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(71) Applicant: **VANCOUVER BIOTECH LTD** [CA/CA]; 9121 Shaughnessy Street, Vancouver, British Columbia, V6P 6R9 (CA).

(72) Inventor; and
(71) Applicant : **LEE, Gregory** [CA/CA]; C/o Ab Pharmatech Ltd., 4133 W 15th Avenue, Vancouver, British Columbia, V6P 6R9 (CA).

(74) Agent: **FETHERSTONHAUGH & CO.**; Box 11115, Royal Centre, Suite 2300, 1055 West Georgia Street, Vancouver, British Columbia V6E 3P3 (CA).

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(54) **Title**: HUMANIZED FORMS OF MONOCLONAL ANTIBODIES TO HUMAN GNRH RECEPTOR

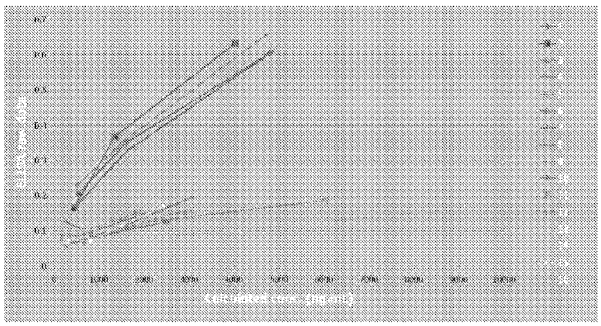

Figure 1

(57) **Abstract**: Humanized forms of murine GHR106 monoclonal antibodies and methods of using them are described. Humanized GHR106 monoclonal antibodies have high affinity and specificity to the corresponding tumor-associated antigen, gonadotropin-releasing hormone (GnRH) receptor comparable to murine GHR106.

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HUMANIZED FORMS OF MONOCLONAL ANTIBODIES TO HUMAN GnRH RECEPTOR

Cross-Reference to Related Applications

[0001] This application claims priority of U.S. Serial No. 61/676,763 filed 27 July 2012 and U.S. Serial No. 13/797,653 filed 12 March 2013. The contents of these documents are incorporated by reference herein in their entirety.

Reference to Sequence Listing Submitted Via EFS-WEB

[0002] The entire content of the following electronic submission of the sequence listing via the USPTO EFS-WEB server, as authorized and set forth in MPEP §1730 II.B.2(a)(C), is incorporated herein by reference in its entirety for all purposes. The sequence listing is identified on the electronically filed text file as follows:

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616342000400seqlist.txt	March 12, 2012	20,735 bytes

Technical Filed

[0003] The invention relates to the field of humanization of GHR106 monoclonal antibody which is of murine origin. GHR106 recognizes specifically the extracellular domains of human GnRH receptor, which is highly expressed on the surface of cancer cells of many human tissue origins. The humanized forms of GHR106 can be utilized for therapeutic applications in human hormone-sensitive cancers as well as in regulating human fertility.

Background Art

[0004] GHR106 monoclonal antibody was generated in mice immunized against synthetic peptides corresponding to the extracellular domains of human GnRH receptor and was found to behave as a GnRH agonist, but with a much longer half-life than agonists known in the art. GnRH agonists have been used to treat a variety of problems such as ovulation disorders, endometriosis, uterine fibroids, precocious puberty, and some types of cancers.

[0005] The murine mAb, GHR106, including the amino acid sequence of its variable regions, is described in PCT publication WO2011/026242, the disclosure of which is

incorporated herein by reference, in particular as to uses of antibodies with specificity similar to that of GHR106.

[0006] Biochemical and immunological experiments demonstrate that GHR106 has high specificity and affinity to GnRH receptor. *In vitro* apoptotic and anti-proliferative assays were performed to document that GHR106 reacts with the surface of almost all cancer cells or cancerous tissues in humans. Complement-dependent cytotoxicity can be induced in cancer cells in the presence of GHR106 at concentrations in the range of µg/ml. *In vivo* growth inhibition by GHR106 of tumor cells implanted in model systems was also demonstrated in nude mouse experiments.

[0007] For use of GHR106-based anti-cancer drugs or fertility regulation drugs in humans, it is essential to modify the original murine GHR106 monoclonal antibody into humanized forms.

Disclosure of the Invention

[0008] The humanized versions of GHR106 of the invention were shown to have affinities and specificities to GnRH receptor which are comparable or equivalent to those of original murine GHR106.

[0009] Thus, in one aspect, the invention is directed to humanized antibodies or fragments that bind the epitope present in residues 1-29 in the extracellular domain of the human GnRH receptor, with specificities and affinities substantially equivalent to that of GHR106. In particular, the antibodies or fragments with variable regions shown in Figure 6 are part of the invention.

[0010] For complete antibodies of the invention, it is preferred that the constant region of the heavy chain be IgG and the constant region of the light chain be kappa. However, other Ig forms, including IgM, IgA and IgE for example, are included as well as those embodiments that have lambda constant regions in their light chains.

[0011] In still other aspects, the invention is directed to methods to use the antibodies of the invention in the treatment of cancer and controlling reproduction in human subjects.

Brief Description of the Drawings

[0012] Figure 1 shows antigen binding affinity of humanized antibodies after a first round of humanization as described herein.

[0013] Figure 2 shows antigen binding affinity of humanized antibodies after a second round.

[0014] Figure 3 shows antigen binding affinity of humanized antibodies after a third round.

[0015] Figure 4 shows SDS-PAGE image of purified recombinant antibodies.

[0016] Figure 5 shows antigen binding affinity of humanized antibodies after a fourth round.

[0017] Figure 6 shows the amino acid sequences of heavy chain and light chain variable regions of humanized forms of GHR106 and of murine GHR106.

[0018] Figure 7 shows the nucleotide sequences encoding the variable regions of Figure 6.

Modes of Carrying Out the Invention

[0019] The humanized antibodies of the invention may be in a variety of forms — including whole antibodies, fragments that are immunoreactive with the epitope present in residues 1-29 in the extracellular domain of the human GnRH receptor, including Fab, Fab', and $F(ab')_2$ fragments as well as recombinantly produced single-chain antibodies. The resulting humanized forms as noted below are of equivalent affinity and specificity to the murine GHR106 and contain substantially similar or identical CDR regions.

[0020] The CDR regions of the variable region of both heavy and light chains can be determined by a number of art-known methods, including the numbering system of Kabat which defines, in the light chain, CDR1 as residues 24-34, CDR2 as residues 50-56, CDR3 as residues 89-97 and, in the heavy chain, CDR1 as residues 31-35, CDR2 as residues 50-65 and CDR3 as residues 95-102 (Wu, T. T., and Kabat, E. A., *Exp. Med.* (1970) 132:211-250). CDRs can also be determined according to the system of Chothia which gives slightly different results (Chothia, C., *et al.*, *Nature* (1989) 342:877-883; Al-Laziken, *et al.*, *J. Mol. Biol.* (1997) 273:927-948). Various subsequent authors have suggested some minor modifications. The CDRs as assigned by both Kabat and Chothia systems are included within the scope of the present invention.

[0021] Sandwich and/or binding immunoassays were used to demonstrate the substantial equivalence between the humanized forms herein and murine GHR106. Their respective affinity and specificity to the cognate antigen, the epitope present in residues 1-29 in the extracellular domain of the human GnRH receptor, are two important parameters to establish their substantial equivalence.

[0022] The previously established sandwich and/or binding immunoassays were used as a tool to demonstrate the substantial equivalence or comparability between the humanized forms and murine GHR106. Their respective affinity and specificity to the cognate antigen in the GnRH receptor establish their substantial equivalence and demonstrates their utility as described for GHR106, but with respect to human subjects.

[0023] The following example is offered to illustrate but not to limit the invention.

Example 1

[0024] Human framework donor selection was made through search of germline followed by rearrangement of the human IgG database using VL and VH sequence with or without CDRs. To obtain human IgG results, normally, each hit is reviewed to eliminate inappropriate donors (such as mouse sequence or humanized sequence, etc.). For VL and VH sequences, the best hits in each group were aligned. Finally, one germline FR donor and one rearranged (mature) FR donor based on sequence similarity and other factors were selected. These factors included CDR length (except for CDR-H3), CDR canonical structure, proline residues at key positions or factors which may affect proper folding of humanized antibody.

[0025] The homology modeling was used to obtain template antibody structure by searching the PDB database for the template antibody VL and VH sequences with or without CDR. The following conditions were taken into consideration:

(1) Sequence homology,

(2) CDR length,

(3) CDR canonical structure, and

(4) Model with correct disulfide linkage.

The antigen binding region of the antibody structure model was optimized through the CDR loop database and canonical structure class as well as comparison with the template structure.

CDR Grafting and Back Mutation

[0026] Structural modeling was used to identify residues outside of CDR loops that might affect CDR configurations. The following binding or interaction factors were considered: hydrogen bonding, steric hindrance and other interactions of main chain and side chains of CDR residues.

[0027] Back mutation was performed to those residues that are predicted significantly to affect CDR loop structure. Other critical residues were also verified including those in (1) the heterodimer interface in FR donors for proper VL and VH interactions, (2) the intra-chain domain interface and (3) the direct interactions to antigen/epitopes in the known structure.

[0028] Based on the above considerations, combinations of back mutations were designed to balance the minimal needs of such process. Low immunogenicity to humans and maximal preservation of antigen-binding affinity are obtained.

Preliminary Characterization of Humanized GHR106 Monoclonal Antibodies

[0029] After four rounds of humanization designs, several humanized GHR106 monoclonal antibodies were generated, expressed and affinity-purified.

[0030] To perform antigen binding assays, cancer cell coated ELISA plates were used to test the affinity of the antibodies. Supernatants containing the various recombinantly produced antibodies from transfected CHO cells were serially diluted and added to ELISA wells for 1h incubation at 37°C. The plates were subsequently washed with wash buffer, and then incubated with HRP conjugated with goat anti-human IgG antibody for 60 minutes. Afterwards, the plates were washed with wash buffer, and then HRP substrate, TMB, was added to each well for color development. Raw data were collected and analyzed by a microplate reader (POLARstar Omega from BMG Labtech).

[0031] All antibodies were produced with human IgG heavy chain constant regions and light chain kappa constant regions.

First Round Humanization

[0032] The first round humanization design generated three heavy chains (H41 through H43) and three light chains (L41 through L43). Each designed sequence was gene synthesized and cloned to make both full-length heavy and light chains. Each DNA was sequence confirmed. A 4 x 4 matrix (Table 1) was designed to generate 16 recombinant antibodies (including the parental control antibody composed of H40 and L40). DNA for each antibody pair was transfected into adherent CHO cells to produce recombinant antibody.

Table 1 Antibody pair matrix for the first round 16 recombinant antibodies

	H40	H41	H42	H43
L40	#1	#5	#9	#13
L41	#2	#6	#10	#14
L42	#3	#7	#11	#15
L43	#4	#8	#12	#16

[0033] Five days after transfection, the media from CHO cells were collected and the IgG levels in the conditioned media were measured by an anti-human IgG/Fc ELISA (LakePharma Product catalog number 2001002). Although there is variation in the production levels, each antibody pair was produced and secreted, as shown in Table 2 below.

Table 2 Human IgG levels (ng/mL) in the conditioned media for each antibody pair.

	H40	H41	H42	H43
L40	4777	3011	2178	2130
L41	4024	6026	2488	1726
L42	4718	2341	1829	2401
L43	4854	3035	2886	9256

[0034] Figure 1 shows the results of the antigen binding assay described above and dose response after the first round humanization. All antibodies with humanized light chains with parental H40 produced antibodies with significant binding affinity. None of the antibodies with three humanized heavy chains showed significant binding affinity.

Second Round Humanization

[0035] Three more humanized heavy chains (H41A, H41B and H41C) were designed. Three more antibodies H41A-L40, H41B-L40 and H41C-L40 were produced and assayed. Figure 2 shows the antigen binding assay and dose response after the second round humanization. None of the second round three humanized heavy chains showed significant binding affinity.

Third Round Humanization

[0036] Humanized heavy chain H41ABC therefore was made and two more antibodies (H41ABC-L40, H41ABC-L41) were produced and assayed. Antibody 7149+7150 was included in the assay as the negative control. Figure 3 shows the antigen

binding assay and dose response after the third round humanization. Humanized heavy chain H41ABC did not show significant binding affinity.

Fourth Round Humanization

[0037] The fourth round humanization design started from scratch and generated three new heavy chains (H64 through H66). The binding assays had shown that humanized light chain L42 demonstrated strong binding to the antigen when combined with parental heavy chain H40. Therefore, a set of five antibodies (Table 3) were designed to be tested (including the parental control antibody and a negative control antibody 7149+7150).

[0038] Plasmids for the antibodies, H64-L42, H65-L42, H66-L42, H40-L42 and 7149+7150 were transfected to 100 mL suspension CHO cells using chemically defined media and in the absence of serum to make the antibodies. Seven days after transfection, the conditioned media were collected and clarified. Whole antibodies in the conditioned media were purified using Protein A beads (MabSelect SuRe™, GE Healthcare). The purified samples were resolved by SDS-PAGE (Figure 4), and antibody concentration was quantified by UV spectrophotometer (Table 3).

Table 3 Composition and production yield of recombinant antibodies

	Heavy chain	Light chain	UV 280 (mg/mL)
1	H64	L42	0.37
2	H65	L42	0.26
3	H66	L42	0.41
4	H40	L42	0.43
5	Negative control	Negative control	0.02

[0039] The antigen binding dose response (Table 4) curves are shown in Figure 5, and the binding titer was determined by GraphPad Prism software, as reported in Table 5.

Table 4 Raw antigen binding ELISA data

1	2	3	4	5	6	7
3.597	3.164	3.683	3.663	3.584	2.216	0.271
2.766	2.298	2.575	3.712	2.668	0.934	0.359
2.88	1.625	1.998	3.585	2.257	0.671	0.275
2.129	0.938	1.477	2.778	1.455	0.474	0.257
1.373	0.552	0.665	1.663	0.826	0.247	0.227
0.712	0.31	0.373	0.955	0.357	0.242	0.178
0.396	0.237	0.246	0.531	0.328	0.201	0.175
0.281	0.207	0.218	0.291	0.234	0.181	0.129

Table 5 Binding potency of purified antibodies

	Antibody	Binding Potency (ng/ml)
1	H64L42	13
2	H65L42	50
3	H66L42	43
4	H40L42	7
5	NC	326

[0040] Thus, humanization of GHR106 has been successfully completed after four rounds of humanization. All three humanized light chains showed good potency, comparable to the parental light chain. L42 was selected for later humanized antibody assays. In total, 10 humanized heavy chains of four rounds have been made. H64 from the fourth round showed good potency, comparable to the parental heavy chain H40. In summary, H64L42 appears to be the best humanized pair with comparable potency as the parental antibody. Figure 6 shows the comparison of amino acid sequences of heavy chain and light chain of humanized forms of GHR106 with those of murine GHR106. Figure 7 shows their encoding nucleic acid sequences.

[0041] Thus, various antibodies and fragments of the invention are antibodies Ab1-Ab9 shown in Table 6

Table 6

	L41	L42	L43
H64	Ab1	Ab2	Ab3
H65	Ab4	Ab5	Ab6
H66	Ab7	Ab8	Ab9

Claims

1. A humanized monoclonal antibody (mAb) or fragment thereof that reacts specifically with an epitope present in amino acid residues 1-29 of the extracellular domain of the human GnRH receptor, and

that binds to the GnRH receptor with a dissociation constant (K_D) of less than or equal to 10^{-7}M, and

that competes with GnRH for binding to the receptor.

2. The mAb of claim 1 that is a complete antibody.

3. The fragment of claim 1 which is a $F(ab')_2$, Fab, Fv, or scFv fragment.

4. The mAb or fragment claim 1 which comprises the CDR regions inherent in one of the heavy chain and/or one of the light chain variable regions shown in Figure 6 according to the numbering system of either Kabat or Chothia.

5. The monoclonal antibody (mAb) or fragment of any claim 1, wherein:

a) the CDR1 region of the heavy chain is of the sequence RYSVH;

b) the CDR2 region of the heavy chain is of the sequence MIWGGGSTDYNSPSLKS or MIWGGGSTDYNSSLQS or MIWGGSTDYNSSLQS; and

c) the CDR3 region of the heavy chain is of the sequence GNDGYYSFAY; and

d) the CDR1 region of the light chain is of the sequence KSSQSLLNSRTRKNYLA;

e) the CDR2 region of the light chain is of the sequence WASTRES; and

f) the CDR3 region of light chain is of the sequence KQSYNLYT.

6. The mAb or fragment of claim 1, wherein the heavy chain comprises the variable region of H65, H66 or H64.

7. The mAb or fragment of claim 1, wherein the light chain comprises the variable region of L41, L42 or L43.

8. The mAb or fragment of claim 6, wherein the light chain comprises the variable region of L41, L42 or L43.

9. The mAb or fragment of claim 1, coupled to a detectable marker and/or a therapeutic agent.

10. A pharmaceutical composition comprising the antibody or fragment of claim 1 and a pharmaceutically acceptable excipient.

11. The pharmaceutical composition of claim 10 further comprising an additional therapeutic agent.

12. Recombinant host cells or immortalized cells that produce the mAb or fragment of claim 1.

13. The recombinant host cells of claim 12 which are mammalian cells, microbial cells, insect cells or plant cells.

14. A method to produce an mAb or fragment, which method comprises culturing the cells of claim 13 and recovering said mAb or fragment.

15. A transgenic non-human animal or transgenic plant that produces the mAb or fragment of claim 1.

16. One or more nucleic acid molecules that encode the antibody or fragment of claim 1.

17. A method to treat a proliferative disorder in a human subject, comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 10.

18. A method for controlling ovarian stimulation in a method of assisted reproduction, comprising administering to a human subject in need of such treatment an effective amount of the pharmaceutical composition of claim 10.

19. The method of claim 18, wherein the method of assisted reproduction is *in vitro* fertilization (IVF).

20. A method to treat an estrogen-dependent condition selected from the group consisting of endometriosis, uterine fibroids, endometrial thinning, polycystic ovary disease and precocious puberty, comprising administering to a human subject in need of such treatment an effective amount of the pharmaceutical composition of claim 10.

21. A method for detecting a proliferation disorder, comprising:

a) contacting a biological sample with the monoclonal antibody or fragment of claim 1; and

b) detecting whether or not said monoclonal antibody or fragment binds to said sample, wherein binding to said sample indicates the presence of GnRH receptors on cells in said sample, thereby detecting cells in said sample exhibiting a proliferation disorder.

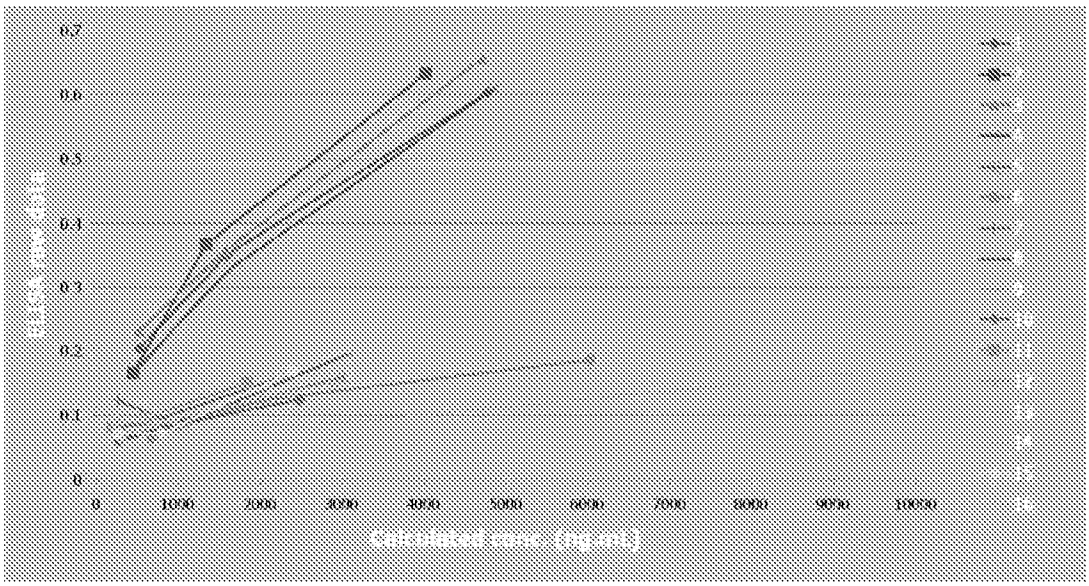


Figure 1

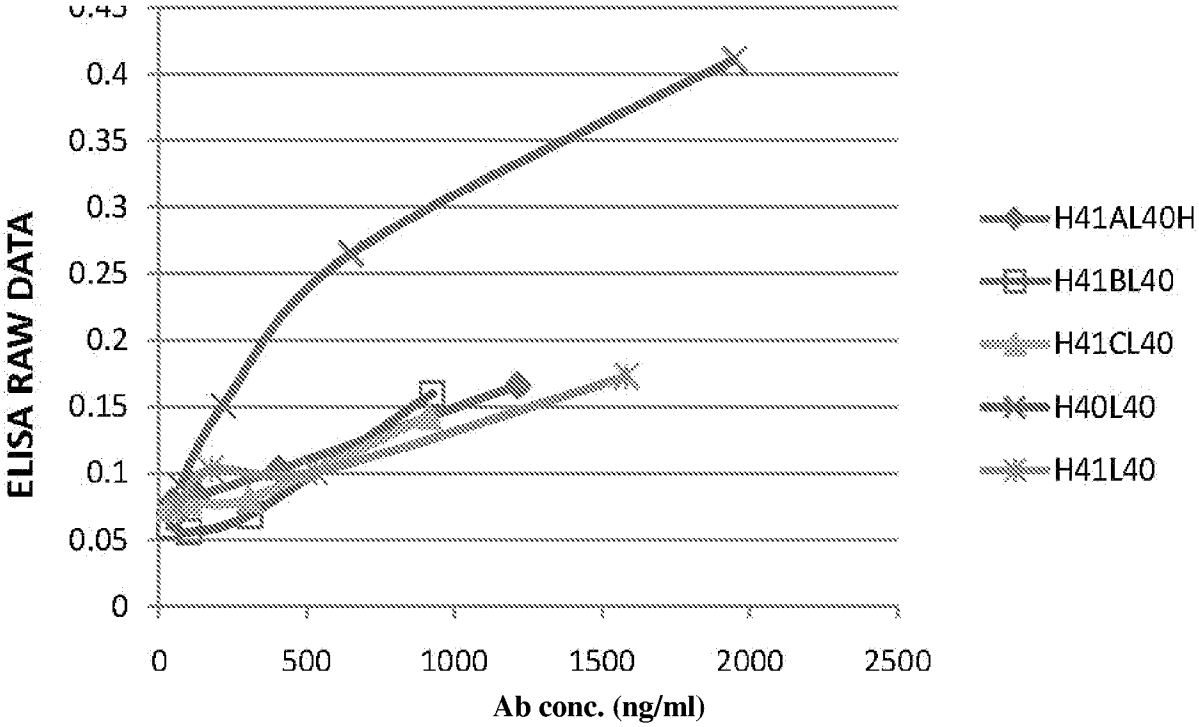


Figure 2

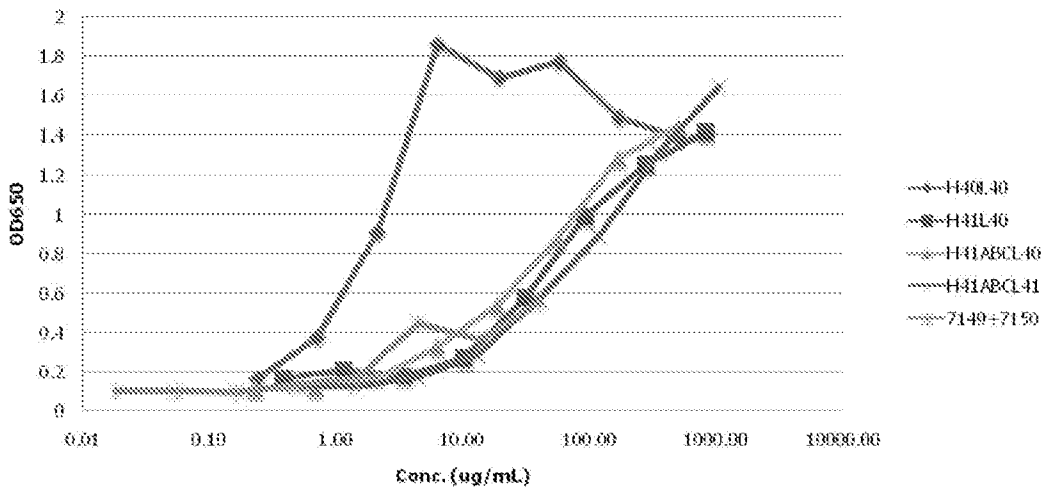
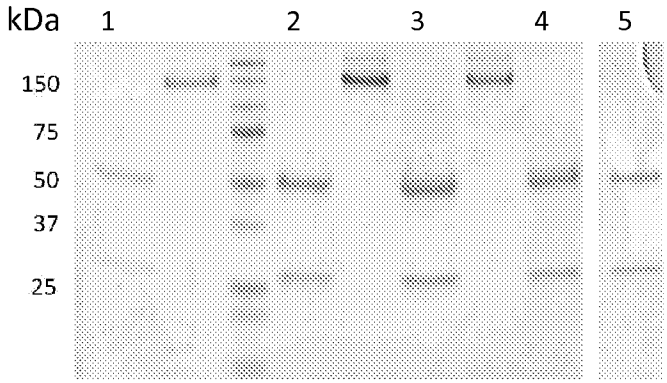


Figure 3



1 H40 L42
2 H64 L42
3 H65 L42
4 H66 L42
5 Negative control

Reducing conditions

Figure 4

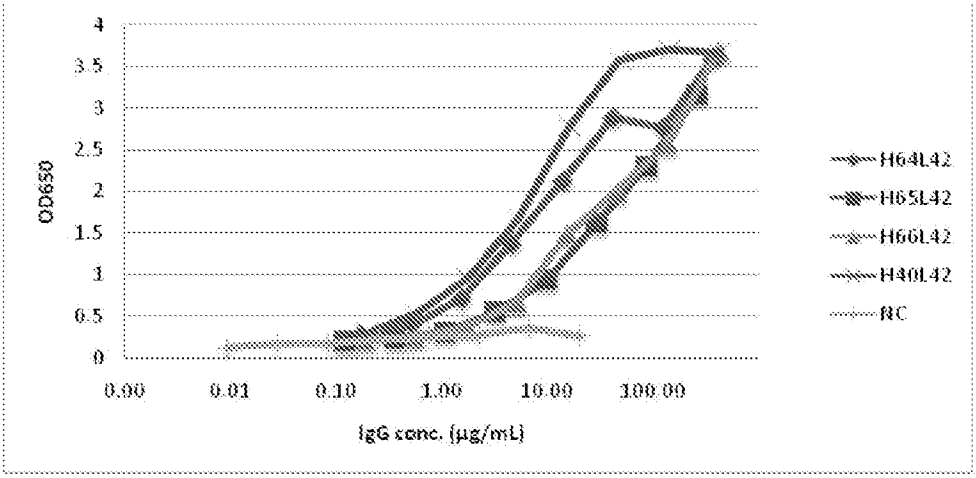


Figure 5

Heavy chain

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                          FR1                 CDR1       FR2          CDR2
hGHR106_H65  QVQLQESGPGLVKPSETLSLVCTVSGFSLS RYSVH WIRQPPGKGLEWIG MIWGG-STDYN 59
hGHR106_H66  QVQLKESGPGLVKPSETLSLVCTVSGFSLS RYSVH WIRQPPGKGLEWIG MIWGGGSTDYN 60
hGHR106_H64  QVQLQESGPGLVKPSETLSLTCTVSGFSLS RYSVH WIRQPPGKGLEWIG MIWGGGSTDYN 60
GHR106_Murine QVQLKESGPGLVAPSQSLSITCTVSGFSLS RYSVH WVRQPPGKGLEWLG MIWGGGSTDYN 60
              ****:******* **::**:.********* ***** *:**********:* ***** *****

                                   FR3                   CDR3       FR4
hGHR106_H65  SSLQS RVTISKDNSKSQVFLKMSSVTAADTAMYYCAR GNDGYYSFAY WGQGTLVTVSS 117
hGHR106_H66  SSLQS RVTISKDNSKSQVFLKMSSVTAADTAMYYCAR GNDGYYSFAY WGQGTLVTVSS 118
hGHR106_H64  PSLKS RVTISKDNSKSQVFLKMSSVTAADTAMYYCAR GNDGYYSFAY WGQGTLVTVSS 118
GHR106_Murine SALKS RLSISKDNSKSQVFLKMNSLQTDDTAMYYCAR GNDGYYSFAY WGQGTLVTVSS 118
              .:*:* *::***************.*: : ********* ********** ***********
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Light chain

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                          FR1                 CDR1              FR2       CDR2
hGHR106_L41  DIVMTQSPDSLAVSLGERATINC KSSQSLLNSRTRKNYLA WYQQKPGQPPKLLIY WASTR 60
hGHR106_L42  DIVMTQSPDSLAVSLGERATINC KSSQSLLNSRTRKNYLA WYQQKPGQSPKLLIY WASTR 60
hGHR106_L43  DIVMTQSPDSLAVSLGERATINC KSSQSLLNSRTRKNYLA WYQQKPGQPPKLLIY WASTR 60
GHR106_Murine DIVMSQSPSSLAVSAGEKVTMSC KSSQSLLNSRTRKNYLA WYQQKPGQSPKLLIY WASTR 60
              ****:***.***** **:.*:.* ***************** ********.****** *****

                              FR3                   CDR3       FR4
hGHR106_L41    ES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC KQSYNLYT FGQGTKLEIK 112
hGHR106_L42    ES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC KQSYNLYT FGQGTKLEIK 112
hGHR106_L43    ES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC KQSYNLYT FGGGTKLEIK 112
GHR106_Murine  ES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYC KQSYNLYT FGGGTKLEIK 112
               ** ******:**************:****:*************** *******
```

Figure 6

Heavy Chains

p7164 (hGHR106_H64)

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCCACCGGACAGGTT
CAGTTGCAAGAGTCTGGTCCCGGCCTGGTTAAACCCTCTGAGACTTTGAGCTTGACATGCACCGTA
AGCGGCTTCTCTCTGAGCCGGTACTCTGTACACTGGATTCGACAGCCTCCTGGCAAGGGCCTGGAA
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GCCATGTACTACTGTGCACGGGGGAATGACGGATACTACAGTTTCGCATATTGGGGCCAGGGAACA
CTGGTTACAGTGTCTAGTGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAG
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GGCCTGTACTCCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATC
TGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGAC
AAGACCCACACCTGCCCTCCCTGCCCCGCCCCCGAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTC
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GTGAGCCACGAGGACCCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCC
AAGACCAAGCCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCTGCCCGCTCCC
ATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGGAGCCTCAGGTGTACACCCTGCCCCCC
AGCCGCGACGAGCTGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCC
GACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCGGTGGCAGCAG
GGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTG
AGCCTGAGCCCCGGAAAGTAA

p7165 (hGHR106_H65)

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AGCGGCTTCTCTCTGAGCCGGTACTCTGTACACTGGATTCGACAGCCTCCTGGCAAGGGCCTGGAA
TGGATTGGCATGATCTGGGGCGGCGGAAGTACAGATTATAACAGCTCCTTGCAGAGCCGCGTCACC
ATCTCTAAGGACAACAGCAAGTCCCAGGTCTTCCTGAAGATGTCAAGCGTCACCGCTGCCGACACC
GCCATGTACTACTGTGCACGGGGGAATGACGGATACTACAGTTTCGCATATTGGGGCCAGGGAACA
CTGGTTACAGTGTCTAGTGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAG
AGCACCAGCGGCGGAACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCCGTGCTGCAGAGCAGC
GGCCTGTACTCCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATC
TGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGAC
AAGACCCACACCTGCCCTCCCTGCCCCGCCCCCGAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTC
CCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGCACCCCCGAGGTGACCTGCGTGGTGGTGGAC
GTGAGCCACGAGGACCCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCC
AAGACCAAGCCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCTGCCCGCTCCC
ATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGGAGCCTCAGGTGTACACCCTGCCCCCC
AGCCGCGACGAGCTGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCC
GACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCGGTGGCAGCAG
GGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTG
AGCCTGAGCCCCGGAAAGTAA

Figure 7 (1st of 3 pages)

p7166 (hGHR106_H66)
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCCACCGGACAGGTT
CAGTTGAAGGAGTCTGGTCCCGGCCTGGTTAAACCCTCTGAGACTTTGAGCTTGGTCTGCACCGTA
AGCGGCTTCTCTCTGAGCCGGTACTCTGTACACTGGATTCGACAGCCTCCTGGCAAGGGCCTGGAA
TGGATTGGCATGATCTGGGGCGGCGGAAGTACAGATTATAACAGCTCCTTGCAGAGCCGCGTCACC
ATCTCTAAGGACAACAGCAAGTCCCAGGTCTTCCTGAAGATGTCAAGCGTCACCGCTGCCGACACC
GCCATGTACTACTGTGCACGGGGGAATGACGGATACTACAGTTTCGCATATTGGGGCCAGGGAACA
CTGGTTACAGTGTCTAGTGCTAGCACCAAGGGCCCCAGCGTGTTCCCTCTGGCCCCCAGCAGCAAG
AGCACCAGCGGCGGAACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACC
GTGTCCTGGAACAGCGGCGCTCTGACCAGCGGAGTGCACACCTTCCCTGCCGTGCTGCAGAGCAGC
GGCCTGTACTCCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATC
TGCAACGTGAACCACAAGCCCTCCAACACCAAGGTGGACAAGAAGGTGGAGCCTAAGAGCTGCGAC
AAGACCCACACCTGCCCTCCCTGCCCCGCCCCCGAGCTGCTGGGCGGACCCAGCGTGTTCCTGTTC
CCTCCCAAGCCCAAGGACACCCTGATGATCAGCCGCACCCCCGAGGTGACCTGCGTGGTGGTGGAC
GTGAGCCACGAGGACCCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCC
AAGACCAAGCCTCGGGAGGAGCAGTACAACTCCACCTACCGCGTGGTGAGCGTGCTGACCGTGCTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCTGCCCGCTCCC
ATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCCCGGGAGCCTCAGGTGTACACCCTGCCCCCC
AGCCGCGACGAGCTGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCTACCCCTCC
GACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCCGTG
CTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCGGTGGCAGCAG
GGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTG
AGCCTGAGCCCCGGAAAGTAA

Light Chains

pCD3_L0041 (hGHR106_L41)
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCCACCGGAGATATC
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TCATCACAAAGCCTCCTTAATTCTAGGACCAGGAAAAACTACCTGGCATGGTATCAACAGAAGCCA
GGACAGCCACCAAAGCTGCTGATCTACTGGGCTTCTACAAGAGAGAGTGGAGTGCCAGACCGCTTC
TCCGGCTCCGGGAGCGGCACTGATTTTACCCTCACTATCAGCTCCCTTCAGGCAGAGGATGTGGCC
GTGTACTATTGCAAGCAGAGCTACAACCTCTACACCTTCGGCCAGGGGACTAAACTGGAAATTAAG
CGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACC
GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTAC
AGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAG
GTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA

pCD3_L0042 (hGHR106_L42)
ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCCACCGGAGATATC
GTAATGACTCAGTCCCCCGATAGCCTCGCTGTGTCATTGGGTGAACGGGCAACTATTAACTGTAAG
TCATCACAAAGCCTCCTTAATTCTAGGACCAGGAAAAACTACCTGGCATGGTATCAACAGAAGCCA
GGACAGTCACCAAAGCTGCTGATCTACTGGGCTTCTACAAGAGAGAGTGGAGTGCCAGACCGCTTC
TCCGGCTCCGGGAGCGGCACTGATTTTACCCTCACTATCAGCTCCCTTCAGGCAGAGGATGTGGCC
GTGTACTATTGCAAGCAGAGCTACAACCTCTACACCTTCGGCCAGGGGACTAAACTGGAAATTAAG
CGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACC
GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTAC
AGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAG
GTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA

Figure 7 (2nd of 3 pages)

pCD3_L0043 (hGHR106_L43)

ATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCCACCGGAGATATC
GTAATGACTCAGTCCCCCGATAGCCTCGCTGTGTCATTGGGTGAACGGGCAACTATTAACTGTAAG
TCATCACAAAGCCTCCTTAATTCTAGGACCAGGAAAAACTACCTGGCATGGTATCAACAGAAGCCA
GGACAGCCACCAAAGCTGCTGATCTACTGGGCTTCTACAAGAGAGAGTGGAGTGCCAGACCGCTTC
TCCGGCTCCGGGAGCGGCACTGATTTTACCCTCACTATCAGCTCCCTTCAGGCAGAGGATGTGGCC
GTGTACTATTGCAAGCAGAGCTACAACCTCTACACCTTCGGCGGAGGGACTAAACTGGAAATTAAG
CGGACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACC
GCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTAC
AGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAG
GTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAA

Figure 7 **(3rd of 3 pages)**