In another aspect, the invention pertains to the use of the binding protein as disclosed herein in the manufacture of a medicament for reducing human PRLR, wherein human PRLR is to be contacted with the medicament such that human PRLR activity is reduced.

In another aspect, the invention pertains to the use of the binding protein as disclosed herein in the manufacture of a medicament for reducing human PRLR activity in a human subject suffering from a disorder in which PRLR activity is detrimental, wherein the medicament is to be administered to the human subject such that human PRLR activity in the human subject is reduced.

In another aspect, the invention pertains to the use of the subject the binding protein as disclosed herein in the manufacture of a medicament for treating a subject for a disease or a disorder in which PRLR activity is detrimental, wherein the medicament is to be administered to the subject, such that treatment is achieved.

In another aspect, the invention pertains to the use of the ADC as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the medicament is to be administered, such that the subject is treated.

In another aspect, the invention pertains to a binding protein capable of binding prolactin receptor (PRLR), wherein said binding protein comprises 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 aspect, the invention pertains to a binding protein capable of binding PRLR and competing with an antibody 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 aspect, the invention pertains to a binding protein capable of binding PRLR and having the same epitopic specificity as an antibody, or antigen-binding portion thereof, wherein the binding protein is Ab19, and wherein the binding protein is a monoclonal antibody.

CLAIMS

We claim:

1. A binding protein capable of binding prolactin receptor (PRLR), wherein said binding protein comprises 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.

2. The binding protein according to claim 1, further comprising a human acceptor framework.

3. The binding protein according to claim 2, wherein said human acceptor framework comprises an amino acid sequence selected from the group consisting of SEQ ID Nos:14-38 or 158.

4. The binding protein according to claim 2, 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.

5. The binding protein according to claim 4, 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 residue capable of interacting with human PRLR;

a residue capable of interacting with a CDR;

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.

6. The binding protein according to claim 5, 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.

7. The binding protein according to claim 6, wherein the binding protein is a consensus human variable domain.

8. The binding protein according to any one of the preceding claims, wherein the binding protein binds the ligand binding D1 domain of PRLR.

9. The binding protein according to any one of the preceding claims, wherein the binding protein inhibits binding of prolactin to PRLR.

10. The binding protein according to any one of the preceding claims, wherein the binding protein is capable of neutralizing PRLR.

11. 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.

12. 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.

13. 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.

14. A binding protein capable of binding PRLR and competing with an antibody 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.

15. A binding protein capable of binding PRLR, that binds to an epitope in PRLR comprising 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, wherein the binding protein is a monoclonal antibody.

16. The binding protein of claim 15, 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.

17. The binding protein of claim 15 or 16, wherein the binding protein is an antibody, or antigen binding portion thereof and wherein the binding protein is Ab19.

18. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising 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, wherein the binding protein is a monoclonal antibody.

19. The binding protein of claim 18, 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.

20. 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, wherein the binding protein is a monoclonal antibody.

21. The binding protein of claim 20, wherein the epitope comprises at least 15 of the amino acid residues.

22. The binding protein of claim 20, 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.

23. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising amino acid residues R25, K185, D187, H188 or W191 of SEQ ID NO:2, wherein the binding protein is a monoclonal antibody.

24. A binding protein capable of binding PRLR that binds to an epitope in PRLR comprising amino acids 91-96 of SEQ ID NO:2, wherein the binding protein is a monoclonal antibody.

25. The binding protein of claim 24, wherein the binding protein comprises an antibody, or antigen binding portion thereof and wherein the binding protein is Ab19.

26. 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, wherein the binding protein is a monoclonal antibody.

27. The binding protein of claim 26, wherein the binding protein is an antibody, or antigen binding portion thereof, and wherein the binding protein is Ab19.

28. A binding protein capable of binding PRLR and having the same epitopic specificity as an antibody, or antigen-binding portion thereof, wherein the binding protein is Ab19, and wherein the binding protein is a monoclonal antibody.

29. The binding protein of any one of claims 14-28, wherein the binding protein binds the ligand binding D1 domain of PRLR.

30. The binding protein of any one of claims 14-29, wherein the binding protein binds an epitope of PRLR which does not inhibit dimerization of PRLR.

31. The binding protein of any one of claims 14-30, wherein the binding protein does not bind the D2 domain of PRLR.

32. The binding protein of any one of claims 14-31, wherein the binding protein inhibits binding of prolactin to PRLR.

33. The binding protein of any one of claims 14-32, wherein the binding protein does not compete with antibody LFA102 for binding of PRLR.

34. The binding protein of any one of claims 1-13, wherein the binding protein is an antibody.

35. An antibody construct comprising the binding protein of any one of claims 1-34, said antibody construct further comprising a linker polypeptide or an immunoglobulin constant domain.

36. The antibody construct according to claim 35, wherein said binding protein is selected from the group consisting of:

an immunoglobulin molecule,
a monoclonal antibody,
a chimeric antibody,
a CDR-grafted antibody,
a humanized antibody,
a Fab,
a Fab',
a F(ab')2,
a Fv,
a disulfide linked Fv,
a scFv,
a single domain antibody,
a diabody,
a multispecific antibody,
a dual specific antibody, and
a bispecific antibody.

37. The antibody construct according to claim 35 or 36, wherein said binding protein comprises 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.

38. The antibody construct according to any one of claims 35-37, comprising an immunoglobulin constant domain having an amino acid sequence selected from the group consisting of SEQ ID Nos:10-13.

39. An antibody conjugate comprising the antibody construct of any one of claims 35-38, 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.

40. The antibody conjugate according to claim 39, 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.

41. The antibody conjugate according to claim 39, 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.

42. The antibody conjugate according to claim 39, 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.

43. The antibody conjugate according to claim 42, 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.

44. The antibody construct according to any one of claims 35-43, wherein said binding protein possesses a human glycosylation pattern.

45. The binding protein according to any one of claims 1-34, wherein said binding protein is a crystallized binding protein.

46. The antibody construct according to any one of claims 35-44, wherein said antibody construct is a crystallized antibody construct.

47. The antibody construct according to claim 46, wherein said crystallized antibody construct is a carrier-free pharmaceutical controlled release crystallized antibody construct.

48. The antibody construct according to claim 46 or 47, wherein said antibody construct has a greater half life *in vivo* than the soluble counterpart of said antibody construct.

49. An isolated nucleic acid encoding an amino acid sequence of the binding protein of any one of claims 1-34.

50. An isolated nucleic acid encoding an antibody construct amino acid sequence of any one of claims 35-44.

51. A vector comprising an isolated nucleic acid according to claim 49 or 50.

52. The vector of claim 50 wherein said vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.

53. A host cell comprising a vector according to claim 51 or 52.

54. The host cell according to claim 53, wherein said host cell is a prokaryotic cell or a eukaryotic cell.

55. The host cell according to claim 54, wherein said prokaryotic host cell is E.Coli.

56. The host cell according to claim 54, wherein said eukaryotic cell is selected from the group consisting of a protist cell, an animal cell, a plant cell and a fungal cell.

57. The host cell according to claim 56, wherein said animal cell is selected from the group consisting of a mammalian cell, an avian cell, and an insect cell.

58. The host cell according to claim 53, 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.

59. The host cell according to claim 58, wherein said yeast cell is *Saccharomyces cerevisiae*.

60. A method of producing a protein capable of binding PRLR, comprising culturing the host cell of any one of claims 53-59 in culture medium under conditions sufficient to produce a binding protein capable of binding PRLR.

61. 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 45, and an ingredient; and
(b) at least one polymeric carrier.

62. The composition according to claim 61, 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.

63. The composition according to claim 61 or 62, wherein said ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-b- cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

64. Use of the composition according to any one of claims 61-63 in the manufacture of a medicament for treating a disease in which PRLR is detrimental in a mammal.

65. A pharmaceutical composition comprising the binding protein of any one of claims 1-34, and a pharmaceutically acceptable carrier.

66. The pharmaceutical composition of claim 65 wherein said pharmaceutically acceptable carrier functions as adjuvant useful to increase the absorption, or dispersion of said binding protein.

67. The pharmaceutical composition of claim 66 wherein said adjuvant is hyaluronidase.

68. The pharmaceutical composition of any one of claims 65-67 further comprising at least one additional therapeutic agent for treating a disorder in which PRLR activity is detrimental.

69. The pharmaceutical composition of claim 68, 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.

70. Use of the binding protein of any one of claims 1-34 in the manufacture of a medicament for reducing PRLR activity in a human subject having a disorder in which PRLR activity is detrimental.

71. Use of the binding protein of any one of claims 1-34 in the manufacture of a medicament for treating a subject having a disorder in which PRLR activity is detrimental.

72. The use of claim 71, wherein the disorder is a cancer.

73. The use of claim 72, 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.

74. The use of claim 72, wherein the cancer is breast cancer.

75. The use method according to any one of claims 71-74, 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.

76. An anti-PRLR antibody, or antigen binding fragment thereof, that specifically competes with an anti-PRLR binding protein of any one of claims 1-34, wherein said competition can be detected in a competitive binding assay using said antibody, the human PRLR polypeptide, and the anti-PRLR binding protein, wherein the binding protein is a monoclonal antibody, and wherein the anti-PRLR antibody, or antigen binding fragment thereof, binds to an epitope overlapping with or identical to the epitope of the binding protein.

77. An anti-PRLR Antibody Drug Conjugate (ADC) comprising the anti-PRLR antibody, or antigen-binding fragment thereof, according to any one of claims 3-5, and at least one drug.

78. The anti-PRLR Antibody Drug Conjugate (ADC) of claim 77, wherein the antibody, or antigen-binding portion thereof, comprises 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.

79. The ADC of claim 77 or 78, 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.

80. The ADC of any one of claims 77-79, 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_I^I, α_2^I, α_3^I, N-acetyl-γ_I^I, PSAG, θ^I_I, 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, ^{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, paclitaxel, 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).

81. A pharmaceutical composition comprising the ADC of any one of claims 77-80.

82. The ADC of any one of claims 77-81 for use in treating cancer in a subject in need thereof.

83. The use of claim 82, 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.

84. The use of claim 82, wherein the cancer is breast cancer.

85. The use according to any one of claims 82-84, 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.