided in Section 1 above.

4. Additional Competing Antibodies

The term "competing antibodies" herein refers to any number of antibodies targeting the same molecular or stably but non-covalently linked supermolecular entity, preferably the same molecule, *i.e.*, PRLR, wherein at least one is capable of specifically reducing the measurable binding of another, preferably by sterically hampering the other's access to its target epitope or by inducing and/or stabilizing a conformation in the target entity that reduces the target's affinity for the other antibody, more preferably by directly blocking access to the other's target epitope by binding to an epitope in sufficiently close vicinity of the former, overlapping with the former or identical to the former, most preferably overlapping or identical, in particular identical. Two epitopes are herein said to be "overlapping" if they share part of their chemical structures, preferably their amino acid sequences, and to be "identical", if their chemical structures, preferably their amino acid sequences, are identical.

In particular embodiments, the competing antibody, or antigen binding portion thereof, is an antibody, or antigen binding portion thereof, that competes with Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab9, chAb9, Ab10, chAb10, Ab11, chAb11, Ab12, chAb12, Ab13, chAb13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 or Ab55. In various embodiments, the binding may be assayed according to the protocol set forth in Example 4.

In one embodiment, the invention is directed to an antibody that competes with Ab1, *i.e.*, comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and (ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54.

In another embodiment, the invention is directed to an antibody that competes with Ab2, *i.e.*, comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and

(ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69.

In another embodiment, the invention is directed to an antibody that competes with Ab3, *i.e.*, comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75 and SEQ ID NO: 76; and (ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:78, SEQ ID NO:82 and SEQ ID NO: 83.

In another embodiment, the invention is directed to an antibody that competes with Ab4, *i.e.*, comprising (i) one variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO:121, SEQ ID NO:122 and SEQ ID NO:123; and (ii) one variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96.

In another embodiment, the invention is directed to an antibody that competes with Ab5, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103.

In another embodiment, the invention is directed to an antibody that competes with Ab6, *i.e.*, the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104.

In another embodiment, the invention is directed to an antibody that competes with Ab7, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105.

In another embodiment, the invention is directed to an antibody that competes with Ab8, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:115 and the variable light chain amino acid sequence set forth in SEQ ID NO:106.

In another embodiment, the invention is directed to an antibody that competes with Ab9, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:116 and the variable light chain amino acid sequence set forth in SEQ ID NO:107.

In another embodiment, the invention is directed to an antibody that competes with Ab10, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:117 and the variable light chain amino acid sequence set forth in SEQ ID NO:108.

In another embodiment, the invention is directed to an antibody that competes with Ab11, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:118 and the variable light chain amino acid sequence set forth in SEQ ID NO:109.

In another embodiment, the invention is directed to an antibody that competes with Ab12, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110.

In another embodiment, the invention is directed to an antibody that competes with Ab13, *i.e.*, comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111.

In another embodiment, the invention is directed to an antibody that competes with Ab14, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 125.

In another embodiment, the invention is directed to an antibody that competes with Ab15, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 126.

In another embodiment, the invention is directed to an antibody that competes with Ab16, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 127.

In another embodiment, the invention is directed to an antibody that competes with Ab17, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 128.

In another embodiment, the invention is directed to an antibody that competes with Ab18, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 125.

In another embodiment, the invention is directed to an antibody that competes with Ab19, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 126.

In another embodiment, the invention is directed to an antibody that competes with Ab20, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 127.

In another embodiment, the invention is directed to an antibody that competes with Ab21, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 128.

In another embodiment, the invention is directed to an antibody that competes with Ab22, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 125.

In another embodiment, the invention is directed to an antibody that competes with Ab23, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 126.

In another embodiment, the invention is directed to an antibody that competes with Ab24, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 127.

In another embodiment, the invention is directed to an antibody that competes with Ab25, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 128.

In another embodiment, the invention is directed to an antibody that competes with Ab26, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 132.

In another embodiment, the invention is directed to an antibody that competes with Ab27, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 133.

In another embodiment, the invention is directed to an antibody that competes with Ab28, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 134.

In another embodiment, the invention is directed to an antibody that competes with Ab29, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 132.

In another embodiment, the invention is directed to an antibody that competes with Ab30, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 133.

In another embodiment, the invention is directed to an antibody that competes with Ab31, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 134.

In another embodiment, the invention is directed to an antibody that competes with Ab32, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 132.

In another embodiment, the invention is directed to an antibody that competes with Ab33, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 133.

In another embodiment, the invention is directed to an antibody that competes with Ab34, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 134.

In another embodiment, the invention is directed to an antibody that competes with Ab35, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 138.

In another embodiment, the invention is directed to an antibody that competes with Ab36, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In another embodiment, the invention is directed to an antibody that competes with Ab37, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 140.

In another embodiment, the invention is directed to an antibody that competes with Ab38, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 138.

In another embodiment, the invention is directed to an antibody that competes with Ab39, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In another embodiment, the invention is directed to an antibody that competes with Ab40, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 140.

In another embodiment, the invention is directed to an antibody that competes with Ab41, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 138.

In another embodiment, the invention is directed to an antibody that competes with Ab42, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In another embodiment, the invention is directed to an antibody that competes with Ab43, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 140.

In another embodiment, the invention is directed to an antibody that competes with Ab44, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 144.

In another embodiment, the invention is directed to an antibody that competes with Ab45, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 145.

In another embodiment, the invention is directed to an antibody that competes with Ab46, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 146.

In another embodiment, the invention is directed to an antibody that competes with Ab47, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 144.

In another embodiment, the invention is directed to an antibody that competes with Ab48, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 145.

In another embodiment, the invention is directed to an antibody that competes with Ab49, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 146.

In another embodiment, the invention is directed to an antibody that competes with Ab50, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 144.

In another embodiment, the invention is directed to an antibody that competes with Ab51, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 145.

In another embodiment, the invention is directed to an antibody that competes with Ab52, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 146.

In another embodiment, the invention is directed to an antibody that competes with Ab53, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 153; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In another embodiment, the invention is directed to an antibody that competes with Ab54, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 154; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In another embodiment, the invention is directed to an antibody that competes with Ab55, *i.e.*, comprising a heavy chain having the amino acid sequence of SEQ ID NO: 155; and a light chain having the amino acid sequence of SEQ ID NO: 139.

In a particular embodiment, the present invention is directed to a binding protein, *e.g.*, antibody, that competes with an antibody comprising a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(1) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54;

(2) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69;

(3) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96;

(4) the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103;

(5) the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104;

(6) the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105; and

(7) the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111.

In another particular embodiment, the present invention is directed to a binding protein, *e.g.*, antibody, that competes with an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110.

5. PRLR Epitopes

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising three, four, five, six, seven, eight, nine or all of the amino acid residues E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises at least five of the amino acid residues. In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2.

In a particular embodiment, the binding protein that binds to said epitope is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab6, chAb6, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, and Ab25.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising three, four, five, six, seven, eight, nine or all of the amino acid residues E8, I9, F10, K11, C12,

R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises at least five of the amino acid residues. In another embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues E8, I9, F10, K11, C12, R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2.

In a particular embodiment, the binding protein that binds to said epitope is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab4, Ab7, chAb7, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab53, Ab54 and Ab55. In another embodiment, the binding protein that binds to said epitope is an antibody or antigen binding portion thereof, selected from the group consisting of Ab2, Ab5, chAb5, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33 and Ab34.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising 13, 14, 15, 16, 17, 18, 19, 20, 21 or all of the amino acid residues R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161, G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191, and W194 of SEQ ID NO:2. In one embodiment, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises at least 15 of the amino acid residues. In some embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161, G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191, and W194 of SEQ ID NO:2.

In a particular embodiment, the binding protein that binds to said epitope is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab3, Ab8, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51 and Ab52.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising at least one, two, three, four or all of the amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2. In some embodiments, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR, binds to an epitope, wherein the epitope comprises all of amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2.

In a particular embodiment, the binding protein that binds to said epitope is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 and Ab55.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope in PRLR comprising amino acids 91-96 of SEQ ID NO:2.

In a particular embodiment, the binding protein that binds to said epitope is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab4, Ab6, Ab7, chAb6, chAb7, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab53, Ab54 and Ab55. In another embodiment, the binding protein that binds to said epitope is an antibody or antigen binding portion thereof, selected from the group consisting of Ab2, Ab5, chAb5, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33 and Ab34.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR that binds to an epitope having residues within at least amino acids 8-100, 185-191, 8-143, or 183-194 of SEQ ID NO:2. In a particular embodiment, the binding protein that binds to said epitope is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 and Ab55.

In another aspect, the invention pertains to a binding protein, *e.g.*, antibody, or antigen binding fragment thereof, capable of binding PRLR and having the same epitopic specificity as an antibody, or antigen-binding portion thereof, selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab9, chAb9, Ab10, chAb10, Ab11, chAb11, Ab12, chAb12, Ab13, chAb13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 and Ab55.

In various embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, is capable of modulating a biological function of PRLR. In other embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen

binding fragment thereof, is capable of neutralizing PRLR. In other embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, binds an epitope of PRLR which does not inhibit dimerization of PRLR. In further embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, does not bind the D2 domain of PRLR. In further embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, binds the ligand binding region of the D1 domain of PRLR. In additional embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, does not compete with antibody LFA102 for binding of PRLR. In additional embodiments of the foregoing aspects, the binding protein, *e.g.*, antibody, or antigen binding fragment thereof, blocks binding of prolactin to PRLR.

C. Production of Antibodies and Antibody-Producing Cell Lines

Preferably, anti-PRLR antibodies of the present invention, exhibit a high capacity to reduce or to neutralize PRLR activity, *e.g.*, as assessed by any one of several *in vitro* and *in vivo* assays known in the art. For example, inhibition of phosphorylation of PRLR, pSTAT5 or ERK1/2in a PRLR expressing cell line, *e.g.,* the human breast carcinoma cell line T47D, can be measured. Alternatively, inhibition of proliferation of PRLR expressing cell lines, *e.g.,* Baf3 pro-B lymphoid cells transfected with human PRLR, or Nb2-11 rat lymphoma cells, can be measured. In preferred embodiments, the isolated antibody, or antigen-binding portion thereof, binds human PRLR, wherein the antibody, or antigen-binding portion thereof, dissociates from human PRLR with a k_{off} rate constant of about $0.1s^{-1}$ or less, as determined by surface plasmon resonance, or which inhibits human PRLR activity with an IC_{50} of about $1 \times 10^{-6}M$ or less. Alternatively, the antibody, or an antigen-binding portion thereof, may dissociate from human PRLR with a k_{off} rate constant of about $1 \times 10^{-2}s^{-1}$ or less, as determined by surface plasmon resonance, or may inhibit human PRLR activity with an IC_{50} of about $1 \times 10^{-7}M$ or less. Alternatively, the antibody, or an antigen-binding portion thereof, may dissociate from human PRLR with a k_{off} rate constant of about $1 \times 10^{-3}s^{-1}$ or less, as determined by surface plasmon resonance, or may inhibit human PRLR with an IC_{50} of about $1 \times 10^{-8}M$ or less. Alternatively, the antibody, or an antigen-binding portion thereof, may dissociate from human PRLR with a k_{off} rate constant of about $1 \times 10^{-4}s^{-1}$ or less, as determined by surface plasmon resonance, or may inhibit PRLR activity with an IC_{50} of about $1 \times 10^{-9}M$ or less. Alternatively, the antibody, or an antigen-binding portion thereof, may dissociate from human PRLR with a k_{off} rate constant of about $1 \times 10^{-5}s^{-1}$ or less, as determined by surface plasmon resonance, or may inhibit PRLR with an IC_{50} of about $1 \times 10^{-10}M$ or less. Alternatively, the antibody, or an antigen-binding portion thereof, may dissociate from human

PRLR with a k_{off} rate constant of about 1 x $10^{-5}s^{-1}$ or less, as determined by surface plasmon resonance, or may inhibit PRLR activity with an IC_{50} of about 1 x 10^{-11}M or less.

Prolactin binds to PRLR and induces homodimerization. PRLR has no intrinsic kinase activity but is associated with protein kinases such as FYN and JAK2 (Kline, J.B., *et al.* (1999) *J. Biol. Chem.* 274:35461-35468). Prolactin binding activates signal transducer and activator of transcription-5 (STAT5) through JAK2 and extracellular signal-related kinase-1 and -2 (ERK1 and ERK2) (Huang, Y., *et al.,* (2006) *Oncogene* 25:7565-7576). JAK2 phosphorylated STAT5A and STAT5B form homo- and heterodimers and modulate gene expression affecting cell growth and differentiation (Hennighausen, L., and Robinson, G.W. (2001) *Develop. Cell* 1:467-475). Activation of PRLR by prolactin alone stimulates cell proliferation, and in combination with dexamethasone, stimulates mammary specific gene expression in cell lines, *e.g.,* γ-casein (Sasaki, M., *et al.* (1996) *Endocrine J.* 43:45-52). Moreover, PRLR has been found to be over-expressed in human breast cancer and prostate cancer tissues (Li *et al., Cancer Res.*, 64:4774-4782, 2004; Gill *et al., J Clin Pathol.*, 54:956-960, 2001; Touraine *et al., J Clin Endocrinol Metab.*, 83:667-674, 1998). Phosphorylation and proliferation assays demonstrated that the antibodies described herein inhibited prolactin mediated phosphorylation and proliferation. For example, as set forth in Example 2 and in Tables 13 and 14, the PRLR antibodies were shown to inhibit phosphorylation of PRLR. In addition, as set forth in Example 2 and in Tables 13 and 14, the PRLR antibodies were shown to inhibit proliferation of PRLR expressing cell lines, *e.g.,* Baf3 pro-B lymphoid cells transfected with human PRLR and Nb2-11 rat lymphoma cells. Moreover, as set forth in Example 3, the PRLR antibodies, in particular, AB5, were shown to reduce tumor growth in *in vivo* studies. One particular antibody disclosed herein, *i.e.*, Ab12, was shown to exhibit PRLR agonist activity.

The antibodies were humanized as described in Example 1. Framework back-mutations were introduced into the CDR-grafted antibody sequences by *de novo* synthesis of the variable domain or by mutagenic oligonucleotide primers and polymerase chain reaction, or by both allowing different combinations of back mutations and other mutations for each of the CDR-grafts. The humanized variable regions of the murine monoclonal PRLR antibodies were cloned into IgG expression vectors for functional characterization.

In certain embodiments, the antibody comprises a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. Preferably, the heavy chain constant region is an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. Furthermore, the antibody can comprise a light chain constant region, either a kappa light chain constant region or a lambda light chain constant region. Preferably, the antibody comprises a kappa light chain constant region. Alternatively, the antibody portion can be, for example, a Fab fragment or a single chain Fv fragment.

Replacements of amino acid residues in the Fc portion to alter antibody effector function are known in the art (Winter, *et al.* US PAT NOs. 5,648,260; 5624821). The Fc portion of an antibody mediates several important effector functions *e.g.* cytokine induction, ADCC, phagocytosis, complement dependent cytotoxicity (CDC) and half-life/ clearance rate of antibody and antigen-antibody complexes. In some cases these effector functions are desirable for therapeutic antibody but in other cases might be unnecessary or even deleterious, depending on the therapeutic objectives. Certain human IgG isotypes, particularly IgG1 and IgG3, mediate ADCC and CDC via binding to FcγRs and complement C1q, respectively. Neonatal Fc receptors (FcRn) are the critical components determining the circulating half-life of antibodies. In still another embodiment at least one amino acid residue is replaced in the constant region of the antibody, for example the Fc region of the antibody, such that effector functions of the antibody are altered.

One embodiment provides a labeled binding protein wherein an antibody or antibody portion of the invention is derivatized or linked to one or more functional molecule(s) (*e.g.*, another peptide or protein). For example, a labeled binding protein of the invention can be derived by functionally linking an antibody or antibody portion of the invention (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, a bispecific antibody or a diabody), a detectable agent, a pharmaceutical agent, a protein or peptide that can mediate the association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag), and/or a cytotoxic or therapeutic agent selected from the group consisting of a mitotic inhibitor, an antitumor antibiotic, an immunomodulating agent, a vector for gene therapy, an alkylating agent, an antiangiogenic agent, an antimetabolite, a boron-containing agent, a chemoprotective agent, a hormone, an antihormone agent, a corticosteroid, a photoactive therapeutic agent, an oligonucleotide, a radionuclide agent, a topoisomerase inhibitor, a tyrosine kinase inhibitor, a radiosensitizer, and a combination thereof.

Useful detectable agents with which an antibody or antibody portion of the invention may be derivatized include fluorescent compounds. Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody may

also be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding.

Another embodiment of the invention provides a crystallized binding protein. Preferably the invention relates to crystals of whole anti-PRLR antibodies and fragments thereof as disclosed herein, and formulations and compositions comprising such crystals. In one embodiment the crystallized binding protein has a greater half-life *in vivo* than the soluble counterpart of the binding protein. In another embodiment the binding protein retains biological activity after crystallization.

Crystallized binding protein of the invention may be produced according methods known in the art and as disclosed in WO 02072636, incorporated herein by reference.

Another embodiment of the invention provides a glycosylated binding protein wherein the antibody or antigen-binding portion thereof comprises one or more carbohydrate residues. Nascent *in vivo* protein production may undergo further processing, known as post-translational modification. In particular, sugar (glycosyl) residues may be added enzymatically, a process known as glycosylation. The resulting proteins bearing covalently linked oligosaccharide side chains are known as glycosylated proteins or glycoproteins. Antibodies are glycoproteins with one or more carbohydrate residues in the Fc domain, as well as the variable domain. Carbohydrate residues in the Fc domain have important effect on the effector function of the Fc domain, with minimal effect on antigen binding or half-life of the antibody (R. Jefferis, *Biotechnol. Prog.* 21 (2005), pp. 11–16). In contrast, glycosylation of the variable domain may have an effect on the antigen binding activity of the antibody. Glycosylation in the variable domain may have a negative effect on antibody binding affinity, likely due to steric hindrance (Co, M.S., *et al.*, *Mol. Immunol.* (1993) 30:1361- 1367), or result in increased affinity for the antigen (Wallick, S.C., *et al.*, *Exp. Med.* (1988) 168:1099-1109; Wright, A., *et al.*, *EMBO J.* (1991) 10:2717-2723).

One aspect of the present invention is directed to generating glycosylation site mutants in which the O- or N-linked glycosylation site of the binding protein has been mutated. One skilled in the art can generate such mutants using standard well-known technologies. Glycosylation site mutants that retain the biological activity, but have increased or decreased binding activity, are another object of the present invention.

In still another embodiment, the glycosylation of the antibody or antigen-binding portion of the invention is modified. For example, an aglycoslated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more

variable region glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in PCT Publication WO2003016466A2, and U.S. Pat. Nos. 5,714,350 and 6,350,861, each of which is incorporated herein by reference in its entirety.

Additionally or alternatively, a modified antibody of the invention can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. See, for example, Shields, R. L. *et al.* (2002) *J. Biol. Chem.* 277:26733-26740; Umana *et al.* (1999) *Nat. Biotech.* 17:176-1, as well as, European Patent No: EP 1,176,195; PCT Publications WO 03/035835; WO 99/54342 80, each of which is incorporated herein by reference in its entirety.

Protein glycosylation depends on the amino acid sequence of the protein of interest, as well as the host cell in which the protein is expressed. Different organisms may produce different glycosylation enzymes (*e.g.*, glycosyltransferases and glycosidases), and have different substrates (nucleotide sugars) available. Due to such factors, protein glycosylation pattern, and composition of glycosyl residues, may differ depending on the host system in which the particular protein is expressed. Glycosyl residues useful in the invention may include, but are not limited to, glucose, galactose, mannose, fucose, n-acetylglucosamine and sialic acid. Preferably the glycosylated binding protein comprises glycosyl residues such that the glycosylation pattern is human.

It is known to those skilled in the art that differing protein glycosylation may result in differing protein characteristics. For instance, the efficacy of a therapeutic protein produced in a microorganism host, such as yeast, and glycosylated utilizing the yeast endogenous pathway may be reduced compared to that of the same protein expressed in a mammalian cell, such as a CHO cell line. Such glycoproteins may also be immunogenic in humans and show reduced half-life *in vivo* after administration. Specific receptors in humans and other animals may recognize specific glycosyl residues and promote the rapid clearance of the protein from the bloodstream. Other adverse effects may include changes in protein folding, solubility, susceptibility to proteases, trafficking, transport, compartmentalization, secretion, recognition by other proteins or factors, antigenicity, or allergenicity. Accordingly, a practitioner may prefer a therapeutic protein with a specific composition and pattern of glycosylation, for example glycosylation composition and

pattern identical, or at least similar, to that produced in human cells or in the species-specific cells of the intended subject animal.

Expressing glycosylated proteins different from that of a host cell may be achieved by genetically modifying the host cell to express heterologous glycosylation enzymes. Using techniques known in the art a practitioner may generate antibodies or antigen-binding portions thereof exhibiting human protein glycosylation. For example, yeast strains have been genetically modified to express non-naturally occurring glycosylation enzymes such that glycosylated proteins (glycoproteins) produced in these yeast strains exhibit protein glycosylation identical to that of animal cells, especially human cells (U.S. patent Publication Nos. 20040018590 and 20020137134 and PCT publication WO2005100584 A2).

In addition to the binding proteins, the present invention is also directed to an anti-idiotypic (anti-Id) antibody specific for such binding proteins of the invention. An anti-Id antibody is an antibody, which recognizes unique determinants generally associated with the antigen-binding region of another antibody. The anti-Id can be prepared by immunizing an animal with the binding protein or a CDR containing region thereof. The immunized animal will recognize, and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody.

Further, it will be appreciated by one skilled in the art that a protein of interest may be expressed using a library of host cells genetically engineered to express various glycosylation enzymes, such that member host cells of the library produce the protein of interest with variant glycosylation patterns. A practitioner may then select and isolate the protein of interest with particular novel glycosylation patterns. Preferably, the protein having a particularly selected novel glycosylation pattern exhibits improved or altered biological properties.

II. Anti-PRLR Antibody Drug Conjugates (ADCs)

The anti-PRLR antibodies described herein may be conjugated to an agent to form an anti-PRLR Antibody Drug Conjugate (ADC). Antibody-drug conjugates (ADCs) may increase the therapeutic efficacy of antibodies in treating disease, *e.g.*, cancer, due to the ability of the ADC to selectively deliver one or more agent(s) to target tissues, such as a tumor-associated antigen, *e.g.*, PRLR expressing tumors. Thus, the invention provides anti-PRLR ADCs for therapeutic use, *e.g.*, treatment of cancer.

The anti-PRLR ADC of the instant invention comprises an anti-PRLR antibody, *i.e.*, an antibody that specifically binds to PRLR, linked to one or more drug moieties. The specificity of the ADC of the invention is defined by the specificity of the antibody, *i.e.*, anti-PRLR. In one embodiment, an anti-PRLR antibody of the invention is linked to one or more cytotoxin(s) which

is delivered internally to a transformed cancer cell expressing PRLR. Examples of drugs that may be used in the anti-PRLR ADC of the invention are provided below, as are linkers that may be used to conjugate the antibody and the one or more drug(s). The terms "drug" and "agent" are used interchangeably herein. The terms "linked" and "conjugated" are also used interchangeably herein.

A. Drugs for Conjugation

Anti-PRLR antibodies of the invention may be used in an ADC to target one or more drug(s) to a cell of interest, *e.g.*, a transformed cancer cell expressing PRLR. The anti-PRLR ADC of the invention provides a targeted therapy that may, for example, reduce the side effects often seen with anti-cancer therapies, as the one or more drug(s) is delivered to a specific cell. Examples of drugs that may be used in ADCs of the invention, *i.e.*, drugs that may be conjugated to the anti-PRLR antibodies of the invention, are provided below, and include mitotic inhibitors, antitumor antibiotics, immunomodulating agents, gene therapy vectors, alkylating agents, antiangiogenic agents, antimetabolites, boron-containing agents, chemoprotective agents, hormone agents, glucocorticoids, photoactive therapeutic agents, oligonucleotides, radioactive isotopes, radiosensitizers, topoisomerase inhibitors, tyrosine kinase inhibitors, and combinations thereof.

1. Mitotic Inhibitors

Anti-PRLR antibodies of the invention may be conjugated to one or more mitotic inhibitor(s) for the treatment of cancer. The term "mitotic inhibitor", as used herein, refers to a cytotoxic and/or therapeutic agent that blocks mitosis or cell division, a biological process particularly important to cancer cells. A mitotic inhibitor disrupts microtubules such that cell division is prevented, often by affecting microtubule polymerization or microtubule depolymerization. Thus, in one embodiment, an anti-PRLR antibody of the invention is conjugated to one or more mitotic inhibitor(s) that disrupts microtubule formation by inhibiting tubulin polymerization. In one embodiment, the mitotic inhibitor used in the ADCs of the invention is Ixempra (ixabepilone). Examples of mitotic inhibitors that may be used in the anti-PRLR ADCs of the invention are provided below.

a. Dolastatins

The anti-PRLR antibody of the invention may be conjugated to at least one dolastatin. Dolastatins are short peptidic compounds isolated from the Indian Ocean sea hare *Dolabella auricularia* (see Pettit *et al.*, J. Am. Chem. Soc., 1976, 98, 4677). Examples of dolastatins include dolastatin 10 and dolatstin 15. Dolastatin 15, a seven-subunit depsipeptide derived from

Dolabella auricularia, and is a potent antimitotic agent structurally related to the antitubulin agent dolastatin 10, a five-subunit peptide obtained from the same organism. Thus, in one embodiment, the anti-PRLR ADC of the invention comprises an anti-PRLR antibody, as described herein, and at least one dolastatin. Auristatins, described below, are synthetic derivatives of dolastatin 10.

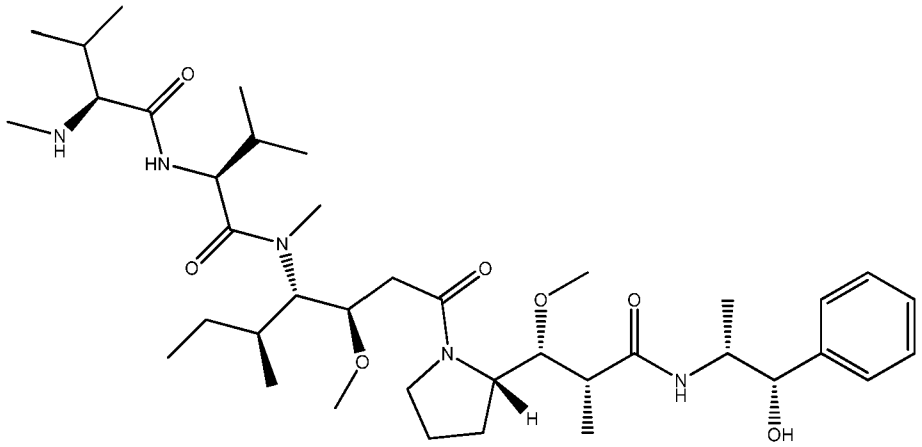
b. Auristatins

The anti-PRLR antibody of the invention may be conjugated to at least one auristatin. Auristatins represent a group of dolastatin analogs that have generally been shown to possess anticancer activity by interfering with microtubule dynamics and GTP hydrolysis, thereby inhibiting cellular division. For example, Auristatin E (U.S. Patent No. 5,635,483) is a synthetic analogue of the marine natural product dolastatin 10, a compound that inhibits tubulin polymerization by binding to the same site on tubulin as the anticancer drug vincristine (G. R. Pettit, Prog. Chem. Org. Nat. Prod, 70: 1-79 (1997)). Dolastatin 10, auristatin PE, and auristatin E are linear peptides having four amino acids, three of which are unique to the dolastatin class of compounds. Exemplary embodiments of the auristatin subclass of mitotic inhibitors include, but are not limited to, monomethyl auristatin D (MMAD or auristatin D derivative), monomethyl auristatin E (MMAE or auristatin E derivative), monomethyl auristatin F (MMAF or auristatin F derivative), auristatin F phenylenediamine (AFP), auristatin EB (AEB), auristatin EFP (AEFP), and 5-benzoylvaleric acid-AE ester (AEVB). The synthesis and structure of auristatin derivatives are described in U.S. Patent Application Publication Nos. 2003-0083263, 2005-0238649 and 2005-0009751; International Patent Publication No. WO 04/010957, International Patent Publication No. WO 02/088172, and U.S. Pat. Nos. 6,323,315; 6,239,104; 6,034,065; 5,780,588; 5,665,860; 5,663,149; 5,635,483; 5,599,902; 5,554,725; 5,530,097; 5,521,284; 5,504,191; 5,410,024; 5,138,036; 5,076,973; 4,986,988; 4,978,744; 4,879,278; 4,816,444; and 4,486,414, each of which is incorporated by reference herein.

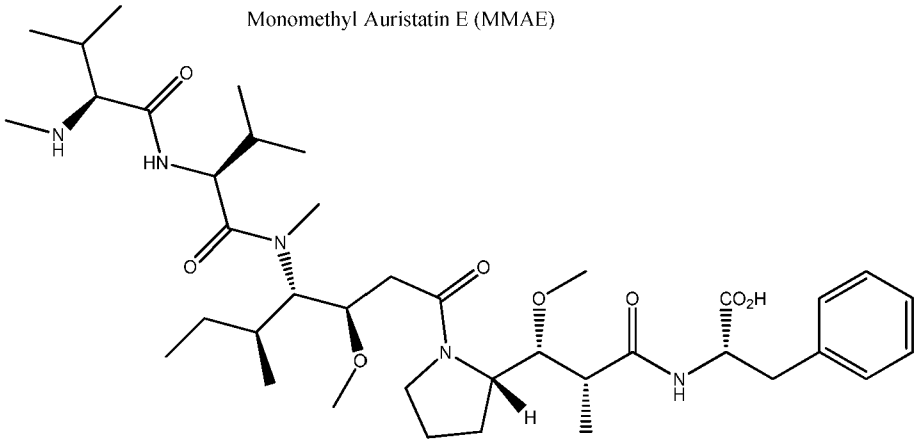
In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one MMAF (monomethylauristatin F). Monomethyl auristatin F (MMAF) inhibits cell division by blocking the polymerization of tubulin. It has a charged C-terminal phenylalanine residue that attenuates its cytotoxic activity compared to its uncharged counterpart MMAE. Because of its super toxicity, it cannot be used as a drug itself, but can be linked to a monoclonal antibody (mAb) that directs it to the cancer cells. In one embodiment, the linker to the anti-PRLR antibody is stable in extracellular fluid, but is cleaved by cathepsin once the conjugate has entered a tumor cell, thus activating the anti-mitotic mechanism.

In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one MMAE (mono-methyl auristatin E). Monomethyl auristatin E (MMAE, vedotin) inhibits cell division by blocking the polymerization of tubulin. Because of its super toxicity, it also cannot be

used as a drug itself. In recent cancer therapy developments, it is linked to a monoclonal antibody (mAb) that recognizes a specific marker expression in cancer cells and directs MMAE to the cancer cells. In one embodiment, the linker linking MMAE to the anti- PRLR antibody is stable in extracellular fluid (*i.e.*, the medium or environment that is external to cells), but is cleaved by cathepsin once the ADC has bound to the specific cancer cell antigen and entered the cancer cell, thus releasing the toxic MMAE and activating the potent anti-mitotic mechanism. The structures of MMAF and MMAE are provided below.



Monomethyl Auristatin E (MMAE)



Monomethyl Auristatin F (MMAF)

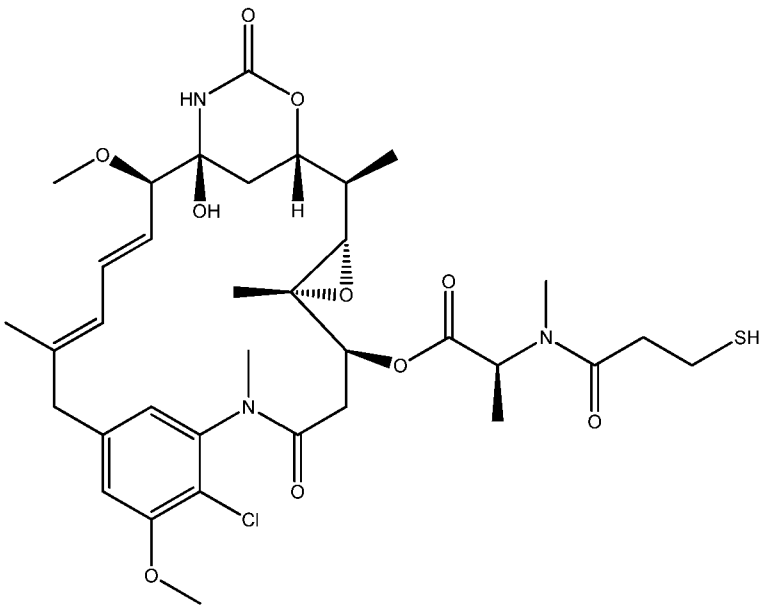
c. Maytansinoids

The anti-PRLR antibody of the invention may be conjugated to at least one maytansinoid. Maytansinoids are potent antitumor agents that were originally isolated from members of the higher plant families Celastraceae, Rhamnaceae and Euphorbiaceae, as well as some species of mosses (Kupchan et al, J. Am. Chem. Soc. 94:1354-1356 [1972]; Wani et al, J. Chem. Soc. Chem. Commun. 390: [1973]; Powell et al, J. Nat. Prod. 46:660-666 [1983]; Sakai et al, J. Nat. Prod. 51 :845-850 [1988]; and Suwanborirux et al, Experientia 46:117-120 [1990]). Evidence suggests that maytansinoids inhibit mitosis by inhibiting polymerization of the microtubule

protein tubulin, thereby preventing formation of microtubules (see, *e.g.*, U.S. Pat. No. 6,441,163 and Remillard *et al.*, Science, 189, 1002-1005 (1975)). Maytansinoids have been shown to inhibit tumor cell growth *in vitro* using cell culture models, and *in vivo* using laboratory animal systems. Moreover, the cytotoxicity of maytansinoids is 1,000-fold greater than conventional chemotherapeutic agents, such as, for example, methotrexate, daunorubicin, and vincristine (see, *e.g.*, U.S. Pat. No. 5,208,020).

Maytansinoids are known in the art to include maytansine, maytansinol, C-3 esters of maytansinol, and other maytansinol analogues and derivatives (see, *e.g.*, U.S. Pat. Nos. 5,208,020 and 6,441,163, each of which is incorporated by reference herein). C-3 esters of maytansinol can be naturally occurring or synthetically derived. Moreover, both naturally occurring and synthetic C-3 maytansinol esters can be classified as a C-3 ester with simple carboxylic acids, or a C-3 ester with derivatives of N-methyl-L-alanine, the latter being more cytotoxic than the former. Synthetic maytansinoid analogues also are known in the art and described in, for example, Kupchan *et al.*, J. Med. Chem., 21, 31-37 (1978).

Suitable maytansinoids for use in ADCs of the invention can be isolated from natural sources, synthetically produced, or semi-synthetically produced using methods known in the art. Moreover, the maytansinoid can be modified in any suitable manner, so long as sufficient cytotoxicity is preserved in the ultimate conjugate molecule. In this regard, maytansinoids lack suitable functional groups to which antibodies can be linked. A linking moiety desirably is utilized to link the maytansinoid to the antibody to form the conjugate, and is described in more detail in section IIB. The structure of an exemplary maytansinoid, mertansine (DM1), is provided below.



Mertansine (DM1)

Representative examples of maytansinoids include, but are not limited, to DM1 ($N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine; also referred to as mertansine, drug maytansinoid 1; ImmunoGen, Inc.; see also Chari *et al.* (1992) *Cancer Res* 52:127), DM2, DM3 ($N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-1-oxopentyl)-maytansine), DM4 (4-methyl-4-mercapto-1-oxopentyl)-maytansine) and maytansinol (a synthetic maytansinoid analog). Other examples of maytansinoids are described in US Patent No. 8,142,784 , incorporated by reference herein.

Ansamitocins are a group of maytansinoid antibiotics that have been isolated from various bacterial sources. These compounds have potent antitumor activities. Representative examples include, but are not limited to ansamitocin P1, ansamitocin P2, ansamitocin P3, and ansamitocin P4.

In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one DM1. In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one DM2. In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one DM3. In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one DM4.

d. Plant Alkaloids

The anti-PRLR antibody of the invention may be conjugated to at least one plant alkaloid, *e.g.*, a taxane or vinca alkaloid. Plant alkaloids are chemotherapy treatments derived made from certain types of plants. The vinca alkaloids are made from the periwinkle plant (*catharanthus rosea*), whereas the taxanes are made from the bark of the Pacific Yew tree (*taxus*). Both the vinca alkaloids and taxanes are also known as antimicrotubule agents, and are described in more detail below.

Taxanes

The anti-PRLR antibody of the invention may be conjugated to at least one taxane. The term "taxane" as used herein refers to the class of antineoplastic agents having a mechanism of microtubule action and having a structure that includes the taxane ring structure and a stereospecific side chain that is required for cytostatic activity. Also included within the term "taxane" are a variety of known derivatives, including both hydrophilic derivatives, and hydrophobic derivatives. Taxane derivatives include, but not limited to, galactose and mannose derivatives described in International Patent Application No. WO 99/18113; piperazino and other derivatives described in WO 99/14209; taxane derivatives described in WO 99/09021, WO 98/22451, and U.S. Pat. No. 5,869,680; 6-thio derivatives described in WO 98/28288; sulfenamide derivatives described in U.S. Pat. No. 5,821,263; and taxol derivative described in U.S. Pat. No. 5,415,869, each of which is incorporated by reference herein. Taxane compounds

have also previously been described in U.S. Pat. Nos. 5,641,803, 5,665,671, 5,380,751, 5,728,687, 5,415,869, 5,407,683, 5,399,363, 5,424,073, 5,157,049, 5,773,464, 5,821,263, 5,840,929, 4,814,470, 5,438,072, 5,403,858, 4,960,790, 5,433,364, 4,942,184, 5,362,831, 5,705,503, and 5,278,324, all of which are expressly incorporated by reference. Further examples of taxanes include, but are not limited to, docetaxel (Taxotere; Sanofi Aventis), paclitaxel (Abraxane or Taxol; Abraxis Oncology), and nanoparticle paclitaxel (ABI-007 / Abraxene; Abraxis Bioscience).

In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one doxetaxel. In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one paclitaxel.

Vinca alkaloids

In one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one vinca alkaloid. Vinca alkaloids are a class of cell-cycle-specific drugs that work by inhibiting the ability of cancer cells to divide by acting upon tubulin and preventing the formation of microtubules. Examples of vinca alkaloids that may be used in the ADCs of the invention include, but are not limited to, vindesine sulfate, vincristine, vinblastine and vinorelbine.

2. Antitumor Antibiotics

Anti-PRLR antibodies of the invention may be conjugated to one or more antitumor antibiotic(s) for the treatment of cancer. As used herein, the term "antitumor antibiotic" means an antineoplastic drug that blocks cell growth by interfering with DNA and is made from a microorganism. Often, antitumor antibiotics either break up DNA strands or slow down or stop DNA synthesis. Examples of antitumor antibiotics that may be included in the anti-PRLR ADCs of the invention include, but are not limited to, actinomycines (*e.g.*, pyrrolo[2,1-c][1,4]benzodiazepines), anthracyclines, calicheamicins, and duocarmycins, described in more detail below.

a. Actinomycines

The anti-PRLR antibody of the invention may be conjugated to at least one actinomycine. Actinomycines are a subclass of antitumor antibiotics isolated from bacteria of the genus *Streptomyces*. Representative examples actinomycines include, but are not limited to, actinomycin D (Cosmegen [also known as actinomycin, dactinomycin, actinomycin IV, actinomycin C1], Lundbeck, Inc.), anthramycin, chicamycin A, DC-18, mazethramycin, neothramycin A, neothramycin B, porothramycin, prothracarcin B, SG2285, sibanomicin, sibiromycin and tomaymycin. In one embodiment, the anti-PRLR antibody of the invention is

conjugated to at least one pyrrolo[2,1-c][1,4]benzodiazepine (PBD). Examples of PDBs include, but are not limited to, anthramycin, chicamycin A, DC-81, mazethramycin, neothramycin A, neothramycin B, porothramycin, prothracarcin B, SG2285, sibanomicin, sibiromycin and tomaymycin. Thus, in one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one actinomycine, *e.g.*, actinomycin D or at least one PBD, *e.g.*, a pyrrolobenzodiazepine (PBD) dimer.

b. Anthracyclines

The anti-PRLR antibody of the invention may be conjugated to at least one anthracycline. Anthracyclines are a subclass of antitumor antibiotics isolated from bacteria of the genus *Streptomyces*. Representative examples include, but are not limited to daunorubicin (Cerubidine, Bedford Laboratories), doxorubicin (Adriamycin, Bedford Laboratories; also referred to as doxorubicin hydrochloride, hydroxydaunorubicin, and Rubex), epirubicin (Ellence, Pfizer), and idarubicin (Idamycin; Pfizer Inc.). Thus, in one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one anthracycline, *e.g.*, doxorubicin.

c. Calicheamicins

The anti-PRLR antibody of the invention may be conjugated to at least one calicheamicin. Calicheamicins are a family of enediyne antibiotics derived from the soil organism *Micromonospora echinospora.* Calicheamicins bind the minor groove of DNA and induce double-stranded DNA breaks, resulting in cell death with a 100 fold increase over other chemotherapeutics (Damle *et al.* (2003) *Curr Opin Pharmacol* 3:386). Preparation of calicheamicins that may be used as drug conjugates in the invention are known in the art, see U.S. Pat. Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001 and 5,877,296. Structural analogues of calicheamicin which may be used include, but are not limited to, γ_1^I, α_2^I, α_3^I, N-acetyl-γ_1^I, PSAG and θ^I_1 (Hinman *et al.*, Cancer Research 53:3336-3342 (1993), Lode *et al.*, Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. Patent Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001 and 5,877,296). Thus, in one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one calicheamicin.

d. Duocarmycins

The anti-PRLR antibody of the invention may be conjugated to at least one duocarmycin. Duocarmycins are a subclass of antitumor antibiotics isolated from bacteria of the genus *Streptomyces*. (see Nagamura and Saito (1998) *Chemistry of Heterocyclic Compounds,* Vol. 34, No. 12). Duocarmycins bind to the minor groove of DNA and alkylate the nucleobase adenine at

the N3 position (Boger (1993) *Pure and Appl Chem* 65(6):1123; and Boger and Johnson (1995) *PNAS USA* 92:3642). Synthetic analogs of duocarmycins include, but are not limited to, adozelesin, bizelesin, and carzelesin. Thus, in one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one duocarmycin.

e. Other antitumor antibiotics

In addition to the foregoing, additional antitumor antibiotics that may be used in the anti-PRLR ADCs of the invention include bleomycin (Blenoxane, Bristol-Myers Squibb), mitomycin, and plicamycin (also known as mithramycin).

3. Immunomodulating Agents

The anti-PRLR antibody of the invention may be conjugated to at least one immunomodulating agent. As used herein, the term "immunomodulating agent" refers to an agent that can stimulate or modify an immune response. In one embodiment, an immunomodulating agent is an immunostimuator which enhances a subject's immune response. In another embodiment, an immunomodulating agent is an immunosuppressant which prevents or decreases a subject's immune response. An immunomodulating agent may modulate myeloid cells (monocytes, macrophages, dendritic cells, meagakaryocytes and granulocytes) or lymphoid cells (T cells, B cells and natural killer (NK) cells) and any further differentiated cell thereof. Representative examples include, but are not limited to, bacillus calmette-guerin (BCG) and levamisole (Ergamisol). Other examples of immunomodulating agents that may be used in the ADCs of the invention include, but are not limited to, cancer vaccines, cytokines, and immunomodulating gene therapy.

a. Cancer vaccines

The anti-PRLR antibody of the invention may be conjugated to a cancer vaccine. As used herein, the term "cancer vaccine" refers to a composition (*e.g.*, a tumor antigen and a cytokine) that elicits a tumor-specific immune response. The response is elicited from the subject's own immune system by administering the cancer vaccine, or, in the case of the instant invention, administering an ADC comprising an anti-PRLR antibody and a cancer vaccine. In preferred embodiments, the immune response results in the eradication of tumor cells in the body (*e.g.*, primary or metastatic tumor cells). The use of cancer vaccines generally involves the administration of a particular antigen or group of antigens that are, for example, present on the surface a particular cancer cell, or present on the surface of a particular infectious agent shown to facilitate cancer formation. In some embodiments, the use of cancer vaccines is for prophylactic purposes, while in other embodiments, the use is for therapeutic purposes. Non-limiting

examples of cancer vaccines that may be used in the anti-PRLR ADCs of the invention include, recombinant bivalent human papillomavirus (HPV) vaccine types 16 and 18 vaccine (Cervarix, GlaxoSmithKline), recombinant quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 vaccine (Gardasil, Merck & Company), and sipuleucel-T (Provenge, Dendreon). Thus, in one embodiment, the anti-PRLR antibody of the invention is conjugated to at least one cancer vaccine that is either an immunostimulator or is an immunosuppressant.

b. Cytokines

The anti-PRLR antibody of the invention may be conjugated to at least one cytokine. The term "cytokine" generally refers to proteins released by one cell population which act on another cell as intercellular mediators. Cytokines directly stimulate immune effector cells and stromal cells at the tumor site and enhance tumor cell recognition by cytotoxic effector cells (Lee and Margolin (2011) *Cancers* 3:3856). Numerous animal tumor model studies have demonstrated that cytokines have broad anti-tumor activity and this has been translated into a number of cytokine-based approaches for cancer therapy (Lee and Margoli, *supra*). Recent years have seen a number of cytokines, including GM-CSF, IL-7, IL-12, IL-15, IL-18 and IL-21, enter clinical trials for patients with advanced cancer (Lee and Margoli, *supra*).

Examples of cytokines that may be used in the ADCs of the invention include, but are not limited to, parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF; platelet-growth factor; transforming growth factors (TGFs); insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon α, β,nd γ, colony stimulating factors (CSFs); granulocyte-macrophage-C-SF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; tumor necrosis factor; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines. Thus, in one embodiment, the invention provides an ADC comprising an anti-PRLR antibody described herein and a cytokine.

c. Colony-stimulating factors (CSFs)

The anti-PRLR antibody of the invention may be conjugated to at least one colony stimulating factor (CSF). Colony stimulating factors (CSFs) are growth factors that assist the

bone marrow in making red blood cells. Because some cancer treatments (*e.g.*, chemotherapy) can affect white blood cells (which help fight infection), colony-stimulating factors may be introduced to help support white blood cell levels and strengthen the immune system. Colony-stimulating factors may also be used following a bone marrow transplant to help the new marrow start producing white blood cells. Representative examples of CSFs that may be used in the anti-PRLR ADCs of the invention include, but are not limited to erythropoietin (epoetin), filgrastim (Neopogen (also known as granulocyte colony-stimulating factor (G-CSF); Amgen, Inc.), sargramostim (leukine (granulocyte-macrophage colony-stimulating factor and GM-CSF); Genzyme Corporation), promegapoietin, and Oprelvekin (recombinant IL-11; Pfizer, Inc.). Thus, in one embodiment, the invention provides an ADC comprising an anti-PRLR antibody described herein and a CSF.

4. Gene Therapy

The anti-PRLR antibody of the invention may be conjugated to at least one nucleic acid (directly or indirectly via a carrier) for gene therapy. Gene therapy generally refers to the introduction of genetic material into a cell whereby the genetic material is designed to treat a disease. As it pertains to immunomoduatory agents, gene therapy is used to stimulate a subject's natural ability to inhibit cancer cell proliferation or kill cancer cells. In one embodiment, the anti-PRLR ADC of the invention comprises a nucleic acid encoding a functional, therapeutic gene that is used to replace a mutated or otherwise dysfuntional (*e.g.* truncated) gene associated with cancer. In other embodiments, the anti-PRLR ADC of the invention comprises a nucleic acid that encodes for or otherwise provides for the production of a therapeutic protein to treat cancer. The nucleic acid that encodes the therapeutic gene may be directly conjugated to the anti-PRLR antibody, or alternatively, may be conjugated to the anti-PRLR antibody through a carrier. Examples of carriers that may be used to deliver a nucleic acid for gene therapy include, but are not limited to, viral vectors or liposomes.

5. Alkylating Agents

The anti-PRLR antibody of the invention may be conjugated to one or more alkylating agent(s). Alkylating agents are a class of antineoplastic compounds that attaches an alkyl group to DNA. Examples of alkylating agents that may be used in the ADCs of the invention include, but are not limited to, alkyl sulfonates, ethylenimimes, methylamine derivatives, epoxides, nitrogen mustards, nitrosoureas, triazines and hydrazines.

a. Alkyl Sulfonates

The anti-PRLR antibody of the invention may be conjugated to at least one alkyl sulfonate. Alkyl sulfonates are a subclass of alkylating agents with a general formula: R-SO_2-O-R^1, wherein R and R^1 are typically alkyl or aryl groups. A representative example of an alkyl sulfonate includes, but is not limited to, busulfan (Myleran, GlaxoSmithKline; Busulfex IV, PDL BioPharma, Inc.).

b. Nitrogen Mustards

The anti-PRLR antibody of the invention may be conjugated to at least one nitrogen mustard. Representative examples of this subclass of anti-cancer compounds include, but are not limited to chlorambucil (Leukeran, GlaxoSmithKline), cyclophosphamide (Cytoxan, Bristol-Myers Squibb; Neosar, Pfizer, Inc.), estramustine (estramustine phosphate sodium or Estracyt), Pfizer, Inc.), ifosfamide (Ifex, Bristol-Myers Squibb), mechlorethamine (Mustargen, Lundbeck Inc.), and melphalan (Alkeran or L-Pam or phenylalanine mustard; GlaxoSmithKline).

c. Nitrosoureas

The anti-PRLR antibody of the invention may be conjugated to at least one nitrosourea. Nitrosoureas are a subclass of alkylating agents that are lipid soluble. Representative examples include, but are not limited to, carmustine (BCNU [also known as BiCNU, *N,N*-Bis(2-chloroethyl)-*N*-nitrosourea, or 1, 3-bis (2-chloroethyl)-*l*-nitrosourea], Bristol-Myers Squibb), fotemustine (also known as Muphoran), lomustine (CCNU or 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea, Bristol-Myers Squibb), nimustine (also known as ACNU), and streptozocin (Zanosar, Teva Pharmaceuticals).

d. Triazines and Hydrazines

The anti-PRLR antibody of the invention may be conjugated to at least one triazine or hydrazine. Triazines and hydrazines are a subclass of nitrogen-containing alkylating agents. In some embodiments, these compounds spontaneously decompose or can be metabolized to produce alkyl diazonium intermediates that facilitate the transfer of an alkyl group to nucleic acids, peptides, and/or polypeptides, thereby causing mutagenic, carcinogenic, or cytotoxic effects. Representative examples include, but are not limited to dacarbazine (DTIC-Dome, Bayer Healthcare Pharmaceuticals Inc.), procarbazine (Mutalane, Sigma-Tau Pharmaceuticals, Inc.), and temozolomide (Temodar, Schering Plough).

e. Other Alkylating Agents

The anti-PRLR antibody of the invention may be conjugated to at least one ethylenimine, methylamine derivative, or epoxide. Ethylenimines are a subclass of alkylating agents that typically containing at least one aziridine ring. Epoxides represent a subclass of alkylating agents that are characterized as cyclic ethers with only three ring atoms.

Representatives examples of ethylenimines include, but are not limited to thiopeta (Thioplex, Amgen), diaziquone (also known as aziridinyl benzoquinone (AZQ)), and mitomycin C. Mitomycin C is a natural product that contains an aziridine ring and appears to induce cytoxicity through cross-linking DNA (Dorr RT, *et al. Cancer Res.* 1985;45:3510; Kennedy KA, et al *Cancer Res.* 1985;45:3541). Representative examples of methylamine derivatives and their analogs include, but are not limited to, altretamine (Hexalen, MGI Pharma, Inc.), which is also known as hexamethylamine and hexastat. Representative examples of epoxides of this class of anti-cancer compound include, but are not limited to dianhydrogalactitol. Dianhydrogalactitol (1,2:5,6-dianhydrodulcitol) is chemically related to the aziridines and generally facilitate the transfer of an alkyl group through a similar mechanism as described above. Dibromodulcitol is hydrolyzed to dianhydrogalactitol and thus is a pro-drug to an epoxide (Sellei C, *et al. Cancer Chemother Rep.* 1969;53:377).

6. Antiangiogenic Agents

The anti-PRLR antibody of the invention may be conjugated to at least one antiangiogenic agent. Antiangiogenic agents inhibit the growth of new blood vessels. Antiangiogenic agents exert their effects in a variety of ways. In some embodiments, these agents interfere with the ability of a growth factor to reach its target. For example, vascular endothelial growth factor (VEGF) is one of the primary proteins involved in initiating angiogenesis by binding to particular receptors on a cell surface. Thus, certain antiangiogenic agents that prevent the interaction of VEGF with its cognate receptor, prevent VEGF from initiating angiogenesis. In other embodiments, these agents interfere with intracellular signaling cascades. For example, once a particular receptor on a cell surface has been triggered, a cascade of other chemical signals is initiated to promote the growth of blood vessels. Thus, certain enzymes, for example, some tyrosine kinases, that are known to facilitate intracellular signaling cascades that contribute to, for example, cell proliferation, are targets for cancer treatment. In other embodiments, these agents interfere with intercellular signaling cascades. Yet, in other embodiments, these agents disable specific targets that activate and promote cell growth or by directly interfering with the growth of blood vessel cells. Angiogenesis inhibitory properties have been discovered in more than 300 substances with numerous direct and indirect inhibitory effects.

Representative examples of antiangiogenic agents that may be used in the ADCs of the invention include, but are not limited to, angiostatin, ABX EFG, C1-1033, PKI-166, EGF vaccine, EKB-569, GW2016, ICR-62, EMD 55900, CP358, PD153035, AG1478, IMC-C225 (Erbitux, ZD1839 (Iressa), OSI-774, Erlotinib (tarceva), angiostatin, arrestin, endostatin, BAY 12-9566 and w/fluorouracil or doxorubicin, canstatin, carboxyamidotriozole and with paclitaxel, EMD121974, S-24, vitaxin, dimethylxanthenone acetic acid, IM862, Interleukin-12, Interleukin-2, NM-3, HuMV833, PTK787, RhuMab, angiozyme (ribozyme), IMC-1C11, Neovastat, marimstat, prinomastat, BMS-275291,COL-3, MM1270, SU101, SU6668, SU11248, SU5416, with paclitaxel, with gemcitabine and cisplatin, and with irinotecan and cisplatin and with radiation, tecogalan, temozolomide and PEG interferon α2b, tetrathiomolybdate, TNP-470, thalidomide, CC-5013 and with taxotere, tumstatin, 2-methoxyestradiol, VEGF trap, mTOR inhibitors (deforolimus, everolimus (Afinitor, Novartis Pharmaceutical Corporation), and temsirolimus (Torisel, Pfizer, Inc.)), tyrosine kinase inhibitors (*e.g.*, erlotinib (Tarceva, Genentech, Inc.), imatinib (Gleevec, Novartis Pharmaceutical Corporation), gefitinib (Iressa, AstraZeneca Pharmaceuticals), dasatinib (Sprycel, Brystol-Myers Squibb), sunitinib (Sutent, Pfizer, Inc.), nilotinib (Tasigna, Novartis Pharmaceutical Corporation), lapatinib (Tykerb, GlaxoSmithKline Pharmaceuticals), sorafenib (Nexavar, Bayer and Onyx), phosphoinositide 3-kinases (PI3K).

7. Antimetabolites

The anti-PRLR antibody of the invention may be conjugated to at least one antimetabolite. Antimetabolites are types of chemotherapy treatments that are very similar to normal substances within the cell. When the cells incorporate an antimetabolite into the cellular metabolism, the result is negative for the cell, *e.g.*, the cell is unable to divide. Antimetabolites are classified according to the substances with which they interfere. Examples of antimetabolies that may be used in the ADCs of the invention include, but are not limited to, a folic acid antagonist (*e.g.*, methotrexate), a pyrimidine antagonist (*e.g.*, 5-Fluorouracil, Foxuridine, Cytarabine, Capecitabine, and Gemcitabine), a purine antagonist (*e.g.*, 6-Mercaptopurine and 6-Thioguanine) and an adenosine deaminase inhibitor (*e.g.*, Cladribine, Fludarabine, Nelarabine and Pentostatin), as described in more detail below.

a. Antifolates

The anti-PRLR antibody of the invention may be conjugated to at least one antifolate. Antifolates are a subclass of antimetabolites that are structurally similar to folate. Representative examples include, but are not limited to, methotrexate, 4-amino-folic acid (also known as

aminopterin and 4-aminopteroic acid), lometrexol (LMTX), pemetrexed (Alimpta, Eli Lilly and Company), and trimetrexate (Neutrexin, Ben Venue Laboratories, Inc.)

b. Purine Antagonists

The anti-PRLR antibody of the invention may be conjugated to at least one purine antagonist. Purine analogs are a subclass of antimetabolites that are structurally similar to the group of compounds known as purines. Representative examples of purine antagonists include, but are not limited to, azathioprine (Azasan, Salix; Imuran, GlaxoSmithKline), cladribine (Leustatin [also known as 2-CdA], Janssen Biotech, Inc.), mercaptopurine (Purinethol [also known as 6-mercaptoethanol], GlaxoSmithKline), fludarabine (Fludara, Genzyme Corporation), pentostatin (Nipent, also known as 2'-deoxycoformycin (DCF)), 6-thioguanine (Lanvis [also known as thioguanine], GlaxoSmithKline).

c. Pyrimidine Antagonists

The anti-PRLR antibody of the invention may be conjugated to at least one pyrimidine antagonist. Pyrimidine antagonists are a subclass of antimetabolites that are structurally similar to the group of compounds known as purines. Representative examples of pyrimidine antagonists include, but are not limited to azacitidine (Vidaza, Celgene Corporation), capecitabine (Xeloda, Roche Laboratories), Cytarabine (also known as cytosine arabinoside and arabinosylcytosine, Bedford Laboratories), decitabine (Dacogen, Eisai Pharmaceuticals), 5-fluorouracil (Adrucil, Teva Pharmaceuticals; Efudex, Valeant Pharmaceuticals, Inc), 5-fluoro-2'-deoxyuridine 5'-phosphate (FdUMP), 5-fluorouridine triphosphate, and gemcitabine (Gemzar, Eli Lilly and Company).

8. Boron-Containing Agents

The anti-PRLR antibody of the invention may be conjugated to at least one boron containing agent. Boron-containing agents comprise a class of cancer therapeutic compounds which interfere with cell proliferation. Representative examples of boron containing agents include, but are not limited, to borophycin and bortezomib (Velcade, Millenium Pharmaceuticals).

9. Chemoprotective Agents

The anti-PRLR antibody of the invention may be conjugated to at least one chemoprotective agent. Chemoprotective drugs are a class of compounds, which help protect the body against specific toxic effects of chemotherapy. Chemoprotective agents may be administered with various chemotherapies in order to protect healthy cells from the toxic effects

of chemotherapy drugs, while simultaneously allowing the cancer cells to be treated with the administered chemotherapeutic. Representative chemoprotective agents include, but are not limited to amifostine (Ethyol, Medimmune, Inc.), which is used to reduce renal toxicity associated with cumulative doses of cisplatin, dexrazoxane (Totect, Apricus Pharma; Zinecard), for the treatment of extravasation caused by the administration of anthracycline (Totect), and for the treatment of cardiac-related complications caused by the administration of the antitumor antibiotic doxorubicin (Zinecard), and mesna (Mesnex, Bristol-Myers Squibb), which is used to prevent hemorrhagic cystitis during chemotherapy treatment with ifocfamide.

10. Hormone agents

The anti-PRLR antibody of the invention may be conjugated to at least one hormone agent. A hormone agent (including synthetic hormones) is a compound that interferes with the production or activity of endogenously produced hormones of the endocrine system. In some embodiments, these compounds interfere with cell growth or produce a cytotoxic effect. Non-limiting examples include androgens, estrogens, medroxyprogesterone acetate (Provera, Pfizer, Inc.), and progestins.

11. Antihormone Agents

The anti-PRLR antibody of the invention may be conjugated to at least one antihormone agent. An "antihormone" agent is an agent that suppresses the production of and/or prevents the function of certain endogenous hormones. In one embodiment, the antihormone agent interferes with the activity of a hormone selected from the group comprising androgens, estrogens, progesterone, and goanadotropin-releasing hormone, thereby interfering with the growth of various cancer cells. Representative examples of antihormone agents include, but are not limited to, aminoglutethimide, anastrozole (Arimidex, AstraZeneca Pharmaceuticals), bicalutamide (Casodex, AstraZeneca Pharmaceuticals), cyproterone acetate (Cyprostat, Bayer PLC), degarelix (Firmagon, Ferring Pharmaceuticals), exemestane (Aromasin, Pfizer Inc.), flutamide (Drogenil, Schering-Plough Ltd), fulvestrant (Faslodex, AstraZeneca Pharmaceuticals), goserelin (Zolodex, AstraZeneca Pharmaceuticals), letrozole (Femara, Novartis Pharmaceuticals Corporation), leuprolide (Prostap), lupron, medroxyprogesterone acetate (Provera, Pfizer Inc.), Megestrol acetate (Megace, Bristol-Myers Squibb Company), tamoxifen (Nolvadex, AstraZeneca Pharmaceuticals), and triptorelin (Decapetyl, Ferring).

12. Corticosteroids

The anti-PRLR antibody of the invention may be conjugated to at least one corticosteroid. Corticosteroids may be used in the ADCs of the invention to decrease

inflammation. An example of a corticosteroid includes, but is not limited to, a glucocorticoid, for example, prednisone (Deltasone, Pharmacia & Upjohn Company, a division of Pfizer, Inc.).

13. Photoactive Therapeutic Agents

The anti-PRLR antibody of the invention may be conjugated to at least one photoactive therapeutic agent. Photoactive therapeutic agents include compounds that can be deployed to kill treated cells upon exposure to electromagnetic radiation of a particular wavelength. Therapeutically relevant compounds absorb electromagnetic radiation at wavelengths which penetrate tissue. In preferred embodiments, the compound is administered in a non-toxic form that is capable of producing a photochemical effect that is toxic to cells or tissue upon sufficient activation. In other preferred embodiments, these compounds are retained by cancerous tissue and are readily cleared from normal tissues. Non-limiting examples include various chromagens and dyes.

14. Oligonucleotides

The anti-PRLR antibody of the invention may be conjugated to at least one oligonucleotide. Oligonucleotides are made of short nucleic acid chains that work by interfering with the processing of genetic information. In some embodiments, the oligonucleotides for use in ADCs are unmodified single-stranded and/or double-stranded DNA or RNA molecules, while in other embodiments, these therapeutic oligonucleotides are chemically-modified single-stranded and/or double-stranded DNA or RNA molecules. In one embodiment, the oligonulceotides used in the ADCs are relatively short (19–25 nucleotides) and hybridize to a unique nucleic acid sequence in the total pool of nucleic acid targets present in cells. Some of the important oligonucleotide technologies include the antisense oligonucleotides (including RNA interference (RNAi)), aptamers, CpG oligonucleotides, and ribozymes.

a. Antisense oligonucleotides

The anti-PRLR antibody of the invention may be conjugated to at least one antisense oligonucleotide. Antisense oligonucleotides are designed to bind to RNA through Watson–Crick hybridization. In some embodiments the antisense oligonucleotide is complementary to a nucleotide encoding a region, domain, portion, or segment of PRLR. In some embodiments, the antisense oligonucleotide comprises from about 5 to about 100 nucleotides, from about 10 to about 50 nucleotides, from about 12 to about 35, and from about 18 to about 25 nucleotides. In some embodiments, the oligonucleotide is at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 100% homologous to a region, portion, domain, or segment of the PRLR gene. In some embodiments

there is substantial sequence homology over at least 15, 20, 25, 30, 35, 40, 50, or 100 consecutive nucleotides of the PRLR gene. In preferred embodiments, the size of these antisense oligonucleotides ranges from 12 to 25 nucleotides in length, with the majority of antisense oligonucleotides being 18 to 21 nucleotides in length. There are multiple mechanisms that can be exploited to inhibit the function of the RNA once the oligonucleotide binds to the target RNA (Crooke ST. (1999). *Biochim. Biophys. Acta*, 1489, 30–42). The best-characterized antisense mechanism results in cleavage of the targeted RNA by endogenous cellular nucleases, such as RNase H or the nuclease associated with the RNA interference mechanism. However, oligonucleotides that inhibit expression of the target gene by non-catalytic mechanisms, such as modulation of splicing or translation arrest, can also be potent and selective modulators of gene function.

Another RNase-dependent antisense mechanism that has recently received much attention is RNAi (Fire *et al.* (1998). *Nature*, 391, 806–811.; Zamore PD. (2002). *Science*, 296, 1265–1269.). RNA interference (RNAi) is a post-transcriptional process where a double stranded RNA inhibits gene expression in a sequence specific fashion. In some embodiments, the RNAi effect is achieved through the introduction of relatively longer double-stranded RNA (dsRNA), while in preferred embodiments, this RNAi effect is achieved by the introduction of shorter double-stranded RNAs, *e.g.* small interfering RNA (siRNA) and/or microRNA (miRNA). In yet another embodiment, RNAi can also be achieved by introducing of plasmid that generate dsRNA complementary to target gene. In each of the foregoing embodiments, the double-stranded RNA is designed to interfere with the gene expression of a particular the target sequence within cells. Generally, the mechanism involves conversion of dsRNA into short RNAs that direct ribonucleases to homologous mRNA targets (summarized, Ruvkun, *Science* 2294:797 (2001)), which then degrades the corresponding endogenous mRNA, thereby resulting in the modulation of gene expression. Notably, dsRNA has been reported to have anti-proliferative properties, which makes it possible also to envisage therapeutic applications (Aubel *et al.*, *Proc. Natl. Acad. Sci., USA* 88:906 (1991)). For example, synthetic dsRNA has been shown to inhibit tumor growth in mice (Levy *et al. Proc. Nat. Acad. Sci. USA,* 62:357-361 (1969)), is active in the treatment of leukemic mice (Zeleznick *et al.*, *Proc. Soc. Exp. Biol. Med.* 130:126-128 (1969)), and inhibits chemically induced tumorigenesis in mouse skin (Gelboin *et al.*, *Science* 167:205-207 (1970)). Thus, in a preferred embodiment, the invention provides for the use of antisense oligonucleotides in ADCs for the treatment of breast cancer. In other embodiments, the invention provides compositions and methods for initiating antisense oligonucleotide treatment, wherein dsRNA interferes with target cell expression of PRLR at the mRNA level. dsRNA, as used above, refers to naturally-occurring RNA, partially purified RNA, recombinantly produced RNA, synthetic RNA, as well as altered RNA that differs from naturally-occurring RNA by the inclusion of non-

standard nucleotides, non-nucleotide material, nucleotide analogs (*e.g.* locked nucleic acid (LNA)), deoxyribonucleotides, and any combination thereof. RNA of the present invention need only be sufficiently similar to natural RNA that it has the ability to mediate the antisense oligonucleotide-based modulation described herein.

b. Aptamers

The anti-PRLR antibody of the invention may be conjugated to at least one aptamer. An aptamer is a nucleic acid molecule that has been selected from random pools based on its ability to bind other molecules. Like antibodies, aptamers can bind target molecules with extraordinary affinity and specificity. In many embodiments, aptamers assume complex, sequence-dependent, three-dimensional shapes that allow them to interact with a target protein, resulting in a tightly bound complex analogous to an antibody-antigen interaction, thereby interfering with the function of said protein. The particular capacity of aptamers to bind tightly and specifically to their target protein underlines their potential as targeted molecular therapies.

c. CpG oligonucleotides

The anti-PRLR antibody of the invention may be conjugated to at least one CpG oligonucleotide. Bacterial and viral DNA are known to be a strong activators of both the innate and specific immunity in humans. These immunologic characteristics have been associated with unmethylated CpG dinucleotide motifs found in bacterial DNA. Owing to the fact that these motifs are rare in humans, the human immune system has evolved the ability to recognize these motifs as an early indication of infection and subsequently initiate immune responses. Therefore, oligonucleotides containing this CpG motif can be exploited to initiate an antitumor immune response.

d. Ribozymes

The anti-PRLR antibody of the invention may be conjugated to at least one ribozyme. Ribozymes are catalytic RNA molecules ranging from about 40 to 155 nucleotides in length. The ability of ribozymes to recognize and cut specific RNA molecules makes them potential candidates for therapeutics. A representative example includes angiozyme.

15. Radionuclide Agents (Radioactive Isotopes)

The anti-PRLR antibody of the invention may be conjugated to at least one radionuclide agent. Radionuclide agents comprise agents that are characterized by an unstable nucleus that is capable of undergoing radioactive decay. The basis for successful radionuclide treatment depends on sufficient concentration and prolonged retention of the radionuclide by the cancer cell. Other

factors to consider include the radionuclide half-life, the energy of the emitted particles, and the maximum range that the emitted particle can travel. In preferred embodiments, the therapeutic agent is a radionuclide selected from the group consisting of ^{111}In, ^{177}Lu, ^{212}Bi, ^{213}Bi, ^{211}At, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{90}Y, ^{125}I, ^{131}I, ^{32}P, ^{33}P, ^{47}Sc, ^{111}Ag, ^{67}Ga, ^{142}Pr, ^{153}Sm, ^{161}Tb, ^{166}Dy, ^{166}Ho, ^{186}Re, ^{188}Re, ^{189}Re, ^{212}Pb, ^{223}Ra, ^{225}Ac, ^{59}Fe, ^{75}Se, ^{77}As, ^{89}Sr, ^{99}Mo, ^{105}Rh, ^{109}Pd, ^{143}Pr, ^{149}Pm, ^{169}Er, ^{194}Ir, ^{198}Au, ^{199}Au, and ^{211}Pb. Also preferred are radionuclides that substantially decay with Auger-emitting particles. For example, Co-58, Ga-67, Br-80m, Tc-99m, Rh-103m, Pt-109, In-111 1, Sb-119, I-125, Ho-161, Os-189m and Ir-192. Decay energies of useful beta-particle-emitting nuclides are preferably Dy-152, At-211, Bi-212, Ra-223, Rn-219, Po-215, Bi-21 1, Ac-225, Fr-221, At-217, Bi-213 and Fm-255. Decay energies of useful alpha-particle-emitting radionuclides are preferably 2,000-10,000 keV, more preferably 3,000-8,000 keV, and most preferably 4,000-7,000 keV. Additional potential radioisotopes of use include ^{11}C, ^{13}N, ^{15}0, ^{75}Br, ^{198}Au, ^{224}Ac, ^{126}I, ^{133}I, ^{77}Br, ^{113m}In, ^{95}Ru, ^{97}Ru, ^{103}Ru, ^{105}Ru, ^{107}Hg, ^{203}Hg, ^{121m}Te, ^{122m}Te, ^{125m}Te, ^{165}Tm, ^{167}Tm, ^{168}Tm, ^{197}Pt, ^{109}Pd, ^{105}Rh, ^{142}Pr, ^{143}Pr, ^{161}Tb, ^{166}Ho, ^{199}Au, ^{57}Co, ^{58}Co, ^{51}Cr, ^{59}Fe, ^{75}Se, ^{201}Tl, ^{225}Ac, ^{76}Br, ^{169}Yb, and the like.

16. Radiosensitizers

The anti-PRLR antibody of the invention may be conjugated to at least one radiosensitizer. The term "radiosensitizer," as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to be radiosensitized to electromagnetic radiation and/or to promote the treatment of diseases that are treatable with electromagnetic radiation. Radiosensitizers are agents that make cancer cells more sensitive to radiation therapy, while typically having much less of an effect on normal cells. Thus, the radiosensitizer can be used in combination with a radiolabeled antibody or ADC. The addition of the radiosensitizer can result in enhanced efficacy when compared to treatment with the radiolabeled antibody or antibody fragment alone. Radiosensitizers are described in D. M. Goldberg (ed.), Cancer Therapy with Radiolabeled Antibodies, CRC Press (1995). Examples of radiosensitizers include gemcitabine, 5-fluorouracil, taxane, and cisplatin.

Radiosensitizers may be activated by the electromagnetic radiation of X-rays. Representative examples of X-ray activated radiosensitizers include, but are not limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, E09, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FUdR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same. Alternatively, radiosensitizers may be activated using photodynamic

therapy (PDT). Representative examples of photodynamic radiosensitizers include, but are not limited to, hematoporphyrin derivatives, Photofrin(r), benzoporphyrin derivatives, NPe6, tin etioporphyrin (SnET2), pheoborbide a, bacteriochlorophyll a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

17. Topoisomerase Inhibitors

The anti-PRLR antibody of the invention may be conjugated to at least one topoisomerase inhibitor. Topoisomerase inhibitors are chemotherapy agents designed to interfere with the action of topoisomerase enzymes (topoisomerase I and II), which are enzymes that control the changes in DNA structure by catalyzing then breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle. Representative examples of DNA topoisomerase I inhibitors include, but are not limited to, camptothecins and its derivatives irinotecan (CPT-11, Camptosar, Pfizer, Inc.) and topotecan (Hycamtin, GlaxoSmithKline Pharmaceuticals). Representative examples of DNA topoisomerase II inhibitors include, but are not limited to, amsacrine, daunorubicin, doxotrubicin, epipodophyllotoxins, ellipticines, epirubicin, etoposide, razoxane, and teniposide.

18. Tyrosine Kinase Inhibitors

The anti-PRLR antibody of the invention may be conjugated to at least one tyrosine kinase inhibitor. Tyrosine kinases are enzymes within the cell that function to attach phosphate groups to the amino acid tyrosine. By blocking the ability of protein tyrosine kinases to function, tumor growth may be inhibited. Examples of tyrosine kinases that may be used on the ADCs of the invention include, but are not limited to, Axitinib, Bosutinib, Cediranib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sunitinib, and Vandetanib.

19. Other Agents

Examples of other agents that may be used in the ADCs of the invention include, but are not limited to, abrin (*e.g.* abrin A chain), alpha toxin, Aleurites fordii proteins, amatoxin, crotin, curcin, dianthin proteins, diptheria toxin (*e.g.* diphtheria A chain and nonbinding active fragments of diphtheria toxin), deoxyribonuclease (Dnase), gelonin, mitogellin, modeccin A chain, momordica charantia inhibitor, neomycin, onconase, phenomycin, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), pokeweed antiviral protein, Pseudomonas endotoxin, Pseudomonas exotoxin (*e.g.* exotoxin A chain (from Pseudomonas aeruginosa)), restrictocin, ricin A chain, ribonuclease (Rnase), sapaonaria officinalis inhibitor, saporin, alpha-sarcin, Staphylcoccal enterotoxin-A, tetanus toxin, cisplatin, carboplatin, and oxaliplatin (Eloxatin,

Sanofi Aventis), proteasome inhibitors (*e.g.* PS-341 [bortezomib or Velcade]), HDAC inhibitors (vorinostat (Zolinza, Merck & Company, Inc.)), belinostat, entinostat, mocetinostat, and panobinostat), COX-2 inhibitors, substituted ureas, heat shock protein inhibitors (*e.g.* Geldanamycin and its numerous analogs), adrenocortical suppressants, and the tricothecenes. (See, for example, WO 93/21232). Other agents also include asparaginase (Espar, Lundbeck Inc.), hydroxyurea, levamisole, mitotane (Lysodren, Bristol-Myers Squibb), and tretinoin (Renova, Valeant Pharmaceuticals Inc.).

It should be noted that the aforementioned groups of drug moieties that may be used in the anti-PRLR ADCs of the invention are not exclusive, in that certain examples of drugs may be found in more than one category, *e.g.*, ansamitocins are both mitotic inhibitors and antitumor antibiotics.

All stereoisomers of the above drug moieties are contemplated for the compounds of the invention, *i.e.* any combination of R and S configurations at the chiral carbons of D.

The above agents (*i.e.*, naked agents not conjugated to an antibody) may also be used in combination therapies with the anti-PRLR antibodies described herein. In one embodiment, the anti-PRLR antibodies of the invention are used with any of the foregoing agents in a combination therapy to treat cancer, where the agent is administered prior to, at the same time as, or following administration of the anti-PRLR anitbody to the subject.

B. Linkers

The present invention provides anti-PRLR ADCs for targeted delivery of drugs. The anti-PRLR ADC of the invention comprises an anti-PRLR antibody and a drug, whereby the antibody and drug may be attached through a linker. Thus, in one embodiment, the antibody drug conjugate (ADC) comprises a linker, a cytotoxic drug, and an anti-PRLR antibody. The term "linker" as used herein, refers to a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches an antibody to a drug moiety. An ADC is prepared using a linker having reactive functionality for binding to the antibody and the drug. For example, a cysteine thiol, or an amine. *e.g.*, N-terminus or amino acid side chain such as lysine, of the antibody may form a bond with a functional group of the linker.

The linkers are preferably stable extracellularly. Before transport or delivery into a cell, the ADC is preferably stable and remains intact, *i.e.* the antibody remains linked to the drug moiety. The linkers are stable outside the target cell and may be cleaved at some efficacious rate inside the cell. An effective linker will: (i) maintain the specific binding properties of the antibody; (ii) allow delivery, *e.g.*, intracellular delivery, of the conjugate or drug moiety; and (iii) maintain a cytotoxic, cell-killing effect, a cytostatic effect, or otherwise a therapeutic effect of a

drug moiety. Stability of the ADC may be measured by standard analytical techniques such as mass spectroscopy, HPLC, and the separation/analysis technique LC/MS.

Generally, ADCs comprise an antibody covalently linked to at least one drug unit. The drug unit(s) can be covalently linked directly or via a linker. Covalent attachment of the antibody and the drug moiety requires the linker to have two reactive functional groups, *i.e.* bivalency in a reactive sense. Bivalent linker reagents which are useful to attach two or more functional or biologically active moieties, such as peptides, nucleic acids, drugs, toxins, antibodies, haptens, and reporter groups are known, and methods have been described their resulting conjugates (Hermanson, G. T. (1996) Bioconjugate Techniques; Academic Press: New York, p234-242).

In some embodiments, the ADC has the following formula (formula I):

$$L\text{-}(LU\text{-}D)_p \qquad (I)$$

or a pharmaceutically acceptable salt or solvate thereof; wherein:

L is the antibody, *e.g.*, anti-PRLR antibody of the present invention, and

(LU-D) is a Linker-Drug moiety, wherein:

LU- is a Linker unit (also referred to as a linker), and

-D is a drug moiety having, for example, cytostatic, cytotoxic, or otherwise therapeutic activity against a target cell, *e.g.*, a cell expressing PRLR; and

p is an integer from 1 to 20.

In some embodiments, p ranges from 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments, p ranges from 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In other embodiments, p is 1, 2, 3, 4, 5 or 6. In some embodiments, p is 2, 4, 6 or 8.

In some embodiments, the -D moieties are the same. In yet another embodiment, the -D moieties are different.

In some embodiments, the ADC has the following formula (II):

$$L\text{-}(A_a\text{-}W_w\text{—}Y_y\text{-}D)_p \qquad (II)$$

or a pharmaceutically acceptable salt or solvate thereof, wherein:

L is the antibody, *e.g.*, anti-PRLR antibody, and

$-A_a-W_w—Y_y-$ is a Linker unit (LU), wherein:

-A- is an optional Stretcher unit,

a is 0 or 1,

each —W— is independently an Amino Acid unit (or in some embodiments, a Glucuronide unit, See also US Publication No. 2012/0107332 A1),

w is an integer ranging from 0 to 12,

—Y— is a self-immolative spacer unit,

y is 0, 1 or 2;

-D is a drug unit having, for example, cytostatic, cytotoxic, or otherwise therapeutic activity against the target cell, *e.g.*, cell expressing PRLR; and

p is an integer from 1 to 20.

In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0, 1 or 2. In some embodiments, a is 0 or 1, w is 0 or 1, and y is 0 or 1. In some embodiments, p ranges from 1 to 10, 1 to 9, 1 to 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, or 1 to 2. In some embodiments, p ranges from 2 to 8, 2 to 7, 2 to 6, 2 to 5, 2 to 4 or 2 to 3. In other embodiments, p is 1, 2, 3, 4, 5 or 6. In some embodiments, p is 2 or 4. In some embodiments, when w is not zero, y is 1 or 2. In some embodiments, when w is 1 to 12, y is 1 or 2. In some embodiments, w is 2 to 12 and y is 1 or 2. In some embodiments, a is 1 and w and y are 0.

For compositions comprising a plurality of antibodies, the drug loading is represented by p, the average number of drug molecules per antibody. Drug loading may range from 1 to 20 drugs (D) per antibody. The average number of drugs per antibody in preparation of conjugation reactions may be characterized by conventional means such as mass spectroscopy, ELISA assay, and HPLC. The quantitative distribution of ADCs in terms of p may also be determined. In some instances, separation, purification, and characterization of homogeneous ADCs where p is a certain value from ADCs with other drug loadings may be achieved by means such as reverse phase HPLC or electrophoresis. In exemplary embodiments, p is from 2 to 8.

The generation of ADCs can be accomplished by any technique known to the skilled artisan. ADCs of the invention comprise anti-PRLR antibodies described herein, a drug, and optionally a linker that joins the drug and the antibody. In one embodiment, the antibody is an anti-PRLR antibody comprising at least one variable region set forth in SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO:48; SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID NO: 54; SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60; SEQ ID NO: 61; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75; SEQ ID NO: 76; SEQ ID NO: 78; SEQ ID NO: 82; SEQ ID NO: 83; SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 91; SEQ ID NO: 95; SEQ ID NO: 96; SEQ ID NO: 103; SEQ ID NO: 104; SEQ ID NO: 105; SEQ ID NO: 106; SEQ ID NO: 107; SEQ ID NO: 108; SEQ ID NO: 109; SEQ ID NO: 110; SEQ ID NO: 111; SEQ ID NO: 112; SEQ ID NO: 113; SEQ ID NO: 114; SEQ ID NO: 115; SEQ ID NO: 116; SEQ ID NO: 117; SEQ ID NO: 118; SEQ ID NO: 119; SEQ ID NO: 120, SEQ ID NO: 121; SEQ ID NO: 122 and SEQ ID NO: 123. A number of different reactions are available for covalent attachment of drugs and linkers to antibodies. This may be accomplished by reaction of the amino acid residues of the antibody, including the amine groups of lysine, the free carboxylic acid groups of glutamic and aspartic acid, the sulfhydryl groups of cysteine and the various moieties of the aromatic amino acids. One of the most commonly used non-specific methods of covalent attachment is the carbodiimide

reaction to link a carboxy (or amino) group of a compound to amino (or carboxy) groups of the antibody. Additionally, bifunctional agents such as dialdehydes or imidoesters have been used to link the amino group of a compound to amino groups of an antibody. Also available for attachment of drugs to antibodies is the Schiff base reaction. This method involves the periodate oxidation of a drug that contains glycol or hydroxy groups, thus forming an aldehyde which is then reacted with the binding agent. Attachment occurs via formation of a Schiff base with amino groups of the antibody. Isothiocyanates can also be used as coupling agents for covalently attaching drugs to antibodies. Other techniques are known to the skilled artisan and within the scope of the present invention.

In certain embodiments, an intermediate, which is the precursor of the linker, is reacted with the drug under appropriate conditions. In certain embodiments, reactive groups are used on the drug or the intermediate. The product of the reaction between the drug and the intermediate, or the derivatized drug, is subsequently reacted with the anti-PRLR antibody under appropriate conditions. The synthesis and structure of exemplary linkers, stretcher units, amino acid units, self-immolative spacer units are described in U.S. Patent Application Publication Nos. 20030083263, 20050238649 and 20050009751, each if which is incorporated herein by reference in its entirety. Examples of linkers are provided below.

In a preferred embodiment, the linker is not substantially sensitive to the extracellular environment. As used herein, "not substantially sensitive to the extracellular environment," in the context of a linker, means that no more than about 20%, typically no more than about 15%, more typically no more than about 10%, and even more typically no more than about 5%, no more than about 3%, or no more than about 1% of the linkers, in a sample of antibody-drug conjugate compound, are cleaved when the ADC presents in an extracellular environment (*e.g.*, in plasma). Whether a linker is not substantially sensitive to the extracellular environment can be determined, for example, by incubating with plasma the antibody-drug conjugate compound for a predetermined time period (*e.g.*, 2, 4, 8, 16, or 24 hours) and then quantitating the amount of free drug present in the plasma.

In some embodiments, the linker is cleavable under intracellular conditions, such that cleavage of the linker releases the drug unit from the antibody in the intracellular environment. In some embodiments, the cleavable linker is pH-sensitive, *i.e.*, sensitive to hydrolysis at certain pH values. Typically, the pH-sensitive linker is hydrolyzable under acidic conditions. For example, an acid-labile linker that is hydrolyzable in the lysosome (*e.g.*, a hydrazone, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like) can be used. (See, *e.g.*, U.S. Pat. Nos. 5,122,368; 5,824,805; 5,622,929; Dubowchik and Walker, 1999, *Pharm. Therapeutics* 83:67-123; Neville *et al.*, 1989, *Biol. Chem.* 264:14653-14661.) Such linkers are relatively stable under neutral pH conditions, such as those in the blood, but are

unstable at below pH 5.5 or 5.0, the approximate pH of the lysosome. In certain embodiments, the hydrolyzable linker is a thioether linker (such as, *e.g.*, a thioether attached to the therapeutic agent via an acylhydrazone bond (see, *e.g.*, U.S. Pat. No. 5,622,929).

In other embodiments, the linker is cleavable under reducing conditions (*e.g.*, a disulfide linker). A variety of disulfide linkers are known in the art, including, for example, those that can be formed using SATA (N-succinimidyl-5-acetylthioacetate), SPDP (N-succinimidyl-3-(2-pyridyldithio)propionate), SPDB (N-succinimidyl-3-(2-pyridyldithio)butyrate) and SMPT (N-succinimidyloxycarbonyl-alpha-methyl-alpha-(2-pyridyl-dithio)toluene), SPDB and SMPT. (See, *e.g.*, Thorpe *et al.*, 1987, Cancer Res. 47:5924-5931; Wawrzynczak *et al.*, In *Immunoconjugates: Antibody Conjugates in Radioimagery and Therapy of Cancer* (C. W. Vogel ed., Oxford U. Press, 1987. See also U.S. Pat. No. 4,880,935.).

In some embodiments, the linker is cleavable by a cleaving agent, *e.g.*, an enzyme, that is present in the intracellular environment (*e.g.*, within a lysosome or endosome or caveolea). The linker can be, *e.g.*, a peptidyl linker that is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. In some embodiments, the peptidyl linker is at least two amino acids long or at least three amino acids long. Cleaving agents can include cathepsins B and D and plasmin, all of which are known to hydrolyze dipeptide drug derivatives resulting in the release of active drug inside target cells (see, *e.g.*, Dubowchik and Walker, 1999, Pharm. Therapeutics 83:67-123). Most typical are peptidyl linkers that are cleavable by enzymes that are present in PRLR-expressing cells. Examples of such linkers are described, *e.g.*, in U.S. Pat. No. 6,214,345, incorporated herein by reference in its entirety and for all purposes. In a specific embodiment, the peptidyl linker cleavable by an intracellular protease is a Val-Cit linker or a Phe-Lys linker (see, *e.g.*, U.S. Pat. No. 6,214,345, which describes the synthesis of doxorubicin with the val-cit linker). One advantage of using intracellular proteolytic release of the therapeutic agent is that the agent is typically attenuated when conjugated and the serum stabilities of the conjugates are typically high.

In other embodiments, the linker of the ADC of the invention is a malonate linker (Johnson *et al.*, 1995, Anticancer Res. 15:1387-93), a maleimidobenzoyl linker (Lau *et al.*, 1995, *Bioorg-Med-Chem.* 3(10):1299-1304), or a 3'-N-amide analog (Lau *et al.*, 1995, *Bioorg-Med-Chem.* 3(10): 1305-12).

In yet other embodiments, the linker unit is not cleavable and the drug is released, for example, by antibody degradation. See U.S. Publication No. 20050238649 incorporated by reference herein in its entirety. An ADC comprising a non-cleavable linker may be designed such that the ADC remains substantially outside the cell and interacts with certain receptors on a target cell surface such that the binding of the ADC initiates (or prevents) a particular cellular signaling pathway.

In some embodiments, the linker unit is substantially hydrophilic linker (*e.g.*, PEG4Mal and sulfo-SPDB). A hydrophilic linker may be used to prevent the drug from being pumped out of resistant cancer cells through MDR (multiple drug resistance) or functionally similar transporters.

In other embodiments, upon cleavage, the linker functions to directly or indirectly inhibit cell growth and/or cell proliferation. For example, in some embodiments, the linker, upon cleavage, can function as an intercalating agent, thereby inhibiting macromolecular biosynthesis (*e.g.* DNA replication, RNA transcription, and/or protein synthesis).

In other embodiments, the linker is designed to facilitate bystander killing (the killing of neighboring cells) through diffusion of the linker unit-drug and/or the drug alone to neighboring cells. In other, embodiments, the linker promotes cellular internalization.

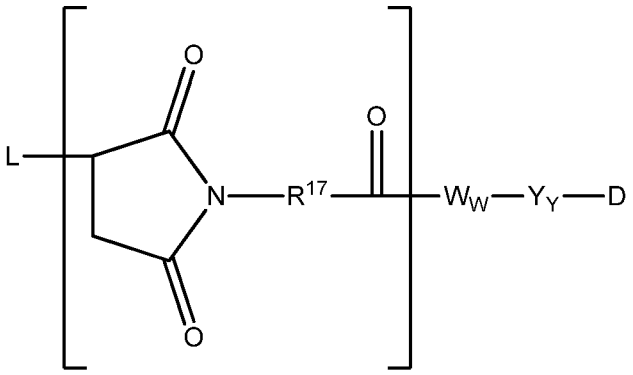
The presence of a sterically hindered disulfide can increase the stability of a particular disulfide bond, enhancing the potency of the ADC. Thus, in one embodiment, the linker includes a sterically hindered disulfide linkage. A sterically hindered disulfide refers to a disulfide bond present within a particular molecular environment, wherein the environment is characterized by a particular spatial arrangement or orientation of atoms, typically within the same molecule or compound, which prevents or at least partially inhibits the reduction of the disulfide bond. Thus, the presence of bulky (or sterically hindering) chemical moieties and/or bulky amino acid side chains proximal to the disulfide bond prevents or at least partially inhibits the disulfide bond from potential interactions that would result in the reduction of the disulfide bond.

Notably, the aforementioned linker types are not mutually exclusive. For example, in one embodiment, the linker used in the ADC of the invention is a non-cleavable linker that promotes cellular internalization.

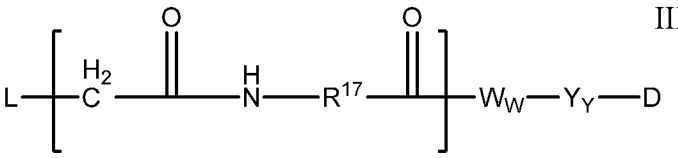
As described in Formula II above, in some embodiments the anti-PRLR ADC of the invention includes a stretcher unit. The stretcher unit (A), when present, is capable of linking an anitbody to an amino acid unit (—W—), if present, to a spacer unit (—Y—), if present; or to a drug (-D) (see Formula II). Useful functional groups that can be present on the anti-PRLR antibodies described herein, either naturally or via chemical manipulation include, but are not limited to, sulfhydryl, amino, hydroxyl, the anomeric hydroxyl group of a carbohydrate, and carboxyl. Suitable functional groups are sulfhydryl and amino. In one example, sulfhydryl groups can be generated by reduction of the intramolecular disulfide bonds of an anti-PRLR antibody. In another embodiment, sulfhydryl groups can be generated by reaction of an amino group of a lysine moiety of an anti-PRLR antibody with 2-iminothiolane (Traut's reagent) or other sulfhydryl generating reagents. In certain embodiments, the anti-PRLR antibody is a recombinant antibody and is engineered to carry one or more lysine moieties. In certain other

embodiments, the recombinant anti-PRLR antibody is engineered to carry additional sulfhydryl groups, *e.g.*, additional cysteines.

In one embodiment, the stretcher unit forms a bond with a sulfur atom of the antibody. The sulfur atom can be derived from a sulfhydryl group of an antibody. Representative stretcher units of this embodiment are depicted within the square brackets of Formulas IIIa and IIIb as shown below,



IIIa

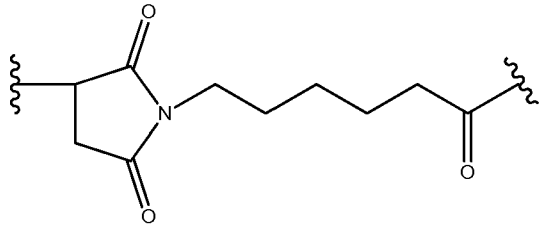


IIIb

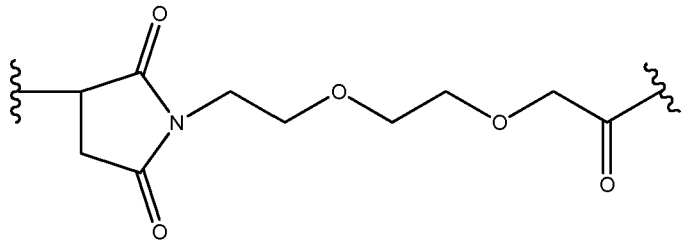
wherein L-, —W—, —Y—, -D, w and y are as defined above, and R^{17} is selected from —C_1-C_{10} alkylene-, —C_1-C_{10} alkenylene-, —C_1-C_{10} alkynylene-, carbocyclo-, —O—(C_1-C_8 alkylene)-, O—(C_1-C_8 alkenylene)-, —O—(C_1-C_8 alkynylene)-, -arylene-, —C_1-C_{10} alkylene-arylene-, —C_2-C_{10} alkenylene-arylene, —C_2-C_{10} alkynylene-arylene, arylene-C_1-C_{10} alkylene-, -arylene-C_2-C_{10} alkenylene-, -arylene-C_2-C_{10} alkynylene-, —C_1-C_{10} alkylene-(carbocyclo)-, —C_2-C_{10} alkenylene-(carbocyclo)-, C_2-C_{10} alkynylene-(carbocyclo)-, -(carbocyclo)-C_1-C_{10} alkylene-, -(carbocyclo)-C_2-C_{10} alkenylene-, -(carbocyclo)-C_2-C_{10} alkynylene, -heterocyclo-, —C_1-C_{10} alkylene-(heterocyclo)-, —C_2-C_{10} alkenylene-(heterocyclo)-, —C_2-C_{10} alkynylene-(heterocyclo)-, -(heterocyclo)-C_1-C_{10} alkylene-, -(heterocyclo)-C_2-C_{10} alkenylene-, -(heterocyclo)-C_1-C_{10} alkynylene-, —$(CH_2CH_2O)_r$—, or —$(CH_2CH_2O)_r$—CH_2—, and r is an integer ranging from 1-10, wherein said alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynyklene, aryl, carbocycle, carbocyclo, heterocyclo, and arylene radicals, whether alone or as part of another group, are optionally substituted. In some embodiments, said alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynyklene, aryl, carbocyle, carbocyclo, heterocyclo, and arylene radicals, whether alone or as part of another group, are unsubstituted. In some embodiments, R^{17} is selected from —C_1-C_{10} alkylene-, -carbocyclo-, —O—(C_1-C_8 alkylene)-, -arylene-, —C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, —C_1-C_{10} alkylene-(carbocyclo)-, -(carbocyclo)-C_1-C_{10} alkylene-, —C_3-C_8

heterocyclo-, —C_1-C_{10} alkylene-(heterocyclo)-, -(heterocyclo)-C_1-C_{10} alkylene-, —$(CH_2CH_2O)_r$—, and — $(CH_2CH_2O)_r$ — CH_2—; and r is an integer ranging from 1-10, wherein said alkylene groups are unsubstituted and the remainder of the groups are optionally substituted.

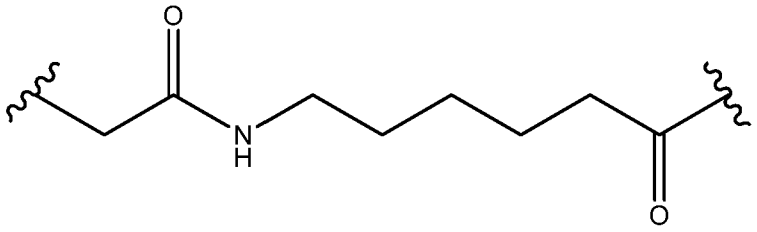
An illustrative stretcher unit is that of Formula IIIa wherein R^{17} is —$(CH_2)_5$—as depicted below (see also U.S. 8,309,093).



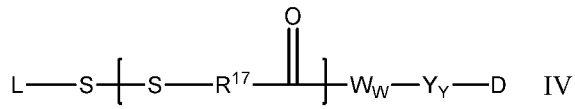
Another illustrative stretcher unit is that of Formula IIIa wherein R^{17} is —$(CH_2CH_2O)_r$—CH_2—; and r is 2, as depicted below (see also U.S. 8,309,093).



Another illustrative stretcher unit is that of Formula IIIa wherein R^{17} is arylene- or arylene-C_1-C_{10} alkylene-. In some embodiments, the aryl group is an unsubstituted phenyl group. Still, another illustrative stretcher unit is that of Formula IIIb wherein R^{17} is —$(CH_2)_5$—, as depicted below (see also U.S. 8,309,093).

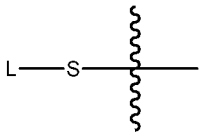


In certain embodiments, the stretcher unit is linked to the anti-PRLR antibody via a disulfide bond between a sulfur atom of the anti-PRLR antibody unit and a sulfur atom of the stretcher unit. A representative stretcher unit of this embodiment is depicted within the square brackets of Formula IV (See below, and see also U.S. 8,309,093)., wherein R^{17}, L-, —W—, —Y—, -D, w, and y are as defined above.

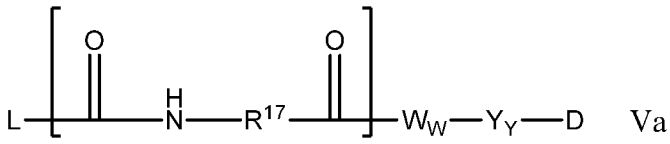


IV

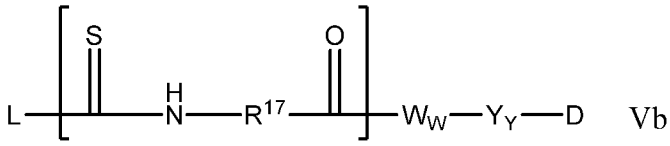
It should be noted that the S moiety in the formula shown below (see also U.S. 8,309,093) refers to a sulfur atom of the antibody, unless otherwise indicated by the context.



In yet other embodiments, the stretcher contains a reactive site that can form a bond with a primary or secondary amino group of an antibody. Examples of these reactive sites include but are not limited to, activated esters such as succinimide esters, 4 nitrophenyl esters, pentafluorophenyl esters, tetrafluorophenyl esters, anhydrides, acid chlorides, sulfonyl chlorides, isocyanates and isothiocyanates. Representative stretcher units of this embodiment are depicted within the square brackets of Formulas Va and Vb (See below (see also U.S. 8,309,093)), wherein R^{17}, L-, —W—, —Y—, -D, w, and y are as defined above.

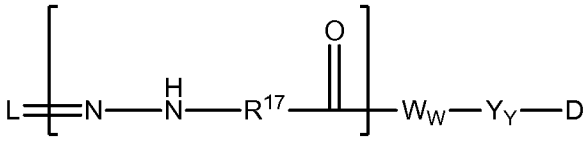


Va

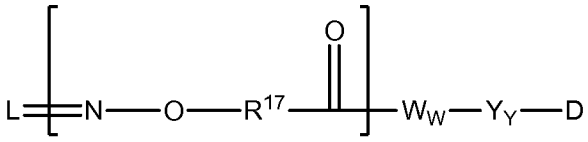


Vb

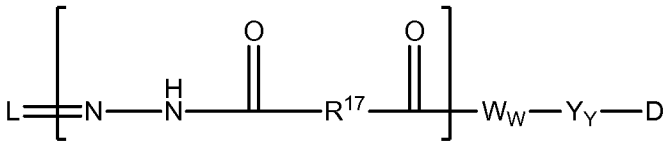
In some embodiments, the stretcher contains a reactive site that is reactive to a modified carbohydrate's (—CHO) group that can be present on an antibody. For example, a carbohydrate can be mildly oxidized using a reagent such as sodium periodate and the resulting (—CHO) unit of the oxidized carbohydrate can be condensed with a Stretcher that contains a functionality such as a hydrazide, an oxime, a primary or secondary amine, a hydrazine, a thiosemicarbazone, a hydrazine carboxylate, and an arylhydrazide such as those described by Kaneko *et al.*, 1991, *Bioconjugate Chem.* 2:133-41. Representative Stretcher units of this embodiment are depicted within the square brackets of Formulas VIa, VIb, and VIc (See below (see also U.S. 8,309,093), wherein —R^{17}-, L-, —W—, —Y—, -D, w and y are as defined as above.



VIa

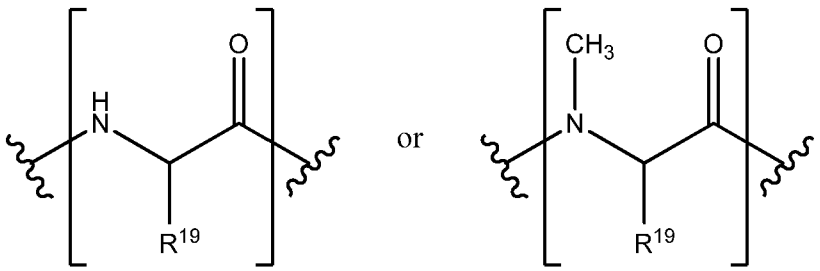


VIb

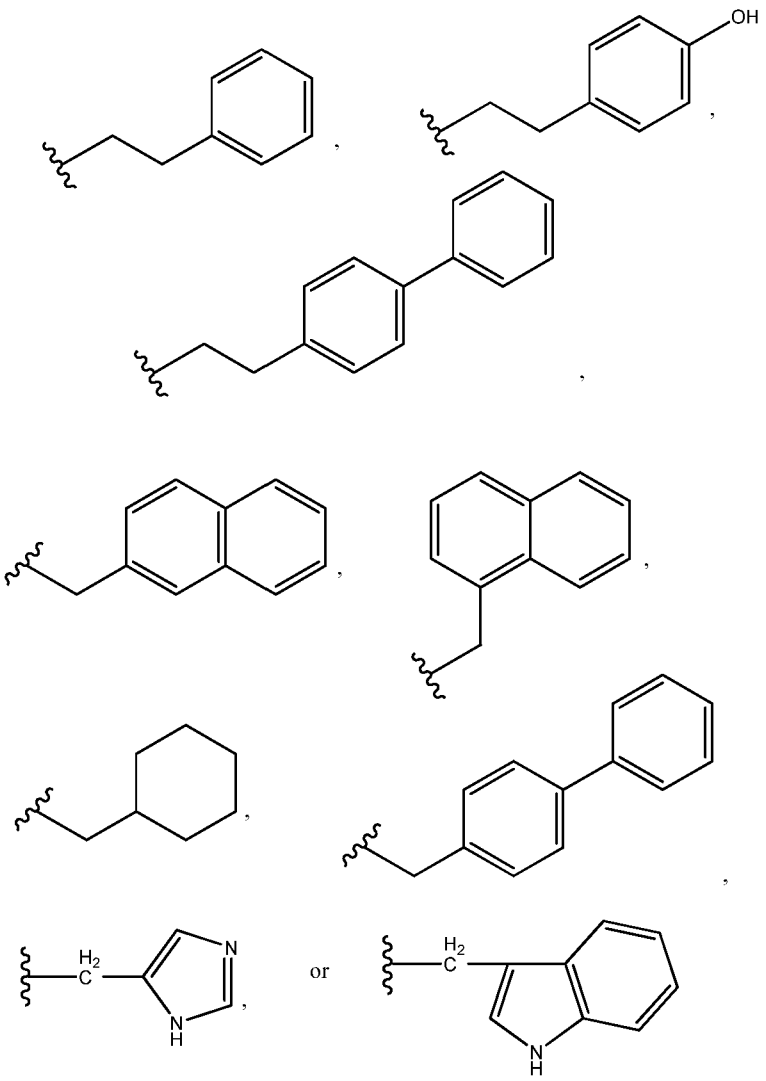


VIc

The amino acid unit (—W—), when present, links the stretcher unit to the spacer unit if the spacer unit is present, links the stretcher unit to the drug moiety if the spacer unit is absent, and links the antibody unit to the drug unit if the stretcher unit and spacer unit are absent. W_w— can be, for example, a monopeptide, dipeptide, tripeptide, tetrapeptide, pentapeptide, hexapeptide, heptapeptide, octapeptide, nonapeptide, decapeptide, undecapeptide or dodecapeptide unit. Each —W— unit independently has the formula denoted below (see also U.S. 8,309,093) in the square brackets, and w is an integer ranging from 0 to 12,

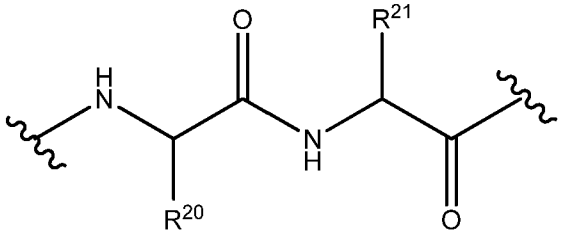


wherein R^{19} is hydrogen, methyl, isopropyl, isobutyl, sec-butyl, benzyl, p-hydroxybenzyl, —CH_2OH, —$CH(OH)CH_3$, —$CH_2CH_2SCH_3$, —CH_2CONH_2, —CH_2COOH, —$CH_2CH_2CONH_2$, --CH_2CH_2COOH, --$(CH_2)_3NHC(=NH)NH_2$, —$(CH_2)_3NH_2$, —$(CH_2)_3NHCOCH_3$, —$(CH_2)_3NHCHO$, —$(CH_2)_4NHC(=NH)NH_2$, —$(CH_2)_4NH_2$, —$(CH_2)_4NHCOCH_3$, —$(CH_2)_4NHCHO$, —$(CH_2)_3NHCONH_2$, —$(CH_2)_4NHCONH_2$, —$CH_2CH_2CH(OH)CH_2NH_2$, 2-pyridylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, phenyl, cyclohexyl, and other non-limiting representative R^{19} groups, as depicted below.



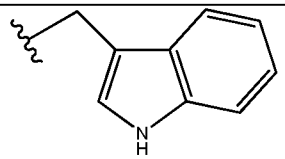
In some embodiments, the amino acid unit can be enzymatically cleaved by one or more enzymes, including a cancer or tumor-associated protease, to liberate the drug (-D), which in one embodiment is protonated *in vivo* upon release to provide a drug.

In certain embodiments, the amino acid unit can comprise natural amino acids. In other embodiments, the amino acid unit can comprise non-natural amino acids. Illustrative W_w units are represented by formula (VII) (as depicted below (see also U.S. 8,309,093),

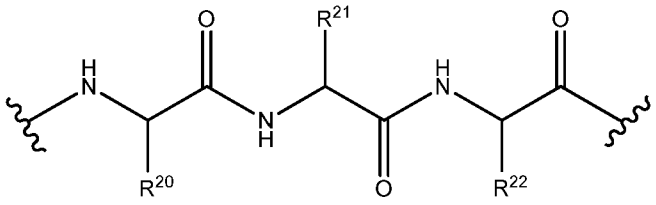


VII

wherein R^{20} and R^{21} are as depicted below;

R^{20}	R^{21}
Benzyl	$(CH_2)_4NH_2$;
Methyl	$(CH_2)_4NH_2$;
Isopropyl	$(CH_2)_4NH_2$;
Isopropyl	$(CH_2)_3NHCONH_2$;
Benzyl	$(CH_2)_3NHCONH_2$;
Isobutyl	$(CH_2)_3NHCONH_2$;
Sec-butyl	$(CH_2)_3NHCONH_2$;
	$(CH_2)_3NHCONH_2$;
Benzyl	Methyl;
Benzyl	$(CH_2)_3NHC(=NH)NH_2$;

formula (VIII) (as depicted below (see also U.S. 8,309,093),

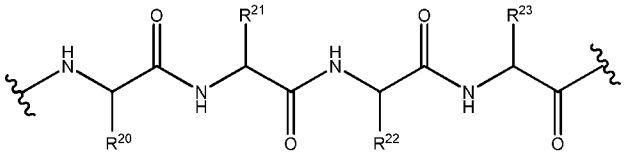


VIII

wherein R^{20}, R^{21}, and R^{22} are as depicted below;

R^{20}	R^{21}	R^{22}
Benzyl	Benzyl	$(CH_2)_4NH_2$;
Isopropyl	Benzyl	$(CH_2)_4NH_2$;
H	Benzyl	$(CH_2)_4NH_2$;

and formula (IX) (as depicted below (see also U.S. 8,309,093),



IX

wherein R^{20}, R^{21}, R^{22}, and R^{23} are as depicted below:

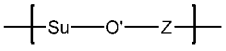
R^{20}	R^{21}	R^{22}	R^{23}
H	Benzyl	Isobutyl	H
Methyl	Isobutyl	Methyl	Isobutyl

Exemplary amino acid units include, but are not limited to, units of formula VII where: R^{20} is benzyl and R^{21} is —$(CH_2)_4NH_2$; R^{20} is isopropyl and R^{21} is —$(CH_2)_4NH_2$; or R^{20} is isopropyl and R^{21} is —$(CH_2)_3NHCONH_2$. Another exemplary amino acid unit is a unit of formula VIII wherein R^{20} is benzyl, R^{21} is benzyl, and R^{22} is —$(CH_2)_4NH_2$.

Useful —W_W— units can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzyme, for example, a tumor-associated protease. In one embodiment, a —W_W— unit is that whose cleavage is catalyzed by cathepsin B, C and D, or a plasmin protease. In one embodiment, —W_W— is a dipeptide, tripeptide, tetrapeptide or pentapeptide. When R^{19}, R^{20}, R^{21}, R^{22} or R^{23} is other than hydrogen, the carbon atom to which R^{19}, R^{20}, R^{21}, R^{22} or R^{23} is attached is chiral. Each carbon atom to which R^{19}, R^{20}, R^{21}, R^{22} or R^{23} is attached is independently in the (S) or (R) configuration.

In one embodiment of the amino acid unit, the amino acid unit is valine-citrulline (vc or val-cit). In another aspect, the amino acid unit is phenylalanine-lysine (*i.e.*, fk). In yet another aspect of the amino acid unit, the amino acid unit is N-methylvaline-citrulline. In yet another aspect, the Amino Acid unit is 5-aminovaleric acid, homo phenylalanine lysine, tetraisoquinolinecarboxylate lysine, cyclohexylalanine lysine, isonepecotic acid lysine, beta-alanine lysine, glycine serine valine glutamine and isonepecotic acid.

Alternatively, in some embodiments, —W— is a glucuronide unit that links a stretcher unit to a spacer unit if the stretcher and spacer units are present, links a stretcher unit to the drug moiety if the spacer unit is absent, and links the linker unit to the drug if the stretcher and spacer units are absent. The glucuronide unit includes a site that can be cleaved by a β-glucuronidase enzyme (See also US 2012/0107332 A1). In some embodiments, the glucuronide unit comprises a sugar moiety (Su) linked via a glycoside bond (—O'—) to a self-immolative group (Z) of the formula as depicted below (See also US 2012/0107332, incorporated by reference herein).



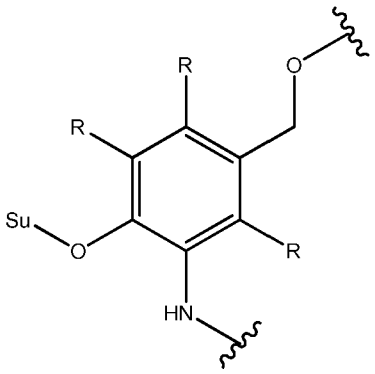
The glycosidic bond (—O'—) is typically a β-glucuronidase-cleavage site, such as a bond cleavable by human, lysosomal β-glucuronidase. In the context of a glucuronide unit, the term "self-immolative group" refers to a di- or tri-functional chemical moiety that is capable of covalently linking together two or three spaced chemical moieties (*i.e.*, the sugar moiety (via a glycosidic bond), a drug unit (directly or indirectly via a spacer unit), and, in some embodiments,

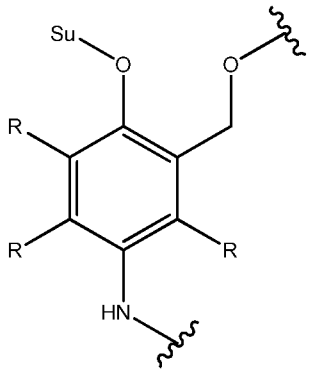
a linker (directly or indirectly via a stretcher unit) into a stable molecule. The self-immolative group will spontaneously separate from the first chemical moiety (*e.g.*, the spacer or drug unit) if its bond to the sugar moiety is cleaved.

In some embodiments, the sugar moiety (Su) is cyclic hexose, such as a pyranose, or a cyclic pentose, such as a furanose. In some embodiments, the pyranose is a glucuronide or hexose. The sugar moiety is usually in the β-D conformation. In a specific embodiment, the pyranose is a β-D-glucuronide moiety (*i.e.*, β-D-glucuronic acid linked to the self-immolative group —Z— via a glycosidic bond that is cleavable by β-glucuronidase). In some embodiments, the sugar moiety is unsubstituted (*e.g.*, a naturally occurring cyclic hexose or cyclic pentose). In other embodiments, the sugar moiety can be a substituted β-D-glucuronide (*i.e.*, glucuronic acid substituted with one or more group, such hydrogen, hydroxyl, halogen, sulfur, nitrogen or lower alkyl.

In some embodiments, the self-immolative group Z is a p-aminobenzyl alcohol (PAB) unit, as further described herein. Other suitable self immolative groups are known in the art.

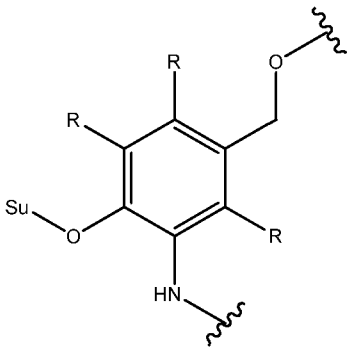
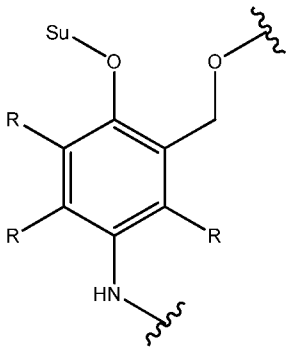
In some embodiments, the glucuronide unit has one of the formulas as depicted below (See also US 2012/0107332 A1),





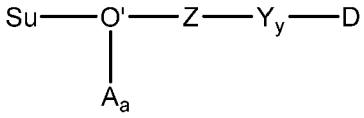
wherein Su is the sugar moiety, the glycosidic bond comprises the oxygen bond between Su and the self immolative group Z, and each R is independently hydrogen, halo (*e.g.*, chloro, bromo, fluoro, etc), —CN, —NO_2, or other electron withdrawing or donating group, provided that the Glucuronide unit (and Z in particular) undergoes self-immolation upon cleavage of the glycosidic bond. In some embodiments, each R is independently hydrogen, halo (*e.g.*, chloro, bromo, fluoro, etc), —CN or —NO_2.

In some embodiments, the glucuronide unit has one of the formulas as depicted below (See also US 2012/0107332 A1),

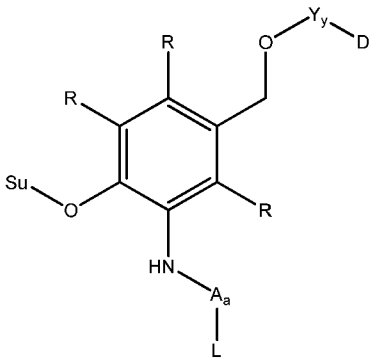
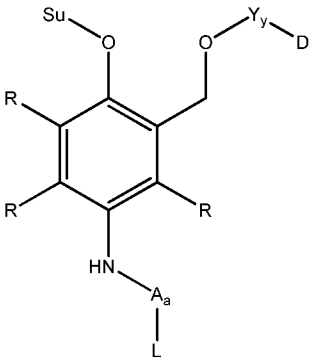
wherein Su is the Sugar moiety, the glycosidic bond (—O'—) comprises the oxygen bond between Su and the self immolative group Z, and each R is independently hydrogen.

In some embodiments, the self-immolative group (Z) is covalently linked to the sugar moiety, to the drug (directly or indirectly via the spacer unit(s)), and to the linker (directly or indirectly via the stretcher unit(s)). In some embodiments, a Drug Linker conjugate has the formula as depicted below (See also US 2012/0107332 A1),

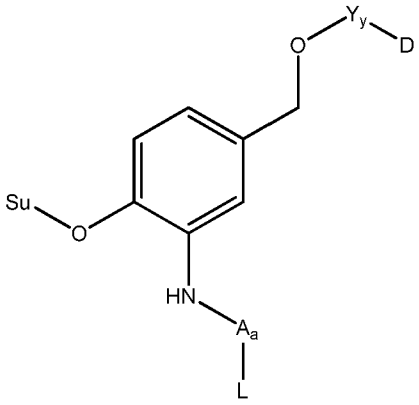


wherein Su, O', Z, Y, y, D, A and a are defined herein. Typically from 1 to 20 of such drug-linker conjugates can be linked to a linker.

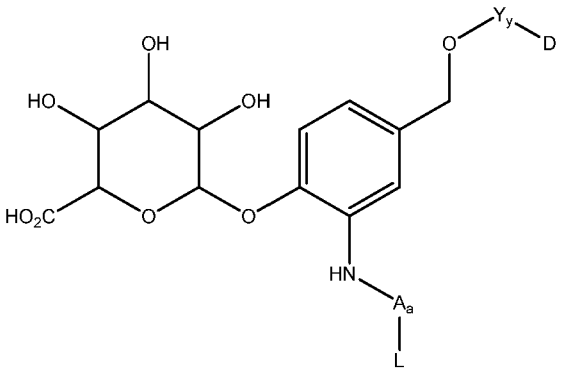
In some embodiments, an ADC comprising the glucuronide unit has one of the formulas as depicted below (See also US 2012/0107332 A1), wherein Su, Y, y, D, A, a, and L are defined as described herein.

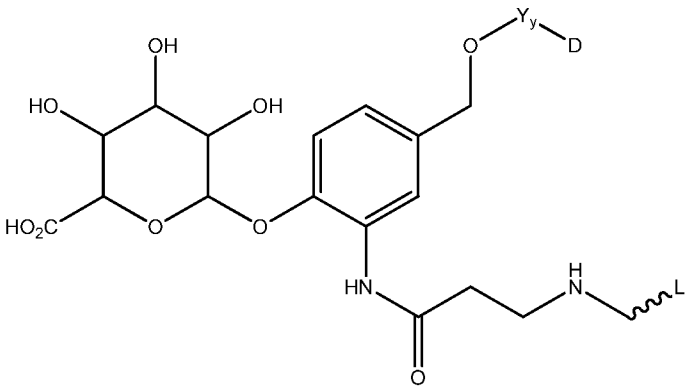
In some embodiments, an ADC comprising the glucuronide unit has the formula as depicted below (See also US 2012/0107332 A1), wherein Y, y, D, A, a, and L are defined herein.



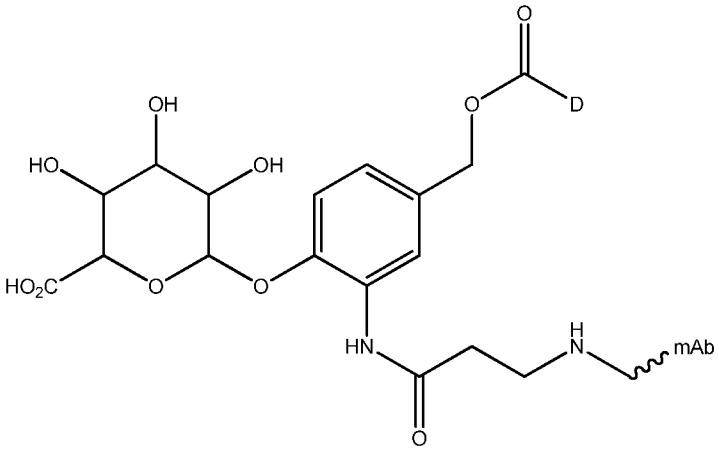
In some embodiments, an ADC comprising the Glucuronide unit has the formula as depicted below (See also US 2012/0107332 A1), wherein Y, y, D and L are defined as described herein.



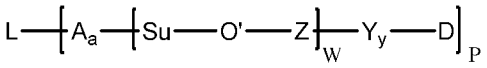
In some embodiments, an ADC comprising the Glucuronide unit has the formula as depicted below (See also US 2012/0107332 A1), wherein Y, y, D and L are defined as described herein.



In some embodiments, an ADC comprising the Glucuronide unit has the formula as depicted below (See also US 2012/0107332 A1), wherein D is as described herein and mAb is a monoclonal antibody.

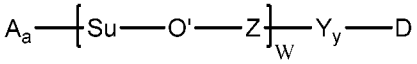


In another group of embodiments, the linker is linked (directly or indirectly) to the sugar moiety (Su), which is linked to the self-immolative group (Z) which is linked (directly or indirectly) to the drug, according to the formula as depicted below (See also US 2012/0107332 A1), wherein A, a, Su, O', Z, w, Y, y, D and L are defined as described herein.



For example, the sugar moiety (Su) can be linked directly to the anitbody or indirectly via a stretcher unit. The self-immolative group (Z) can be linked directly to the drug or indirectly via a spacer unit.

In related embodiments, a drug-linker compound has the following formula as depicted below (See also US 2012/0107332 A1), wherein A, a, Su, O', Z, w, Y, y and D are defined herein.

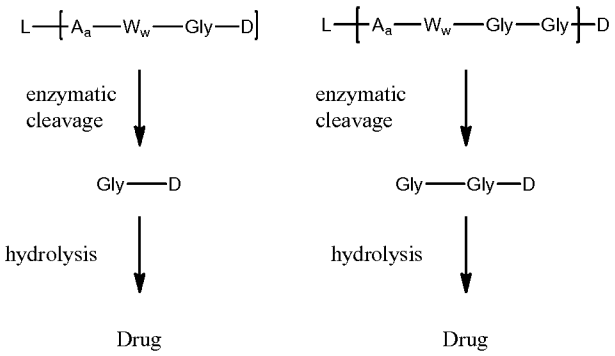


Typically from 1 to 20 of such drug-linker compounds can be linked to an antibody.

The spacer unit (—Y—), when present, links an Amino Acid unit (or Glucuronide unit, See also US 2012/0107332 A1 to the Drug unit when an Amino Acid unit is present. Alternately, the Spacer unit links the Stretcher unit to the Drug unit when the Amino Acid unit is absent. The Spacer unit also links the Drug unit to the Antibody unit when both the Amino Acid unit and Stretcher unit are absent.

Spacer units are of two general types: non self-immolative or self-immolative. A non self-immolative Spacer unit is one in which part or all of the spacer unit remains bound to the drug moiety after cleavage, particularly enzymatic, of an amino acid unit (or glucuronide unit) from the antibody-drug conjugate. Examples of a non self-immolative spacer unit include, but are not limited to a (glycine-glycine) Spacer unit and a glycine spacer unit (both depicted in Scheme 1 below (see also U.S. 8,309,093)).

Scheme 1



When a conjugate containing a glycine-glycine Spacer unit or a glycine Spacer unit undergoes enzymatic cleavage via an enzyme (*e.g.*, a tumor-cell associated-protease, a cancer-cell-associated protease or a lymphocyte-associated protease), a glycine-glycine-drug moiety or a glycine-drug moiety is cleaved from L-A_a-W_w-. In one embodiment, an independent hydrolysis reaction takes place within the target cell, cleaving the glycine-drug moiety bond and liberating the drug.

In some embodiments, a non self-immolative spacer unit (—Y—) is -Gly-. In some embodiments, a non self-immolative spacer unit (—Y—) is -Gly-Gly-.

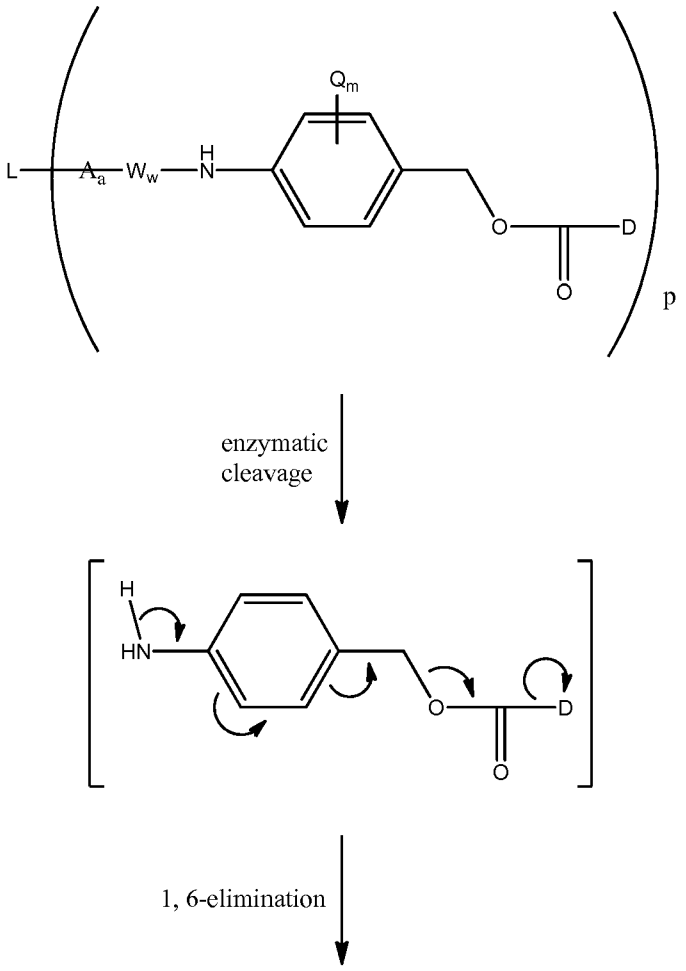
In one embodiment, a drug-linker conjugate is provided in which the spacer unit is absent (y=0), or a pharmaceutically acceptable salt or solvate thereof.

Alternatively, a conjugate containing a self-immolative spacer unit can release -D. As used herein, the term "self-immolative spacer" refers to a bifunctional chemical moiety that is capable of covalently linking together two spaced chemical moieties into a stable tripartite molecule. It will spontaneously separate from the second chemical moiety if its bond to the first moiety is cleaved.

In some embodiments, —Y_y— is a p-aminobenzyl alcohol (PAB) unit whose phenylene portion is substituted with Q_m wherein Q is –C_1-C_8 alkyl, —C_1-C_8 alkenyl, —C_1-C_8 alkynyl, —O—(C_1-C_8 alkyl), —O—(C_1-C_8 alkenyl), —O—(C_1-C_8 alkynyl), -halogen, -nitro or -cyano; and m is an integer ranging from 0-4. The alkyl, alkenyl and alkynyl groups, whether alone or as part of another group, can be optionally substituted.

In some embodiments, —Y— is a PAB group that is linked to —W_w— via the amino nitrogen atom of the PAB group, and connected directly to -D via a carbonate, carbamate or ether group. Without being bound by any particular theory or mechanism, Scheme 2 below (see also U.S. 8,309,093) depicts a possible mechanism of drug release of a PAB group which is attached directly to -D via a carbamate or carbonate group as described by Toki *et al.*, 2002, J. Org. Chem. 67:1866-1872.

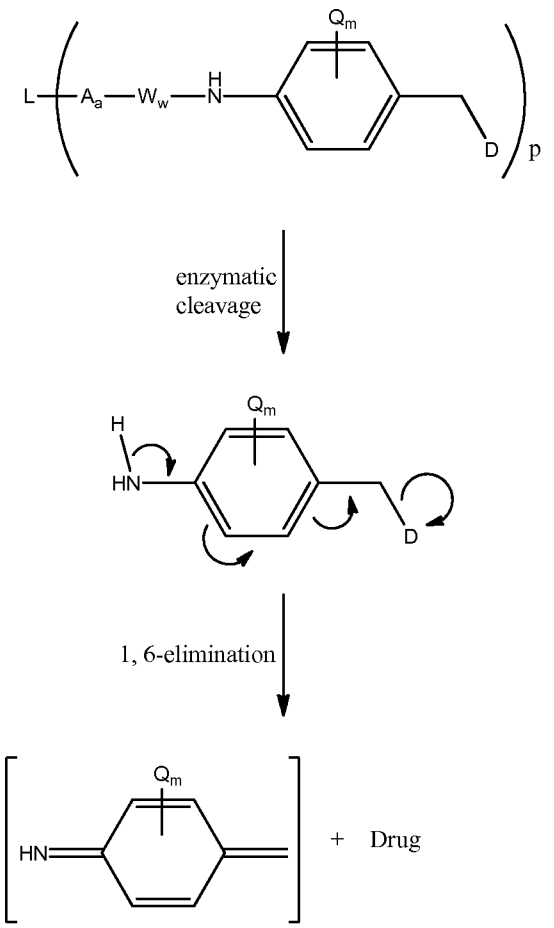
Scheme 2



In Scheme 2, Q is —C_1-C_8 alkyl, —C_1-C_8 alkenyl, —C_1-C_8 alkynyl, —O—(C_1-C_8 alkyl), —O—(C_1-C_8 alkenyl), —O—(C_1-C_8 alkynyl), -halogen, -nitro or -cyano; m is an integer ranging from 0-4; and p ranges from 1 to about 20. The alkyl, alkenyl and alkynyl groups, whether alone or as part of another group, can be optionally substituted.

Without being bound by any particular theory or mechanism, Scheme 3 below (see also U.S. 8,309,093) depicts a possible mechanism of Drug release of a PAB group which is attached directly to -D via an ether or amine linkage, wherein D includes the oxygen or nitrogen group that is part of the drug.

Scheme 3

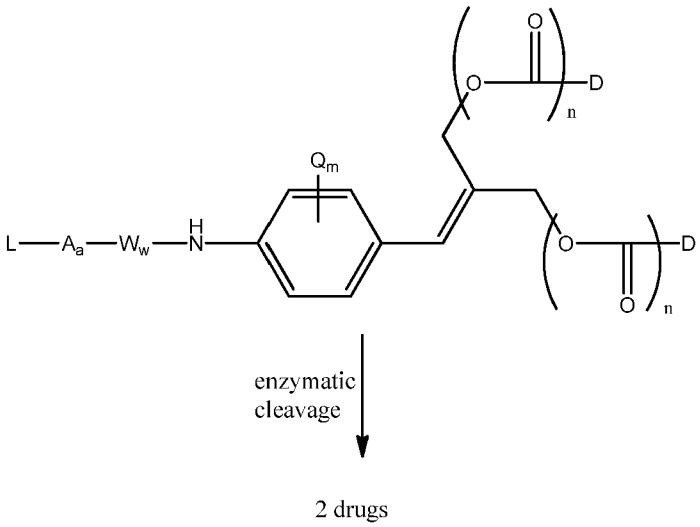


In Scheme 3, Q is —C_1-C_8 alkyl, —C_1-C_8 alkenyl, —C_1-C_8 alkynyl, —O—(C_1-C_8 alkyl), —O—(C_1-C_8 alkenyl), —O—(C_1-C_8 alkynyl), -halogen, -nitro or -cyano; m is an integer ranging from 0-4; and p ranges from 1 to about 20. The alkyl, alkenyl and alkynyl groups, whether alone or as part of another group, can be optionally substituted.

Other examples of self-immolative spacers include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (Hay *et al.*, 1999, Bioorg. Med. Chem. Lett. 9:2237) and ortho or para-aminobenzylacetals. Spacers can be used that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-aminobutyric acid amides (Rodrigues *et al.*, 1995, Chemistry Biology 2:223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (Storm *et al.*, 1972, J. Amer. Chem. Soc. 94:5815) and 2-aminophenylpropionic acid amides (Amsberry *et al.*, 1990, J. Org. Chem. 55:5867). Elimination of amine-containing drugs that are substituted at the α-position of glycine (Kingsbury *et al.*, 1984, J. Med. Chem. 27:1447) are also examples of self-immolative spacers.

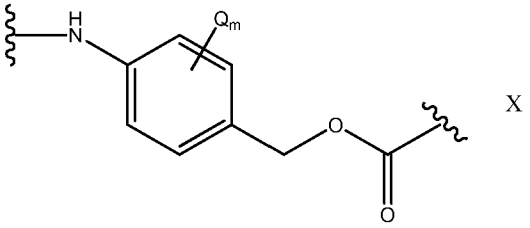
In one embodiment, the spacer unit is a branched bis(hydroxymethyl)-styrene (BHMS) unit as depicted in Scheme 4 below (see also U.S. 8,309,093), which can be used to incorporate and release multiple drugs.

Scheme 4

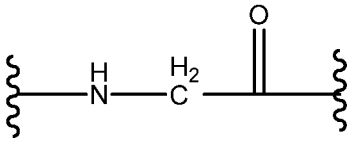


In Scheme 4 above, Q is —C_1-C_8 alkyl, —C_1-C_8 alkenyl, —C_1-C_8 alkynyl, —O—(C_1-C_8 alkyl), —O—(C_1-C_8 alkenyl), —O—(C_1-C_8 alkynyl), -halogen, -nitro or -cyano; m is an integer ranging from 0-4; n is 0 or 1; and p ranges from 1 to about 20. The alkyl, alkenyl and alkynyl groups, whether alone or as part of another group, can be optionally substituted.

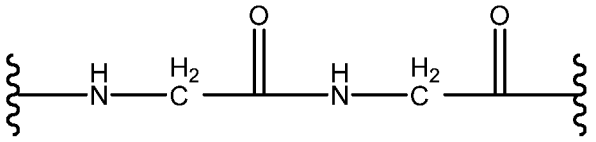
In one aspect, spacer units (—Y_y—) are represented by Formulas (X)-(XII) (See below (see also U.S. 8,309,093) wherein Q is —C_1-C_8 alkyl, —C_1-C_8 alkenyl, —C_1-C_8 alkynyl, —O—(C_1-C_8 alkyl), —O—(C_1-C_8 alkenyl), —O—(C_1-C_8 alkynyl), -halogen, -nitro or -cyano; and m is an integer ranging from 0-4.



X



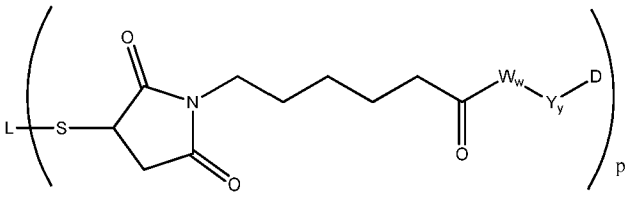
XI



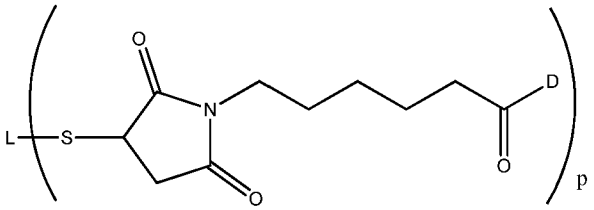
XII

The alkyl, alkenyl and alkynyl groups, whether alone or as part of another group, can be optionally substituted.

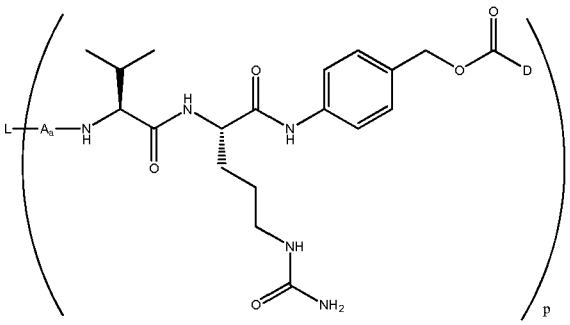
Embodiments of the Formula I and II comprising ADCs can also include, the compound with the structure as depicted below (see also U.S. 8,309,093),

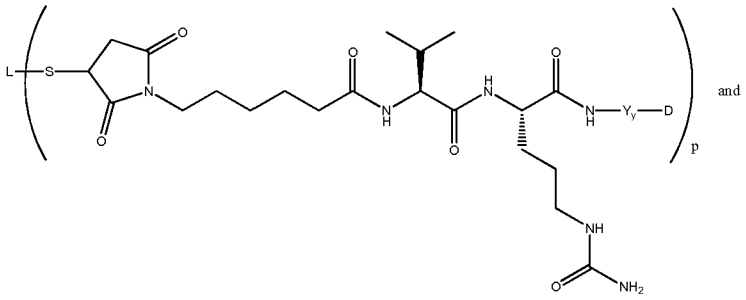


wherein w and y are each 0, 1 or 2, and, the compound with the structure as depicted below (see also U.S. 8,309,093),

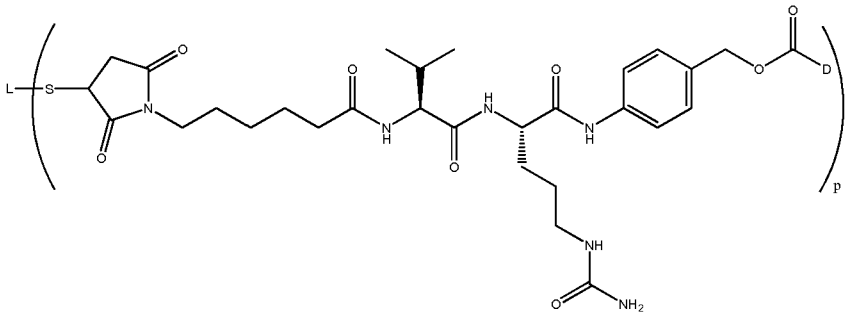


wherein w and y are each 0, and the compounds as depicted below (see also U.S. 8,309,093).





and



In yet other embodiments, the spacer unit (—Y—), when present, links a glucuronide unit, when present, to the drug moiety. In some embodiments, the spacer unit(s) of these embodiments are self-immolative spacers. In this context, the term "self-immolative spacer" refers to a bifunctional chemical moiety that is capable of covalently linking together two spaced chemical moieties into a normally stable tripartite molecule. It will spontaneously separate from the second chemical moiety if its bond to the first moiety is cleaved.

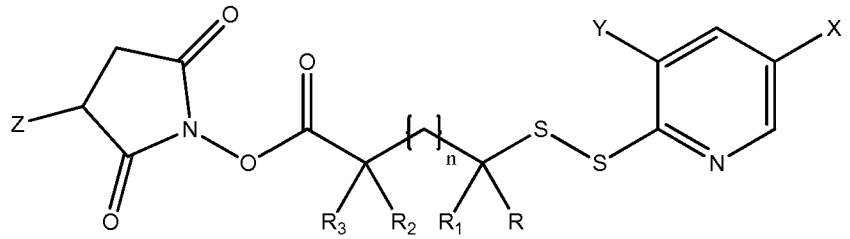
In some embodiments, —Y— is linked to -W_w- via the methylene carbon atom of the self-immolative group, and linked connected directly to -D via a carbonate, carbamate or ether group.

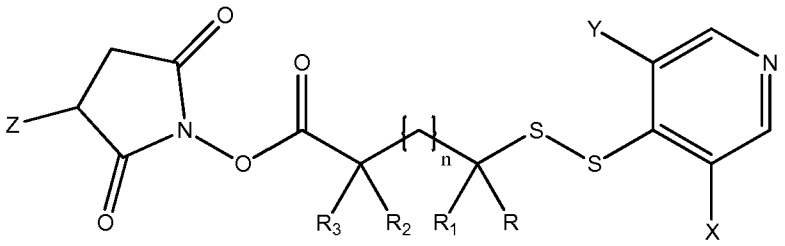
In some embodiments, -Yy- is a p-aminobenzyl alcohol (PAB) unit whose phenylene portion is substituted with Q_m wherein Q is as defined herein, and m is an integer ranging from 0-4. In another embodiment, -Y_y- can be a carbonate group.

Other examples of self-immolative spacers include, but are not limited to, aromatic compounds that are electronically similar to the PAB group such as 2-aminoimidazol-5-methanol derivatives (see, *e.g.*, Hay *et al.*, 1999, *Bioorg. Med. Chem. Lett.* 9:2237) and ortho or para-aminobenzylacetals. Spacers can be used that undergo cyclization upon amide bond hydrolysis, such as substituted and unsubstituted 4-aminobutyric acid amides (see, *e.g.*, Rodrigues *et al.*, 1995, *Chemistry Biology* 2:223), appropriately substituted bicyclo[2.2.1] and bicyclo[2.2.2] ring systems (see, *e.g.*, Storm *et al.*, 1972, *J. Amer. Chem. Soc.* 94:5815) and 2-aminophenylpropionic acid amides (see, *e.g.*, Amsberry *et al.*, 1990, J. Org. Chem. 55:5867). Elimination of amine-containing drugs that are substituted at the a-position of glycine (see, *e.g.*, Kingsbury *et al.*, 1984, *J. Med. Chem.* 27:1447) are also examples of self-immolative spacers.

Other suitable spacer units are disclosed in Published U.S. Patent Application No. 2005-0238649, the disclosure of which is incorporated by reference herein.

Another approach for the generation of ADCs involves the use of heterobifunctional cross-linkers which link the anti-PRLR antibody to the drug of interest. Preferably, the cross-linkers are N-succinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate or the highly water-soluble analog N-sulfosuccinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate, N-succinimidyl-4-(2-pyridyldithio) butyrate (SPDB), N-succinimidyl-4-(5-nitro-2-pyridyldithio) butyrate (SNPB), and N-sulfosuccinimidyl-4-(5-nitro-2-pyridyldithio) butyrate (SSNPB), N-succinimidyl-4-methyl-4-(5-nitro-2-pyridyldithio)pentanoate (SMNP), N-succinimidyl-4-(5-N,N-dimethylcarboxamido-2-pyridyldithio) butyrate (SCPB) or N-sulfosuccinimidyl4-(5-N,N-dimethylcarboxamido-2-pyridyldithio) butyrate (SSCPB)). The antibodies of the present invention modified with the cross-linkers N-succinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate, N-sulfosuccinimidyl 4-(5-nitro-2-pyridyldithio)-pentanoate, SPDB, SNPB, SSNPB, SMNP, SCPB, or SSCPB can then react with a small excess of a particular drug that contains a thiol moiety to give excellent yields of an ADC. Preferably, the cross-linkers are compounds of the formula as depicted below (See also U.S. Patent No. 6,913,748),

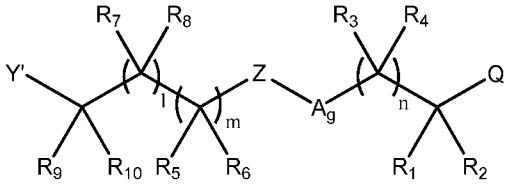




wherein R, R_1, R_2 and R_3 are the same or different and are H, methyl, ethyl, or linear, branched, or cyclic alkyl having 3 to 6 carbon atoms, n is 0 or an integer from 1 to 4, X and Y are the same or different and are H, $CONR_4R_5$ or NO_2, provided that X and Y are not both H at the same time, R_4 and R_5 are the same or different and are each H, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl, and Z is $SO_3^-M^+$ or H, wherein M^+ represents a metal ion or a tetra alkyl ammonium ion, provided that when X and/or Y is NO_2, Z is not H. Additional heterobifunctional crosslinkers and methods of making ADCs using the same are described in U.S. Patent No. 6,913,748, which is expressly incorporated by reference herein.

In one embodiment, charged linkers (also referred to as pro-charged linkers) are used to conjugate anti-PRLR antibodies to drugs to form ADCs. Charged linkers include linkers that become charged after cell processing. The presence of a charged group(s) in the linker of a particular ADC or on the drug after cellular processing provides several advantages, such as (i) greater water solubility of the ADC, (ii) ability to operate at a higher concentration in aqueous solutions, (iii) ability to link a greater number of drug molecules per antibody, potentially resulting in higher potency, (iv) potential for the charged conjugate species to be retained inside the target cell, resulting in higher potency, and (v) improved sensitivity of multidrug resistant cells, which would be unable to export the charged drug species from the cell. Examples of some suitable charged or pro-charged cross-linkers and their synthesis are shown in Figures 1 to 10 of U.S. Patent No. 8,236, 319 and are incorporated by reference herein. Preferably, the charged or pro-charged cross-linkers are those containing sulfonate, phosphate, carboxyl or quaternary amine substituents that significantly increase the solubility of the ADCs, especially for ADCs with 2 to 20 conjugated drugs. Conjugates prepared from linkers containing a pro-charged moiety would produce one or more charged moieties after the conjugate is metabolized in a cell.

In a further embodiment, the ADC of the invention comprises a linker having the formula as depicted below (see also U.S. Patent No. 8,236, 319),



wherein Y' represents a functional group that enables reaction with an antibody; Q represents a functional group that enables linkage of a drug via a disulfide, thioether, thioester, peptide, hydrazone, ester, ether, carbamate or amide bond; R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} are the same or different and are H, linear alkyl having from 1 to 6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl having from 2 to 6 carbon atoms, anions, such as but not limited to, SO_3^-, X—SO_3^-, OPO_3^{2-}, X—OPO_3^{2-}, PO_3^{2-}, X—PO_3^{2-}, CO_2—, cations, such as but not limited to, a nitrogen containing heterocycle, $N^+R_{11}R_{12}R_{13}$, or X—$N^+R_{11}R_{12}R_{13}$ or a phenyl, wherein: R_{11}, R_{12}, and R_{13} are the same or different and are H, linear alkyl having from 1 to 6 carbon atoms, or branched or cyclic alkyl having from 3 to 6 carbon atoms and X represents phenyl or a linear alkyl having from 1 to 6 carbon atoms, or a branched or cyclic alkyl having from 3 to 6 carbon atoms; l, m, and n are 0 or an integer from 1 to 4; A is a phenyl or substituted phenyl, wherein the substituent is a linear alkyl having from 1 to 6 carbon atoms, or a branched or cyclic alkyl having from 3 to 6 carbon atoms, or a charged substituent selected from anions, such as but not limited to, SO_3^-, X—SO_3^-, OPO_3^{2-}, X—OPO_3^{2-}, PO_3^{2-}, X—PO_3^{2-}, CO_2—, and cations, such as but not limited to, a nitrogen containing heterocycle, $N^+R_{11}R_{12}R_{13}$ or X—$N^+R_{11}R_{12}R_{13}$, wherein X has the same definition as above, and wherein g is 0 or 1; Z is an optional polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is 0 or an integer from 2 to about 1000, or F1-E1-P-E2-F2 unit in which E1 and E2 are the same or different and are C=O, O, or NR14, wherein R_{14} is H, a linear alkyl having from 1 to 6 carbon atoms, a branched or cyclic alkyl having from 3 to 6 carbon atoms, a linear, branched or cyclic alkenyl or alkynyl having from 2 to 6 carbon atoms; P is a peptide unit between 2 and 20 amino acids in length, wherein E1 or E2 can be linked to the peptide through the terminal nitrogen, terminal carbon or through a side chain of one of the amino acids of the peptide; and F1 and F2 are the same or different and are an optional polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is 0 or an integer from 2 to about 1000, provided that when Z is not F1-E1-P-E2-F2, at least one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is a charged substituent or when g is 1, at least one of A, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10} is a charged substituent.

Examples of the functional group, Y', that enables reaction with an antibody include amine reacting agents such as but not limited to N-hydroxysuccinmide esters, p-nitrophenyl esters, dinitrophenyl esters, pentafluorophenyl esters; thiol reactive agents such as but not limited

to pyridyldisulfides, nitropyridyldisulfides, maleimides, haloacetates and carboxylic acid chlorides.

Examples of the functional group, Q, which enables linkage of a drug, include groups that enable linkage via a disulfide, thioether, thioester, peptide, hydrazone, ester, carbamate, or amide bond. Such functional groups include, but are not limited to, thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines, and hydroxy.

Examples of linear alkyls include methyl, ethyl, propyl, butyl, pentyl and hexyl. Examples of branched or cyclic alkyls having 3 to 6 carbon atoms include isopropyl, sec-butyl, isobutyl, tert-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Examples of linear alkenyls having 2 to 6 carbon atoms include ethenyl, propenyl, butenyl, pentenyl, hexenyl. Examples of branched or cyclic alkenyls having 2 to 6 carbon atoms include isobutenyl, isopentenyl, 2-methyl-1-pentenyl, 2-methyl-2-pentenyl.

Examples of linear alkynyls having 2 to 6 carbon atoms include ethynyl, propynyl, butynyl, pentynyl, hexynyl. Examples of branched or cyclic alkynyls having up to 6 carbon atoms include 3-methyl-1-butynyl, 3-methyl-1-penynyl, 4-methyl-2-hexynyl.

In one embodiment, one of R_1, R_2, R_3, R_4, R_9, or R_{10} is a charged substituent selected from sulfonate, phosphate or trialkylammonium, and the rest are H, l, g and m are each 0, n=1, Q and Y' are each independently, a disulfide substituent, a maleimido, a haloacetyl group, or a N-hydroxy succinimide ester. In another more preferred embodiment, one of R_1, R_2, R_3, R_4, R_9, or R_{10} is a sulfonate, and the rest are H, l, g and m are each 0, n=1, Q is a disulfide, maleimido or haloacetyl moiety, and Y' is a maleimido moiety or a N-hydroxy succinimide ester. In a further more preferred embodiment, one of R_1, R_2, R_3, R_4, R_9, or R_{10} is a sulfonate, and the rest are H, l, g and m are each 0, n=1, Q is a pyridyldithio or nitropyridyldithio group, maleimido or haloacetyl moiety, and Y' is a N-hydroxy succinimide ester.

Additional examples of linkers that can be used with the present compositions and methods include valine-citrulline; maleimidocaproyl; amino benzoic acids; p-aminobenzylcarbamoyl (PAB); lysosomal enzyme-cleavable linkers; maleimidocaproyl-polyethylene glycol (MC(PEG)6-OH); N-methyl-valine citrulline; N-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC); N-Succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); and N-Succinimidyl 4-(2-pyridylthio)pentanoate (SPP) (See also US 2011/0076232). Another linker for use in the present invention includes an avidin-biotin linkage to provide an avidin-biotin-containing ADC (See also U.S. Patent No. 4,676,980, PCT publication Nos. WO1992/022332A2, WO1994/016729A1, WO1995/015770A1, WO1997/031655A2, WO1998/035704A1, WO1999/019500A1, WO2001/09785A2, WO2001/090198A1, WO2003/093793A2, WO2004/050016A2, WO2005/081898A2, WO2006/083562A2, WO2006/089668A1, WO2007/150020A1, WO2008/135237A1,

WO2010/111198A1, WO2011/057216A1, WO2011/058321A1, WO2012/027494A1, and EP77671B1), wherein some such linkers are resistant to biotinidase cleavage. Additional linkers for use in the present invention may contain a cohesin/dockerin pair to provide a cohesion-dockerin-containing ADC (See PCT publication Nos. WO2008/097866A2, WO2008/097870A2, WO2008/103947A2, and WO2008/103953A2).

Additional linkers for use in the present invention may contain non-peptide polymers (examples include, but are not limited to, polyethylene glycol, polypropylene glycol, polyoxyethylated polyols, polyvinyl alcohol, polysaccharides, dextran, polyvinyl ethyl ether, PLA (poly(lactic acid)), PLGA (poly(lactic acid-glycolic acid)), and combinations thereof, wherein a preferred polymer is polyethylene glycol) (See also PCT publication No. WO2011/000370). Additional linkers are also described in WO 2004-010957, U.S. Publication No. 20060074008, U.S. Publication No. 20050238649, and U.S. Publication No. 20060024317 (each of which is incorporated by reference herein in its entirety and for all purposes).

For an ADC of the invention comprising a maytansinoid, many positions on maytansinoids can serve as the position to chemically link the linking moiety. In one embodiment, maytansinoids comprise a linking moiety that contains a reactive chemical group are C-3 esters of maytansinol and its analogs where the linking moiety contains a disulfide bond and the chemical reactive group comprises a N-succinimidyl or N-sulfosuccinimidyl ester. For example, the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with hydroxy and the C-20 position having a hydroxy group are all useful. The linking moiety most preferably is linked to the C-3 position of maytansinol.

III. Uses of Anti-PRLR Antibodies

Given their ability to bind to human PRLR, the anti-human PRLR antibodies, or portions thereof, of the invention can be used to detect human PRLR (*e.g.*, in a biological sample, such as serum or plasma), using a conventional immunoassay, such as an enzyme linked immunosorbent assays (ELISA), an radioimmunoassay (RIA) or tissue immunohistochemistry. The invention provides a method for detecting human PRLR in a biological sample comprising contacting a biological sample with an antibody, or antibody portion, of the invention and detecting either the antibody (or antibody portion) bound to human PRLR or unbound antibody (or antibody portion), to thereby detect human PRLR in the biological sample. The antibody is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples

of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of suitable radioactive material include ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, or ^{153}Sm.

Alternative to labeling the antibody, human PRLR can be assayed in biological fluids by a competition immunoassay utilizing rhPRLR standards labeled with a detectable substance and an unlabeled anti-human PRLR antibody. In this assay, the biological sample, the labeled rhPRLR standards and the anti-human PRLR antibody are combined and the amount of labeled rhPRLR standard bound to the unlabeled antibody is determined. The amount of human PRLR in the biological sample is inversely proportional to the amount of labeled rhPRLR standard bound to the anti-PRLR antibody. Similarly, human PRLR can also be assayed in biological fluids by a competition immunoassay utilizing rhPRLR standards labeled with a detectable substance and an unlabeled anti-human PRLR antibody.

The antibodies and antibody portions of the invention preferably are capable of neutralizing human PRLR activity both *in vitro* and *in vivo*. Accordingly, such antibodies and antibody portions of the invention can be used to inhibit hPRLR activity, *e.g.*, in a cell culture containing hPRLR, in human subjects or in other mammalian subjects having PRLR with which an antibody of the invention cross-reacts. In one embodiment, the invention provides a method for inhibiting hPRLR activity comprising contacting hPRLR with an antibody or antibody portion of the invention such that hPRLR activity is inhibited. For example, in a cell culture containing, or suspected of containing hPRLR, an antibody or antibody portion of the invention can be added to the culture medium to inhibit hPRLR activity in the culture.

In another embodiment, the invention provides a method for reducing hPRLR activity in a subject, advantageously from a subject suffering from a disease or disorder in which PRLR activity is detrimental. The invention provides methods for reducing PRLR activity in a subject suffering from such a disease or disorder, which method comprises administering to the subject an antibody or antibody portion of the invention such that PRLR activity in the subject is reduced. Preferably, the PRLR is human PRLR, and the subject is a human subject. Alternatively, the subject can be a mammal expressing a PRLR to which an antibody of the invention is capable of binding. Still further the subject can be a mammal into which PRLR has been introduced (*e.g.*, by administration of PRLR or by expression of a PRLR transgene). An antibody of the invention can be administered to a human subject for therapeutic purposes. Moreover, an antibody of the invention can be administered to a non-human mammal expressing a PRLR with which the antibody is capable of binding for veterinary purposes or as an animal model of human disease. Regarding the latter, such animal models may be useful for evaluating

the therapeutic efficacy of antibodies of the invention (*e.g.*, testing of dosages and time courses of administration).

As used herein, the term "a disorder in which PRLR activity is detrimental" is intended to include diseases and other disorders in which the presence of PRLR in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, a disorder in which PRLR activity is detrimental is a disorder in which reduction of PRLR activity is expected to alleviate the symptoms and/or progression of the disorder. Such disorders may be evidenced, for example, by an increase in the concentration of PRLR in a biological fluid of a subject suffering from the disorder (*e.g.*, an increase in the concentration of PRLR in serum, plasma, synovial fluid, *etc.* of the subject), which can be detected, for example, using an anti-PRLR antibody as described above. Non-limiting examples of disorders that can be treated with the antibodies of the invention, for example, Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab9, chAb9, Ab10, chAb10, Ab11, chAb11, Ab13, chAb13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 or Ab55, variants thereof, or antigen binding fragments thereof, include those disorders discussed in the section below pertaining to pharmaceutical compositions of the antibodies of the invention. For example, suitable disorders include, but are not limited to, a variety of cancers including, but not limited to, melanoma, lymphoma, breast cancer, ovarian cancer, renal carcinoma, gastrointestinal cancer, colon cancer, lung cancer, pancreatic cancer, endometrial cancer and prostate cancer. In particular embodiments, the cancer is breast cancer, renal cancer, prostate cancer, ovarian cancer, endometrial cancer or lung cancer. In a particular embodiment, the cancer is breast cancer. In a particular embodiment, the cancer is prostate cancer.

In another embodiment, the present invention is directed to treatment of "a disorder associated with underexpression or reduced activity of PRLR." As used herein the term "a disorder associated with underexpression or reduced activity of PRLR" is intended to include diseases and other disorders in which the underexpression or reduced activity of PRLR has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, increasing the activity of PRLR activity is expected to alleviate the symptoms and/or progression of these disorders. Such disorders may be evidenced, for example, by a decrease in the concentration of PRLR in a biological fluid of a subject suffering from the disorder (*e.g.*, a decrease in the concentration of PRLR in serum, plasma, synovial fluid, *etc.* of the subject), which can be detected, for example, using an anti-PRLR antibody as described above. Non-limiting examples of disorders that can be

treated with the antibodies of the invention, for example, Ab12, chAb12 variants thereof, or antigen binding fragments thereof, include enhancing mammary development or increasing lactation.

IV. Pharmaceutical Compositions

The invention also provides pharmaceutical compositions comprising an antibody, or antigen-binding portion thereof, of the invention and a pharmaceutically acceptable carrier. The pharmaceutical compositions comprising antibodies of the invention are for use in, but not limited to, diagnosing, detecting, or monitoring a disorder, in preventing, treating, managing, or ameliorating of a disorder or one or more symptoms thereof, and/or in research. In a specific embodiment, a composition comprises one or more antibodies of the invention. In another embodiment, the pharmaceutical composition comprises one or more antibodies of the invention and one or more prophylactic or therapeutic agents other than antibodies of the invention for treating a disorder in which PRLR activity is detrimental. Preferably, the prophylactic or therapeutic agents known to be useful for or having been or currently being used in the prevention, treatment, management, or amelioration of a disorder or one or more symptoms thereof. In accordance with these embodiments, the composition may further comprise of a carrier, diluent or excipient.

The antibodies and antibody-portions of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody or antibody portion of the invention and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

Various delivery systems are known and can be used to administer one or more antibodies of the invention or the combination of one or more antibodies of the invention and a prophylactic agent or therapeutic agent useful for preventing, managing, treating, or ameliorating a disorder or one or more symptoms thereof, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment,

receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of administering a prophylactic or therapeutic agent of the invention include, but are not limited to, parenteral administration (*e.g.*, intradermal, intramuscular, intraperitoneal, intravenous and subcutaneous), epidural administration, intratumoral administration, and mucosal administration (*e.g.*, intranasal and oral routes). In addition, pulmonary administration can be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent. See, *e.g.*, U.S. Pat. Nos. 6,019,968, 5,985, 320, 5,985,309, 5,934, 272, 5,874,064, 5,855,913, 5,290, 540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entireties. In one embodiment, an antibody of the invention, combination therapy, or a composition of the invention is administered using Alkermes AIR® pulmonary drug delivery technology (Alkermes, Inc., Cambridge, Mass.). In a specific embodiment, prophylactic or therapeutic agents of the invention are administered intramuscularly, intravenously, intratumorally, orally, intranasally, pulmonary, or subcutaneously. The prophylactic or therapeutic agents may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

In a specific embodiment, it may be desirable to administer the prophylactic or therapeutic agents of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion, by injection, or by means of an implant, said implant being of a porous or non-porous material, including membranes and matrices, such as sialastic membranes, polymers, fibrous matrices (*e.g.*, Tissuel®), or collagen matrices. In one embodiment, an effective amount of one or more antibodies of the invention antagonists is administered locally to the affected area to a subject to prevent, treat, manage, and/or ameliorate a disorder or a symptom thereof. In another embodiment, an effective amount of one or more antibodies of the invention is administered locally to the affected area in combination with an effective amount of one or more therapies (*e.g.*, one or more prophylactic or therapeutic agents) other than an antibody of the invention of a subject to prevent, treat, manage, and/or ameliorate a disorder or one or more symptoms thereof.

In another embodiment, the prophylactic or therapeutic agent of the invention can be delivered in a controlled release or sustained release system. In one embodiment, a pump may be used to achieve controlled or sustained release (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:20; Buchwald *et al.*, 1980, Surgery 88:507; Saudek *et al.*, 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used to achieve controlled or

sustained release of the therapies of the invention (see *e.g.*, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J., Macromol. Sci. Rev. Macromol. Chem.* 23:61; see also Levy *et al.*, 1985, *Science* 228:190; During *et al.*, 1989, *Ann. Neurol.* 25:351; Howard *et al.*, 1989, *J. Neurosurg.* 7 1:105); U.S. Pat. No. 5,679,377; U.S. Pat. No. 5, 916,597; U. S. Pat. No. 5,912,015; U.S. Pat. No. 5,989,463; U.S. Pat. No. 5,128,326; PCT Publication No. WO 99/15154; and PCT Publication No. WO 99/20253. Examples of polymers used in sustained release formulations include, but are not limited to, poly(2-hydroxy ethyl methacrylate), poly(methyl methacrylate), poly(acrylic acid), poly(ethylene-co-vinyl acetate), poly(methacrylic acid), polyglycolides (PLG), polyanhydrides, poly(N- vinyl pyrrolidone), poly(vinyl alcohol), polyacrylamide, poly(ethylene glycol), polylactides (PLA), poly(lactide-co-glycolides) (PLGA), and polyorthoesters. In a preferred embodiment, the polymer used in a sustained release formulation is inert, free of leachable impurities, stable on storage, sterile, and biodegradable. In yet another embodiment, a controlled or sustained release system can be placed in proximity of the prophylactic or therapeutic target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

Controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533). Any technique known to one of skill in the art can be used to produce sustained release formulations comprising one or more therapeutic agents of the invention. See, *e.g.*, U. S. Pat. No. 4,526, 938, PCT publication WO 91/05548, PCT publication WO 96/20698, Ning *et al.*, 1996, "Intratumoral Radioimmunotheraphy of a Human Colon Cancer Xenograft Using a Sustained-Release Gel," *Radiotherapy & Oncology* 39:179-189, Song *et al.*, 1995, "Antibody Mediated Lung Targeting of Long- Circulating Emulsions," *PDA Journal of Pharmaceutical Science & Technology* 50:372-397, Cleek *et al.*, 1997, "Biodegradable Polymeric Carriers for a bFGF Antibody for Cardiovascular Application," *Pro. Int'l. Symp. Control. Rel. Bioact. Mater.* 24:853-854, and Lam *et al.*, 1997, "Microencapsulation of Recombinant Humanized Monoclonal Antibody for Local Delivery," *Proc. Int'l. Symp. Control Rel. Bioact. Mater.* 24:759- 760, each of which is incorporated herein by reference in their entireties.

In a specific embodiment, where the composition of the invention is a nucleic acid encoding a prophylactic or therapeutic agent, the nucleic acid can be administered *in vivo* to promote expression of its encoded prophylactic or therapeutic agent, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see U. S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like

peptide which is known to enter the nucleus (see, *e.g.*, Joliot *et al.*, 1991, *Proc. Natl. Acad. Sci. USA* 88:1864-1868). Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression by homologous recombination.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral, intranasal (*e.g.*, inhalation), transdermal (*e.g.*, topical), transmucosal, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocamne to ease pain at the site of the injection.

If the compositions of the invention are to be administered topically, the compositions can be formulated in the form of an ointment, cream, transdermal patch, lotion, gel, shampoo, spray, aerosol, solution, emulsion, or other form well-known to one of skill in the art. See, *e.g.*, Remington's Pharmaceutical Sciences and Introduction to Pharmaceutical Dosage Forms, 19th ed., Mack Pub. Co., Easton, Pa. (1995). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity preferably greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (*e.g.*, preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (*e.g.*, a gaseous propellant, such as freon) or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art.

If the method of the invention comprises intranasal administration of a composition, the composition can be formulated in an aerosol form, spray, mist or in the form of drops. In particular, prophylactic or therapeutic agents for use according to the present invention can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (*e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a

metered amount. Capsules and cartridges (composed of, *e.g.*, gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

If the method of the invention comprises oral administration, compositions can be formulated orally in the form of tablets, capsules, cachets, gel caps, solutions, suspensions, and the like. Tablets or capsules can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, polyvinylpyrrolidone, or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose, or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate) ; or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets may be coated by methods well-known in the art. Liquid preparations for oral administration may take the form of, but not limited to, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives, or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol, or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring, and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated for slow release, controlled release, or sustained release of a prophylactic or therapeutic agent(s).

The method of the invention may comprise pulmonary administration, *e.g.*, by use of an inhaler or nebulizer, of a composition formulated with an aerosolizing agent. See, *e.g.*, U.S. Pat. Nos. 6,019, 968, 5,985, 320, 5, 985,309, 5,934,272, 5,874,064, 5,855,913, 5,290,540, and 4,880,078; and PCT Publication Nos. WO 92/19244, WO 97/32572, WO 97/44013, WO 98/31346, and WO 99/66903, each of which is incorporated herein by reference their entireties. In a specific embodiment, an antibody of the invention, combination therapy, and/or composition of the invention is administered using Alkermes AIR® pulmonary drug delivery technology (Alkermes, Inc., Cambridge, Mass.).

The method of the invention may comprise administration of a composition formulated for parenteral administration by injection (*e.g.*, by bolus injection or continuous infusion). Formulations for injection may be presented in unit dosage form (*e.g.*, in ampoules or in multi-dose containers) with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active

ingredient may be in powder form for constitution with a suitable vehicle (*e.g.*, sterile pyrogen-free water) before use.

The methods of the invention may additionally comprise of administration of compositions formulated as depot preparations. Such long acting formulations may be administered by implantation (*e.g.*, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compositions may be formulated with suitable polymeric or hydrophobic materials (*e.g.*, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (*e.g.*, as a sparingly soluble salt).

The methods of the invention encompass administration of compositions formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2- ethylamino ethanol, histidine, procaine, etc.

Generally, the ingredients of compositions are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the mode of administration is infusion, composition can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the mode of administration is by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

In particular, the invention also provides that one or more of the prophylactic or therapeutic agents, or pharmaceutical compositions of the invention is packaged in a hermetically sealed container such as an ampoule or sachette indicating the quantity of the agent. In one embodiment, one or more of the prophylactic or therapeutic agents, or pharmaceutical compositions of the invention is supplied as a dry sterilized lyophilized powder or water free concentrate in a hermetically sealed container and can be reconstituted (*e.g.*, with water or saline) to the appropriate concentration for administration to a subject. Preferably, one or more of the prophylactic or therapeutic agents or pharmaceutical compositions of the invention is supplied as a dry sterile lyophilized powder in a hermetically sealed container at a unit dosage of at least 5 mg, more preferably at least 10 mg, at least 15 mg, at least 25 mg, at least 35 mg, at least 45 mg, at least 50 mg, at least 75 mg, or at least 100 mg. The lyophilized prophylactic or therapeutic agents or pharmaceutical compositions of the invention should be stored at between 2° C. and 8° C. in its original container and the prophylactic or therapeutic agents, or pharmaceutical compositions of the invention should be administered within 1 week, preferably within 5 days, within 72 hours, within 48 hours, within 24 hours, within 12 hours, within 6 hours, within 5 hours, within 3 hours, or within 1 hour after being reconstituted. In an alternative embodiment,

one or more of the prophylactic or therapeutic agents or pharmaceutical compositions of the invention is supplied in liquid form in a hermetically sealed container indicating the quantity and concentration of the agent. Preferably, the liquid form of the administered composition is supplied in a hermetically sealed container at least 0.25 mg/ml, more preferably at least 0.5 mg/ml, at least 1 mg/ml, at least 2.5 mg/ml, at least 5 mg/ml, at least 8 mg/ml, at least 10 mg/ml, at least 15 mg/kg, at least 25 mg/ml, at least 50 mg/ml, at least 75 mg/ml or at least 100 mg/ml. The liquid form should be stored at between 2° C. and 8° C. in its original container.

The antibodies and antibody-portions of the invention can be incorporated into a pharmaceutical composition suitable for parenteral administration. Preferably, the antibody or antibody-portions will be prepared as an injectable solution containing 0.1-250 mg/ml antibody. The injectable solution can be composed of either a liquid or lyophilized dosage form in a flint or amber vial, ampule or pre-filled syringe. The buffer can be L-histidine (1-50 mM), optimally 5-10 mM, at pH 5.0 to 7.0 (optimally pH 6.0). Other suitable buffers include but are not limited to, sodium succinate, sodium citrate, sodium phosphate or potassium phosphate. Sodium chloride can be used to modify the toxicity of the solution at a concentration of 0-300 mM (optimally 150 mM for a liquid dosage form). Cryoprotectants can be included for a lyophilized dosage form, principally 0-10% sucrose (optimally 0.5-1.0%). Other suitable cryoprotectants include trehalose and lactose. Bulking agents can be included for a lyophilized dosage form, principally 1-10% mannitol (optimally 2-4%). Stabilizers can be used in both liquid and lyophilized dosage forms, principally 1-50 mM L-Methionine (optimally 5-10 mM). Other suitable bulking agents include glycine, arginine, can be included as 0-0.05% polysorbate-80 (optimally 0.005-0.01%). Additional surfactants include but are not limited to polysorbate 20 and BRIJ surfactants. The pharmaceutical composition comprising the antibodies and antibody-portions of the invention prepared as an injectable solution for parenteral administration, can further comprise an agent useful as an adjuvant, such as those used to increase the absorption, or dispersion of a therapeutic protein (*e.g.*, antibody). A particularly useful adjuvant is hyaluronidase, such as Hylenex® (recombinant human hyaluronidase). Addition of hyaluronidase in the injectable solution improves human bioavailability following parenteral administration, particularly subcutaneous administration. It also allows for greater injection site volumes (*i.e.* greater than 1 ml) with less pain and discomfort, and minimum incidence of injection site reactions. (see WO2004078140, US2006104968 incorporated herein by reference).

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.*, injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible

solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active compound (*i.e.*, antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile, lyophilized powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and spray-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including, in the composition, an agent that delays absorption, for example, monostearate salts and gelatin.

The antibodies and antibody-portions of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is subcutaneous injection, intravenous injection or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, *e.g.*, *Sustained and Controlled Release Drug Delivery Systems*, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

In certain embodiments, an antibody or antibody portion of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic

administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

In other embodiments, an antibody or antibody portion of the invention may be conjugated to a polymer-based species such that said polymer-based species may confer a sufficient size upon said antibody or antibody portion of the invention such that said antibody or antibody portion of the invention benefits from the enhanced permeability and retension effect (EPR effect) (See also PCT Publication No. WO2006/042146A2 and U.S. Publication Nos. 2004/0028687A1, 2009/0285757A1, and 2011/0217363A1, and U.S. Patent No. 7,695,719 (each of which is incorporated by reference herein in its entirety and for all purposes).

Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, an antibody or antibody portion of the invention is formulated with and/or co-administered with one or more additional therapeutic agents that are useful for treating disorders in which PRLR activity is detrimental. For example, an anti-hPRLR antibody or antibody portion of the invention may be formulated and/or co-administered with one or more additional antibodies that bind other targets (*e.g.*, antibodies that bind cytokines or that bind cell surface molecules). Furthermore, one or more antibodies of the invention may be used in combination with two or more of the foregoing therapeutic agents. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

In certain embodiments, an antibody to PRLR or fragment thereof is linked to a half-life extending vehicle known in the art. Such vehicles include, but are not limited to, the Fc domain, polyethylene glycol, and dextran. Such vehicles are described, *e.g.*, in U.S. Application Serial No. 09/428,082 and published PCT Application No. WO 99/25044, which are hereby incorporated by reference for any purpose.

In a specific embodiment, nucleic acid sequences comprising nucleotide sequences encoding an antibody of the invention or another prophylactic or therapeutic agent of the invention are administered to treat, prevent, manage, or ameliorate a disorder or one or more symptoms thereof by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded antibody or prophylactic or therapeutic agent of the invention that mediates a prophylactic or therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. For general reviews of the methods of gene therapy, see Goldspiel *et al.*, 1993,

Clinical Pharmacy 12:488-505; Wu and Wu, 1991, *Biotherapy* 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, *Science* 260:926- 932 (1993); and Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; May, 1993, *TIBTECH* 11(5):155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel *et al.* (eds.), *Current Protocols in Molecular Biology*, John Wiley &Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990). Detailed description of various methods of gene therapy is provided in US20050042664 A1 which is incorporated herein by reference.

In another aspect, this application features a method of treating (*e.g.*, curing, suppressing, ameliorating, delaying or preventing the onset of, or preventing recurrence or relapse of) or preventing a PRLR-associated disorder, in a subject. The method includes: administering to the subject a PRLR binding agent (particularly an antagonist), *e.g.*, an anti-PRLR antibody or fragment thereof as described herein, in an amount sufficient to treat or prevent the PRLR-associated disorder. The PRLR antagonist, *e.g.*, the anti-PRLR antibody or fragment thereof, can be administered to the subject, alone or in combination with other therapeutic modalities as described herein.

In another aspect, this application provides a method for detecting the presence of PRLR in a sample *in vitro* (*e.g.*, a biological sample, such as serum, plasma, tissue, biopsy). The subject method can be used to diagnose a disorder, *e.g.*, a cancer. The method includes: (i) contacting the sample or a control sample with the anti-PRLR antibody or fragment thereof as described herein; and (ii) detecting formation of a complex between the anti-PRLR antibody or fragment thereof, and the sample or the control sample, wherein a statistically significant change in the formation of the complex in the sample relative to the control sample is indicative of the presence of PRLR in the sample.

In yet another aspect, this application provides a method for detecting the presence of PRLR *in vivo* (*e.g.*, *in vivo* imaging in a subject). The subject method can be used to diagnose a disorder, *e.g.*, a PRLR-associated disorder. The method includes: (i) administering the anti-PRLR antibody or fragment thereof as described herein to a subject or a control subject under conditions that allow binding of the antibody or fragment to PRLR; and (ii) detecting formation of a complex between the antibody or fragment and PRLR, wherein a statistically significant change in the formation of the complex in the subject relative to the control subject is indicative of the presence of PRLR.

Antibodies of the invention, or antigen binding portions thereof can be used alone or in combination to treat such diseases. It should be understood that the antibodies of the invention or antigen binding portion thereof can be used alone or in combination with an additional agent, *e.g.*, a therapeutic agent, said additional agent being selected by the skilled artisan for its intended

purpose. For example, the additional agent can be a therapeutic agent art-recognized as being useful to treat the disease or condition being treated by the antibody of the present invention. The additional agent also can be an agent that imparts a beneficial attribute to the therapeutic composition, *e.g.*, an agent which affects the viscosity of the composition.

It should further be understood that the combinations which are to be included within this invention are those combinations useful for their intended purpose. The agents set forth below are illustrative for purposes and not intended to be limited. The combinations, which are part of this invention, can be the antibodies of the present invention and at least one additional agent selected from the lists below. The combination can also include more than one additional agent, *e.g.*, two or three additional agents if the combination is such that the formed composition can perform its intended function.

The combination therapy can include one or more PRLR antagonists, *e.g.*, anti-PRLR antibodies or fragments thereof, formulated with, and/or co-administered with, one or more additional therapeutic agents, *e.g.*, one or more cytokine and growth factor inhibitors, immunosuppressants, anti-inflammatory agents (*e.g.*, systemic anti-inflammatory agents), anti-fibrotic agents, metabolic inhibitors, enzyme inhibitors, and/or cytotoxic or cytostatic agents, mitotic inhibitors, antitumor antibiotics, immunomodulating agents, vectors for gene therapy, alkylating agents, antiangiogenic agents, antimetabolites, boron-containing agents, chemoprotective agents, hormones, antihormone agents, corticosteroids, photoactive therapeutic agents, oligonucleotides, radionuclide agents, topoisomerase inhibitors, tyrosine kinase inhibitors, or radiosensitizers, as described in more herein.

In a particular embodiment, the anti-PRLR binding proteins described herein, for example, anti-PRLR antibodies, are used in combination with an anti-cancer agent or an antineoplastic agent. The terms "anti-cancer agent" and "antineoplastic agent" refer to drugs used to treat malignancies, such as cancerous growths. Drug therapy may be used alone, or in combination with other treatments such as surgery or radiation therapy. Several classes of drugs may be used in cancer treatment, depending on the nature of the organ involved. For example, breast cancers are commonly stimulated by estrogens, and may be treated with drugs which inactive the sex hormones. Similarly, prostate cancer may be treated with drugs that inactivate androgens, the male sex hormone. Anti-cancer agents that may be used in conjunction with the anti-PRLR antibodies of the present invention include, among others, the following agents:

Anti-Cancer Agent	Comments	Examples
Antibodies (a) antibodies other than anti-PRLR antibodies; and (b) anti-PRLR antibodies which bind different epitopes	Antibodies which bind IGF-1R (insulin-like growth factor type 1 receptor), which is expressed on the cell surface of most human cancers	A12 (fully humanized mAb) 19D12 (fully humanized mAb) Cp751-871 (fully humanized mAb) H7C10 (humanized mAb) alphaIR3 (mouse) ScFV/FC (mouse/human chimera) EM/164 (mouse)
	Antibodies which bind EGFR (epiderman growth factor receptor); Mutations affecting EGFR expression or activity could result in cancer	Matuzumab (EMD72000) Erbitux® / Cetuximab (Imclone) Vectibix® / Panitumumab (Amgen) mAb 806 Nimotuxumab (TheraCIM)
	Antibodies which bind cMET (Mesechymal epithelial transition factor); a member of the MET family of receptor tyrosine kinases)	AVEO (AV299) (AVEO) AMG102 (Amgen) 5D5 (OA-5d5) (Genentech) H244G11 (Pierre Fabre)
	Anti-ErbB3 antibodies which bind different epitopes	Ab #14 (MM 121-14) Herceptin® (Trastuzumab; Genentech) 1B4C3; 2D1D12 (U3 Pharma AG)
Small Molecules Targeting IGF1R	Insulin-like growth factor type 1 receptor which is expressed on the cell surface of many human cancers	NVP-AEW541-A BMS-536,924 (1H-benzoimidazol-2-yl)-1H-pyridin-2-one) BMS-554,417 Cycloligan TAE226 PQ401
Small Molecules Targeting EGFR	EGFR (epiderman growth factor receptor); Overexpression or mutations affecting EGFR expression or activity could result in cancer	Iressa® / Gefitinib (AstraZeneca) CI-1033 (PD 183805) (Pfizer) Lapatinib (GW-572016) (GlaxoSmithKline) Tykerb® / Lapatinib Ditosylate (Smith Kline Beecham) Tarceva ® / Erlotinib HCL (OSI-774) (OSI Pharma) PKI-166 (Novartis) PD-158780 EKB-569 Tyrphostin AG 1478 (4-(3-Chloroanillino)-6,7-dimethoxyquinazoline)

Small Molecules Targeting cMET	cMET (Mesenchymal epithelial transition factor); a member of the MET family of receptor tyrosine kinases)	PHA665752 ARQ 197
Antimetabolites		Flourouracil (5-FU) Capecitabine / XELODA® (HLR Roche) 5-Trifluoromethyl-2'-deoxyuridine Methotrexate sodium (Trexall) (Barr) Raltitrexed/ Tomudex® (AstraZeneca) Pemetrexed / Alimta® (Lilly) Tegafur Cytosine Arabinoside (Cytarabine, Ara-C) / Thioguanine® (GlaxoSmithKline) 5-azacytidine 6-mercaptopurine (Mercaptopurine, 6-MP) Azathioprine / Azasan® (AAIPHARMA LLC) 6-thioguanine (6-TG) / Purinethol® (TEVA) Pentostatin / Nipent® (Hospira Inc.) Fludarabine phosphate / Fludara® (Bayer Health Care) Cladribine (2-CdA, 2-chlorodeoxyadenosine) / Leustatin® (Ortho Biotech)
Alkylating agents	An alkylating antineoplastic agent is an alkylating agent that attaches an alkyl group to DNA. Since cancer cells generally proliferate unrestrictively more than do healthy cells they are more sensitive to DNA damage, and alkylating agents are used clinically to treat a variety of tumors.	Ribonucleotide Reductase Inhibitor (RNR) Cyclophosphamide / Cytoxan (BMS) Neosar (TEVA) Ifosfamide / Mitoxana® (ASTA Medica) Thiotepa (Bedford, Abraxis, Teva) BCNU→ 1,3-bis(2-chloroethyl)-1-nitosourea CCNU→ 1, -(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (methyl CCNU) Hexamethylmelamine (Altretamine, HMM) / Hexalen® (MGI Pharma Inc.) Busulfan / Myleran (GlaxoSmithKline) Procarbazine HCL/ Matulane (Sigma Tau Pharmaceuticals, Inc.) Dacarbazine (DTIC) Chlorambucil / Leukara® (SmithKline Beecham) Melphalan / Alkeran® (GlaxoSmithKline) Cisplatin (Cisplatinum, CDDP) / Platinol (Bristol Myers) Carboplatin / Paraplatin (BMS) Oxaliplatin /Eloxitan® (Sanofi-Aventis US)

Topoisomerase inhibitors	Topoisomerase inhibitors are chemotherapy agents designed to interfere with the action of topoisomerase enzymes (topoisomerase I and II), which are enzymes that control the changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle.	Doxorubicin HCL / Doxil® (Alza) Daunorubicin citrate / Daunoxome® (Gilead) Mitoxantrone HCL / Novantrone (EMD Serono) Actinomycin D Etoposide / Vepesid® (BMS)/ Etopophos® (Hospira, Bedford, Teva Parenteral, Etc.) Topotecan HCL / Hycamtin® (GlaxoSmithKline) Teniposide (VM-26) / Vumon® (BMS) Irinotecan HCL(CPT-ll) / Camptosar® (Pharmacia & Upjohn)
Microtubule targeting agents	Microtubules are one of the components of the cytoskeleton. They have diameter of ~24 nm and length varying from several micrometers to possibly millimeters in axons of nerve cells. Microtubules serve as structural components within cells and are involved in many cellular processes including mitosis, cytokinesis, and vesicular transport.	Vincristine / Oncovin® (Lilly) Vinblastine sulfate / Velban®(discontinued) (Lilly) Vinorelbine tartrate / Navelbine® (PierreFabre) Vindesine sulphate / Eldisine® (Lilly) Pac1itaxel / Taxol® (BMS) Docetaxel / Taxotere® (Sanofi Aventis US) Nanoparticle paclitaxel (ABI-007) / Abraxane® (Abraxis BioScience, Inc.) Ixabepilone / IXEMPRA™ (BMS)
Kinase inhibitors	Tyrosine kinases are enzymes within the cell that function to attach phosphate groups to the amino acid tyrosine. By blocking the ability of protein tyrosine kinases to function, these compounds provide a tool for controlling cancerous cell growth.	Imatinib mesylate / Gleevec (Novartis) Sunitinib malate / Sutent® (Pfizer) Sorafenib toslate / Nexavar® (Bayer) Nilotinib hydrochloride monohydrate / Tasigna® (Novartis)
Protein synthesis inhibitors	Induces cell apoptosis	L-asparaginase / Elspar® (Merck & Co.)
Immunotherapeutic agents	Induces cancer patients to exhibit immune responsiveness	Alpha interferon Angiogenesis Inhibitor / Avastin® (Genentech) IL-2→ Interleukin 2 (Aldesleukin) / Proleukin ® (Chiron) IL-12→ Interleukin 12

Hormones	Hormone therapies associated with menopause and aging seek to increase the amount of certain hormones in your body to compensate for age- or disease-related hormonal declines. Hormone therapy as a cancer treatment either reduces the level of specific hormones or alters the cancer's ability to use these hormones to grow and spread.	Toremifene citrate / Fareston® (GTX, Inc.) Fulvestrant / Faslodex® (AstraZeneca) Raloxifene HCL / Evista® (Lilly) Anastrazole / Arimidex® (AstraZeneca) Letrozole / Femara® (Novartis) Fadrozole (CGS 16949A) Exemestane / Aromasin® (Pharmacia & Upjohn) Leuprolide acetate / Eligard® (QTL USA) Lupron® (TAP Pharm) Goserelin acetate / Zoladex® (AstraZeneca) Triptorelin pamoate / Trelstar® (Watson Labs) Buserelin / Suprefact® (Sanofi Aventis) Nafarelin Cetrorelix / Cetrotide® (EMD Serono) Bicalutamide / Casodex® (AstraZeneca) Nilutamide / Nilandron® (Aventis Pharm.) Megestrol acetate / Megace® (BMS) Somatostatin Analogs (Octreotide acetate / Sandostatin® (Novartis)
Glucocorticoids	Anti-inflammatory drugs used to reduce swelling that causes cancer pain.	Predinsolone Dexamethasone / Decadron® (Wyeth)
Aromatose inhibitors	Includes imidazoles	Ketoconazole
mTOR inhibitors	the mTOR signaling pathway was originally discovered during studies of the immunosuppressive agent rapamycin. This highly conserved pathway regulates cell proliferation and metabolism in response to environmental factors, linking cell growth factor receptor signaling via phosphoinositide-3-kinase(PI-3K) to cell growth, proliferation, and angiogenesis.	Sirolimus (Rapamycin) / Rapamune® (Wyeth) Temsirolimus (CCI-779) / Torisel® (Wyeth) Deforolimus (AP23573) / (Ariad Pharm.) Everolimus (RAD00I) / Certican® (Novartis)

In addition to the above anti-cancer agents, the anti-PRLR antibodies described herein may be administered in combination with the agents described in section II. Further, the aforementioned anti-cancer agents may also be used in the ADCs of the invention.

In particular embodiments, the anti-PRLR antibodies can be administered alone or with another anti-cancer agent which acts in conjunction with or synergistically with the antibody to treat the disease associated with PRLR activity. Such anti-cancer agents include, for example,

agents well known in the art (*e.g.*, cytotoxins, chemotherapeutic agents, small molecules and radiation). Examples of anti-cancer agents include, but are not limited to, Panorex (Glaxo-Welcome), Rituxan (IDEC/Genentech/Hoffman la Roche), Mylotarg (Wyeth), Campath (Millennium), Zevalin (IDEC and Schering AG), Bexxar (Corixa/GSK), Erbitux (Imclone/BMS), Avastin (Genentech) and Herceptin (Genentech/Hoffman la Roche). Other anti-cancer agents include, but are not limited to, those disclosed in U.S. Patent No. 7,598,028 and International Publication No. WO2008/100624, the contents of which are hereby incorporated by reference. One or more anti-cancer agents may be administered either simultaneously or before or after administration of an antibody or antigen binding portion thereof of the present invention.

Further examples of preferred additional therapeutic agents that can be co-administered and/or formulated with one or more PRLR antagonists, *e.g.*, anti- PRLR antibodies or fragments thereof, include, but are not limited to, one or more of: inhaled steroids; beta-agonists, *e.g.*, short-acting or long- acting beta-agonists; antagonists of leukotrienes or leukotriene receptors; combination drugs such as ADVAIR; IgE inhibitors, *e.g.*, anti-IgE antibodies (*e.g.*, XOLAIR); phosphodiesterase inhibitors (*e.g.*, PDE4 inhibitors); xanthines; anticholinergic drugs; mast cell-stabilizing agents such as cromolyn; IL-4 inhibitors; IL-5 inhibitors; eotaxin/CCR3 inhibitors; antagonists of histamine or its receptors including H1, H2, H3, and H4, and antagonists of prostaglandin D or its receptors (DP1 and CRTH2). Such combinations can be used to treat asthma and other respiratory disorders. Additional examples of therapeutic agents that can be co-administered and/or formulated with one or more anti-PRLR antibodies or fragments thereof include one or more of: TNF antagonists (*e.g.*, a soluble fragment of a TNF receptor, *e.g.*, p55 or p75 human TNF receptor or derivatives thereof, *e.g.*, 75 kD TNFR-IgG (75 kD TNF receptor-IgG fusion protein, ENBREL)); TNF enzyme antagonists, *e.g.*, TNF converting enzyme (TACE) inhibitors; muscarinic receptor antagonists; TGF-beta antagonists; interferon gamma; perfenidone; chemotherapeutic agents, *e.g.*, methotrexate, leflunomide, or a sirolimus (raparnycin) or an analog thereof, *e.g.*, CCI-779; COX2 and cPLA2 inhibitors; NSAIDs; immunomodulators; p38 inhibitors, TPL-2, MK-2 and NFkB inhibitors, among others.

Other preferred combinations are cytokine suppressive anti-inflammatory drug(s) (CSAIDs); antibodies to or antagonists of other human cytokines or growth factors, for example, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-15, IL-16, IL-18, IL-21, IL-31, interferons, EMAP-II, GM-CSF, FGF, EGF, PDGF, and edothelin-1, as well as the receptors of these cytokines and growth factors. Antibodies of the invention, or antigen binding portions thereof, can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, CTLA or their ligands including CD154 (gp39 or CD40L).

Preferred combinations of therapeutic agents may interfere at different points in the inflammatory cascade; preferred examples include TNF antagonists like chimeric, humanized or human TNF antibodies, adalimumab, (HUMIRA; D2E7; PCT Publication No. WO 97/29131), CA2 (RemicadeTM), CDP 571, and soluble p55 or p75 TNF receptors, derivatives, thereof, (p75TNFR1gG (EnbrelTM) or p55TNFR1gG (Lenercept), and also TNF converting enzyme (TACE) inhibitors; similarly IL-1 inhibitors (Interleukin-1-converting enzyme inhibitors, IL-1RA etc.) may be effective for the same reason. Other preferred combinations include Interleukin 4.

The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may be determined by a person skilled in the art and may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody, or antibody portion, are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Dosage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.1-20 mg/kg, more preferably 1-10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to

be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the methods of the invention described herein are obvious and may be made using suitable equivalents without departing from the scope of the invention or the embodiments disclosed herein. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

Example 1: Generation and isolation of anti human PRLR monoclonal antibodies

1 Humanization of PRLR antibodies

1.1 Human germline sequence selections for constructing CDR-grafted, humanized PRLR antibodies

By applying the humanization methodology, the CDR sequences of VH and VL chains of monoclonal antibodies Ab5, Ab6, Ab7 and Ab8 were grafted onto different human heavy and light chain acceptor sequences as follows:

1.1.1 Ab6

Ab1 refers to humanized antibodies derived from murine Ab6. Based on the alignments with the VH and VL sequences of monoclonal antibody Ab6 of the present invention, the following known human sequences were selected:

1. IGHV1-69*02 and IGHJ6*01 for constructing heavy chain acceptor sequences
2. IGKV1-12*01 or IGKV3-15*01 and IGKJ4*01 for constructing light chain acceptor sequences

By grafting the corresponding VH and VL CDRs of Ab6 into said acceptor sequences, the CDR-grafted, humanized, and modified VH and VL sequences were prepared.

1.1.2 Ab5

Ab2 refers to humanized antibodies derived from murine Ab5. Based on the alignments with the VH and VL sequences of monoclonal antibody Ab5 of the present invention, the following known human sequences were selected:

1. IGHV1-69*01 and IGHJ4*01 for constructing heavy chain acceptor sequences
2. IGKV2-29*02 and IGKJ4*01 for constructing light chain acceptor sequences

By grafting the corresponding VH and VL CDRs of Ab5 into said acceptor sequences, the CDR-grafted, humanized, and modified VH and VL sequences were prepared.

1.1.3 Ab8

Ab3 refers to humanized antibodies derived from murine Ab8. Based on the alignments with the VH and VL sequences of monoclonal antibody Ab8 of the present invention the following known human sequences were selected:

1. IGHV1-18*01 and IGHJ6*01 for constructing heavy chain acceptor sequences
2. IGKV1D-39*01 and IGKJ2*01 for constructing light chain acceptor sequences

By grafting the corresponding VH and VL CDRs of Ab8 into said acceptor sequences, the CDR-grafted, humanized, and modified VH and VL sequences were prepared.

1.1.4 Ab7

Ab4 refers to humanized antibodies derived from murine Ab7. Based on the alignments with the VH and VL sequences of monoclonal antibody Ab7 of the present invention the following known human sequences were selected:

1. IGHV1-69*06 and IGHJ4*01 for constructing heavy chain acceptor sequences
2. IGKV2-29*02 and IGKJ4*01 for constructing light chain acceptor sequences

By grafting the corresponding VH and VL CDRs of Ab7 into said acceptor sequences, the CDR-grafted, humanized, and modified VH and VL sequences were prepared.

1.2 Introducing potential framework back-mutations in CDR-grafted antibodies

To generate humanized antibody with potential framework back-mutations, the mutations were identified and introduced into the CDR-grafted antibody sequences by *de novo* synthesis of the variable domain, or mutagenic oligonucleotide primers and polymerase chain reactions, or both by methods well known in the art. Different combinations of back mutations and other mutations were constructed for each of the CDR-grafts as follows. Residue numbers for these mutations were based on the Kabat numbering system.

1.2.1 Ab1

For heavy chains Ab1VH.1z, one or more of the following residues were back mutated as follows: M48→I, V67→A, I69→L, and A71→V. Additional mutations included the following: Q1→E, Y27→G, N60→A, K64→Q, and D65→G.

For light chain Ab1VL.1, one or more of the following residues were back mutated as follows: A43→S, G64→D, and Y87→F.

1.2.2 Ab2

For heavy chains Ab2VH.1z, one or more of the following residues were back mutated as follows: M48→I, V67→A, I69→L, A71→V, and T75→S. Additional mutations included the following: Q1→E, Y27→G, N60→A, and K64→Q.

For light chain Ab2VL.1, one or more of the following residues were back mutated as follows: I2→V and Y87→F.

1.2.3 Ab3

For heavy chains Ab3VH.1z, one or more of the following residues were back mutated as follows: M48→I, V67→A, M69→L, T71→V, and T73→N. Additional mutations included the following: Q1→E, N60→A, F63→L, K64→Q, and S65→G.

For light chain Ab3VL.1, one or more of the following residues were back mutated as follows: A43→P and I48→V.

1.2.4 Ab4

For heavy chains Ab4 VH.1z, one or more of the following residues were back mutated as follows: M48→I, V67→A, I69→L, A71→V, K73→R, T75→S, and A93→G. Additional mutations included the following: Q1→E.

For light chain Ab4 VL.1, one or more of the following residues were back mutated as follows: I2→V and Y87→F.

1.3 Generation of humanized antibodies to PRLR containing framework back-mutations in CDR-grafted antibodies

The following humanized variable regions of the murine monoclonal PRLR antibodies were cloned into IgG expression vectors for functional characterization.

1.3.1 Ab1

TABLE 9: Sequences of humanized variable regions for Ab1 antibody

SEQ ID NO:	Protein region	Sequence
		123456789**0**123456789**0**123456789**0**
39	Ab1 VH.1z	QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTTYWM** **H**WVRQAPGQGLEWMG**EIDPSDSYSNYNQKFKD**RV TITADKSTSTAYMELSSLRSEDTAVYYCAR**NGGL** **GPAWFSY**WGQGTLVTVSS
43	Ab1 VH.1	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTTYWM** **H**WVRQAPGQGLEWMG**EIDPSDSYSNYNQKFKD**RV TITADKSTSTAYMELSSLRSEDTAVYYCAR**NGGL** **GPAWFSY**WGQGTLVTVSS
44	Ab1 VH.1a	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTTYWM** **H**WVRQAPGQGLEWIG**EIDPSDSYSNYNQKFKD**RA TLTVDKSTSTAYMELSSLRSEDTAVYYCAR**NGGL** **GPAWFSY**WGQGTLVTVSS
45	Ab1 VH.1b	EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFTTYWM** **H**WVRQAPGQGLEWIG**EIDPSDSYSNYAQKF**QGRV TITVDKSTSTAYMELSSLRSEDTAVYYCAR**NGGL** **GPAWFSY**WGQGTLVTVSS

SEQ ID NO:	Protein region	Sequence
		123456789012345678901234567890
48	Ab1 VL.1	DIQMTQSPSSVSASVGDRVTITC**KASQYVGT** **AVA**WYQQKPGKAPKLLIY**SASNRYT**GVPSRF SGSGSGTDFTLTISSLQPEDFATYYC**QQYSS** **YPWT**FGGGTKVEIK
52	Ab1 VL.1a	DIQMTQSPSSVSASVGDRVTITC**KASQYVGT** **AVA**WYQQKPGKSPKLLIY**SASNRYT**GVPSRF SDSGSGTDFTLTISSLQPEDFATYFC**QQYSS** **YPWT**FGGGTKVEIK
53	Ab1 VL.2	EIVMTQSPATLSVSPGERATLSC**KASQYVGT** **AVA**WYQQKPGQAPRLLIY**SASNRYT**GIPARF SGSGSGTEFTLTISSLQSEDFAVYYC**QQYSS** **YPWT**FGGGTKVEIK
54	Ab1 VL.2a	EIVMTQSPATLSVSPGERATLSC**KASQYVGT** **AVA**WYQQKPGQSPRLLIY**SASNRYT**GVPARF SDSGSGTEFTLTISSLQSEDFAVYFC**QQYSS** **YPWT**FGGGTKVEIK

- **Ab1 VH.1z** is a CDR-grafted, humanized Ab6 VH containing IGHV1-69*02 and IGHJ6*01 framework sequences.
- **Ab1 VH.1** is based on .1z with a Q1E change.
- **Ab1 VH.1a** is a humanized design based on .1 and contains four proposed framework back-mutations M48I, V67A, I69L, and A71V.
- **Ab1 VH.1b** is an intermediate design between .1 and .1a and only has two back-mutations M48I and A71V. It also has four CDR human germlining changes Y27G, N60A, K64Q, and D65G.
- **Ab1 VL.1** is a CDR-grafted humanized Ab6 VL containing IGKV1-12*01 and IGKJ4*01 framework sequences.
- **Ab1 VL.1a** is a humanized design based on .1 with 3 proposed framework back-mutations (A43S, G64D, and Y87F).
- **Ab1 VL.2** is a CDR-grafted humanized Ab6 VL containing IGKV3-15*01 and IGKJ4*01 framework sequences.
- **Ab1 VL.2a** is a humanized design based on .1 with 4 proposed framework back-mutations (A43S, I58V, G64D, and Y87F).

1.3.2 Ab2

TABLE 10: Sequences of humanized variable regions for Ab2 Antibody

SEQ ID NO:	Protein region	Sequence
		1234567890123456789012345678900
55	Ab2 VH.1z	QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSFWM** **H**WVRQAPGQGLEWMG**VIDPSDTYTNYNQKFKG**RV TITADESTSTAYMELSSLRSEDTAVYYCAR**GDYS** **NWFTY**WGQGTLVTVSS
59	Ab2 VH.1	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSFWM** **H**WVRQAPGQGLEWMG**VIDPSDTYTNYNQKFKG**RV TITADESTSTAYMELSSLRSEDTAVYYCAR**GDYS** **NWFTY**WGQGTLVTVSS
60	Ab2 VH.1a	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSFWM** **H**WVRQAPGQGLEWIG**VIDPSDTYTNYNQKFKG**RA TLTVDESSSTAYMELSSLRSEDTAVYYCAR**GDYS** **NWFTY**WGQGTLVTVSS
61	Ab2 VH.1b	EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFTSFWM** **H**WVRQAPGQGLEWIG**VIDPSDTYTNYAQKFQG**RV TITVDESTSTAYMELSSLRSEDTAVYYCAR**GDYS** **NWFTY**WGQGTLVTVSS
64	Ab2 VL.1	DIVMTQTPLSLSVTPGQPASISC**RSSQRLVH** **SNGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC **SQSTHVPWT**FGGGTKVEIK
68	Ab2 VL.1a	DVVMTQTPLSLSVTPGQPASISC**RSSQRLVH** **SNGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYFC **SQSTHVPWT**FGGGTKVEIK
69	Ab2 VL.1b	DVVMTQTPLSLSVTPGQPASISC**RSSQRLVH** **SNGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC **SQSTHVPWT**FGGGTKVEIK

- **Ab2 VH.1z** is a CDR-grafted, humanized Ab5 VH containing IGHV1-69*01 and IGHJ4*01 framework sequences.
- **Ab2 VH.1** is based on .1z with a Q1E change.
- **Ab2 VH.1a** is a humanized design based on .1 and contains five proposed framework back-mutations M48I, V67A, I69L, A71V, and T75S.
- **Ab2 VH.1b** is an intermediate design between .1 and .1a and only has two back-mutations M48I and A71V. It also has three CDR human germlining changes Y27G, N60A, and K64Q.
- **Ab2VL.1** is a CDR-grafted humanized Ab5 VL containing IGKV2-29*02 and IGKJ4*01 framework sequences.
- **Ab2 VL.1a** is a humanized design based on .1 with 2 proposed framework back-mutations (I2V and Y87F).
- **Ab2 VL.1b** is an intermediate design between .1 and .1a with 1 proposed framework back-mutation I2V.

Ab3

TABLE 11: Sequences of humanized variable regions for Ab3 Antibody

SEQ ID NO:	Protein region	Sequence
		12345678901234567890123456789 0
70	Ab3 VH.1z	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDYNI** **H**WVRQAPGQGLEWMG**YIYPNNDGTGYNQKFKS**RV TMTTDTSTSTAYMELRSLRSDDTAVYYCAR**GDGN** **YVGDMDY**WGQGTTVTVSS
74	Ab3 VH.1	EVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDYNI** **H**WVRQAPGQGLEWMG**YIYPNNDGTGYNQKFKS**RV TMTTDTSTSTAYMELRSLRSDDTAVYYCAR**GDGN** **YVGDMDY**WGQGTTVTVSS
75	Ab3 VH.1a	EVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDYNI** **H**WVRQAPGQGLEWIG**YIYPNNDGTGYNQKFKS**RA TLTVDNSTSTAYMELRSLRSDDTAVYYCAR**GDGN** **YVGDMDY**WGQGTTVTVSS
76	Ab3 VH.1b	EVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDYNI** **H**WVRQAPGQGLEWIG**YIYPNNDGTGYAQKLQG**RV TMTVDTSTSTAYMELRSLRSDDTAVYYCAR**GDGN** **YVGDMDY**WGQGTTVTVSS
78	Ab3 VL.1	DIQMTQSPSSLSASVGDRVTITC**RASENIYS** **YLA**WYQQKPGKAPKLLIY**NAKTLAE**GVPSRF SGSGSGTDFTLTISSLQPEDFATYYC**QHHYA** **TPFT**FGQGTKLEIK
82	Ab3 VL.1a	DIQMTQSPSSLSASVGDRVTITC**RASENIYS** **YLA**WYQQKPGKPPKLLVY**NAKTLAE**GVPSRF SGSGSGTDFTLTISSLQPEDFATYYC**QHHYA** **TPFT**FGQGTKLEIK
83	Ab3 VL.1b	DIQMTQSPSSLSASVGDRVTITC**RASENIYS** **YLA**WYQQKPGKAPKLLVY**NAKTLAE**GVPSRF SGSGSGTDFTLTISSLQPEDFATYYC**QHHYA** **TPFT**FGQGTKLEIK

- **Ab3 VH.1z** is a CDR-grafted, humanized Ab8 VH containing IGHV1-18*01 and IGHJ6*01 framework sequences.
- **Ab3 VH.1** is based on .1z with a Q1E change.
- **Ab3 VH.1a** is a humanized design based on .1 and contains five proposed framework back-mutations M48I, V67A, M69L, T71V, and T73N.
- **Ab3 VH.1b** is an intermediate design between .1 and .1a and only has two back-mutations M48I and T71V. It also has four HCDR2 human germlining changes N60A, F63L, K64Q, and S65G.
- **Ab3 VL.1** is a CDR-grafted humanized Ab8 VL containing IGKV1D-39*01 and IGKJ2*01 framework sequences.
- **Ab3 VL.1a** is a humanized design based on .1 with 2 proposed framework back-mutations (A43P and I48V).
- **Ab3 VL.1b** is an intermediate design between .1 and .1a with 1 proposed framework back-mutation I48V.

1.3.3 Ab4

TABLE 12: Sequences of humanized variable regions for Ab4 antibody

SEQ ID NO:	Protein region	Sequence
		123456789**0**123456789**0**1234567890
84	Ab4 VH.1z	QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSYWI** **H**WVRQAPGQGLEWMG**EIDPSDSYTNYNQKFKG**RV TITADKSTSTAYMELSSLRSEDTAVYYCAR**SFFT** **NWFAY**WGQGTLVTVSS
88	Ab4 VH.1	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSYWI** **H**WVRQAPGQGLEWMG**EIDPSDSYTNYNQKFKG**RV TITADKSTSTAYMELSSLRSEDTAVYYCAR**SFFT** **NWFAY**WGQGTLVTVSS
89	Ab4 VH.1a	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSYWI** **H**WVRQAPGQGLEWI**GEIDPSDSYTNYNQKFKG**RA TLTVDKSSSTAYMELSSLRSEDTAVYYCAR**SFFT** **NWFAY**WGQGTLVTVSS
121	Ab4 VH.1a.2	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSYWI** **H**WVRQAPGQGLEWI**GEIDPSDSYTNYNQKFKG**RA TLTVDRSSSTAYMELSSLRSEDTAVYYCGR**SFFT** **NWFAY**WGQGTLVTVSS
122	Ab4 VH.1a.3	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSYWI** **H**WVRQAPGQGLEWI**GEIDPSDSYTNYNQKFKG**RA TLTVDKSSSTAYMELSSLRSEDTAVYYCGR**SFFT** **NWFAY**WGQGTLVTVSS
90	Ab4 VH.1b	EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFTSYWI** **H**WVRQAPGQGLEWI**GEIDPSDSYTNYAQKFQG**RV TITVDKSTSTAYMELSSLRSEDTAVYYCAR**SFFT** **NWFAY**WGQGTLVTVSS
123	Ab4 VH.1b.2	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSYWI** **H**WVRQAPGQGLEWI**GEIDPSDSYTNYNQKFKG**RV TITVDKSTSTAYMELSSLRSEDTAVYYCAR**SFFT** **NWFAY**WGQGTLVTVSS
91	Ab4 VL.1	DIVMTQTPLSLSVTPGQPASISC**RSSQSLVH** **SNGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC **SQSTHVPFT**FGGGTKVEIK
95	Ab4 VL.1a	DVVMTQTPLSLSVTPGQPASISC**RSSQSLVH** **SNGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYFC **SQSTHVPFT**FGGGTKVEIK
96	Ab4 VL.1b	DVVMTQTPLSLSVTPGQPASISC**RSSQSLVH** **SNGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**G VPDRFSGSGSGTDFTLKISRVEAEDVGVYYC **SQSTHVPFT**FGGGTKVEIK

- **Ab4 VH.1z** is a CDR-grafted, humanized Ab7 VH containing IGHV1-69*6 and JH4 framework sequences.
- **Ab4 VH.1** is based on .1z with a Q1E change.
- **Ab4 VH.1a** is a humanized design based on .1 and contains seven proposed framework back-mutations M48I, V67A, I69L, A71V, K73R, T75S, and A93G.
- **Ab4 VH.1b** is an intermediate design between .1 and .1a and only has two back-mutations M48I and A71V.

- **Ab4 VL.1** is a CDR-grafted humanized Ab7 VL containing IGKV2-29 and Jk4 framework sequences.
- **Ab4 VL.1a** is a humanized design based on .1 with 2 proposed framework back-mutations (I2V and Y87F).
- **Ab4 VL.1b** is an intermediate design between .1 and .1a with 1 proposed framework back-mutation I2V.

Example 2: Assaying Binding and Activity of PRLR Antibodies

The binding and activity of the PRLR antibodies of the invention were assayed as follows.

2.1 T47D pPRLR ELISA

T47D cells were plated at 60,000/well in 96-well plate in RPMI1640 medium containing 10% FBS, and were incubated overnight. The next day, the cell culture medium was switched to RPMI1640 medium without FBS. Cells were then treated with testing PRLR antibodies diluted in PBS buffer containing 0.1%BSA at concentrations ranging from 0.001 to 10 ug/mL for 60 min at 37C. At the end of treatment, cells were stimulated with 100 ng/mL hPRL (R&D Systems) for 15 min at 37C. Cells were then lysed with cell lysis buffer (Cell Signaling) for 20min at 4C. The cell lysates were analyzed for phospho-PRLR levels using the human phosphor-PRLR ELISA DuoSet IC kit from R&D System (#DYC4058). Results are depicted in Table 13.

This assay was used as an initial screen because phosphorylation of PRLR is a direct response to stimulation of the receptor, and blocking of this activity is correlated to inhibition of PRLR signaling. All antibodies exhibited inhibition of phosphorylation of PRLR.

2.2 Cell Proliferation Assays

2.2.1 Baf3-xPRLR cell proliferation assay

Engineered Baf3-xPRLR cell lines were maintained in RPMI1640 medium with 10%FBS and 10ng/mL hPRL (R&D Systems). Cells were seeded in 96-well plate at 10,000/well in regular culture medium containing 10ng/mL hPRL. Cells were then treated with testing PRLR antibodies diluted in PBS buffer with 0.1%BSA at concentrations 0.001-10ug/mL for 3 days at 37C. After incubation, cell proliferation was measured using standard CellTiter- Glo Luminescent Viability Assay kit (Promega). Results are depicted in Table 13.

2.2.2 Nb2-11 cell proliferation assay

Nb2-11 cells (Sigma) were maintained in Complete medium (RPMI1640, 10% FBS, 10% horse serum, 0.05mM 2-mercaptoethanol, 0.075% sodium bicarbonate). Cells were switched to

Stationary medium (RPMI1640, 10% horse serum, 0.05mM 2-mercaptoethanol, 0.075% sodium bicarbonate) plus 1% FBS on the day before the assay. For PRL-dependent proliferation assay, Nb2-11 cells were washed and resuspended in Stationary medium plus 1ng/mL hPRL (R&D Systems) at 250k cells / mL. Cells were plated in 96-well plate at 90uL/well, and were treated with 10uL of testing PRLR antibodies diluted in PBS buffer with 0.1%BSA at final concentrations 0.001-10ug/mL for 3 days at 37C. After incubation, cell proliferation was measured using standard CellTiter- Glo Luminescent Viability Assay kit (Promega). Results are depicted in Table 13.

2.2.3 Conclusions

Rat Nb-211 and Ba/F3 cells expressing mouse, cyno, and human PRLR expression are all dependent on PRLR signaling for proliferation, so this sensitive assay was used to assess blockage of PRLR signaling on cells for these different species *in vitro*. The human results paralleled those seen with the pPRLR assay. Activity was generally maintained in the humanized versions, *e.g.*, Ab1, Ab2, Ab3 and Ab4. Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab8, Ab9, Ab11 and Ab13 demonstrated PRLR inhibition for cynoPRLR and human PRLR, with Ab1, Ab2, Ab4, Ab5, Ab6, Ab7, Ab9 and Ab13 being particularly efficacious. Ab2, Ab4 and Ab7 demonstrated particularly efficacious PRLR inhibitory activity for mouse and rat PRLR.

2.3 ELISA binding assay for extra cellular domains (ECD)

Plates were coated overnight with goat anti-human Fc region antibody (1 ug/ml) for human, mouse and rat PRLR ECD-Fc fusion proteins, and mouse anti-his for cyno PRLR ECD-his6 protein in 1x PBS (pH 7.4). For cyno PRLR ECD binding experiments to mouse antibodies, cyno PRLR ECD-his6 protein was directly bound to the ELISA plate. Plates were blocked for 1 hour with Superblock (Pierce) and washed (3x) with wash buffer (1x PBS (pH 7.4), 0.05% Tween 20). ECD proteins were bound to the appropriate antibody (1 hour) in binding buffer (wash buffer plus 10% Superblock), washed (3x, wash buffer), and then incubated with serial dilutions of antibodies (1 hour) in binding buffer. After washing (3x, wash buffer), secondary antibodies conjugated to HRP were bound (1 hour) in binding buffer, washed (3x, wash buffer), and incubated with TMB substrate (Pierce) to develop signal for 3-5 minutes, stopped with 2N H_2SO_4 and scanned at 450 nM. Curves were fit with GraphPad 5 (Prizm) and EC50's were determined with curve fitting function of GraphPad 5. Results are depicted in Table 13.

The binding ELISA data correlated to the proliferation inhibition data.

2.4 FACS binding assay:

Nb2-11 and Baf3-xPRLR cells were resuspended in FACS buffer (PBS + 1%FBS) at 2 millions cells / mL. Cells were added to round bottom 96-well plate (100uL/well) and treated with testing PRLR antibodies for 1hr at 4C. Cells were then washed with FACS buffer twice and incubated with 2nd antibody conjugated to ALEXA488 (Invitrogen) for 1hr at 4C. After two washes in FACS buffer, cells were resuspended in 1% formaldehyde in PBS. Cells were analyzed using LSRII flowcytometer. Results are depicted in Table 13.

The FACS data also correlated with the proliferation data. Humanized antibodies were not subjected to the FACS binding assay.

2.5 Biacore binding

Running buffer was HBS-EP+ (10mM Hepes, pH7.5, 150mM NaCl, 3mM EDTA, 0.05% Tween 20). [PRLR] at 600nM, 66.67nM and 7.41nM (3 point, 9-fold dilution series), fit to a 1:1 binding model (local Rmax, MT term included) using Biacore T200 Evaluation Software. Results are depicted in Table 14.

The Biacore data provides more detailed biochemical binding information. The lower affinity binding of the humanized antibodies to mouse PRLR are more accurately quantified with this assay.

Analysis of the results in Figure 11 demonstrate that chAb7 has a high affinity for human PRLR. Further, upon humanization of the chimeric antibody to make the humanized antibodies Ab36 and Ab39, the affinity decreases by ~45-fold and ~22-fold, respectively. The decreases in affinity are primarily due to changes in the k_{off} rate. While back mutations performed on Ab36 (*i.e.*, Ab53) did not improve the antibody affinity, back mutations performed on Ab39 (*i.e.*, Ab54 and Ab55) increased the affinity to a level that was approximately 4-fold and 5-fold weaker than that observed with chAb7. Analysis of the results in Figure 10 indicated that all the mAbs show significantly and proportionally weaker binding kinetics for murine PRLR.

TABLE 13: SUMMARY OF FINDINGS FROM EXAMPLES 2.1 (T47D pPRLR ELISA), 2.2 (Baf3-xPRLR and NB2-11 CELL PROLIFERATION ASSAYS), 2.3 (ELISA BINDING ASSAY FOR ECD) & 2.4 (FACS BINDING ASSAY)

		Cell Phospho-ELISA	Cell Proliferation Assay				Binding ELISA				FACS (GeoMean-neg)		
Antibody	**Isotype**	**T47D pPRLR IC50 (ug/mL)**	**Baf3-hPRLR IC50 (ug/mL)**	**Baf3-cyPRLR IC50 (ug/mL)**	**Baf3-mPRLR IC50 (ug/mL)**	**Nb2-11 IC50 (ug/mL)**	**Human EC50 (pM)**	**Cyno EC50 (pM)**	**Rat EC50 (pM)**	**Mouse EC50 (pM)**	**T47D 10ug/mL**	**Nb2-11 20ug/mL**	**Baf3-mPRLR 10ug/mL**
Ab6	G1	0.039	0.26	0.44	>30	>30	86	>5000	>5000	>5000	1838	0	0
Ab5	G2a	0.038	0.24	0.38	1.03	0.91	71	95	80	98	1607	90	166
Ab8	G2b	0.219	1.15	1.64	>30	>30	98	>5000	205	342	1532	17	1
Ab7	G1	0.080	0.28	0.30	3.55	4.42	98	202	135	143	2380	82	27
Ab13	G2a	0.047	0.32	0.85	4.69	7.56	70	143	85	88	1499	60	143
Ab9	G2b	0.072	0.51	6.40	>30	>30	72	>5000	>5000	>5000	1871	0	1
Ab10	G2a	0.362	3.14	>10	>30	>30	147	>5000	234	1137	2723	16	49
Ab11	G1	0.047	1.11	1.20	18.52	>30	93	153	87	86	2220	94	25
Ab12	G2a	0.538	stimulatory	>30	>30	stimulatory	69	<4000	146	121	1680	17	90
chAb6	G1		0.28	12.17	no	no	103	72	>1000	>10000			
chAb5	G1		0.15	0.42	2.51	0.69	98	103	147	120			
chAb8	G1		0.30	2.94	no	no	80	191	305	1017			
chAb7	G1		1.2	1.9	3.6	16.8	151	118	157	184			
chAb9	G1		0.20	10.44	no	no							
chAb12	G1		10.74	>10	no	41.37							
Ab14	G1		0.30	1.15	>30		32.86	30.98	>10000	>10000			
Ab15	G1		0.13	0.19	>30		78.06	55.05	>10000	>10000			
Ab16	G1		0.46	1.73	>30		64.07	67.14	>10000	>10000			
Ab17	G1		0.14	0.27	>30		76.58	78.79	>10000	>10000			
Ab18	G1		0.15	0.40	>30		67.52	110.8	>10000	>10000			

		Cell Phospho-ELISA	Cell Proliferation Assay				Binding ELISA				FACS (GeoMean-neg)		
Antibody	**Isotype**	**T47D pPRLR IC50 (ug/mL)**	**Baf3-hPRLR IC50 (ug/mL)**	**Baf3-cyPRLR IC50 (ug/mL)**	**Baf3-mPRLR IC50 (ug/mL)**	**Nb2-11 IC50 (ug/mL)**	**Human EC50 (pM)**	**Cyno EC50 (pM)**	**Rat EC50 (pM)**	**Mouse EC50 (pM)**	**T47D 10ug/mL**	**Nb2-11 20ug/mL**	**Baf3-mPRL 10ug/mL**
Ab19	G1		0.12	0.13	>30		61.36	57.55	>10000	>10000			
Ab20	G1		0.20	0.50	>30		83.57	71.08	>10000	>10000			
Ab21	G1		0.15	0.15	>30		72.76	53.75	>10000	>10000			
Ab22	G1		>30				>10000	>10000	>10000	>10000			
Ab23	G1		>30				>10000	>10000	>10000	>10000			
Ab24	G1		>30				>10000	>10000	>10000	>10000			
Ab25	G1		>30				>10000	>10000	>10000	>10000			
Ab26	G1		0.23	0.25	y*		198.9	151.3	163.7	201.3			
Ab27	G1		0.16	0.22	y		169.7	101.9	125.2	185.1			
Ab28	G1		0.22	0.31	y		196.8	96.5	416.2	291.6			
Ab29	G1		0.15	0.23	y		269.2	153.1	688.5	238.2			
Ab30	G1		0.14	0.24	y		220.5	100.1	423.1	197.5			
Ab31	G1		0.17	0.39	y		452.6	255.5	717.6	332.7			
Ab32	G1		>30				>10000	>10000	>10000	>10000			
Ab33	G1		>30				>10000	>10000	>10000	>10000			
Ab34	G1		>30				>10000	>10000	>10000	>10000			
Ab35	G1		0.38	0.65	>30		2495	320.4	>10000	>10000			
Ab36	G1		0.28	0.41	>30		556.4	538	>10000	>10000			
Ab37	G1		0.43	0.44	>30		183.7	185.8	>10000	>10000			
Ab38	G1		0.42	0.25	>30		346.3	263.5	>10000	>10000			
Ab39	G1		0.27	0.25	>30		180.3	459.8	>10000	>10000			
Ab40	G1		0.40	0.32	>30		4405	862.3	>10000	>10000			
Ab41	G1		4.38				>10000	>10000	>10000	>10000			
Ab42	G1		4.76				>10000	>10000	>10000	>10000			
Ab43	G1		6.75				>10000	>10000	>10000	>10000			
Ab44	G1		0.30	1.76	>30		43.45	94.52	>10000	>10000			

		Cell Phospho-ELISA	Cell Proliferation Assay				Binding ELISA				FACS (GeoMean-neg)		
Antibody	**Isotype**	**T47D pPRLR IC50 (ug/mL)**	**Baf3-hPRLR IC50 (ug/mL)**	**Baf3-cyPRLR IC50 (ug/mL)**	**Baf3-mPRLR IC50 (ug/mL)**	**Nb2-11 IC50 (ug/mL)**	**Human EC50 (pM)**	**Cyno EC50 (pM)**	**Rat EC50 (pM)**	**Mouse EC50 (pM)**	**T47D 10ug/mL**	**Nb2-11 20ug/mL**	**Baf3-mPRLR 10ug/mL**
Ab45	G1		0.31	2.24	>30		68.37	201	>10000	977.5			
Ab46	G1		0.30	1.72	>30		62.57	81.4	>10000	568.2			
Ab47	G1		0.40	3.01	>30		81.88	119.3	>10000	>10000			
Ab48	G1		0.40	4.87	>30		74.65	236.2	>10000	>10000			
Ab49	G1		0.37	3.49	>30		95.44	360.7	>10000	>10000			
Ab50	G1		0.51	41.58	>30		109.1	>10000	>10000	>10000			
Ab51	G1		0.55	100.04	>30		287.4	>10000	>10000	>10000			
Ab52	G1		0.51	304.52	>30		91.32	>10000	>10000	>10000			
Ab53	G1		1.03										
Ab54	G1		0.77										
Ab55	G1		0.92										
LFA102	G1	0.069	0.56	>30	>30	0.93	53	154	157		1636	98	4

TABLE 14: SUMMARY OF FINDINGS FROM EXAMPLE 2.5 (BIACORE BINDING ASSAY)

		Biacore: binding to human PRLR			Biacore: binding to cyno PRLR			Biacore: binding to murine PRLR		
	Isotype	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
Ab6	G1	1.28E+06	5.76E-04	4.50E-10	1.36E+06	1.09E-03	8.07E-10	6.22E+05	3.94E-01	6.35E-07
Ab5	G2a	3.55E+05	2.03E-04	5.72E-10	3.36E+05	2.35E-04	7.00E-10	2.02E+05	2.91E-03	1.44E-08
Ab8	G2b	5.36E+05	8.19E-05	1.53E-10	5.26E+05	1.16E-03	2.20E-09	1.80E+05	4.66E-02	2.59E-07
Ab7	G1	2.80E+05	4.27E-05	1.53E-10	2.59E+05	3.29E-05	1.27E-10	8.40E+04	3.50E-03	4.17E-08
Ab 13	G2a	4.33E+05	4.31E-04	9.97E-10						
Ab9	G2b	5.77E+05	1.31E-04	2.26E-10						
Ab10	G2a	1.61E+05	2.28E-04	1.41E-09						
Ab11	G1	3.05E+05	2.11E-02	6.92E-08						
Ab12	G2a	2.82E+05	1.86E-03	6.60E-09						
chAb6	G1	1.14E+06	5.36E-04	4.69E-10	1.30E+06	1.03E-03	7.94E-10	5.91E+05	3.60E-01	6.08E-07
chAb5	G1	3.56E+05	1.99E-04	5.58E-10	3.33E+05	2.23E-04	6.71E-10	2.00E+05	2.77E-03	1.38E-08
chAb8	G1	4.96E+05	9.10E-05	1.83E-10	5.14E+05	1.77E-03	3.44E-09	1.85E+05	5.38E-02	2.91E-07
chAb7	G1	2.48E+05	4.46E-05	1.80E-10	2.35E+05	3.61E-05	1.54E-10	7.95E+04	3.57E-03	4.49E-08
chAb9	G1									
chAb12	G1									
Ab14	G1	1.10E+06	4.58E-03	4.16E-09						
Ab15	G1	1.16E+06	9.72E-04	8.37E-10						
Ab16	G1	1.39E+06	5.62E-03	4.05E-09						
Ab17	G1	1.25E+06	1.32E-03	1.06E-09						
Ab18	G1	1.06E+06	1.71E-03	1.62E-09						
Ab19	G1	9.85E+05	4.03E-04	4.09E-10	1.05E+06	7.28E-04	6.91E-10	4.09E+05	2.52E-01	6.16E-07
Ab20	G1	1.04E+06	2.08E-03	2.00E-09				**	**	6.20E-07
Ab21	G1	1.06E+06	5.86E-04	5.54E-10				5.00E+05	2.60E-01	5.30E-07

		Biacore: binding to human PRLR			Biacore: binding to cyno PRLR			Biacore: binding to murine PRLR		
	Isotype	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
Ab22	G1	4.03E+05	1.67E-01	4.16E-07						
Ab23	G1									
Ab24	G1									
Ab25	G1									
Ab26	G1									
Ab27	G1	3.56E+05	4.43E-04	1.25E-09	3.33E+05	5.20E-04	1.56E-09	1.34E+05	5.12E-03	3.83E-08
Ab28	G1	3.44E+05	5.33E-04	1.55E-09	3.15E+05	6.19E-04	1.97E-09	1.17E+05	6.06E-03	5.20E-08
Ab29	G1	3.13E+05	5.60E-04	1.79E-09	3.01E+05	6.75E-04	2.24E-09	1.20E+05	6.34E-03	5.30E-08
Ab30	G1	3.39E+05	4.37E-04	1.29E-09	3.30E+05	5.23E-04	1.59E-09	1.40E+05	5.60E-03	4.00E-08
Ab31	G1	3.22E+05	5.37E-04	1.67E-09	3.10E+05	6.43E-04	2.08E-09	1.22E+05	6.82E-03	5.57E-08
Ab32	G1									
Ab33	G1									
Ab34	G1									
Ab35	G1	1.20E+05	1.60E-03	1.33E-08	1.05E+05	1.42E-03	1.35E-08	4.98E+04	7.85E-02	1.58E-06
Ab36	G1	1.57E+05	1.28E-03	8.13E-09	1.33E+05	1.14E-03	8.51E-09	4.98E+04	5.68E-02	1.14E-06
Ab37	G1	1.19E+05	1.46E-03	1.23E-08	1.07E+05	1.32E-03	1.23E-08	4.11E+04	6.87E-02	1.67E-06
Ab38	G1	1.41E+05	8.79E-04	6.22E-09	1.25E+05	7.56E-04	6.04E-09	5.30E+04	5.27E-02	9.94E-07
Ab39	G1	1.68E+05	7.15E-04	4.25E-09	1.53E+05	6.13E-04	4.01E-09	5.76E+04	4.27E-02	7.42E-07
Ab40	G1	1.53E+05	8.23E-04	5.38E-09	1.34E+05	7.19E-04	5.38E-09	4.50E+04	5.34E-02	1.19E-06
Ab41	G1									
Ab42	G1									
Ab43	G1									
Ab44	G1									
Ab45	G1									
Ab46	G1									
Ab47	G1									
Ab48	G1	5.46E+05	9.84E-05	1.80E-10	5.76E+05	5.63E-03	9.77E-09	2.17E+05	9.83E-02	4.53E-07
Ab49	G1	5.58E+05	1.20E-04	2.14E-10						

		Biacore: binding to human PRLR			Biacore: binding to cyno PRLR			Biacore: binding to murine PRLR		
	Isotype	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**
Ab50	G1									
Ab51	G1									
Ab52	G1									
Ab53	G1	1.2E+05	1.0E-03	8.5E-09	1.1E+05	8.9E-04	7.8E-09	4.0E+04	5.2E-02	1.3E-06
Ab54	G1	1.4E+05	1.4E-04	1.0E-09	1.4E+05	1.2E-04	8.5E-10	4.1E+04	7.0E-03	1.7E-07
Ab55	G1	1.7E+05	1.2E-04	6.7E-10	1.7E+05	9.8E-05	5.9E-10	4.4E+04	6.3E-03	1.4E-07
LFA102		5.6E+05	7.3E-04	1.3E-09	8.8E+05	9.5E-03	1.1E-08	6.2E+05	1.6E-02	2.6E-08

Example 3: Xenograft tumor growth inhibition assay

The effect of PRLR antibodies on the growth of Nb2-11 rat lymphoma xenograft tumors was evaluated. One million cancer cells suspended in S-MEM media (no calcium, no glutamine, Life Technologies Corporation) containing Matrigel (phenol red free, Becton Dickinson Biosciences Discovery Labware) were inoculated subcutaneously into the right hind flank of female SCID-beige mice (Charles Rivers Labs, 10 per group) on study day 0. Administration (IP) of antibodies or vehicle (normal saline) was initiated at the time of size match on day 7. The tumors were measured by a pair of calipers twice a week starting at the time of size match and tumor volumes were calculated according to the formula $V = L \times W^2/2$ (V: volume, mm^3; L: length, mm. W: width, mm). Tumor volume was measured for the duration of the experiment until the mean tumor volume in each group reached an endpoint of >1000 mm^3. Results are shown in Figure 5 and Table 15.

Table 15. Summary of the effects of PRLR antibodies in Nb2-11 xenograft model

Treatment	Dose route, regimen	% TGI[a]	% TGD[b]
Ab7	30 mg/kg IP, Q7Dx3	12	17
Ab6	30 mg/kg IP, Q7Dx3	-15	9
Ab11	30 mg/kg IP, Q7Dx3	-5	13
Ab5	30 mg/kg IP, Q7Dx3	78***	84***
Ab9	30 mg/kg IP, Q7Dx3	2	17

a. Tumor growth inhibition, %TGI = 100 - mean tumor volume of treatment group / mean tumor volume of control group x 100. The p values (as indicated by asterisks) are derived from Student's T test comparison of treatment group vs. control group. Based on day 26. *p<0.05, ** p<0.01, *** p<0.001.

b. Tumor growth delay, %TGD = (T – C) / C x 100, where T = median time to endpoint of treatment group and C = median time to endpoint of control group. The p values (as indicated by asterisks) derived from Kaplan Meier log-rank comparison of treatment group vs. treatment control group. Based on an endpoint of 1000 mm^3. *p<0.05, ** p<0.01, *** p<0.001.

Example 4: Anti-PRLR Epitope Grouping

The epitope groupings of the PRLR antibodies of the invention were determined using the pair-wise binding assay as follows.

Murine Antibodies: Ab5-Ab12

Running buffer was HBS-EP+ (10mM Hepes, pH7.4, 150mM NaCl, 3mM EDTA, 0.05% surfactant). Assay was performed using Biacore T100 and CM5 sensor chips with anti-mouse IgG (Pierce) or anti-human IgG (Pierce) in each flow cell. A PRLR antibody was captured in a flow cell. The flow cell was then blocked by injection of a control antibody (50µg/ml) prior to

the injection of the antigen. A second PRLR antibody (10µg/ml) was then injected. The binding response as a function of time was analyzed for each pairwise binding assay. Reciprocal binding assays were also performed. Results of assays performed with murine antibodies Ab5, Ab6, Ab7, Ab8, Ab9, Ab10, Ab11 and Ab12 are depicted in Figure 6.

Chimeric and Humanized Antibodies

Running buffer was HBS-EP+ (10mM Hepes, pH7.4, 150mM NaCl, 3mM EDTA, 0.05% surfactant). Assay was performed at 12°C using Biacore T200 and CM5 sensor chips with anti-human IgG (Pierce) amine-coupled in all 4 flow cells to ~2000 RU.

Separate test mAbs were captured in flowcells 2, 3 & 4 (flowcell 1 was reference, no test mAb). All 4 flowcells were then blocked by injection with isotype control mAb at 50ug/ml. All 4 flowcells were then injected with antigen or buffer only (buffer only is for double referencing, done for each mAb pair individually). All 4 flowcells were then injected with 2nd test mAb at 10ug/ml. All 4 flowcells were then regenerated with glycine, pH1.5.

The binding response as a function of time was analyzed for each pairwise binding assay. Reciprocal binding assays were also performed. Results of simultaneous binding assays performed with chAb7, Ab39, Ab40, chAb5, Ab30, chAb6, Ab19, Ab21, chAb8, Ab48, Ab49 and LFA102 are depicted in Figure 7 and Figure 8.

These assays, performed using both chimeric and humanzied antibodies, demonstrated that both the chimeric and the humanized antibodies recognized the same region of PRLR. Figure 7 shows the results of an antibody binding assay performed to determine if the chimeric and humanized forms of each root mean antibody compete with each other for binding to PRLR. These results indicate that the chimeric and humanized forms of each root mean antibody do compete with each other, thus suggesting that the humanization of the chimeric antibody did not significantly change the core epitope for any given root mean antibody. In other words, chimeric engineering or humanization did not change the relative epitope grouping for most antibodies when compared to the epitope grouping of the parental mouse antibodies. However, there was a small shift in the epitope grouping for the Ab5 derived mAbs relative to the Ab8 derived mAbs when compared to the prior epitope grouping for the mouse mAbs. This difference is more likely to be due to steric differences between mouse and human frameworks as opposed to a change in the actual epitope. For similar results see Zettlitz, K.A., et al., *Mol Biotechnol* (2010) 46: 265-278.

Example 5: Crystallization of chAb6 (Fab)-PRLR complex

Crystallization of the structure of the chAb6 Fab fragment-PRLR complex was performed and analyzed as follows.

Preparation and purification of the chAb6 Fab fragment:

The Fab fragment of chAb6 was prepared by papain cleavage of the parent mAb as detailed below. Papain was activated with 50mM cysteine in PBS, pH 7.4 buffer. The mAb chAb6 in PBS, pH 7.4 buffer was mixed with papain at 1:77 weight ratio of papain to mAb and incubated for 1 h at 37° C. The reaction was quenched with 6.25mM iodoacetamide. The mixture was purified on 8 ml Mab SelectSure resin (GE Healthcare) where the Fab fragment was collected as flow through. The flow through was concentrated using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). The concentrated mixture was purified on a 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare), pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer. Fractions containing the Fab fragment (monitored by UV absorbance at 280 nm) were pooled and frozen at – 80° C. Sample purity was assessed by analytical SEC, SDS-PAGE and mass spectrometry.

chAb6 Fab-PRLR complex preparation:

Recombinant human PRLR was expressed in a mammalian expression system and subsequently purified using techniques well known in the art. Recombinant human PRLR and the chAb6 Fab protein were mixed at a 1.15:1 molar ratio and incubated for 2 h at 22° C. The complex sample was loaded onto a 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer at 1 ml/min. Fractions containing the complex (monitored by UV absorbance at 280 nm) were pooled and concentrated to 44 mg/ml using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). Sample purity was assessed by analytical SEC and SDS-PAGE. Excess Fab-Complex protein was stored frozen at -80° C.

Crystallization of the chAb6 Fab - PRLR complex:

The protein complex was delivered at 43.9 mg/ml in 50mM HEPES pH 7.5, 50mM NaCl and was used diluted to 30 mg/ml for crystallization trials. Crystals grew using the vapor diffusion technique at 17°C. The reservoir solution was 25%(w/v) PEG 3350, 0.1M Bis-Tris pH 5.5, 0.1M ammonium sulfate. Crystallization drops were made using a 1:1 ratio of protein and reservoir solution. The crystals were cryo-protected using 10%(v/v) propylene glycol. Diffraction data were collected under gaseous nitrogen at 100K at the Canadian Light Source (Saskatoon, Canada).

X-ray structure of the chAb6 Fab - PRLR complex:

X-ray diffraction data extended to 1.93 Å resolution, and a full data set was processed with HKL2000 (HKL Research, Inc). The crystallographic space group is orthorhombic P212121 with unit cell parameters a=62 Å, b=83 Å, and c=135 Å. The statistics for the data set collected are provided in Table 16.

TABLE 16. X-RAY DIFFRACTION STATISTICS FOR chAb6 FAB-PRLR COMPLEX

Resolution (Å)	50 – 1.93
Unique Reflections	53,147
Rmerge (%)	9.9
Completeness (%)	99
Multiplicity	7.2

Structure determination:

The crystal structure was determined by molecular replacement. Partial search model for the VhVl, ChCl, and PRLR portions were generated and sequentially placed using the program MOLREP (Vagin et al, 1997) in the CCP4 suite of programs (Winn et al. 2011). The asymmetric unit contains one molecular complex, and symmetry mates complete the crystalline lattice with intermolecular contacts. The coordinates were refined against the data using the program autoBUSTER (Global Phasing, Ltd) and iterative rounds of graphical analysis and rebuilding into electron density with the program COOT (Emsley et al, 2010). Statistics for the resulting structure are provided in Table 17:

TABLE 17. REFINEMENT STATISTICS FOR THE chAb6 FAB-PRLR COMPLEX

Resolution (Å)	50 – 1.93
R / Rfree (%)	20.2 / 23.6
RMSDideal bonds (Å)	0.010
RMSDideal angles (°)	1.11

Intermolecular contacts are observed between the PRLR extracellular domain and multiple chAb6 Fab CDRs. The contacts are comprised of critical hydrophobic and hydrophilic interactions and include bridging water molecules. These contacts directly engage CDR's H1, H2, H3, and L2 of SEQ ID Nos: 104 and 113. The contact area on the antigen covers an epitope surface at the intersection of the PRLR domains, comprising the topographical region defined by PRLR residues: E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2 . The foregoing amino acid residues of PRLR are within 4Å of the chAb6 Fab upon binding thereto.

An illustration of the epitope surfaces mapped onto the structure of the PRL-PRLR ternary complex for Ab6 and LFA102 are shown in Figure 9.

Example 6: Crystallization of chAb7 (Fab)-PRLR complex

Crystallization of the structure of the chAb7 Fab fragment-PRLR complex was performed and analyzed as follows.

Preparation and purification of the chAb7 Fab fragment:

The Fab fragment of chAb7 was prepared by papain cleavage of the parent mAb as detailed below. Papain was activated with 50mM cysteine in PBS, pH 7.4 buffer. The mAb chAb7 in PBS, pH 7.4 buffer was mixed with papain at 1:100 weight ratio of papain to mAb and incubated for 1 h at 37° C. The reaction was quenched with 6mM iodoacetamide. The mixture was purified on 5 ml Mab SelectSure resin (GE Healthcare) where the Fab fragment was collected as flow through. The flow through was concentrated using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). The concentrated mixture was purified on 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer. Fractions containing Fab fragment (monitored by UV absorbance at 280 nm) were pooled and frozen at – 80° C. Sample purity was assessed by analytical SEC, SDS-PAGE and mass spectrometry.

chAb7 Fab-PRLR complex preparation:

Recombinant human PRLR was expressed in mammalian expression system and subsequently purified using techniques well known in the art. Recombinant human PRLR and the chAb7 Fab protein were mixed at a 2:1 molar ratio and incubated for 2 h at 4° C. The complex sample was loaded onto a 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer at 1 ml/min. Fractions containing the complex (monitored by UV absorbance at 280 nm) were pooled and concentrated to 18 mg/ml using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). Sample purity was assessed by analytical SEC and SDS-PAGE. Excess Fab-Complex protein was stored frozen at -80° C.

Crystallization of the chAb7 Fab-PRLR complex:

The protein delivered at 17.6 mg/ml in 50mM HEPES pH 7.5, 50mM NaCl, 1mM sodium azide and was used at the delivered concentration. Crystals grew using the vapor diffusion technique at 4°C. The reservoir solution was 22%(w/v) PEG 4000, 0.1M sodium acetate, 0.2M ammonium sulfate. Crystallization drops were made using a 1:1 ratio of protein and reservoir solution. The crystals were cryo protected using 15%(v/v) propylene glycol. Diffraction data were collected under gaseous nitrogen at 100K the 17ID line (IMCA-cat) at the Advanced Photon Source (Argonne, IL).

X-ray structure of the chAb7 Fab-PRLR complex:

X-ray diffraction data extended to 2.0 Å resolution, and a full data set was processed with autoPROC (Global Phasing, Ltd). The crystal space group is monoclinic P21 with unit cell parameters a=99 Å, b=85 Å, c=101 Å, and beta=93°. The statistics for the data set collected are provided in Table 18.

TABLE 18. X-RAY DIFFRACTION STATISTICS FOR chAb7 FAB-PRLR COMPLEX

Resolution (Å)	49 – 2.0
Unique Reflections	103,942
Rmerge (%)	7.0
Completeness (%)	98
Multiplicity	3.4

Structure determination:

The crystal structure was determined by molecular replacement. Partial search model for the VhVl, ChCl, and PRLR portions were generated and sequentially placed using the program MOLREP (Vagin et al, 1997) in the CCP4 suite of programs (Winn et al. 2011). The asymmetric unit contains 2 molecular complexes that are arranged similarly and pack with symmetry mates for complete crystalline lattice with intermolecular contacts. The coordinates were refined against the data using the program autoBUSTER (Global Phasing, Ltd) and iterative rounds of graphical analysis and rebuilding into electron density with the program COOT (Emsley et al, 2010). Statistics for the resulting structure are provided in Table 19:

TABLE 19. REFINEMENT STATISTICS FOR THE chAb7 FAB-PRLR COMPLEX

Resolution (Å)	20 – 2.0
R / Rfree (%)	18.4 / 21.6
RMSDideal bonds (Å)	0.010
RMSDideal angles (°)	1.12

PRLR / chAb7 Fab Complex Structure:

Intermolecular contacts are observed between the PRLR extracellular domain and multiple chAb7 Fab CDRs. The buried surface area of the receptor upon binding of antibody is 1198 $Å^2$. The contacts are comprised of critical hydrophobic and hydrophilic interactions and include bridging water molecules. These contacts directly engage CDR's H1, H2, H3, L1, and L2 of SEQ ID Nos: 105 and 114. The contact area on the antigen covers an epitope surface at the intersection of the PRLR domains, comprising the topographical region defined by PRLR residues: E8, I9, F10, K11, C12, R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2. The foregoing amino acid residues of PRLR are within 4Å of the chAb7 Fab upon binding thereto.

The position of bound chAb7 to PRLR suggests that chAb7 would prevent prolactin binding to PRLR.

The findings of Examples 5 and 6 are consistent in demonstrating that chAb6 and chAb7 exhibit complementary interactions for roughly the same epitope. Conserved heavy chain features between the two antibodies suggest the importance of heavy chain interactions in PRLR binding.

Example 7: Crystallization of chAb8 (Fab)-PRLR complexes

Crystallization of the structure of the chAb8 Fab fragment-PRLR complex was performed and analyzed as follows.

Preparation and purification of the chAb8 Fab fragment:

The Fab fragment of chAb8 was prepared by papain cleavage of the parent mAb as detailed below. Papain was activated with 50mM cysteine in PBS, pH 7.4 buffer. The mAb chAb8 in PBS, pH 7.4 buffer was mixed with papain at 1:93 weight ratio of papain to mAb and incubated for 1 h at 37° C. The reaction was quenched with 5mM iodoacetamide. The mixture was purified on 8 ml Mab SelectSure resin (GE Healthcare) where the Fab fragment was collected as flow through. The flow through was concentrated using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). The concentrated mixture was purified on 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer. Fractions containing Fab fragment (monitored by UV absorbance at 280 nm) were pooled and frozen at – 80° C. Sample purity was assessed by analytical SEC, SDS-PAGE and mass spectrometry.

chAb8 Fab-PRLR complex preparation:

Recombinant human PRLR was expressed in a mammalian expression system and subsequently purified using techniques well known in the art. Recombinant human PRLR and the chAb8 Fab protein were mixed at a 1.16:1 molar ratio and incubated for 2 h at 22° C. The complex sample was loaded onto a 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer at 1 ml/min. Fractions containing the complex (monitored by UV absorbance at 280 nm) were pooled and concentrated to 38 mg/ml using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). Sample purity was assessed by analytical SEC and SDS-PAGE. Excess Fab-Complex protein was stored frozen at -80° C.

Crystallization of the chAb8-PRLR complex:

The protein complex was delivered at 38 mg/ml in 50mM HEPES pH 7.5, 50mM NaCl and was used diluted to 30 mg/ml for crystallization trials. Crystals grew using the vapor diffusion technique at 17°C. The reservoir solution was 20%(w/v) PEG 8000, 0.1M sodium cacodylate pH 5.5, 0.2 ammonium sulfate. Crystallization drops were made using a 1:1 ratio of protein and reservoir solution. The crystals were cryo-protected using 10%(v/v) propylene glycol. Diffraction data were collected under gaseous nitrogen at 100K at the Canadian Light Source (Saskatoon, Canada).

X-ray structure of the chAb8 Fab-PLR complex:

X-ray diffraction data extended to 2.55 Å resolution, and a full data set was processed with HKL2000 (HKL Research, Inc). The crystallographic space group is orthorhombic P212121

with unit cell parameters a=55 Å, b=89 Å, and c=186 Å. The statistics for the data set collected are provided in Table 20.

TABLE 20. X-RAY DIFFRACTION STATISTICS FOR chAb8 FAB-PRLR COMPLEX

Resolution (Å)	50 – 2.55
Unique Reflections	30,353
Rmerge (%)	12.7
Completeness (%)	99
Multiplicity	7.2

Structure determination:

The crystal structure was determined by molecular replacement. Partial search model for the VhVl, ChCl, and PRLR portions were generated and sequentially placed using the program MOLREP (Vagin et al, 1997) in the CCP4 suite of programs (Winn et al. 2011). The asymmetric unit contains one molecular complex, and symmetry mates complete the crystalline lattice with intermolecular contacts. The coordinates were refined against the data using the program autoBUSTER (Global Phasing, Ltd) and iterative rounds of graphical analysis and rebuilding into electron density with the program COOT (Emsley et al, 2010). Statistics for the resulting structure are provided in Table 21:

TABLE 21. REFINEMENT STATISTICS FOR THE chAb8 FAB-PRLR COMPLEX

Resolution (Å)	44 – 2.55
R / Rfree (%)	23.1 / 28.3
RMSDideal bonds (Å)	0.010
RMSDideal angles (°)	1.28

PRLR / chAb8 Fab Complex Structure:

Intermolecular contacts are observed between the PRLR extracellular domain and multiple chAb8 Fab CDRs. The contacts are comprised of critical hydrophobic and hydrophilic interactions and include bridging water molecules. These contacts directly engage CDR's H1, H2, H3, L1 and L3 of SEQ ID Nos: 106 and 115. The contact area on the antigen covers an epitope surface at the intersection of the PRLR domains, comprising the topographical region defined by PRLR residues: R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161, G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191, and W194 of SEQ ID NO:2. The foregoing amino acid residues of PRLR are within 4Å of the chAb8 Fab upon binding thereto.

Example 8: Crystallization of chAb5 (Fab)

Crystallization of the structure of the chAb5 Fab fragment was performed and analyzed as follows.

Preparation and purification of the chAb5 Fab fragment:

The Fab fragment of chAb5 was prepared by papain cleavage of the parent mAb as detailed below. Papain was activated with 50mM cysteine in PBS, pH 7.4 buffer. The mAb chAb5 in PBS, pH 7.4 buffer was mixed with papain at 1:100 weight ratio of papain to mAb and incubated for 1 h at 37° C. The reaction was quenched with 5.5mM iodoacetamide. The mixture was purified on 5 ml Mab SelectSure resin (GE Healthcare) where the Fab fragment was collected as flow through. The flow through was concentrated using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). The concentrated mixture was purified on 2.6 cm x 60 cm Sephacryl 200 HiPrep column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer. Fractions containing Fab fragment (monitored by UV absorbance at 280 nm) were pooled and concentrated to 31.3 mg/ml using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). Sample purity was assessed by analytical SEC, SDS-PAGE and mass spectrometry.

Crystallization of the chAb5:

The protein was delivered at 31.3 mg/mL in 50mM HEPES pH 7.5, 50mM NaCl, 1mM sodium azide and was diluted to 20mg/ml for crystallization trials using protein buffer. Crystals grew using the vapor diffusion technique at 4°C. The reservoir solution was 20%(w/v) PEG 3350, 0.2M sodium formate. Crystallization drops were made using a 1:1 ratio of protein and reservoir solution. The crystals were cryo-protected using 15%(v/v) propylene glycol. Diffraction data were collected under gaseous nitrogen at 100K the 17ID line (IMCA-CAT) at the Advanced Photon Source (Argonne, IL).

X-ray structure of the chAb5

X-ray diffraction data extended to 2.1 Å resolution, and a full data set was processed with autoPROC (Global Phasing, Ltd). The crystal space group is monoclinic P21 with unit cell parameters a=72 Å, b=66 Å, c=92 Å, and beta=96°. The statistics for the data set collected are provided in Table 22.

TABLE 22. X-RAY DIFFRACTION STATISTICS FOR chAb5 FAB

Resolution (Å)	66 – 2.1
Unique Reflections	51,329
Rmerge (%)	10.5
Completeness (%)	99
Multiplicity	3.4

Structure determination:

The crystal structure was determined by molecular replacement. Partial search models for the VhVl and ChCl portions were generated and sequentially placed using the program MOLREP (Vagin et al, 1997) in the CCP4 suite of programs (Winn et al. 2011). The asymmetric unit contains two (2) Fab molecules of similar conformation and pack with symmetry mates for complete crystalline lattice with intermolecular contacts. The coordinates were refined against the data using the program autoBUSTER (Global Phasing, Ltd) and iterative rounds of graphical analysis and rebuilding into electron density with the program COOT (Emsley et al, 2010). Statistics for the resulting structure are provided in Table 23:

TABLE 23. REFINEMENT STATISTICS FOR THE chAb5 FAB

Resolution (Å)	42 – 2.1
R / Rfree (%)	21.2 / 26.2
RMSDideal bonds (Å)	0.010
RMSDideal angles (°)	1.23

chAb5 Fab Structure:

Overlay of the chAb5 with chAb7 Fab from the complex with PRLR reveals close structural alignment, yielding 0.67 Å RMSD for the aligned C-alpha coordinates of the VhVl domains. The comparison highlighted the expected aspect of very similar structural conformation for these closely related Fabs, and provided evidence for similar conformations at the locations of different amino acids. Inspection of the interface with PRLR for the aligned structures reveals no severe clashes with the conformation of chAb5.

An overlay of a model of chAb5 with chAb7, based on their respective crystal structures, suggests that the antibodies have few differences and share similar conformations. Based on the foregoing, chAb5 is expected to have a similar epitope as chAb7 with similar PRLR interactions.

Example 9: Crystallization of LFA-102-PRLR complexes

Crystallization of the structure of the LFA102-PRLR complex was performed and analyzed as follows.

Preparation and purification of the LFA-102 Fab fragment:

The Fab fragment of LFA-102 was prepared by papain cleavage of the parent mAb as detailed below. Papain was activated with 50mM cysteine in PBS, pH 7.4 buffer. mAb LFA-102 in PBS, pH 7.4 buffer was mixed with papain at 1:100 weight ratio of papain to mAb and incubated for 1 h at 37° C. The reaction was quenched with 5mM iodoacetamide. The mixture was purified on 20 ml Mab SelectSure resin (GE Healthcare) where the Fab fragment was collected as flow through. The flow through was concentrated using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). The concentrated mixture

was purified on 2.6 cm x 60 cm Sephacryl 300 HR column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer. Fractions containing Fab fragment (monitored by UV absorbance at 280 nm) were pooled and frozen at – 80° C. Sample purity was assessed by analytical SEC, SDS-PAGE and mass spectrometry.

LFA-102 Fab-PRLR complex preparation:

Recombinant human PRLR was expressed in mammalian expression system and subsequently purified using techniques well known in the art. Recombinant human PRLR and LFA-102 Fab protein were mixed at a 1.1:1 molar ratio and incubated for 3 h at 4° C. The complex sample was loaded onto a 2.6 cm x 60 cm Sephacryl 300 HR column (GE Healthcare) pre-equilibrated in 50mM HEPES, 50mM NaCl, pH 7.5 buffer at 1 ml/min. Fractions containing the complex (monitored by UV absorbance at 280 nm) were pooled and concentrated to 18 mg/ml using an Ultrafree-15 Biomax 30 kDa molecular weight cut-off (MWCO) centrifugal device (Millipore). Sample purity was assessed by analytical SEC and SDS-PAGE. Excess Fab-Complex protein was stored frozen at -80° C.

Crystallization of the LFA-102 Fab-PRLR complex:

The protein was delivered at 20.7 mg/ml in 50mM HEPES pH 7.5, 50mM NaCl, 1mM sodium azide and was used at the delivered concentration. Crystals grew using the vapor diffusion technique at 4°C with the reservoir being 45% (w/v) 2-methyl-2, 4-pentanediol (MPD), 0.1M Tris-HCl pH 8.5, 0.1M ammonium dihydrogen phosphate. With these solution conditions no additional cryo-protectant was required so crystals were retrieved directly from the drop and cryo-cooled in liquid nitrogen. Diffraction data were collected under gaseous nitrogen at 100K the 17ID line (IMCA-cat) at the Advanced Photon Source (Argonne, IL).

X-ray structure of the LFA-102 Fab-PRLR complex:

X-ray diffraction data extended to 2.25 Å resolution, and a full data set was processed with autoPROC (Global Phasing, Ltd). The crystallographic space group is monoclinic C2 with unit cell parameters a=98 Å, b=119 Å, c=81 Å, and beta=107°. The statistics for the data set collected are provided in Table 24.

TABLE 24. X-RAY DIFFRACTION STATISTICS FOR LFA-102 FAB-PRLR COMPLEX

Resolution (Å)	77 – 2.25
Unique Reflections	41,794
Rmerge (%)	3.9
Completeness (%)	99
Multiplicity	3.4

Structure determination:

The crystal structure was determined by molecular replacement. Partial search model for the VhVl, ChCl, and PRLR portions were generated and sequentially placed using the program

MOLREP (Vagin et al, 1997) in the CCP4 suite of programs (Winn *et al.* 2011). The asymmetric unit contains one molecular complex, and symmetry mates complete the crystalline lattice with intermolecular contacts. The coordinates were refined against the data using the program autoBUSTER (Global Phasing, Ltd) and iterative rounds of graphical analysis and rebuilding into electron density with the program COOT (Emsley et al, 2010). Statistics for the resulting structure are provided in Table 25:

TABLE 25. REFINEMENT STATISTICS FOR THE LFA-102 FAB-PRLR COMPLEX

Resolution (Å)	77 – 2.25
R / Rfree (%)	19.7 / 23.1
RMSDideal bonds (Å)	0.010
RMSDideal angles (°)	1.17

PRLR / chAb7 Fab Complex Structure:

Intermolecular contacts are between PRLR and LFA102 involve CDR's L1, L3, H2 and H3of LFA102 (Seq ID Nos 156 and 157). The contact area on the antigen covers an epitope defined by PRLR residues: E145, E155, W156, E157, I158, H159, F160, A161, G162, Q164, L170 and S171 of SEQ ID NO:2. The foregoing amino acid residues of PRLR are within 4Å of LFA102 upon binding thereto.

The position of bound LFA102 to PRLR suggests that LFA102 would inhibit PRLR dimerization, but appears to nearly allow simultaneous binding of prolactin to PRLR.

Example 10: Binding of Anti-PRLR Antibodies to cyPRLR and muPRLR

Assays were performed to assess the binding of certain anti-PRLR antibodies to cyPRLR and muPRLR as follows.

Running buffer was HBS-EP+ (10mM Hepes, pH7.4, 150mM NaCl, 3mM EDTA, 0.05% P20). Assay was performed using Biacore T200 and CM5 sensor chips with anti-mouse Fc (Pierce 31170) or anti-human Fc (Pierce 31125), amine coupled in all 4 flow cells to ~8000.

mAb was captured in flow cells 2, 3 or 4. Antigen was injected (2 min at 80µl/ min). Concentrations were a 3 point, 9 fold dilution series from 500 nM – 7.4 nM, and buffer only. Dissociation was monitored for 15 minutes. Regeneration was performed with 2 consecutive injections (60 and 10 sec at 60 µ/min) of 10 mM glycine, pH 1.5.

Results are depicted in Figure 10. Cyno and human PRLR binding kinetics are virtually identical for the tested antibodies. However, each tested antibody shows significantly and proportionally weaker binding kinetics for muPRLR.

Sequence Listing

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:1	Human PRLR	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEKGK SEELLSALGCQDFPPTSDYEDLLVEYLEVDDS EDQHLMSVHSKEHPSQGMKPTYLDPDTDSGRG SCDSPSLLSEKCEEPQANPSTFYDPEVIEKPE NPETTHTWDPQCISMEGKIPYFHAGGSKCSTW PLPQPSQHNPRSSYHNITDVCELAVGPAGAPA TLLNEAGKDALKSSQTIKSREEGKATQQREVE SFHSETDQDTPWLLPQEKTPFGSAKPLDYVEI HKVNKDGALSLLPKQRENSGKPKKPGTPENNK EYAKVSGVMDNNILVLVPDPHAKNVACFEESA KEAPPSLEQNQAEKALANFTATSSKCRLQLGG LDYLDPACFTHSFH
SEQ ID NO.:2	Human PRLR Extracellular Domain	QLPPGKPEIFKCRSPNKETFTCWWRPGTDGGL PTNYSLTYHREGETLMHECPDYITGGPNSCHF GKQYTSMWRTYIMMVNATNQMGSSFSDELYVD VTYIVQPDPPLELAVEVKQPEDRKPYLWIKWS PPTLIDLKTGWFTLLYEIRLKPEKAAEWEIHF AGQQTEFKILSLHPGQKYLVQVRCKPDHGYWS AWSPATFIQIPSDFTMN
SEQ ID NO.:3	Human PRLR Isoform 2	MKENVASATVFTLLLFLNTCLLNVQPDPPLEL AVEVKQPEDRKPYLWIKWSPPTLIDLKTGWFT LLYEIRLKPEKAAEWEIHFAGQQTEFKILSLH PGQKYLVQVRCKPDHGYWSAWSPATFIQIPSD FTMNDTTVWISVAVLSAVICLIIVWAVALKGY SMVTCIFPPVPGPKIKGFDAHLLEKGKSEELL SALGCQDFPPTSDYEDLLVEYLEVDDSEDQHL MSVHSKEHPSQGMKPTYLDPDTDSGRGSCDSP SLLSEKCEEPQANPSTFYDPEVIEKPENPETT HTWDPQCISMEGKIPYFHAGGSKCSTWPLPQP SQHNPRSSYHNITDVCELAVGPAGAPATLLNE AGKDALKSSQTIKSREEGKATQQREVESFHSE TDQDTPWLLPQEKTPFGSAKPLDYVEIHKVNK DGALSLLPKQRENSGKPKKPGTPENNKEYAKV SGVMDNNILVLVPDPHAKNVACFEESAKEAPP SLEQNQAEKALANFTATSSKCRLQLGGLDYLD PACFTHSFH
SEQ ID NO.:4	Human PRLR Isoform 3	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSAW

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:5	Human PRLR Isoform 4	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEKGK SEELLSALGCQDFPPTSDYEDLLVEYLEVDDS EDQHLMSVHSKEHPSQGDPLMLGASHYKNLKS YRPRKISSQGRLAVFTKATLTTVQ
SEQ ID NO.:6	Human PRLR Isoform 5	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEKGK SEELLSALGCQDFPPTSDYEDLLVEYLEVDDS EDQHLMSVHSKEHPSQEREQRQAQEARDS
SEQ ID NO.:7	Human PRLR Isoform 6	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSDFTMNDTTVWISVAVLSAVICLIIVWAV ALKGYSMVTCIFPPVPGPKIKGFDAHLLEVTP
SEQ ID NO.:8	Human PRLR Isoform 7	MKENVASATVFTLLLFLNTCLLNGQLPPGKPE IFKCRSPNKETFTCWWRPGTDGGLPTNYSLTY HREGETLMHECPDYITGGPNSCHFGKQYTSMW RTYIMMVNATNQMGSSFSDELYVDVTYIVQPD PPLELAVEVKQPEDRKPYLWIKWSPPTLIDLK TGWFTLLYEIRLKPEKAAEWEIHFAGQQTEFK ILSLHPGQKYLVQVRCKPDHGYWSAWSPATFI QIPSGDPLMLGASHYKNLKSYRPRKISSQGRL AVFTKATLTTVQ
SEQ ID NO.:9	Human PRLR Isoform 8	MHECPDYITGGPNSCHFGKQYTSMWRTYIMMV NATNQMGSSFSDELYVDVTYIVQPDPPLELAV EVKQPEDRKPYLWIKWSPPTLIDLKTGWFTLL YEIRLKPEKAAEWEIHFAGQQTEFKILSLHPG QKYLVQVRCKPDHGYWSAWSPATFIQIPSDFT MNDTTVWISVAVLSAVICLIIVWAVALKGYSM VTCIFPPVPGPKIKGFDAHLLEVTP
SEQ ID NO.:10	Ig gamma-1 constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:11	Ig gamma-1 constant region mutant	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
SEQ ID NO.:12	Ig Kappa constant region	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDST YSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO.:13	Ig Lambda constant region	QPKAAPSVTLFPPSSEELQANKATLVCLISDF YPGAVTVAWKADSSPVKAGVETTTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS
SEQ ID NO.:14	VH1-18&JH6 FR1 21/28&JH4 FR1 VH1-46&JH6 FR1	QVQLVQSGAEVKKPGASVKVSCKASGYTFT
SEQ ID NO.:15	VH1-18&JH6 FR2 VH1-46&JH6 FR2	WVRQAPGQGLEWMG
SEQ ID NO.:16	VH1-18&JH6 FR3	RVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR
SEQ ID NO.:17	VH1-18&JH6 FR4 VH2-26&JH6 FR4 VH1-46&JH6 FR4	WGQGTTVTVSS
SEQ ID NO.:18	21/28&JH4 FR2	WVRQAPGQRLEWMG
SEQ ID NO.:19	21/28&JH4 FR3	RVTITRDTSASTAYMELSSLRSEDTAVYYCAR
SEQ ID NO.:20	21/28&JH4 FR4 M60&JH4 FR4	WGQGTLVTVSS
SEQ ID NO.:21	VH2-26&JH6 FR1	QVTLKESGPVLVKPTETLTLTCTVSGFSLS
SEQ ID NO.:22	VH2-26&JH6 FR2	WIRQPPGKALEWLAH
SEQ ID NO.:23	VH2-26&JH6 FR3	RLTISKDTSKSQVVLTMTNMDPVDTATYYCAR
SEQ ID NO.:24	M60&JH4 FR1	QVTLRESGPALVKPTQTLTLTCTLYGFSLS
SEQ ID NO.:25	M60&JH4 FR2	WIRQPPGKALEWLA
SEQ ID NO.:26	M60&JH4 FR3	RLTISKDTSKNQVVLTMTNMDPVDTATYYCAR
SEQ ID NO.:27	VH1-46&JH6 FR3	RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
SEQ ID NO.:28	A20&JK4 FR1 III-3R&JK4 FR1	DIQMTQSPSSLSASVGDRVTITC
SEQ ID NO.:29	A20&JK4 FR2 III-3R&JK4 FR2	WYQQKPGKVPKLLIY

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		123456789012345678901234567890 12
SEQ ID NO.:30	A20&JK4 FR3	GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC
SEQ ID NO.:31	A20&JK4 FR4 III-3R&JK4 FR4 A1&JK4 FR4	FGGGTKVEIKR
SEQ ID NO.:32	III-3R&JK4 FR3	GVPSRISGSGSGTDFTFTISSLQPEDIATYYC
SEQ ID NO.:33	A1&JK4 FR1	DVVMTQSPLSLPVTLGQPASISC
SEQ ID NO.:34	A1&JK4 FR2	WFQQRPGQSPRRLIY
SEQ ID NO.:35	A1&JK4 FR3 01&JK2 FR3	GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC
SEQ ID NO.:36	01&JK2 FR1	DIVMTQTPLSLPVTPGEPASISC
SEQ ID NO.:37	01&JK2 FR2	WYLQKPGQSPQLLIY
SEQ ID NO.:38	01&JK2 FR4	FGQGTKLEIKR
SEQ ID NO.:39	Ab1 VH.1z	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTTY WMHWVRQAPGQGLEWMGEIDPSDSYSNYNQKF KDRVTITADKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSS
SEQ ID NO.:40	Ab1 VH.1z CDRH1 Ab1 VH.1 CDRH1 Ab1 VH.1a CDRH1	GYTFTTYWMH
SEQ ID NO.:41	Ab1 VH.1z CDRH2 Ab1 VH.1 CDRH2 Ab1 VH.1a CDRH2	EIDPSDSYSNYNQKFKD
SEQ ID NO.:42	Ab1 VH.1z CDRH3 Ab1 VH.1 CDRH3 Ab1 VH.1a CDRH3 Ab1 VH.1b CDRH3	NGGLGPAWFSY
SEQ ID NO.:43	Ab1 VH.1	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTTY WMHWVRQAPGQGLEWMGEIDPSDSYSNYNQKF KDRVTITADKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSS
SEQ ID NO.:44	Ab1 VH.1a	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTTY WMHWVRQAPGQGLEWIGEIDPSDSYSNYNQKF KDRATLTVDKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSS
SEQ ID NO.:45	Ab1 VH.1b	EVQLVQSGAEVKKPGSSVKVSCKASGGTFTTY WMHWVRQAPGQGLEWIGEIDPSDSYSNYAQKF QGRVTITVDKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSS
SEQ ID NO.:46	Ab1 VH.1b CDRH1	GGTFTTYWMH
SEQ ID NO.:47	Ab1 VH.1b CDRH2	EIDPSDSYSNYAQKF
SEQ ID NO.:48	Ab1 VL.1	DIQMTQSPSSVSASVGDRVTITC**KASQYVGTA** **VA**WYQQKPGKAPKLLIY**SASNRYT**GVPSRFSG SGSGTDFTLTISSLQPEDFATYYC**QQYSSYPW** **T**FGGGTKVEIK
SEQ ID NO.:49	Ab1 VL.1 CDRL1 Ab1 VL.1a CDRL1 Ab1 VL.2 CDRL1 Ab1 VL.2a CDRL1	**KASQYVGTAVA**

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		123456789012345678901234567890 12
SEQ ID NO.:50	Ab1 VL.1 CDRL2 Ab1 VL.1a CDRL2 Ab1 VL.2 CDRL2 Ab1 VL.2a CDRL2	**SASNRYT**
SEQ ID NO.:51	Ab1 VL.1 CDRL3 Ab1 VL.1a CDRL3 Ab1 VL.2 CDRL3 Ab1 VL.2a CDRL3	**QQYSSYPWT**
SEQ ID NO.:52	Ab1 VL.1a	DIQMTQSPSSVSASVGDRVTITC**KASQYVGTA** **VA**WYQQKPGKSPKLLIY**SASNRYT**GVPSRFSD SGSGTDFTLTISSLQPEDFATYFC**QQYSSYPW** **T**FGGGTKVEIK
SEQ ID NO.:53	Ab1 VL.2	EIVMTQSPATLSVSPGERATLSC**KASQYVGTA** **VA**WYQQKPGQAPRLLIY**SASNRYT**GIPARFSG SGSGTEFTLTISSLQSEDFAVYYC**QQYSSYPW** **T**FGGGTKVEIK
SEQ ID NO.:54	Ab1 VL.2a	EIVMTQSPATLSVSPGERATLSC**KASQYVGTA** **VA**WYQQKPGQSPRLLIY**SASNRYT**GVPARFSD SGSGTEFTLTISSLQSEDFAVYFC**QQYSSYPW** **T**FGGGTKVEIK
SEQ ID NO.:55	Ab2 VH.1z	QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSF** **WMH**WVRQAPGQGLEWMG**VIDPSDTYTNYNQKF** **KG**RVTITADESTSTAYMELSSLRSEDTAVYYC AR**GDYSNWFTY**WGQGTLVTVSS
SEQ ID NO.:56	Ab2 VH.1z CDRH1 Ab2 VH.1 CDRH1 Ab2 VH.1a CDRH1	**GYTFTSFWMH**
SEQ ID NO.:57	Ab2 VH.1z CDRH2 Ab2 VH.1 CDRH2 Ab2 VH.1a CDRH2	**VIDPSDTYTNYNQKFKG**
SEQ ID NO.:58	Ab2 VH.1z CDRH3 Ab2 VH.1 CDRH3 Ab2 VH.1a CDRH3 Ab2 VH.1b CDRH3	**GDYSNWFTY**
SEQ ID NO.:59	Ab2 VH.1	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSF** **WMH**WVRQAPGQGLEWMG**VIDPSDTYTNYNQKF** **KG**RVTITADESTSTAYMELSSLRSEDTAVYYC AR**GDYSNWFTY**WGQGTLVTVSS
SEQ ID NO.:60	Ab2 VH.1a	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSF** **WMH**WVRQAPGQGLEWIG**VIDPSDTYTNYNQKF** **KG**RATLTVDESSSTAYMELSSLRSEDTAVYYC AR**GDYSNWFTY**WGQGTLVTVSS
SEQ ID NO.:61	Ab2 VH.1b	EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFTSF** **WMH**WVRQAPGQGLEWIG**VIDPSDTYTNYAQKF** **QG**RVTITVDESTSTAYMELSSLRSEDTAVYYC AR**GDYSNWFTY**WGQGTLVTVSS
SEQ ID NO.:62	Ab2 VH.1b CDRH1	**GGTFTSFWMH**
SEQ ID NO.:63	Ab2 VH.1b CDRH2	**VIDPSDTYTNYAQKFQG**
SEQ ID NO.:64	Ab2 VL.1	DIVMTQTPLSLSVTPGQPASISC**RSSQRLVHS** **NGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**GVP DRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQS** **THVPWT**FGGGTKVEIK
SEQ ID NO.:65	Ab2 VL.1 CDRL1 Ab2 VL.1a CDRL1 Ab2 VL.1b CDRL1	**RSSQRLVHSNGNTYLH**
SEQ ID NO.:66	Ab2 VL.1 CDRL2 Ab2 VL.1a CDRL2 Ab2 VL.1b CDRL2	**KVSNRFS**

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		123456789012345678901234567890 12
SEQ ID NO.:67	Ab2 VL.1 CDRL3 Ab2 VL.1a CDRL3 Ab2 VL.1b CDRL3	**SQSTHVPWT**
SEQ ID NO.:68	Ab2 VL.1a	DVVMTQTPLSLSVTPGQPASISC**RSSQRLVHS** **NGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**GVP DRFSGSGSGTDFTLKISRVEAEDVGVYFC**SQS** **THVPWT**FGGGTKVEIK
SEQ ID NO.:69	Ab2 VL.1b	DVVMTQTPLSLSVTPGQPASISC**RSSQRLVHS** **NGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**GVP DRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQS** **THVPWT**FGGGTKVEIK
SEQ ID NO.:70	Ab3 VH.1z	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDY** **NIH**WVRQAPGQGLEWMG**YIYPNNDGTGYNQKF** **KS**RVTMTTDTSTSTAYMELRSLRSDDTAVYYC AR**GDGNYVGDMDY**WGQGTTVTVSS
SEQ ID NO.:71	Ab3 VH.1z CDRH1 Ab3 VH.1 CDRH1 Ab3 VH.1a CDRH1 Ab3 VH.1b CDRH1	**GYTFTDYNIH**
SEQ ID NO.:72	Ab3 VH.1z CDRH2 Ab3 VH.1 CDRH2 Ab3 VH.1a CDRH2	**YIYPNNDGTGYNQKFKS**
SEQ ID NO.:73	Ab3 VH.1z CDRH3 Ab3 VH.1 CDRH3 Ab3 VH.1a CDRH3 Ab3 VH.1b CDRH3	**GDGNYVGDMDY**
SEQ ID NO.:74	Ab3 VH.1	EVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDY** **NIH**WVRQAPGQGLEWMG**YIYPNNDGTGYNQKF** **KS**RVTMTTDTSTSTAYMELRSLRSDDTAVYYC AR**GDGNYVGDMDY**WGQGTTVTVSS
SEQ ID NO.:75	Ab3 VH.1a	EVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDY** **NIH**WVRQAPGQGLEWIG**YIYPNNDGTGYNQKF** **KS**RATLTVDNSTSTAYMELRSLRSDDTAVYYC AR**GDGNYVGDMDY**WGQGTTVTVSS
SEQ ID NO.:76	Ab3 VH.1b	EVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDY** **NIH**WVRQAPGQGLEWIG**YIYPNNDGTGYAQKL** **QG**RVTMTVDTSTSTAYMELRSLRSDDTAVYYC AR**GDGNYVGDMDY**WGQGTTVTVSS
SEQ ID NO.:77	Ab3 VH.1b CDRH2	**YIYPNNDGTGYAQKLQG**
SEQ ID NO.:78	Ab3 VL.1	DIQMTQSPSSLSASVGDRVTITC**RASENIYSY** **LA**WYQQKPGKAPKLLIY**NAKTLAE**GVPSRFSG SGSGTDFTLTISSLQPEDFATYYC**QHHYATPF** **T**FGQGTKLEIK
SEQ ID NO.:79	Ab3 VL.1 CDRL1 Ab3 VL.1a CDRL1 Ab3 VL.1b CDRL1	**RASENIYSYLA**
SEQ ID NO.:80	Ab3 VL.1 CDRL2 Ab3 VL.1a CDRL2 Ab3 VL.1b CDRL2	**NAKTLAE**
SEQ ID NO.:81	Ab3 VL.1 CDRL3 Ab3 VL.1a CDRL3 Ab3 VL.1b CDRL3	**QHHYATPFT**
SEQ ID NO.:82	Ab3 VL.1a	DIQMTQSPSSLSASVGDRVTITC**RASENIYSY** **LA**WYQQKPGKPPKLLVY**NAKTLAE**GVPSRFSG SGSGTDFTLTISSLQPEDFATYYC**QHHYATPF** **T**FGQGTKLEIK

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:83	Ab3 VL.1b	DIQMTQSPSSLSASVGDRVTITC**RASENIYSY LA**WYQQKPGKAPKLLVY**NAKTLAE**GVPSRFSG SGSGTDFTLTISSLQPEDFATYYC**QHHYATPF T**FGQGTKLEIK
SEQ ID NO.:84	Ab4 VH.1z	QVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSY WIH**WVRQAPGQGLEWMG**EIDPSDSYTNYNQKF KG**RVTITADKSTSTAYMELSSLRSEDTAVYYC AR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:85	Ab4 VH.1z CDRH1 Ab4 VH.1 CDRH1 Ab4 VH.1a CDRH1 Ab4 VH.1a.2 CDRH1 Ab4 VH.1a.3 CDRH1 Ab4 VH.1b.2 CDRH1	**GYTFTSYWIH**
SEQ ID NO.:86	Ab4 VH.1z CDRH2 Ab4 VH.1 CDRH2 Ab4 VH.1a CDRH2 Ab4 VH.1a.2 CDRH2 Ab4v VH.1a.3 CDRH2 Ab4 VH.1b.2 CDRH2	**EIDPSDSYTNYNQKFKG**
SEQ ID NO.:87	Ab4 VH.1z CDRH3 Ab4 VH.1 CDRH3 Ab4 VH.1a CDRH3 Ab4 VH.1a.2 CDRH3 Ab4 VH.1a.3 CDRH3 Ab4 VH.1b CDRH3 Ab4 VH.1b.2 CDRH3	**SFFTNWFAY**
SEQ ID NO.:88	Ab4 VH.1	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSY WIH**WVRQAPGQGLEWMG**EIDPSDSYTNYNQKF KG**RVTITADKSTSTAYMELSSLRSEDTAVYYC AR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:89	Ab4 VH.1a	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSY WIH**WVRQAPGQGLEWIG**EIDPSDSYTNYNQKF KG**RATLTVDRSSSTAYMELSSLRSEDTAVYYC GR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:90	Ab4 VH.1b.2	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSY WIH**WVRQAPGQGLEWIG**EIDPSDSYTNYNQKF KG**RVTITVDKSTSTAYMELSSLRSEDTAVYYC AR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:91	Ab4 VL.1	DIVMTQTPLSLSVTPGQPASISC**RSSQSLVHS NGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**GVP DRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQS THVPFT**FGGGTKVEIK
SEQ ID NO.:92	Ab4 VL.1 CDRH1 Ab4 VL.1a CDRH1 Ab4 VL.1b CDRH1	**RSSQSLVHSNGNTYLH**
SEQ ID NO.:93	Ab4 VL.1 CDRH2 Ab4 VL.1a CDRH2 Ab4 VL.1b CDRH2	**KVSNRFS**

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		123456789012345678901234567890123456789012
SEQ ID NO.:94	Ab4 VL.1 CDRH3 Ab4 VL.1a CDRH3 Ab4 VL.1b CDRH3	**SQSTHVPFT**
SEQ ID NO.:95	Ab4 VL.1a	DVVMTQTPLSLSVTPGQPASISC**RSSQSLVHS** **NGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**GVP DRFSGSGSGTDFTLKISRVEAEDVGVYFC**SQS** **THVPFT**FGGGTKVEIK
SEQ ID NO.:96	Ab4 VL.1b	DVVMTQTPLSLSVTPGQPASISC**RSSQSLVHS** **NGNTYLH**WYLQKPGQSPQLLIY**KVSNRFS**GVP DRFSGSGSGTDFTLKISRVEAEDVGVYYC**SQS** **THVPFT**FGGGTKVEIK
SEQ ID NO.:97	CDR Region: CDRH1	Consensus sequence: 26 27 28 29 30 31 32 33 34 35 35a X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} G Y T F T S Y W M H F S I S D F N I F N T D Y A W
SEQ ID NO.:98	CDR Region: CDRH2	Consensus sequence: 50 51 52 52a 53 54 55 56 57 58 59 60 61 62 63 64 65 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} X_{17} Y I D P S D G Y T N Y N Q K F K G V F Y N Y N S G S G F P D E L S E S N G D H A Y P T V D G G S T S S S N R
SEQ ID NO.:99	CDR Region: CDRH3	Consensus sequence: 95 96 97 98 99 100 100a 100b 100c 100d 100e 101102 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} G D G S Y W F D M A M D Y S F F N N V G W F T N G Y T G P A F A Q L W L I G Y A G S G M Y S R G Y - A
SEQ ID NO.:100	CDR Region: CDRL1	Consensus sequence: 24 25 26 27 27a 27b 27c 27d 27e 28 29 30 31 32 33 34 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} R A S Q - - - - - N G N T Y L H K S E S L V H S Y I Y S A V A S S R I - V G M T S V E
SEQ ID NO.:101	CDR Region: CDRL2	Consensus sequence: 50 51 52 53 54 55 56 X_1 X_2 X_3 X_4 X_5 X_6 X_7 K A S N R F S N V K T L A E S T Y T L S
SEQ ID NO.:102	CDR Region: CDRL3	Consensus sequence: 89 90 91 92 93 94 95 95a 96 97 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} Q Q S S H V P - F T S H H T S T P W F G Y A Y L Y G W V
SEQ ID NO.:103	Murine Ab5 Variable Light Chain	DVVMTQTPLSLPVSLGDQASISCRSSQRLVHS NGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDLGVYFCSQS THVPWTFGGGTKLEIK
SEQ ID NO.:104	Murine Ab6 Variable Light Chain	DIVMTQSQKFMSTTVGDRVSITCKASQYVGTA VAWYQQKPGQSPKLLIYSASNRYTGVPDRFTD SGSGTDFTLTISNLQSEDLADYFCQQYSSYPW TFGGGTKLEIK
SEQ ID NO.:105	Murine Ab7 Variable Light Chain	DVVMTQTPLSLPVSLGDQASISCRSSQSLVHS NGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVP DRFSGSGSGTDFTLKINRVEAEDLGVYFCSQS THVPFTFGSGTKLEIK

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		123456789012345678901234567890 12
SEQ ID NO.:106	Murine Ab8 Variable Light Chain	DIQMTQSPASLSASVGETVTITCRASENIYSY LAWYQQKQGKPPQLLVYNAKTLAEGVPSRFSG GGSGTQFSLKINSLQPEDFGSYYCQHHYATPF TFGSGTKLEIK
SEQ ID NO.:107	Murine Ab9 Variable Light Chain	DIQMTQSPASLSASVGETVTITCRASENIYSY LAWYQQKQGKSPQLLVYNAKTLAEGVPSRFSG SGSGTQFSLKINSLQPEDFGSYYCQHHSGTPF TFGSGTKLEIK
SEQ ID NO.:108	Murine Ab10 Variable Light Chain	DIQMTQSPASLSASVGETVTITCRASENIYSY LTWYQQKQGKSPQLLVYNAKTLAEGVPSRFSG SGSGTQFSLKINSLQPEDFGSYHCQHHSVTPL TFGAGTKLELK
SEQ ID NO.:109	Murine Ab11 Variable Light Chain	DVLMTQTPLSLPVSLGDQASISCRSSQSIVHS NGNTYLEWYLQKPGQSPKLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDLGVYYCFQG SHVPFTFGSGTKLEIK
SEQ ID NO.:110	Murine Ab12 Variable Light Chain	QIVLTQSPGIMSASPGEKVTMTCSASSSVTYM YWYQQKPRSSPKPWIYLTSNLASGVPARFSGS GSGTSYSLTISSMEAEDGATYYCQQWSSTPPL TFGGGTKLELN
SEQ ID NO.:111	Murine Ab13 Variable Light Chain	DVVMTQTPFSLPVSLGDQASISCRSSQSLVHS NGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDLELYFCSQS THVPWTFGGGTKLEIK
SEQ ID NO.:112	Murine Ab5 Variable Heavy Chain	QVQLQQPGAELVRPGTSVKLSCKASGYTFTSF WMHWVKQRPGQGLEWIGVIDPSDTYTNYNQKF KGKATLTVDTSSSTAYMQLSSLTSEDSAVYYC ARGDYSNWFTYWGQGTLVTVSA
SEQ ID NO.:113	Murine Ab6 Variable Heavy Chain	QVQLQQPGAELVMPGSSVKLSCKASGYTFTTY WMHWVKQRPGQGLEWIGEIDPSDSYSNYNQKF KDKATLTVDKSSSTAYMQLSSLTSEDSAVYYC ARNGGLGPAWFSYWGQGTLVTVSA
SEQ ID NO.:114	Murine Ab7 Variable Heavy Chain	QVQLQQPGAELVMPGTSVKLSCKASGYTFTSY WIHWVKQRPGQGLEWIGEIDPSDSYTNYNQKF KGKATLTVDRSSSTAYMQLSSLTSEDSAVYYC GRSFFTNWFAYWGQGTLVTVSA
SEQ ID NO.:115	Murine Ab8 Variable Heavy Chain	EVQLQQSGPELVKPGASVKISCKASGYTFTDY NIHWVKQSHGKSLEWIGYIYPNNDGTGYNQKF KSKATLTVDNSSSTAYMEVRSLTSEDSAVYYC ARGDGNYVGDMDYWGQGTSVTVSS
SEQ ID NO.:116	Murine Ab9 Variable Heavy Chain	EVQLQQSGPELVRPGASVKISCKASGYSFTDY NMHWVKQSHGKSLEWIGYIYPYNGGAGYNQKF KSKATMNVGISSSTAYMELRSLTSEDSAVYYC ARGDGNYVGDMDYWGQGTSVTVSS
SEQ ID NO.:117	Murine Ab10 Variable Heavy Chain	EVQLHQSGPELVKPGASVKISCKASGYTFTDY NMHWMKQSHGKSLEWIGYFYPYNGGTGYNQEF KNKATLTVDISSSTAYMELRRLTSEDSAVYYC ARGGWGIYYAMDYWGQGTSVTVSS
SEQ ID NO.:118	Murine Ab11 Variable Heavy Chain	EVKLVESGGGLVQPGGSLKLSCAASGFTFSDY YMFWVRQTPEKSLEWVAYISNGGGSTYYPDTV KGRFTISRDNAKNTLYLQMSRLKSEDTAMYYC SRQLFYYGSRGAMGYWGQGTSVTVSS
SEQ ID NO.:119	Murine Ab12 Variable Heavy Chain	DVQLQESGPGLVKPSQSLSLTCTVTGYSITSD YAWNWIRQFPGNKLEWMGYIGYSGRTSFNPSL KSRISITRDTSKNQFFLQLNSVTTEDTATYYC ARGGFAMDYWGQGTSVTVSS
SEQ ID NO.:120	Murine Ab13 Variable Heavy Chain	DVVMTQTPFSLPVSLGDQASISCRSSQSLVHS NGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDLELYFCSQS THVPWTFGGGTKLEIK

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:121	Ab4 VH.1a.2	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSY WIH**WVRQAPGQGLEWIG**EIDPSDSYTNYNQKF KG**RATLTVDRSSSTAYMELSSLRSEDTAVYYC GR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:122	Ab4 VH.1a.3	EVQLVQSGAEVKKPGSSVKVSCKAS**GYTFTSY WIH**WVRQAPGQGLEWIG**EIDPSDSYTNYNQKF KG**RATLTVDKSSSTAYMELSSLRSEDTAVYYC GR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:123	Ab4 VH.1b	EVQLVQSGAEVKKPGSSVKVSCKAS**GGTFTSY WIH**WVRQAPGQGLEWIG**EIDPSDSYTNYAQKF QG**RVTITVDKSTSTAYMELSSLRSEDTAVYYC AR**SFFTNWFAY**WGQGTLVTVSS
SEQ ID NO.:124	Ab1 HC.1	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTTY WMHWVRQAPGQGLEWMGEIDPSDSYSNYNQKF KDRVTITADKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO.:125	Ab1 LC.1	DIQMTQSPSSVSASVGDRVTITCKASQYVGTA VAWYQQKPGKAPKLLIYSASNRYTGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQYSSYPW TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:126	Ab1 LC.1a	DIQMTQSPSSVSASVGDRVTITCKASQYVGTA VAWYQQKPGKSPKLLIYSASNRYTGVPSRFSD SGSGTDFTLTISSLQPEDFATYFCQQYSSYPW TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:127	Ab1 LC.2	EIVMTQSPATLSVSPGERATLSCKASQYVGTA VAWYQQKPGQAPRLLIYSASNRYTGIPARFSG SGSGTEFTLTISSLQSEDFAVYYCQQYSSYPW TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:128	Ab1 LC.2a	EIVMTQSPATLSVSPGERATLSCKASQYVGTA VAWYQQKPGQSPRLLIYSASNRYTGVPARFSD SGSGTEFTLTISSLQSEDFAVYFCQQYSSYPW TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:129	Ab1 HC.1a	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTTY WMHWVRQAPGQGLEWIGEIDPSDSYSNYNQKF KDRATLTVDKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO.:130	Ab1 HC.1b	EVQLVQSGAEVKKPGSSVKVSCKASGGTFTTY WMHWVRQAPGQGLEWIGEIDPSDSYSNYAQKF QGRVTITVDKSTSTAYMELSSLRSEDTAVYYC ARNGGLGPAWFSYWGQGTLVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO.:131	Ab2 HC.1	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSF WMHWVRQAPGQGLEWMGVIDPSDTYTNYNQKF KGRVTITADESTSTAYMELSSLRSEDTAVYYC ARGDYSNWFTYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:132	Ab2 LC.1	DIVMTQTPLSLSVTPGQPASISCRSSQRLVHS NGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQS THVPWTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:133	Ab2 LC.1a	DVVMTQTPLSLSVTPGQPASISCRSSQRLVHS NGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYFCSQS THVPWTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:134	Ab2 LC.1b	DVVMTQTPLSLSVTPGQPASISCRSSQRLVHS NGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQS THVPWTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:135	Ab2 HC.1a	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSF WMHWVRQAPGQGLEWIGVIDPSDTYTNYNQKF KGRATLTVDESSSTAYMELSSLRSEDTAVYYC ARGDYSNWFTYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:136	Ab2 HC.1b	EVQLVQSGAEVKKPGSSVKVSCKASGGTFTSF WMHWVRQAPGQGLEWIGVIDPSDTYTNYAQKF QGRVTITVDESTSTAYMELSSLRSEDTAVYYC ARGDYSNWFTYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:137	Ab4 HC.1	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSY WIHWVRQAPGQGLEWMGEIDPSDSYTNYNQKF KGRVTITADKSTSTAYMELSSLRSEDTAVYYC ARSFFTNWFAYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:138	Ab4 LC.1	DIVMTQTPLSLSVTPGQPASISCRSSQSLVHS NGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQS THVPFTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:139	Ab4 LC.1a	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHS NGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYFCSQS THVPFTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:140	Ab4 LC.1b	DVVMTQTPLSLSVTPGQPASISCRSSQSLVHS NGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQS THVPFTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:141	Ab4 HC.1a	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSY WIHWVRQAPGQGLEWIGEIDPSDSYTNYNQKF KGRATLTVDKSSSTAYMELSSLRSEDTAVYYC ARSFFTNWFAYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:142	Ab4 HC.1b	EVQLVQSGAEVKKPGSSVKVSCKASGGTFTSY WIHWVRQAPGQGLEWIGEIDPSDSYTNYAQKF QGRVTITVDKSTSTAYMELSSLRSEDTAVYYC ARSFFTNWFAYWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:143	Ab3 HC.1	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDY NIHWVRQAPGQGLEWMGYIYPNNDGTGYNQKF KSRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARGDGNYVGDMDYWGQGTTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:144	Ab3 LC.1	DIQMTQSPSSLSASVGDRVTITCRASENIYSY LAWYQQKPGKAPKLLIYNAKTLAEGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQHHYATPF TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:145	Ab3 LC.1a	DIQMTQSPSSLSASVGDRVTITCRASENIYSY LAWYQQKPGKPPKLLVYNAKTLAEGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQHHYATPF TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:146	Ab3 LC.1b	DIQMTQSPSSLSASVGDRVTITCRASENIYSY LAWYQQKPGKAPKLLVYNAKTLAEGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQHHYATPF TFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC
SEQ ID NO.:147	Ab3 HC.1a	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDY NIHWVRQAPGQGLEWIGYIYPNNDGTGYNQKF KSRATLTVDNSTSTAYMELRSLRSDDTAVYYC ARGDGNYVGDMDYWGQGTTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO.:148	Ab3 HC.1b	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDY NIHWVRQAPGQGLEWIGYIYPNNDGTGYAQKL QGRVTMTVDTSTSTAYMELRSLRSDDTAVYYC ARGDGNYVGDMDYWGQGTTVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
SEQ ID NO.:149	Ab4 VH.1b CDRH1	**GGTFTSYWIH**
SEQ ID NO.:150	Ab4 VH.1b CDRH2	**EIDPSDSYTNYAQKFQG**
SEQ ID NO.:151	CDR Region: CDRH1	Consensus sequence: 26 27 28 29 30 31 32 33 34 35 35a X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} G Y T F T S Y W M H F S I S D F N I F N G T D Y A W

Sequence Identifier	Protein	Sequence
		123456789012345678901234567890 12
SEQ ID NO.:152	CDR Region: CDRH2	Consensus sequence: 50 51 52 52a 53 54 55 56 57 58 59 60 61 62 63 64 65 X_1 X_2 X_3 X_4 X_5 X_6 X_7 X_8 X_9 X_{10} X_{11} X_{12} X_{13} X_{14} X_{15} X_{16} X_{17} Y I D P S D G Y T N Y N Q K F K G V F Y N Y N S G S G F P D E L Q S E S N G D H A Y A P T V D G G S T S S S N R
SEQ ID NO.:153	Ab4 HC.1b.2	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWIHW VRQAPGQGLEWIGEIDPSDSYTNYNQKFKGRVTITV DKSTSTAYMELSSLRSEDTAVYYCARSFFTNWFAYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
SEQ ID NO.:154	Ab4 HC.1a.3	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWIHW VRQAPGQGLEWIGEIDPSDSYTNYNQKFKGRATLTV DKSSSTAYMELSSLRSEDTAVYYCGRSFFTNWFAYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
SEQ ID NO.:155	Ab4 HC.1a.2	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWIHW VRQAPGQGLEWIGEIDPSDSYTNYNQKFKGRATLTV DRSSSTAYMELSSLRSEDTAVYYCGRSFFTNWFAYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
SEQ ID NO.:156	LFA102 Heavy Chain	EVQLVESGGGLVQPGGSLRLSCAVSGFTFSSYGMSW VRQAPGKRLEWVATVSSGGTYTYYPDSVKGRFTISR DNSKNTLYLQMNSLRAEDTAMYYCARHRGNYYATYY YAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
SEQ ID NO.:157	LFA102 Light Chain	DIVLTQSPDSLAVSLGERATINCKASKSVSTSGYTY MHWYQQKPGQPPKLLIYLASNRESGVPDRFSGSGSG TDFTLTISPVQAEDVATYYCQHSGELPPSFGQGTKL EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC

CLAIMS

We claim:

1. A binding protein comprising an antigen binding domain, said binding protein capable of binding prolactin receptor (PRLR), said antigen binding domain comprising at least one CDR comprising an amino acid sequence selected from the group consisting of SEQ ID Nos:97, 98, 99, 100, 101, 102, 151 and 152.

2. The binding protein according to claim 1, wherein said at least one CDR comprises an amino acid sequence selected from the group consisting of SEQ ID Nos:40-42, 46, 47, 49-51, 56-58, 62, 63, 65-67, 71-73, 77, 79-81, 85-87, 92-94, 149 and 150.

3. The binding protein according to claim 1 or 2, wherein said binding protein comprises at least 3 CDRs.

4. The binding protein according to any one of claims 1-3, wherein said at least 3 CDRs are a heavy chain variable domain CDR set (CDR1, CDR2, and CDR3) selected from the group consisting of SEQ ID NOs: 40, 41, and 42; SEQ ID NOs: 46, 47, and 42; SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 62, 63, and 58; SEQ ID NOs: 71, 72, and 73; SEQ ID NOs: 71, 77, and 73; SEQ ID NOs: 85, 86, and 87; SEQ ID NOs: 149, 150, and 87.

5. The binding protein according any one of claims 1-3, wherein said at least 3 CDRs are a light chain variable domain CDR set (CDR1, CDR2, and CDR3) selected from the group consisting of SEQ ID NOs: 49, 50, and 51; SEQ ID NOs: 65, 66, and 67; SEQ ID NOs: 79, 80, and 81; and SEQ ID NOs: 92, 93, and 94.

6. The binding protein according to claim 5, further comprising a heavy chain variable domain CDR set selected from the group consisting of SEQ ID NOs: 40, 41, and 42; SEQ ID NOs: 46, 47, and 42; SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 62, 63, and 58; SEQ ID NOs: 71, 72, and 73; SEQ ID NOs: 71, 77, and 73; SEQ ID NOs: 85, 86, and 87; SEQ ID NOs: 149, 150, and 87.

7. The binding protein according to claim 6, wherein said at least two variable domain CDR sets are selected from a group consisting of:

(1) either of the heavy chain variable domain CDR sets SEQ ID Nos:40, 41 and 42 or SEQ ID Nos:46, 47 and 42, and the light chain variable domain CDR set SEQ ID Nos:49, 50 and 51;

(2) either of the heavy chain variable domain CDR sets SEQ ID Nos:56, 57 and 58 or SEQ ID Nos: 62, 63 and 58, and the light chain variable domain CDR set SEQ ID Nos 65, 66 and 67;

(3) either of the heavy chain variable domain CDR sets SEQ ID Nos: 71, 72 and 73 or SEQ ID Nos: 71, 77 and 73, and the light chain variable domain CDR set SEQ ID Nos: 79, 80 and 81; and

(4) either of the heavy chain variable domain CDR sets SEQ ID Nos:85, 86 and 87 or SEQ ID Nos: 149, 150 and 87, and the light chain variable domain CDR set SEQ ID Nos: 92, 93 and 94.

8. The binding protein according to any one of the preceding claims, further comprising a human acceptor framework.

9. The binding protein according to claim 8, wherein said human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID Nos:14-38.

10. The binding protein according to claim 8, wherein said human acceptor framework comprises at least one Framework Region amino acid substitution, wherein the amino acid sequence of the framework is at least 65% identical to the sequence of said human acceptor framework and comprises at least 70 amino acid residues identical to said human acceptor framework.

11. The binding protein according to claim 10, wherein said human acceptor framework comprises at least one Framework Region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;

a glycosylation site residue;

a rare residue;

a residue capable of interacting with human PRLR;

a residue capable of interacting with a CDR;

a canonical residue;

a contact residue between heavy chain variable region and light chain variable region;

a residue within a Vernier zone; and

a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

12. The binding protein according to claim 10, wherein said key residue is selected from the group consisting of 2L, 43L, 48L, 58L, 64L, 87L, 27H, 48H, 60H, 63H, 64H, 65H, 67H, 69H, 71H, 73H, 75H, 93H.

13. The binding protein according to claim 12, wherein the binding protein is a consensus human variable domain.

14. The binding protein according to any one of the preceding claims, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44; SEQ ID NO: 45; SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60; SEQ ID NO: 61; SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75; SEQ ID NO: 76; SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122 and SEQ ID NO: 123.

15. The binding protein according to any one of the preceding claims, wherein said binding protein comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of:

(1) one of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 or SEQ ID NO: 45; and one of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 or SEQ ID NO:54;
(2) one of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 or SEQ ID NO: 61; and one of SEQ ID NO:64, SEQ ID NO:68 or SEQ ID NO: 69;
(3) one of SEQ ID NO: 70; SEQ ID NO: 74; SEQ ID NO: 75 or SEQ ID NO: 76; and one of SEQ ID NO:78, SEQ ID NO:82 or SEQ ID NO: 83; and
(4) one of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122 or SEQ ID NO: 123; and one of SEQ ID NO:91, SEQ ID NO:95 or SEQ ID NO:96.

16. The binding protein according to any one of the preceding claims, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 48; SEQ ID NO: 52; SEQ ID NO: 53; SEQ ID

NO: 54; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 69; SEQ ID NO: 78; SEQ ID NO: 82; SEQ ID NO: 83; SEQ ID NO: 91; SEQ ID NO: 95; and SEQ ID NO: 96.

17. The binding protein according to any one of the preceding claims, wherein said binding protein comprises a heavy chain sequence and a light chain sequence selected from the group consisting of:

(a) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 125;

(b) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 126;

(c) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 127;

(d) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 128;

(e) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 125;

(f) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 126;

(g) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 127;

(h) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 128;

(i) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 125;

(j) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 126;

(k) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 127;

(l) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 128;

(m) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 132;

(n) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 133;

(o) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 134;

(p) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 132;

(q) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 133;

(r) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 134;

(s) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 132;

(t) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 133;

(u) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 134;

(v) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 138;

(w) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(x) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 140;

(y) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 138;

(z) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(aa) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 140;

(bb) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 138;

(cc) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(dd) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 140;

(ee) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 144;

(ff) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 145;

(gg) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 146;

(hh) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 144;

(ii) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 145;

(jj) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 146;

(kk) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 144;

(ll) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 145;

(mm) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 146;

(nn) a heavy chain having the amino acid sequence of SEQ ID NO: 153; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(oo) a heavy chain having the amino acid sequence of SEQ ID NO: 154; and a light chain having the amino acid sequence of SEQ ID NO: 139; and

(pp) a heavy chain having the amino acid sequence of SEQ ID NO: 155; and a light chain having the amino acid sequence of SEQ ID NO: 139.

18. The binding protein according to any one of the preceding claims, wherein the binding protein binds the ligand binding D1 domain of PRLR.

19. The binding protein according to any one of the preceding claims, wherein the binding protein inhibits binding of prolactin to PRLR.

20. The binding protein according to any one of the preceding claims, wherein the binding protein is capable of modulating a biological function of PRLR.

21. The binding protein according to any one of the preceding claims, wherein the binding protein is capable of neutralizing PRLR.

22. The binding protein according to any one of the preceding claims, wherein said binding protein has an on rate constant (K_{on}) to PRLR selected from the group consisting of: at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; and at least about $10^6 M^{-1}s^{-1}$; as measured by surface plasmon resonance.

23. The binding protein according to any one of the preceding claims, wherein said binding protein has an off rate constant (K_{off}) to PRLR selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

24. The binding protein according to any one of the preceding claims, wherein said binding protein has a dissociation constant (K_D) to PRLR selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

25. A binding protein capable of binding PRLR that competes with an antibody comprising a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(1) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54;

(2) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69;

(3) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96;

(4) the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103;

(5) the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104;

(6) the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105;

(7) the variable heavy chain amino acid sequence set forth in SEQ ID NO:116 and the variable light chain amino acid sequence set forth in SEQ ID NO:107;

(8) the variable heavy chain amino acid sequence set forth in SEQ ID NO:117 and the variable light chain amino acid sequence set forth in SEQ ID NO:108;

(9) the variable heavy chain amino acid sequence set forth in SEQ ID NO:118 and the variable light chain amino acid sequence set forth in SEQ ID NO:109;

(10) the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110; and

(11) the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111.

26. The binding protein of claim 25, wherein the binding protein competes with an antibody comprising a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(1) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54;

(2) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 55; SEQ ID NO: 59; SEQ ID NO: 60 and SEQ ID NO: 61; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:64, SEQ ID NO:68 and SEQ ID NO: 69;

(3) a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96;

(4) the variable heavy chain amino acid sequence set forth in SEQ ID NO:112 and the variable light chain amino acid sequence set forth in SEQ ID NO:103;

(5) the variable heavy chain amino acid sequence set forth in SEQ ID NO:113 and the variable light chain amino acid sequence set forth in SEQ ID NO:104;

(6) the variable heavy chain amino acid sequence set forth in SEQ ID NO:114 and the variable light chain amino acid sequence set forth in SEQ ID NO:105; and

(7) the variable heavy chain amino acid sequence set forth in SEQ ID NO:120 and the variable light chain amino acid sequence set forth in SEQ ID NO:111.

27. The binding protein of claim 25, wherein the binding protein competes with an antibody comprising the variable heavy chain amino acid sequence set forth in SEQ ID NO:119 and the variable light chain amino acid sequence set forth in SEQ ID NO:110.

28. The binding protein of claim 25, wherein the binding protein competes with an antibody comprising a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 39; SEQ ID NO: 43; SEQ ID NO: 44 and SEQ ID NO: 45; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO: 53 and SEQ ID NO:54.

29. The binding protein of claim 25, wherein the binding protein competes with an antibody comprising a variable heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 89; SEQ ID NO: 90; SEQ ID NO: 121; SEQ ID NO: 122; and SEQ ID NO: 123; and a variable light chain having an amino acid sequence selected from the group consisting of SEQ ID NO:91, SEQ ID NO:95 and SEQ ID NO:96.

30. A binding protein capable of binding PRLR that competes with an antibody comprising a heavy chain sequence and a light chain sequence selected from the group consisting of:

(a) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 125;

(b) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 126;

(c) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 127;

(d) a heavy chain having the amino acid sequence of SEQ ID NO: 124; and a light chain having the amino acid sequence of SEQ ID NO: 128;

(e) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 125;

(f) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 126;

(g) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 127;

(h) a heavy chain having the amino acid sequence of SEQ ID NO: 129; and a light chain having the amino acid sequence of SEQ ID NO: 128;

(i) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 125;

(j) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 126;

(k) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 127;

(l) a heavy chain having the amino acid sequence of SEQ ID NO: 130; and a light chain having the amino acid sequence of SEQ ID NO: 128;

(m) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 132;

(n) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 133;

(o) a heavy chain having the amino acid sequence of SEQ ID NO: 131; and a light chain having the amino acid sequence of SEQ ID NO: 134;

(p) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 132;

(q) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 133;

(r) a heavy chain having the amino acid sequence of SEQ ID NO: 135; and a light chain having the amino acid sequence of SEQ ID NO: 134;

(s) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 132;

(t) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 133;

(u) a heavy chain having the amino acid sequence of SEQ ID NO: 136; and a light chain having the amino acid sequence of SEQ ID NO: 134;

(v) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 138;

(w) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(x) a heavy chain having the amino acid sequence of SEQ ID NO: 137; and a light chain having the amino acid sequence of SEQ ID NO: 140;

(y) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 138;

(z) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(aa) a heavy chain having the amino acid sequence of SEQ ID NO: 141; and a light chain having the amino acid sequence of SEQ ID NO: 140;

(bb) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 138;

(cc) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(dd) a heavy chain having the amino acid sequence of SEQ ID NO: 142; and a light chain having the amino acid sequence of SEQ ID NO: 140;

(ee) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 144;

(ff) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 145;

(gg) a heavy chain having the amino acid sequence of SEQ ID NO: 143; and a light chain having the amino acid sequence of SEQ ID NO: 146;

(hh) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 144;

(ii) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 145;

(jj) a heavy chain having the amino acid sequence of SEQ ID NO: 147; and a light chain having the amino acid sequence of SEQ ID NO: 146;

(kk) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 144;

(ll) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 145;

(mm) a heavy chain having the amino acid sequence of SEQ ID NO: 148; and a light chain having the amino acid sequence of SEQ ID NO: 146;

(nn) a heavy chain having the amino acid sequence of SEQ ID NO: 153; and a light chain having the amino acid sequence of SEQ ID NO: 139;

(oo) a heavy chain having the amino acid sequence of SEQ ID NO: 154; and a light chain having the amino acid sequence of SEQ ID NO: 139; and

(pp) a heavy chain having the amino acid sequence of SEQ ID NO: 155; and a light chain having the amino acid sequence of SEQ ID NO: 139.

31. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising three, four, five, six, seven, eight, nine or all of the amino acid residues E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2.

32. The binding protein of claim 31, wherein the epitope comprises at least five of the amino acid residues.

33. The binding protein of claim 31, wherein the epitope comprises all of amino acid residues E8, F10, C12, R25, E43, G44, I76, D91, E92, L93, Y94, V95, D96, Y99, I100, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2.

34. The binding protein of any one of claims 31-33, wherein the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab6, chAb6, and Ab14-Ab25.

35. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising three, four, five, six, seven, eight, nine or all of the amino acid residues E8, I9, F10, K11, C12, R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2.

36. The binding protein of claim 35, wherein the epitope comprises at least five of the amino acid residues.

37. The binding protein of claim 35, wherein the epitope comprises all of amino acid residues E8, I9, F10, K11, C12, R25, E43, G44, W72, T74, I76, D91, E92, L93, Y94, V95, D96, T98, Y99, I100, W139, L143, E145, F160, K185, D187, H188, Y190 and W191 of SEQ ID NO:2.

38. The binding protein of any one of claims 35-37, wherein the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab4, Ab7, chAb7, Ab35-Ab43 and Ab53-Ab55.

39. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising 13, 14, 15, 16, 17, 18, 19, 20, 21 or all of the amino acid residues R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161, G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191 and W194 of SEQ ID NO:2.

40. The binding protein of claim 39, wherein the epitope comprises at least 15 of the amino acid residues.

41. The binding protein of claim 39, wherein the epitope comprises all of amino acid residues R25, T141, L143, E145, R147, E155, W156, E157, I158, H159, F160, A161,

G162, Q163, Q164, F167, S171, R183, K185, D187, H188, W191, and W194 of SEQ ID NO:2.

42. The binding protein of any one of claims 39-41, wherein the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab3, Ab8, chAb8 and Ab44-Ab52.

43. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising at least one, two, three, four or all of the amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2.

44. The binding protein of claim 43, wherein the epitope comprises all of amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2.

45. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising amino acids 91-96 of SEQ ID NO:2.

46. The binding protein of claim 45, wherein the binding protein comprises an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab4, Ab6, Ab7, chAb6, chAb7, Ab14-Ab25, Ab35-Ab43 and Ab53-Ab55.

47. A binding protein capable of binding PRLR that binds to an epitope having residues within at least amino acids 8-100, 185-191, 8-143, or 183-194 of SEQ ID NO:2.

48. The binding protein of claim 44 or 47, wherein the binding protein is an antibody, or antigen binding portion thereof, selected from the group consisting of Ab1, Ab3, Ab4, Ab6-Ab8, chAb6, chAb7, chAb8, Ab14-Ab25 and Ab35-Ab55.

49. A binding protein capable of binding PRLR and having the same epitopic specificity as an antibody, or antigen-binding portion thereof, selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, chAb5, Ab6, chAb6, Ab7, chAb7, Ab8, chAb8, Ab9, chAb9, Ab10, chAb10, Ab11, chAb11, Ab12, chAb12, Ab13, chAb13, Ab14, Ab15, Ab16, Ab17, Ab18, Ab19, Ab20, Ab21, Ab22, Ab23, Ab24, Ab25, Ab26, Ab27, Ab28, Ab29, Ab30, Ab31, Ab32, Ab33, Ab34, Ab35, Ab36, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42,

Ab43, Ab44, Ab45, Ab46, Ab47, Ab48, Ab49, Ab50, Ab51, Ab52, Ab53, Ab54 and Ab55.

50. The binding protein of any one of claims 25-49, wherein the binding protein is capable of modulating a biological function of PRLR.

51. The binding protein of any one of claims 25-50, wherein the binding protein binds the ligand binding D1 domain of PRLR.

52. The binding protein of any one of claims 25-51, wherein the binding protein binds an epitope of PRLR which does not inhibit dimerization of PRLR.

53. The binding protein of any one of claims 25-52, wherein the binding protein does not bind the D2 domain of PRLR.

54. The binding protein of any one of claims 25-53, wherein the binding protein inhibits binding of prolactin to PRLR.

55. The binding protein of any one of claims 25-54, wherein the binding protein does not compete with antibody LFA102 for binding of PRLR.

56. The binding protein of any one of claims 1-55, wherein the binding protein is an antibody.

57. An antibody construct comprising the binding protein of any one of claims 1-56, said antibody construct further comprising a linker polypeptide or an immunoglobulin constant domain.

58. The antibody construct according to claim 57, wherein said binding protein is selected from the group consisting of:

an immunoglobulin molecule,	a disulfide linked Fv,
a monoclonal antibody,	a scFv,
a chimeric antibody,	a single domain antibody,
a CDR-grafted antibody,	a diabody,
a humanized antibody,	a multispecific antibody,
a Fab,	a dual specific antibody, and

a Fab',
a F(ab')2,
a Fv,
a bispecific antibody.

59. The antibody construct according to any one of claims 57-58, wherein said binding protein comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

a human IgM constant domain,
a human IgG1 constant domain,
a human IgG2 constant domain,
a human IgG3 constant domain,
a human IgG4 constant domain,
a human IgE constant domain,
and
a human IgA constant domain.

60. The antibody construct according to any one of claims 57-59, comprising an immunoglobulin constant domain having an amino acid sequence selected from the group consisting of SEQ ID Nos:10-13.

61. An antibody conjugate comprising the antibody construct of any one of claims 57-60, said antibody conjugate further comprising an agent selected from the group consisting of: an immunoadhension molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

62. The antibody conjugate according to claim 61, wherein said agent is an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

63. The antibody conjugate according to claim 61, wherein said imaging agent is a radiolabel selected from the group consisting of: ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm.

64. The antibody conjugate according to claim 61, wherein said agent is a therapeutic or cytotoxic agent selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

65. The antibody conjugate according to claim 64, wherein the anti-mitotic agent is selected from the group consisting of a dolastatin, an auristatin, a maytansinoid, a plant alkaloid, a taxane, and a vinca alkaloid.

66. The antibody construct according to any one of claims 57-65, wherein said binding protein possesses a human glycosylation pattern.

67. The binding protein according to any one of claims 1-56, wherein said binding protein is a crystallized binding protein.

68. The antibody construct according to any one of claims 57-66, wherein said antibody construct is a crystallized antibody construct.

69. The antibody construct according to claim 68, wherein said crystallized antibody construct is a carrier-free pharmaceutical controlled release crystallized antibody construct.

70. The antibody construct according to claim 68 or 69, wherein said antibody construct has a greater half life *in vivo* than the soluble counterpart of said antibody construct.

71. The antibody construct according to any one of claims 68-70, wherein said antibody construct retains biological activity.

72. An isolated nucleic acid encoding a binding protein amino acid sequence of any one of claims 1-56.

73. An isolated nucleic acid encoding an antibody construct amino acid sequence of any one of claims 57-66.

74. A vector comprising an isolated nucleic acid according to claim 73.

75. The vector of claim 74 wherein said vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.

76. A host cell comprising a vector according to claim 74 or 75.

77. The host cell according to claim 76, wherein said host cell is a prokaryotic cell or a eukaryotic cell, .

78. The host cell according to claim 77, wherein said prokaryotic host cell is E.Coli.

79. The host cell according to claim 77, wherein said eukaryotic cell is selected from the group consisting of a protist cell, an animal cell, a plant cell and a fungal cell.

80. The host cell according to claim 79, wherein said animal cell is selected from the group consisting of a mammalian cell, an avian cell, and an insect cell.

81. The host cell according to claim 76, wherein said host cell is selected from the group consisting of a CHO cell, a COS cell, a yeast cell, and an insect Sf9 cell,.

82. The host cell according to claim 81, wherein said yeast cell is *Saccharomyces cerevisiae*.

83. A method of producing a protein capable of binding PRLR, comprising culturing a host cell of any one of claims 76-82 in culture medium under conditions sufficient to produce a binding protein capable of binding PRLR.

84. A protein produced according to the method of claim 83.

85. A composition for the release of a binding protein said composition comprising:
(a) a formulation, wherein said formulation comprises a crystallized binding protein, according to claim 67, and an ingredient; and
(b) at least one polymeric carrier.

86. The composition according to claim 85, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutryate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo) phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin,

gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polysaccharides, blends and copolymers thereof.

87. The composition according to claim 85 or 86, wherein said ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

88. A method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition according to any one of claims 85-87.

89. A pharmaceutical composition comprising the binding protein of any one of claims 1-56, and a pharmaceutically acceptable carrier.

90. The pharmaceutical composition of claim 89 wherein said pharmaceutically acceptable carrier functions as adjuvant useful to increase the absorption, or dispersion of said binding protein.

91. The pharmaceutical composition of claim 90 wherein said adjuvant is hyaluronidase.

92. The pharmaceutical composition of any one of claims 89-91 further comprising at least one additional therapeutic agent for treating a disorder in which PRLR activity is detrimental.

93. The pharmaceutical composition of claim 92, wherein said additional agent is selected from the group consisting of: therapeutic agent, imaging agent, cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an anti-rheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an oral steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

94. A method for reducing human PRLR activity comprising contacting human PRLR with the binding protein of any one of claims 1-56 such that human PRLR activity is reduced.

95. A method for reducing human PRLR activity in a human subject suffering from a disorder in which PRLR activity is detrimental, comprising administering to the human subject the binding protein of any one of claims 1-56 such that human PRLR activity in the human subject is reduced.

96. A method for treating a subject for a disease or a disorder in which PRLR activity is detrimental by administering to the subject the binding protein of any one of claims 1-56, such that treatment is achieved.

97. The method of claim 96, wherein the disorder is a cancer.

98. The method of claim 97, wherein the cancer is selected from the group consisting of melanoma, endometrial cancer, lymphoma, breast cancer, ovarian cancer, renal carcinoma, gastrointestinal cancer, colon cancer, lung cancer, pancreatic cancer, and prostate cancer.

99. The method of claim 97, wherein the cancer is breast cancer.

100. The method according to any one of claims 96-99, wherein said binding protein is administered to the subject by a mode selected from the group consisting of parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

101. An anti-PRLR antibody, or antigen binding fragment thereof, that specifically competes with an anti-PRLR binding protein of any one of claims 1-56, wherein said competition can be detected in a competitive binding assay using said antibody, the human PRLR polypeptide, and the anti-PRLR binding protein.

102. An anti-PRLR Antibody Drug Conjugate (ADC) comprising an anti-PRLR antibody, or antigen-binding fragment thereof, and at least one drug, wherein the antibody, or antigen-binding portion thereof, comprises at least 3 CDRs.

103. The anti-PRLR Antibody Drug Conjugate (ADC) of claim 102, wherein the antibody, or antigen-binding portion thereof, comprises at least 3 CDRs selected from a heavy chain variable domain CDR set (CDR1, CDR2, and CDR3) consisting of SEQ ID NOs: 40, 41, and 42; SEQ ID NOs: 46, 47, and 42; SEQ ID NOs: 56, 57, and 58; SEQ ID NOs: 62, 63, and 58; SEQ ID NOs: 71, 72, and 73; SEQ ID NOs: 71, 77, and 73; SEQ ID NOs: 85, 86, and 87; SEQ ID NOs: 149, 150, and 87.

104. The anti-PRLR Antibody Drug Conjugate (ADC) of claim 102 or 103, wherein the antibody, or antigen-binding portion thereof, comprises at least 3 CDRs selected from a light chain variable domain CDR set (CDR1, CDR2, and CDR3) consisting of SEQ ID NOs: 49, 50, and 51; SEQ ID NOs: 65, 66, and 67; SEQ ID NOs: 79, 80, and 81; and SEQ ID NOs: 92, 93, and 94.

105. The ADC of any one of claims 102-104, wherein the drug is selected from the group consisting of a mitotic inhibitor, an antitumor antibiotic, an immunomodulating agent, a vector for gene therapy, an alkylating agent, an antiangiogenic agent, an antimetabolite, a boron-containing agent, a chemoprotective agent, a hormone, an antihormone agent, a corticosteroid, a photoactive therapeutic agent, an oligonucleotide, a radionuclide agent, a topoisomerase inhibitor, a tyrosine kinase inhibitor, and a radiosensitizer.

106. The ADC of any one of claims 102-105, wherein the drug is selected from the group consisting of Ixempra, dolastatin 10, dolatstin 15, auristatin E, auristatin PE, monomethyl auristatin D (MMAD or auristatin D derivative), monomethyl auristatin E (MMAE or auristatin E derivative), monomethyl auristatin F (MMAF or auristatin F derivative), auristatin F phenylenediamine (AFP), auristatin EB (AEB), auristatin EFP (AEFP), 5-benzoylvaleric acid-AE ester (AEVB), methotrexate, daunorubicin, vincristine, maytansine, maytansinol, C-3 esters of maytansinol, ansamitocin P1, ansamitocin P2, ansamitocin P3, ansamitocin P4, docetaxel, paclitaxel, nanoparticlae paclitaxel, vindesine sulfate, vincristine, vinblastine, vinorelbine, actinomycines, pyrrolo[2,1-c][1,4]benzodiazepines, pyrrolobenzodiazepine (PBD) dimer,actinomycin D, anthramycin, chicamycin A, DC-18, mazethramycin, neothramycin A, neothramycin B,

porothramycin, prothracarcin B, SG2285, sibanomicin, sibiromycin, tomaymycin, anthracyclines, daunorubicin, doxorubicin, epirubicin, idarubicin, calicheamicins, γ_1^I, α_2^I, α_3^I, N-acetyl-γ_1^I, PSAG, θ^I_1, duocarmycins, adozelesin, bizelesin, and carzelesin, bleomycin, mitomycin, plicamycin, bacillus calmette-guerin (BCG), levamisole, cancer vaccines, recombinant bivalent human papillomavirus (HPV) vaccine types 16 and 18 vaccine, recombinant quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 vaccine, sipuleucel-T, cytokines, parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH), hepatic growth factor; fibroblast growth factor, prolactin, placental lactogen, tumor necrosis factor, mullerian-inhibiting substance, mouse gonadotropin-associated peptide, inhibin, activin, vascular endothelial growth factor, integrin, thrombopoietin (TPO), nerve growth factors such as NGF, platelet-growth factor, transforming growth factors (TGFs), insulin-like growth factor-I and -II, erythropoietin (EPO), osteoinductive factors, interferons such as interferon α, β,nd γ, colony stimulating factors (CSFs), granulocyte-macrophage-C-SF (GM-CSF), and granulocyte-CSF (G-CSF), interleukins (ILs) such as IL-1, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, tumor necrosis factor and other polypeptide factors including LIF and kit ligand (KL), colony-stimulating factors, erythropoietin (epoetin), filgrastim, sargramostim, promegapoietin, Oprelvekin, immunomodulating gene therapeutics, nucleic acid encoding a functional, therapeutic gene that is used to replace a mutated or otherwise dysfuntional (*e.g.* truncated) gene associated with cancer, nucleic acid that encodes for or otherwise provides for the production of a therapeutic protein to treat cancer, alkyl sulfonates, busulfan, nitrogen mustards, chlorambucil, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, and melphalan, nitrosoureas, carmustine, fotemustine, lomustine, nimustine, streptozocin, triazines and hydrazines, dacarbazine, procarbazine, temozolomide, ethylenimimes, thiopeta, diaziquone, mitomycin C, methylamine derivatives, epoxides, altretamine, dianhydrogalactitol, dibromodulcitol, angiostatin, ABX EFG, C1-1033, PKI-166, EGF vaccine, EKB-569, GW2016, ICR-62, EMD 55900, CP358, PD153035, AG1478, IMC-C225, OSI-774, Erlotinib, angiostatin, arrestin, endostatin, BAY 12-9566 and w/fluorouracil or doxorubicin, canstatin, carboxyamidotriozole and with paclitaxel, EMD121974, S-24, vitaxin, dimethylxanthenone acetic acid, IM862, Interleukin-12, Interleukin-2, NM-3, HuMV833, PTK787, RhuMab, angiozyme, IMC-1C11, Neovastat, marimstat, prinomastat, BMS-275291,COL-3, MM1270, SU101, SU6668, SU11248, SU5416, with paclitaxel, with gemcitabine and cisplatin, and with irinotecan and cisplatin and with radiation, tecogalan, temozolomide and PEG interferon α2b,

tetrathiomolybdate, TNP-470, thalidomide, CC-5013 and with taxotere, tumstatin, 2-methoxyestradiol, VEGF trap, mTOR inhibitors (deforolimus, everolimus, and temsirolimus), tyrosine kinase inhibitors (*e.g.*, imatinib, gefitinib, dasatinib, sunitinib, nilotinib, lapatinib, sorafenib, phosphoinositide 3-kinases (PI3K), folic acid antagonists, methotrexate, 4-amino-folic acid, lometrexol, pemetrexed, trimetrexate, a pyrimidine antagonists, azacitidine, capecitabine, cytarabine, decitabine, 5-fluorouracil, 5-fluoro-2'-deoxyuridine 5'-phosphate, 5-fluorouridine triphosphate, gemcitabine, foxuridine, a purine antagonist azathioprine, cladribine, mercaptopurine, fludarabine, pentostatin, 6-thioguanine, adenosine deaminase inhibitors, Cladribine, Fludarabine, Nelarabine, Pentostatin, borophycin, bortezomib, chemoprotective agents, amifostine, dexrazoxane, mesna, androgens, estrogens, medroxyprogesterone acetate, progestins, aminoglutethimide, anastrozole, bicalutamide, chlorotrianises, cyproterone acetate, degarelix, exemestane, flutamide, fulvestrant, goserelin, letrozole, leuprolide, lupron, medroxyprogesterone acetate, Megestrol acetate, tamoxifen, triptorelin, asparaginase, dacarbazine, hydroxyurea, levamisole, mitotane, procarbazane, tretinoin, glucocorticoids, prednisone, chromagens, dyes, antisense oligonucleotides whether naturally occurring or synthesized using standard and/or non-standard nucleotides (including RNA interference (RNAi)), double-stranded RNA (dsRNA), small interferring RNA (siRNA), microRNA (miRNA), aptamers, CpG oligonucleotides, ribozymes, angiozyme, ^{111}In, ^{177}Lu, ^{212}Bi, ^{213}Bi, ^{211}At, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{90}Y, ^{I25}I, ^{I31}I, ^{32}P, ^{33}P, ^{47}Sc, ^{111}Ag, ^{67}Ga, ^{142}Pr, ^{153}Sm, ^{161}Tb, ^{166}Dy, ^{166}Ho, ^{186}Re, ^{188}Re, ^{189}Re, ^{212}Pb, ^{223}Ra, ^{225}Ac, ^{59}Fe, ^{75}Se, ^{77}As, ^{89}Sr, ^{99}Mo, ^{105}Rh, ^{I09}Pd, ^{143}Pr, ^{149}Pm, ^{169}Er, ^{194}Ir, ^{198}Au, ^{199}Au, ^{211}Pb, Co-58, Ga-67, Br-80m, Tc-99m, Rh-103m, Pt-109, In-111 1, Sb-119, I-125, Ho-161 , Os-189m, Ir-192, Dy-152, At-211 , Bi-212, Ra-223, Rn-219, Po-215, Bi-21 1, Ac-225, Fr-221, At-217, Bi-213, Fm-255, ^{11}C, ^{13}N, ^{15}0, ^{75}Br, ^{198}Au, ^{224}Ac, ^{126}I, ^{133}I, ^{77}Br, ^{113m}In, ^{95}Ru, ^{97}Ru, ^{I03}Ru, ^{105}Ru, ^{107}Hg, ^{203}Hg, ^{121m}Te, ^{122m}Te, ^{125m}Te, ^{165}Tm, ^{I67}Tm, ^{168}Tm, ^{197}Pt, ^{109}Pd, ^{105}Rh, ^{142}Pr, ^{143}Pr, ^{161}Tb, ^{I66}Ho, ^{199}Au, ^{57}Co, ^{58}Co, ^{51}Cr, ^{59}Fe, ^{75}Se, ^{201}Tl, ^{225}Ac, ^{76}Br, ^{I69}Yb, taxane, cisplatin, metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, E09, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5-iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FUdR), hydroxyurea, hematoporphyrin derivatives, Photofrin(r), benzoporphyrin derivatives, NPe6, tin etioporphyrin (SnET2), pheoborbide a, bacteriochlorophyll a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, camptothecins, irinotecan, topotecan, amsacrine, daunorubicin, doxotrubicin, epipodophyllotoxins, ellipticines, epirubicin, etoposide, razoxane, teniposide, Axitinib, Bosutinib, Cediranib, Dasatinib, Erlotinib, Gefitinib, Imatinib, Lapatinib, Lestaurtinib,

Nilotinib, Semaxanib, Sunitinib, Vandetanib, abrin, abrin A chain, alpha toxin, Aleurites fordii proteins, amatoxin, crotin, curcin, dianthin proteins, diptheria toxin, diphtheria A chain, nonbinding active fragments of diphtheria toxin, deoxyribonuclease (Dnase), gelonin, mitogellin, modeccin A chain, momordica charantia inhibitor, neomycin, onconase, phenomycin, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), pokeweed antiviral protein, Pseudomonas endotoxin, Pseudomonas exotoxin, exotoxin A chain from Pseudomonas aeruginosa, restrictocin, ricin, ricin A chain, ribonuclease (Rnase), sapaonaria officinalis inhibitor, saporin, alpha-sarcin, Staphylcoccal enterotoxin-A, tetanus toxin, cisplatin, carboplatin, and oxaliplatin (Eloxatin, Sanofi Aventis), proteasome inhibitors, PS-341, HDAC inhibitors, vorinostat, belinostat, entinostat, mocetinostat, panobinostat, COX-2 inhibitors, substituted ureas, heat shock protein inhibitors, Geldanamycin, adrenocortical suppressants, tricothecenes, A12, 19D12, Cp751-871, H7C10, alphaIR3, ScFV/FC, EM/164, Matuzumab, Erbitux, Vectibix, mAb 806, Nimotuxumab, AVEO, AMG102, 5D5 (OA-5d5), H244G11, Ab #14 (MM 121-14), Herceptin, 1B4C3; 2D1D12, NVP-AEW541-A, BMS-536,924 (1H-benzoimidazol-2-yl)-1H-pyridin-2-one), BMS-554,417, Cycloligan, TAE226, PQ401 , Iressa, CI-1033 (PD 183805), Lapatinib (GW-572016), Tykerb, Tarceva, PKI-166, PD-158780, EKB-569, Tyrphostin AG 1478 (4-(3-Chloroanillino)-6,7-dimethoxyquinazoline), PHA665752, ARQ 197, Capecitabine, 5-Trifluoromethyl-2'-deoxyuridine, Methotrexate sodium, Raltitrexed, Pemetrexed, Tegafur, Cytosine Arabinoside (Cytarabine), 5-azacytidine, 6-mercaptopurine (Mercaptopurine, 6-MP), Azathioprine, 6-thioguanine, Pentostatin, Fludarabine phosphate, Cladribine (2-CdA, 2-chlorodeoxyadenosine), Ribonucleotide Reductase Inhibitor, Cyclophosphamide, Neosar, ifosfamide, Thiotepa, BCNU→ 1,3-bis(2-chloroethyl)-1-nitosourea, CCNU→ 1, -(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (methyl CCNU), Hexamethylmelamine, busulfan, Procarbazine HCL, Dacarbazine (DTIC), chlorambucil, melphalan, carboplatin, oxaliplatin, doxorubicin HCL, daunorubicin citrate, mitoxantrone HCL, actinomycin D, etoposide, topotecan HCL, teniposide, irinotecan HCL(CPT-ll), vincristine, vinblastine sulfate, vinorelbine tartrate, vindesine sulphate, pac1itaxel, docetaxel, abraxane, ixabepilone, imatinib mesylate, sunitinib malate, sorafenib toslate, nilotinib hydrochloride monohydrate, L-asparaginase, alpha interferon, Avastin, IL-2, Aldesleukin, Proleukin, IL-12, Toremifene citrate, Fulvestrant, raloxifene HCL, anastrazole, letrozole, Fadrozole (CGS 16949A), exemestane, leuprolide acetate, Lupron, goserelin acetate, triptorelin pamoate, buserelin, Nafarelin, cetrorelix, bicalutamide, nilutamide, megestrol acetate, somatostatin Analogs, prendinsolone, dexamethasone, ketoconazole, sirolimus, temsirolimus (CCI-779), deforolimus (AP23573), and everolimus (RAD00I).

107. A pharmaceutical composition comprising the ADC of any one of claims 102-106.

108. A method of treating cancer in a subject in need thereof, said method comprising administering the ADC of any one of claims 102-107, such that the subject is treated.

109. The method of claim 108, wherein the cancer is selected from the group consisting of melanoma, endometrial cancer, lymphoma, breast cancer, ovarian cancer, renal carcinoma, gastrointestinal cancer, colon cancer, lung cancer, pancreatic cancer, and prostate cancer.

110. The method of claim 108, wherein the cancer is breast cancer.

111. The method according to any one of claims 108-110, wherein the ADC is administered to the subject by a mode selected from the group consisting of parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.