a. 006-H08 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 46, and an amino acid sequence according to SEQ ID NO: 34, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 52, and an amino acid sequence according to SEQ ID NO: 40.

b. 006-H08-12-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 331, and an amino acid sequence according to SEQ ID NO: ~~353~~143, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~165~~353, and an amino acid sequence according to SEQ ID NO: ~~143~~165,

c. 006-H08-13-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 332, ,and an amino acid sequence according to SEQ ID NO: ~~354~~144, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~166~~354, and an amino acid sequence according to SEQ ID NO: ~~144~~166,

d. 006-H08-13-6-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 333, and an amino acid sequence according to SEQ ID NO: ~~355~~145, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~167~~355, and an amino acid sequence according to SEQ ID NO: ~~145~~167,

e. 006-H08-14-6-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 334, and an amino acid sequence according to SEQ ID NO: ~~356~~146, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~168~~356, and an amino acid sequence according to SEQ ID NO: ~~146~~168,

f. 006-H08-15-5 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 335, and an amino acid sequence according to SEQ ID NO: ~~357~~147, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~169~~357, and an amino acid sequence according to SEQ ID NO: ~~147~~169,

g. 006-H08-19-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 336, and an amino acid sequence according to SEQ ID NO: ~~358~~148, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~170~~358, and an amino acid sequence according to SEQ ID NO: ~~148~~170,

h. 006-H08-29-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 337, and an amino acid sequence according to SEQ ID NO: ~~359~~149, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~171~~359, and an amino acid sequence according to SEQ ID NO: ~~149~~171,

i. 006-H08-32-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 338, and an amino acid sequence according to SEQ ID NO: ~~360~~150, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~172~~360, and an amino acid sequence according to SEQ ID NO: ~~150~~172,

j. 006-H08-33-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 339, and an amino acid sequence according to SEQ ID NO: ~~361~~151, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~173~~361, and an amino acid sequence according to SEQ ID NO: ~~151~~173,

k. 006-H08-33-16-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 340, and an amino acid sequence according to SEQ ID NO: ~~362~~152, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~174~~362, and an amino acid sequence according to SEQ ID NO: ~~152~~174,

l. 006-H08-35-17-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 341, and an amino acid sequence according to SEQ ID NO: ~~363~~153, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~175~~363, and an amino acid sequence according to SEQ ID NO: ~~153~~175,

m. 006-H08-35-17-4 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 342, and an amino acid sequence according to SEQ ID NO: ~~364~~154, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~176~~364, and an amino acid sequence according to SEQ ID NO: ~~154~~176,

n. 006-H08-35-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 343, and an amino acid sequence according to SEQ ID NO: ~~365~~155, and a variable light

chain domain with a nucleic acid sequence according to SEQ ID NO: ~~177~~365, and an amino acid sequence according to SEQ ID NO: ~~155~~177,

o. 006-H08-36-17-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 344, and an amino acid sequence according to SEQ ID NO: ~~366~~156, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~178~~366, and an amino acid sequence according to SEQ ID NO: ~~156~~178,

p. 006-H08-37-19-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 345, and an amino acid sequence according to SEQ ID NO: ~~367~~157, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~179~~367, and an amino acid sequence according to SEQ ID NO: ~~157~~179,

q. 006-H08-39-7 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 346, and an amino acid sequence according to SEQ ID NO: ~~368~~158, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~180~~368, and an amino acid sequence according to SEQ ID NO: ~~158~~180,

r. 006-H08-48-5 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 347, and an amino acid sequence according to SEQ ID NO: ~~369~~159, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~181~~369, and an amino acid sequence according to SEQ ID NO: ~~159~~181,

s. 006-H08-53-27-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 348, and an amino acid sequence according to SEQ ID NO: ~~370~~160, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~182~~370, and an amino acid sequence according to SEQ ID NO: ~~160~~182,

t. 006-H08-59-30-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 349, and an amino acid sequence according to SEQ ID NO: ~~371~~161, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~183~~371, and an amino acid sequence according to SEQ ID NO: ~~161~~183,

u. 006-H08-63-32-4 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 350, and an amino acid sequence according to SEQ ID NO: ~~372~~162, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~184~~372, and an amino acid sequence according to SEQ ID NO: ~~162~~184,

v. 006-H08-65-33-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 351, and an amino acid sequence according to SEQ ID NO: ~~373~~163, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~185~~373, and an amino acid sequence according to SEQ ID NO: ~~163~~185,

w. 006-H08-68-35-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 352, and an amino acid sequence according to SEQ ID NO: ~~374~~164, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: ~~186~~374, and an amino acid sequence according to SEQ ID NO: ~~164~~186.

In yet another embodiment antibody or antigen-binding fragment of the afore mentioned antibodies are disclosed whereby

a. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 7, 13, 18, 24, 29, or

b. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 74, 13, 78, 24, 90, or

c. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 75, 13, 82, 24, 91, or

d. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 7, 13, 82, 24, 29, or

e. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 7, 13, 86, 24, 29, or

f. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 74, 13, 87, 24, 100, or

g. the antibody contains one, two, three, four, five or six of the CDRs corresponding to SEQ ID NO: 1, 74, 13, 87, 24, 92 or

<210> 29
<211> 11
<212> PRT
<213> Homo sapiens

<400> 29

Cys Gln Ser Tyr Asp Thr Gly Leu Ser Gly Trp Val
1 5 10

<210> 30
<211> 11
<212> PRT
<213> Homo sapiens

<400> 30

Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Val
1 5 10

<210> 31
<211> 12
<212> PRT
<213> Homo sapiens

<400> 31

Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Trp Val
1 5 10

<210> 32
<211> 11
<212> PRT
<213> Homo sapiens

<400> 32

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Val
1 5 10

<210> 33
<211> 11
<212> PRT
<213> Homo sapiens

<400> 33

Cys Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Leu
1 5 10

<210> 34
<211> 119
<212> PRT
<213> Homo sapiens

<400> 34

Gln Val Glu Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr

Claims:

1. Antibody 006-H08 or defined maturated variants thereof or antigen-binding fragments thereof which antagonize prolactin receptor-mediated signaling and which bind to epitopes of the extracellular domain of the prolactin receptor and human polymorphic variants thereof whereby the amino acid sequence of the extracellular domain of the prolactin receptor corresponds to SEQ ID NO: 70, and the nucleic acid sequence corresponds to SEQ ID NO: 71.

2. Antibody 006-H08 or antigen-binding fragment thereof according to claim 1 comprising the CDRs of the antibody of claim 1, whereby
   a. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7 and 13 and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, and 29, or
   b. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 78, 24, 90; or
   c. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 75, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 82, 24, 91; or
   d. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 82, 24, 29; or
   e. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 86, 24, 29; or
   f. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 87, 24, 100; or
   g. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 87, 24, 92; or
   h. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 89, 24, 93; or

i. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 79, 24, 101; or

j. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 76, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 89, 24, 90; or

k. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 100; or

l. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 97; or

m. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 98; or

n. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 83, 24, 99; or

o. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 96; or

p. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 94; or

q. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 88, 24, 90; or

r. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 74, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 81, 24, 95; or

s. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 75, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 29; or

t. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 77, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 18, 24, 29; or

u. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 80, 24, 29; or

v. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 85, 24, 29; or

w. the variable heavy chain contains the CDR sequences corresponding to SEQ ID NO: 1, 7, 13, and the variable light chain contains the CDR sequences corresponding to SEQ ID NO: 84, 24, 29.

3. Antibody or antigen-binding fragment according to claim 1 to 2, whereby the antibody

a. 006-H08 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 46, and an amino acid sequence according to SEQ ID NO: 34, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 52, and an amino acid sequence according to SEQ ID NO: 40,

b. 006-H08-12-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 331, and an amino acid sequence according to SEQ ID NO: 353, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 165, and an amino acid sequence according to SEQ ID NO: 143,

c. 006-H08-13-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 332, ,and an amino acid sequence according to SEQ ID NO: 354, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 166, and an amino acid sequence according to SEQ ID NO: 144,

d. 006-H08-13-6-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 333, and an amino acid sequence according to SEQ ID NO: 355, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 167, and an amino acid sequence according to SEQ ID NO: 145,

e. 006-H08-14-6-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 334, and an amino acid sequence according to SEQ ID NO: 356, and a variable light chain

domain with a nucleic acid sequence according to SEQ ID NO: 168, and an amino acid sequence according to SEQ ID NO: 146,

f. 006-H08-15-5 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 335, and an amino acid sequence according to SEQ ID NO: 357, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 169, and an amino acid sequence according to SEQ ID NO: 147,

g. 006-H08-19-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 336, and an amino acid sequence according to SEQ ID NO: 358, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 170, and an amino acid sequence according to SEQ ID NO: 148,

h. 006-H08-29-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 337, and an amino acid sequence according to SEQ ID NO: 359, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 171, and an amino acid sequence according to SEQ ID NO: 149,

i. 006-H08-32-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 338, and an amino acid sequence according to SEQ ID NO: 360, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 172, and an amino acid sequence according to SEQ ID NO: 150,

j. 006-H08-33-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 339, and an amino acid sequence according to SEQ ID NO: 361, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 173, and an amino acid sequence according to SEQ ID NO: 151,

k. 006-H08-33-16-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 340, and an amino acid sequence according to SEQ ID NO: 362, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 174, and an amino acid sequence according to SEQ ID NO: 152,

l. 006-H08-35-17-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 341, and an amino acid sequence according to SEQ ID NO: 363, and a

variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 175, and an amino acid sequence according to SEQ ID NO: 153,

m. 006-H08-35-17-4 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 342, and an amino acid sequence according to SEQ ID NO: 364, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 176, and an amino acid sequence according to SEQ ID NO: 154,

n. 006-H08-35-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 343, and an amino acid sequence according to SEQ ID NO: 365, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 177, and an amino acid sequence according to SEQ ID NO: 155,

o. 006-H08-36-17-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 344, and an amino acid sequence according to SEQ ID NO: 366, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 178, and an amino acid sequence according to SEQ ID NO: 156,

p. 006-H08-37-19-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 345, and an amino acid sequence according to SEQ ID NO: 367, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 179, and an amino acid sequence according to SEQ ID NO: 157,

q. 006-H08-39-7 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 346, and an amino acid sequence according to SEQ ID NO: 368, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 180, and an amino acid sequence according to SEQ ID NO: 158,

r. 006-H08-48-5 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 347, and an amino acid sequence according to SEQ ID NO: 369, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 181, and an amino acid sequence according to SEQ ID NO: 159,

s. 006-H08-53-27-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 348, and an amino acid sequence according to SEQ ID NO: 370, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 182, and an amino acid sequence according to SEQ ID NO: 160,

t. 006-H08-59-30-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 349, and an amino acid sequence according to SEQ ID NO: 371, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 183, and an amino acid sequence according to SEQ ID NO: 161,

u. 006-H08-63-32-4 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 350, and an amino acid sequence according to SEQ ID NO: 372, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 184, and an amino acid sequence according to SEQ ID NO: 162,

v. 006-H08-65-33-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 351, and an amino acid sequence according to SEQ ID NO: 373, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 185, and an amino acid sequence according to SEQ ID NO: 163,

w. 006-H08-68-35-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 352, and an amino acid sequence according to SEQ ID NO: 374, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 186, and an amino acid sequence according to SEQ ID NO: 164.

4. Antibody according to claim 1 to 3, whereby the antibody consists of an antigen-binding region that binds specifically to or has a high affinity of for one or more regions of PRLR, whose amino acid sequence is depicted by SEQ ID NO: 70 and human polymorphic variants of SEQ ID NO: 70, amino acid position 1 to

210, whereby the affinity is at least 100 nM, preferably less than about 100 nM, more preferably less than about 30 nM, even more preferred with an affinity of less than about 10 nM, or even more preferred with an affinity of less than 1 nM.

5. Antibody of claim 1 to 4 wherein the heavy constant is a modified or unmodified IgG1, IgG2, IgG3 or IgG4.

6. An isolated nucleic acid sequence encoding an antibody or antigen-binding fragment according to any of the claims 1 to 5.

7. An isolated nucleic acid sequence according to claim 6, whereby the nucleic acid sequences are according to table 5.

8. Expression vector comprising a nucleic acid sequence of claim 6 and 7.

9. Host cell comprising the vector of claim 8 or a nucleic acid molecule of claim 6 and 7, whereby the host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, and may be a prokaryotic cell, such as a bacterial cell.

10. A method of using the host cell of claim 9 to produce an antibody or antigen-binding fragment, comprising culturing the host cell of claim under suitable conditions and recovering said antibody.

11. An antibody or antigen-binding fragment produced by the method of claim 10.

12. An antibody or antigen-binding fragment of any of claims 1 to 5 that is purified to at least 95% homogeneity by weight.

13. An antibody or antigen-binding fragment according to claims 1 to 5 as a medicament.

14. A pharmaceutical composition comprising the antibody or antigen-binding fragment according to claim 1 to 5 and a pharmaceutically acceptable carrier comprising excipients and auxiliaries.

15. Kits comprising an antibody of claim 1 to 5 comprising a therapeutically effective amount of antibody 006-H08 or maturated variants thereof, packaged in a container, said kit optionally containing a second therapeutic agent, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding the use of the contents of the container to treat endometriosis, adenomyosis, benign breast disease and mastalgia, lactation inhibition, hyper- and normoprolactinemic hair loss, benign prostate hyperplasia, fibroids or for use in non-hormonal female contraception or to treat women under combined hormone therapy (i.e. estrogen plus progestin therapy) to inhibit mammary epithelial cell proliferation.

16. Antibody or antigen-binding fragment according to claim 1 to 5 for the treatment and/or prevention of endometriosis and adenomyosis (endometriosis interna).

17. Antibody or antigen-binding fragment according to claim 1 to 5 for female contraception.

18. Antibody or antigen-binding fragment according to claim 1 to 5 for the treatment of benign breast disease and mastalgia.

19. Antibody or antigen-binding fragment according to claim 1 to 5 for the inhibition of lactation.

20. Antibody or antigen-binding fragment according to claim 1 to 5 for the treatment of benign prostate hyperplasia.

21. Antibody or antigen-binding fragment according to claim 1 to 5 for the treatment of hyper- and normoprolactinemic hair loss.

22. Antibody or antigen-binding fragment according to claim 1 to 5 for the treatment of women receiving combined hormone therapy.

23. Antibody or antigen-binding fragment according to claim 1 to 5 for the treatment of women receiving combined hormone therapy, whereby the combined hormone therapy is an estrogen plus progestin therapy.

24. Antibody or antigen-binding fragment according to claim 1 to 5 or in form of a pharmaceutical composition according to claim 14 comprising PRLR antibodies or antigen-binding fragment according to claim 1 to 5 for parenteral administration, whereby methods of parenteral delivery include topical, intra-arterial, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, intrauterine, vaginal, or intranasal administration.

25. Pharmaceutical composition according to claim 14 comprising PRLR antibodies or antigen-binding fragment according to claim 1 to 5, in combination with at least one other agent.

CLAIMS

1. Isolated antibody or defined maturated variants thereof according to table 5 or antigen-binding fragments thereof which antagonize prolactin receptor-mediated signaling and which bind to epitopes of the extracellular domain of the prolactin receptor and human polymorphic variants thereof, whereby the amino acid sequence of the extracellular domain of the prolactin receptor corresponds to SEQ ID NO: 70, and the nucleic acid sequence corresponds to SEQ ID NO: 71, whereby SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3, and whereby

    a. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 78 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 90 corresponds to LCDR3; or
    b. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 75 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 82 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 91 corresponds to LCDR3; or
    c. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 82 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3; or
    d. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 86 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3; or
    e. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to

HCDR3, and SEQ ID NO: 87 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 100 corresponds to LCDR3; or

f. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 87 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 92 corresponds to LCDR3; or

g. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 89 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 93 corresponds to LCDR3; or

h. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 79 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 101 corresponds to LCDR3, or

i. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 76 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 89 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 90 corresponds to LCDR3; or

j. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 100 corresponds to LCDR3; or

k. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 97 corresponds to LCDR3; or

l. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to

LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 98 corresponds to LCDR3; or

m. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 83 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 99 corresponds to LCDR3; or

n. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 96 corresponds to LCDR3; or

o. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 94 corresponds to LCDR3; or

p. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 88 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 90 corresponds to LCDR3; or

q. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 74 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 81 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 95 corresponds to LCDR3; or

r. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 75 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3; or

s. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 77 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 18 of the variable light chain corresponds to

LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3; or

t. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 80 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3; or

u. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 85 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3 9; or

v. SEQ ID NO: 1 of the variable heavy chain corresponds to HCDR1, SEQ ID NO: 7 corresponds to HCDR2, SEQ ID NO: 13 corresponds to HCDR3, and SEQ ID NO: 84 of the variable light chain corresponds to LCDR 1, SEQ ID NO: 24 corresponds to LCDR2 and SEQ ID NO: 29 corresponds to LCDR3.

2. Isolated antibody or antigen-binding fragment according to claim 1, whereby the antibody

a. 006-H08 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 46, and an amino acid sequence according to SEQ ID NO: 34, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 52, and an amino acid sequence according to SEQ ID NO: 40,

b. 006-H08-12-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 331, and an amino acid sequence according to SEQ ID NO: 143, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 353, and an amino acid sequence according to SEQ ID NO: 165,

c. 006-H08-13-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 332, ,and an amino acid sequence according to SEQ ID NO: 144, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 354, and an amino acid sequence according to SEQ ID NO: 166,

d. 006-H08-13-6-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 333, and an amino acid sequence according to SEQ ID NO: 145, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 355, and an amino acid sequence according to SEQ ID NO: 167,

e. 006-H08-14-6-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 334, and an amino acid sequence according to SEQ ID NO: 146, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 356, and an amino acid sequence according to SEQ ID NO: 168,

f. 006-H08-15-5 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 335, and an amino acid sequence according to SEQ ID NO: 147, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 357, and an amino acid sequence according to SEQ ID NO: 169,

g. 006-H08-19-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 336, and an amino acid sequence according to SEQ ID NO: 148, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 358, and an amino acid sequence according to SEQ ID NO: 170,

h. 006-H08-29-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 337, and an amino acid sequence according to SEQ ID NO: 149, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 359, and an amino acid sequence according to SEQ ID NO: 171,

i. 006-H08-32-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 338, and an amino acid sequence according to SEQ ID NO: 150, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 360, and an amino acid sequence according to SEQ ID NO: 172,

j. 006-H08-33-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 339, and an amino acid sequence according to SEQ ID NO: 151, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 361, and an amino acid sequence according to SEQ ID NO: 173,

k. 006-H08-33-16-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 340, and an amino acid sequence according to SEQ ID NO: 152, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 362, and an amino acid sequence according to SEQ ID NO: 174,

l. 006-H08-35-17-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 341, and an amino acid sequence according to SEQ ID NO: 153, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 363, and an amino acid sequence according to SEQ ID NO: 175,

m. 006-H08-35-17-4 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 342, and an amino acid sequence according to SEQ ID NO: 154, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 364, and an amino acid sequence according to SEQ ID NO: 176,

n. 006-H08-35-1 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 343, and an amino acid sequence according to SEQ ID NO: 155, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 365, and an amino acid sequence according to SEQ ID NO: 177,

o. 006-H08-36-17-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 344, and an amino acid sequence according to SEQ ID NO: 156, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 366, and an amino acid sequence according to SEQ ID NO: 178,

p. 006-H08-37-19-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 345, and an amino acid sequence according to SEQ ID NO: 157, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 367, and an amino acid sequence according to SEQ ID NO: 179,

q. 006-H08-39-7 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 346, and an amino acid sequence according to SEQ ID NO: 158, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 368, and an amino acid sequence according to SEQ ID NO: 180,

r. 006-H08-48-5 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 347, and an amino acid sequence according to SEQ ID NO: 159, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 369, and an amino acid sequence according to SEQ ID NO: 181,

s. 006-H08-53-27-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 348, and an amino acid sequence according to SEQ ID NO: 160, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 370, and an amino acid sequence according to SEQ ID NO: 182,

t. 006-H08-59-30-0 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 349, and an amino acid sequence according to SEQ ID NO: 161, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 371, and an amino acid sequence according to SEQ ID NO: 183,

u. 006-H08-63-32-4 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 350, and an amino acid sequence according to SEQ ID NO: 162, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 372, and an amino acid sequence according to SEQ ID NO: 184,

v. 006-H08-65-33-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 351, and an amino acid sequence according to SEQ ID NO: 163, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 373, and an amino acid sequence according to SEQ ID NO: 185,

w. 006-H08-68-35-2 comprises a variable heavy chain domain corresponding to a nucleic acid sequence according to SEQ ID NO: 352,

and an amino acid sequence according to SEQ ID NO: 164, and a variable light chain domain with a nucleic acid sequence according to SEQ ID NO: 374, and an amino acid sequence according to SEQ ID NO: 186.

3. Isolated antibody according to claim 1 to 2, whereby the antibody consists of an antigen-binding region that binds specifically to or has a high affinity of for one or more regions of PRLR, whose amino acid sequence is depicted by SEQ ID NO: 70 and human polymorphic variants of SEQ ID NO: 70, amino acid position 1 to 210, whereby the affinity is at least 100 nM, preferably less than about 100 nM, more preferably less than about 30 nM, even more preferred with an affinity of less than about 10 nM, or even more preferred with an affinity of less than 1 nM.

4. Isolated antibody of claim 1 to 3 wherein the heavy constant is a modified or unmodified IgG1, IgG2, IgG3 or IgG4.

5. An isolated nucleic acid sequence encoding an antibody or antigen-binding fragment according to any of the claims 1 to 4.

6. Expression vector comprising a nucleic acid sequence of claim 5.

7. Host cell comprising the vector of claim 6 or a nucleic acid molecule of claim 5, whereby the host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, and may be a prokaryotic cell, such as a bacterial cell.

8. A method of using the host cell of claim 7 to produce an antibody or antigen-binding fragment, comprising culturing the host cell of claim 7 under suitable conditions and recovering said antibody.

9. An antibody or antigen-binding fragment of any of claims 1 to 4 that is purified to at least 95% homogeneity by weight.

10. Use of an antibody or antigen-binding fragment according to any of claims 1 to 4 as a medicament.

11. A pharmaceutical composition comprising the antibody or antigen-binding fragment according to any of claims 1 to 4 and a pharmaceutically acceptable carrier comprising excipients and auxiliaries.

12. Kits comprising an antibody of any of claims 1 to 4 comprising a therapeutically effective amount of antibody 006-H08 or maturated variants thereof, packaged in a container, said kit optionally containing a second therapeutic agent.

13. Antibody or antigen-binding fragment according to any of claims 1 to 4 for use as a medicament for the treatment and/or prevention of endometriosis and adenomyosis (endometriosis interna).

14. Antibody or antigen-binding fragment according to any of claims 1 to 4 for use as a medicament for the treatment of benign breast disease and mastalgia.

15. Antibody or antigen-binding fragment according to any of claims 1 to 4 for use as a medicament for the inhibition of lactation.

16. Antibody or antigen-binding fragment according to any of claims 1 to 4 for use as a medicament for the treatment of hyper- and normoprolactinemic hair loss.

17. Use of the antibodies according to any of claims 1 to 4 or in form of a pharmaceutical composition according to claim 11 comprising PRLR antibodies or antigen-binding fragment according to any of claims 1 to 4 in preparation of a pharmaceutical formulation for parenteral administration, whereby methods of parenteral delivery include topical, intra-arterial, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, intrauterine, vaginal, or intranasal administration.

18. Pharmaceutical composition according to claim 11 comprising PRLR antibodies or antigen-binding fragment according to any of claims 1 to 4, in combination with at least one other agent.