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(54) **METHOD FOR TREATING BREAST CANCER**

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(57) **ABSTRACT**

Breast cancer cells lacking ER protein expression, PgR protein expression and/or showing absence of HER2 protein over-expression (i.e., triple-negative breast cancer cells, basal-like) can be efficiently targeted with an anti-KAAG1 antibody and killed upon delivery of a therapeutic moiety. Antibodies and antigen binding fragments that specifically binds to KAAG1 may thus be used for the, detection and therapeutic treatment of breast cancer cells that are negative for at least one of these markers. The use of antibody conjugates in the treatment of triple-negative breast cancer and/or basal-like breast cancer is disclosed herein.

Figure 1a

3A4-VL

```
murine       DVVMTQTPLSLAVSLGDQASISCRSSQSLLHSNGNTYLEWYLQKPGQSPKLLIHTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPLTFGAGTRLELK   11/80 (86.3%)
Humanized1   DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPQLLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKLEIK    0/80 (100%)
Humanized2   DVVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPKLLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKLEIK    2/80 (97.5%)
                                      CDR-L1                  CDR-L2                                  CDR-L3
```

Figure 1b

3A4-VH

```
mouse        QIQLVQSGPEMVKPGASVKMSCKASGYTFTDDYMSWVKQSHGKSLEWIGDINPYNGDTNYNQKFKGKAILTVDKSSSTAYMQLNSLTSEDSAVYYCARDPGAMDYWGQGTSVTVSS   21/82 (74.4%)
Humanized1   QVQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNYNQKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS    0/82 (100%)
Humanized2   QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNYNQKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS    2/82 (97.5%)
Humanized3   QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWIGDINPYNGDTNYNQKFKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS    6/82 (92.7%)
Humanized4   QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVKQAPGQGLEWIGDINPYNGDTNYNQKFKGKATLTVDKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS    8/82 (90.2%)
                                      CDR-H1                  CDR-H2                                  CDR-H3
```

Figure 2a

Variable light chain alignment

```
Mouse VL            DVVMTQTPLSLAVSLGDQASISCRSSQSLLHSNGNTYLEWYLQKPGQSPKLLIHTVSNRF 60
SEQ ID NO.33        DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPQLLIYTVSNRF 60
                    *:*********.*: *: ********************************:***:******

Mouse VL            SGVPDRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPLTFGAGTRLELK 112
SEQ ID NO.33        SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKLEIK 112
                    ***************************:**************** **:**:*
```

Figure 2b

Variable heavy chain alignment

```
Mouse VH        QIQLVQSGPEMVKPGASVKMSCKASGYTFTDDYMSWVKQSHGKSLEWIGDINPYNGDTNY 60
SEQ ID NO.38    QVQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNY 60
                *:*******.*: *******:******************:*: *:.***:************

Mouse VH        NQKFKGKAILTVDKSSSTAYMQLNSLTSEDSAVYYCARDPGAMDYWGQGTSVTVSS 116
SEQ ID NO.38    NQKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS 116
                ******:. :*.*.*:*****:*.** ***:******************** *****
```

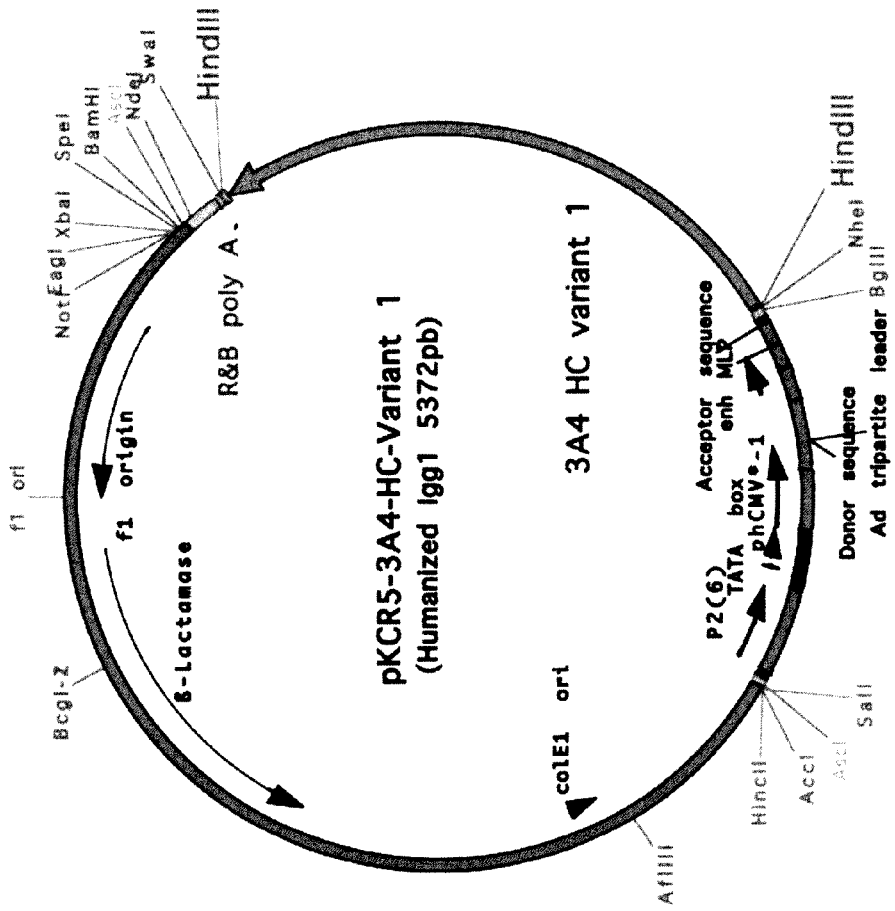

pKCR5-3A4-HC-Variant 1
(Humanized Igg1 5372pb)
3A4 HC variant 1
R&B poly A.
HindIII
SpeI
BamHI
AscI
NdeI
SwaI
NotI
EagI
XbaI
f1 ori
f1 origin
β-Lactamase
BcgI-Z
colE1 ori
AflIII
HincII
AccI
AscI
SalI
P2(6)
TATA box
PhCMV*-1
Acceptor sequence
enh MLP
Donor sequence
Ad tripartite leader
NheI
HindIII
BglII

Figure 3a

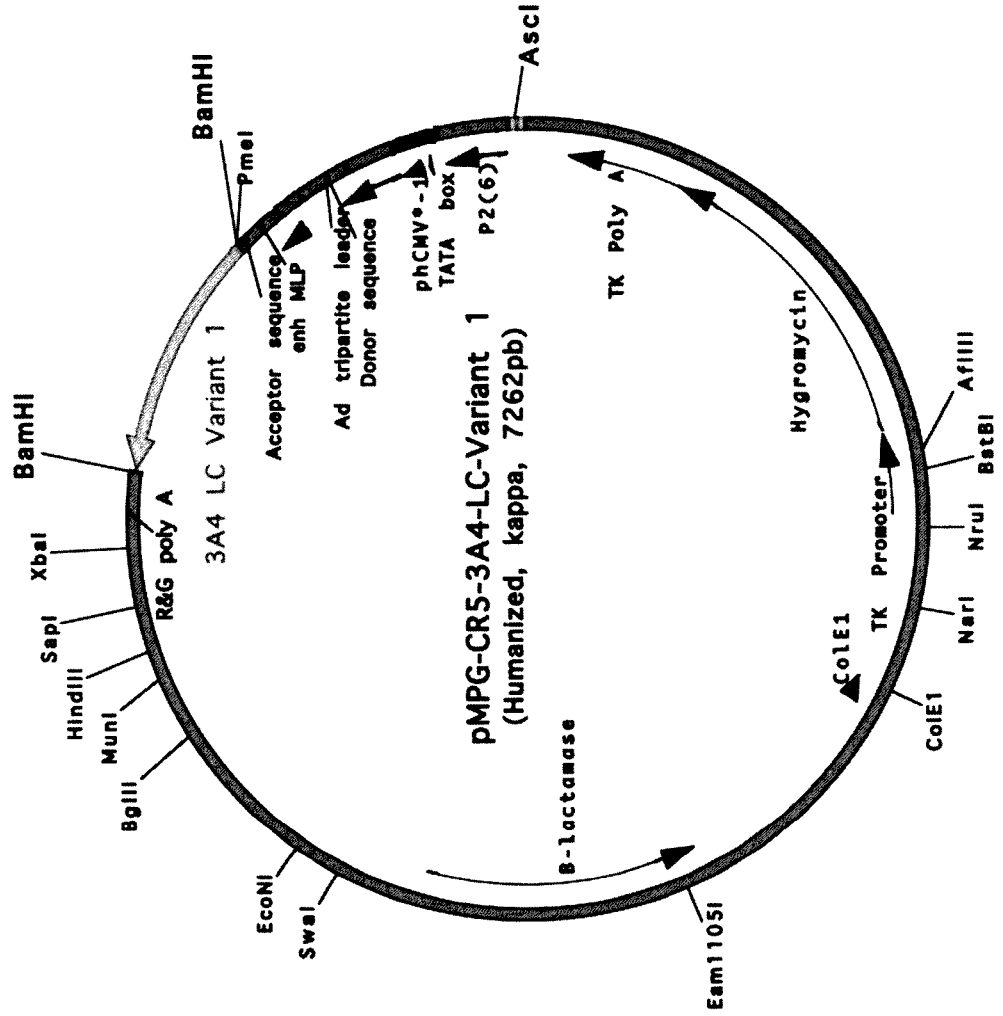

pMPG-CR5-3A4-LC-Variant 1
(Humanized, kappa, 7262pb)
3A4 LC Variant 1
BamHI
PmeI
AscI
BamHI
XbaI
SapI
HindIII
MunI
BglII
EcoNI
SwaI
Eam1105I
ColE1
NarI
NruI
BstBI
AflIII
Acceptor sequence
enh MLP
Ad tripartite leader
Donor sequence
phCMV*-1
TATA box
P2(6)
TK Poly A
Hygromycin
TK Promoter
ColE1
B-lactamase
R&G poly A

Figure 3b

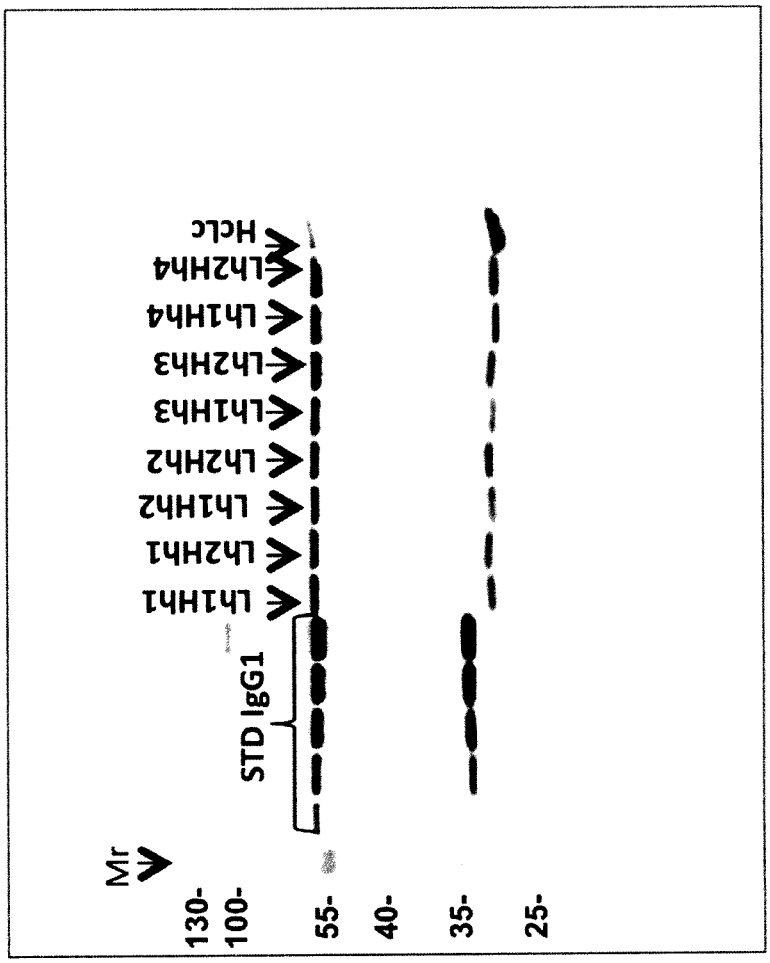
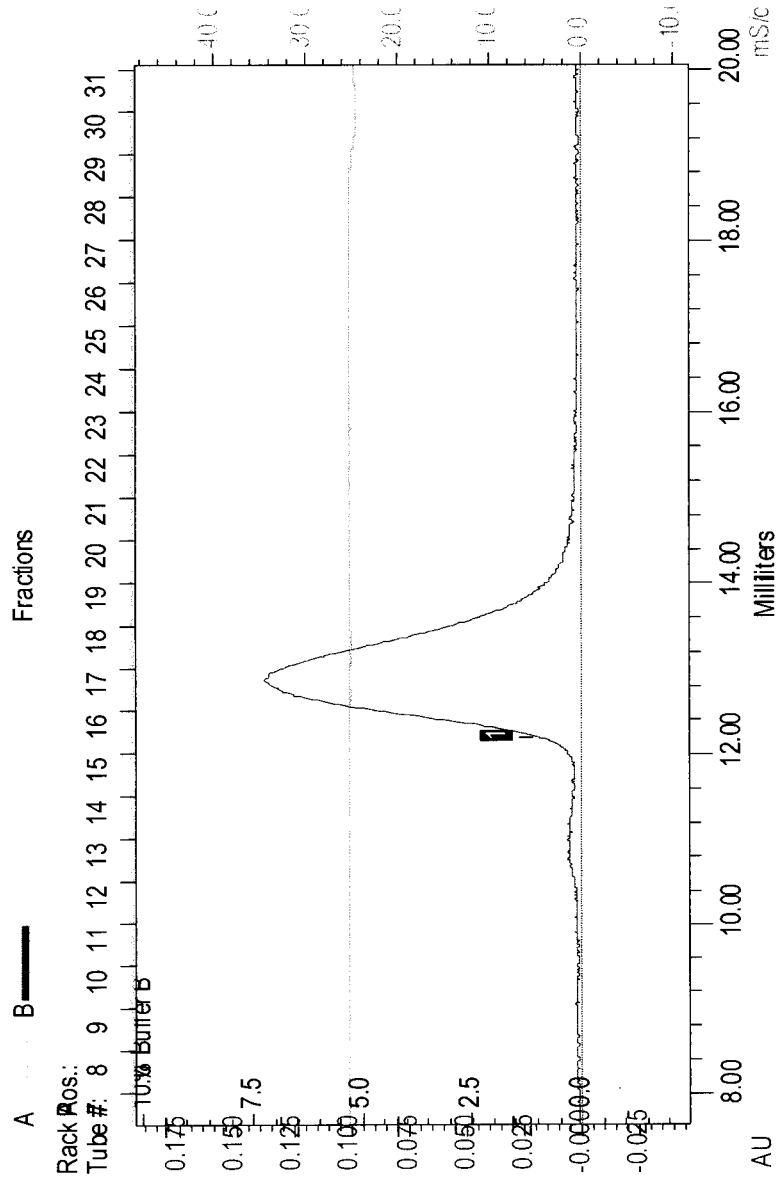

Mr
130-
100-
55-
40-
35-
25-
STD IgG1
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4
Hc/Lc

Figure 4

Figure 5


Fractions
A
B
Rack Pos.:
Tube #: 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
10% Buffer B
0.175
0.150
0.125
0.100
0.075
0.050
0.025
-0.000
-0.025
AU
7.5
5.0
2.5
0.0
8.00
10.00
12.00
14.00
16.00
18.00
20.00
Milliliters
mS/c

Antibody	ka (1/Ms)	kd (1/s)	K_D (nM)	Fold diff.
LcHc	7.72×10^{6}	1.21×10^{-4}	0.016	-
Lh1Hh1	6.93×10^{6}	3.28×10^{-3}	0.474	29.6
Lh2Hh1	6.97×10^{6}	2.37×10^{-3}	0.341	21.3
Lh1Hh2	5.65×10^{6}	1.19×10^{-3}	0.211	13.2
Lh2Hh2	7.40×10^{6}	1.81×10^{-3}	0.245	15.3
Lh1Hh3	6.46×10^{6}	9.60×10^{-4}	0.149	9.3
Lh2Hh3	4.46×10^{6}	1.02×10^{-3}	0.228	14.3
Lh1Hh4	5.14×10^{6}	7.64×10^{-4}	0.149	9.3
Lh2Hh4	4.57×10^{6}	4.70×10^{-4}	0.103	6.4

Figure 6

Figure 7a

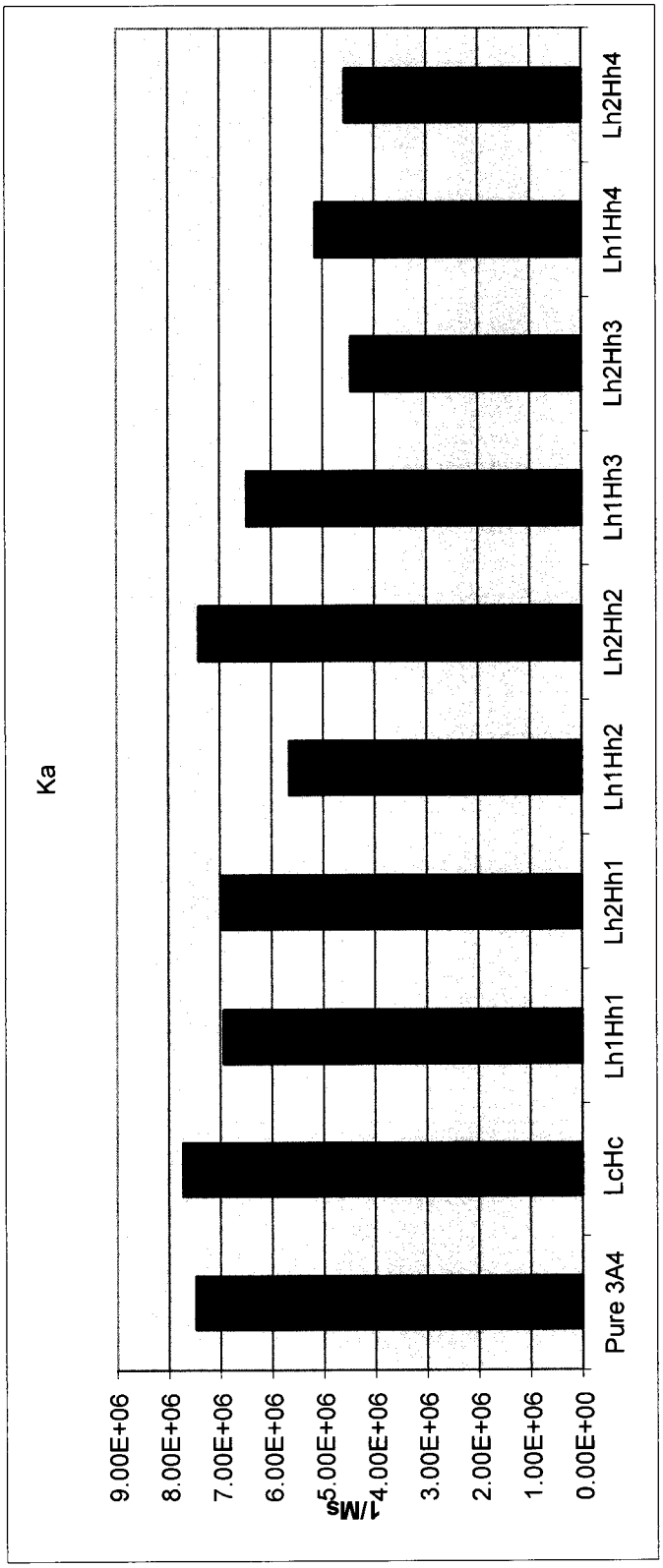

Ka
1/Ms
9.00E+06
8.00E+06
7.00E+06
6.00E+06
5.00E+06
4.00E+06
3.00E+06
2.00E+06
1.00E+06
0.00E+00
Pure 3A4
LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4

Figure 7b

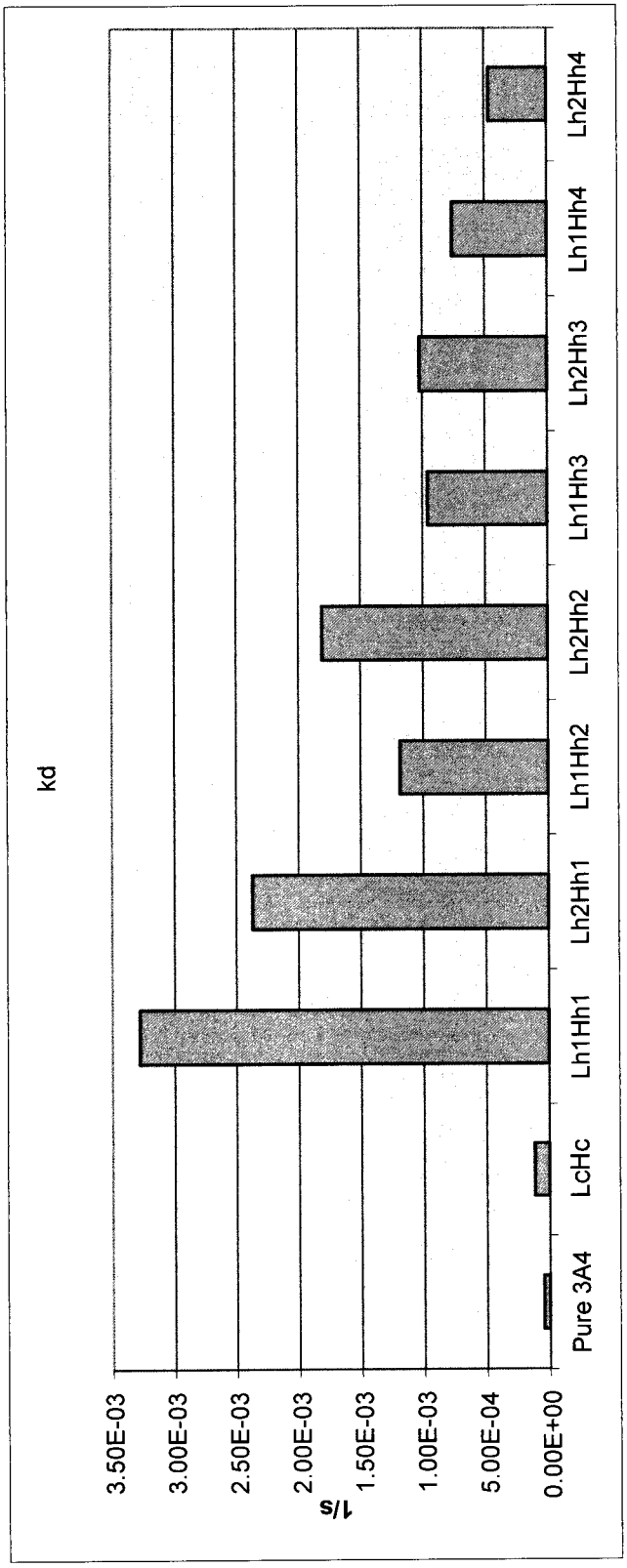

kd
1/s
3.50E-03
3.00E-03
2.50E-03
2.00E-03
1.50E-03
1.00E-03
5.00E-04
0.00E+00
Pure 3A4
LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4

Figure 7c

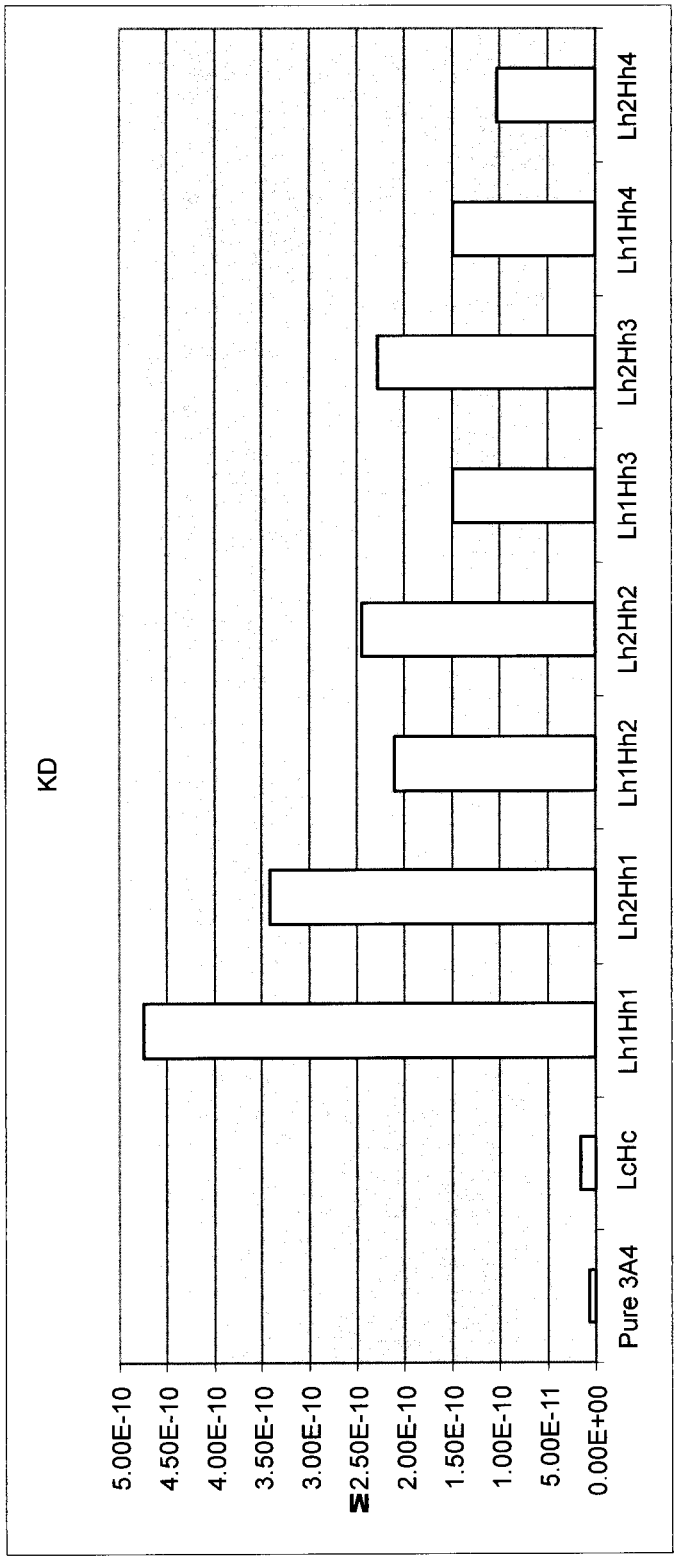

KD
5.00E-10
4.50E-10
4.00E-10
3.50E-10
3.00E-10
2.50E-10
2.00E-10
1.50E-10
1.00E-10
5.00E-11
0.00E+00
Pure 3A4
LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4

Figure 8a

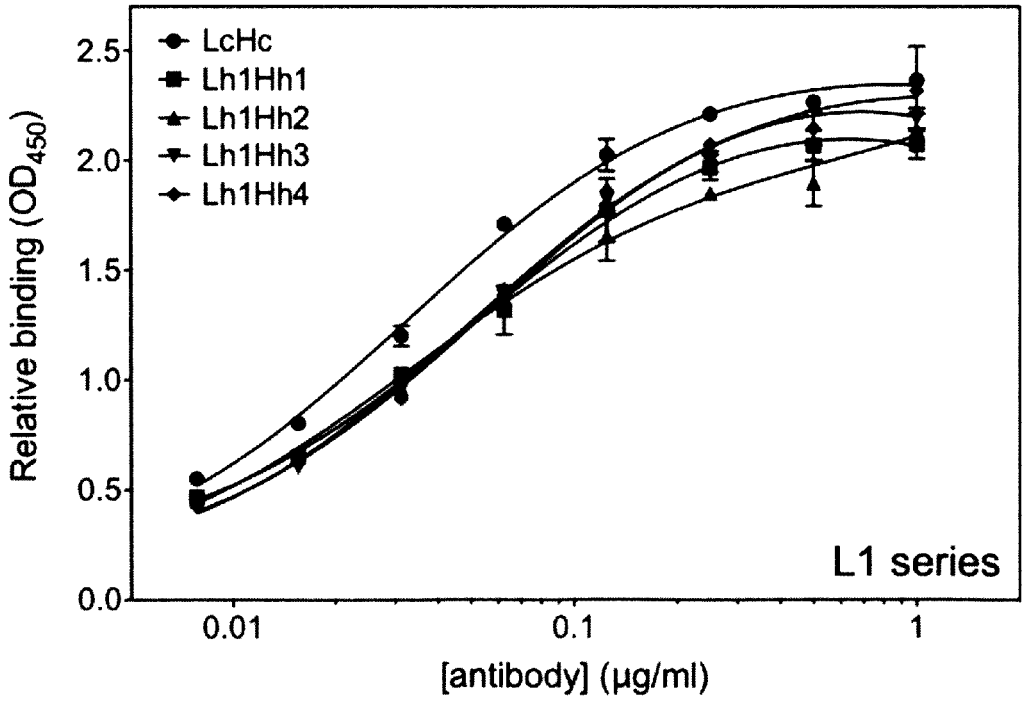

LcHc
Lh1Hh1
Lh1Hh2
Lh1Hh3
Lh1Hh4
Relative binding (OD_{450})
2.5
2.0
1.5
1.0
0.5
0.0
0.01
0.1
1
[antibody] (µg/ml)
L1 series

Figure 8b

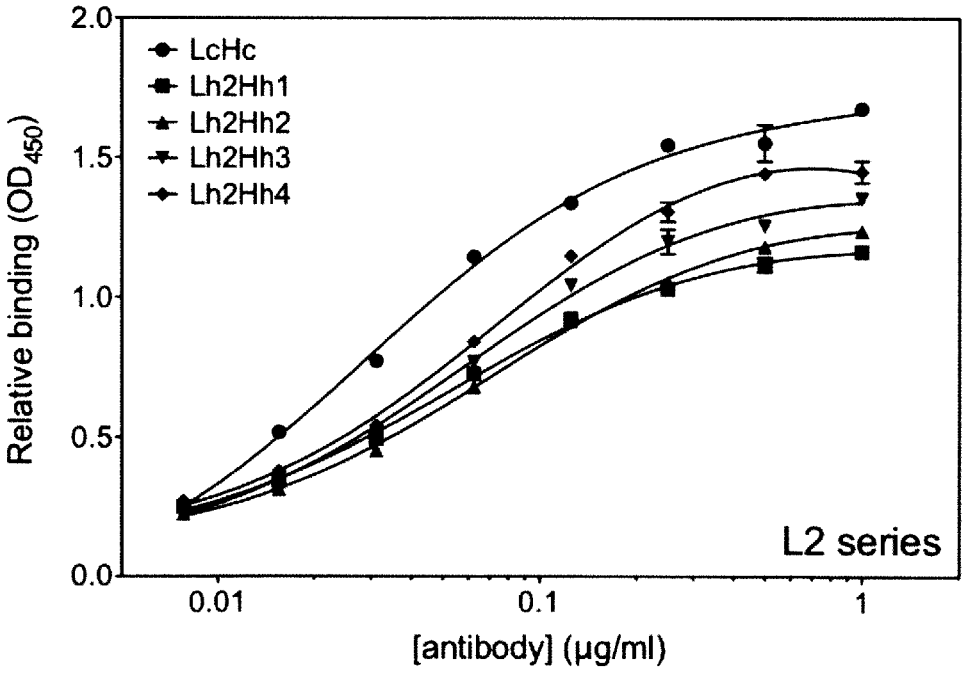
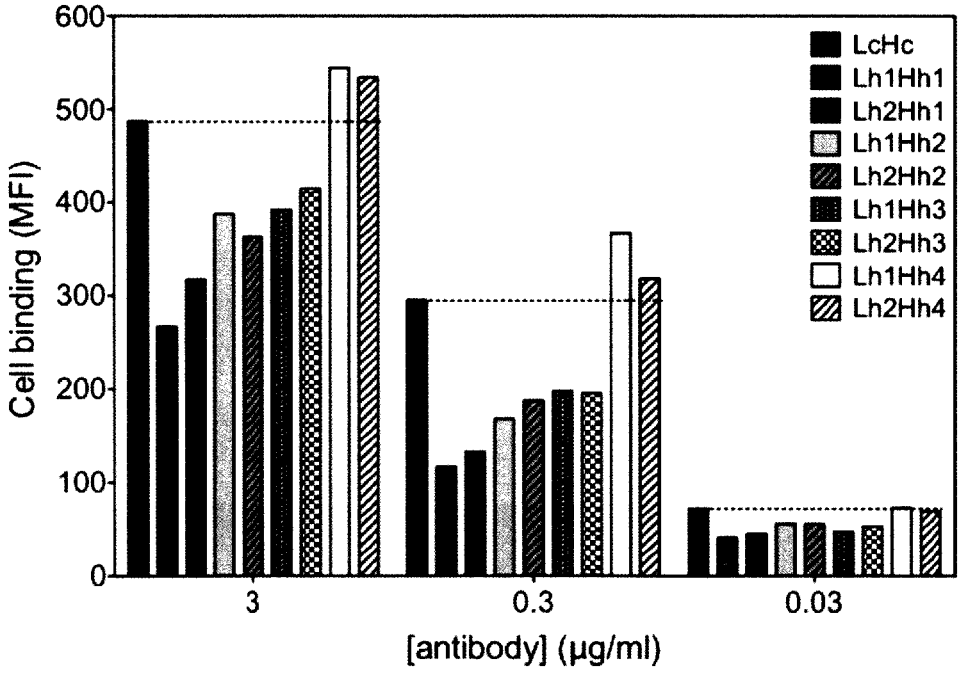
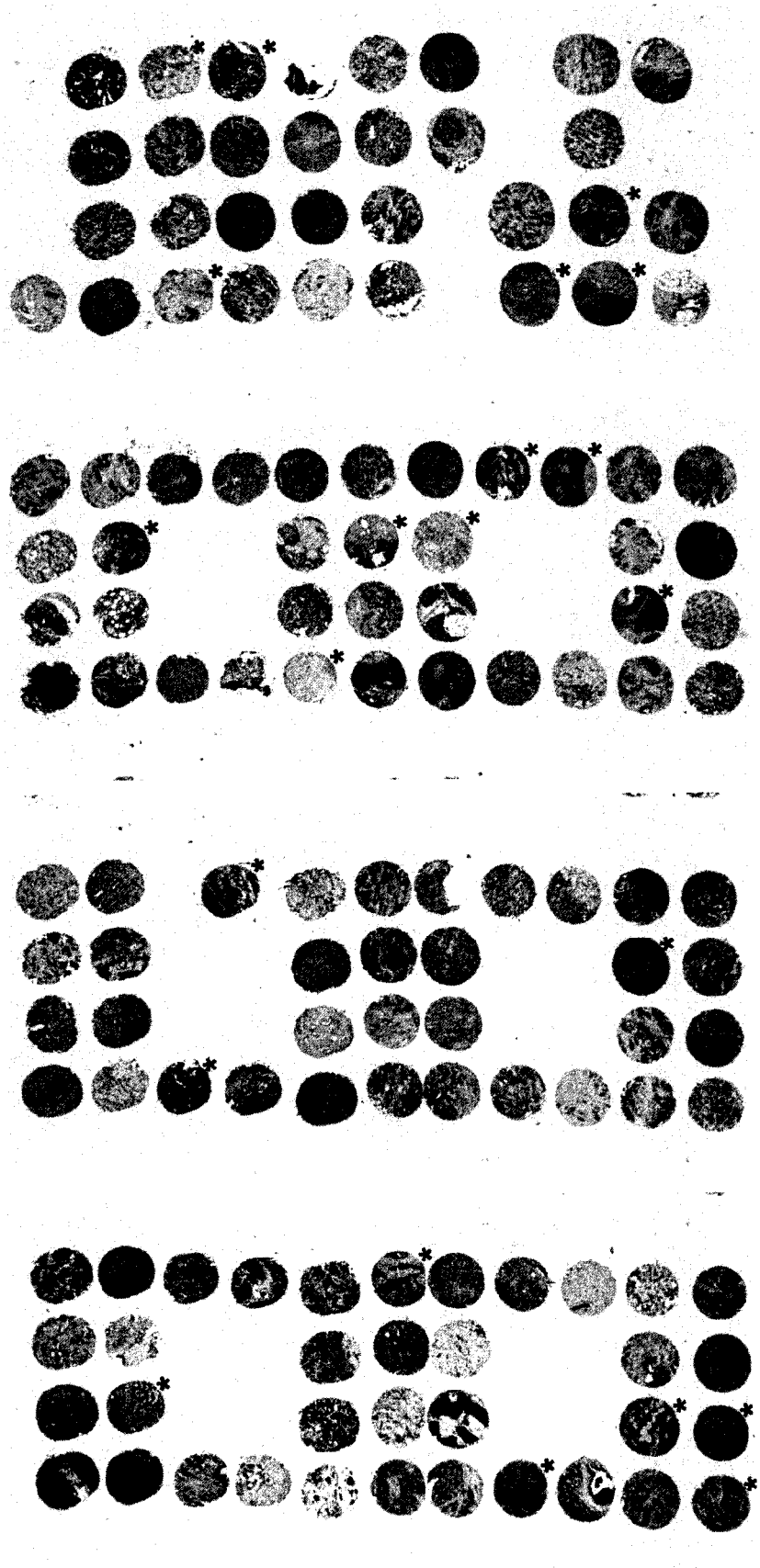

2.0
1.5
1.0
0.5
0.0
Relative binding (OD_{450})
LcHc
Lh2Hh1
Lh2Hh2
Lh2Hh3
Lh2Hh4
L2 series
0.01
0.1
1
[antibody] (µg/ml)

Figure 9

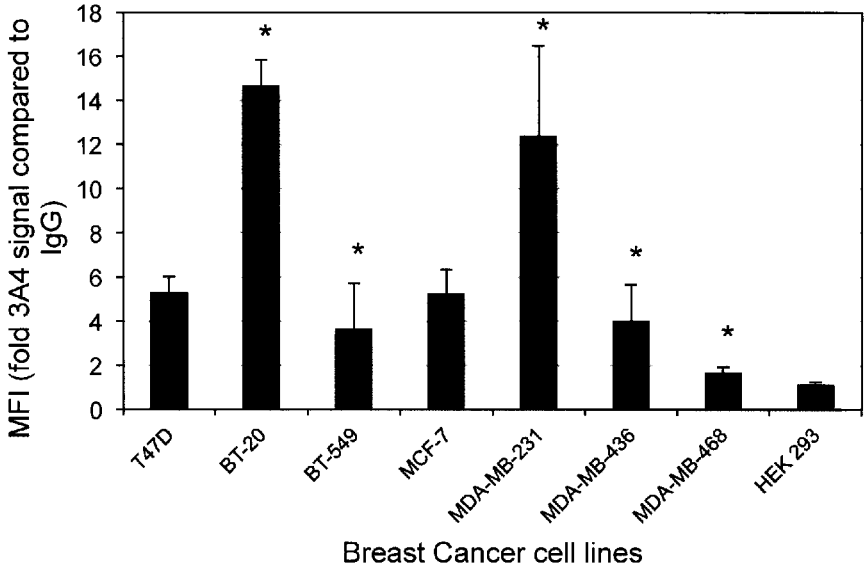

600
500
400
300
200
100
0
Cell binding (MFI)
3
0.3
0.03
[antibody] (µg/ml)
LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4



*, TNBC samples

Figure 10

Figure 11



*, TNBC cell lines

Figure 12

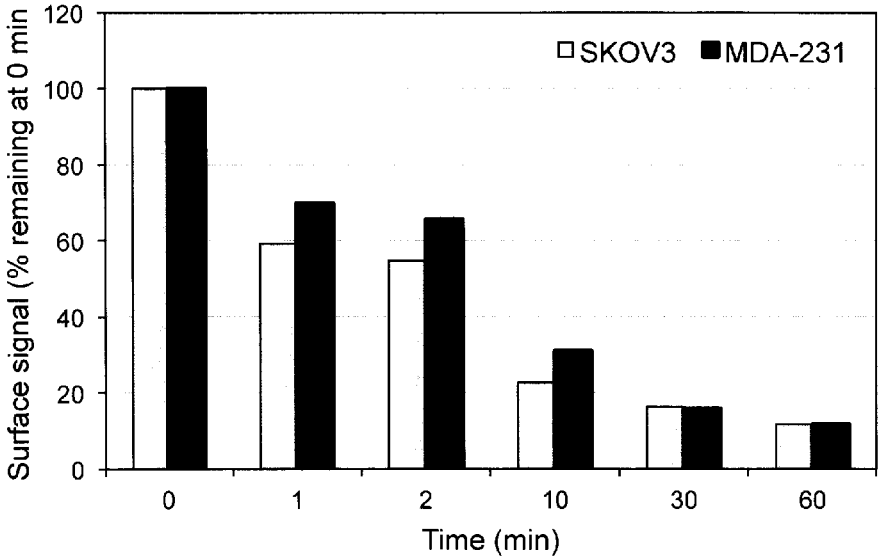

Surface signal (% remaining at 0 min
120
100
80
60
40
20
0
SKOV3
MDA-231
0
1
2
10
30
60
Time (min)

Figure 13

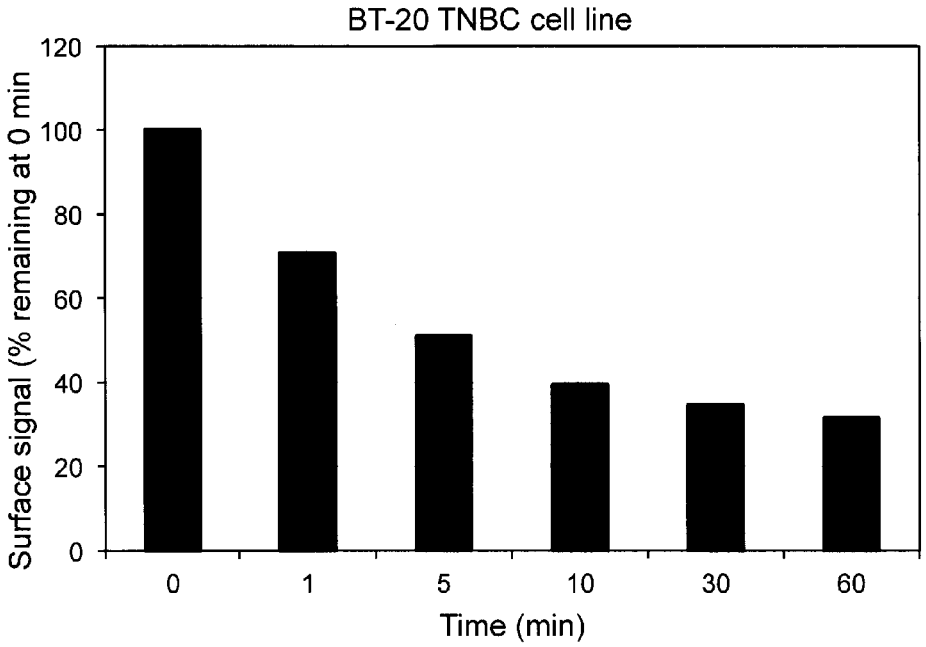

BT-20 TNBC cell line
Surface signal (% remaining at 0 min
120
100
80
60
40
20
0
0
1
5
10
30
60
Time (min)

Figure 14

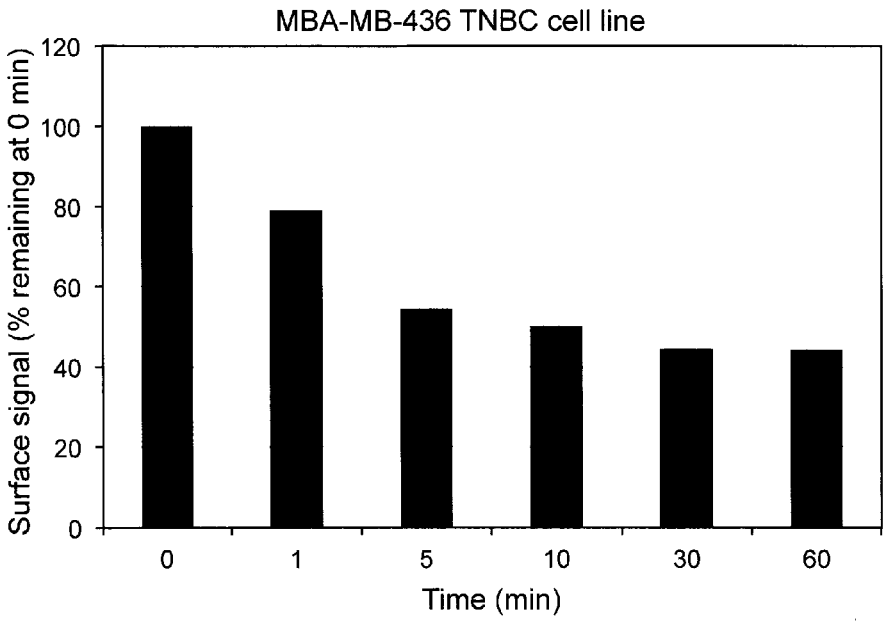
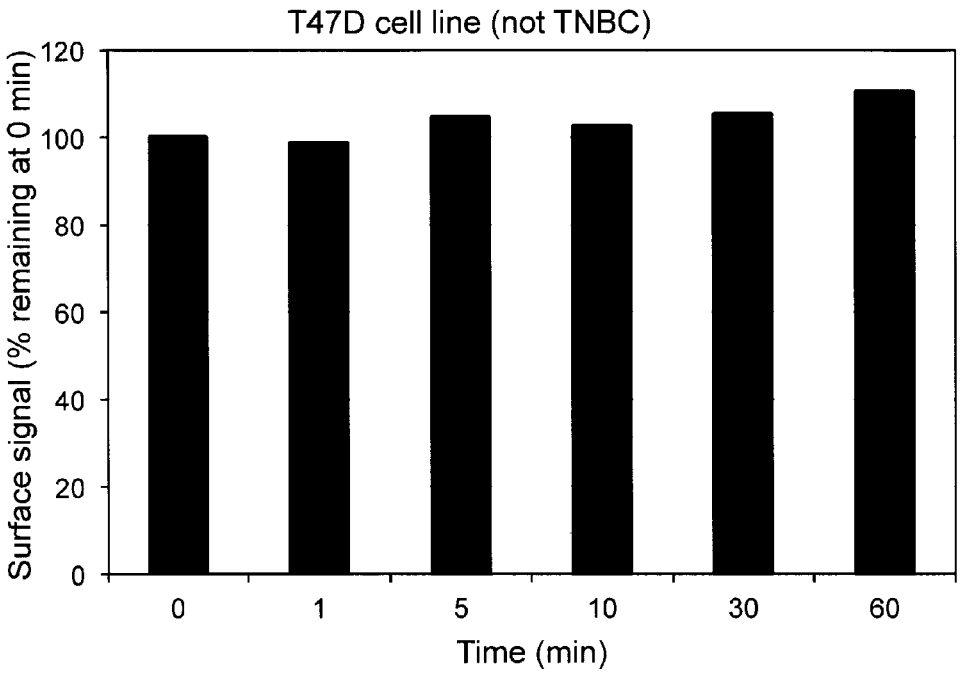

MBA-MB-436 TNBC cell line
Surface signal (% remaining at 0 min)
120
100
80
60
40
20
0
0
1
5
10
30
60
Time (min)

Figure 15


T47D cell line (not TNBC)
Surface signal (% remaining at 0 min)
120
100
80
60
40
20
0
0
1
5
10
30
60
Time (min)

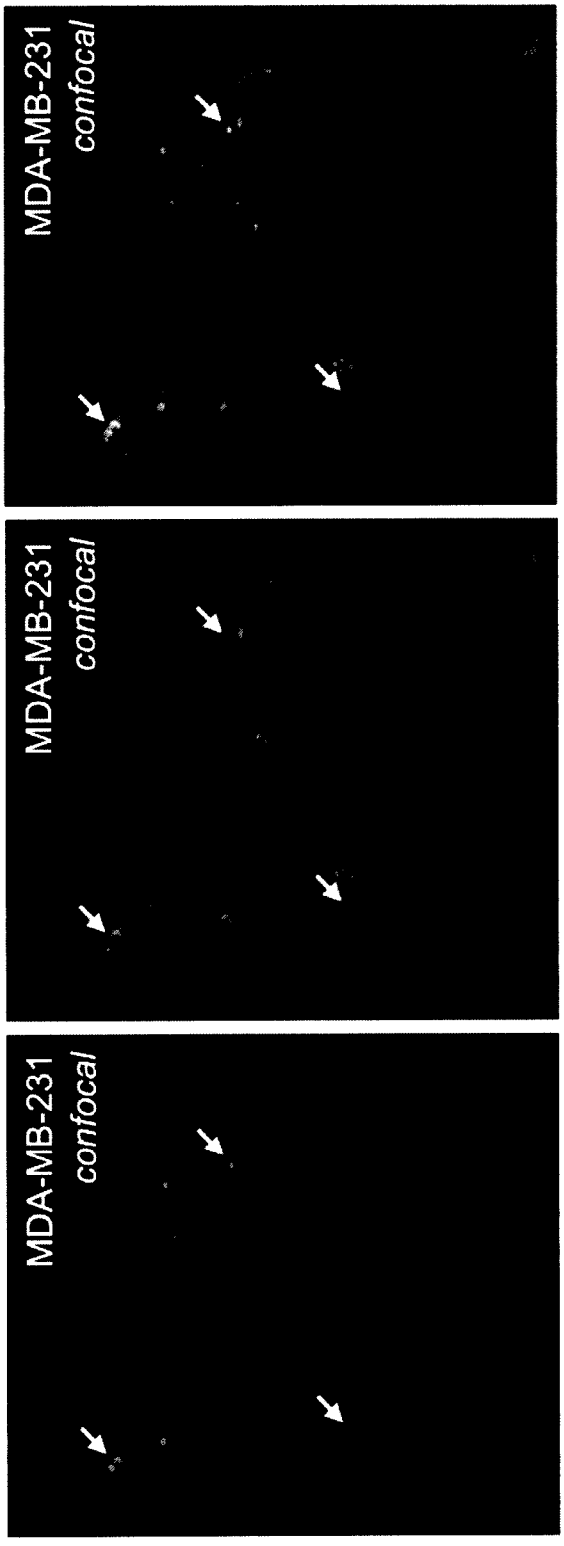

MDA-MB-231
confocal
KAAG1
MDA-MB-231
confocal
LAMP1
MDA-MB-231
confocal
Merge

Figure 16

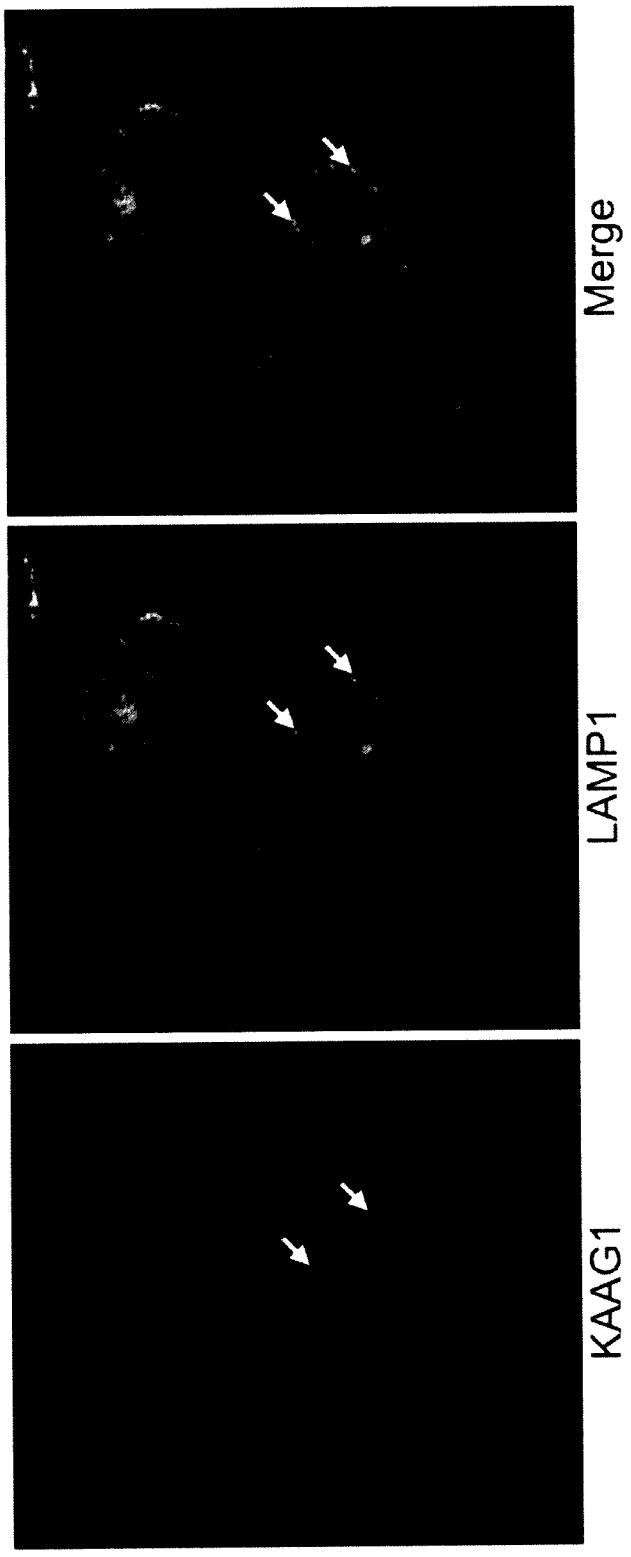


Figure 17

METHOD FOR TREATING BREAST CANCER

BACKGROUND

[0001] World wide, greater than 1 million women are diagnosed with breast cancer each year. Breast cancer is a very heterogeneous disease made up of dozens of different types that are distinguished using a histological classification system. A large subtype and a majority of cases are histologically identified as luminal A or luminal B which can be grossly characterized as exhibiting estrogen receptor (ER) expression with low grade or higher grade histology, respectively (Santana-Davila and Perez, 2010). Immunohistochemical methods are used to measure the expression of progesterone receptor (PgR) which, when coupled with ER-positive status allows the classification of a tumor as being hormone responsive. Furthermore, the over-expression or amplification of human epidermal growth factor receptor 2 (HER2) can be monitored either with immunohistochemistry or fluorescence in situ hybridization (FISH). Generally, the expression of these three markers in breast tumors is associated with a better clinical outcome because there are several treatment options available for patients that target these proteins (de Ruijter et al., 2011), including tamoxifen, Arimidex™ (anastrozole), Aromasin™ (exemestane), Femara™ (letrozole), Faslodex™ (fulvestrant), Herceptin™ (trastuzumab) or Tykerb™ (lapatinib).

[0002] Another histological subtype of breast cancer consists of the basal-like cancers which are associated with, among others, a higher histological grade, increase mitotic index and high Ki67 expression (Santana-Davila and Perez, 2010). The vast majority of basal-like cancers are comprised of triple-negative breast cancer (TNBC) cases, which make up a between 15-20% of all diagnosed breast cancer cases (Ismail-Khan and Bui, 2010). TNBC is defined by the lack of protein expression of ER, PgR and the absence of HER2 protein over-expression. The relationship between basal-like cancer and TNBC is not easily delineated since not all TNBC are basal-like and not all basal-like cancers are TNBC, but approximately 75% of cases in these categories share characteristics of both. TNBC is associated with poor prognosis consisting of low five-year survival rates and high recurrence.

[0003] Patients with TNBC develop their disease earlier in life compared with other breast cancer subtypes and are often diagnoses at the pre-menopausal stage (Carey et al., 2006). Triple-negative breast cancer shows an increased propensity of recurrence after treatment and seem to be more aggressive than other breast carcinoma subtypes (Nofech-Mozes et al., 2009), similar to those of the basal-like breast cancer subtype. Consequently, the overall five-year survival of TNBC patients is significantly lower than those diagnosed with other subtypes of breast cancer. There is currently no acceptable specific molecular marker for TNBC. Despite this lack, these tumors do respond to chemotherapy (Kriege et al., 2009). Patients have shown better response to cytotoxic agents in the adjuvant setting as well as in the neoadjuvant setting when administered agents such as 5-fluorouracil, doxorubicin and cyclophosphamide (Rouzier et al. 2005). Other agents that have shown some efficacy include platinum based compounds such as cisplatin and anti-tubulin compounds such as taxanes (Santana-Davila and Perez, 2010).

[0004] As mentioned above, there are no specific targets for TNBC but this has not impeded the trial of target agents such as the inhibition of Poly [ADP-ribose] polymerase 1 (PARP1). PARP1 is an enzyme that participates in the repair of DNA single-strand breaks by associating with corrupted DNA strands and mediating the recruitment of enzymes needed to repair single-strand breaks (de Ruijter et al., 2011). Thus the strategy has been to inhibit PARP1 activity as a means of allowing cancer cells to accumulate more DNA single-strand breaks, which ultimately leads to genetic instability, mitotic arrest and apoptosis. Promising clinical results were achieved in patients that showed mutations in BRCA1 and/or BRCA2, important mediators of genetic maintenance and homologous recombination required for proper cell division. Indeed, patients with BRCA1 mutations, which are presumably deficient in these genetic stability pathways, showed greater response to PARP1 inhibitors compared with those who were wild type for BRCA1 (Fong et al., 2009). It is clear that targeting PARP1 in TNBC patients who are carriers of BRCA mutation represents a promising strategy. The combination of ER/PgR/HER2 status with that of the genetic profile of the BRCA1/2 genes might offer the best characterization for deciding the proper treatment options for TNBC patients.

[0005] Other strategies also examined the use of EGFR inhibitors, either as monoclonal antibodies or small molecule inhibitors or anti-angiogenic compounds to target VEGF. Several clinical trials have evaluated the efficacy of these compounds but none of them have shown significant response when administered alone. However, mild efficacy was observed in patients treated with these inhibitors in combination with other cytotoxic agents (Santana-Davila and Perez, 2010).

[0006] Notwithstanding the recent advances in the understanding and the treatment for breast cancer, the use of chemotherapy is invariably associated with severe adverse reactions, which limit their use. Consequently, the need for more specific strategies such as combining antigen tissue specificity with the selectivity of monoclonal antibodies should permit a significant reduction in off-target-associated side effects. There are no TNBC specific antigens that are currently under investigation as therapeutic targets for monoclonal antibodies. Thus, TNBC patients have little options because of the inability to target a specific marker of protein that is expressed in these tumors. There are urgent needs to identify new proteins expressed in TNBC for applications as new diagnostic markers and novel targeted therapies.

[0007] Kidney associated antigen 1 (KAAG1), the protein sequence which is identified herein as SEQ ID NO.:2, was originally cloned from a cDNA library derived from a histocompatibility leukocyte antigen-B7 renal carcinoma cell line as an antigenic peptide presented to cytotoxic T lymphocytes (Van den Eynde et al., 1999; Genebank accession no. Q9UBP8, the cDNA sequence is represented by nucleotides 738-992 of SEQ ID NO.:1). The locus containing KAAG1 was found to encode two genes transcribed in both directions on opposite strands. The sense strand was found to encode a transcript that encodes a protein termed DCDC2. Expression studies by these authors found that the KAAG1 antisense transcript was tumor specific and exhibited very little expression in normal tissues whereas the DCDC2 sense transcript was ubiquitously expressed (Van den Eynde et al., 1999). The expression of the KAAG1

transcript in cancer, and in particular ovarian cancer, renal cancer, lung cancer, colon cancer, breast cancer and melanoma was disclosed in international application No. PCT/CA2007/001134 published on Dec. 27, 2007 under No. WO 2007/147265. Van den Eynde et al., also observed RNA expression in renal carcinomas, colorectal carcinomas, melanomas, sarcomas, leukemias, brain tumors, thyroid tumors, mammary carcinomas, prostatic carcinomas, oesophageal carcinomas, bladder tumor, lung carcinomas and head and neck tumors. Recently, strong genetic evidence obtained through linkage disequilibrium studies found that the VMP/DCDC2/KAAG1 locus was associated with dyslexia (Schumacher et al., 2006; Cope et al., 2005). One of these reports pointed to the DCDC2 marker as the culprit in dyslexic patients since the function of this protein in cortical neuron migration was in accordance with symptoms of these patients who often display abnormal neuronal migration and maturation (Schumacher et al., 2006).

[0008] The Applicant has obtained a panel of antibodies and antigen binding fragment that bind to the KAAG1 protein. These antibodies or antigen binding fragments were shown to target three regions of the protein; amino acids 1 to 35, amino acids 36 to 60 amino acids 61 to 84. The Applicant found that antibodies targeting a region between amino acids 30 to 84 were the most advantageous for therapeutic purposes as they recognized KAAG1 located at the surface of tumor cells. The Applicant has shown that some of these antibodies and antigen binding fragments can mediate antibody-dependent cell cytotoxicity and/or are internalized by tumor cells, which makes them good candidates to deliver a payload to tumor cells. The Applicant has also generated chimeric and humanized antibodies based on selected antibody candidates and has shown that these antibodies can inhibit tumor cell formation and invasion (see PCT/CA2009/001586 published on Jun. 3, 2010 under No. WO2010/060186 and PCT/CA2010/001785 published on May 12, 2011 under No. WO2011/054112). Finally, the Applicant found that these antibodies could be used for the treatment and diagnosis of ovarian cancer, skin cancer, renal cancer, colorectal cancer, sarcoma, leukemia, brain tumor, thyroid tumor, breast cancer, prostate cancer, oesophageal tumor, bladder tumor, lung tumor and head and neck tumor and metastatic form of these cancers.

[0009] The Applicant has now come to the unexpected discovery that breast cancer cells lacking ER protein expression, PgR protein expression and/or showing absence of HER2 protein over-expression (i.e., triple-negative breast cancer cells, basal-like) can be efficiently targeted with an antibody or antigen binding fragment that specifically binds to KAAG1. Anti-KAAG1 antibodies may thus be used for the, detection and therapeutic treatment of breast cancer cells that are negative for at least one of these markers.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. **1***a* is an amino acid sequence alignment of the 3A4 variable domains of the murine and humanized light chains. The light chain has two humanized variants (Lh1 an Lh2). The CDRs are shown in bold and indicted by CDRL1, CDRL2 and CDRL3. Back mutations in the human framework regions that are murine amino acids are underlined in the humanized sequences.

[0011] FIG. **1***b* is an amino acid sequence alignment of the 3A4 variable domains of the murine and humanized heavy chains. The heavy chain has four humanized variants (Hh1 to Hh4). The CDRs are shown in bold and indicted by CDRH1, CDRH2 and CDRH3. Back mutations in the human framework regions that are murine amino acids are underlined in the humanized sequences.

[0012] FIG. **2***a* is an alignment of murine 3A4 light chain variable region (SEQ ID NO.:4) with a light chain variable region variant (SEQ ID NO.:33) using the ClustalW2 program (Larkin M. A., et al., (2007) ClustalW and ClustalX version 2. *Bioinformatics* 2007 23(21): 2947-2948) where an "*" (asterisk) indicates positions which have a single, fully conserved residue, wherein ":" (colon) indicates conservation between groups of strongly similar properties—scoring>0.5 in the Gonnet PAM 250 matrix and where "." (period) indicates conservation between groups of weakly similar properties—scoring=<0.5 in the Gonnet PAM 250 matrix.

[0013] FIG. **2***b* is an alignment of murine 3A4 heavy chain variable region (SEQ ID NO.:2) with a light chain variable region variant (SEQ ID NO.:38) using the ClustalW2 program (Larkin M. A., et al., (2007) ClustalW and ClustalX version 2. *Bioinformatics* 2007 23(21): 2947-2948) where an "*" (asterisk) indicates positions which have a single, fully conserved residue, wherein ":" (colon) indicates conservation between groups of strongly similar properties—scoring>0.5 in the Gonnet PAM 250 matrix and where "." (period) indicates conservation between groups of weakly similar properties—scoring=<0.5 in the Gonnet PAM 250 matrix.

[0014] FIG. **3***a* represents plasmid map of pKCR5-3A4-HC-Variant 1. The heavy chains of the humanized 3A4 variants were cloned in the same manner into the HindIII site of pK-CR5. Consequently the resulting plasmids are identical to pKCR5-3A4-HC variant 1 except for the sequence of the heavy chain immunoglobulin variable domain.

[0015] FIG. **3***b* represents plasmid map of pMPG-CR5-3A4-LC-Variant 1. The light chains of the humanized variants 1 and 2 of 3A4 antibody were cloned in the same manner into the BamHI site of pMPG-CR5. Consequently, the resulting plasmid is identical to pMPG-CR5-3A4-LC-Variant 1, except for the sequence of the light chain immunoglobulin variable domain.

[0016] FIG. **4** represents an analysis of antibody production after transient transfection in CHO cells. Supernatant (13 days post-transfection) of CHOcTA cells transfected with the different combinations of light and heavy chains of humanized 3A4 antibody were analyzed by western blot. Quantification of antibody produced in the supernatants was determined after scanning the bands of the western blot against dilution of a known standard (human purified IgG antibody). Mr molecular weight marker (kDa).

[0017] FIG. **5** is a graph of a Superdex G75 gel filtration of recombinant KAAG1 sample. KAAG1 was injected over the gel filtration and separated at 0.4 ml/min. The largest peak between fractions 15-19.

[0018] FIG. **6** is a Table listing the rate and affinity constants for the murine and humanized variants of the 3A4 antibody.

[0019] FIG. **7***a* is an histogram illustrating the association rates (K_a) of the humanized antibodies.

[0020] FIG. **7***b* is an histogram illustrating the dissociation rates (K_d) of the humanized antibodies.

[0021] FIG. **7***c* is an histogram illustrating the affinity constants (K_D) of the humanized antibodies.

[0022] FIG. **8***a* illustrates humanized 3A4 variants binding to KAAG1 in an ELISA. This figure shows the comparative binding of 3A4 humanized antibody variants and the murine 3A4. Concentration-dependent binding profiles of the humanized heavy chains (Hh1, Hh2, Hh3 and Hh4) assembled with the Lh1 light chain variant.

[0023] FIG. **8***b* illustrates humanized 3A4 variants binding to KAAG1 in an ELISA. This figure shows the comparative binding of 3A4 humanized antibody variants and the murine 3A4. Concentration-dependent binding profiles of the humanized heavy chains (Hh1, Hh2, Hh3 and Hh4) assembled with the Lh2 light chain variant.

[0024] FIG. **9** illustrates humanized 3A4 variants binding to KAAG1 on the surface of cancer cells. This illustration shows the comparative binding activity of the humanized and the murine 3A4 antibodies on the unpermeabilized SKOV-3 ovarian cancer cells.

[0025] FIG. **10** shows a scan of a tissue microarray containing 139 biopsy samples obtained from breast cancer patients. The samples were blotted with the 3A4 anti-KAAG1 antibody and showed that the vast majority of the breast tumors expressed very high level of KAAG1 antigen. The confirmed TNBC samples are marked with an asterisk.

[0026] FIG. **11** shows the results of flow cytometry performed using MDA-MB-231, MDA-MB-436, MDA-MB-468, BT-20, BT-549, T47D, MCF-7 and 293-6E cell lines incubated with the 3A4 anti-KAAG1 antibody (blue bars of the histogram) compared with a control IgG (red bars). This is a representative results from an experiment that was performed in triplicate. The TNBC cell lines are marked with an asterisk.

[0027] FIG. **12** represents the detection of the KAAG1 antigen on the surface of MDA-MB-231 cells by flow cytometry with the 3A4 anti-KAAG1 antibody. The fluorescence signal decreases with time when the cells were incubated at 37° C., which suggests that the KAAG1/antibody complex was internalized during the incubation when the cells were incubated with 3A4.

[0028] FIG. **13** represents the detection of the KAAG1 antigen on the surface of MDA-MB-436 cells by flow cytometry with the 3A4 anti-KAAG1 antibody. The fluorescence signal decreases with time when the cells were incubated at 37° C., which suggests that the KAAG1/antibody complex was internalized during the incubation when the cells were incubated with 3A4.

[0029] FIG. **14** represents the detection of the KAAG1 antigen on the surface of BT-20 cells by flow cytometry with the 3A4 anti-KAAG1 antibody. The fluorescence signal decreases with time when the cells were incubated at 37° C., which suggests that the KAAG1/antibody complex was internalized during the incubation when the cells were incubated with 3A4.

[0030] FIG. **15** represents the detection of the KAAG1 antigen on the surface of T47D cells by flow cytometry with the 3A4 anti-KAAG1 antibody. The fluorescence signal decreases with time when the cells were incubated at 37° C., which suggests that the KAAG1/antibody complex was internalized during the incubation when the cells were incubated with 3A4.

[0031] FIG. **16** represents immunofluorescence data performed on live MDA-MB-231 cells with the 3A4 anti-KAAG1 antibody and the anti-LAMP1 antibody. The immunofluorescence signal associated with the anti-KAAG1 antibody is shown in the left panel, the immunofluorescence signal associated LAMP1 is shown in the middle panel and the merging of both images is shown in the right panel. These data illustrates the co-localization of KAAG1 and LAMP1 near the peri-nuclear area.

[0032] FIG. **17** represents immunofluorescence data performed on live MDA-MB-231 cells with the 3A4 anti-KAAG1 antibody and the anti-LAMP1 antibody. The immunofluorescence signal associated with the anti-KAAG1 antibody is shown in the left panel, the immunofluorescence signal associated LAMP1 is shown in the middle panel and the merging of both images is shown in the right panel. These data illustrates the localization of KAAG1 with LAMP1 a marker of late endosomes/lysosomes.

SUMMARY OF THE INVENTION

[0033] The present invention provides a method of treating or detecting cancer or cancer cells (in vitro or in vivo) in an individual in need.

[0034] In accordance with the present invention, methods of treatment or detection may be carried out with an antibody capable of binding to KAAG1 or an antigen binding fragment thereof.

[0035] The individual in need may comprise, for example, an individual having or suspected of having cancer. Such individual may have a cancer or cancer cells originating from a breast carcinoma.

[0036] The cancer or cancer cells may more particularly originate from a breast carcinoma characterized as being triple-negative or basal-like.

[0037] Therefore, the individuals who may benefit from methods of treatment or detection described herein may include those suffering from breast carcinoma.

[0038] The breast carcinoma may comprise tumors cells showing a decrease or a lost in the expression of the estrogen receptor.

[0039] The breast carcinoma may comprise tumor cells showing a decrease or a lost in the expression of the progesterone receptor.

[0040] The breast carcinoma may comprise tumor cells showing a decrease or a lost in the expression of Her2.

[0041] The breast carcinoma may comprise tumor cells showing a decrease or a lost in Her2 overexpression.

[0042] More particularly, the breast carcinoma may comprise tumor cells showing either 1) a decrease or a loss in expression of the estrogen receptor and the progesterone receptor, 2) a decrease or a loss in expression of the estrogen receptor and a decrease or a loss of Her2 overexpression, 3) a decrease or a loss in expression of the progesterone receptor and a decrease or a loss of Her2 overexpression or 4) a decrease or a loss in expression of the estrogen receptor, a decrease or a loss in expression of the progesterone receptor and a decrease or a loss of Her2 overexpression.

[0043] Even more particularly, the breast carcinoma may comprise tumor cells showing either 1) a loss in expression of the estrogen receptor and the progesterone receptor, 2) a loss in expression of the estrogen receptor and a loss of Her2 expression, 3) a loss in expression of the progesterone receptor and a loss of Her2 expression or 4) a loss in expression of the estrogen receptor, a loss in expression of the progesterone receptor and a loss of Her2 expression.

[0044] In accordance with the present invention, the individual may carry breast cancer cells that are characterized as being triple-negative or may have a tumor categorized as being a triple-negative breast cancer.

[0045] In accordance with the present invention, the individual may carry breast cancer cells that are characterized as basal-like, or may have a tumor categorized as being a basal-like breast cancer.

[0046] Other individuals who would benefit from treatment with an anti-KAAG1 include those having carcinoma comprising tumors cells exhibiting an epithelial-to-mesenchymal transition (EMT) phenotype.

[0047] Commonly used molecular markers of EMT include, for example, a reduced expression of E-cadherin, cytokeratin and β-catenin (in the membrane) and/or an increased expression of Snail, Slug, Twist, ZEB1, ZEB2, N-cadherin, vimentin, α-smooth muscle actin, matrix metalloproteinases etc. (see for example, Kalluri and Weinberg, The Journal of Clinical Investigation, 119(6), p 1420-1428; 2009; Fassina et al., Modern Pathology, 25; p 86-99; 2012; Lee et al., JCB; 172; p 973-981; 2006). An EMT phenotype may also be distinguished by an increased capacity for migration, invasion of by resistance to anoikis/apoptosis. Cells that are undergoing epithelial-to-mesenchymal transition may thus be detected by a reduction of epithelial markers and apparition of mesenchymal markers or EMT phenotypes.

[0048] In accordance with the present invention, the method may thus comprise, for example, administering an antibody or antigen binding fragment which is capable of specific binding to KAAG1 to an individual in need. The individual in need is preferentially selected on the basis of their tumor lacking ER expression, PgR expression and/or by the absence of HER2 protein over-expression. Clinical testing for these markers is usually performed using histopathologic methods (immunohistochemistry, FISH, etc.) and/or by gene expression studies (see for example Dent et al, 2007, Bernstein and Lacey, 2011). The individual in need may thus be an individual who has received a diagnosis of triple-negative breast cancer or basal-like breast cancer. The individual in need may be an individual which is unresponsive to hormonal therapy and/or to transtuzumab therapy (or other anti-Her2 antibodies). Alternatively, the individual in need may be an individual carrying tumor cells that have the ability of undergoing epithelial-to-mesenchymal transition or that have acquired a mesenchymal phenotype.

[0049] The present invention thus provides a method of treating triple-negative breast cancer or basal-like breast cancer by administering an inhibitor of KAAG1 activity or expression to an individual in need.

[0050] In accordance with the present invention, the KAAG1 inhibitor may thus comprise an antibody described herein or an antigen binding fragment thereof.

[0051] Also in accordance with the present invention, the KAAG1 inhibitor may comprise a nucleotide sequence complementary to SEQ ID NO.:1 or to a fragment thereof. More particularly, the KAAG1 inhibitor may comprise a nucleotide sequence complementary to nucleotides 738 to 992 (inclusively) of SEQ ID NO.:1 or to a fragment thereof. For example, the inhibitor may include at least 10 consecutive nucleotides (at least 15, at least 20) which are complementary to SEQ ID NO.:1 or to nucleotides 738 to 992 (inclusively) of SEQ ID NO.:1. More particular type of KAAG1 inhibitor includes a siRNA which inhibit expression of SEQ ID NO.:1.

[0052] Suitable antibodies or antigen binding fragments include those that are capable of binding to KAAG1 at the surface of tumor cells. Such antibodies or antigen binding fragments thereof may preferentially bind an epitope included within amino acids 30 to 84 of KAAG1 inclusively.

[0053] Alternatively such antibodies or antigen binding fragments thereof may bind an epitope located within amino acids 36 to 60 (inclusively) or within amino acids 61 to 84 (inclusively) of KAAG1.

[0054] The epitope may particularly be located or comprised within amino acids 50 to 70, 50 to 65, 51 to 65, 52 to 65, 53 to 65, 54 to 65, 54 to 64, 54 to 63, 54 to 62, 54 to 61, 54 to 60, 50 to 62; 50 to 61, or 50 to 60 (inclusively or exclusively).

[0055] In accordance with an embodiment of the invention, the antibody or antigen binding fragment may bind an epitope comprised within amino acids 50 to 70 of KAAG1.

[0056] In a further embodiment of the invention, the antibody or antigen binding fragment may bind an epitope comprised within amino acids 50 to 62 of KAAG1.

[0057] In yet a further embodiment, the antibody or antigen binding fragment may bind an epitope comprised within amino acids 54 to 65 of KAAG1.

[0058] Suitable antibodies for therapeutic treatment include for example, those which mediate antibody-dependent cell cytotoxicity.

[0059] Other even more suitable antibodies for therapeutic treatment include those that are conjugated with a therapeutic moiety.

[0060] In accordance with the present invention, the antibody may be, for example, a monoclonal antibody, a chimeric antibody, a humanized antibody a human antibody or an antigen binding fragment thereof.

DETAILED DESCRIPTION OF THE INVENTION

Method of Treatment

[0061] As indicated herein, the present invention encompass administering an antibody or antigen binding fragment to an individual having a breast cancer characterized as being "triple negative breast cancer" or "basal-like breast cancer".

[0062] Classification of breast cancer subtypes as being "triple negative breast cancer" or "basal-like breast cancer" is known in the art (see for example, Foulkes et al., N. Engl. J. Med., 2010; 363:1938-1948) and includes, for example, the following definitions:

[0063] "Basal-like breast cancer", may include for example, a subtype of breast cancer comprising a heterogenous group of tumors characterized by the absence of or low levels of expression of estrogen receptors, very low prevalence of Her2 overexpression and expression of genes usually found in the basal or myoepithelial cells of the human breast. Such expression may be determined by microarray analysis.

[0064] "Triple-negative breast cancer", may include for example, a tumor characterized by lack of estrogen receptor (ER), progesterone receptor (PR) and Her2 expression. Some investigators accept tumors as being negative for expression of ER or PR only if less than 1% of the cells are positive for ER or PR expression; others consider tumors to be negative for ER or PR expression when up to 10% of cells are positive for expression. Different definitions of HER2-negativity have been used. The two most frequently adopted include tumors with immunohistochemical scores of 0/1+ or 2+ that are lacking HER2 gene amplification after in situ

hybridization. Such expression may be especially determined by immunohistochemical staining.

[0065] In accordance with the present invention, the method of treatment includes administering a KAAG1 inhibitor to an individual in need. Such KAAG1 inhibitor includes, for example, an antibody or antigen binding fragment thereof which specifically binds to KAAG1.

[0066] It is likely that the most potent antibodies or antigen binding fragments may be those having a high affinity for KAAG1. It is also likely that the most potent antibodies or antigen binding fragments may be those that are internalized within a cells compartment such as, for example, a lysosome or an endosome.

[0067] As such, the present invention especially encompasses antibodies or antigen binding fragments having a high affinity for KAAG1.

[0068] Suitable antibodies or antigen binding fragments include those that are capable of binding to KAAG1 at the surface of tumor cells with a high affinity. Such high affinity antibodies or antigen binding fragments thereof may preferentially bind an epitope included within amino acids 30 to 84 of KAAG1 inclusively.

[0069] Alternatively such high affinity antibodies or antigen binding fragments thereof may bind an epitope located within amino acids 36 to 60 (inclusively) or within amino acids 61 to 84 (inclusively) of KAAG1.

[0070] The high affinity antibodies or antigen binding fragments may bind, for example, an epitope may particularly be located or comprised within amino acids 50 to 70, 50 to 65, 51 to 65, 52 to 65, 53 to 65, 54 to 65, 54 to 64, 54 to 63, 54 to 62, 54 to 61, 54 to 60, 50 to 62; 50 to 61, or 50 to 60 (inclusively or exclusively).

[0071] In accordance with an embodiment of the invention, the high affinity antibody or antigen binding fragment may bind an epitope comprised within amino acids 50 to 70 of KAAG1.

[0072] In a further embodiment of the invention, the high affinity antibody or antigen binding fragment may bind an epitope comprised within amino acids 50 to 62 of KAAG1.

[0073] In yet a further embodiment, the high affinity antibody or antigen binding fragment may bind an epitope comprised within amino acids 54 to 65 of KAAG1.

[0074] Preferred antibodies including high affinity antibodies are those than may be internalized in a cell or cell compartment (e.g., lysosomes or endosomes). The ability of antibodies to be internalized may be determined by method known in the art such as for example and without limitation, by immunofluorescence studies similar to those performed herein.

[0075] Antibodies having CDRs identical to those of the 3A4 antibodies are particularly encompassed by the present invention. As such, antibodies having a light chain variable region and/or heavy chain variable region consensus sequences set forth in any of SEQ ID NOs.:186 to 188 and 191 to 193 and specific sequences set forth in SEQ ID No.:46, 48, 189, 190, or 194 to 198 are encompassed by the present invention. Among those, antibodies having a light chain variable region and/or heavy chain variable region consensus sequences set forth in any of SEQ ID NO.: 188 and 196 or specific sequences set forth in SEQ ID NO.:46, 48, 189, 190, or 194 to 198 are particularly contemplated.

[0076] The antibodies or antigen binding fragments thereof may preferably be conjugated with a therapeutic moiety.

[0077] The antibodies or antigen binding fragments thereof, may have a human constant region. Preferably the antibodies or antigen binding fragments thereof may have a human IgG1 constant region. Alternatively, the antibodies or antigen binding fragments thereof may have an IgG2 constant region.

[0078] The method of the present invention may also include administering a KAAG1 inhibitor such as an antibody (e.g., conjugated with a therapeutic moiety) or antigen binding fragment in combination with an anticancer agent such as for example, a small molecule drug, an antibody or antigen binding fragment binding to a target other than KAAG1, a chemotherapeutic or a cytotoxic agent. Example of anticancer agent that could be administered with the KAAG1 inhibitor may include for example, doxorubicin, taxanes, anti-angiogenic agents, platinum salts, PARP inhibitors.

[0079] Other methods of treatment encompassed by the present invention include administering other types of KAAG1 inhibitors such as antisense-based therapeutics (siRNA, antisenses, ribozymes, etc.).

Antibodies and Antigen Binding Fragments that Binds to KAAG1

[0080] The term "antibody or antigen binding fragment" or similar terms such as "antibodies and antigen binding fragments" encompasses, for example "variant antibody or antigen binding fragment" such as, for example, "humanized antibody or antigen binding fragment".

[0081] The term "antibody" refers to intact antibody, monoclonal or polyclonal antibodies. The term "antibody" also encompasses multispecific antibodies such as bispecific antibodies. Human antibodies are usually made of two light chains and two heavy chains each comprising variable regions and constant regions. The light chain variable region comprises 3 CDRs, identified herein as CDRL1, CDRL2 and CDRL3 flanked by framework regions. The heavy chain variable region comprises 3 CDRs, identified herein as CDRH1, CDRH2 and CDRH3 flanked by framework regions.

[0082] The term "antigen-binding fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to bind to an antigen (e.g., KAAG1, secreted form of KAAG1 or variants thereof). It has been shown that the antigen-binding function of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR), e.g., V_H CDR3. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single polypeptide chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibod-

ies are also intended to be encompassed within the term "antigen-binding fragment" of an antibody. Furthermore, the antigen-binding fragments include binding-domain immunoglobulin fusion proteins comprising (i) a binding domain polypeptide (such as a heavy chain variable region, a light chain variable region, or a heavy chain variable region fused to a light chain variable region via a linker peptide) that is fused to an immunoglobulin hinge region polypeptide, (ii) an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii) an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region. The hinge region may be modified by replacing one or more cysteine residues with serine residues so as to prevent dimerization. Such binding-domain immunoglobulin fusion proteins are further disclosed in US 2003/0118592 and US 2003/0133939. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0083] A typical antigen binding site is comprised of the variable regions formed by the pairing of a light chain immunoglobulin and a heavy chain immunoglobulin. The structure of the antibody variable regions is very consistent and exhibits very similar structures. These variable regions are typically comprised of relatively homologous framework regions (FR) interspaced with three hypervariable regions termed Complementarity Determining Regions (CDRs). The overall binding activity of the antigen binding fragment is often dictated by the sequence of the CDRs. The FRs often play a role in the proper positioning and alignment in three dimensions of the CDRs for optimal antigen binding.

[0084] As used herein the term "high affinity" refers to an affinity of 10 nM or less. The term "high affinity" especially includes antibodies having an affinity of 5 nM or less. The term "high affinity" even more particularly includes antibodies having an affinity of 1 nM or less, or 0.1 nM or less.

[0085] Antibodies and/or antigen binding fragments of the present invention may originate, for example, from a mouse, a rat or any other mammal or from other sources such as through recombinant DNA technologies.

[0086] An-KAAG1 antibodies were initially isolated from Fab libraries for their specificity towards the antigen of interest. Exemplary methods on how to convert Fab into full immunoglobulins are provided herein.

[0087] The variable regions described herein may be fused with constant regions of a desired species thereby allowing recognition of the antibody by effector cells of the desired species. The constant region may originate, for example, from an IgG1, IgG2, IgG3, or IgG4 subtype. Cloning or synthesizing a constant region in frame with a variable region is well within the scope of a person of skill in the art and may be performed, for example, by recombinant DNA technology.

[0088] In certain embodiments of the present invention, antibodies that bind to KAAG1 may be of the IgG1, IgG2, IgG3, or IgG4 subtype. More specific embodiments of the invention relates to an antibody of the IgG1 subtype or especially human IgG1 subtype. Other specific embodiments of the invention relates to an antibody of the IgG2 subtype or especially of the human IgG2 subtype.

[0089] The antibody may be a humanized antibody of the IgG1 subtype subtype or especially human IgG1 subtype. Alternatively, the antibody may be a humanized antibody of the IgG2 subtype or especially of the human IgG2 subtype.

[0090] The antibody may be, for example, biologically active in mediating antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CMC), or associated with immune complexes. The typical ADCC involves activation of natural killer (NK) cells and is reliant on the recognition of antibody-coated cells by Fc receptors on the surface of the NK cells. The Fc receptors recognize the Fc domain of antibodies such as is present on IgG1, which bind to the surface of a target cell, in particular a cancerous cell that expresses an antigen, such as KAAG1. Once bound to the Fc receptor of IgG the NK cell releases cytokines and cytotoxic granules that enter the target cell and promote cell death by triggering apoptosis.

[0091] The present invention described a collection of antibodies that bind to KAAG1 or to a KAAG1 variant. In certain embodiments, the antibodies may be selected from the group consisting of polyclonal antibodies, monoclonal antibodies such as chimeric or humanized antibodies, antibody fragments such as antigen binding fragments, single chain antibodies, domain antibodies, and polypeptides with an antigen binding region.

[0092] In an aspect of the invention, the isolated antibody or antigen binding fragment of the present invention may be capable of inducing killing (elimination, destruction, lysis) of KAAG1-expressing tumor cells or KAAG1 variant-expressing tumor cells (e.g., in an ADCC-dependent manner).

[0093] In a further aspect of the invention, the isolated antibody or antigen binding fragment of the present invention may especially be characterized by its capacity of reducing spreading of tumor cells expressing KAAG1 or a KAAG1 variant.

[0094] In an additional aspect of the invention, the isolated antibody or antigen binding fragment of the present invention may be characterized by its capacity of decreasing or impairing formation of tumors expressing KAAG1 or a KAAG1 variant.

[0095] In an exemplary embodiment of the invention, the isolated antibody or antigen binding fragment may comprise amino acids of a constant region, which may originate, for example, from a human antibody.

[0096] In another exemplary embodiment of the invention, the isolated antibody or antigen binding fragment may comprise framework amino acids of a human antibody.

[0097] Without being limited to the exemplary embodiments presented herein, the Applicant as generated specific antibodies and antigen binding fragments that may be useful for the purposes described herein.

[0098] The following is a list of antibodies that were generated and shown to bind in a specific manner to KAAG1; 3D3, 3A4, 3C4, 3G10, 3A2, 3F6, 3E8, 3E10, 3A9, 3B1, 3G5, 3B2, 3B8, 3G8, 3F7, 3E9, 3G12, 3C3, 3E12, 4A2, 3F10, 3F4, 3611, 3D1, 3C2, 3E6 and 3H3. Sequences of the antibody light chain or heavy chain, variable regions or complementary determining regions (CDRs) are available in international application No. PCT/CA2009/001586 published on Jun. 3, 2010 under No. WO2010/060186A8, in international application No. PCT/CA2010/001795 published on May 12, 2011 under No. WO2011/054112A1 or in international application No. PCT/CA2012/000296 published on Oct. 4, 2012 under No. WO2012/129668A1.

[0099] In most instances, the sequence of the CDRs has been provided separately or is shown in bold herein.

[0100] Amongst, these antibodies, the 3D3, 3A4, 3G10 and 3C4 were selected for in vitro and/or in vivo biological testing. The 3A4 antibody appeared to have the best characteristics. Based on our experiments, the 3A4 antibody when conjugated with a therapeutic moiety (e.g. a cytotoxic agent) is more effective in killing cancer cells than its non-conjugated version.

[0101] In an exemplary embodiment, the antibody or antigen binding fragment may comprise any individual CDR or a combination of CDR1, CDR2 and/or CDR3 of the light chain variable region. The CDR3 may more particularly be selected. Combination may include for example, CDRL1 and CDRL3; CDRL1 and CDRL2; CDRL2 and CDRL3 and; CDRL1, CDRL2 and CDRL3.

[0102] In another exemplary embodiment, the antibody or antigen binding fragment may comprise any individual CDR or a combination of CDR1, CDR2 and/or CDR3 of the heavy chain variable region. The CDR3 may more particularly be selected. Combination may include for example, CDRH1 and CDRH3; CDRH1 and CDRH2; CDRH2 and CDRH3 and; CDRH1, CDRH2 and CDRH3.

[0103] In accordance with the present invention, the antibody or antigen binding fragment may comprise at least two CDRs of a CDRL1, a CDRL2 or a CDRL3.

[0104] Also in accordance with the present invention, the antibody or antigen binding fragment may comprise one CDRL1, one CDRL2 and one CDRL3.

[0105] Further in accordance with the present invention, the antibody or antigen binding fragment may comprise:

[0106] a. At least two CDRs of a CDRL1, CDRL2 or CDRL3 and;

[0107] b. At least two CDRs of a CDRH1, one CDRH2 or one CDRH3.

[0108] The antibody or antigen binding fragment may more preferably comprise one CDRL1, one CDRL2 and one CDRL3.

[0109] The antibody or antigen binding fragment may also more preferably comprise one CDRH1, one CDRH2 and one CDRH3.

[0110] When only one of the light chain variable region or the heavy chain variable region is available, an antibody or antigen-binding fragment may be reconstituted by screening a library of complementary variable regions using methods known in the art (Portolano et al. The Journal of Immunology (1993) 150:880-887, Clarkson et al., Nature (1991) 352:624-628).

[0111] Exemplary embodiments of the present invention encompass antibodies or antigen binding fragments having the CDRs of the light chain and/or heavy chains of the 3D3, 3A4, 3C4, 3G10, 3A2, 3F6, 3E8, 3E10, 3A9, 3B1, 3G5, 3B2, 368, 3G8, 3F7, 3E9, 3G12, 3C3, 3E12, 4A2, 3F10, 3F4, 3611, 3D1, 3C2, 3E6 or 3H3 antibodies. More particular embodiments of the invention include antibodies or antigen binding fragments having the CDRs of the light chain and/or heavy chains of the 3D3, 3A4, 3C4 or 3G10 antibodies. Even more particular embodiments of the invention include antibodies or antigen binding fragments having the CDRs of the light chain and/or heavy chains of the 3A4 antibody. The invention thus encompassed any monoclonal, chimeric, human, or humanized antibody comprising one or more CDRs of the 3A4 antibody.

[0112] Antibodies or antigen binding fragments that may be used in methods of the present invention, include those having CDRs of the 3A4 antibody and may comprise, for example, a CDRH1 as set forth in SEQ ID NO.:49, a CDRH2 as set forth in SEQ ID NO.:50 or in SEQ ID NO.:212, a CDRH3 as set forth in SEQ ID NO.:51, a CDRL1 as set forth in SEQ ID NO.: 52, a CDRL2 as set forth in SEQ ID NO.:53 and a CDRL3 as set forth in SEQ ID NO.: 54.

[0113] The present invention therefore encompass, antibodies and antigen binding fragment which are capable of specific binding to KAAG1 and which may comprise sequences selected from the group consisting of:

[0114] a. the 3CDRs of a light chain variable region defined in SEQ ID NO.:16 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.:18,

[0115] b. the 3CDRs of a light chain variable region defined in SEQ ID NO.:20 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.:22;

[0116] c. the 3CDRs of a light chain variable region defined in SEQ ID NO.:24 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.:26;

[0117] d. the 3CDRs of a light chain variable region defined in SEQ ID NO.:48 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.:46;

[0118] e. the 3CDRs of a light chain variable region defined in SEQ ID NO.:103 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 126,

[0119] f. the 3CDRs of a light chain variable region defined in SEQ ID NO.:104 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 127,

[0120] g. the 3CDRs of a light chain variable region defined in SEQ ID NO.:105 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 128,

[0121] h. the 3CDRs of a light chain variable region defined in SEQ ID NO.:106 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 145,

[0122] i. the 3CDRs of a light chain variable region defined in SEQ ID NO.:107 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 129,

[0123] j. the 3CDRs of a light chain variable region defined in SEQ ID NO.:108 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 130,

[0124] k. the 3CDRs of a light chain variable region defined in SEQ ID NO.:109 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 141,

[0125] l. the 3CDRs of a light chain variable region defined in SEQ ID NO.:110 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 131,

[0126] m. the 3CDRs of a light chain variable region defined in SEQ ID NO.:111 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 134,

[0127] n. the 3CDRs of a light chain variable region defined in SEQ ID NO.:112 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 135,

[0128] o. the 3CDRs of a light chain variable region defined in SEQ ID NO.:113 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 136,

[0129] p. the 3CDRs of a light chain variable region defined in SEQ ID NO.:114 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 133,

[0130] q. the 3CDRs of a light chain variable region defined in SEQ ID NO.:115 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 140,

[0131] r. the 3CDRs of a light chain variable region defined in SEQ ID NO.:116 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 137,

[0132] s. the 3CDRs of a light chain variable region defined in SEQ ID NO.:117 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 144,

[0133] t. the 3CDRs of a light chain variable region defined in SEQ ID NO.:118 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 139,

[0134] u. the 3CDRs of a light chain variable region defined in SEQ ID NO.:119 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 132,

[0135] v. the 3CDRs of a light chain variable region defined in SEQ ID NO.:120 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 142,

[0136] w. the 3CDRs of a light chain variable region defined in SEQ ID NO.:121 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 138,

[0137] x. the 3CDRs of a light chain variable region defined in SEQ ID NO.:122 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 146,

[0138] y. the 3CDRs of a light chain variable region defined in SEQ ID NO.:123 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 153,

[0139] z. the 3CDRs of a light chain variable region defined in SEQ ID NO.:124 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 143,

[0140] aa. the 3CDRs of a light chain variable region defined in SEQ ID NO.:189 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 194,

[0141] bb. the 3CDRs of a light chain variable region defined in SEQ ID NO.:189 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 195,

[0142] cc. the 3CDRs of a light chain variable region defined in SEQ ID NO.:189 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 196,

[0143] dd. the 3CDRs of a light chain variable region defined in SEQ ID NO.:189 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 197,

[0144] ee. the 3CDRs of a light chain variable region defined in SEQ ID NO.:190 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 194,

[0145] ff. the 3CDRs of a light chain variable region defined in SEQ ID NO.:190 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 195,

[0146] gg. the 3CDRs of a light chain variable region defined in SEQ ID NO.:190 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 196, or

[0147] hh. the 3CDRs of a light chain variable region defined in SEQ ID NO.:190 and/or the 3CDRs of a heavy chain variable region defined in SEQ ID NO.: 197.

[0148] Other exemplary embodiments of the invention encompass antibodies or antigen binding fragments having the light chain and/or heavy chains of the 3D3, 3A4, 3C4, 3G10, 3A2, 3F6, 3E8, 3E10, 3A9, 361, 3G5, 3B2, 368, 3G8, 3F7, 3E9, 3G12, 3C3, 3E12, 4A2, 3F10, 3F4, 3611, 3D1, 3C2, 3E6 or 3H3 antibodies. More particular embodiments of the invention include antibodies or antigen binding fragments having the light chain and/or heavy chains of the 3D3, 3A4, 3C4 or 3G10 antibodies. Even more particular embodiments of the invention include antibodies or antigen binding fragments having the light chain and/or heavy chains of the 3A4 antibody (humanized and non-humanized).

[0149] The present invention therefore encompass, antibodies and antigen binding fragment which are capable of specific binding to KAAG1 and which may comprise sequences selected from the group consisting of:

[0150] a. the light chain variable region defined in SEQ ID NO.:16 (encoded by SEQ ID NO.:15) and/or the heavy chain variable region defined in SEQ ID NO.:18 (encoded by SEQ ID NO.:17),

[0151] b. the light chain variable region defined in SEQ ID NO.:20 (encoded by SEQ ID NO.:19) and/or the heavy chain variable region defined in SEQ ID NO.:22 (encoded by SEQ ID NO.:21);

[0152] c. the light chain variable region defined in SEQ ID NO.:24 (encoded by SEQ ID NO.:23) and/or the heavy chain variable region defined in SEQ ID NO.:26 (encoded by SEQ ID NO.:25);

[0153] d. the light chain variable region defined in SEQ ID NO.:48 and/or the heavy chain variable region defined in SEQ ID NO.:46,

[0154] e. the light chain variable region defined in SEQ ID NO.:103 and/or the heavy chain variable region defined in SEQ ID NO.:126,

[0155] f. the light chain variable region defined in SEQ ID NO.:104 and/or the heavy chain variable region defined in SEQ ID NO.:127,

[0156] g. the light chain variable region defined in SEQ ID NO.:105 and/or the heavy chain variable region defined in SEQ ID NO.:128,

[0157] h. the light chain variable region defined in SEQ ID NO.:106 and/or the heavy chain variable region defined in SEQ ID NO.:145,

[0158] i. the light chain variable region defined in SEQ ID NO.:107 and/or the heavy chain variable region defined in SEQ ID NO.:129,

[0159] j. the light chain variable region defined in SEQ ID NO.:108 and/or the heavy chain variable region defined in SEQ ID NO.:130,

[0160] k. the light chain variable region defined in SEQ ID NO.:109 and/or the heavy chain variable region defined in SEQ ID NO.:141,

[0161] l. the light chain variable region defined in SEQ ID NO.:110 and/or the heavy chain variable region defined in SEQ ID NO.:131,

[0162] m. the light chain variable region defined in SEQ ID NO.:111 and/or the heavy chain variable region defined in SEQ ID NO.:134,

[0163] n. the light chain variable region defined in SEQ ID NO.:112 and/or the heavy chain variable region defined in SEQ ID NO.:135,

[0164] o. the light chain variable region defined in SEQ ID NO.:113 and/or the heavy chain variable region defined in SEQ ID NO.:140,

[0165] p. the light chain variable region defined in SEQ ID NO.:114 and/or the heavy chain variable region defined in SEQ ID NO.:133,

[0166] q. the light chain variable region defined in SEQ ID NO.:115 and/or the heavy chain variable region defined in SEQ ID NO.:140,

[0167] r. the light chain variable region defined in SEQ ID NO.:116 and/or the heavy chain variable region defined in SEQ ID NO.:137,

[0168] s. the light chain variable region defined in SEQ ID NO.:117 and/or the heavy chain variable region defined in SEQ ID NO.:144,

[0169] t. the light chain variable region defined in SEQ ID NO.:118 and/or the heavy chain variable region defined in SEQ ID NO.:139,

[0170] u. the light chain variable region defined in SEQ ID NO.:119 and/or the heavy chain variable region defined in SEQ ID NO.:132,

[0171] v. the light chain variable region defined in SEQ ID NO.:120 and/or the heavy chain variable region defined in SEQ ID NO.:142,

[0172] w. the light chain variable region defined in SEQ ID NO.:121 and/or the heavy chain variable region defined in SEQ ID NO.:138,

[0173] x. the light chain variable region defined in SEQ ID NO.:122 and/or the heavy chain variable region defined in SEQ ID NO.:146,

[0174] y. the light chain variable region defined in SEQ ID NO.:123 and/or the heavy chain variable region defined in SEQ ID NO.:147;

[0175] z. the light chain variable region defined in SEQ ID NO.:124 and/or the heavy chain variable region defined in SEQ ID NO.:144;

[0176] aa. the light chain variable region defined in SEQ ID NO.:189 and/or the heavy chain variable region defined in SEQ ID NO.:194,

[0177] bb. the light chain variable region defined in SEQ ID NO.:189 and/or the heavy chain variable region defined in SEQ ID NO.:195,

[0178] cc. the light chain variable region defined in SEQ ID NO.:190 and/or the heavy chain variable region defined in SEQ ID NO.:194,

[0179] dd. the light chain variable region defined in SEQ ID NO.:190 and/or the heavy chain variable region defined in SEQ ID NO.:195,

[0180] ee. the light chain variable region defined in SEQ ID NO.:190 and/or the heavy chain variable region defined in SEQ ID NO.:196, or

[0181] ff. the light chain variable region defined in SEQ ID NO.:190 and/or the heavy chain variable region defined in SEQ ID NO.:197.

[0182] The framework region of the heavy and/or light chains described herein may be derived from one or more of the framework regions illustrated in the antibodies described herein. The antibody or antigen binding fragments may thus comprise one or more of the CDRs described herein (e.g., selected from the specific CDRs or consensus CDRs of SEQ ID NO.:72 to 88 or CDR variants of SEQ ID NO.:89-102) and framework regions originating from those described herein. In SEQ ID Nos. 103-154, the expected CDRs are shown in bold, while the framework regions are not.

[0183] Table 1 refers to the complete sequences of light and heavy chain of some of the anti-KAAG1 antibodies which were selected for biological testing.

TABLE 1

Antibody designation	Chain type	Nucleotide sequence (SEQ ID NO.:)	Amino acid sequence (SEQ ID NO.:)
3D3	Light (L)	3	4
3D3	Heavy (H)	5	6
3G10	Light	7	8
3G10	Heavy	9	10
3C4	Light	11	12
3C4	Heavy	13	14
Humanized 3D3	Light		166
Humanized 3D3	Heavy		167
Humanized 3C4	Light		170
Humanized 3C4	Heavy		171
Humanized 3A4	Light (Lh1)		199
Humanized 3A4	Light (Lh2)		200
Humanized 3A4	Heavy (Hh1)		202
Humanized 3A4	Heavy (Hh2)		203
Humanized 3A4	Heavy (Hh3)		204
Humanized 3A4	Heavy (Hh4)		205

[0184] Epitope mapping studies revealed that the 3D3 antibody interacts with a KAAG1 epitope spanned by amino acids 36-60, inclusively. The 3G10 and 3A4 antibodies interact with a KAAG1 epitope spanned by amino acids 61-84, inclusively and the 3C4 antibody interacts with a KAAG1 epitope spanned by amino acids 1-35. Although, the 3G10 and 3A4 binds a similar region, the 3G10 antibody does not bind to KAAG1 as efficiently as the 3A4 antibody.

[0185] It is to be understood herein, that the light chain variable region of the specific combination provided above may be changed for any other light chain variable region. Similarly, the heavy chain variable region of the specific combination provided above may be changed for any other heavy chain variable region.

[0186] Sequences of light and heavy chain variable regions of selected antibodies that bind to KAAG1 are disclosed in Table 2.

TABLE 2

Ab. designation	Variable region type	Nucleotide (SEQ ID NO.:)	Amino acid (SEQ ID NO.:)
3D3	Light (VL)	15	16
3D3	Heavy (VH)	17	18

TABLE 2-continued

Ab. designation	Variable region type	Nucleotide (SEQ ID NO.:)	Amino acid (SEQ ID NO.:)
3G10	Light	19	20
3G10	Heavy	21	22
3C4	Light	23	24
3C4	Heavy	25	26
3A2	Light		103
3A2	Heavy		126
3E10	Light		106
3E10	Heavy		145
3G12	Light		121
3G12	Heavy		138
3A4	Light	47	48
3A4	Heavy	45	46
Humanized 3D3	Light		168
Humanized 3D3	Heavy		169
Humanized 3C4	Light		172
Humanized 3C4	Heavy		173
Humanized 3A4	Light (Lvh1)		189
Humanized 3A4	Light (Lvh2)		190
Humanized 3A4	Heavy (Hvh1)		194
Humanized 3A4	Heavy (Hvh2)		195
Humanized 3A4	Heavy (Hvh3)		197
Humanized 3A4	Heavy (Hvh4)		198

[0187] SEQ ID NOs. 103-154 correspond to the light chain and heavy chain variable regions of other antibodies which were shown to bind KAAG1.

[0188] CDR sequence of the light and heavy chain variable regions of selected antibodies that bind to KAAG1 are disclosed in Table 3.

TABLE 3

Ab. desig-nation	Chain type	CDR	SEQ ID NO.:	a.a. sequence
3D3	Light (L)	CDR L1	27	KSSQSLLNSNFQKNFLA
3D3	Light	CDR L2	28	FASTRES
3D3	Light	CDR L3	29	QQHYSTPLT
3D3	Heavy (H)	CDR H1	30	GYIFTDYEIH
3D3	Heavy	CDR H2	31	VIDPETGNTA
3D3	Heavy	CDR H3	32	MGYSDY
3G10	Light	CDR L1	33	RSSQSLLHSNGNTYLE
3G10	Light	CDR L2	34	KVSNRFS
3G10	Light	CDR L3	35	FQGSHVPLT
3G10	Heavy	CDR H1	36	GYTFTDNYMN
3G10	Heavy	CDR H2	37	DINPYYGTTT
3G10	Heavy	CDR H3	38	ARDDWFDY
3C4	Light	CDR L1	39	KASQDIHNFLN
3C4	Light	CDR L2	40	RANRLVD
3C4	Light	CDR L3	41	LQYDEIPLT
3C4	Heavy	CDR H1	42	GFSITSGYGWH
3C4	Heavy	CDR H2	43	YINYDGHND
3C4	Heavy	CDR H3	44	ASSYDGLFAY

TABLE 3-continued

Ab. desig-nation	Chain type	CDR	SEQ ID NO.:	a.a. sequence
3A2	Light	CDR L1	148	KSSQSLLHSDGKTYLN
3A2	Light	CDR L2	149	LVSKLDS
3A2	Light	CDR L3	150	WQGTHFPRT
3A2	Heavy	CDR H1	151	GYTFTD YNMH
3A2	Heavy	CDR H2	152	YINPYNDVTE
3A2	Heavy	CDR H3	153	AWFGL RQ
3E10	Light	CDR L1	154	RSSKSLLHSNGN TYLY
3E10	Light	CDR L2	155	RMSNLAS
3E10	Light	CDR L3	156	MQHLEYPYT
3E10	Heavy	CDR H1	157	GDTFTD YYMN
3E10	Heavy	CDR H2	158	DINPNYGGIT
3E10	Heavy	CDR H3	159	QAYYRNS DY
3G12	Light	CDR L1	160	KASQDVGTAVA
3G12	Light	CDR L2	161	VVTSTRHT
3G12	Light	CDR L3	162	QQHYSIPLT
3G12	Heavy	CDR H1	163	GYIFTDYEIH
3G12	Heavy	CDR H2	164	VIDPETGNTA
3G12	Heavy	CDR H3	165	MGYSDY
3A4	Light	CDR L1	52	RSSQSLLHSNGNTYLE
3A4	Light	CDR L2	53	TVSNRFS
3A4	Light	CDR L3	54	FQGSHVPLT
3A4	Heavy	CDR H1	49	GYTFTDDYMS
3A4	Heavy	CDR H2	50 or 212	DINPYNGDTNYNQKFKG or DINPYNGDTN
3A4	Heavy	CDR H3	51	DPGAMDY

Variant Antibody and Antigen Binding Fragments

[0189] The present invention also encompasses variants of the antibodies or antigen binding fragments described herein. Variant antibodies or antigen binding fragments included are those having a variation in the amino acid sequence. For example, variant antibodies or antigen binding fragments included are those having at least one variant CDR (two, three, four, five or six variant CDRs, etc. or even twelve variant CDRs), a variant light chain variable region, a variant heavy chain variable region, a variant light chain and/or a variant heavy chain. Variant antibodies or antigen binding fragments included in the present invention are those having, for example, similar or improved binding affinity in comparison with the original antibody or antigen binding fragment.

[0190] As used herein the term "variant" applies to any of the sequence described herein and includes for example, a

variant CDR (either CDRL1, CDRL2, CDRL3, CDRH1, CDRH2 and/or CDRH3), a variant light chain variable region, a variant heavy chain variable region, a variant light chain, a variant heavy chain, a variant antibody, a variant antigen binding fragment and a KAAG1 variant.

[0191] The sites of greatest interest for substitutional mutagenesis include the hypervariable regions (CDRs), but modifications in the framework region or even in the constant region are also contemplated. Exemplary embodiments of CDR variants are provided in SEQ ID NOs.: 72-102.

[0192] Conservative substitutions may be made by exchanging an amino acid (of a CDR, variable chain, antibody, etc.) from one of the groups listed below (group 1 to 6) for another amino acid of the same group.

[0193] Other exemplary embodiments of conservative substitutions are shown in Table 1A under the heading of "preferred substitutions". If such substitutions result in a undesired property, then more substantial changes, denominated "exemplary substitutions" in Table 1A, or as further described below in reference to amino acid classes, may be introduced and the products screened.

[0194] It is known in the art that variants may be generated by substitutional mutagenesis and retain the biological activity of the polypeptides of the present invention. These variants have at least one amino acid residue in the amino acid sequence removed and a different residue inserted in its place. For example, one site of interest for substitutional mutagenesis may include a site in which particular residues obtained from various species are identical. Examples of substitutions identified as "conservative substitutions" are shown in Table 1A. If such substitutions result in a change not desired, then other type of substitutions, denominated "exemplary substitutions" in Table 1A, or as further described herein in reference to amino acid classes, are introduced and the products screened.

[0195] Substantial modifications in function or immunological identity are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation. (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side chain properties:

(group 1) hydrophobic: norleucine, methionine (Met), Alanine (Ala), Valine (Val), Leucine (Leu), Isoleucine (Ile)

(group 2) neutral hydrophilic: Cysteine (Cys), Serine (Ser), Threonine (Thr)

(group 3) acidic: Aspartic acid (Asp), Glutamic acid (Glu)

(group 4) basic: Asparagine (Asn), Glutamine (Gln), Histidine (His), Lysine (Lys), Arginine (Arg)

(group 5) residues that influence chain orientation: Glycine (Gly), Proline (Pro); and

(group 6) aromatic: Tryptophan (Trp), Tyrosine (Tyr), Phenylalanine (Phe)

[0196] Non-conservative substitutions will entail exchanging a member of one of these classes for another.

TABLE 1A

Amino acid substitution

Original residue	Exemplary substitution	Conservative substitution
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln, His, Lys, Arg, Asp	Gln
Asp (D)	Glu, Asn	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp, Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn, Gln, Lys, Arg,	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Leu, Met, Phe, Ala, Norleucine	Leu

[0197] Variation in the amino acid sequence of the variant antibody or antigen binding fragment may include an amino acid addition, deletion, insertion, substitution etc., one or more modification in the backbone or side-chain of one or more amino acid, or an addition of a group or another molecule to one or more amino acids (side-chains or backbone).

[0198] Variant antibody or antigen binding fragment may have substantial sequence similarity and/or sequence identity in its amino acid sequence in comparison with that the original antibody or antigen binding fragment amino acid sequence. The degree of similarity between two sequences is based upon the percentage of identities (identical amino acids) and of conservative substitution.

[0199] Generally, the degree of similarity and identity between variable chains has been determined herein using the Blast2 sequence program (Tatiana A. Tatusova, Thomas L. Madden (1999), "Blast 2 sequences—a new tool for comparing protein and nucleotide sequences", FEMS Microbiol Lett. 174:247-250) using default settings, i.e., blastp program, BLOSUM62 matrix (open gap 11 and extension gap penalty 1; gapx dropoff 50, expect 10.0, word size 3) and activated filters.

[0200] Percent identity will therefore be indicative of amino acids which are identical in comparison with the original peptide and which may occupy the same or similar position. Percent similarity will be indicative of amino acids that are identical and those that are replaced with conservative amino acid substitution in comparison with the original peptide at the same or similar position.

[0201] Variants of the present invention therefore comprise those which may have at least 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with an original sequence or a portion of an original sequence.

[0202] Exemplary embodiments of variants are those having at least 81% sequence identity to a sequence described

herein and 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

[0203] Other exemplary embodiments of variants are those having at least 82% sequence identity to a sequence described herein and 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

[0204] Further exemplary embodiments of variants are those having at least 85% sequence identity to a sequence described herein and 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

[0205] Other exemplary embodiments of variants are those having at least 90% sequence identity to a sequence described herein and 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

[0206] Additional exemplary embodiments of variants are those having at least 95% sequence identity to a sequence described herein and 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

[0207] Yet additional exemplary embodiments of variants are those having at least 97% sequence identity to a sequence described herein and 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

[0208] For a purpose of concision the applicant provides herein a Table 1B illustrating exemplary embodiments of individual variants encompassed by the present invention and comprising the specified % sequence identity and % sequence similarity. Each "X" is to be construed as defining a given variant.

[0209] The present invention encompasses CDRs, light chain variable regions, heavy chain variable regions, light chains, heavy chains, antibodies and/or antigen binding fragments which comprise at least 70% identity or at least 80% identity with the sequence described herein.

[0210] The present invention therefore encompass, antibodies and antigen binding fragment which are capable of specific binding to KAAG1 and which may comprise sequences selected from the group consisting of:

[0211] a. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:16 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:18,

[0212] b. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:20 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:22;

[0213] c. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:24 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:26;

[0214] d. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:48 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:46;

[0215] e. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:103 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:126,

[0216] f. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:104 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:127,

[0217] g. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:105 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:128,

[0218] h. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:106 and a

TABLE 1B

		Percent (%) sequence identity																				
		80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
Percent (%)	80	X																				
	81	X	X																			
	82	X	X	X																		
	83	X	X	X	X																	
	84	X	X	X	X	X																
	85	X	X	X	X	X	X															
	86	X	X	X	X	X	X	X														
	87	X	X	X	X	X	X	X	X													
	88	X	X	X	X	X	X	X	X	X												
	89	X	X	X	X	X	X	X	X	X	X											
	90	X	X	X	X	X	X	X	X	X	X	X										
	91	X	X	X	X	X	X	X	X	X	X	X	X									
	92	X	X	X	X	X	X	X	X	X	X	X	X	X								
	93	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
	94	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
	95	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
	96	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
	97	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	98	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	99	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	100	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:145,

[0219] i. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:107 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:128,

[0220] j. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:108 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:130,

[0221] k. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:109 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:141,

[0222] l. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:110 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:131,

[0223] m. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:111 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:134,

[0224] n. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:112 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:135,

[0225] o. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:113 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:136,

[0226] p. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:114 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:133,

[0227] q. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:115 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:140,

[0228] r. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:116 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:137,

[0229] s. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:117 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:144,

[0230] t. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:118 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:139,

[0231] u. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:119 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:132,

[0232] v. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:120 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:142,

[0233] w. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:121 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:138,

[0234] x. the light chain variable region having at least 70% sequence identity with SEQ ID NO.:122 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:146,

[0235] y. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:123 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:147, or;

[0236] z. a light chain variable region having at least 70% sequence identity with SEQ ID NO.:124 and a heavy chain variable region having at least 70% sequence identity with SEQ ID NO.:143.

[0237] In accordance with the present invention, the variant antibodies or antigen binding fragments may comprise CDRs that are identical to those of the corresponding light chain and/or heavy chain variable region. In other instance the variant antibodies or antigen binding fragments may comprise variant CDR(s).

[0238] Therefore, exemplary embodiments of a variant antibody or antigen binding fragment of the present invention are those comprising a light chain variable region comprising a sequence which is at least 70%, 75%, 80% identical to SEQ ID NOs.:16, 20, 24, 103, 106 or 121. The CDRs of such variant may be identical to those of the corresponding non-variant (wild type sequence) antibody or antigen binding fragment or may vary by 1-3 amino acids.

[0239] Another exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:16 and having for example from 1 to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:16. A SEQ ID NO.:16 variant is provided in SEQ ID NO.:168.

[0240] An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:20 and having for example from 1 to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:20.

[0241] An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:24 and having for example from 1 to 21 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:24. A SEQ ID NO.:24 variant is provided in SEQ ID NO.:172.

[0242] An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:103 and having for example from 1 to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:103.

[0243] An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:106 and having for example from 1 to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:106.

[0244] An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are

100% identical to the CDR amino acid sequence of SEQ ID NO.:121 and having for example from 1 to 21 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:121.

[0245] In some instances, the variant antibody light chain variable region may comprise amino acid deletions or additions (in combination or not with amino acid substitutions). Often 1, 2, 3, 4 or 5 amino acid deletions or additions may be tolerated.

[0246] Other exemplary embodiments of a variant antibody or antigen binding fragment of the present invention are those comprising a heavy chain variable region comprising a sequence which is at least 70%, 75%, 80% identical to 18, 22, 26, 126, 138 or 145. The CDRs of such variant may be identical to those of the corresponding non-variant (wild type sequence) antibody or antigen binding fragment or may vary by 1-3 amino acids.

[0247] An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:18 and having, for example, from 1 to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:18. A SEQ ID NO.:18 variant is provided in SEQ ID NO.:169.

[0248] An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:22 and having, for example, from 1 to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:22.

[0249] An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:26 and having, for example, from 1 to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:26. A SEQ ID NO.:26 variant is provided in SEQ ID NO.:173.

[0250] An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:126 and having, for example, from 1 to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:126.

[0251] An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:145 and having, for example, from 1 to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:145.

[0252] An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:138 and having, for example, from 1 to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:138.

[0253] In some instances, the variant antibody heavy chain variable region may comprise amino acid deletions or additions (in combination or not with amino acid substitutions). Often 1, 2, 3, 4 or 5 amino acid deletions or additions may be tolerated.

Variant CDRS

[0254] Also encompassed by the present invention are polypeptides, antibodies or antigen binding fragments comprising variable chains having at least one conservative amino acid substitution in at least one of the CDRs described herein (in comparison with the original CDR).

[0255] The present invention also encompasses are polypeptides, antibodies or antigen binding fragments comprising variable chains having at least one conservative amino acid substitution in at least two of the CDRs (in comparison with the original CDRs).

[0256] The present invention also encompasses are polypeptides, antibodies or antigen binding fragments comprising variable chains having at least one conservative amino acid substitution in the 3 CDRs (in comparison with the original CDRs).

[0257] The present invention also encompasses are polypeptides, antibodies or antigen binding fragments comprising variable chains having at least two conservative amino acid substitutions in at least one of the CDRs (in comparison with the original CDRs).

[0258] The present invention also encompasses are polypeptides, antibodies or antigen binding fragments comprising variable chains having at least two conservative amino acid substitutions in at least two of the CDRs (in comparison with the original CDRs).

[0259] The present invention also encompasses are polypeptides, antibodies or antigen binding fragments comprising variable chains having at least two conservative amino acid substitutions in the 3 CDRs (in comparison with the original CDRs).

[0260] Comparison of the amino acid sequences of the light chain variable regions or the heavy chain variable regions of antibodies showing the greatest characteristics allowed us to derive consensus sequences within the CDRs and within the variable regions. The consensus for CDRs are provided in SEQ ID Nos: 72 to 88.

[0261] The present invention therefore provides in an exemplary embodiment, an isolated antibody or antigen binding fragment comprising a light chain variable region having;

[0262] a. a CDRL1 sequence selected from the group consisting of SEQ ID NO.:72 and SEQ ID NO.:73;

[0263] b. a CDRL2 sequence selected from the group consisting of SEQ ID NO.:74, SEQ ID NO.: 75 and SEQ ID NO.:76, or;

[0264] c. a CDRL3 sequence selected from the group consisting of SEQ ID NO.:77, SEQ ID NO.:78 and SEQ ID NO.:79.

[0265] The present invention therefore provides in an exemplary embodiment, an isolated antibody or antigen binding fragment comprising a heavy chain variable region having;

[0266] a. a CDRH1 sequence comprising SEQ ID NO.: 80;

[0267] b. a CDRH2 sequence selected from the group consisting of SEQ ID NO.:81, SEQ ID NO.:82, SEQ ID NO.:83, SEQ ID NO.:84 and SEQ ID NO.:85, or;

[0268] c. a CDRH3 sequence selected from the group consisting of SEQ ID NO.:86, SEQ ID NO.:87 and SEQ ID NO.:88.

[0269] In accordance with the present invention, the antibody may comprise a CDRL1 sequence comprising or consisting of formula:

(SEQ ID NO.: 72)
$X_{1a}SSX2_aSLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$

[0270] wherein X_{1a} may be a basic amino acid;

[0271] wherein X_{2a} may be a basic amino acid;

[0272] wherein X_{3a} may be H, Y or N;

[0273] wherein X_{4a} may be S, T, N or R;

[0274] wherein X_{5a} may be absent, S or N;

[0275] wherein X_{6a} may be D, F or N;

[0276] wherein X_{7a} may be G or Q;

[0277] wherein X_{8a} may be K, L or N;

[0278] wherein X_{9a} may be T or N;

[0279] wherein X_{10a} may be an aromatic amino acid, and;

[0280] wherein X_{11a} may be A, N, E or Y.

[0281] In an exemplary embodiment of the invention X_{1a} may be K or R.

[0282] In a further embodiment of the invention X_{2a} may be Q or K.

[0283] In yet a further embodiment of the invention X_3, may be N or H.

[0284] In an additional embodiment of the invention X_{10a} may be Y or F.

[0285] More specific embodiments of the invention include CDRL1 of SEQ ID NO.:72 where: X_{1a} is K; X_{2a} is Q; X_{3a} is N; X_{3a} is H; X_{4a} is S; X_{4a} is T; X_{5a} is S; X_{5a} is absent; X_{6a} is N; X_{7a} is Q; X_{7a} is G; X_{8a} is K; X_{9a} is N; X_{9a} is T; X_{10a} is Y; or X_{11a} is A.

[0286] In accordance with the present invention, the antibody may comprise a CDRL1 sequence comprising or consisting of formula:

(SEQ ID NO.: 73)
$KASQDX_{1b}X_{2b}X_{3b}X_{4b}X5_bX_{6b}$

[0287] wherein X_{1b} may be an hydrophobic amino acid;

[0288] wherein X_{2b} may be G or H;

[0289] wherein X_{3b} may be T, N or R;

[0290] wherein X_{4b} may be F, Y or A;

[0291] wherein X_{5b} may be an hydrophobic amino acid, and;

[0292] wherein X_{6b} may be N or A.

[0293] In an exemplary embodiment of the invention X_{1b} may be V or I.

[0294] In another exemplary embodiment of the invention X_{5b} may be V or L.

[0295] More specific embodiments of the invention include CDRL1 of SEQ ID NO.:73 where X_{1b} is I; X_{2b} is H; X_{3b} is T; X_{3b} is N; X_{4b} is Y; X_{4b} iS F; X_{5b} is L or X_{6b} is N.

[0296] Other exemplary embodiments of CDRL1 are provided in SEQ ID NOs. 89 and 90.

[0297] In accordance with the present invention, the antibody may comprise a CDRL2 sequence comprising or consisting of formula:

(SEQ ID NO.: 74)
$FX_{1c}STX_{2c}X_{3c}S$

[0298] Wherein X_{1c} is A or G;

[0299] Wherein X_{2c} is R or T, and;

[0300] Wherein X_{3c} is E, K or A.

[0301] In an exemplary embodiment of the invention X_{1c} may be A and X_{2c} may be T.

[0302] In another exemplary embodiment of the invention X_{1c} may be A and X_{2c} may be R.

[0303] Other specific embodiments of the invention include CDRL2 of SEQ ID NO.:74 where X_{1c} is A; X_{2c} is R or X_{3c} is E.

[0304] In accordance with the present invention, the antibody may comprise a CDRL2 sequence comprising or consisting of formula:

(SEQ ID NO.: 75)
$X_{1d}VSX_{2d}X_{3d}X_{4d}S$

[0305] Wherein X_{1d} may be L or K;

[0306] Wherein X_{2d} may be a basic amino acid;

[0307] Wherein X_{3d} may be L or R and;

[0308] Wherein X_{4d} may be D or F.

[0309] In an exemplary embodiment of the invention X_{2d} may be K or N.

[0310] Other specific embodiments of the invention include CDRL2 of SEQ ID NO.:75 where X_{1d} is L; X_{2d} is K; X_{3d} is L or X_{4d} is D.

[0311] In accordance with the present invention, the antibody may comprise a CDRL2 sequence comprising or consisting of formula:

(SEQ ID NO.: 76)
$X_{1e}ANRLVX_{2e}$

[0312] Wherein X_{1e} may be a basic amino acid, and;

[0313] Wherein X_{2e} may be D or A.

[0314] In an exemplary embodiment of the invention X_{1e} may be R or H.

[0315] Other specific embodiments of the invention include CDRL2 of SEQ ID NO.:76 where X_{1e} is R or X_{2e} is D.

[0316] Other exemplary embodiments of CDRL2 are provided in SEQ ID NOs.: 91-93.

[0317] In accordance with the present invention, the antibody may comprise a CDRL3 sequence comprising or consisting of formula:

(SEQ ID NO.: 77)
$X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$

[0318] Wherein X_{1f} may be Q or L;

[0319] Wherein X_{2f} may be an aromatic amino acid;

[0320] Wherein X_{3f} may be D, F or Y;

[0321] Wherein X_{4f} may be E, A, N or S, and;

[0322] Wherein X_{5f} may be I, F or T.

[0323] In an exemplary embodiment of the invention X_{2f} may be Y or H.

[0324] In another exemplary embodiment of the invention X_{3f} may be Y or D.

[0325] In yet another exemplary embodiment of the invention X_{5f} may be I or T.

[0326] Other specific embodiments of the invention include CDRL3 of SEQ ID NO.:77 where X_{1f} is Q; X_{2f} iS H; X_{3f} is D; X_{3f} is Y; X_{4f} is S; X_{4f} is E; X_{4f} is A; X_{5f} is T, or X_{5f} is I.

[0327] In accordance with the present invention, the antibody may comprise a CDRL3 sequence comprising or consisting of formula:

(SEQ ID NO.: 78)

$QQHX_{1g}X_{2g}X_{3g}PLT$

[0328] Wherein X_{1g} may be an aromatic amino acid;

[0329] Wherein X_{2g} may be N or S, and;

[0330] Wherein X_{3g} may be I or T.

[0331] In an exemplary embodiment of the invention X_{1g} may be F or Y

[0332] Other specific embodiments of the invention include CDRL3 of SEQ ID NO.:78 where X_{2g} is S or X_{3g} is T.

[0333] In accordance with the present invention, the antibody may comprise a CDRL3 sequence comprising or consisting of formula:

(SEQ ID NO.: 79)

$X_{1h}QGX_{2h}HX_{3h}PX_{4h}T$

[0334] Wherein X_{1h} may be an aromatic amino acid;

[0335] Wherein X_{2h} may be a neutral hydrophilic amino acid;

[0336] Wherein X_{3h} may be F or V, and;

[0337] Wherein X_{4h} may be R or L.

[0338] In an exemplary embodiment of the invention X_{1h} may be W or F.

[0339] In another exemplary embodiment of the invention X_{2h} may be S or T.

[0340] Other specific embodiments of the invention include CDRL3 of SEQ ID NO.:79 where X_{1h} is W; X_{2h} is T; X_{3h} is F, or X_{4h} is R.

[0341] Other exemplary embodiments of CDRL3 are provided in SEQ ID NOs. 94 and 95.

[0342] In accordance with the present invention, the antibody may comprise a CDRH1 sequence comprising or consisting of formula:

(SEQ ID NO.: 80)

$GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$

[0343] Wherein X_{1i} may be T, I or K;

[0344] Wherein X_{2i} may be a neutral hydrophilic amino acid;

[0345] Wherein X_{3i} may be an acidic amino acid;

[0346] Wherein X_{4i} may be E, N or D, and;

[0347] Wherein X_{5i} may be hydrophobic amino acid.

[0348] In an exemplary embodiment of the invention X_{2i} may be T or S.

[0349] In another exemplary embodiment of the invention X_{3i} may be D or E.

[0350] In yet another exemplary embodiment of the invention X_{4i} may be N or E.

[0351] In a further exemplary embodiment of the invention X_{5i} may be M, I or v.

[0352] Other specific embodiments of the invention include CDRH1 of SEQ ID NO.:80 where X_{2i} is T; X_{3i} is D; X_{4i} is E; X_{5i} is I or X_{5i} is M.

[0353] Other exemplary embodiments of CDRH1 are provided in SEQ ID NOs.: 96 and 97.

[0354] In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

(SEQ ID NO.: 81)

$X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$

[0355] Wherein X_{1j} may be V or G

[0356] Wherein X_{2j} may be a hydrophobic amino acid;

[0357] Wherein X_{3j} may be A, G or E;

[0358] Wherein X_{4j} may be R, G, D, A, S, N or V, and;

[0359] Wherein X_{5j} may be a hydrophobic amino acid.

[0360] In an exemplary embodiment of the invention X_{2j} may be I or L.

[0361] In another exemplary embodiment of the invention X_{5j} may be A or V.

[0362] Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:81 where X_{1j} is V; X_{2j} is I; X_{3j} is E; X_{4j} is D or X_{5j} is A.

[0363] In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

(SEQ ID NO.: 82)

$VX_{1k}DPX_{2k}TGX_{3k}TA$

[0364] Wherein X_{1k} may be an hydrophobic amino acid;

[0365] Wherein X_{2k} may be A, E or G;

[0366] Wherein X_{3k} may be R, G, A, S, N V or D.

[0367] In an exemplary embodiment of the invention X_{1k} may be L or I.

[0368] Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:82 where X_{1k} is I; X_{2k} is E, or X_{3k} is D.

[0369] In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

(SEQ ID NO.: 83)

$YIX_{1l}X_{2l}X_{3l}GX_{4l}X_{5l}X_{6l}$

[0370] Wherein $X1_l$ may be S or N;

[0371] Wherein X_{2l} may be an aromatic amino acid

[0372] Wherein X_{3l} may be D, E or N;

[0373] Wherein $X4_l$ may be a D or H;

[0374] Wherein X_{5l} may be Y, S or N;

[0375] Wherein X_{6l} may be D, E or N.

[0376] In an exemplary embodiment of the invention X_{3l} may be D or N.

[0377] In another exemplary embodiment of the invention X_{6l} may be D or N.

[0378] Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:83 where X_{2l} is F or Y, X_{3l} is N, X_{4l} is D or X_{6l} is N.

[0379] In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

$X_{1m}INPYNX_{2m}VTE$ (SEQ ID NO.:84)

[0380] wherein X_{1m} may be N or Y, and;

[0381] wherein X_{2m} may be E, D or N.

[0382] In an exemplary embodiment of the invention X_{2m} may be D or N.

[0383] Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:84 where X_{1m} is N or X_{2m} is D.

[0384] In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

(SEQ ID NO.: 85)

$DINPX_{1n}YGX_{2n}X_{3n}T$

[0385] Wherein X_{1n} may be N or Y,
[0386] Wherein X_{2n} may be G or T and;
[0387] wherein X_{3n} may be I or T.
[0388] Other exemplary embodiments of CDRH2 are provided in SEQ ID NOs. 98 and 99.
[0389] In accordance with the present invention, the antibody may comprise a CDRH3 sequence comprising or consisting of formula:

(SEQ ID NO.: 86)

$MX_{1o}X_{2o}X_{3o}DY$

[0390] Wherein X_{1o} may be G or S;
[0391] Wherein X_{2o} may be Y or H, and;
[0392] wherein X_{3o} may be A or S.
[0393] Other specific embodiments of the invention include CDRH3 of SEQ ID NO.:86 where X_{1o} is G; X_{2o} is Y or X_{3o} is S.
[0394] In accordance with the present invention, the antibody may comprise a CDRH3 sequence comprising or consisting of formula:

(SEQ ID NO.: 87)

$IX_{1p}YAX_{2p}DY$

[0395] Wherein X_{1p} may be G or S and;
[0396] Wherein X_{2p} may be absent or M.
[0397] Other specific embodiments of the invention include CDRH3 of SEQ ID NO.:87 where X_{1p} is S or X_{2p} is M.
[0398] In accordance with the present invention, the antibody may comprise a CDRH3 sequence comprising or consisting of formula:

(SEQ ID NO.: 88)

$AX_{1q}X_{2q}GLRX_{3q}$

[0399] Wherein X_{1q} may be R or W;
[0400] Wherein X_{2q} may be an aromatic amino acid and;
[0401] wherein X_{3q} may be a basic amino acid.
[0402] In an exemplary embodiment of the invention X_{2q} may be W or F.
[0403] In another exemplary embodiment of the invention X_{3q} may be Q or N.
[0404] Other specific embodiments of the invention include CDRH3 of SEQ ID NO.:88 where X_{1q} is R; X_{2q} is W or X_{3q} is N.
[0405] Variant antibodies or antigen binding fragments encompassed by the present invention include those that may comprise an insertion, a deletion or an amino acid substitution (conservative or non-conservative). These variants may have at least one amino acid residue in its amino acid sequence removed and a different residue inserted in its place.

Humanized Antibodies

[0406] Exemplary embodiments of variant antibodies and antigen binding fragments of the present invention are a group of antibodies and antigen binding fragments capable of binding to KAAG1 and characterized herein as being humanized.

[0407] The humanized antibodies and antigen binding fragments of the present invention includes more particularly, humanized 3D3, 3A4 or 3C4 antibodies and antigen binding fragments. The humanized 3D3, 3A4 or 3C4 antibodies have at least one amino acid difference in a framework region in comparison with the monoclonal 3D3, 3A4 or 3C4 antibody.

[0408] Humanized 3A4 antibodies having CDRs identical to those of the monoclonal 3A4 antibody (VL: SEQ ID NO.:48, VH: SEQ ID NO.:46) were generated and tested. These humanized antibodies comprise up to 11 amino acid substitutions (from one to eleven) in the variable light chain framework region and up to 23 amino acid substitutions (from one to twenty-three) in the variable heavy chain framework region in comparison with the monoclonal 3A4 antibody. The applicant has shown that these humanized 3A4 antibodies bind to KAAG1 as efficiently as the monoclonal 3A4 antibody.

[0409] Exemplary embodiments of variant antibody or antigen binding fragments include those having a light chain variable region as set forth in SEQ ID NO.:186:

SEQ ID NO.: 186

DXVMTQTPLSLXVXXGXXASISCRSSQSLLHSNGNTYLEWYLQKPGQSPX

LLIHTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDXGVYYCFQGSHVP

LTFGXGTXLEXK,

wherein at least one of the amino acids identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48. The amino acid substitution may be, for example, an amino acid found at a corresponding position of a natural human antibody or a human antibody consensus. The amino acid substitution may be, for example conservative.

[0410] Another exemplary embodiment of a variant antibody or antigen binding fragment include those having a light chain variable region as set forth in SEQ ID NO.:187:

SEQ ID NO.: 187

DX_{e1}VMTQTPLSLX_{e2}V$X_{e3}X_{e4}GX_{e5}X_{e6}$ASISCRSSQSLLHSNGNTYLEWY

LQKPGQSPX_{e7}LLIHTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAED

X_{e8}GVYYCFQGSHVPLTFGX_{e9}GTX_{e10}LEX_{e11}K,

Wherein X_{e1} may be a hydrophobic amino acid;

Wherein X_{e2} may be A or P;

[0411] Wherein X_{e3} may be neutral hydrophilic amino acid;

Wherein X_{e4} may be L or P;

[0412] Wherein X_{e5} may be an acidic amino acid;

Wherein X_{e6} may be Q or P;

[0413] Wherein X_{e7} may be a basic amino acid; Wherein X_{e8} may be a hydrophobic amino acid;

Wherein X_{e9} may be A or Q;

[0414] Wherein X_{e10} may be a basic amino acid; or Wherein X_{e11} may be a hydrophobic amino acid, wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48.

[0415] An additional exemplary embodiment of a variant antibody or antigen binding fragment include those having a light chain variable region as set forth in SEQ ID NO.:188:

SEQ ID NO.: 188

DX_{e1}VMTQTPLSLX$_{e2}$VX$_{e3}$X$_{e4}$GX$_{e5}$X$_{e6}$ASISCRSSQSLLHSNGNTYLEWY

LQKPGQSPX$_{e7}$LLIHTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAED

X$_{e8}$GVYYCFQGSHVPLTFGX$_{e9}$GTX$_{e10}$LEX$_{e11}$K

Wherein X_{E1} may be V or I

Wherein X_{E2} may be A or P

Wherein X_{E3} may be S or T

Wherein X_{E4} may be L or P

Wherein X_{E5} may be D or E

Wherein X_{E6} may be Q or P

Wherein X_{E7} may be K or Q

Wherein X_{E8} may be L or V

Wherein X_{E9} may be A or Q

Wherein X_{E10} may be R or K or

Wherein X_{E11} may be L or I,

[0416] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48.

[0417] In accordance with an embodiment, the light chain variable domain variant may have a sequence as set forth in SEQ ID NO.:189 or 190:

SEQ ID NO.: 189

DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPQ

LLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVP

LTFGQGTKLEIK.

SEQ ID NO.: 190

DVVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPK

LLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVP

LTFGQGTKLEIK.

[0418] Exemplary embodiments of variant antibody or antigen binding fragments include those having a heavy chain variable region as set forth in SEQ ID NO.:191.

SEQ ID NO.: 191

QXQLVQSGXEXXKPGASVKXSCKASGYTFTDDYMSWVXQXXGXXLEWXGD

INPYNGDTNYNQKFKGXXXXTXDXSXSTAYMXLXSLXSEDXAVYYCARDP

GAMDYWGQGTXVTVSS,

wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46. The amino acid substitution may be, for example, an amino acid found at a corresponding position of a natural human antibody or a human antibody consensus. The amino acid substitution may be, for example conservative.

[0419] Another exemplary embodiment of a variant antibody or antigen binding fragment include those having a heavy chain variable region as set forth in SEQ ID NO.:192:

SEQ ID NO.: 192

QX$_{f1}$QLVQSGX$_{f2}$EX$_{f3}$X$_{bf4}$KPGASVKX$_{f5}$SCKASGYTFTDDYMSWVX$_{f6}$QX$_{f7}$

X$_{f8}$GX$_{f9}$X$_{f10}$LEWX$_{f11}$GDINPYNGDTNYNQKFKGX$_{f12}$X$_{f13}$X$_{b14}$X$_{f15}$TX$_{f16}$

DX$_{f17}$SX$_{f18}$STAYMX$_{f19}$LX$_{f20}$SLX$_{f21}$SEDX$_{f22}$AVYYCARDPGAMDYWGQGT

X$_{f23}$VTVSS,

Wherein X_{f1} may be a hydrophobic amino acid;

Wherein X_{bf2} may be P or A;

[0420] Wherein X_{f3} may be a hydrophobic amino acid;

Wherein X_{f4} may be V or K;

[0421] Wherein X_{f5} may be a hydrophobic amino acid; Wherein X_{f6} may be a basic amino acid;

Wherein X_{f7} may be S or A;

Wherein X_{f8} may be H or P;

[0422] Wherein X_{f9} may be a basic amino acid;

Wherein X_{f10} may be S or G;

[0423] Wherein X_{f11} may be a hydrophobic amino acid; Wherein X_{f12} may be a basic amino acid; Wherein X_{f13} may be a hydrophobic amino acid;

Wherein X_{f14} may be I or T;

[0424] Wherein X_{f15} may be a hydrophobic amino acid; Wherein X_{f16} may be a hydrophobic amino acid;

Wherein X_{f17} may be K or T;

[0425] Wherein X_{f18} may be a neutral hydrophilic amino acid;

Wherein X_{f19} may be Q or E;

Wherein X_{f20} may be N or S;

Wherein X_{f21} may be T or R;

[0426] Wherein X_{f22} may be a neutral hydrophilic amino acid; or

Wherein X_{f23} may be S or L,

[0427] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46.

[0428] An additional exemplary embodiment of a variant antibody or antigen binding fragment include those having a heavy chain variable region as set forth in SEQ ID NO.:193:

SEQ ID NO.: 193

$QX_{F1}QLVQSGX_{F2}EX_{F3}X_{F4}KPGASVKX_{F5}SCKASGYTFTDDYMSWVX_{F6}QX_{F7}$

$X_{F8}GX_{F9}X_{F10}LEWX_{F11}GDINPYNGDTNYNQKFKGX_{F12}X_{F13}X_{F14}X_{F15}TX_{F16}$

$DX_{F17}SX_{F18}STAYMX_{F19}LX_{F20}SLX_{F21}SEDX_{F22}AVYYCARDPGAMDYWGQG$

$TX_{F23}VTVSS$

Wherein X_{F1} may be I or V;

Wherein X_{F2} may be P or A;

Wherein X_{F3} may be M or V;

Wherein X_{F4} may be V or K;

Wherein X_{F5} may be M or V;

Wherein X_{F6} may be K or R;

Wherein X_{F7} may be S or A;

Wherein X_{F8} may be H or P;

Wherein X_{F9} may be K or Q;

Wherein X_{F10} may be S or G;

Wherein X_{F11} may be I or M;

Wherein X_{F12} may be K or R;

Wherein X_{F13} may be A or V;

Wherein X_{F14} may be I or T;

Wherein X_{F15} may be L or I;

Wherein X_{F16} may be V or A;

Wherein X_{F17} may be K or T;

Wherein X_{F18} may be S or T;

Wherein X_{F19} may be Q or E;

Wherein X_{F20} may be N or S;

Wherein X_{F21} may be T or R;

Wherein X_{F22} may be S or T; or

Wherein X_{F23} is S or L,

[0429] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46.

[0430] In accordance with an embodiment, the heavy chain variable domain variant may have a sequence as set forth in any one of SEQ ID NO. 194 to 197:

SEQ ID NO.: 194

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGD

INPYNGDTNYNQKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCARDP

GAMDYWGQGTLVTVSS.

SEQ ID NO.: 195

QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGD

INPYNGDTNYNQKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDP

GAMDYWGQGTLVTVSS.

SEQ ID NO.: 196

QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWIGD

INPYNGDTNYNQKFKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARDP

GAMDYWGQGTLVTVSS.

SEQ ID NO.: 197

QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVKQAPGQGLEWIGD

INPYNGDTNYNQKFKGKATLTVDKSTSTAYMELSSLRSEDTAVYYCARDP

GAMDYWGQGTLVTVSS.

[0431] In accordance with an embodiment of the invention, the humanized 3D3 antibody may have a light chain variable region of formula:

(SEQ ID NO.: 174)

DIVMTQSPXSLAVSXGXXXTXNC**KSSQSLLNSNFQKNFLA**WYQQKPGQXP

KLLIY**FASTRES**SXPDRFXGSGSGTDFTLTISSXQAEDXAXYXC**QQHYST**

PLTFGXGTKLEXK;

[0432] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:16. The amino acid substitution may be, for example conservative.

[0433] In accordance with a more specific embodiment, the humanized 3D3 antibody may have a light chain variable region of formula:

(SEQ ID NO.: 175)

$DIVMTQSPX_{A1}SLAVSX_{A2}GX_{A3}X_{A4}X_{A5}TX_{A6}NC$**KSSQSLLNSNFQKNFLA**WY

$QQKPGQX_{A7}PKLLIY$**FASTRES**$SX_{A8}PDRFX_{A9}GSGSGTDFTLTISSX_{A10}QA$

$EDX_{A11}AX_{A12}YX_{A13}C$**QQHYSTPLT**$FGX_{A14}GTKLEX_{A15}K;$

[0434] Wherein X_{A1} may be, for example, D or S;

[0435] Wherein X_{A2} may be, for example, a hydrophobic amino acid or more particularly L or I;

[0436] Wherein X_{A3} may be, for example, E or Q;

[0437] Wherein X_{A4} may be, for example, a basic amino acid or more particularly R or K;

[0438] Wherein X_{A5} may be, for example, a hydrophobic amino acid or more particularly A or V;

[0439] Wherein X_{A6} may be, for example, a hydrophobic amino acid or more particularly I or M;

[0440] Wherein X_{A7} may be, for example, P or S;

[0441] Wherein X_{A8} may be, for example, a hydrophobic amino acid or more particularly V or I;

[0442] Wherein X_{A9} may be, for example, S or I;

[0443] Wherein X_{A10} may be, for example, a hydrophobic amino acid or more particularly L or V;

[0444] Wherein X_{A11} may be, for example, a hydrophobic amino acid or more particularly V or L;

[0445] Wherein X_{A12} may be, for example, V or D;

[0446] Wherein X_{A13} may be, for example, an aromatic amino acid or more particularly Y or F;

[0447] Wherein X_{A14} may be, for example, Q or A and;

[0448] Wherein X_{A15} may be, for example, a hydrophobic amino acid or more particularly I or L.

[0449] In accordance with an even more specific embodiment, the humanized 3D3 antibody may have a light chain variable region of formula:

(SEQ ID NO.: 176)

DIVMTQSPX$_{a1}$SLAVSX$_{a2}$GX$_{a3}$X$_{a4}$X$_{a5}$TX$_{a6}$NC**KSSQSLLNSNFQKNFLA**WY

QQKPGQX$_{a7}$PKLLIY**FASTRES**SX$_{a8}$PDRFX$_{a9}$GSGSGTDFTLTISSX$_{a10}$

QAEDX$_{a11}$AX$_{a12}$YX$_{a13}$C**QQHYSTPLT**FGX$_{a14}$GTKLEX$_{a15}$K;

[0450] Wherein X_{a1} may be, for example, D or S;

[0451] Wherein X_{a2} may be, for example, L or I;

[0452] Wherein X_{a3} may be, for example, E or Q;

[0453] Wherein X_{a4} may be, for example, R or K;

[0454] Wherein X_{a5} may be, for example, A or V;

[0455] Wherein X_{a6} may be, for example, I or M;

[0456] Wherein X_{a7} may be, for example, P or S;

[0457] Wherein X_{a8} may be, for example, V or I;

[0458] Wherein X_{a9} may be, for example, S or I;

[0459] Wherein X_{a10} may be, for example, L or V;

[0460] Wherein X_{a11} may be, for example, V or L;

[0461] Wherein X_{a12} may be, for example, V or D;

[0462] Wherein X_{a13} may be, for example, Y or F;

[0463] Wherein X_{a14} may be, for example, Q or A and;

[0464] Wherein X_{a15} is for example, I or L.

[0465] In accordance with an embodiment of the present invention, the humanized 3D3 antibody may have a heavy chain variable region of formula:

(SEQ ID NO.: 177)

EVQLXQSXAEXXXPGASVXXSCKAS**GYIFTDYEIH**WVXQXPXXGLEWXG**V**

IDPETGNTAFNQKFKGXXTXTADXSXSTAYMELSSLTSEDXAVYYC**MGYS**

DYWGQGTXXTVSS;

wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:18. The amino acid substitution may be, for example conservative.

[0466] In accordance with a more specific embodiment, the humanized 3D3 antibody may have a heavy chain variable region of formula:

(SEQ ID NO.: 178)

EVQLX$_{B1}$QSX$_{B2}$AEX$_{B3}$XNX$_{B5}$PGASVX$_{B6}$X$_{B7}$SCKAS**GYIFTDYEIH**WVX$_{B8}$Q

X$_{B9}$PX$_{B10}$X$_{B11}$GLEWX$_{B12}$G**VIDPETGNTA**FNQKFKGX$_{B13}$X$_{B14}$TX$_{B15}$TAD

X$_{B16}$SX$_{B17}$STAYMELSSLTSEDX$_{B18}$AVYYC**MGYSD**YWGQGTX$_{B19}$X$_{B20}$TV

SS,

[0467] Wherein X_{B1} may be, for example, V or Q;

[0468] Wherein X_{B2} may be, for example, G or V;

[0469] Wherein X_{B3} may be, for example, a hydrophobic amino acid or more particularly V or L;

[0470] Wherein X_{B4} may be, for example, K or V;

[0471] Wherein X_{B5} may be, for example, a basic amino acid or more particularly K or R;

[0472] Wherein X_{B6} may be, for example, K or T;

[0473] Wherein X_{B7} may be, for example, a hydrophobic amino acid or more particularly V or L;

[0474] Wherein X_{B8} may be, for example, a basic amino acid or more particularly R or K;

[0475] Wherein X_{B9} may be, for example, A or T;

[0476] Wherein X_{B10} may be, for example, G or V;

[0477] Wherein X_{B11} may be, for example, Q or H;

[0478] Wherein X_{B12} may be, for example, a hydrophobic amino acid or more particularly M or I;

[0479] Wherein X_{B13} may be, for example, a basic amino acid or more particularly R or K;

[0480] Wherein X_{B14} may be, for example, a hydrophobic amino acid or more particularly V or A;

[0481] Wherein X_{B15} may be, for example, a hydrophobic amino acid or more particularly I or L;

[0482] Wherein X_{B16} may be, for example, T or I;

[0483] Wherein X_{B17} may be, for example, a neutral hydrophilic amino acid or more particularly T or S;

[0484] Wherein X_{B18} may be, for example, a neutral hydrophilic amino acid or more particularly T or S;

[0485] Wherein X_{B19} may be, for example, L or T and;

[0486] Wherein X_{B20} may be, for example, a hydrophobic amino acid or more particularly V or L.

[0487] In accordance with a more specific embodiment, the humanized 3D3 antibody may have a heavy chain variable region of formula:

(SEQ ID NO.: 179)

EVQLX$_{b1}$QSX$_{b2}$AEX$_{b3}$X$_{b4}$X$_{b5}$PGASVX$_{b6}$X$_{b7}$SCKAS**GYIFTDYEIH**WVX$_{b8}$Q

X$_{b9}$PX$_{b10}$X$_{b11}$GLEWX$_{b12}$G**VIDPETGNTA**FNQKFKGX$_{b13}$X$_{b14}$TX$_{b15}$TADX$_{b16}$

SX$_{b17}$STAYMELSSLTSEDX$_{b18}$AVYYC**MGYSDY**WGQGTX$_{b19}$X$_{b20}$TVSS;

[0488] Wherein X_{b1} may be, for example, V or Q;

[0489] Wherein X_{b2} may be, for example, G or V;

[0490] Wherein X_{b3} may be, for example, V or L;

[0491] Wherein X_{b4} may be, for example, K or V;

[0492] Wherein X_{b5} may be, for example, K or R;

[0493] Wherein X_{b6} may be, for example, K or T;

[0494] Wherein X_{b7} may be, for example, V or L;

[0495] Wherein X_{b8} may be, for example, R or K;

[0496] Wherein X_{b9} may be, for example, A or T;

[0497] Wherein X_{b10} may be, for example, G or V;

[0498] Wherein X_{b11} may be, for example, Q or H;

[0499] Wherein X_{b12} may be, for example, M or I;

[0500] Wherein X_{b13} may be, for example, R or K;

[0501] Wherein X_{b14} may be, for example, V or A;

[0502] Wherein X_{b15} may be, for example, I or L;

[0503] Wherein X_{b16} may be, for example, T or I;

[0504] Wherein X_{b17} may be, for example, T or S;

[0505] Wherein X_{b18} may be, for example, T or S;

[0506] Wherein X_{b19} may be, for example, L or T;

[0507] Wherein X_{b20} may be, for example, V or L.

[0508] In accordance with an embodiment of the present invention, the humanized 3C4 antibody may have a light chain variable region of formula:

(SEQ ID NO.: 180)

DIVMXQSPSSXXASXGXRVTITC**KASQDIHNFLN**WFQQKPGKXPKTLIF**R**

ANRLVDGVPSRFSGSGSGXDYXLTISSLXXEDXXXYSC**LQYDEIPLT**FGX

GTKLEXX;

wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:24. The amino acid substitution may be, for example conservative.

[0509] In accordance with a more specific embodiment, the humanized 3C4 antibody may have a light chain variable region of formula:

(SEQ ID NO.: 181)

DIVMX$_{C1}$QSPSSX$_{C2}$X$_{C3}$ASX$_{C4}$GX$_{C5}$RVTITC**KASQDIHNFLN**WFQQKPGK

X$_{C6}$PKTLIF**RANRLVD**GVPSRFSGSGSGX$_{C7}$DYX$_{C8}$LTISSLX$_{C9}$X$_{C10}$ED

X$_{C11}$X$_{C12}$X$_{C13}$YSC**LQYDEIPLT**FGX$_{C14}$GTKLEX$_{C15}$X$_{C16}$;

[0510] Wherein X_{C1} may be, for example, a neutral hydrophilic amino acid or more particularly T or S;

[0511] Wherein X_{C2} may be, for example, a hydrophobic amino acid or more particularly L or M;

[0512] Wherein X_{C3} may be, for example, S or Y;

[0513] Wherein X_{C4} may be, for example, a hydrophobic amino acid or more particularly V or L;

[0514] Wherein X_{C5} may be, for example, an acidic amino acid or more particularly D or E;

[0515] Wherein X_{C6} may be, for example, A or S;

[0516] Wherein X_{C7} may be, for example, T or Q;

[0517] Wherein X_{C8} may be, for example, a neutral hydrophilic amino acid or more particularly T or S;

[0518] Wherein X_{C9} may be, for example, Q or E;

[0519] Wherein X_{C10} may be, for example, P or F;

[0520] Wherein X_{C11} may be, for example, F or L;

[0521] Wherein X_{C12} may be, for example, A or G;

[0522] Wherein X_{C13} may be, for example, T or I;

[0523] Wherein X_{C14} may be, for example, Q or A;

[0524] Wherein X_{C15} may be, for example, a hydrophobic amino acid or more particularly I or L, and; wherein X_{C16} may be, for example, a basic amino acid or more particularly K or R.

[0525] In accordance with a more specific embodiment, the humanized 3C4 antibody may have a light chain variable region of formula:

(SEQ ID NO.: 182)

DIVMX$_{c1}$QSPSSX$_{c2}$X$_{c3}$ASX$_{c4}$GX$_{c5}$RVTITC**KASQDIHNFLN**WFQQKPGK

X$_{c6}$PKTLIF**RANRLVD**GVPSRFSGSGSGX$_{c7}$DYX$_{c8}$LTISSLX$_{c9}$X$_{c10}$ED

X$_{c11}$X$_{c12}$X$_{c13}$YSC**LQYDEIPLT**FGX$_{c14}$GTKLEX$_{c15}$X$_{c16}$;

[0526] Wherein X_{c1} may be, for example, T or S;

[0527] Wherein X_{c2} may be, for example, L or M;

[0528] Wherein X_{c3} may be, for example, S or Y;

[0529] Wherein X_{c4} may be, for example, V or L;

[0530] Wherein X_{c5} may be, for example, D or E;

[0531] Wherein X_{c6} may be, for example, A or S;

[0532] Wherein X_{c7} may be, for example, T or Q;

[0533] Wherein X_{c8} may be, for example, T or S;

[0534] Wherein X_{c9} may be, for example, Q or E;

[0535] Wherein X_{c10} may be, for example, P or F;

[0536] Wherein X_{c11} may be, for example, F or L;

[0537] Wherein X_{c12} may be, for example, A or G;

[0538] Wherein X_{c13} may be, for example, T or I;

[0539] Wherein X_{c14} may be, for example, Q or A;

[0540] Wherein X_{c15} may be, for example, I or L and;

[0541] wherein X_{c16} may be, for example, K or R.

[0542] In accordance with an embodiment of the present invention, the humanized 3C4 antibody may have a heavy chain variable region of formula:

(SEQ ID NO.: 183)

EVQLQESGPXLVKPSQXLSLTCTVX**GFSITSGYGWH**WIRQXPGXXLEWX

G**YINYDGHND**YNPSLKSRXXIXQDTSKNQFXLXLXSVTXXDTAXYYC**AS**

SYDGLFAYWGQGTLVTVSX;

wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:26. The amino acid substitution may be, for example conservative.

[0543] In accordance with a more specific embodiment, the humanized 3C4 antibody may have a heavy chain variable region of formula:

(SEQ ID NO.: 184)

EVQLQESGPX$_{D1}$LVKPSQX$_{D2}$LSLTCTVX$_{D3}$**GFSITSGYGWH**WIRQX$_{D4}$P

GX$_{D5}$X$_{D6}$LEWX$_{D7}$G**YINYDGHND**YNPSLKSRX$_{D8}$X$_{D9}$IX$_{D10}$QDTSKNQF

X$_{D11}$LX$_{D12}$LX$_{D13}$SVTX$_{D14}$X$_{D15}$DTAX$_{D16}$YYC**ASSYDGLFAY**WGQGT

LVTVSX$_{D17}$;

[0544] Wherein X_{D1} may be, for example, G or D;

[0545] Wherein X_{D2} may be, for example, a neutral hydrophilic amino acid or more particularly T or S;

[0546] Wherein X_{D3} may be, for example, a neutral hydrophilic amino acid or more particularly S or T;

[0547] Wherein X_{D4} may be, for example, H or F;

[0548] Wherein X_{D5} may be, for example, K or N;

[0549] Wherein X_{D6} may be, for example, G or K;

[0550] Wherein X_{D7} may be, for example, a hydrophobic amino acid or more particularly I or M;

[0551] Wherein X_{D8} may be, for example, a hydrophobic amino acid or more particularly V or I;

[0552] Wherein X_{D9} may be, for example, a neutral hydrophilic amino acid or more particularly T or S;

[0553] Wherein X_{D10} may be, for example, a neutral hydrophilic amino acid or more particularly S or T;

[0554] Wherein X_{D11} may be, for example, a neutral hydrophilic amino acid or more particularly S or F;

[0555] Wherein X_{D12} may be, for example, a basic amino acid or more particularly K or Q;

[0556] Wherein X_{D13} may be, for example, S or N;

[0557] Wherein X_{D14} may be, for example, A or T;

[0558] Wherein X_{D15} may be, for example, A or E;

[0559] Wherein X_{D16} may be, for example, V or T and;

[0560] Wherein X_{D17} may be any amino acid, A or absent.

[0561] In accordance with a more specific embodiment, the humanized 3C4 antibody may have a heavy chain variable region of formula:

(SEQ ID NO.: 185)

EVQLQESGPX$_{d1}$LVKPSQX$_{d2}$LSLTCTVX$_{d3}$**GFSITSGYGWH**WIRQX$_{d4}$P

GX$_{d5}$X$_{d6}$LEWX$_{d7}$G**YINYDGHND**YNPSLKSRX$_{d8}$X$_{d9}$IX$_{d10}$QDTSKNQF

X$_{d11}$LX$_{d12}$LX$_{d13}$SVTX$_{d14}$X$_{d15}$DTAX$_{d16}$YYC**ASSYDGLFAY**WGQGT

LVTVSX$_{d17}$;

[0562] Wherein X_{d1} may be, for example, G or D;

[0563] Wherein X_{d2} may be, for example, T or S;

[0564] Wherein X_{d3} may be, for example, S or T;

[0565] Wherein X_{d4} may be, for example, H or F;

[0566] Wherein X_{d5} may be, for example, K or N;

[0567] Wherein X_{d6} may be, for example, G or K;

[0568] Wherein X_{d7} may be, for example, I or M;

[0569] Wherein X_{d8} may be, for example, V or I;

[0570] Wherein X_{d9} may be, for example, T or S;

[0571] Wherein X_{d10} may be, for example, S or T;

[0572] Wherein X_{d11} may be, for example, S or F;

[0573] Wherein X_{d12} may be, for example, K or Q;

[0574] Wherein X_{d13} may be, for example, S or N;

[0575] Wherein X_{d14} may be, for example, A or T;

[0576] Wherein X_{d15} may be, for example, A or E;

[0577] Wherein X_{d16} may be, for example, V or T and;

[0578] Wherein X_{d17}, A or absent.

[0579] Accordingly, the present invention provides in one aspect, an antibody or antigen binding fragment thereof capable of specific binding to Kidney associated antigen 1 (KAAG1) which may have a light chain variable region at least 70% identical to SEQ ID NO.:16 and/or a heavy chain variable region at least 70% identical to SEQ ID NO.:18. The antibody or antigen binding fragment thereof may also comprise at least one amino acid substitution in comparison with SEQ ID NO.:16 or SEQ ID NO.:18.

[0580] The present invention also provides in another aspect, an antibody or antigen binding fragment thereof which may have a light chain variable region at least 70% identical to SEQ ID NO.:24 and/or a heavy chain variable region at least 70% identical to SEQ ID NO.:26. The antibody or antigen binding fragment thereof may also comprise at least one amino acid substitution in comparison with SEQ ID NO.:24 or SEQ ID NO.:26.

[0581] The present invention also provides in another aspect, an antibody or antigen binding fragment thereof which may have a light chain variable region at least 70% identical to SEQ ID NO.:48 and/or a heavy chain variable region at least 70% identical to SEQ ID NO.:46. The antibody or antigen binding fragment thereof may also comprise at least one amino acid substitution in comparison with SEQ ID NO.:48 or SEQ ID NO.:46.

[0582] In accordance with an embodiment of the invention, the amino acid substitution may be outside of a complementarity determining region (CDR). An antibody or antigen binding fragment having such an amino acid sequence encompasses, for example, a humanized antibody or antigen binding fragment.

[0583] As used herein the term "from one to twenty-five" includes every individual values and ranges such as for example, 1, 2, 3, and up to 25; 1 to 25; 1 to 24, 1 to 23, 1 to 22, 1 to 21, 1 to 20, 1 to 19; 1 to 18; 1 to 17; 1 to 16; 1 to 15 and so on; 2 to 25, 2 to 24, 2 to 23, 2 to 22, 2 to 21, 2 to 20; 2 to 19; 2 to 18; 2 to 17 and so on; 3 to 25, 3 to 24, 3 to 23, 3 to 22, 3 to 21, 3 to 20; 3 to 19; 3 to 18 and so on; 4 to 25, 4 to 24, 4 to 23, 4 to 22, 4 to 21, 4 to 20; 4 to 19; 4 to 18; 4 to 17; 4 to 16 and so on; 5 to 25, 5 to 24, 5 to 23, 5 to 22, 5 to 21, 5 to 20; 5 to 19; 5 to 18; 5 to 17 and so on, etc.

[0584] As used herein the term "from one to twenty-three" includes every individual values and ranges such as for example, 1, 2, 3, and up to 23; 1 to 23, 1 to 22, 1 to 21, 1 to 20, 1 to 19; 1 to 18; 1 to 17; 1 to 16; 1 to 15 and so on; 2 to 23, 2 to 22, 2 to 21, 2 to 20; 2 to 19; 2 to 18; 2 to 17 and so on; 3 to 23, 3 to 22, 3 to 21, 3 to 20; 3 to 19; 3 to 18 and so on; 4 to 23, 4 to 22, 4 to 21, 4 to 20; 4 to 19; 4 to 18; 4 to 17; 4 to 16 and so on; 5 to 25, 5 to 24, 5 to 23, 5 to 22, 5 to 21, 5 to 20; 5 to 19; 5 to 18; 5 to 17 and so on, etc.

[0585] As used herein the term "from one to twenty" includes every individual values and ranges such as for example, 1, 2, 3, and up to 20; 1 to 20; 1 to 19; 1 to 18; 1 to 17; 1 to 16; 1 to 15 and so on; 2 to 20; 2 to 19; 2 to 18; 2 to 17 and so on; 3 to 20; 3 to 19; 3 to 18 and so on; 4 to 20; 4 to 19; 4 to 18; 4 to 17; 4 to 16 and so on; 5 to 20; 5 to 19; 5 to 18; 5 to 17 and so on, etc.

[0586] Likewise, the term "from one to fifteen" includes every individual values and ranges such as for example, 1, 2, 3, and up to 15; 1 to 15; 1 to 14; 1 to 13; 1 to 12; 1 to 11; 1 to 10 and so on; 2 to 15; 2 to 14; 2 to 13; 2 to 12 and so on; 3 to 15; 3 to 14; 3 to 13 and so on; 4 to 15; 4 to 14; 4 to 13; 4 to 12; 4 to 11 and so on; 5 to 15; 5 to 14; 5 to 13; 5 to 12 and so on, etc.

[0587] Likewise, the term "from one to eleven" includes every individual values and ranges such as for example, 1, 2, 3, and up to 11; 1 to 11; 1 to 10, 1 to 9, 1 to 8, 1 to 7, and so on; 2 to 11; 2 to 10; 2 to 9; 2 to 8 and so on; 3 to 11; 3 to 10; 3 to 9 and so on; 4 to 11; 4 to 10; 4 to 9; 4 to 8; 4 to 7 and so on; 5 to 11; 5 to 10; 5 to 9; 5 to 8 and so on, etc.

[0588] In a more specific embodiment of the invention, the number of amino acid substitutions that may be accommodated in a humanized light chain variable region derived from SEQ ID NO.:16 may be for example, from 1 to 15 amino acid substitutions.

[0589] In yet a more specific embodiment of the invention, the number of amino acid substitutions that may be accommodated in a humanized heavy chain variable region derived from SEQ ID NO.:18 may be for example, from 1 to 20 amino acid substitutions. In some instances, when considering a humanized version of SEQ ID NO.:18, it may be useful to have at least three amino acid substitutions.

[0590] In a further more specific embodiment of the invention, the number of amino acid substitutions that may be accommodated in a humanized light chain variable region derived from SEQ ID NO.:24 may be for example, from 1 to 16 amino acid substitutions.

[0591] In yet a further more specific embodiment of the invention, the number of amino acid substitutions that may

be accommodated in a humanized heavy chain variable region of SEQ ID NO.:26 may be for example, from 1 to 17 amino acid substitutions.

[0592] In a further more specific embodiment of the invention, the number of amino acid substitutions that may be accommodated in a humanized light chain variable region derived from SEQ ID NO.:48 may be for example, from 1 to 11 amino acid substitutions.

[0593] In yet a further more specific embodiment of the invention, the number of amino acid substitutions that may be accommodated in a humanized heavy chain variable region of SEQ ID NO.:46 may be for example, from 1 to 23 amino acid substitutions.

[0594] In accordance with an embodiment of the invention, the one to twenty amino acid substitutions may be for example, in the light chain variable region.

[0595] In accordance with an embodiment of the invention, the one to twenty amino acid substitutions may be for example, in the heavy chain variable region.

[0596] A humanized antibody or antigen binding fragment may therefore have a light chain variable region having up to twenty amino acid substitutions in comparison with SEQ ID NO.:16 or SEQ ID NO.:24 and may have a heavy chain variable region having up to twenty amino acid substitutions in comparison with SEQ ID NO.:18 or SEQ ID NO.:26. A humanized antibody or antigen binding fragment may therefore have a light chain variable region having up to twenty-five amino acid substitutions in comparison with SEQ ID NO.:48 and may have a heavy chain variable region having up to twenty-five amino acid substitutions in comparison with SEQ ID NO.:46.

[0597] It is to be understood herein that when the humanized antibody or antigen binding fragment has two light chain variable regions and two heavy chain variable regions, each one of the light chain variable regions may independently have up to twenty-five, twenty-four, twenty-three, twenty-two, twenty-one, twenty, nineteen, eighteen, seventeen, sixteen, fifteen, fourteen, thirteen, twelve, eleven, ten, nine, eight, seven, six, five, four, three, two, one amino acid substitutions and each one of the heavy chain variable regions may have up to twenty-five, twenty-four, twenty-three, twenty-two, twenty-one, twenty, nineteen, eighteen, seventeen, sixteen, fifteen, fourteen, thirteen, twelve, eleven, ten, nine, eight, seven, six, five, four, three, two, one amino acid substitutions.

[0598] As discussed herein the amino acid substitutions may be conservative or non-conservative. In an exemplary embodiment the amino acid substitutions may be conservative.

[0599] It is to be understood herein that the humanized antibody or antigen binding fragment of the invention may also have a light chain variable region and/or heavy chain variable region showing a deletion in comparison with SEQ ID NO.:16, SEQ ID NO.:18, SEQ ID NO.:189, SEQ ID NO.:190, SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196, SEQ ID NO.:197, SEQ ID NO.:24 and/or SEQ ID NO.:26. Such deletion may be found, for example, at an amino- or carboxy-terminus of the light chain variable region and/or heavy chain variable region.

[0600] Another exemplary embodiment of the humanized antibody or antigen binding fragment of the present invention includes for example, an antibody or antigen binding fragment having a light chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:186, SEQ ID NO.:187, SEQ ID NO.:188, SEQ ID NO.:189 or SEQ ID NO.:190.

[0601] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:186" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, or at least 112 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:186" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:186 and especially those sequences which include the 3 CDRs of SEQ ID NO.:186, such as, for example a sequence comprising amino acids 6 to 108, 5 to 109, 13 to 103, 14 to 111 of SEQ ID NO.:186 and so on.

[0602] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:187" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, or at least 112 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:187" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:187 and especially those sequences which include the 3 CDRs of SEQ ID NO.:187, such as, for example a sequence comprising amino acids 7 to 109, 12 to 104, 22 to 113, 18 to 112 of SEQ ID NO.:187 and so on.

[0603] The terms "at least 90 consecutive amino acids of SEQ ID NO.:188", "at least 90 consecutive amino acids of SEQ ID NO.:189" or "at least 90 consecutive amino acids of SEQ ID NO.:190" has a similar meaning.

[0604] In accordance with the present invention, the antibody or antigen binding fragment of the present invention may have, for example, a light chain variable region as set forth in SEQ ID NO.:189 or 190.

[0605] The humanized antibody or antigen binding fragment of the invention includes (or further includes) for example, a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NOs.:191, 192, 193, 194, 195, 196 or 197.

[0606] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:191" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 or at least 116 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:191" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:191 and especially those sequences which include the 3 CDRs of SEQ ID NO.:191, such as, for example a sequence comprising amino acids 1 to 106, 2 to 112, 11 to 113, 7 to 102 of SEQ ID NO.:191 and so on.

[0607] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:192" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 or at least 116 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:192" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:192 and especially those sequences which include the 3 CDRs of SEQ ID NO.:192, for example a sequence comprising amino acids 6 to 109, 8 to 113, 1 to 102, 2 to 105 of SEQ ID NO.:192 and so on.

[0608] The terms "at least 90 consecutive amino acids of SEQ ID NO.:193", "at least 90 consecutive amino acids of SEQ ID NO.:194", "at least 90 consecutive amino acids of SEQ ID NO.:195", "at least 90 consecutive amino acids of

SEQ ID NO.:196" or "at least 90 consecutive amino acids of SEQ ID NO.:197" has a similar meaning.

[0609] In accordance with the present invention, the antibody or antigen binding fragment of the present invention may have, for example, a heavy chain variable region as set forth in SEQ ID NO.:194, 195, 196 or 197.

[0610] In accordance with the present invention the antibody or antigen binding fragment may comprise, for example,

[0611] a) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:186 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:191, SEQ ID NO.:192, SEQ ID NO.:193, SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197;

[0612] b) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:187 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:191, SEQ ID NO.:192, SEQ ID NO.:193, SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197;

[0613] c) a light chain variable region which may comprise amino acids at least 90 consecutive amino acids of SEQ ID NO.:188 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:191, SEQ ID NO.:192, SEQ ID NO.:193, SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197;

[0614] d) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:189 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:191, SEQ ID NO.:192, SEQ ID NO.:193, SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197 or

[0615] e) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:190 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:191, SEQ ID NO.:192, SEQ ID NO.:193, SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197.

[0616] In accordance with a more specific embodiment of the invention, the light chain variable region may comprise at least 90 consecutive amino acids of SEQ ID NO.:189 or 190 and the heavy chain variable region may comprise at least 90 consecutive amino acids of SEQ ID NO.:194, 195, 196 or 197.

[0617] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:189 and the heavy chain variable region may be as set forth in SEQ ID NO.:194.

[0618] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:189 and the heavy chain variable region may be as set forth in SEQ ID NO.:195.

[0619] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:189 and the heavy chain variable region may be as set forth in SEQ ID NO.:196.

[0620] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:189 and the heavy chain variable region may be as set forth in SEQ ID NO.:197.

[0621] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:190 and the heavy chain variable region may be as set forth in SEQ ID NO.:194.

[0622] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:190 and the heavy chain variable region may be as set forth in SEQ ID NO.:195.

[0623] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:190 and the heavy chain variable region may be as set forth in SEQ ID NO.:196.

[0624] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:190 and the heavy chain variable region may be as set forth in SEQ ID NO.:197.

[0625] Another exemplary embodiment of the humanized antibody or antigen binding fragment of the present invention includes for example, an antibody or antigen binding fragment having a light chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:174, SEQ ID NO.:175, SEQ ID NO.:176 or SEQ ID NO.:168.

[0626] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:174" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112 or at least 113 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:174" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:174 and especially those sequences which include the 3 CDRs of SEQ ID NO.:174, such as, for example a sequence comprising amino acids 6 to 108, 5 to 109, 13 to 103, 14 to 111 of SEQ ID NO.:174 and so on.

[0627] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:175" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112 or at least 113 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:175" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:175 and especially those sequences which include the 3 CDRs of SEQ ID NO.:175, such as, for example a sequence comprising amino acids 7 to 109, 12 to 104, 22 to 113, 18 to 112 of SEQ ID NO.:175 and so on.

[0628] The terms "at least 90 consecutive amino acids of SEQ ID NO.:176" or "at least 90 consecutive amino acids of SEQ ID NO.:168" has a similar meaning.

[0629] In accordance with the present invention, the antibody or antigen binding fragment of the present invention may have, for example, a light chain variable region as set forth in SEQ ID NO.:168.

[0630] The humanized antibody or antigen binding fragment of the invention includes (or further includes) for example, a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NOs.:177, 178, 179 or 169.

[0631] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:177" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112 or at least 113 consecutive amino acids". The term "at least 90 consecutive

amino acids of SEQ ID NO.:177" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:177 and especially those sequences which include the 3 CDRs of SEQ ID NO.:177, such as, for example a sequence comprising amino acids 1 to 106, 2 to 112, 11 to 113, 7 to 102 of SEQ ID NO.:177 and so on.

[0632] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:178" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112 or at least 113 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:178" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:178 and especially those sequences which include the 3 CDRs of SEQ ID NO.:178, for example a sequence comprising amino acids 6 to 109, 8 to 113, 1 to 102, 2 to 105 of SEQ ID NO.:178 and so on.

[0633] The terms "at least 90 consecutive amino acids of SEQ ID NO.:179" or "at least 90 consecutive amino acids of SEQ ID NO.:169" has a similar meaning.

[0634] In accordance with the present invention, the antibody or antigen binding fragment of the present invention may have, for example, a heavy chain variable region as set forth in SEQ ID NO.:169.

[0635] In accordance with the present invention the antibody or antigen binding fragment may comprise, for example,

[0636] f) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:174 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:177, SEQ ID NO.:178, SEQ ID NO.:179 or SEQ ID NO.:169;

[0637] g) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:175 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:177, SEQ ID NO.:178, SEQ ID NO.:179 or SEQ ID NO.:169;

[0638] h) a light chain variable region which may comprise amino acids at least 90 consecutive amino acids of SEQ ID NO.:176 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:177, SEQ ID NO.:178, SEQ ID NO.:179 or SEQ ID NO.:169 or;

[0639] i) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:168 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:177, SEQ ID NO.:178, SEQ ID NO.:179 or SEQ ID NO.:169.

[0640] In accordance with a more specific embodiment of the invention, the light chain variable region may comprise at least 90 consecutive amino acids of SEQ ID NO.:168 and the heavy chain variable region may comprise at least 90 consecutive amino acids of SEQ ID NO.:169.

[0641] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:168 and the heavy chain variable region may be as set forth in SEQ ID NO.:169.

[0642] Other exemplary embodiments of the humanized antibodies or antigen binding fragments of the invention are those which may comprise a light chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID Nos. 180, 181, 182 or 172.

[0643] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:180" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106 or at least 107, consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:180" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:180 and especially those sequences which include the 3 CDRs of SEQ ID NO.:180, for example a sequence comprising amino acids 6 to 102, 11 to 106, 1 to 106, 3 to 95, 5 to 95 of SEQ ID NO.:180 and so on.

[0644] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:181" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106 or at least 107, consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:181" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:181 and especially those sequences which include the 3 CDRs of SEQ ID NO.:181, for example a sequence comprising amino acids 9 to 106, 10 to 101, 1 to 98, 3 to 99, 7 to 107 of SEQ ID NO.:181 and so on.

[0645] The terms "at least 90 consecutive amino acids of SEQ ID NO.:182" or "at least 90 consecutive amino acids of SEQ ID NO.:172" has a similar meaning.

[0646] In accordance with the present invention, the antibody or antigen binding fragment of the present invention may have, for example, a light chain variable region as set forth in SEQ ID NO.:172.

[0647] The humanized antibody or antigen binding fragment of the invention includes (or further includes) for example, a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NOs.:183, 184, 185 or 173.

[0648] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:183" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 or at least 116 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:183" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:183 and especially those sequences which include the 3 CDRs of SEQ ID NO.:183, such as, for example a sequence comprising amino acids 6 to 111, 1 to 106, 2 to 104, 5 to 106, 10 to 107 of SEQ ID NO.:183 and so on.

[0649] As used herein the term "at least 90 consecutive amino acids of SEQ ID NO.:185" also includes the terms "at least 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115 or at least 116 consecutive amino acids". The term "at least 90 consecutive amino acids of SEQ ID NO.:185" encompasses any possible sequence of at least 90 consecutive amino acids found in SEQ ID NO.:185 and especially those sequences which include the 3 CDRs of SEQ ID NO.:185, such as, for example a sequence comprising amino acids 3 to 107, 1 to 115, 1 to 110, 22 to 116, 20 to 115 of SEQ ID NO.:185 and so on.

[0650] The terms "at least 90 consecutive amino acids of SEQ ID NO.:184" or "at least 90 consecutive amino acids of SEQ ID NO.:173" has a similar meaning.

[0651] In accordance with the present invention, the antibody or antigen binding fragment of the present invention may have, for example, a heavy chain variable region as set forth in SEQ ID NO.:173.

[0652] In accordance with the present invention the antibody or antigen binding fragment may comprise, for example,

[0653] a) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:180 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:183, SEQ ID NO.:184, SEQ ID NO.:185 or SEQ ID NO.:173;

[0654] b) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:181 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:183, SEQ ID NO.:184, SEQ ID NO.:185 or SEQ ID NO.:173;

[0655] c) a light chain variable region which may comprise amino acids at least 90 consecutive amino acids of SEQ ID NO.:182 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:183, SEQ ID NO.:184, SEQ ID NO.:185 or SEQ ID NO.:173 or;

[0656] d) a light chain variable region which may comprise at least 90 consecutive amino acids of SEQ ID NO.:172 and a heavy chain variable region which may comprise at least 90 consecutive amino acids of any of SEQ ID NO.:183, SEQ ID NO.:184, SEQ ID NO.:185 or SEQ ID NO.:173.

[0657] In accordance with a more specific embodiment of the invention, the light chain variable region may have at least 90 consecutive amino acids of SEQ ID NO.:172 and the heavy chain variable region may have at least 90 consecutive amino acids of SEQ ID NO.:173.

[0658] In accordance with an even more specific embodiment of the invention, the light chain variable region may be as set forth in SEQ ID NO.:172 and the heavy chain variable region may be as set forth in SEQ ID NO.:173.

[0659] The antibody or antigen binding fragment of the present invention may have a light chain variable region and/or heavy chain variable region as described above and may further comprise amino acids of a constant region, such as, for example, amino acids of a constant region of a human antibody.

[0660] In an exemplary embodiment, the antibody or antigen binding fragment of the present invention may comprise, for example, a human IgG1 constant region.

[0661] In accordance with another exemplary embodiment of the invention, the antigen binding fragment may be, for example, a scFv, a Fab, a Fab' or a $(Fab)_2$.

Production of the Antibodies in Cells

[0662] The anti-KAAG1 antibodies that are disclosed herein can be made by a variety of methods familiar to those skilled in the art, such as hybridoma methodology or by recombinant DNA methods.

[0663] In an exemplary embodiment of the invention, the anti-KAAG1 antibodies may be produced by the conventional hybridoma technology, where a mouse is immunized with an antigen, spleen cells isolated and fused with myeloma cells lacking HGPRT expression and hybrid cells selected by hypoxanthine, aminopterin and thymine (HAT) containing media.

[0664] In an additional exemplary embodiment of the invention, the anti-KAAG1 antibodies may be produced by recombinant DNA methods.

[0665] In order to express the anti-KAAG1 antibodies, nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein or any other may be inserted into an expression vector, i.e., a vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host. These elements may include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination.

[0666] A variety of expression vector/host cell systems known to those of skill in the art may be utilized to express a polypeptide or RNA derived from nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with baculovirus vectors; plant cell systems transformed with viral or bacterial expression vectors; or animal cell systems. For long-term production of recombinant proteins in mammalian systems, stable expression in cell lines may be effected. For example, nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be transformed into cell lines using expression vectors that may contain viral origins of replication and/or endogenous expression elements and a selectable or visible marker gene on the same or on a separate vector. The invention is not to be limited by the vector or host cell employed. In certain embodiments of the present invention, the nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may each be ligated into a separate expression vector and each chain expressed separately. In another embodiment, both the light and heavy chains able to encode any one of a light and heavy immunoglobulin chains described herein may be ligated into a single expression vector and expressed simultaneously.

[0667] Alternatively, RNA and/or polypeptide may be expressed from a vector comprising nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein using an in vitro transcription system or a coupled in vitro transcription/translation system respectively.

[0668] In general, host cells that contain nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein and/or that express a polypeptide encoded by the nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein, or a portion thereof, may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA/DNA or DNA/RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques that include membrane, solution, or chip based technologies for the detection

and/or quantification of nucleic acid or amino acid sequences. Immunological methods for detecting and measuring the expression of polypeptides using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). Those of skill in the art may readily adapt these methodologies to the present invention.

[0669] Host cells comprising nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may thus be cultured under conditions for the transcription of the corresponding RNA (mRNA, siRNA, shRNA etc.) and/or the expression of the polypeptide from cell culture. The polypeptide produced by a cell may be secreted or may be retained intracellularly depending on the sequence and/or the vector used. In an exemplary embodiment, expression vectors containing nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be designed to contain signal sequences that direct secretion of the polypeptide through a prokaryotic or eukaryotic cell membrane.

[0670] Due to the inherent degeneracy of the genetic code, other DNA sequences that encode the same, substantially the same or a functionally equivalent amino acid sequence may be produced and used, for example, to express a polypeptide encoded by nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein. The nucleotide sequences of the present invention may be engineered using methods generally known in the art in order to alter the nucleotide sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

[0671] In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed polypeptide in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. In an exemplary embodiment, anti-KAAG1 antibodies that contain particular glycosylation structures or patterns may be desired. Post-translational processing, which cleaves a "prepro" form of the polypeptide, may also be used to specify protein targeting, folding, and/or activity. Different host cells that have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and W138) are available commercially and from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the expressed polypeptide.

[0672] Those of skill in the art will readily appreciate that natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence resulting in translation of a fusion polypeptide containing heterologous polypeptide moieties in any of the aforementioned host systems. Such heterologous polypeptide moieties may facilitate purification of fusion polypeptides using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein, thioredoxin, calmodulin binding peptide, 6-His (His), FLAG, c-myc, hemaglutinin (HA), and antibody epitopes such as monoclonal antibody epitopes.

[0673] In yet a further aspect, the present invention relates to a polynucleotide which may comprise a nucleotide sequence encoding a fusion protein. The fusion protein may comprise a fusion partner (e.g., HA, Fc, etc.) fused to the polypeptide (e.g., complete light chain, complete heavy chain, variable regions, CDRs etc.) described herein.

[0674] Those of skill in the art will also readily recognize that the nucleic acid and polypeptide sequences may be synthesized, in whole or in part, using chemical or enzymatic methods well known in the art. For example, peptide synthesis may be performed using various solid-phase techniques and machines such as the ABI 431A Peptide synthesizer (PE Biosystems) may be used to automate synthesis. If desired, the amino acid sequence may be altered during synthesis and/or combined with sequences from other proteins to produce a variant protein.

Antibody Conjugates

[0675] The antibody or antigen binding fragment of the present invention may be conjugated with a detectable moiety (i.e., for detection or diagnostic purposes) or with a therapeutic moiety (for therapeutic purposes)

[0676] A "detectable moiety" is a moiety detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical and/or other physical means. A detectable moiety may be coupled either directly and/or indirectly (for example via a linkage, such as, without limitation, a DOTA or NHS linkage) to antibodies and antigen binding fragments thereof of the present invention using methods well known in the art. A wide variety of detectable moieties may be used, with the choice depending on the sensitivity required, ease of conjugation, stability requirements and available instrumentation. A suitable detectable moiety include, but is not limited to, a fluorescent label, a radioactive label (for example, without limitation, ^{125}I, In^{111}, Tc^{99}, I^{131} and including positron emitting isotopes for PET scanner etc), a nuclear magnetic resonance active label, a luminiscent label, a chemiluminescent label, a chromophore label, an enzyme label (for example and without limitation horseradish peroxidase, alkaline phosphatase, etc.), quantum dots and/or a nanoparticle. Detectable moiety may cause and/or produce a detectable signal thereby allowing for a signal from the detectable moiety to be detected.

[0677] In another exemplary embodiment of the invention, the antibody or antigen binding fragment thereof may be coupled (modified) with a therapeutic moiety (e.g., drug, cytotoxic moiety).

[0678] In an exemplary embodiment, the anti-KAAG1 antibodies and antigen binding fragments may comprise an inhibitor, a chemotherapeutic or cytotoxic agent. For example, the antibody and antigen binding fragments may be conjugated to the chemotherapeutic or cytotoxic agent. Such chemotherapeutic or cytotoxic agents include, but are not limited to, Yttrium-90, Scandium-47, Rhenium-186, Iodine-131, Iodine-125, and many others recognized by those skilled in the art (e.g., lutetium (e.g., Lu^{177}), bismuth (e.g., Bi^{213}), copper (e.g., Cu^{67})). In other instances, the chemotherapeutic or cytotoxic agent may comprise, without limitation, 5-fluorouracil, adriamycin, irinotecan, platinum-

based compounds such as cisplatin and anti-tubulin or anti-mitotic compounds such as, taxanes, doxorubicin and cyclophosphamide, *pseudomonas* endotoxin, ricin and other toxins. Suitable antibody drug conjugates are selected amongst those having an IC_{50} in the range of 0.001 nM to 150 nM, 0.001 nM to 100 nM, 0.001 nM to 50 nM, 0.001 nM to 20 nM or 0.001 nM to 10 nM (inclusively). The cytotoxic drug used for conjugation is thus selected on the basis of these criteria.

[0679] Alternatively, in order to carry out the methods of the present invention and as known in the art, the antibody or antigen binding fragment of the present invention (conjugated or not) may be used in combination with a second molecule (e.g., a secondary antibody, etc.) which is able to specifically bind to the antibody or antigen binding fragment of the present invention and which may carry a desirable detectable, diagnostic or therapeutic moiety.

Pharmaceutical Compositions of the Antibodies and their Use

[0680] Pharmaceutical compositions of the anti-KAAG1 antibodies or antigen binding fragments (conjugated or not) are also encompassed by the present invention. The pharmaceutical composition may comprise an anti-KAAG1 antibody or an antigen binding fragment and may also contain a pharmaceutically acceptable carrier.

[0681] Other aspects of the invention relate to a composition which may comprise the antibody or antigen binding fragment described herein and a carrier.

[0682] The present invention also relates to a pharmaceutical composition which may comprise the antibody or antigen binding fragment described herein and a pharmaceutically acceptable carrier.

[0683] In addition to the active ingredients, a pharmaceutical composition may contain pharmaceutically acceptable carriers comprising water, PBS, salt solutions, gelatins, oils, alcohols, and other excipients and auxiliaries that facilitate processing of the active compounds into preparations that may be used pharmaceutically. In other instances, such preparations may be sterilized.

[0684] As used herein, "pharmaceutical composition" means therapeutically effective amounts of the agent together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCl., acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts). Solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal, oral, vaginal, rectal routes. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, intracranially and intratumorally.

[0685] Further, as used herein "pharmaceutically acceptable carrier" or "pharmaceutical carrier" are known in the art and include, but are not limited to, 0.01-0.1 M or 0.05 M phosphate buffer or 0.8% saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's orfixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

[0686] For any compound, the therapeutically effective dose may be estimated initially either in cell culture assays or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the concentration range and route of administration. Such information may then be used to determine useful doses and routes for administration in humans. These techniques are well known to one skilled in the art and a therapeutically effective dose refers to that amount of active ingredient that ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating and contrasting the ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population) statistics. Any of the therapeutic compositions described above may be applied to any subject in need of such therapy, including, but not limited to, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and humans.

[0687] The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Methods of Use

[0688] The term "treatment" for purposes of this disclosure refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or

disorder. Those in need of treatment include those already having the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

[0689] The present invention provides in one aspect thereof, a method of treating an individual having or suspected of having breast cancer with an antibody or antigen binding fragment which is capable of specific binding to KAAG1.

[0690] In accordance with the present invention, the individual may have a breast cancer that is negative for the estrogen receptor expression, the progesterone receptor expression and/or Her2 expression (or overexpression).

[0691] Also in accordance with the present invention, the individual may have a breast cancer that has low expression for at least one of estrogen receptor, progesterone receptor and/or Her2.

[0692] For example, the tumor may be negative for (or have low expression of) both estrogen receptor expression and progesterone receptor expression.

[0693] In accordance with the present invention, the individual may have a breast cancer that is characterized as being triple-negative or basal-like.

[0694] Yet other aspects of the invention relate to the use of the isolated antibody or antigen binding fragment described herein in the treatment or diagnosis of breast cancer characterized by a lack of estrogen receptor expression, progesterone receptor expression and/or Her2 overexpression or by low expression of at least one of these three markers.

[0695] In accordance with the present invention, the method may comprise, for example, administering an antibody or antigen binding fragment which is capable of specific binding to KAAG1 to an individual in need. The individual in need is preferentially selected on the basis of a lack of ER expression, PgR expression and/or by the absence of HER2 protein over-expression. Clinical testing for these markers is usually performed using histopathologic methods (immunohistochemistry, FISH, etc.) and/or by gene expression studies (see for example Dent et al, 2007, Bernstein and Lacey, 2011). The individual in need may thus be an individual who has received a diagnosis of triple-negative breast cancer or basal-like breast cancer.

[0696] The present invention thus particularly relates to the therapeutic treatment of individual having triple-negative breast cancer or basal-like cancer with an anti-KAAG1 antibody.

[0697] Suitable antibodies or antigen binding fragments include those that are capable of specific binding to KAAG1 at the surface of tumor cells. Such antibodies may preferentially bind an epitope included within amino acids 30 to 84 of KAAG1 inclusively (e.g., within amino acids 36 to 60 (inclusively) or within amino acids 61 to 84 (inclusively) of KAAG1).

[0698] Suitable antibodies may be those which mediate antibody-dependent cell cytotoxicity and those that are conjugated with a therapeutic moiety.

[0699] In accordance with the present invention, the antibody may be, for example, a monoclonal antibody, a chimeric antibody or a humanized antibody or an antigen binding fragment thereof.

[0700] The method of the present invention may include administering the antibody or antigen binding fragment in combination with an inhibitor, a chemotherapeutic or a cytotoxic agent.

[0701] Other methods of treatment encompassed by the present invention include administering other types of KAAG1 inhibitors such as antisense-based therapeutics (siRNA, antisenses, ribozymes, etc.).

[0702] The present invention thus provides a method of treating triple-negative breast cancer or basal-like breast cancer by administering an inhibitor of KAAG1 activity or expression to an individual in need.

[0703] The inhibitor may comprise a nucleotide sequence complementary to SEQ ID NO.:1 or to a fragment thereof. More particularly, the inhibitor may comprise a nucleotide sequence complementary to nucleotides 738 to 992 (inclusively) of SEQ ID NO.:1 or to a fragment thereof. For example, the inhibitor may include at least 10 consecutive nucleotides (at least 15, at least 20) which are complementary to SEQ ID NO.:1 or to nucleotides 738 to 992 (inclusively) of SEQ ID NO.:1.

[0704] In certain instances, the anti-KAAG1 antibodies and fragments may interact with cancer cells that express KAAG1 and induce an immunological reaction by mediating ADCC. In other instances, the anti-KAAG1 antibodies and fragments may block the interaction of KAAG1 with its protein partners.

[0705] In certain instances, the anti-KAAG1 antibodies and antigen binding fragments thereof may be administered concurrently with other treatments given for the same condition (inhibitors, chemotherapeutics or cytotoxic agents). As such, the antibodies may be administered with a PARP1 inhibitor, a EGFR inhibitor, anti-mitotics (eg., taxanes), platinum-based agents (eg., cisplatin), DNA damaging agents (eg. Doxorubicin) and other anti-cancer therapies that are known to those skilled in the art. In other instances, the anti-KAAG1 antibodies and antigen binding fragments thereof may be administered with other therapeutic antibodies. These include, but are not limited to, antibodies that target EGFR, CD-20, and Her2.

[0706] The present invention relates in a further aspect thereof to a method for inhibiting the growth of KAAG1-expressing cell that are estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−), the method may comprise contacting the cell with an effective amount of the antibody or antigen binding fragment described herein.

[0707] The present invention also encompasses method of treating cancer or inhibiting the growth of a KAAG1 expressing cells that are estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−), in a mammal, the method may comprise administering the antibody or antigen binding fragment described herein to a mammal in need.

[0708] In further aspects, the present invention provides method of treatment, diagnostic methods and method of detection using the antibody or antigen binding fragment of the present invention and the use of these antibodies or antigen binding fragment in the manufacture of a pharmaceutical composition or drug for such purposes.

[0709] Method of treatment encompassed by the present invention includes administering an antibody or antigen binding fragment described herein to a mammal in need, and especially to a patient having or susceptible of having a cancer characterized as being estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−),

[0710] The invention also provides in further aspects, methods for reducing tumor spread, tumor invasion, tumor formation or for inducing tumor lysis, which may comprise administering an isolated antibody or antigen binding fragment to a mammal in need.

[0711] The invention therefore relates to the use of the isolated antibody or antigen binding fragment described herein in the (manufacture of a pharmaceutical composition for) treatment of cancer, reduction of tumor spread, tumor invasion, tumor formation or for inducing tumor lysis of KAAG1-expressing tumor cells that are estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−).

[0712] The antibody or antigen binding fragment may more particularly be applicable for malignant tumor including, for example, a malignant tumor having the ability to metastasize and/or tumor cells characterized by anchorage-independent growth. The antibody or antigen binding fragment of the present invention may also be used in the diagnosis of cancer. The diagnosis of cancer may be performed in vivo by administering the antibody or antigen binding fragment of the present invention to a mammal having or suspected of having a cancer. The diagnosis may also be performed ex vivo by contacting a sample obtained from the mammal with the antibody or antigen binding fragment and determining the presence or absence of cells (tumor cells) expressing KAAG1 or a KAAG1 variant.

[0713] The present invention also encompasses method of detecting cancer or detecting a KAAG1 expressing cells that are estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−), in a mammal, the method may comprise administering the antibody or antigen binding fragment described herein to a mammal in need.

[0714] The present invention relates in another aspect thereof to a method for detecting a cell expressing KAAG1 or a KAAG1 variant, the method may comprise contacting the cell with an antibody or antigen binding fragment described herein and detecting a complex formed by the antibody and the KAAG1- or KAAG1 variant-expressing cell. Exemplary embodiments of antibodies or antigen binding fragments used in detection methods are those which are capable of binding to the extracellular region of KAAG1.

[0715] Other exemplary embodiments of antibodies or antigen binding fragments used in detection methods are those which bind to KAAG1 or KAAG1 variant expressed at the surface of tumor cells that are estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−).

[0716] Another aspect of the invention relates a method for detecting KAAG1 (SEQ ID NO.:2), a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2 or a secreted form of circulating form of KAAG1 or KAAG1 variant, the method may comprise contacting a cell expressing KAAG1 or the KAAG1 variant or a sample (biopsy, serum, plasma, urine etc.) comprising or suspected of comprising KAAG1 or the KAAG1 variant with the antibody or antigen binding fragments described herein and measuring binding. The sample may originate from a mammal (e.g., a human) which may have cancer (e.g., breast cancer that is characterized as being estrogen receptor-negative (ER−), progesterone receptor negative (PgR−) and/or that lacks Her2 overexpression (Her2−), such as basal-like breast cancer or triple-negative breast cancer) or may be suspected of having cancer. The sample may be a tissue sample obtained from the mammal or a cell culture supernatant.

[0717] In accordance with the invention the sample may be a serum sample, a plasma sample, a blood sample or ascitic fluid obtained from the mammal. The antibody or antigen binding fragment described herein may advantageously detect a secreted or circulating form (circulating in blood) of KAAG1.

[0718] The method may comprise quantifying the complex formed by the antibody or antigen binding fragment bound to KAAG1 or to the KAAG1 variant.

[0719] The binding of an antibody to an antigen will cause an increase in the expected molecular weight of the antigen. A physical change therefore occurs upon specific binding of the antibody or antigen binding fragment and the antigen.

[0720] Such changes may be detected using, for example, electrophoresis followed by Western blot and coloration of the gel or blot, mass spectrometry, HPLC coupled with a computer or else. Apparatus capable of computing a shift in molecular weight are known in the art and include for example, Phosphorimager™.

[0721] When the antibody comprises for example a detectable label, the antigen-antibody complex may be detected by the fluorescence emitted by the label, radiation emission of the label, enzymatic activity of a label provided with its substrate or else.

[0722] Detection and/or measurement of binding between an antibody or antigen binding fragment and an antigen may be performed by various methods known in the art. Binding between an antibody or antigen binding fragment and an antigen may be monitored with an apparatus capable of detecting the signal emitted by the detectable label (radiation emission, fluorescence, color change etc.). Such apparatus provides data which indicates that binding as occurred and may also provide indication as to the amount of antibody bound to the antigen. The apparatus (usually coupled with a computer) may also be capable of calculating the difference between a background signal (e.g., signal obtained in the absence of antigen-antibody binding) or background noise and the signal obtained upon specific antibody-antigen binding. Such apparatuses may thus provide the user with indications and conclusions as to whether the antigen has been detected or not.

[0723] Additional aspects of the invention relate to kits which may include one or more container containing one or more antibodies or antigen binding fragments described herein.

Nucleic Acids, Vectors and Cells

[0724] Antibodies are usually made in cells allowing expression of the light chain and heavy chain expressed from a vector(s) comprising a nucleic acid sequence encoding the light chain and/or heavy chain.

[0725] The present therefore encompasses nucleic acids capable of encoding any of the CDRs, light chain variable regions, heavy chain variable regions, light chains, heavy chains described herein.

[0726] The present invention therefore relates in a further aspect to a nucleic acid encoding a light chain variable region and/or a heavy chain variable region of an antibody which is capable of specific binding to KAAG1.

[0727] Exemplary embodiments of nucleic acids encompassed by the present invention includes a nucleic acid selected from the group consisting of a nucleic acid having

at least 70% sequence identity (i.e., at least 75%, at least 80% sequence identity) with any one of SEQ ID NOs.:3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 45 and 47, fragments (e.g., of at least 10, at least 15, at least 20 consecutive nucleotides) and complement thereof.

[0728] In accordance with an embodiment of the invention, the nucleic acid may especially encode a light chain variable region and/or heavy chain variable region of an antibody which may be capable of inducing killing (elimination, destruction, lysis) of KAAG1- or KAAG1 variant-expressing tumor cells.

[0729] In accordance with another embodiment of the invention, the nucleic acid may especially encode a light chain variable region and/or heavy chain variable region of an antibody which may be capable of reducing spreading of KAAG1- or KAAG1 variant-expressing tumor cells.

[0730] In accordance with yet another embodiment of the invention, the nucleic acid may particularly encode a light chain variable region and/or heavy chain variable region of an antibody which may be capable of decreasing or impairing formation of KAAG1- or KAAG1 variant-expressing tumors.

[0731] Exemplary embodiments of nucleic acids of the present invention include nucleic acids encoding a light chain variable region comprising:

[0732] a. a CDRL1 sequence selected from the group consisting of SEQ ID NO.:72 and SEQ ID NO.:73;

[0733] b. a CDRL2 sequence selected from the group consisting of SEQ ID NO.:74, SEQ ID NO.: 75 and SEQ ID NO.:76, or;

[0734] c. a CDRL3 sequence selected from the group consisting of SEQ ID NO.:77, SEQ ID NO.:78 and SEQ ID NO.:79.

[0735] In accordance with the present invention, the nucleic acid may encode a light chain variable region which may comprise at least two CDRs of a CDRL1, a CDRL2 or a CDRL3.

[0736] Also in accordance with the present invention, the nucleic acid may encode a light chain variable region which may comprise one CDRL1, one CDRL2 and one CDRL3.

[0737] The present invention also relates to a nucleic acid encoding a heavy chain variable region comprising:

[0738] a. a CDRH1 sequence comprising SEQ ID NO.: 80;

[0739] b. a CDRH2 sequence selected from the group consisting of SEQ ID NO.:81, SEQ ID NO.:82, SEQ ID NO.:83, SEQ ID NO.:84 and SEQ ID NO.:85, or;

[0740] c. a CDRH3 sequence selected from the group consisting of SEQ ID NO.:86, SEQ ID NO.:87 and SEQ ID NO.:88.

[0741] In accordance with the present invention, the nucleic acid may encode a heavy chain variable region which may comprise at least two CDRs of a CDRH1, a CDRH2 or a CDRH3.

[0742] In accordance with the present invention, the nucleic acid may encode a heavy chain variable region which may comprise one CDRH1, one CDRH2 and one CDRH3.

[0743] Also encompassed by the present invention are nucleic acids encoding antibody variants having at least one conservative amino acid substitution.

[0744] In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution.

[0745] In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution in at least two of the CDRs.

[0746] In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution in the 3 CDRs.

[0747] In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitutions in at least one of the CDRs.

[0748] In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitutions in at least two of the CDRs.

[0749] In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitutions in the 3 CDRs.

[0750] Other aspects of the invention relate to a nucleic acid encoding a light chain variable region having at least 70%, 75%, 80% sequence identity with a sequence selected from the group consisting of SEQ ID NO.:16, SEQ ID NO.:20, SEQ ID NO.:24, SEQ ID NO.:103, SEQ ID NO.: 104, SEQ ID NO.:105, SEQ ID NO.:106, SEQ ID NO.:107, SEQ ID NO.:108, SEQ ID NO.:109, SEQ ID NO.:110, SEQ ID NO.:111, SEQ ID NO.:112, SEQ ID NO.:113, SEQ ID NO.:114, SEQ ID NO.:115, SEQ ID NO.:116, SEQ ID NO.:117, SEQ ID NO.:118, SEQ ID NO.:119, SEQ ID NO.:120, SEQ ID NO.:121, SEQ ID NO.:122, SEQ ID NO.:123, SEQ ID NO.:124 and SEQ ID NO.:125.

[0751] Yet other aspects of the invention relate to a nucleic acid encoding a heavy chain variable region having at least 70%. 75%, 80% sequence identity to a sequence selected from the group consisting of SEQ ID NO.:18, SEQ ID NO.:22, SEQ ID NO.:26, SEQ ID NO.:126, SEQ ID NO.: 127, SEQ ID NO.:128, SEQ ID NO.:129, SEQ ID NO.:130, SEQ ID NO.:131, SEQ ID NO.:132, SEQ ID NO.:133, SEQ ID NO.:134, SEQ ID NO.:135, SEQ ID NO.:136, SEQ ID NO.:137, SEQ ID NO.:138, SEQ ID NO.:139, SEQ ID NO.:140, SEQ ID NO.:141, SEQ ID NO.:142, SEQ ID NO.:143, SEQ ID NO.:144, SEQ ID NO.:145, SEQ ID NO.:146 and SEQ ID NO.:147.

[0752] In yet another aspect, the present invention relates to a vector comprising the nucleic acids described herein.

[0753] In accordance with the present invention, the vector may be an expression vector.

[0754] Vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host are known in the art. These elements may include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination.

[0755] In another aspect the present invention relates to an isolated cell that may comprise the nucleic acid described herein.

[0756] The isolated cell may comprise a nucleic acid encoding a light chain variable region and a nucleic acid encoding a heavy chain variable region either on separate vectors or on the same vector. The isolated cell may also

comprise a nucleic acid encoding a light chain and a nucleic acid encoding a heavy chain either on separate vectors or on the same vector.

[0757] In accordance with the present invention, the cell may be capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

[0758] In another aspect, the present invention provides a cell which may comprise and/or may express the antibody described herein.

[0759] In accordance with the invention, the cell may comprise a nucleic acid encoding a light chain variable region and a nucleic acid encoding a heavy chain variable region.

[0760] The cell may be capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

[0761] The examples below are presented to further outline details of the present invention.

EXAMPLES

Example 1

[0762] This example discloses the methods used to convert the Fabs into full IgG1 chimeric monoclonal antibodies.

[0763] Aside from the possibility of conducting interaction studies between the Fab monoclonals and the KAAG1 protein, the use of Fabs may be limited with respect to conducting meaningful in vitro and in vivo studies to validate the biological function of the antigen. Thus, it was necessary to transfer the light and heavy chain variable regions contained in the Fabs to full antibody scaffolds, to generate mouse-human chimeric IgG1s. The expression vectors for both the light and heavy immunoglobulin chains were constructed such that i) the original bacterial signal peptide sequences upstream of the Fab expression vectors were replaced by mammalian signal peptides and ii) the light and heavy chain constant regions in the mouse antibodies were replaced with human constant regions. The methods to accomplish this transfer utilized standard molecular biology techniques that are familiar to those skilled in the art.

[0764] Light chain expression vector—an existing mammalian expression plasmid, called pTTVH8G (Durocher et al., 2002), designed to be used in the 293E transient transfection system was modified to accommodate the mouse light chain variable region. The resulting mouse-human chimeric light chain contained a mouse variable region followed by the human kappa constant domain. The cDNA sequence encoding the human kappa constant domain was amplified by PCR with primers OGS1773 and OGS1774 (SEQ ID NOS:55 and 56, respectively). The nucleotide sequence and the corresponding amino acid sequence for the human kappa constant region are shown in SEQ ID NOS: 57 and 58, respectively. The resulting 321 base pair PCR product was ligated into pTTVH8G immediately downstream of the signal peptide sequence of human VEGF A (NM_003376). This cloning step also positioned unique restriction endonuclease sites that permitted the precise positioning of the cDNAs encoding the mouse light chain variable regions. The sequence of the final expression plasmid, called pTTVK1, is shown in SEQ ID NO.:59. Based on the sequences disclosed in Table 2, PCR primers specific for the light chain variable regions of antibodies 3D3, 3G10, 3C4 and 3A4 (SEQ ID NOS:15, 19, 23 and 47, respectively) were designed that incorporated, at their 5'-end, a sequence identical to the last 20 base pairs of the VEGF A signal peptide. The sequences of these primers are shown in SEQ ID NOS:60, 61, 62 and 213. The same reverse primer was used to amplify all three light chain variable regions of 3D3, 3G10 and 3C4 since the extreme 3'-ends were identical. This primer (SEQ ID NO.:63) incorporated, at its 3'-end, a sequence identical to the first 20 base pairs of the human kappa constant domain. Primer SE ID NO.:214 was used to amplify the 3A4 light chain variable region. Both the PCR fragments and the digested pTTVK1 were treated with the 3'-5' exonuclease activity of T4 DNA polymerase resulting in complimentary ends that were joined by annealing. The annealing reactions were transformed into competent *E. coli* and the expression plasmids were verified by sequencing to ensure that the mouse light chain variable regions were properly inserted into the pTTVK1 expression vector. Those skilled in the art will readily recognize that the method used for construction of the light chain expression plasmids applies to all anti-KAAG1 antibodies contained in the original Fab library.

[0765] Heavy chain expression vector—the expression vector that produced the heavy chain immunoglobulins was designed in a similar manner to the pTTVK1 described above for production of the light chain immunoglobulins. Plasmid pYD11 (Durocher et al., 2002), which contains the human IgGK signal peptide sequence as well as the CH2 and CH3 regions of the human Fc domain of IgG1, was modified by ligating the cDNA sequence encoding the human constant CH1 region. PCR primers OGS1769 and OGS1770 (SEQ ID NOS:64 and 65), designed to contain unique restriction endonuclease sites, were used to amplify the human IgG1 CH1 region containing the nucleotide sequence and corresponding amino acid sequence shown in SEQ ID NOS:66 and 67. Following ligation of the 309 base pair fragment of human CH1 immediately downstream of the IgGK signal peptide sequence, the modified plasmid (SEQ ID NO.:68) was designated pYD15. When a selected heavy chain variable region is ligated into this vector, the resulting plasmid encodes a full IgG1 heavy chain immunoglobulin with human constant regions. Based on the sequences disclosed in Table 2, PCR primers specific for the heavy chain variable regions of antibodies 3D3, 3G10, 3C4 and 3A4 (SEQ ID NOS:17, 21, 25 and 45, respectively) were designed that incorporated, at their 5'-end, a sequence identical to the last 20 base pairs of the IgGK signal peptide. The sequences of these primers are shown in SEQ ID NOS:69 (3D3 and 3G10 have the same 5'-end sequence), SEQ ID NO.: 70 or SEQ ID NO.:215 for 3A4. The same reverse primer was used to amplify all three heavy chain variable regions of 3D3, 3C4 and 3G10 since the extreme 3'-ends were identical. This primer (SEQ ID NO.:71) incorporated, at its 3'-end, a sequence identical to the first 20 base pairs of the human CH1 constant domain. For the 3A4 heavy chain variable region, SEQ ID NO.:216 was used. Both the PCR fragments and the digested pYD15 were treated with the 3'-5' exonuclease activity of T4 DNA polymerase resulting in complimentary ends that were joined by annealing. The annealing reactions were transformed into competent *E. coli* and the expression plasmids were verified by sequencing to ensure that the mouse heavy chain variable regions were properly inserted into the pYD15 expression vector. Those skilled in the art will readily recognize that the method used

for construction of the heavy chain expression plasmids applies to all anti-KAAG1 antibodies contained in the original Fab library.

[0766] Expression of human IgG1s in 293E cells—The expression vectors prepared above that encoded the light and heavy chain immunoglobulins were expressed in 293E cells using the transient transfection system (Durocher et al., 2002). Other methods of transient or stable expression may be used. The ratio of light to heavy chain was optimized in order to achieve the most yield of antibody in the tissue culture medium and it was found to be 9:1 (L:H). The ability of the anti-KAAG1 antibodies (monoclonal, chimeric or humanized) to bind to recombinant Fc-KAAG1 was measured by ELISA and compared with the original mouse Fabs.

[0767] The scheme used to convert other Fabs into a complete IgG (including the 3A4) and for expression of the antibodies is described in more details in international application No. PCT/CA2012/000296, the entire content of which is incorporated herein by reference.

Example 2

Humanization of the 3A4 Mouse Monoclonal Antibody

[0768] International patents No. PCT/CA2009/001586, PCT/CA2010/001795 and No. PCT/CA2012/000296, described exemplary methodology used to generate the humanized light chain and heavy chain variable regions.

[0769] Humanization of the 3A4 antibody light chain variable region involved 11 mutations to its proposed humanized framework for 100% framework humanization. Humanization of the 3A4 antibody heavy chain variable region involved 23 mutations to its proposed humanized framework for 100% framework humanization. These 100% humanized variable region sequences are labelled Lvh1 and Hvh1, respectively (SEQ ID NOs:189 and 194). Additional humanized sequences were also designed in which several residues from the 3A4 mouse sequences were retained based on careful structural and comparative sequence analyses that indicate a high probability of altering antigen-binding affinity if mutations are to be introduced at these positions. These sequences of the variable regions are labelled Lvh2, Hvh2, Hvh3 and Hvh4 (SEQ ID NOs: 190, 195, 196 and 197).

[0770] The two humanized light chain variants (including the constant region) are identified herein as Lh1 (SEQ ID NO.: 199) and Lh2 (SEQ ID NO.:200). The four humanized heavy chain variants (including the constant region are identified herein as Hh1 (SEQ ID NO.:202), Hh2 (SEQ ID NO.:203), Hh3 (SEQ ID NO.:204) and Hh4 (SEQ ID NO.:205). The two humanized light chain and 4 humanized heavy chain can be assembled into 8 humanized antibodies (Lh1Hh1, Lh1Hh2, Lh1Hh3, Lh1Hh4, Lh2Hh1, Lh2Hh2, Lh2Hh3, and Lh2Hh4).

[0771] In the case of 3A4 light-chain humanized sequence Lvh2 (SEQ ID NO:190), framework residues Val-L2 and Lys-L45 were retained from the mouse sequence since residue L2 is semi-buried, contacts both CDR-L1 and CDR-L3, and has antigen-contacting propensity, while residue L45 approaches the heavy-chain. We note that both these murine residues may occur in human frameworks. In the case of 3A4 heavy-chain humanized sequence Hvh2 (SEQ ID NO:195), framework residues Ile-H2 and Lys-L73 were retained from the mouse sequence since residue H2 is semi-buried, contacts both CDR-H1 and CDR-H3, and has antigen-contacting propensity, while residue H73 belongs to the Vernier zone supporting CDR-H2, and both these murine residues may occur in human frameworks. In the case of 3A4 heavy-chain humanized sequence Hvh3 (SEQ ID NO:196), Ile-H2 and Lys-L73 back-mutations were retained and in addition to these, framework residues Ile-H48, Ala-H67, Leu-H69 and Val-H71 were retained from the mouse sequence since all these additional murine residues are buried residues and belong to the Vernier zone supporting CDR-H2, and also murine residue H71 may occur in human frameworks. In the case of 3A4 heavy-chain humanized sequence Hvh4 (SEQ ID NO:197), all 6 back-mutations of the Hvh3 humanized variant were included plus additional two mouse framework residues Lys-H38 and Lys-H66 since they represent semi-buried residues close to CDR-H2. The resulting amino acid sequences of the murine and humanized chains are listed in Table 1. The alignment of the murine and humanized light chain variable regions is shown in FIG. **1***a* and the alignment of the murine and humanized heavy chain variable regions is shown in FIG. **1***b*.

[0772] FIGS. **2***a* and **2***b* is an alignment of the murine light chain variable region with the 100% humanized light chain variable region and the murine heavy chain variable region with the 100% humanized heavy chain variable region respectively. This figure illustrates the amino acids that are preserved and those that have been chosen for substitution.

Example 3

Assembly and Expression of 3A4 Humanized Variant Antibodies

[0773] The purpose of these investigations is to determine the kinetics parameters of anti-clusterin antibodies. In particular, to determine whether the humanization of the 3A4 anti-KAAG1 monoclonal antibody affects the kinetics parameters of its binding to human KAAG1. To this end, a kinetic analysis method was developed using the ProteOn XPR36 instrument from BioRad. Human KAAG1 was immobilized on a sensor chip. Full length antibodies or Fab fragments were injected and allowed to interact with the immobilized KAAG1.

Construction of Plasmid Encoding the Chimeric (Murine) Heavy and Light Chains of 3A4

[0774] The heavy and light chains of the chimeric antibody were amplified by PCR from the original murine immunoglobulin chains using the following oligonucleotide primer pairs: heavy chain, 5'-oligo encoded by SEQ ID NO: 206 and 3'-oligo encoded by SEQ ID NO:207; light chain, 5'-oligo encoded by SEQ ID NO: 208 and 3'-oligo encoded by SEQ ID NO:209. The resulting PCR products were digested by Hind III and cloned into pK-CR5 (SEQ ID NO:210) previously digested with Hind III.

Construction of Plasmids Encoding the Humanized Heavy Chain 3A4 Variants 1, 2, 3 and 4

[0775] The fragments coding for the humanized heavy chain region of the antibody 3A4 (Hh1, Hh2, Hh3 and Hh4) were ordered from GenScript (Piscataway, USA). The DNA fragments including the kozak and stop codon sequences were digested with HindIII and cloned into the HindIII site of plasmid pK-CR5 previously dephosphorylated with calf intestinal phosphatase (NEB) to prevent recircularization. FIG. **3***a* shows the map of the plasmid pK-CR5-3A4-HC-

variant1. All heavy chain variants of the humanized 3A4 were constructed in a similar manner.

Construction of Plasmids Encoding the Humanized Light Chain 3A4 Variants 1 and 2

[0776] The fragments coding for the human light chain regions of the antibody 3A4 (Lh1 and Lh2) were ordered from GenScript. The DNA fragments including the kozak and stop codon sequences was digested with BamHI and cloned into the BamHI site of plasmid pMPG-CR5 (SEQ ID NO:211) previously dephosphorylated with calf intestinal phosphatase (NEB) to prevent recircularization. FIG. **3***b* shows the map of the plasmid pMPG-CR5-3A4-LC-variant1. All light chain variants of the humanized 3A4 were constructed in a similar manner.

Transient Transfection Study

[0777] Plasmid DNA was isolated from small cultures of *E. coli* using the Mini-Prep kit (Qiagen Inc, Mississauga, ON) according to the manufacturer's recommendation. Briefly, 2 ml of LB medium containing 100 μg/ml of ampicillin were inoculated with a single colony picked after ligation and transformation. The cultures were incubated at 37° C. overnight with vigorous shaking (250 RPM). The plasmid was then isolated from 1.5 ml of culture using the protocols, buffers, and columns provided by the kit. The DNA was eluted using 50 μl of sterile water. Plasmid DNA was isolated from large culture of *E. coli* using the Plasmid Plus Maxi kit (Qiagen Inc, Mississauga, ON) according to the manufacturer's recommendation. 200 mL of LB medium containing 100 μg/mL ampicillin were inoculated with a single fresh colony of *E. coli* and incubated overnight at 37° C. with vigorous shaking (250 RPM). The bacteria (130 mL of culture for the heavy chain and 180 mL of culture for the light chain) were pelleted by centrifugation at 6000×g, for 15 min, at 4° C. and the plasmid was isolated using the protocols, buffers and columns provided by the kit. The pure plasmids was resuspended in sterile 50 mM Tris, pH8 and quantified by measuring the optical density at 260 nm. Before transfection the purified plasmid were sterilized by extraction with phenol/chloroform followed by ethanol precipitation. The plasmid were resuspended in sterile 50 mM Tris, pH 8 and quantified by optical density at 260 nm.

[0778] Before transfection, the cells (CHO-cTA) were washed with PBS and resuspended at a concentration of 4.0×10^6 cell/ml in growth medium (CD-CHO, Invitrogen) without dextran sulfate for 3 h in suspension culture. For each plasmid combination, 45 ml of cells were transfected by adding slowly 5 ml of CDCHO medium supplemented with 10 μg/ml of each plasmid and 50 μg/ml of polyethylenimine (PEI Max; Polysciences). The final concentration was 1 μg/ml of each plasmid and 5 μg/ml of PEI. After 2 h, the cells were transferred at 30° C. The next days, 50 μg/mL of dextran sulfate and 3.75 ml of each supplement (Efficient Feed A and B Invitrogen) were added to the cells and they were incubated at 30° C. for 13 days. 2.5 ml of Feed A and 2.5 ml of Feed B were added at day 4, 6, 8 and 11. On day 13, the supernatant was clarified by centrifugation and filtered through a 0.22 μM filter.

[0779] CHO cells (CHOcTA) were transfected with plasmids encoding the different variants of humanized heavy and light chains of the 3A4 antibody regulated by the CR5 promoter. Transfection with different combinations of light and heavy chains was performed. As control, cells were also transfected with plasmids encoding the chimeric/murine antibody.

Purification of Antibody

[0780] 15 ml of supernatant from the CHO cell transfections were concentrated by centrifugation using the Amicon Ultra (Ultacell-50k) cassette at 1500 rpm. The concentrated antibody (550 μl) was purified using the Nab spin kit Protein A Plus (Thermo Scientific) according to the manufacture's recommendations. The purified antibodies were then desalted using PBS and the concentrating Amicon Ultra (Ultracel-10K) cassette at 2500 rpm to a final volume of 250 μl. The purified antibody was quantified by reading the OD_{280} using the Nanodrop spectrophotometer and kept frozen at −20° C. An aliquote of the purified antibody was resuspended into an equal volume of Laemmli 2× and heated at 95° C. for 5 min and chilled on ice. A standard curve was made using known amount of purified human IgG1 kappa from Human Myeloma plasma (Athens Research). The samples were separated on a polyacrylamide Novex 10% Tris-Glycine gel (Invitrogen Canada Inc., Burlington, ON) and transferred onto a Hybond-N nitrocellulose membrane (Amersham Bioscience Corp., Baie d'Urfée, QC) for 1 h at 275 mA. The membrane was blocked for 1 h in 0.15% Tween 20, 5% skimmed milk in PBS and incubated for 1 hr with an Goat anti-Human IgG (H+L) conjugated to Cy5 (Jackson, Cat#109-176-099). The signal was revealed and quantified by scanning with the Typhoon Trio+ scanner (GE Healthcare). As shown in FIG. **4**, all combinations of the 3A4 humanized antibody variants were expressed in CHO cells.

Example 4

Kinetic Analysis of Murine and Humanized 3A4 Antibody

Supplies

[0781] GLM sensorchips, the Biorad ProteOn amine coupling kit (EDC, sNHS and ethanolamine), and 10 mM sodium acetate buffers were purchased from Bio-Rad Laboratories (Mississauga, ON). HEPES buffer, EDTA, and NaCl were purchased from from Sigma-Aldrich (Oakville, ON). Ten percent Tween 20 solution was purchased from Teknova (Hollister, Calif.). The goat anti-human IgG Fc fragment specific antibody was purchased from Jackson ImmunoResearch. The gel filtration column Superdex 75 10/300 GL was purchased from GE Healthcare.

Gel Filtration

[0782] The KAAG1 protein at a concentration of 3.114 mg/ml and a volume of 220 μL was injected onto the Superdex G75 column. The separation was done at 0.4 ml/min in HBST running buffer (see below) without Tween 20. The volume of the fractions collected was 500 μL. Concentration of KAAG1 in each fraction was determined by OD_{280} using an extension coefficient of 5500 and a MW of 8969. FIG. **5** represents the profile of the gel filtration of KAAG1. A small peak of potential aggregate is eluting at around 11 ml. The protein eluting at 13 ml was used as analyte for the SPR assay (fractions 15-19).

SPR Biosensor Assays

[0783] All surface plasmon resonance assays were carried out using a BioRad ProteOn XPR36 instrument (Bio-Rad Laboratories Ltd. (Mississauga, ON) with HBST running buffer (10 mM HEPES, 150 mM NaCl, 3.4 mM EDTA, and 0.05% Tween 20 pH 7.4) at a temperature of 25° C. The anti-mouse Fc capture surface was generated using a GLM sensorchip activated by a 1:5 dilution of the standard Bio-Rad sNHS/EDC solutions injected for 300 s at 30 μL/min in the analyte (horizontal) direction. Immediately after the activation, a 13 μg/mL solution of anti-human IgG Fc fragment specific in 10 mM NaOAc pH 4.5 was injected in the analyte direction at a flow rate of 25 μL/min until approximately 8000 resonance units (RUs) were immobilized. Remaining active groups were quenched by a 300 s injection of 1M ethanolamine at 30 μL/min in the analyte direction, and this also ensures mock-activated interspots are created for blank referencing. The screening of the 3A4 variants for binding to KAAG1 occurred in two steps: an indirect capture of 3A4 variants from cell supernatant onto the anti-human IgG Fc fragment specific surface in the ligand direction (vertical) followed by a KAAG1 injection in the analyte direction. Firstly, one buffer injection for 30 s at 100 uL/min in the ligand direction was used to stabilize the baseline. For each 3A4 capture, unpurified 3A4 variants in cell-culture media were diluted to 4% in HBST, or approximately 1.25 μg/mL of purifed 3A4 in HBST was used. Four to five 3A4 variants along with wild-type 3A4 were simultaneously injected in individual ligand channels for 240 s at flow 25 μL/min. This resulted in a saturating 3A4 capture of approximately 400-700 RUs onto the anti-human IgG Fc fragment specific surface. The first ligand channel was left empty to use as a blank control if required. This 3A4 capture step was immediately followed by two buffer injections in the analyte direction to stabilize the baseline, and then the gel filtration purified KAAG1 was injected. For a typical screen, five KAAG1 concentrations (8, 2.66, 0.89, 0.29, and 0.098 nM) and buffer control were simultaneously injected in individual analyte channels at 50 μL/min for 120 s with a 600s dissociation phase, resulting in a set of binding sensorgrams with a buffer reference for each of the captured 3A4 variants. The anti-human IgG Fc fragment specific-3A4 complexes were regenerated by a 18 s pulse of 0.85% phosphoric acid for 18 s at 100 μL/min to prepare the anti-human IgG Fc fragment specific surface for the next injection cycle. Sensorgrams were aligned and double-referenced using the buffer blank injection and interspots, and the resulting sensorgrams were analyzed using ProteOn Manager software v3.0. The kinetic and affinity values were determined by fitting the referenced sensorgrams to the 1:1 Langmuir binding model using local R_{max}, and affinity constants (K_D M) were derived from the resulting rate constants (k_d s^{-1}/k_a $M^{-1}s^{-1}$).

Determination of Rate and Affinity Constants

[0784] FIG. **6** summarizes the association (k_a, 1/Ms) and dissociation (k_d, 1/s) rate constants as well as affinity (K_D, M) constants for the interaction of KAAG1 with purified murine 3A4, murine 3A4 transiently expressed as a chimeric and transiently expressed humanized variants. These constants are graphically represented in FIG. **7***a-c*. The association rate constant is very similar for the pure parental, chimeric and humanized 3A4 variants (FIG. **7***a*). The dissociation rate constants is similar for the transiently express chimeric as compared to the pure parental 3A4 with suggest that the transfection procedure did not alter the parameters of the interaction of KAAG1 with the antibody (FIG. **7***b*). However, all humanized variants seem to have a slightly altered off rate, i.e. quicker dissociation rate (FIG. **7***b*). This is reflected in the affinity constants (FIG. **7***c*). In summary, there is a linear correlation between the binding affinity (log K_D) of the humanized variant and the number of back-mutations made in the parent antibody (LcHc) with a decrease in the binding affinity as the number of mutations is increasing. However, the difference in binding affinity is only 4 fold different between the worse variant (H1L1, 0.47 nM) which has no mouse residue retained and the best variant which has 10 mouse residues retained (H4L2, 0.1 nM). Finally, the binding affinity of all variants for KAAG1 was found to be sub-nanomolar and the best variant (H4L2, 0.1 nM) exhibited an affinity about 6-fold weaker than the murine (LcHc, 0.057 nM). Overall, these results indicate that humanization was successful as all of the variants displayed high affinity for KAAG1.

Example 5

Binding of 3A4 Humanized Variants to KAAG1 in an ELISA

[0785] ELISA methods were also used to compare the binding activity of the humanized 3A4 variants to the murine 3A4 antibody. Recombinant human KAAG1 was coated in 96-well plates O/N, washed and incubated for 1 h at RT with increasing quantities of murine or humanized 3A4 variants. Following another round of washing steps, an anti-human antibody conjugated to HRP was added to the wells and the bound 3A4 antibody was measured calorimetrically at Abs_{450}. As shown in FIG. **8***a*, the humanized variants (Lh1Hh1, Lh1Hh2, Lh1Hh3 and Lh1Hh4) displayed very similar binding to KAAG1 when compared to the murine 3A4 (LcHc), which has a high affinity of 0.016 nM. This result indicated that all four humanized heavy chain variants were comparable to the original h3A4 heavy chain when assembled with the L1 variant of the humanized light chain. FIG. **8***a* shows the results when the heavy chain variants were assembled with Lh2 variant of the 3A4 humanized light chain. In this instance, there was a difference in the binding of the variants. For example, Lh2hh4 was the variant with the closest profile compared to the murine 3A4. This was in agreement with the SPR data, which showed that the variant 4 of the heavy chain had the highest affinity for KAAG1. Taken together, these binding results show that the humanized variants all interact with human KAAG1 in this assay. Although there were some subtle differences, the binding in ELISA was in concordance with the SPR results.

Example 6

Binding of 3A4 Humanized Variants on the Surface of Cancer Cells

[0786] Flow cytometry was used to evaluate the capacity of the humanized 3A4 variants to interact with KAAG1 expressed on the surface of cancer cells. To this end, SKOV-3 ovarian cancer cells, which we had previously showed were efficiently bound by 3A4 by flow cytometry, were incubated with the eight humanized variants and the

original murine antibody. Briefly, SKOV-3 cells were detached from the plate with EDTA and incubated on ice with either 3.0 mg/ml, 0.3 mg/ml or 0.3 mg/ml of the antibodies for 1 h. After three washing steps, the cells were incubated with the secondary antibody, anti-human IgG-conjugated to FITC for 1 h on ice. Cell surface fluorescence was measured in a flow cytometer and the values are shown in the histogram of FIG. **9**. As depicted, all variants could detect KAAG1 on the surface on unpermeabilized and the strongest signals were obtained at the highest concentration of 3A4 antibodies (3 mg/ml) and decreased as the concentration of the antibody was decreased. Among the different variants, the ones with the most murine back-mutations (FIG. **9**, see Lh1Hh4 and Lh2Hh4) interacted with KAAG1 on the surface of cells with the highest activity. In fact, Lh1Hh4 and Lh2hh4 appeared to be slight improved cell surface binding to KAAG1 compared to the murine 3A4 antibody (LcHc).

Example 7

[0787] This example describes the use of anti-KAAG1 antibodies for detecting the expression of KAAG1 in TNBC.

[0788] As a means of determining if the KAAG1 antigen was present in TNBC samples, immunohistochemistry was conducted. Tissue microarrays were obtained that contained 139 breast tumor samples generated from patient biopsies. Paraffin-embedded epithelial breast tumor samples were placed on glass slides and fixed for 15 min at 50° C. Deparaffinization was conducted by treating 2× with xylene followed by dehydration in successive 5 min washes in 100%, 80%, and 70% ethanol. The slides were washed 3× in PBS for 5 min and treated with antigen retrieval solution (1 mM EDTA, pH 8.0) to unmask the antigen. Endogenous peroxide reactive species were removed by incubating slides with H_2O_2 in methanol and blocking was performed by incubating the slides with serum-free blocking solution (Santa Cruz Biotech) for 5 min at room temperature. The primary antibody (anti-KAAG1 3A4) was added for 1 h at room temperature. KAAG1-reactive antigen was detected by incubating with biotin-conjugated mouse anti-kappa followed by streptavidin-HRP tertiary antibody. Positive staining was revealed by treating the slides with DAB-hydrogen peroxide substrate for less than 5 min and subsequently counterstained with hematoxylin. The KAAG1 protein was found to be expressed at very high levels in the vast majority of breast tumor samples. A representative array containing 139 tumors is depicted in FIG. **10**. In particular, 15/20 biopsy samples confirmed to be TNBC (FIG. **10**, samples identified by an asterisk) were stained strongly for KAAG1 expression with the 3A4 antibody. Taken together, these immunohistochemical studies illustrate the utility of detecting KAAG1 in breast cancer, in particular TNBC, with the monoclonal antibodies.

Example 8

[0789] This example describes the use of anti-KAAG1 antibodies for detecting the expression of KAAG1 in TNBC cell lines.

[0790] Combined results from the bioinformatics analysis of the primary structure of the cDNA encoding KAAG1, biochemical studies, and immunohistochemical detection of the protein in epithelial cells suggested that the KAAG1 antigen was located at the cell surface. However, more direct evidence was required to demonstrate that KAAG1 is indeed expressed on the surface of TNBC cells. To conduct this analysis, breast cancer cell lines were obtained from a commercial vendor (ATCC, Manassas, Va.) and used in flow cytometry experiments. RT-PCR expression analyses using KAAG1 mRNA specific primers previously showed that certain breast cancer cell lines expressed KAAG1 mRNA (see PCT/CA2007/001134). Therefore some of these cell lines were selected to determine the presence of the KAAG1 antigen at their surface. To verify this, the triple-negative MDA-MB-231, MDA-MB-436, MDA-MB-468, BT-20 and BT-549 cell lines were tested for surface expression of KAAG1 using the 3A4 anti-KAAG1 antibody. In addition, breast cancer cell lines, which are not triple-negative, namely T47D and MCF-7, were also included in the analysis. Finally, a control cell line, 293-6E, that exhibits undetectable level of KAAG1 antigen expression was included as a negative control for the flow cytometry experiment (FCM). For the purpose of FCM analysis, the cells were harvested using 5 mM EDTA, counted with a hemocytometer, and resuspended in FCM buffer (0.5% BSA, 0.01% goat serum in 1×PBS) at a cell density of 2×10^6 cells/ml. Chimeric 3A4 anti-KAAG1 antibody or a control IgG were added to 100 μl of cells at a final concentration of 0.5 μg/ml and incubated on ice for 1 h. The cells were washed in cold FCM buffer to remove unbound antibodies, resuspended in 100 μl FCM buffer containing anti-human IgG conjugated to FITC secondary antibody (diluted 1:200) and incubated on ice for 45 min. Following another washing step in cold FCM buffer, the cells were resuspended in 300 μl FCM buffer and analyzed with a flow cytometer. 10 μg/ml propidium iodide was added to each sample to allow for gating of dead cells. The results from three independent experiments are shown in FIG. **11**, where the mean fluorescence intensity (MFI) fold Induction represents the geometric mean value of the signal obtained when the cells were incubated with 3A4 antibody over that of the negative human IgG control, which was arbitrarily set to 1. Incubation of the antibodies with the control 293-6EHEK-293 cells resulted in fluorescence signals that were similar to the signal obtained when the cells were incubated in the absence of the primary antibody. Furthermore, there was no significant difference between the signal obtained with 3A4 compared to the control IgG. Moreover, when the control IgG was incubated with the breast cancer cell lines, the signals were very similar to those obtained with the control 293-6E cells. By contrast, detectable fluorescence signal was observed when the 3A4 antibody was incubated with all breast cancer cells lines. Although variable amount of fluorescence was observed, the highest amount of KAAG1 was detected on the surface of MDA-MB-231 and BT-20 cell lines, two TNBC cell lines (see FIG. **11**, TNBC cell lines are indicated with an asterisk). In fact all five TNBC cell lines were positive for KAAG1 expression under these conditions. T47 D and MCF-7 cells also expressed KAAG1. Taken together, this flow cytometry analysis shows that TNBC cell line express high level of KAAG1 on their cell surface.

Example 9

[0791] Methods for Use of the 3A4 Anti-KAAG1 Antibody as an Antibody Conjugate

[0792] As demonstrated above, the KAAG1 antigen was detected by 3A4 on the surface of cancer cells using flow cytometry. There are several different molecular events that

can occur upon binding of an antibody to its target on the surface of cells. These include i) blocking accessibility to another cell-surface antigen/receptor or a ligand, ii) formation of a relatively stable antibody-antigen complex to allow cells to be targeted via ADCC or CDC, iii) signalling events can occur as exemplified by agonistic antibodies, iv) the complex can be internalized, or v) the complex can be shed from the cell surface. To address this question we examined the behavior of the 3A4 antibody-KAAG1 complex on the surface of the cells. The ovarian cancer cell line, SKOV3, was used as a positive control in this experiment since it was successfully used in previous internalization experiments (see PCT/CA2009/001586). MDA-MB-231 TNBC cells were plated, washed, and incubated with 0.5 μg/ml chimeric 3A4 antibody as described in Example 3. After washing, complete medium was added and the cells placed at 37° C. for up to 60 minutes. The cells were removed at the indicated times (see FIG. **12**), rapidly cooled, prepared for flow cytometry with FITC-conjugated anti-human IgG and the results were expressed as the percentage of mean fluorescence intensity remaining on the cell surface compared with the signal at time 0 minutes (see FIG. **12**, Surface signal (% remaining at 0 min). As illustrated in FIG. **12**, the fluorescence signal decreased rapidly when 3A4 was incubated with MDA-MB-231 cells (FIG. **12**, black bars, indicated by MDA-231 in the figure) and seemed to achieve a maximum loss of signal by 30-45 minutes. The loss of signal was comparable to that observed when 3A4 was incubated with the SKOV3 cells (FIG. **12**, grey bars). This result indicates that the 3A4/KAAG1 complex disappeared from the cells which indicated that an internalization of the complex likely occurred. Preliminary studies to elucidate the mechanism responsible for this decrease in cell-surface fluorescence have revealed that the complex appears to be internalized. Similar results are expected with humanized 3A4 antibodies.

[0793] Similar results were observed in two additional TNBC cell lines, namely MDA-MB-436 (FIG. **13**) and BT-20 (FIG. **14**) confirming that the internalization of the 3A4/KAAG1 complex on the surface of multiple TNBC cell lines. By contrast, despite similar MFI levels of 3A4 binding on the surface of MDA-MB-436 and T47D (FIG. **11**), the loss of signal at the cell surface was not observed when 3A4 was incubated with the T47D cell line. This finding suggests the possibility that internalization of the 3A4/KAAG1 complex might occur to a higher degree in TNBC cells (FIG. **15**) compared with cells that are not triple-negative.

[0794] These findings were further confirmed by conducting immunofluorescence on live cells to see if this internalization could be microscopically observed. MDA-MB-231 cells were seeded on cover slips and once the cells were properly adhered, fresh medium was added containing the 3A4 anti-KAAG1 chimeric antibody at 10 ug/ml and incubating at 37 C for 4 h. The cells were washed in PBS then fixed in 4% paraformaldehyde (in PBS) for 20 min. After washing, the cells were permeabilized with 0.1% Triton X-100 in PBS for 5 min. Blocking was performed with 1.5% dry milk in PBS for 1 h. Lysosomal-associated membrane protein 1 (LAMP1, Chang et al., 2002) was detected by incubating with anti-LAMP1 (Santa Cruz, sc-18821, diluted 1:100) in 1.5% milk in PBS for 2 h. After washing in PBS, the secondary antibodies were added together in 1.5% milk and incubated for 1 h. For the anti-KAAG1 chimeric antibody the secondary antibody was a Rhodamine Red-X conjugated donkey anti-human IgG (H+L) diluted 1:300. For the anti-LAMP1 antibody the secondary antibody was a DyLight488-conjugated goat anti-mouse IgG (H+L) diluted 1:300. Both secondary antibodies were from Jackson ImmunoResearch. The coverslips were washed in PBS and mounted in ProLong Gold antifade reagent with DAPI. As seen in FIG. **7**, after 4 hours of incubation at 37 C in the presence of MDA-MB-231 cancer cells, the 3A4 antibody was able to be detected in complexes predominantly near the peri-nuclear area (arrows, see red staining in the left panel in FIG. **16**), which is typical of endosomal-lysosomal-based internalization pathways. This observation was further confirmed when a lysosomal marker, LAMP1 was visualized and was found to be also expressed in these areas (arrows, see green staining in the middle panel in FIG. **16**). Importantly, the merging of the two images resulted in the appearance of yellow-orange structures indicating that the 3A4 and the anti-LAMP1 antibodies were present in the same structures (arrows, see yellow staining in the right panel in FIG. **16**). The co-localization of 3A4, which binds to KAAG1 on the surface of cancer cells, with LAMP1, a marker of late endosomes/lysosomes, shows that the antibody/antigen complex was internalized and that it follows a pathway that is amenable for the release of a payload that would be conjugated to the 3A4 antibody. Identical results were observed in another TNBC cell line, BT-20 (see FIG. **17**).

[0795] Taken together, these studies demonstrated that antibodies specific for KAAG1 such as 3A4 might have uses as an antibody conjugate, in particular, as an antibody-drug conjugate (ADC). Thus, the high level of TNBC specificity of KAAG1 coupled with the capacity of this target to be internalized in cells support the development of applications as an ADC.

Example 10

[0796] In order to demonstrate that anti-KAAG1 antibodies can efficiently target and kill cells lacking ER protein expression, PgR protein expression and/or showing absence of HER2 protein over-expression, we generated two antibody drug conjugates (ADCs); 3A4-ADC1 and 3A4-ADC2.

[0797] To that effect, we used the chimeric 3A4 antibody and conjugated a cytotoxic drug via a highly stable peptide linker that is selectively cleaved by lysosomal enzymes after internalization (3A4-ADC1), or conjugated with another anti-mitotic drug via a non-cleavable linker (3A4-ADC2). The cytotoxic drug may become active once internalized in the cells.

[0798] The ability of the 3A4 ADCs to detect KAAG1 on the surface of TNBC cells was determined using flow cytometry using the methods described herein. Briefly, unconjugated 3A4, 3A4-ADC1, 3A4-ADC2 and a control IgG were incubated in the presence of MDA-231 TNBC cells, which are KAAG1 positive. Results indicated that the conjugation of 3A4 with either drug did not affect its binding to triple negative breast cancer cells such as MDA-231 (data not shown).

[0799] Having confirmed that the 3A4 ADCs could bind to KAAG1 expressed on the surface of TNBC cells, their cytotoxicity against these cells was evaluated in cell proliferation assays. MDA-231 or TOV-112D cells were cultured as described above in previous examples. The cells were seeded at 3000 cells/well in 96-well plates in 200 μl of media per well overnight at 37° C., in 5% CO_2. The next day, media was replaced with fresh media containing antibodies, at concentrations ranging from 0.122 nM to 500 nM, and

incubated at 37° C. for 72 h. All conditions were performed in triplicate wells. The number of surviving cells was determined by performing a cellular proliferation assay, using CellTiter 96 Aqueous One Solution (Promega, Madison, Wis.), following manufacturer's protocol. Following the collection of the raw data, the results were expressed as the percentage survival compared to the number of cells in the wells treated with PBS, which was set to 100%. Results indicated that the unconjugated 3A4 did not affect the proliferation of MDA-231 cells at all concentrations tested. In contrast, the 3A4 ADCs tested showed significant cytotoxicity.

[0800] These results indicate that 3A4 antibody conjugates may be used as an alternative treatment for patients having triple negative breast cancer or basal-like breast cancer. Similar results are expected for conjugates based on humanized 3A4 antibodies.

[0801] The present description refers to a number of documents, the content of which is incorporated herein by reference in their entirety.

Sequences Referred to in the Description

[0802]

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SEQ ID NO.: 17
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CAAGGCTTCGGGCTACATATTTACTGACTATGAGATACACTGGGTGAAGCAGACTCCTGTGCATG

GCCTGGAATGGATTGGGGTTATTGATCCTGAAACTGGTAATACTGCCTTCAATCAGAAGTTCAAG

GGCAAGGCCACACTGACTGCAGACATATCCTCCAGCACAGCCTACATGGAACTCAGCAGTTTGAC

ATCTGAGGACTCTGCCGTCTATTACTGTATGGGTTATTCTGATTATTGGGGCCAAGGCACCACTC

TCACAGTCTCCTCA

SEQ ID NO.: 18
EVQLQQSVAELVRPGASVTLSCKASGYIFTDYEIHWVKQTPVHGLEWIGVIDPETGNTAFNQKFK

GKATLTADISSSTAYMELSSLTSEDSAVYYCMGYSDYWGQGTTLTVSS

SEQ ID NO.: 19
GATGTTTTGATGACCCAAACTCCACGCTCCCTGTCTGTCAGTCTTGGAGATCAAGCCTCCATCTC

TTGTAGATCGAGTCAGAGCCTTTTACATAGTAATGGAAACACCTATTTAGAATGGTATTTGCAGA

AACCAGGCCAGCCTCCAAAGGTCCTGATCTACAAAGTTTCCAACCGATTTTCTGGGGTCCCAGAC

AGGTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCGGAGTGGAGGCTGAGGA

TCTGGGAGTTTATTACTGCTTTCAAGGTTCACATGTTCCTCTCACGTTCGGTGCTGGGACCAAGC

TGGAGCTGAAA

SEQ ID NO.: 20
DVLMTQTPRSLSVSLGDQASISCRSSQSLLHSNGNTYLEWYLQKPGQPPKVLIYKVSNRFSGVPD

RFSGSGSGTDFTLKISGVEAEDLGVYYCFQGSHVPLTFGAGTKLELK

SEQ ID NO.: 21
GAGATCCAGCTGCAGCAGTCTGGACCTGAGTTGGTGAAGCCTGGGGCTTCAGTGAAGATATCCTG

TAAGGCTTCTGGATACACCTTCACTGACAACTACATGAACTGGGTGAAGCAGAGCCATGGAAAGA

GCCTTGAGTGGATTGGAGATATTAATCCTTACTATGGTACTACTACCTACAACCAGAAGTTCAAG

GGCAAGGCCACATTGACTGTAGACAAGTCCTCCCGCACAGCCTACATGGAGCTCCGCGGCCTGAC

ATCTGAGGACTCTGCAGTCTATTACTGTGCAAGAGATGACTGGTTTGATTATTGGGGCCAAGGGA

CTCTGGTCACTGTCTCTGCA

SEQ ID NO.: 22
EIQLQQSGPELVKPGASVKISCKASGYTFTDNYMNWVKQSHGKSLEWIGDINPYYGTTTYNQKFK

GKATLTVDKSSRTAYMELRGLTSEDSAVYYCARDDWFDYWGQGTLVTVSA

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SEQ ID NO.: 23
GACATCGTTATGTCTCAGTCTCCATCTTCCATGTATGCATCTCTAGGAGAGAGAGTCACTATCAC

TTGCAAGGCGAGTCAGGACATTCATAACTTTTTAAACTGGTTCCAGCAGAAACCAGGAAAATCTC

CAAAGACCCTGATCTTTCGTGCAAACAGATTGGTAGATGGGGTCCCATCAAGGTTCAGTGGCAGT

GGATCTGGGCAAGATTATTCTCTCACCATCAGCAGCCTGGAGTTTGAAGATTTGGGAATTTATTC

TTGTCTACAGTATGATGAGATTCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAGA

SEQ ID NO.: 24
DIVMSQSPSSMYASLGERVTITCKASQDIHNFLNWFQQKPGKSPKTLIFRANRLVDGVPSRFSGS

GSGQDYSLTISSLEFEDLGIYSCLQYDEIPLTFGAGTKLELR

SEQ ID NO.: 25
GAGGTGCAGCTTCAGGAGTCAGGACCTGACCTGGTGAAACCTTCTCAGTCACTTTCACTCACCTG

CACTGTCACTGGCTTCTCCATCACCAGTGGTTATGGCTGGCACTGGATCCGGCAGTTTCCAGGAA

ACAAACTGGAGTGGATGGGCTACATAAACTACGATGGTCACAATGACTACAACCCATCTCTCAAA

AGTCGAATCTCTATCACTCAAGACACATCCAAGAACCAGTTCTTCCTGCAGTTGAATTCTGTGAC

TACTGAGGACACAGCCACATATTACTGTGCAAGCAGTTACGACGGCTTATTTGCTTACTGGGGCC

AAGGGACTCTGGTCACTGTCTCTGCA

SEQ ID NO.: 26
EVQLQESGPDLVKPSQSLSLTCTVTGFSITSGYGWHWIRQFPGNKLEWMGYINYDGHNDYNPSLK

SRISITQDTSKNQFFLQLNSVTTEDTATYYCASSYDGLFAYWGQGTLVTVSA

SEQ ID NO.: 27
KSSQSLLNSNFQKNFLA

SEQ ID NO.: 28
FASTRES

SEQ ID NO.: 29
QQHYSTPLT

SEQ ID NO.: 30
GYIFTDYEIH

SEQ ID NO.: 31
VIDPETGNTA

SEQ ID NO.: 32
MGYSDY

SEQ ID NO.: 33
RSSQSLLHSNGNTYLE

SEQ ID NO.: 34
KVSNRFS

SEQ ID NO.: 35
FQGSHVPLT

SEQ ID NO.: 36
GYTFTDNYMN

SEQ ID NO.: 37
DINPYYGTTT

SEQ ID NO.: 38
ARDDWFDY

SEQ ID NO.: 39
KASQDIHNFLN

SEQ ID NO.: 40
RANRLVD

SEQ ID NO.: 41
LQYDEIPLT

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SEQ ID NO.: 42
GFSITSGYGWH

SEQ ID NO.: 43
YINYDGHND

SEQ ID NO.: 44
ASSYDGLFAY

SEQ ID NO.: 45 - 3A4 heavy chain variable region nucleotide sequence
CAGATCCAGTTGGTGCAATCTGGACCTGAGATGGTGAAGCCTGGGGCTTCAGTGAAGATGTCCTG

TAAGGCTTCTGGATACACATTCACTGACGACTACATGAGCTGGGTGAAACAGAGCCATGGAAAGA

GCCTTGAGTGGATTGGAGATATTAATCCTTACAACGGTGATACTAACTACAACCAGAAGTTCAAG

GGCAAGGCCATATTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAGCTCAACAGCCTGAC

ATCGGAAGACTCAGCAGTCTATTACTGTGCAAGAGACCCGGGGGCTATGGACTACTGGGGTCAAG

GAACCTCAGTCACCGTCTCCTCA

SEQ ID NO.: 46 - 3A4 heavy chain variable region polypeptide sequence
QIQLVQSGPEMVKPGASVKMSCKASGYTFTDDYMSWVKQSHGKSLEWIGDINPYNGDTNYNQKFK

GKAILTVDKSSSTAYMQLNSLTSEDSAVYYCARDPGAMDYWGQGTSVTVSS

SEQ ID NO.: 47 - 3A4 light chain variable region nucleotide sequence
GATGTTGTGATGACCCAAACTCCACTCTCCCTGGCTGTCAGTCTTGGAGATCAAGCCTCCATCTC

TTGCAGATCTAGTCAGAGCCTTCTACATAGTAATGGAAACACCTATTTAGAATGGTACCTTCAGA

AACCAGGCCAGTCTCCAAAGCTCCTGATCCACACAGTTTCCAACCGATTTTCTGGGGTCCCAGAC

AGATTCAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGA

TCTGGGAGTTTATTACTGCTTTCAAGGTTCACATGTTCCGCTCACGTTCGGTGCTGGGACCAGGC

TGGAGCTGAAA

SEQ ID NO.: 48 - 3A4 light chain variable region polypeptide sequence
DVVMTQTPLSLAVSLGDQASISCRSSQSLLHSNGNTYLEWYLQKPGQSPKLLIHTVSNRFSGVPD

RFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPLTFGAGTRLELK

SEQ ID NO.: 49 - 3A4 heavy chain CDR1 polypeptide sequence
GYTFTDDYMS

SEQ ID NO.: 50 - 3A4 heavy chain CDR2 polypeptide sequence
DINPYNGDTNYNQKFKG

SEQ ID NO.: 51 - 3A4 heavy chain CDR3 polypeptide sequence
DPGAMDY

SEQ ID NO.: 52 - 3A4 light chain CDR1 polypeptide sequence
RSSQSLLHSNGNTYLE

SEQ ID NO.: 53 - 3A4 light chain CDR2 polypeptide sequence
TVSNRFS

SEQ ID NO.: 54 - 3A4 light chain CDR3 polypeptide sequence
FQGSHVPLT

SEQ ID NO.: 55
GTAAGCAGCGCTGTGGCTGCACCATCTGTCTTC

SEQ ID NO.: 56
GTAAGCGCTAGCCTAACACTCTCCCCTGTTGAAGC

SEQ ID NO.: 57
GCTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGC

CTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATA

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ACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTAC

AGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA

AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

SEQ ID NO.: 58
AVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY

SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO.: 59
CTTGAGCCGGCGGATGGTCGAGGTGAGGTGTGGCAGGCTTGAGATCCAGCTGTTGGGGTGAGTAC

TCCCTCTCAAAAGCGGGCATTACTTCTGCGCTAAGATTGTCAGTTTCCAAAAACGAGGAGGATTT

GATATTCACCTGGCCCGATCTGGCCATACACTTGAGTGACAATGACATCCACTTTGCCTTTCTCT

CCACAGGTGTCCACTCCCAGGTCCAAGTTTAAACGGATCTCTAGCGAATTCATGAACTTTCTGCT

GTCTTGGGTGCATTGGAGCCTTGCCTTGCTGCTCTACCTCCACCATGCCAAGTGGTCCCAGGCTT

GAGACGGAGCTTACAGCGCTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG

TTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT

ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACA

GCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACAC

AAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAG

GGGAGAGTGTTAGGGTACCGCGGCCGCTTCGAATGAGATCCCCCGACCTCGACCTCTGGCTAATA

AAGGAAATTTATTTTCATTGCAATAGTGTGTTGGAATTTTTTGTGTCTCTCACTCGGAAGGACAT

ATGGGAGGGCAAATCATTTGGTCGAGATCCCTCGGAGATCTCTAGCTAGAGCCCCGCCGCCGGAC

GAACTAAACCTGACTACGGCATCTCTGCCCCTTCTTCGCGGGGCAGTGCATGTAATCCCTTCAGT

TGGTTGGTACAACTTGCCAACTGGGCCCTGTTCCACATGTGACACGGGGGGGGACCAAACACAAA

GGGGTTCTCTGACTGTAGTTGACATCCTTATAAATGGATGTGCACATTTGCCAACACTGAGTGGC

TTTCATCCTGGAGCAGACTTTGCAGTCTGTGGACTGCAACACAACATTGCCTTTATGTGTAACTC

TTGGCTGAAGCTCTTACACCAATGCTGGGGGACATGTACCTCCCAGGGGCCCAGGAAGACTACGG

GAGGCTACACCAACGTCAATCAGAGGGGCCTGTGTAGCTACCGATAAGCGGACCCTCAAGAGGGC

ATTAGCAATAGTGTTTATAAGGCCCCCTTGTTAACCCTAAACGGGTAGCATATGCTTCCCGGGTA

GTAGTATATACTATCCAGACTAACCCTAATTCAATAGCATATGTTACCCAACGGGAAGCATATGC

TATCGAATTAGGGTTAGTAAAAGGGTCCTAAGGAACAGCGATATCTCCCACCCCATGAGCTGTCA

CGGTTTTATTTACATGGGGTCAGGATTCCACGAGGGTAGTGAACCATTTTAGTCACAAGGGCAGT

GGCTGAAGATCAAGGAGCGGGCAGTGAACTCTCCTGAATCTTCGCCTGCTTCTTCATTCTCCTTC

GTTTAGCTAATAGAATAACTGCTGAGTTGTGAACAGTAAGGTGTATGTGAGGTGCTCGAAAACAA

GGTTTCAGGTGACGCCCCCAGAATAAAATTTGGACGGGGGGTTCAGTGGTGGCATTGTGCTATGA

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GAATTTATGGCTATGGGCAACACATAATCCTAGTGCAATATGATACTGGGGTTATTAAGATGTGT

CCCAGGCAGGGACCAAGACAGGTGAACCATGTTGTTACACTCTATTTGTAACAAGGGGAAAGAGA

GTGGACGCCGACAGCAGCGGACTCCACTGGTTGTCTCTAACACCCCCGAAAATTAAACGGGGCTC

CACGCCAATGGGGCCCATAAACAAAGACAAGTGGCCACTCTTTTTTTTGAAATTGTGGAGTGGGG

GCACGCGTCAGCCCCCACACGCCGCCCTGCGGTTTTGGACTGTAAAATAAGGGTGTAATAACTTG

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CGGGGAATACCTGCATAAGTAGGTGGGCGGGCCAAGATAGGGGCGCGATTGCTGCGATCTGGAGG

ACAAATTACACACACTTGCGCCTGAGCGCCAAGCACAGGGTTGTTGGTCCTCATATTCACGAGGT

CGCTGAGAGCACGGTGGGCTAATGTTGCCATGGGTAGCATATACTACCCAAATATCTGGATAGCA

TATGCTATCCTAATCTATATCTGGGTAGCATAGGCTATCCTAATCTATATCTGGGTAGCATATGC

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CTGTATCCGGGTAGCATATGCTATCCTCACGATGATAAGCTGTCAAACATGAGAATTAATTCTTG

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AGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATA

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TATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTG

CCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTA

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CCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTT

GAGATCCTTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTG

GTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCA

GATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCAC

CGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGT

CTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGG

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GGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGG

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TTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGC

TCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATAC

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GGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCT

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CGACCGGATCGGAAAACCTCTCGAGAAAGGCGTCTAACCAGTCACAGTCGCAAGGTAGGCTGAGC

ACCGTGGCGGGCGGCAGCGGGTGGCGGTCGGGGTTGTTTCTGGCGGAGGTGCTGCTGATGATGTA

ATTAAAGTAGGCGGT

SEQ DI NO.: 60
ATGCCAAGTGGTCCCAGGCTGACATTGTGATGACCCAGTCTCC

SEQ ID NO.: 61
ATGCCAAGTGGTCCCAGGCTGATGTTTTGATGACCCAAACTCC

SEQ ID NO.: 62
ATGCCAAGTGGTCCCAGGCTGACATCGTTATGTCTCAGTCTCC

SEQ ID NO.: 63
GGGAAGATGAAGACAGATGGTGCAGCCACAGC

SEQ ID NO.: 64
GTAAGCGCTAGCGCCTCAACGAAGGGCCCATCTGTCTTTCCCCTGGCCCC

SEQ ID NO.: 65
GTAAGCGAATTCACAAGATTTGGGCTCAACTTTCTTG

SEQ ID NO.: 66
GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC

AGCAGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAG

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AGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA

CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGT

SEQ ID NO.: 67
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL

SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

SEQ ID NO.: 68
CTTGAGCCGGCGGATGGTCGAGGTGAGGTGTGGCAGGCTTGAGATCCAGCTGTTGGGGTGAGTAC

TCCCTCTCAAAAGCGGGCATTACTTCTGCGCTAAGATTGTCAGTTTCCAAAAACGAGGAGGATTT

GATATTCACCTGGCCCGATCTGGCCATACACTTGAGTGACAATGACATCCACTTTGCCTTTCTCT

CCACAGGTGTCCACTCCCAGGTCCAAGTTTGCCGCCACCATGGAGACAGACACACTCCTGCTATG

GGTACTGCTGCTCTGGGTTCCAGGTTCCACTGGCGGAGACGGAGCTTACGGGCCCATCTGTCTTT

CCCCTGGCCCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA

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TCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC

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CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGT

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CCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACC

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CCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGA

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TGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTC

CTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAA

CCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGT

CAGTGAGCGAGGAAGCGTACATTTATATTGGCTCATGTCCAATATGACCGCCATGTTGACATTGA

TTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTT

CCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGA

CGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTG

-continued

GAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTCCGCCCCC

TATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTACGGGACT

TTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAG

TACACCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGT

CAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAATAACCCCGCCC

CGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCGTTTAGTG

AACCGTCAGATCCTCACTCTCTTCCGCATCGCTGTCTGCGAGGGCCAGCTGTTGGGCTCGCGGTT

GAGGACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAACCCGTCGGCCTCCGAACGGT

ACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAACCTCTCGAGAAAGGC

GTCTAACCAGTCACAGTCGCAAGGTAGGCTGAGCACCGTGGCGGGCGGCAGCGGGTGGCGGTCGG

GGTTGTTTCTGGCGGAGGTGCTGCTGATGATGTAATTAAAGTAGGCGGT

SEQ ID NO.: 69
GGGTTCCAGGTTCCACTGGCGAGGTTCAGCTGCAGCAGTCTGT

SEQ ID NO.: 70
GGGTTCCAGGTTCCACTGGCGAGGTGCAGCTTCAGGAGTCAGG

SEQ ID NO: 71
GGGGCCAGGGGAAAGACAGATGGGCCCTTCGTTGAGGC

SEQ ID NO.: 89: Exemplary embodiment of CDRL1
K-S-S-Q-S-L-L-N/H-S/T-S/N/D-N/G-Q/N/K-K/L-N-Y-L-A

SEQ ID NO.: 90: Exemplary embodiment of CDRL1
K-A-S-Q-D-I-H-N/T-Y/F-L-N

SEQ ID NO.: 91: Exemplary embodiment of CDRL2
F-A-S-T-R-E-S

SEQ ID NO.: 92: Exemplary embodiment of CDRL2
L-V-S-K-L-D-S

SEQ ID NO.: 93: Exemplary embodiment of CDRL2
R-A-N-R-L-V-D

SEQ ID NO.: 94: Exemplary embodiment of CDRL3
Q-Q-H-Y-S-T-P-L-T

SEQ ID NO.: 95: Exemplary embodiment of CDRL3
W/L-Q-Y/G-D/T-A/E/H-F-P-R-T

SEQ ID NO.: 96: Exemplary embodiment of CDRH1 1
G-Y-T/I-F-T-D/E-Y-E/N-M/I/V-H

SEQ ID NO.: 97: Exemplary embodiment of CDRH1
G-F-T/S-I-T-S-G-Y-G-W-H

SEQ ID NO.: 98: Exemplary embodiment of CDRH2
V/N/G-I/L-D-P-E/A/G-T/Y-G-X-T-A

SEQ ID NO.: 99: Exemplary embodiment of CDRH2
Y-I-N/S-F/Y-N/D-G

SEQ ID NO.: 100: Exemplary embodiment of CDRH3
M-G-Y-S/A-D-Y

SEQ ID NO.: 101: Exemplary embodiment of CDRH3
A-S-S-Y-D-G-F-L-A-Y

SEQ ID NO.: 102: Exemplary embodiment of CDRH3 3
A-R/W-W/F-G-L-R-Q/N

SEQ ID NO. 103- 3A2 light chain variable region
DAVMTQIPLTLSVTIGQPASLSC**KSSQSLLHSDGKTYLN**WLLQRPGQSPKRLIS**LVSKLDS**GVPD

RFTGSGSGTDFTLKISRVEAEDLGLYYC**WQGTHFPRT**FAGGTNLEIK

-continued

SEQ ID NO. 104 3F6 light chain variable region
SIVMTQTPLTLSVTIGQPASITC**KSSQSLLYSDGKTYLN**WLLQRPGQSPKRLIS**LVSKLDS**GVPD

GFTGSGSGTDFTLKISRVEAEDLGVYYC**WQGTHFPRT**FGGGTKLEIK

SEQ ID NO. 105- 3E8 light chain variable region
DAVMTQIPLTLSVTIGQPASISC**KSSQSLLHSDGKTYLN**WLLQRPGQSPKRLIY**LVSKLDS**GVPD

RFTGSGSGTDFTLKISRVEAEDLGVYYC**WQGTHFPRT**FGGGTKLEIK

SEQ ID NO. 106- 3E10 light chain variable region
DIVMTQAAPSVPVTPGESVSISC**RSSKSLLHSNGNTYLY**WFLQRPGQSPQLLIY**RMSNLAS**GVPD

RFSGSGSGTAFTLRISRVEAEDVGVYYC**MQHLEYPYT**FGGGTKLEIK

SEQ ID NO. 107- 3A9 light chain variable region
DIVMTQSPSSLAMSLGQKVTMSC**KSSQSLLNSNNQLNYLA**WYQQKPGQSPKLLVY**FASTRKS**GVP

DRFIGSGSGTDFTLTITSVQAEDLADYFC**QQHFNTPLT**FGAGTKLELK

SEQ ID NO. 108- 3B1 light chain variable region
DIVMTQSPSSLAISVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVF**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSIPLT**FGAGTKLELK

SEQ ID NO. 109- 3G5 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVF**FASTRES**GVP

DRFIGSGSGTDFTLTITSVQAEDLADYFC**QQHYSIPLT**FGSGTKLELK

SEQ ID NO. 110- 3B2 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVY**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSIPLT**FGAGTKLELK

SEQ ID NO. 111- 3B8 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVY**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 112- 3G8 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVY**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 113- 3F7 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLIY**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 114- 3E9 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVY**FASTRES**GVP

DRFIGSGSGTEFTLTITSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 115- 3C3 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVY**FGSTRES**GVP

DRFIGSGSGTDFTLTISGVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 116- 3E12 light chain variable region
DIVMTQSPSSLAMSVGQKVTMNC**KSSQSLLNRSNQKNYLA**WYQQKPGQSPKLLVY**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSIPLT**FGAGTKLELK

SEQ ID NO. 117- 4A2 light chain variable region
DIVMTQSPSSLAMSVGQKVTMNC**KSSQSLLNNSNQKNYLA**WYQQKPGQSPKLLLY**FASTRES**GVP

DRFIGSGSGTYFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLDLK

SEQ ID NO. 118- 3F10 light chain variable region
DIVMTQSPSSLTMSVGQKVTMSC**KSSQSLLNTSNQLNYLA**WYQQKPGQSPKLLVY**FASTTES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

-continued

SEQ ID NO. 119- 3F4 light chain variable region
DIVMTQSPSSLTVTAGEKVTMSC**KSSQSLLNTSNQKNYLA**WYQQKPGQSPKLLVY**FASTRAS**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 120- 3B11 light chain variable region
DIVMTQSPSSLAMSVGQKVTMSC**KSSQSLLNSSNQKNYLA**WYQQKPGQSPKLLVY**FASTRES**GVP

DRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK

SEQ ID NO. 121- 3G12 light chain variable region
DIVMTQSPKFMSTSVGDRVSITC**KASQDVGTAVA**WYQQKPGQSPELLIY**WTSTRHT**GVPDRFSGS

GSGTDFTLTISSVQAEDLADYFC**QQHYSIPLT**FGAGTKLELR

SEQ ID NO. 122- 3D1 light chain variable region
DIKMTQSPSSMYASLGERVTITC**KASQDIHTYLN**WFQQKPGKSPETLIY**RANRLVD**GVPSRFSGS

GSGQDYSLTISSLEYEDMGIYYC**LQYDEFPLT**FGAGTKLELK

SEQ ID NO. 123- 3C2 light chain variable region
DIQMTQSPSSMYASLGERVTLTC**KASQDIHNYLN**WFQQKPGKSPKTLIH**RANRLVA**GVPSRFSGS

GSGQDYSLTISSLEYEDLGIYYC**LQYDAFPLT**FGAGTKLELK

SEQ ID NO. 124- 3E6 light chain variable region
DIQMTQSPSSMYASLGERVTLTC**KASQDIHNYLN**WFQQKPGKSPKTLIH**RANRLVA**GVPSRFSGS

GSGQDYSLTISSLEYEDLGIYYC**LQYDAFPLT**FGAGTKLELK

SEQ ID NO. 125- 3H3 light chain variable region
DIVMSQSPSSMYASLGERVTITC**KASQDIHRFLN**WFQQKPGKSPKTLIF**HANRLVD**GVPSRFSGS

GSGLDYSLTISSLEYEDMGIYFC**LQYDAFPLT**FGAGTKLELK

SEQ ID NO. 126- 3A2 heavy chain variable region
HEIQLQQSGPELVKPGASVKMSCKTS**GYTFTDYNMH**WVKQKPGQGLEWIG**YINPYNDVTE**YNEKF

KGRATLTSDKSSSTAYMDLSSLTSDDSAVYFC**AWFGLRQ**WGQGTLVTVST

SEQ ID NO. 127- 3F6 heavy chain variable region
HEVQLQQSGPELVKPGASVKMSCKAS**GYIFTEYNIH**WVKQKPGQGPEWIG**NINPYNDVTE**YNEKF

KGKATLTSDKASSTAYMDLSSLTSEDSAVYYC**ARWGLRN**WGQGTLVTVSA

SEQ ID NO. 128- 3E8 heavy chain variable region
HEVQLQQSVPELVKPGASVKMSCKTS**GYTFTEYNMH**WVKQKPGQGPEWIG**NINPYNNVTE**YNEKF

KGKATLTSDKSSSTAYLDLSSLTSEDSAVYYC**ARWGLRN**WGQGTLVTVSA

SEQ ID NO. 129- 3A9 heavy chain variable region
HQVQVQQPGAELVRPGASVTLSCKAS**GYIFTDYEVH**WVRQRPVHGLEWIG**VIDPETGDTA**YNQKF

KGKATLTADKSSSTAYMELSSLTAEDSAVYYC**IGYADY**WGQGTTLTVSS

SEQ ID NO. 130- 3B1 heavy chain variable region
HQVQLQQPGAELVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGGTA**YNQKF

KGKATLTTDKSSSTAYMELRSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 131- 3B2 heavy chain variable region
HEVQLQQSGAELVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGATA**YNQKF

KGKATLTADKSSSTAYMELSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 132- 3F4 heavy chain variable region
HEVQLQQSGAELVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGSTA**YNQKF

KGKATLTADKASSTAYMELSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 133- 3E9 heavy chain variable region
HEVQLQQSGAELVRPGASATLSCKAS**GYTFTDYEMH**WVKQTPVHGLEWIG**VIDPETGSTA**YNQKF

KGKATLTADKSSSTAYMELSSLTSEDSAVYYC**MGYADY**WGQGTTLTVSS

-continued

SEQ ID NO. 134- 3B8 heavy chain variable region
HEVQLQQSGAELVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGDTA**YNQNF

TGKATLTADKSSSTAYMELSSLTSEDSAVYYC**MGYADY**WGQGTTLTVSS

SEQ ID NO. 135- 3G8 heavy chain variable region
HQVQLKQSGAELVRPGASVTLSCKAS**GYTFTDYEVH**WVKQTPVHGLEWIG**VIDPATGDTA**YNQKF

KGKATLTADKSSSTAYMEVSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 136- 3F7 heavy chain variable region
HQAYLQQSGAELVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGDTA**YNQKF

KDKATLTADKASSTAYMELSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 137- 3E12 heavy chain variable region
HQVQLQQSEAELVKPGASVKLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGDTA**YNQKF

KGKATLTADKSSSTAYMELSRLTSEDSAVYYC**MGHSDY**WGQGTTLTVSS

SEQ ID NO. 138- 3G12 heavy chain variable region
HEVQLQQSVAELVRPGASVTVSCKAS**GYIFTDYEIH**WVKQTPAHGLEWIG**VIDPETGNTA**FNQKF

KGKATLTADISSSTAYMELSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 139- 3F10 heavy chain variable region
HEVQLQQSVAELVRPGAPVTLSCKAS**GYTFTDYEVH**WVKQTPVHGLEWIG**VIDPETGATA**YNQKF

KGKATLTADKSSSAAYMELSRLTSEDSAVYYC**MSYSDY**WGQGTTLTVSS

SEQ ID NO. 140- 3C3 heavy chain variable region
HEVQLQQSVAEVVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VIDPETGVTA**YNQRF

RDKATLTTDKSSSTAYMELSSLTSEDSAVYFC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 141- 3G5 heavy chain variable region
HQVQLQQPGAELVRPGASVTLSCKAS**GYTFTDYEIH**WVKQTPVHGLEWIG**VLDPGTGRTA**YNQKF

KDKATLSADKSSSTAYMELSSLTSEDSAVYYC**MSYSDY**WGPGTTLTVSS

SEQ ID NO. 142- 3B11 heavy chain variable region
HEVQLQQSVAELVRPGASVTLSCKAS**GYTFTDYEMH**WVKQTPVRGLEWIG**VIDPATGDTA**YNQKF

KGKATLTADKSSSAAFMELSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS

SEQ ID NO. 143- 3E6 heavy chain variable region
HQVQLQQSGAELVRPGASVTLSCKAS**GYTFSDYEMH**WVKQTPVHGLEWIG**GIDPETGDTV**YNQKF

KGKATLTADKSSSTAYMELSSLTSEDSAVYYC**ISYAMDY**WGQGTSVTVSS

SEQ ID NO. 144- 4A2 heavy chain variable region
HQVKLQQSGTELVRPGASVTLSCKAS**GYKFTDYEMH**WVKQTPVHGLEWIG**GIDPETGGTA**YNQKF

KGKAILTADKSSTTAYMELRSLTSEDSAVYYC**ISYAMDY**WGQGTSVTVSS

SEQ ID NO. 145- 3E10 heavy chain variable region
HEVQLQQSGPELVKPGASVKISCKAS**GDTFTDYYMN**WVKQSHGKSLEWIG**DINPNYGGIT**YNQKF

KGKATLTVDTSSSTAYMELRGLTSEDSAVYYC**QAYYRNSDY**WGQGTTLTVSS

SEQ ID NO. 146- 3D1 heavy chain variable region
HEVQLQESGPDLVKPSQSLSLTCTVT**GFSITSGYGWH**WIRQFPGDKLEWMG**YISFNGDYN**YNPSL

KSRISITRDTSKNQFFLQLSSVTTEDTATYYC**ASSYDGLFAY**WGQGTLVTVSA

SEQ ID NO. 147- 3C2 heavy chain variable region
HDVQLQESGPDLVKPSQSLSLTCTVT**GFSITSGYGWH**WIRQFPGNKLEWMG**YISFNGDSN**YNPSL

KSRISITRDTSKNQFFLQLNSVTSEDTATYYC**ASSYDGLFAY**WGQGPLVTVSA

A

SEQ ID NO.: 148
KSSQSLLHSDGKTYLN

SEQ ID NO.: 149
LVSKLDS

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SEQ ID NO.: 150
WQGTHFPRT

SEQ ID NO.: 151
GYTFTD YNMH

SEQ ID NO.: 152
YINPYNDVTE

SEQ ID NO.: 153
AWFGL RQ

SEQ ID NO.: 154
RSSKSLLHSNGN TYLY

SEQ ID NO.: 155
RMSNLAS

SEQ ID NO.: 156
MQHLEYPYT

SEQ ID NO.: 157
GDTFTD YYMN

SEQ ID NO.: 158
DINPNYGGIT

SEQ ID NO.: 159
QAYYRNS DY

SEQ ID NO.: 160
KASQDVGTAVA

SEQ ID NO.: 161
WTSTRHT

SEQ ID NO.: 162
QQHYSIPLT

SEQ ID NO.: 163
GYIFTDYEIH

SEQ ID NO.: 164
VIDPETGNTA

SEQ ID NO.: 165
MGYSDY

SEQ ID NO.: 166
MVLQTQVFISLLLWISGAYGDIVMTQSPDSLAVSLGERATINCKSSQSLLNSNFQKNFLAWYQQK

PGQPPKLLIYFASTRESSVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHYSTPLTFGQGTKL

EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK

DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO.: 167
MDWTWRILFLVAAATGTHAEVQLVQSGAEVKKPGASVKVSCKASGYIFTDYEIHWVRQAPGQGLE

WMGVIDPETGNTAFNQKFKGRVTITADTSTSTAYMELSSLTSEDTAVYYCMGYSDYWGQGTLVTV

SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY

SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPP

KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH

QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS

DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS

LSLSPGK

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SEQ ID N: 168
DIVMTQSPDSLAVSLGERATINCKSSQSLLNSNFQKNFLAWYQQKPGQPPKLLIYFASTRESSVP

DRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHYSTPLTFGQGTKLEIK

SEQ ID NO.: 169
EVQLVQSGAEVKKPGASVKVSCKASGYIFTDYEIHWVRQAPGQGLEWMGVIDPETGNTAFNQKFK

GRVTITADTSTSTAYMELSSLTSEDTAVYYCMGYSDYWGQGTLVTVSS

SEQ ID NO.: 170
MVLQTQVFISLLLWISGAYGDIVMTQSPSSLSASVGDRVTITCKASQDIHNFLNWFQQKPGKAPK

TLIFRANRLVDGVPSRFSGSGSGTDYTLTISSLQPEDFATYSCLQYDEIPLTFGQGTKLEIKRTV

AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL

SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO.: 171
MDWTWRILFLVAAATGTHAEVQLQESGPGLVKPSQTLSLTCTVSGFSITSGYGWHWIRQHPGKGL

EWIGYINYDGHNDYNPSLKSRVTISQDTSKNQFSLKLSSVTAADTAVYYCASSYDGLFAYWGQGT

LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS

SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF

LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL

TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG

FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY

TQKSLSLSPGK

SEQ ID No.: 172
DIVMTQSPSSLSASVGDRVTITCKASQDIHNFLNWFQQKPGKAPKTLIFRANRLVDGVPSRFSGS

GSGTDYTLTISSLQPEDFATYSCLQYDEIPLTFGQGTKLEIK

SEQ ID NO.: 173
EVQLQESGPGLVKPSQTLSLTCTVSGFSITSGYGWHWIRQHPGKGLEWIGYINYDGHNDYNPSLK

SRVTISQDTSKNQFSLKLSSVTAADTAVYYCASSYDGLFAYWGQGTLVTVS

SEQ ID NO.: 186 (3A4 variant light chain variable region consensus 1)
DXVMTQTPLSLXVXXGXXASISCRSSQSLLHSNGNTYLEWYLQKPGQSPXLLIHTVSNRFSGVP

DRFSGSGSGTDFTLKISRVEAEDXGVYYCFQGSHVPLTFGXGTXLEXK

wherein at least one of the amino acids identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48. The amino acid substitution may be, for example conservative.

(3A4 variant light chain variable region consensus 2)
SEQ ID NO.: 187
DX_{a1}VMTQTPLSLX_{a2}V$X_{a3}X_{a4}GX_{a5}X_{a6}$ASISCRSSQSLLHSNGNTYL

EWYLQKPGQSPX_{a7}LLIHTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAE

DX_{a8}GVYYCFQGSHVPLTFG$X_{a9}GTX_{a10}LEX_{a11}K$

Wherein X_{a1} may be a hydrophobic amino acid;

Wherein X_{a2} may be A or P;

[0803] Wherein X_{a3} may be neutral hydrophilic amino acid;

Wherein X_{a4} may be L or P;

[0804] Wherein X_{a5} may be an acidic amino acid;

Wherein X_{a6} may be Q or P;

[0805] Wherein X_{a7} may be a basic amino acid;

Wherein X_{a8} may be a hydrophobic amino acid;

Wherein X_{a9} may be A or Q;

[0806] Wherein X_{a10} may be a basic amino acid; or

Wherein X_{a11} may be a hydrophobic amino acid,

wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48.

(3A4 variant light chain variable region consensus 3)

SEQ ID NO.: 188

$DX_{A1}VMTQTPLSLX_{A2}VX_{A3}X_{A4}GX_{A5}X_{A6}ASISCRSSQSLLHSNGNTYL$

$EWYLQKPGQSPX_{A7}LLIHTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAE$

$DX_{A8}GVYYCFQGSHVPLIFGX_{A9}GTX_{A10}LEX_{A11}K$

Wherein X_{A1} may be V or I

Wherein X_{A2} may be A or P

Wherein X_{A3} may be S or T

Wherein X_{A4} may be L or P

Wherein X_{A5} may be D or E

Wherein X_{A6} may be Q or P

Wherein X_{A7} may be K or Q

Wherein X_{A8} may be L or V

Wherein X_{A9} may be A or Q

Wherein X_{A10} may be R or K or

Wherein X_{A11} may be L or I,

[0807] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48.

(3A4 variant 1 light chain variable region: Lvh1)

SEQ ID NO.: 189

DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPQ

LLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVP

LTFGQGTKLEIK

(3A4 variant 2 light chain variable region: Lvh2)

SEQ ID NO.: 190

DVVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPK

LLIYTVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVP

LTFGQGTKLEIK

(3A4 variant heavy chain variable region consensus 1)

SEQ ID NO.: 191

QXQLVQSGXEXXKPGASVKXSCKASGYTFTDDYMSWVXQXXGXXLEWXGD

INPYNGDTNYNQKFKGXXXXTXDXSXSTAYMXLXSLXSEDXAVYYCARDP

GAMDYWGQGTXVTVSS

wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46. The amino acid substitution may be, for example conservative.

(3A4 variant heavy chain variable region consensus 2)

SEQ ID NO.: 192

$QX_{b1}QLVQSGX_{b2}EX_{b3}X_{b4}KPGASVKX_{b5}SCKASGYTFTDDYMSWVX_{b6}$

$QX_{b7}X_{b8}GX_{b9}X_{b10}LEWX_{b11}GDINPYNGDTNYNCKPKGX_{b12}X_{b13}$

$X_{b14}X_{b15}TX_{b16}DX_{b17}SX_{b18}STAYMX_{b19}LX_{b20}SLX_{b21}SEDX_{b22}$

$AVYYCARDPGAMDYWGQGTX_{b23}VTVSS$

Wherein X_{b1} may be a hydrophobic amino acid;

Wherein X_{b2} may be P or A;

[0808] Wherein X_{b3} may be a hydrophobic amino acid;

Wherein X_{b4} may be V or K;

[0809] Wherein X_{b5} may be a hydrophobic amino acid;
Wherein X_{b6} may be a basic amino acid;

Wherein X_{b7} may be S or A;

Wherein X_{b8} may be H or P;

[0810] Wherein X_{b9} may be a basic amino acid;

Wherein X_{b10} may be S or G;

[0811] Wherein X_{b11} may be a hydrophobic amino acid;
Wherein X_{b12} may be a basic amino acid;
Wherein X_{b13} may be a hydrophobic amino acid;

Wherein X_{b14} may be I or T;

[0812] Wherein X_{b15} may be a hydrophobic amino acid;
Wherein X_{b16} may be a hydrophobic amino acid;

Wherein X_{b17} may be K or T;

[0813] Wherein X_{b18} may be a neutral hydrophilic amino acid;

Wherein X_{b19} may be Q or E;

Wherein X_{b20} may be N or S;

Wherein X_{b21} may be T or R;

[0814] Wherein X_{b22} may be a neutral hydrophilic amino acid; or

Wherein X_{b23} may be S or L,

[0815] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46.

(3A4 variant heavy chain variable region consensus 3)

SEQ ID NO.: 193

$QX_{B1}QLVQSGX_{B2}EX_{B3}X_{B4}KPGASVKX_{B5}SCKASGYTFTDDYMSWVX_{B6}$

$QX_{B7}X_{B8}GX_{B9}X_{B10}LEWX_{B11}GDINPYNGDTNYNQKFKGX_{B12}X_{B13}$

$X_{B14}X_{B15}TX_{B16}DX_{B17}SX_{B18}STAYMX_{B19}LX_{B20}SLX_{B21}SEDX_{B22}$

$AVYYCARDPGAMDYWGQGTX_{B23}VTVSS$

Wherein X_{B1} may be I or V;

Wherein X_{B2} may be P or A;

Wherein X_{B3} may be M or V;

Wherein X_{B4} may be V or K;

Wherein X_{B5} may be M or V;

Wherein X_{B6} may be K or R;

Wherein X_{B7} may be S or A;

Wherein X_{B8} may be H or P;

Wherein X_{B9} may be K or Q;

Wherein X_{B10} may be S or G;

Wherein X_{B11} may be I or M;

Wherein X_{B12} may be K or R;

Wherein X_{B13} may be A or V;

Wherein X_{B14} may be I or T;

Wherein X_{B15} may be L or I;

Wherein X_{B16} may be V or A;

Wherein X_{B17} may be K or T;

Wherein X_{B18} may be S or T;

Wherein X_{B19} may be Q or E;

Wherein X_{B20} may be N or S;

Wherein X_{B21} may be T or R;

Wherein X_{B22} may be S or T; or

Wherein X_{B23} may be S or L,

[0816] wherein at least one of the amino acid identified by X is an amino acid substitution (conservative or non-conservative) in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46.

(3A4 variant 1 heavy chain variable region: Hvh1)
SEQ ID NO.: 194
QVQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNYN

QKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS

(3A4 variant 2 heavy chain variable region: Hvh2)
SEQ ID NO.: 195
QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNYNQ

KFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS

(3A4 variant 3 heavy chain variable region: Hvh3)
SEQ ID NO.: 196
QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWIGDINPYNGDTNYNQK

FKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS

(3A4 variant 4 heavy chain variable region: Hvh4)
SEQ ID NO.: 197
QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVKQAPGQGLEWIGDINPYNGDTNYNQK

FKGKATLTVDKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSS

3A4 murine light (kappa) chain
SEQ ID NO: 198
DVVMTQTPLSLAVSLGDQASISCRSSQSLLHSNGNTYLEWYLQKPGQSPKLLIHTVSNRFSGVP

DRFSGSGSGTDFTLKISRVEAEDLGVYYCFQGSHVPLTFGAGTRLELKRTVAAPSVFIFPPSDEQ

LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK

HKVYACEVTHQGLSSPVTKSFNRGEC

3A4 humanized light (kappa) chain variant 1; Lh1
SEQ ID NO: 199
DIVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPQLLIYTVSNRFSGVPD

RFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQL

KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK

HKVYACEVTHQGLSSPVTKSFNRGEC

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3A4 humanized light (kappa) chain variant 2; Lh2

SEQ ID NO: 200

DVVMTQTPLSLPVTPGEPASISCRSSQSLLHSNGNTYLEWYLQKPGQSPKLLIYTVSNRFSGVPD

RFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQL

KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK

HKVYACEVTHQGLSSPVTKSFNRGEC

3A4 murine heavy (Igg1) chain

SEQ ID NO: 201

QIQLVQSGPEMVKPGASVKMSCKASGYTFTDDYMSWVKQSHGKSLEWIGDINPYNGDTNYNQ

KFKGKAILTVDKSSSTAYMQLNSLTSEDSAVYYCARDPGAMDYWGQGTSVTVSSASTKGPSVF

PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS

SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR

TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE

YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES

NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

K

3A4 humanized heavy (Igg1) chain variant 1; Hh1

SEQ ID NO: 202

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNYN

QKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSSASTKGPSVF

PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS

SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR

TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE

YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES

NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

K

3A4 humanized heavy (Igg1) chain variant 2; Hh2

SEQ ID NO: 203

QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWMGDINPYNGDTNYNQ

KFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSSASTKGPSVFP

LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS

SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT

PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY

KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN

GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

3A4 humanized heavy (Igg1) chain variant 3; Hh3

SEQ ID NO: 204

QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVRQAPGQGLEWIGDINPYNGDTNYNQK

FKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSSASTKGPSVFP

LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS

SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT

PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY

KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN

GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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3A4 humanized heavy (Igg1) chain variant 4: Hh4

SEQ ID NO: 205

QIQLVQSGAEVKKPGASVKVSCKASGYTFTDDYMSWVKQAPGQGLEWIGDINPYNGDTNYNQK

FKGKATLTVDKSTSTAYMELSSLRSEDTAVYYCARDPGAMDYWGQGTLVTVSSASTKGPSVFP

LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS

SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT

PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY

KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN

GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 206

ATACCCAAGCTTGCCACCATGGAGACAGACACAC

SEQ ID NO: 207

ATACCCAAGCTTCATTTCCCGGGAGACAGGGAG

SEQ ID NO: 208

ATACCCAAGCTTGGGCCACCATGAACTTTCTGCTGTCTTGG

SEQ ID NO: 209

ATACCCAAGCTTCTAACACTCTCCCCTGTTGAAG

pK-CR5

SEQ ID NO: 210

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CAAGGCGATTAAGTTGGGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGC

CAGTGAGCGCGCGTAATACGACTCACTATAGGGCGAATTGGAGCTCCACCGCGGTGGCGG

CCGCTCTAGAACTAGTGGATCCACATCGGCGCGCCAAATGATTTGCCCTCCCATATGTCCTT

CCGAGTGAGAGACACAAAAAATTCCAACACACTATTGCAATGAAAATAAATTTCCTTTATTAG

CCAGAGGTCGAGATTTAAATAAGCTTGCTAGCAGATCTTTGGACCTGGGAGTGGACACCTGT

GGAGAGAAAGGCAAAGTGGATGTCATTGTCACTCAAGTGTATGGCCAGATCGGGCCAGGTG

AATATCAAATCCTCCTCGTTTTTGGAAACTGACAATCTTAGCGCAGAAGTAATGCCCGCTTTT

GAGAGGGAGTACTCACCCCAACAGCTGGATCTCAAGCCTGCCACACCTCACCTCGACCATC

CGCCGTCTCAAGACCGCCTACTTTAATTACATCATCAGCAGCACCTCCGCCAGAAACAACCC

CGACCGCCACCCGCTGCCGCCCGCCACGGTGCTCAGCCTACCTTGCGACTGTGACTGGTT

AGACGCCTTTCTCGAGAGGTTTTCCGATCCGGTCGATGCGGACTCGCTCAGGTCCCTCGGT

GGCGGAGTACCGTTCGGAGGCCGACGGGTTTCCGATCCAAGAGTACTGGAAAGACCGCGA

AGAGTTTGTCCTCAACCGCGAGCCCAACAGCTGGCCCTCGCAGACAGCGATGCGGAAGAG

AGTGACCGCGGAGGCTGGATCGGTCCCGGTGTCTTCTATGGAGGTCAAAACAGCGTGGATG

GCGTCTCCAGGCGATCTGACGGTTCACTAAACGAGCTCTGCTTATATAGGCCTCCCACCGTA

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CACGCCTACCTCGACCCGGGTACCAATCTTATAATACAAACAGACCAGATTGTCTGTTTGTTA

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GGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGC

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GGTCTGACGCTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAA

AGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATG

AGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGT

CTATTTCGTTCATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGG

CTTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCACCGGCTCCAGAT

TTATCAGCAATAAACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTAT

CCGCCTCCATCCAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAAT

AGTTTGCGCAACGTTGTTGCCATTGCTACAGGCATCGTGGTGTCACGCTCGTCGTTTGGTAT

GGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCA

AAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTA

TCACTCATGGTTATGGCAGCACTGCATAATTCTCTTACTGTCATGCCATCCGTAAGATGCTTT

TCTGTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTG

CTCTTGCCCGGCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCA

TCATTGGAAAACGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGT

TCGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCT

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pMPG-CR5

SEQ ID NO: 211

GTCGACGATACCGTGCACTTAATTAAGCGCGCTCGACCAAATGATTTGCCCTCCCATATGTC

CTTCCGAGTGAGAGACACAAAAAATTCCAACACACTATTGCAATGAAAATAAATTTCCTTTATT

AGCCAGAGGTCGAGGTCGGGGGATCCGTTTAAACTTGGACCTGGGAGTGGACACCTGTGG

AGAGAAAGGCAAAGTGGATGTCATTGTCACTCAAGTGTATGGCCAGATCGGGCCAGGTGAA

TATCAAATCCTCCTCGTTTTTGGAAACTGACAATCTTAGCGCAGAAGTAATGCCCGCTTTTGA

GAGGGAGTACTCACCCCAACAGCTGGATCTCAAGCCTGCCACACCTCACCTCGACCATCCG

CCGTCTCAAGACCGCCTACTTTAATTACATCATCAGCAGCACCTCCGCCAGAAACAACCCCG

ACCGCCACCCGCTGCCGCCCGCCACGGTGCTCAGCCTACCTTGCGACTGTGACTGGTTAGA

CGCCTTTCTCGAGAGGTTTTCCGATCCGGTCGATGCGGACTCGCTCAGGTCCCTCGGTGGC

GGAGTACCGTTCGGAGGCCGACGGGTTTCCGATCCAAGAGTACTGGAAAGACCGCGAAGA

GTTTGTCCTCAACCGCGAGCCCAACAGCTGGCCCTCGCAGACAGCGATGCGGAAGAGAGT

GACCGCGGAGGCTGGATCGGTCCCGGTGTCTTCTATGGAGGTCAAAACAGCGTGGATGGC

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CGCCTACCTCGACCCGGGTACCAATCTTATAATACAAACAGACCAGATIGTCTGTTTGTTATA

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CCCACGGGGCCAGTGGCTATGGCAGGGCCTGCCGCCCCGACGTTGGCTGCGAGCCCTGG

GCCTTCACCCGAACTTGGGGGGTGGGGTGGGGAAAAGGAAGAAACGCGGGCGTATTGGCC

CCAATGGGGTCTCGGTGGGGTATCGACAGAGTGCCAGCCCTGGGACCGAACCCCGCGTTT

ATGAACAAACGACCCAACACCCGTGCGTTTTATTCTGTCTTTTTATTGCCGTCATAGCGCGG

GTTCCTTCCGGTATTGTCTCCTTCCGTGTTTCAGTTAGCCTCCCCCATCTCCCCTATTCCTTT

GCCCTCGGACGAGTGCTGGGGCGTCGGTTTCCACTATCGGCGAGTACTTCTACACAGCCAT

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CAAGCTCTGATAGAGTTGGTCAAGACCAATGCGGAGCATATACGCCCGGAGCCGCGGCGAT

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GCGTGCACGAGGTGCCGGACTTCGGGGCAGTCCTCGGCCCAAAGCATCAGCTCATCGAGA

GCCTGCGCGACGGACGCACTGACGGTGTCGTCCATCACAGTTTGCCAGTGATACACATGGG

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GACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTCTCCTGTTC

CGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTGGCGCTTTC

TCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGGGCTGTG

TGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGAGTC

CAACCCGGTAAGACACGACTTATCGCCACTGGCAGCAGCCACTGGTAACAGGATTAGCAGA

GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTA

GAAGGACAGTATTTGGTATCTGCGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAGAGTTGGT

AGCTCTTGATCCGGCAAACAAACCACCGCTGGTAGCGGTGGTTTTTTTGTTTGCAAGCAGCA

GATTACGCGCAGAAAAAAAGGATCTCAAGAAGATCCTTTGATCTTTTCTACGGGGTCTGACG

CTCAGTGGAACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTATCAAAAAGGATCTTCA

CCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTG

GTCTGACAGTTACCAATGCTTAATCAGTGAGGCACCTATCTCAGCGATCTGTCTATTTCGTTC

ATCCATAGTTGCCTGACTCCCCGTCGTGTAGATAACTACGATACGGGAGGGCTTACCATCTG

GCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCACCGGCTCCAGATTTATCAGCAAT

AAACCAGCCAGCCGGAAGGGCCGAGCGCAGAAGTGGTCCTGCAACTTTATCCGCCTCCATC

CAGTCTATTAATTGTTGCCGGGAAGCTAGAGTAAGTAGTTCGCCAGTTAATAGTTTGCGCAA

CGTTGTTGCCATTGCTGCAGGCATCGTGGTGTCACGCTCGTCGTTTGGTATGGCTTCATTCA

GCTCCGGTTCCCAACGATCAAGGCGAGTTACATGATCCCCCATGTTGTGCAAAAAAGCGGTT

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TGAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTTGCTCTTGCCCGG

CGTCAACACGGGATAATACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAA

CGTTCTTCGGGGCGAAAACTCTCAAGGATCTTACCGCTGTTGAGATCCAGTTCGATGTAACC

CACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTTTCACCAGCGTTTCTGGGTGAGCAAA

AACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTC

ATACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGAGCGGATACA

TATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGC

CACCTGACGTCTAAGAAACCATTATTATCATGACATTAACCTATAAAAATAGGCGTATCACGA

GGCCCTTTCGTCTTCAAGAATTCTCATGTTTGACAGCTTATCTCTAGCAGATCCGGAATTCCC

CTCCCCAATTTAAATGAGGACCTAACCTGTGGAAATCTACTGATGTGGGAGGCTGTAACTGT

ACAAACAGAGGTTATTGGAATAACTAGCATGCTTAACCTTCATGCAGGGTCACAAAAAGTGC

ATGACGATGGTGGAGGAAAACCTATTCAAGGCAGTAATTTCCACTTCTTTGCTGTTGGTGGA

GACCCCTTGGAAATGCAGGGAGTGCTAATGAATTACAGGACAAAGTACCCAGATGGTACTAT

AACCCCTAAAAACCCAACAGCCCAGTCCCAGGTAATGAATACTGACCATAAGGCCTATTTGG

ACAAAAACAATGCTTATCCAGTTGAGTGCTGGGTTCCTGATCCTAGTAGAAATGAAAATACTA

GGTATTTTGGGACTTTCACAGGAGGGGAAAATGTTCCCCCAGTACTTCATGTGACCAACACA

GCTACCACAGTGTTGCTAGATGAACAGGGTGTGGGGCCTCTTTGTAAAGCTGATAGCCTGTA

TGTTTCAGCTGCTGATATTTGTGGCCTGTTTACTAACAGCTCTGGAACACAACAGTGGAGAG

GCCTTGCAAGATATTTTAAGATCCGCCTGAGAAAAAGATCTGTAAAGAATCCTTACCTAATTT

CCTTTTTGCTAAGTGACCTTATAAACAGGAGAACCCAGAGAGTGGATGGGCAGCCTATGTAT

GGTATGGAATCCCAGGTAGAAGAGGTTAGGGTGTTTGATGGCACAGAAAGACTTCCAGGGG

ACCCAGATATGATAAGATATATTGACAAACAGGGACAATTGCAAACCAAAATGCTTTAAACAG

GTGCTTTTATTGTACATATACATTTAATAAATGCTGCTTTTGTATAAGCCACTTTTAAGCTTGT

GTTATTTTGGGGGTGGTGTTTTAGGCCTTTTAAAACACTGAAAGCCTTTACACAAATGCAACT

CTTGACTATGGGGGTCTGACCTTTGGGAATGTTCAGCAGGGGCTGAAGTATCTGAGACTTG

GGAAGAGCATTGTGATTGGGATTCAGTGCTTGATCCATGTCCAGAGTCTTCAGTTTCTGAAT

CCTCTTCTCTTGTAATATCAAGAATACATTTCCCCATGCATATATTATATTTCATCCTTGAAAAA

GTATACATACTTATCTCAGAATCCAGCCTTTCCTTCCATTCAACAATTCTAGAAGTTAAAACTG

GGGTAGATGCTATTACAGAGGTAGAATGCTTCCTAAACCCAGAAATGGGGGATCTGC

3A4 humanized heavy chain CDR2 polypeptide sequence

SEQ ID NO.: 212

DINPYNGDTN

OGS18500

SEQ ID NO.: 213

ATGCCAAGTGGTCCCAGGCTGATGTTGTGATGACCCAAACTCC

OGS2084

SEQ ID NO:. 214

GGGAAGATGAAGACAGATGGTGCAGCCACAGTCCG

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OGS1879

SEQ ID NO.: 215

GGGTTCCAGGTTCCACTGGCCAGATCCAGTTGGTGCAATCTGG

OGS1810

EQ ID NO.: 216

GGGGCCAGGGGAAAGACAGATGGGCCCTTCGTTGAGGC

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SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 216

<210> SEQ ID NO 1
<211> LENGTH: 885
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<300> PUBLICATION INFORMATION:
<308> DATABASE ACCESSION NUMBER: UniProtKB/Q9UBP8
<309> DATABASE ENTRY DATE: 1999-12-20
<313> RELEVANT RESIDUES IN SEQ ID NO: (1)..(885)

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ggggagaccg actcacttga gtttcttgaa ggcttcctgg cctccagcca cgtaattgcc 180

cccgctctgg atctggtcta gcttccggat tcggtggcca gtccgcgggg tgtagatgtt 240

cctgacggcc ccaaagggtg cctgaacgcc gccggtcacc tccttcagga agacttcgaa 300

gctggacacc ttcttctcat ggatgacgac gcggcgcccc gcgtagaagg ggtccccgtt 360

gcggtacaca agcacgctct tcacgacggg ctgagacagg tggctggacc tggcgctgct 420

gccgctcatc ttccccgctg gccgccgcct cagctcgctg cttcgcgtcg ggaggcacct 480

ccgctgtccc agcggcctca ccgcacccag ggcgcgggat cgcctcctga aacgaacgag 540

aaactgacga atccacaggt gaaagagaag taacggccgt gcgcctaggc gtccacccag 600

aggagacact aggagcttgc aggactcgga gtagacgctc aagtttttca ccgtggcgtg 660

cacagccaat caggacccgc agtgcgcgca ccacaccagg ttcacctgct acgggcagaa 720

tcaaggtgga cagcttctga gcaggagccg gaaacgcgcg gggccttcaa acaggcacgc 780

ctagtgaggg caggagagag gaggacgcac acacacacac acacacaaat atggtgaaac 840

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<212> TYPE: PRT
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<300> PUBLICATION INFORMATION:
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<309> DATABASE ENTRY DATE: 1999-12-20
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<400> SEQUENCE: 2

Met Asp Asp Asp Ala Ala Pro Arg Val Glu Gly Val Pro Val Ala Val
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His Lys His Ala Leu His Asp Gly Leu Arg Gln Val Ala Gly Pro Gly
            20 25 30

Ala Ala Ala Ala His Leu Pro Arg Trp Pro Pro Pro Gln Leu Ala Ala
        35 40 45

Ser Arg Arg Glu Ala Pro Pro Leu Ser Gln Arg Pro His Arg Thr Gln
    50 55 60

Gly Ala Gly Ser Pro Pro Glu Thr Asn Glu Lys Leu Thr Asn Pro Gln
65 70 75 80

Val Lys Glu Lys

<210> SEQ ID NO 3
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 light chain

<400> SEQUENCE: 3

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atgaactgca agtccagtca gagcctttta aatagtaact ttcaaaagaa ctttttggcc 120

tggtaccagc agaaaccagg ccagtctcct aaacttctga tatactttgc atccactcgg 180

gaatctagta tccctgatcg cttcataggc agtggatctg ggacagattt cactcttacc 240

atcagcagtg tgcaggctga agacctggca gattacttct gtcagcaaca ttatagcact 300

ccgctcacgt tcggtgctgg gaccaagctg gagctgaaag ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> SEQ ID NO 4
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 light chain

<400> SEQUENCE: 4

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Ile Gly
1 5 10 15

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser

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            20                  25                  30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Ile
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 5
<211> LENGTH: 1329
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain

<400> SEQUENCE: 5

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tcctgcaagg cttcgggcta catatttact gactatgaga tacactgggt gaagcagact    120

cctgtgcatg gcctggaatg gattggggtt attgatcctg aaactggtaa tactgccttc    180

aatcagaagt tcaagggcaa ggccacactg actgcagaca tatcctccag cacagcctac    240

atggaactca gcagtttgac atctgaggac tctgccgtct attactgtat gggttattct    300

gattattggg gccaaggcac cactctcaca gtctcctcag cctcaacgaa gggcccatct    360

gtctttcccc tggccccctc ctccaagagc acctctgggg gcacagcggc cctgggctgc    420

ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgccctgacc    480

agcggcgtgc acaccttccc ggctgtccta cagtcctcag gactctactc cctcagcagc    540

gtggtgaccg tgccctccag cagcttgggc acccagacct acatctgcaa cgtgaatcac    600

aagcccagca acaccaaggt ggacaagaaa gttgagccca aatcttgtga attcactcac    660

acatgcccac cgtgcccagc acctgaactc ctgggggggac cgtcagtctt cctcttcccc    720

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg    780

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg    840
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cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 900

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc 960

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1020

gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1080

ctgacctgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat 1140

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1200

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1260

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1320

cccgggaaa 1329

<210> SEQ ID NO 6
<211> LENGTH: 443
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain

<400> SEQUENCE: 6

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

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys Glu Phe Thr His Thr Cys Pro Pro
210 215 220

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225 230 235 240

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
245 250 255

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Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
            260                 265                 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        275                 280                 285

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    290                 295                 300

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305                 310                 315                 320

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
                325                 330                 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
            340                 345                 350

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        355                 360                 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    370                 375                 380

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385                 390                 395                 400

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
                405                 410                 415

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            420                 425                 430

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 7
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 light chain

<400> SEQUENCE: 7

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atctcttgta gatcgagtca gagcctttta catagtaatg gaaacaccta tttagaatgg    120

tatttgcaga aaccaggcca gcctccaaag gtcctgatct acaaagtttc caaccgattt    180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc    240

agcggagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct    300

ctcacgttcg gtgctgggac caagctggag ctgaaagctg tggctgcacc atctgtcttc    360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg    420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg    480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc    540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc    600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt          654


<210> SEQ ID NO 8
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<212> TYPE: PRT
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<223> OTHER INFORMATION: 3G10 light chain
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<400> SEQUENCE: 8

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1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Gly Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
115 120 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 9
<211> LENGTH: 1335
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain

<400> SEQUENCE: 9

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tcctgtaagg cttctggata caccttcact gacaactaca tgaactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggagat attaatcctt actatggtac tactacctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctcccg cacagcctac 240

atggagctcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgac 300

tggtttgatt attggggcca agggactctg gtcactgtct ctgcagcctc aacgaagggc 360

ccatctgtct ttcccctggc cccctcctcc aagagcacct ctgggggcac agcggccctg 420

ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgcc 480

ctgaccagcg gcgtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 540

agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc agacctacat ctgcaacgtg 600

aatcacaagc ccagcaacac caaggtggac aagaaagttg agcccaaatc ttgtgaattc 660

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actcacacat gcccaccgtg cccagcacct gaactcctgg ggggaccgtc agtcttcctc    720

ttccccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacatgcgtg    780

gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg    840

gaggtgcata atgccaagac aaagccgcgg gaggagcagt acaacagcac gtaccgtgtg    900

gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgcaag    960

gtctccaaca aagccctccc agcccccatc gagaaaacca tctccaaagc caaagggcag   1020

ccccgagaac cacaggtgta caccctgccc ccatcccggg atgagctgac caagaaccag   1080

gtcagcctga cctgcctggt caaaggcttc tatcccagcg acatcgccgt ggagtgggag   1140

agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc   1200

tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc   1260

ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc   1320

ctgtctcccg ggaaa                                                    1335


<210> SEQ ID NO 10
<211> LENGTH: 445
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain

<400> SEQUENCE: 10

Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Asp Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195                 200                 205

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Glu Phe Thr His Thr Cys
    210                 215                 220
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Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
            260                 265                 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    370                 375                 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385                 390                 395                 400

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                405                 410                 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            420                 425                 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 11
<211> LENGTH: 639
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain

<400> SEQUENCE: 11

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atcacttgca aggcgagtca ggacattcat aacttttttaa actggttcca gcagaaacca    120

ggaaaatctc caaagaccct gatctttcgt gcaaacagat tggtagatgg ggtcccatca    180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagttt    240

gaagatttgg gaatttattc ttgtctacag tatgatgaga ttccgctcac gttcggtgct    300

gggaccaagc tggagctgag agctgtggct gcaccatctg tcttcatctt cccgccatct    360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc    420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag    480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg    540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg    600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt                            639


<210> SEQ ID NO 12
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<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain

<400> SEQUENCE: 12

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Phe
65 70 75 80

Glu Asp Leu Gly Ile Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg Ala Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 13
<211> LENGTH: 1341
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain

<400> SEQUENCE: 13

gaggtgcagc ttcaggagtc aggacctgac ctggtgaaac cttctcagtc actttcactc 60

acctgcactg tcactggctt ctccatcacc agtggttatg gctggcactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataaact acgatggtca caatgactac 180

aacccatctc tcaaaagtcg aatctctatc actcaagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagcagttac 300

gacggcttat ttgcttactg gggccaaggg actctggtca ctgtctctgc agcctcaacg 360

aagggcccat ctgtctttcc cctggccccc tcctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

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```
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac    540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc    600

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt    660

gaattcactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc    720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca    780

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac    840

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac    900

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag    960

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa   1020

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag   1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc   1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1320

ctctccctgt ctcccgggaa a                                             1341
```

<210> SEQ ID NO 14
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain

<400> SEQUENCE: 14

```
Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
1               5                   10                  15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser Gly
            20                  25                  30

Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Gln Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190
```

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```
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Glu Phe Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> SEQ ID NO 15
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 light chain variable region

<400> SEQUENCE: 15

```
gacattgtga tgacccagtc tccatcctcc ctggctgtgt caataggaca gaaggtcact     60

atgaactgca agtccagtca gagcctttta aatagtaact ttcaaaagaa ctttttggcc    120

tggtaccagc agaaaccagg ccagtctcct aaacttctga tactttgc atccactcgg    180

gaatctagta tccctgatcg cttcataggc agtggatctg ggacagattt cactcttacc    240

atcagcagtg tgcaggctga agacctggca gattacttct gtcagcaaca ttatagcact    300

ccgctcacgt tcggtgctgg gaccaagctg gagctgaaa                           339
```

<210> SEQ ID NO 16
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: 3D3 light chain variable region

<400> SEQUENCE: 16

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Ile Gly
1 5 10 15

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Ile
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 17
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain variable region

<400> SEQUENCE: 17

gaggttcagc tgcagcagtc tgtagctgag ctggtgaggc ctggggcttc agtgacgctg 60

tcctgcaagg cttcgggcta catatttact gactatgaga tacactgggt gaagcagact 120

cctgtgcatg gcctggaatg gattggggtt attgatcctg aaactggtaa tactgccttc 180

aatcagaagt tcaagggcaa ggccacactg actgcagaca tatcctccag cacagcctac 240

atggaactca gcagtttgac atctgaggac tctgccgtct attactgtat gggttattct 300

gattattggg gccaaggcac cactctcaca gtctcctca 339

<210> SEQ ID NO 18
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain variable region

<400> SEQUENCE: 18

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

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

-continued

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
100 105 110

Ser

<210> SEQ ID NO 19
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 light chain variable region

<400> SEQUENCE: 19

gatgttttga tgacccaaac tccacgctcc ctgtctgtca gtcttggaga tcaagcctcc 60

atctcttgta gatcgagtca gagcctttta catagtaatg gaaacaccta tttagaatgg 120

tatttgcaga aaccaggcca gcctccaaag gtcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcggagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct 300

ctcacgttcg gtgctgggac caagctggag ctgaaa 336

<210> SEQ ID NO 20
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 light chain variable region

<400> SEQUENCE: 20

Asp Val Leu Met Thr Gln Thr Pro Arg Ser Leu Ser Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Gly Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> SEQ ID NO 21
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain variable region

<400> SEQUENCE: 21

gagatccagc tgcagcagtc tggacctgag ttggtgaagc ctggggcttc agtgaagata 60

tcctgtaagg cttctggata caccttcact gacaactaca tgaactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggagat attaatcctt actatggtac tactacctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctcccg cacagcctac 240

-continued

atggagctcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgac 300

tggtttgatt attggggcca agggactctg gtcactgtct ctgca 345

<210> SEQ ID NO 22
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain variable region

<400> SEQUENCE: 22

Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Asp Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> SEQ ID NO 23
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain variable region

<400> SEQUENCE: 23

gacatcgtta tgtctcagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattcat aacttttttaa actggttcca gcagaaacca 120

ggaaaatctc caaagaccct gatctttcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagttt 240

gaagatttgg gaatttattc ttgtctacag tatgatgaga ttccgctcac gttcggtgct 300

gggaccaagc tggagctgag a 321

<210> SEQ ID NO 24
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain variable region

<400> SEQUENCE: 24

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
20 25 30

-continued

```
Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
        35                  40                  45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Phe
65                  70                  75                  80

Glu Asp Leu Gly Ile Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
            100                 105
```

<210> SEQ ID NO 25
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain variable region

<400> SEQUENCE: 25

```
gaggtgcagc ttcaggagtc aggacctgac ctggtgaaac cttctcagtc actttcactc     60

acctgcactg tcactggctt ctccatcacc agtggttatg gctggcactg gatccggcag    120

tttccaggaa acaaactgga gtggatgggc tacataaact acgatggtca caatgactac    180

aacccatctc tcaaaagtcg aatctctatc actcaagaca catccaagaa ccagttcttc    240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagcagttac    300

gacggcttat ttgcttactg gggccaaggg actctggtca ctgtctctgc a             351
```

<210> SEQ ID NO 26
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain variable region

<400> SEQUENCE: 26

```
Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
1               5                   10                  15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser Gly
            20                  25                  30

Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Gln Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ala
        115
```

<210> SEQ ID NO 27
<211> LENGTH: 17
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 light chain CDR1

<400> SEQUENCE: 27

Lys Ser Ser Gln Ser Leu Leu Asn Ser Asn Phe Gln Lys Asn Phe Leu
1 5 10 15

Ala

<210> SEQ ID NO 28
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 light chain CDR2

<400> SEQUENCE: 28

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 light chain CDR3

<400> SEQUENCE: 29

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> SEQ ID NO 30
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain CDR1

<400> SEQUENCE: 30

Gly Tyr Ile Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> SEQ ID NO 31
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain CDR2

<400> SEQUENCE: 31

Val Ile Asp Pro Glu Thr Gly Asn Thr Ala
1 5 10

<210> SEQ ID NO 32
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D3 heavy chain CDR3

<400> SEQUENCE: 32

Met Gly Tyr Ser Asp Tyr
1 5

-continued

<210> SEQ ID NO 33
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 light chain CDR1

<400> SEQUENCE: 33

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> SEQ ID NO 34
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 light chain CDR2

<400> SEQUENCE: 34

Lys Val Ser Asn Arg Phe Ser
1 5

<210> SEQ ID NO 35
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 light chain CDR3

<400> SEQUENCE: 35

Phe Gln Gly Ser His Val Pro Leu Thr
1 5

<210> SEQ ID NO 36
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain CDR1

<400> SEQUENCE: 36

Gly Tyr Thr Phe Thr Asp Asn Tyr Met Asn
1 5 10

<210> SEQ ID NO 37
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain CDR2

<400> SEQUENCE: 37

Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr
1 5 10

<210> SEQ ID NO 38
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G10 heavy chain CDR3

<400> SEQUENCE: 38

Ala Arg Asp Asp Trp Phe Asp Tyr

-continued

1 5

<210> SEQ ID NO 39
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain CDR1

<400> SEQUENCE: 39

Lys Ala Ser Gln Asp Ile His Asn Phe Leu Asn
1 5 10

<210> SEQ ID NO 40
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain CDR2

<400> SEQUENCE: 40

Arg Ala Asn Arg Leu Val Asp
1 5

<210> SEQ ID NO 41
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 light chain CDR3

<400> SEQUENCE: 41

Leu Gln Tyr Asp Glu Ile Pro Leu Thr
1 5

<210> SEQ ID NO 42
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain CDR1

<400> SEQUENCE: 42

Gly Phe Ser Ile Thr Ser Gly Tyr Gly Trp His
1 5 10

<210> SEQ ID NO 43
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain CDR2

<400> SEQUENCE: 43

Tyr Ile Asn Tyr Asp Gly His Asn Asp
1 5

<210> SEQ ID NO 44
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C4 heavy chain CDR3

<400> SEQUENCE: 44

-continued

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr
1 5 10

<210> SEQ ID NO 45
<211> LENGTH: 348
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 heavy chain variable region

<400> SEQUENCE: 45

cagatccagt tggtgcaatc tggacctgag atggtgaagc ctggggcttc agtgaagatg 60

tcctgtaagg cttctggata cacattcact gacgactaca tgagctgggt gaaacagagc 120

catggaaaga gccttgagtg gattggagat attaatcctt acaacggtga tactaactac 180

aaccagaagt tcaagggcaa ggccatattg actgtagaca aatcctccag cacagcctac 240

atgcagctca acagcctgac atcggaagac tcagcagtct attactgtgc aagagacccg 300

ggggctatgg actactgggg tcaaggaacc tcagtcaccg tctcctca 348

<210> SEQ ID NO 46
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 heavy chain variable region

<400> SEQUENCE: 46

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Met Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 47
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 light chain variable region

<400> SEQUENCE: 47

gatgttgtga tgacccaaac tccactctcc ctggctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagccttcta catagtaatg gaaacaccta tttagaatgg 120

taccttcaga aaccaggcca gtctccaaag ctcctgatcc acacagtttc caaccgattt 180

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tctggggtcc cagacagatt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttccg 300

ctcacgttcg gtgctgggac caggctggag ctgaaa 336

<210> SEQ ID NO 48
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 light chain variable region

<400> SEQUENCE: 48

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile His Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Arg Leu Glu Leu Lys
100 105 110

<210> SEQ ID NO 49
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 heavy chain CDR1

<400> SEQUENCE: 49

Gly Tyr Thr Phe Thr Asp Asp Tyr Met Ser
1 5 10

<210> SEQ ID NO 50
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 heavy chain CDR2

<400> SEQUENCE: 50

Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 51
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 heavy chain CDR3

<400> SEQUENCE: 51

Asp Pro Gly Ala Met Asp Tyr

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1 5

<210> SEQ ID NO 52
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 light chain CDR1

<400> SEQUENCE: 52

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> SEQ ID NO 53
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 light chain CDR2

<400> SEQUENCE: 53

Thr Val Ser Asn Arg Phe Ser
1 5

<210> SEQ ID NO 54
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 light chain CDR3

<400> SEQUENCE: 54

Phe Gln Gly Ser His Val Pro Leu Thr
1 5

<210> SEQ ID NO 55
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer OSG 1773

<400> SEQUENCE: 55

gtaagcagcg ctgtggctgc accatctgtc ttc 33

<210> SEQ ID NO 56
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer OSG 1774

<400> SEQUENCE: 56

gtaagcgcta gcctaacact ctcccctgtt gaagc 35

<210> SEQ ID NO 57
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human kappa constant region

<400> SEQUENCE: 57

gctgtggctg caccatctgt cttcatcttc ccgccatctg atgagcagtt gaaatctgga 60

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actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120

aaggtggata acgccctcca atcgggtaac tcccaggaga gtgtcacaga gcaggacagc 180

aaggacagca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240

cacaaagtct acgcctgcga agtcacccat cagggcctga gctcgcccgt cacaaagagc 300

ttcaacaggg gagagtgtta g 321

<210> SEQ ID NO 58
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human kappa constant region

<400> SEQUENCE: 58

Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1 5 10 15

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
20 25 30

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
35 40 45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65 70 75 80

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> SEQ ID NO 59
<211> LENGTH: 6385
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Plasmid pTTVK1

<400> SEQUENCE: 59

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aggaggattt gatattcacc tggcccgatc tggccataca cttgagtgac aatgacatcc 180

actttgcctt tctctccaca ggtgtccact cccaggtcca agtttaaacg gatctctagc 240

gaattcatga actttctgct gtcttgggtg cattggagcc ttgccttgct gctctacctc 300

caccatgcca agtggtccca ggcttgagac ggagcttaca gcgctgtggc tgcaccatct 360

gtcttcatct tcccgccatc tgatgagcag ttgaaatctg gaactgcctc tgttgtgtgc 420

ctgctgaata acttctatcc cagagaggcc aaagtacagt ggaaggtgga taacgccctc 480

caatcgggta actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc 540

ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaagt ctacgcctgc 600

gaagtcaccc atcagggcct gagctcgccc gtcacaaaga gcttcaacag gggagagtgt 660

tagggtaccg cggccgcttc gaatgagatc ccccgacctc gacctctggc taataaagga 720

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aatttatttt cattgcaata gtgtgttgga atttttttgtg tctctcactc ggaaggacat 780

atgggagggc aaatcatttg gtcgagatcc ctcggagatc tctagctaga gccccgccgc 840

cggacgaact aaacctgact acggcatctc tgccccttct tcgcggggca gtgcatgtaa 900

tcccttcagt tggttggtac aacttgccaa ctgggccctg ttccacatgt gacacggggg 960

gggaccaaac acaaaggggt tctctgactg tagttgacat ccttataaat ggatgtgcac 1020

atttgccaac actgagtggc tttcatcctg gagcagactt tgcagtctgt ggactgcaac 1080

acaacattgc ctttatgtgt aactcttggc tgaagctctt acaccaatgc tgggggacat 1140

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tgtgtagcta ccgataagcg gaccctcaag agggcattag caatagtgtt tataaggccc 1260

ccttgttaac cctaaacggg tagcatatgc ttcccgggta gtagtatata ctatccagac 1320

taaccctaat tcaatagcat atgttaccca acgggaagca tatgctatcg aattagggtt 1380

agtaaaaggg tcctaaggaa cagcgatatc tcccacccca tgagctgtca cggttttatt 1440

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aagatcaagg agcgggcagt gaactctcct gaatcttcgc ctgcttcttc attctccttc 1560

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tacactctat ttgtaacaag gggaaagaga gtggacgccg acagcagcgg actccactgg 1980

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gacaagtggc cactcttttt tttgaaattg tggagtgggg gcacgcgtca gcccccacac 2100

gccgccctgc ggttttggac tgtaaaataa gggtgtaata acttggctga ttgtaacccc 2160

gctaaccact gcggtcaaac cacttgccca caaaaccact aatggcaccc cggggaatac 2220

ctgcataagt aggtgggcgg gccaagatag gggcgcgatt gctgcgatct ggaggacaaa 2280

ttacacacac ttgcgcctga gcgccaagca cagggttgtt ggtcctcata ttcacgaggt 2340

cgctgagagc acggtgggct aatgttgcca tgggtagcat atactaccca aatatctgga 2400

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aaaaggaaga gtatgagtat tcaacatttc cgtgtcgccc ttattccctt ttttgcggca 3240

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cagttgggtg cacgagtggg ttacatcgaa ctggatctca acagcggtaa gatccttgag 3360

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gaggaagcgg aagagcgccc aatacgcaaa ccgcctctcc ccgcgcgttg gccgattcat 5040

taatgcagct ggcacgacag gtttcccgac tggaaagcgg gcagtgagcg caacgcaatt 5100

aatgtgagtt agctcactca ttaggcaccc caggctttac actttatgct tccggctcgt 5160

atgttgtgtg gaattgtgag cggataacaa tttcacacag gaaacagcta tgaccatgat 5220

tacgccaagc tctagctaga ggtcgaccaa ttctcatgtt tgacagctta tcatcgcaga 5280

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tgacgtcaat gggagtttgt tttggcacca aaatcaacgg gactttccaa aatgtcgtaa 6000

taaccccgcc ccgttgacgc aaatgggcgg taggcgtgta cggtgggagg tctatataag 6060

cagagctcgt ttagtgaacc gtcagatcct cactctcttc cgcatcgctg tctgcgaggg 6120

ccagctgttg ggctcgcggt tgaggacaaa ctcttcgcgg tctttccagt actcttggat 6180

cggaaacccg tcggcctccg aacggtactc cgccaccgag ggacctgagc gagtccgcat 6240

cgaccggatc ggaaaacctc tcgagaaagg cgtctaacca gtcacagtcg caaggtaggc 6300

tgagcaccgt ggcgggcggc agcgggtggc ggtcggggtt gtttctggcg gaggtgctgc 6360

tgatgatgta attaaagtag gcggt 6385

<210> SEQ ID NO 60
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 60

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<210> SEQ ID NO 61
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 61

atgccaagtg gtcccaggct gatgttttga tgacccaaac tcc 43

<210> SEQ ID NO 62
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 62

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<210> SEQ ID NO 63

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<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 63

gggaagatga agacagatgg tgcagccaca gc 32

<210> SEQ ID NO 64
<211> LENGTH: 50
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 64

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<210> SEQ ID NO 65
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 65

gtaagcgaat tcacaagatt tgggctcaac tttcttg 37

<210> SEQ ID NO 66
<211> LENGTH: 309
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 CH1 region

<400> SEQUENCE: 66

gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg 60

ggcacagcag ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc 240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 300

aaatcttgt 309

<210> SEQ ID NO 67
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Human IgG1 CH1 region

<400> SEQUENCE: 67

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

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    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys
            100


<210> SEQ ID NO 68
<211> LENGTH: 5379
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Plasmid pYD15

<400> SEQUENCE: 68

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agtactccct ctcaaaagcg ggcattactt ctgcgctaag attgtcagtt tccaaaaacg    120

aggaggattt gatattcacc tggcccgatc tggccataca cttgagtgac aatgacatcc    180

actttgcctt tctctccaca ggtgtccact cccaggtcca agtttgccgc caccatggag    240

acagacacac tcctgctatg ggtactgctg ctctgggttc caggttccac tggcggagac    300

ggagcttacg ggcccatctg tctttcccct ggccccctcc tccaagagca cctctggggg    360

cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg    420

gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg    480

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cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga    900

gtacaagtgc aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa    960

agccaaaggg cagccccgag aaccacaggt gtacaccctg cccccatccc gggatgagct   1020

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cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct   1140

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gcaggggaac gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca   1260

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taatcccttc agttggttgg tacaacttgc caactgaacc ctaaacgggt agcatatgct   1560

tcccgggtag tagtatatac tatccagact aaccctaatt caatagcata tgttacccaa   1620

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tcctaattta tatctgggta gcatatacta cccaaatatc tggatagcat atgctatcct 2160

aatctatatc tgggtagcat atgctatcct aatctatatc tgggtagcat aggctatcct 2220

aatctatatc tgggtagcat atgctatcct aatctatatc tgggtagtat atgctatcct 2280

aatttatatc tgggtagcat aggctatcct aatctatatc tgggtagcat atgctatcct 2340

aatctatatc tgggtagtat atgctatcct aatctgtatc cgggtagcat atgctatcct 2400

cacgatgata agctgtcaaa catgagaatt aattcttgaa gacgaaaggg cctcgtgata 2460

cgcctatttt tataggttaa tgtcatgata ataatggttt cttagacgtc aggtggcact 2520

tttcggggaa atgtgcgcgg aacccctatt tgtttatttt tctaaataca ttcaaatatg 2580

tatccgctca tgagacaata accctgataa atgcttcaat aatattgaaa aaggaagagt 2640

atgagtattc aacatttccg tgtcgccctt attccctttt ttgcggcatt ttgccttcct 2700

gtttttgctc acccagaaac gctggtgaaa gtaaaagatg ctgaagatca gttgggtgca 2760

cgagtgggtt acatcgaact ggatctcaac agcggtaaga tccttgagag ttttcgcccc 2820

gaagaacgtt ttccaatgat gagcactttt aaagttctgc tatgtggcgc ggtattatcc 2880

cgtgttgacg ccgggcaaga gcaactcggt cgccgcatac actattctca gaatgacttg 2940

gttgagtact caccagtcac agaaaagcat cttacggatg gcatgacagt aagagaatta 3000

tgcagtgctg ccataaccat gagtgataac actgcggcca acttacttct gacaacgatc 3060

ggaggaccga aggagctaac cgcttttttg cacaacatgg gggatcatgt aactcgcctt 3120

gatcgttggg aaccggagct gaatgaagcc ataccaaacg acgagcgtga caccacgatg 3180

cctgcagcaa tggcaacaac gttgcgcaaa ctattaactg gcgaactact tactctagct 3240

tcccggcaac aattaataga ctggatggag gcggataaag ttgcaggacc acttctgcgc 3300

tcggcccttc cggctggctg gtttattgct gataaatctg gagccggtga gcgtgggtct 3360

cgcggtatca ttgcagcact ggggccagat ggtaagccct cccgtatcgt agttatctac 3420

acgacgggga gtcaggcaac tatggatgaa cgaaatagac agatcgctga gataggtgcc 3480

tcactgatta agcattggta actgtcagac caagtttact catatatact ttagattgat 3540

ttaaaacttc atttttaatt taaaaggatc taggtgaaga tccttttttga taatctcatg 3600

accaaaatcc cttaacgtga gttttcgttc cactgagcgt cagaccccgt agaaaagatc 3660

aaaggatctt cttgagatcc ttttttttctg cgcgtaatct gctgcttgca aacaaaaaaa 3720

ccaccgctac cagcggtggt ttgtttgccg gatcaagagc taccaactct ttttccgaag 3780

gtaactggct tcagcagagc gcagatacca aatactgtcc ttctagtgta gccgtagtta 3840

ggccaccact tcaagaactc tgtagcaccg cctacatacc tcgctctgct aatcctgtta 3900

ccagtggctg ctgccagtgg cgataagtcg tgtcttaccg ggttggactc aagacgatag 3960

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ttaccggata aggcgcagcg gtcgggctga acgggggttt cgtgcacaca gcccagcttg 4020

gagcgaacga cctacaccga actgagatac ctacagcgtg agcattgaga aagcgccacg 4080

cttcccgaag ggagaaaggc ggacaggtat ccggtaagcg gcagggtcgg aacaggagag 4140

cgcacgaggg agcttccagg gggaaacgcc tggtatcttt atagtcctgt cgggtttcgc 4200

cacctctgac ttgagcgtcg atttttgtga tgctcgtcag gggggcggag cctatggaaa 4260

aacgccagca acgcggcctt tttacggttc ctggcctttt gctggccttt tgctcacatg 4320

ttctttcctg cgttatcccc tgattctgtg gataaccgta ttaccgcctt tgagtgagct 4380

gataccgctc gccgcagccg aacgaccgag cgcagcgagt cagtgagcga ggaagcgtac 4440

atttatattg gctcatgtcc aatatgaccg ccatgttgac attgattatt gactagttat 4500

taatagtaat caattacggg gtcattagtt catagcccat atatggagtt ccgcgttaca 4560

taacttacgg taaatggccc gcctggctga ccgcccaacg acccccgccc attgacgtca 4620

ataatgacgt atgttcccat agtaacgcca atagggactt tccattgacg tcaatgggtg 4680

gagtatttac ggtaaactgc ccacttggca gtacatcaag tgtatcatat gccaagtccg 4740

ccccctattg acgtcaatga cggtaaatgg cccgcctggc attatgccca gtacatgacc 4800

ttacgggact ttcctacttg gcagtacatc tacgtattag tcatcgctat taccatggtg 4860

atgcggtttt ggcagtacac caatgggcgt ggatagcggt ttgactcacg gggatttcca 4920

agtctccacc ccattgacgt caatgggagt ttgttttggc accaaaatca acgggacttt 4980

ccaaaatgtc gtaataaccc cgccccgttg acgcaaatgg gcggtaggcg tgtacggtgg 5040

gaggtctata taagcagagc tcgtttagtg aaccgtcaga tcctcactct cttccgcatc 5100

gctgtctgcg agggccagct gttgggctcg cggttgagga caaactcttc gcggtctttc 5160

cagtactctt ggatcggaaa cccgtcggcc tccgaacggt actccgccac cgagggacct 5220

gagcgagtcc gcatcgaccg gatcggaaaa cctctcgaga aaggcgtcta accagtcaca 5280

gtcgcaaggt aggctgagca ccgtggcggg cggcagcggg tggcggtcgg ggttgtttct 5340

ggcggaggtg ctgctgatga tgtaattaaa gtaggcggt 5379

<210> SEQ ID NO 69
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 69

gggttccagg ttccactggc gaggttcagc tgcagcagtc tgt 43

<210> SEQ ID NO 70
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 70

gggttccagg ttccactggc gaggtgcagc ttcaggagtc agg 43

<210> SEQ ID NO 71
<211> LENGTH: 38

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 71

ggggccaggg gaaagacaga tgggcccttc gttgaggc 38

<210> SEQ ID NO 72
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR1 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be H, Y or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be S, T, N or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa may be absent, S or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be D, F or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be G or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Xaa may be K, L or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Xaa may be T or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be A, N, E or Y

<400> SEQUENCE: 72

Xaa Ser Ser Xaa Ser Leu Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu
1 5 10 15

Xaa

<210> SEQ ID NO 73
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR1 consensus
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be G or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be T, N or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be F, Y or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be N or A

<400> SEQUENCE: 73

Lys Ala Ser Gln Asp Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> SEQ ID NO 74
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be A or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be R or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be E, K or A

<400> SEQUENCE: 74

Phe Xaa Ser Thr Xaa Xaa Ser
1 5

<210> SEQ ID NO 75
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be L or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be L or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)

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<223> OTHER INFORMATION: Xaa may be D or F

<400> SEQUENCE: 75

Xaa Val Ser Xaa Xaa Xaa Ser
1 5

<210> SEQ ID NO 76
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be D or A

<400> SEQUENCE: 76

Xaa Ala Asn Arg Leu Val Xaa
1 5

<210> SEQ ID NO 77
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Q or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be D, F or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be E, A, N or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be I, F or T

<400> SEQUENCE: 77

Xaa Gln Xaa Xaa Xaa Xaa Pro Leu Thr
1 5

<210> SEQ ID NO 78
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be N or S

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be I or T

<400> SEQUENCE: 78

Gln Gln His Xaa Xaa Xaa Pro Leu Thr
1 5

<210> SEQ ID NO 79
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: light chain CDR3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be F or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be R or L

<400> SEQUENCE: 79

Xaa Gln Gly Xaa His Xaa Pro Xaa Thr
1 5

<210> SEQ ID NO 80
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR1 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be T, I or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be an acidic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be E, N or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid

<400> SEQUENCE: 80

Gly Tyr Xaa Phe Xaa Xaa Tyr Xaa Xaa His
1 5 10

<210> SEQ ID NO 81
<211> LENGTH: 10
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be V or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be A, G or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be R, G, D, A, S, N or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid

<400> SEQUENCE: 81

Xaa Xaa Asp Pro Xaa Thr Gly Xaa Thr Xaa
1 5 10

<210> SEQ ID NO 82
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be A, E or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be R, G, A, S, N, V or D

<400> SEQUENCE: 82

Val Xaa Asp Pro Xaa Thr Gly Xaa Thr Ala
1 5 10

<210> SEQ ID NO 83
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be S or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be D, E or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)

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<223> OTHER INFORMATION: Xaa may be D or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Y, S or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be D, E or N

<400> SEQUENCE: 83

Tyr Ile Xaa Xaa Xaa Gly Xaa Xaa Xaa
1 5

<210> SEQ ID NO 84
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be N or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be E, D or N

<400> SEQUENCE: 84

Xaa Ile Asn Pro Tyr Asn Xaa Val Thr Glu
1 5 10

<210> SEQ ID NO 85
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be N or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be G or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be I or T

<400> SEQUENCE: 85

Asp Ile Asn Pro Xaa Tyr Gly Xaa Xaa Thr
1 5 10

<210> SEQ ID NO 86
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be G or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Y or H

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be A or S

<400> SEQUENCE: 86

Met Xaa Xaa Xaa Asp Tyr
1 5

<210> SEQ ID NO 87
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be G or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be absent or M

<400> SEQUENCE: 87

Ile Xaa Tyr Ala Xaa Asp Tyr
1 5

<210> SEQ ID NO 88
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain CDR3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be R or W
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be a basic amino acid

<400> SEQUENCE: 88

Ala Xaa Xaa Gly Leu Arg Xaa
1 5

<210> SEQ ID NO 89
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL1 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be N or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be S or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa may be S, N or D
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be N or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be Q, N or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Xaa may be K or L

<400> SEQUENCE: 89

Lys Ser Ser Gln Ser Leu Leu Xaa Xaa Xaa Xaa Xaa Xaa Asn Tyr Leu
1 5 10 15

Ala

<210> SEQ ID NO 90
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL1 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be N or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be Y or F

<400> SEQUENCE: 90

Lys Ala Ser Gln Asp Ile His Xaa Xaa Leu Asn
1 5 10

<210> SEQ ID NO 91
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL2 consensus

<400> SEQUENCE: 91

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> SEQ ID NO 92
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL2 consensus

<400> SEQUENCE: 92

Leu Val Ser Lys Leu Asp Ser
1 5

<210> SEQ ID NO 93
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL2 consensus

<400> SEQUENCE: 93

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Arg Ala Asn Arg Leu Val Asp
1 5

<210> SEQ ID NO 94
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL3 consensus

<400> SEQUENCE: 94

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> SEQ ID NO 95
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRL3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be W or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Y or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be D or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be A, E or H

<400> SEQUENCE: 95

Xaa Gln Xaa Xaa Xaa Phe Pro Arg Thr
1 5

<210> SEQ ID NO 96
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH1 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be T or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be D or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be E or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be M, I or V

<400> SEQUENCE: 96

Gly Tyr Xaa Phe Thr Xaa Tyr Xaa Xaa His
1 5 10

<210> SEQ ID NO 97

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<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH1 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be T or S

<400> SEQUENCE: 97

Gly Phe Xaa Ile Thr Ser Gly Tyr Gly Trp His
1 5 10

<210> SEQ ID NO 98
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be V, N or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be I or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be E, A or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be T or Y
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 98

Xaa Xaa Asp Pro Xaa Xaa Gly Xaa Thr Ala
1 5 10

<210> SEQ ID NO 99
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH2 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be N or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be F or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be N or D

<400> SEQUENCE: 99

Tyr Ile Xaa Xaa Xaa Gly
1 5

<210> SEQ ID NO 100
<211> LENGTH: 6

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be S or A

<400> SEQUENCE: 100

Met Gly Tyr Xaa Asp Tyr
1 5

<210> SEQ ID NO 101
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH3 consensus

<400> SEQUENCE: 101

Ala Ser Ser Tyr Asp Gly Phe Leu Ala Tyr
1 5 10

<210> SEQ ID NO 102
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDRH3 consensus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be R or W
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be W or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Q or N

<400> SEQUENCE: 102

Ala Xaa Xaa Gly Leu Arg Xaa
1 5

<210> SEQ ID NO 103
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 light chain variable region

<400> SEQUENCE: 103

Asp Ala Val Met Thr Gln Ile Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Ser Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

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Ser Arg Val Glu Ala Glu Asp Leu Gly Leu Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Arg Thr Phe Ala Gly Gly Thr Asn Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 104
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F6 light chain variable region

<400> SEQUENCE: 104

Ser Ile Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Ser Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Gly Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 105
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E8 light chain variable region

<400> SEQUENCE: 105

Asp Ala Val Met Thr Gln Ile Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 106
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 light chain variable region

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<400> SEQUENCE: 106

Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
85 90 95

Leu Glu Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 107
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A9 light chain variable region

<400> SEQUENCE: 107

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Leu Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Asn Gln Leu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Lys Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Thr Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Phe Asn Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 108
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B1 light chain variable region

<400> SEQUENCE: 108

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Ile Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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Ser Pro Lys Leu Leu Val Phe Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys


<210> SEQ ID NO 109
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G5 light chain variable region

<400> SEQUENCE: 109

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1               5                   10                  15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Phe Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Thr Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys


<210> SEQ ID NO 110
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B2 light chain variable region

<400> SEQUENCE: 110

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1               5                   10                  15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
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100 105 110

Lys

<210> SEQ ID NO 111
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B8 light chain variable region

<400> SEQUENCE: 111

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 112
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G8 light chain variable region

<400> SEQUENCE: 112

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 113
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: 3F7 light chain variable region

<400> SEQUENCE: 113

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 114
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E9 light chain variable region

<400> SEQUENCE: 114

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
65 70 75 80

Ile Thr Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 115
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C3 light chain variable region

<400> SEQUENCE: 115

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Tyr Phe Gly Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Gly Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys


<210> SEQ ID NO 116
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E12 light chain variable region

<400> SEQUENCE: 116

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1               5                   10                  15

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Arg
            20                  25                  30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys


<210> SEQ ID NO 117
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 4A2 light chain variable region

<400> SEQUENCE: 117

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1               5                   10                  15

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Asn
            20                  25                  30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Leu Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Tyr Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
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                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Asp Leu
            100                 105                 110

Lys


<210> SEQ ID NO 118
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F10 light chain variable region

<400> SEQUENCE: 118

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Thr Met Ser Val Gly
1               5                   10                  15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Thr
            20                  25                  30

Ser Asn Gln Leu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Thr Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys


<210> SEQ ID NO 119
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F4 light chain variable region

<400> SEQUENCE: 119

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Thr Val Thr Ala Gly
1               5                   10                  15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Thr
            20                  25                  30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Ala Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys


<210> SEQ ID NO 120
<211> LENGTH: 113
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B11 light chain variable region

<400> SEQUENCE: 120

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Met Ser Val Gly
1 5 10 15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> SEQ ID NO 121
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 light chain variable region

<400> SEQUENCE: 121

Asp Ile Val Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Glu Leu Leu Ile
35 40 45

Tyr Trp Thr Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln His Tyr Ser Ile Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105

<210> SEQ ID NO 122
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D1 light chain variable region

<400> SEQUENCE: 122

Asp Ile Lys Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Thr Tyr
20 25 30

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Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Glu Thr Leu Ile
35 40 45

Tyr Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> SEQ ID NO 123
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C2 light chain variable region

<400> SEQUENCE: 123

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Gln Asp Ile His Asn Tyr
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

His Arg Ala Asn Arg Leu Val Ala Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Ala Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> SEQ ID NO 124
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E6 light chain variable region

<400> SEQUENCE: 124

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Gln Asp Ile His Asn Tyr
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

His Arg Ala Asn Arg Leu Val Ala Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Ala Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys

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100 105

<210> SEQ ID NO 125
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3H3 light chain variable region

<400> SEQUENCE: 125

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Arg Phe
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Phe His Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Leu Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Phe Cys Leu Gln Tyr Asp Ala Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> SEQ ID NO 126
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 heavy chain variable region

<400> SEQUENCE: 126

His Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Asn Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Glu Tyr Asn Glu Lys
50 55 60

Phe Lys Gly Arg Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Asp Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe
85 90 95

Cys Ala Trp Phe Gly Leu Arg Gln Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Thr
115

<210> SEQ ID NO 127
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F6 heavy chain variable region

<400> SEQUENCE: 127

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```
His Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1               5                   10                  15

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Glu
            20                  25                  30

Tyr Asn Ile His Trp Val Lys Gln Lys Pro Gly Gln Gly Pro Glu Trp
        35                  40                  45

Ile Gly Asn Ile Asn Pro Tyr Asn Asp Val Thr Glu Tyr Asn Glu Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ala Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Trp Gly Leu Arg Asn Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ala
        115


<210> SEQ ID NO 128
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E8 heavy chain variable region

<400> SEQUENCE: 128

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

Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu
            20                  25                  30

Tyr Asn Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Pro Glu Trp
        35                  40                  45

Ile Gly Asn Ile Asn Pro Tyr Asn Asn Val Thr Glu Tyr Asn Glu Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Leu Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Trp Gly Leu Arg Asn Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ala
        115


<210> SEQ ID NO 129
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A9 heavy chain variable region

<400> SEQUENCE: 129

His Gln Val Gln Val Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp
            20                  25                  30

Tyr Glu Val His Trp Val Arg Gln Arg Pro Val His Gly Leu Glu Trp
```

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```
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ala Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ile Gly Tyr Ala Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 130
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B1 heavy chain variable region

<400> SEQUENCE: 130

His Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 131
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B2 heavy chain variable region

<400> SEQUENCE: 131

His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95
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```
Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 132
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F4 heavy chain variable region

<400> SEQUENCE: 132

His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ser Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ala Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 133
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E9 heavy chain variable region

<400> SEQUENCE: 133

His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Ala Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ser Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ala Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 134
<211> LENGTH: 114
<212> TYPE: PRT
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-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B8 heavy chain variable region

<400> SEQUENCE: 134

His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Asn
    50 55 60

Phe Thr Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85 90 95

Cys Met Gly Tyr Ala Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100 105 110

Ser Ser

<210> SEQ ID NO 135
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G8 heavy chain variable region

<400> SEQUENCE: 135

His Gln Val Gln Leu Lys Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20 25 30

Tyr Glu Val His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35 40 45

Ile Gly Val Ile Asp Pro Ala Thr Gly Asp Thr Ala Tyr Asn Gln Lys
    50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Val Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100 105 110

Ser Ser

<210> SEQ ID NO 136
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F7 heavy chain variable region

<400> SEQUENCE: 136

His Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp

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```
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ala Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 137
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E12 heavy chain variable region

<400> SEQUENCE: 137

His Gln Val Gln Leu Gln Gln Ser Glu Ala Glu Leu Val Lys Pro Gly
1               5                   10                  15

Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly His Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 138
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 heavy chain variable region

<400> SEQUENCE: 138

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Ala His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala
65                  70                  75                  80
```

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```
Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 139
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3F10 heavy chain variable region

<400> SEQUENCE: 139

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Pro Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Val His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Ala Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Ser Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser


<210> SEQ ID NO 140
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C3 heavy chain variable region

<400> SEQUENCE: 140

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Val Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Val Thr Ala Tyr Asn Gln Arg
    50                  55                  60

Phe Arg Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
```

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<210> SEQ ID NO 141
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G5 heavy chain variable region

<400> SEQUENCE: 141

His Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Leu Asp Pro Gly Thr Gly Arg Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Asp Lys Ala Thr Leu Ser Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Ser Tyr Ser Asp Tyr Trp Gly Pro Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> SEQ ID NO 142
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3B11 heavy chain variable region

<400> SEQUENCE: 142

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val Arg Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Ala Thr Gly Asp Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Ala Ala
65 70 75 80

Phe Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> SEQ ID NO 143
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E6 heavy chain variable region

<400> SEQUENCE: 143

His Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly

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```
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp
            20                  25                  30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Gly Ile Asp Pro Glu Thr Gly Asp Thr Val Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ile Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
            100                 105                 110

Val Ser Ser
        115


<210> SEQ ID NO 144
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 4A2 heavy chain variable region

<400> SEQUENCE: 144

His Gln Val Lys Leu Gln Gln Ser Gly Thr Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Lys Phe Thr Asp
            20                  25                  30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Ile Leu Thr Ala Asp Lys Ser Ser Thr Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ile Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
            100                 105                 110

Val Ser Ser
        115


<210> SEQ ID NO 145
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 heavy chain variable region

<400> SEQUENCE: 145

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

Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Asp
            20                  25                  30

Tyr Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp
        35                  40                  45
```

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```
Ile Gly Asp Ile Asn Pro Asn Tyr Gly Gly Ile Thr Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Gln Ala Tyr Tyr Arg Asn Ser Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 146
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3D1 heavy chain variable region

<400> SEQUENCE: 146

His Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser
1               5                   10                  15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser
            20                  25                  30

Gly Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asp Lys Leu Glu
        35                  40                  45

Trp Met Gly Tyr Ile Ser Phe Asn Gly Asp Tyr Asn Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Phe Leu Gln Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ala
        115


<210> SEQ ID NO 147
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3C2 heavy chain variable region

<400> SEQUENCE: 147

His Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser
1               5                   10                  15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser
            20                  25                  30

Gly Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu
        35                  40                  45

Trp Met Gly Tyr Ile Ser Phe Asn Gly Asp Ser Asn Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Phe Leu Gln Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr
                85                  90                  95
```

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Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Pro
100 105 110

Leu Val Thr Val Ser Ala
115

<210> SEQ ID NO 148
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 light chain CDR1

<400> SEQUENCE: 148

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> SEQ ID NO 149
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 light chain CDR2

<400> SEQUENCE: 149

Leu Val Ser Lys Leu Asp Ser
1 5

<210> SEQ ID NO 150
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 light chain CDR3

<400> SEQUENCE: 150

Trp Gln Gly Thr His Phe Pro Arg Thr
1 5

<210> SEQ ID NO 151
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 heavy chain CDR1

<400> SEQUENCE: 151

Gly Tyr Thr Phe Thr Asp Tyr Asn Met His
1 5 10

<210> SEQ ID NO 152
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 heavy chain CDR2

<400> SEQUENCE: 152

Tyr Ile Asn Pro Tyr Asn Asp Val Thr Glu
1 5 10

<210> SEQ ID NO 153
<211> LENGTH: 7
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A2 heavy chain CDR3

<400> SEQUENCE: 153

Ala Trp Phe Gly Leu Arg Gln
1 5

<210> SEQ ID NO 154
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 light chain CDR1

<400> SEQUENCE: 154

Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> SEQ ID NO 155
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 light chain CDR2

<400> SEQUENCE: 155

Arg Met Ser Asn Leu Ala Ser
1 5

<210> SEQ ID NO 156
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 light chain CDR3

<400> SEQUENCE: 156

Met Gln His Leu Glu Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 157
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 heavy chain CDR1

<400> SEQUENCE: 157

Gly Asp Thr Phe Thr Asp Tyr Tyr Met Asn
1 5 10

<210> SEQ ID NO 158
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 heavy chain CDR2

<400> SEQUENCE: 158

Asp Ile Asn Pro Asn Tyr Gly Gly Ile Thr
1 5 10

<210> SEQ ID NO 159

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3E10 heavy chain CDR3

<400> SEQUENCE: 159

Gln Ala Tyr Tyr Arg Asn Ser Asp Tyr
1 5

<210> SEQ ID NO 160
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 light chain CDR1

<400> SEQUENCE: 160

Lys Ala Ser Gln Asp Val Gly Thr Ala Val Ala
1 5 10

<210> SEQ ID NO 161
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 light chain CDR2

<400> SEQUENCE: 161

Trp Thr Ser Thr Arg His Thr
1 5

<210> SEQ ID NO 162
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 light chain CDR3

<400> SEQUENCE: 162

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> SEQ ID NO 163
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 heavy chain CDR1

<400> SEQUENCE: 163

Gly Tyr Ile Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> SEQ ID NO 164
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 heavy chain CDR2

<400> SEQUENCE: 164

Val Ile Asp Pro Glu Thr Gly Asn Thr Ala
1 5 10

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<210> SEQ ID NO 165
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3G12 heavy chain CDR3

<400> SEQUENCE: 165

Met Gly Tyr Ser Asp Tyr
1 5

<210> SEQ ID NO 166
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3D3 light chain

<400> SEQUENCE: 166

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
20 25 30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
35 40 45

Leu Leu Asn Ser Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg
65 70 75 80

Glu Ser Ser Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
85 90 95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
100 105 110

Tyr Cys Gln Gln His Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr
115 120 125

Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
130 135 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145 150 155 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
165 170 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
180 185 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
195 200 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
210 215 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235 240

<210> SEQ ID NO 167
<211> LENGTH: 462
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3D3 heavy chain

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<400> SEQUENCE: 167

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Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                  10                  15

Thr His Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe
        35                  40                  45

Thr Asp Tyr Glu Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val
        115                 120                 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
    130                 135                 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400
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Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        435                 440                 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210> SEQ ID NO 168
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3D3 light chain variable region

<400> SEQUENCE: 168

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys


<210> SEQ ID NO 169
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3D3 heavy chain variable region

<400> SEQUENCE: 169

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
            20                  25                  30

Glu Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
            100                 105                 110
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Ser

<210> SEQ ID NO 170
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3C4 light chain

<400> SEQUENCE: 170

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp
35 40 45

Ile His Asn Phe Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

Lys Thr Leu Ile Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser
85 90 95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln Tyr Asp
100 105 110

Glu Ile Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
115 120 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
195 200 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
210 215 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230

<210> SEQ ID NO 171
<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3C4 heavy chain

<400> SEQUENCE: 171

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1 5 10 15

Thr His Ala Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile
35 40 45

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Thr Ser Gly Tyr Gly Trp His Trp Ile Arg Gln His Pro Gly Lys Gly
    50                  55                  60

Leu Glu Trp Ile Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn
65                  70                  75                  80

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Gln Asp Thr Ser Lys Asn
                85                  90                  95

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
    130                 135                 140

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
145                 150                 155                 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                165                 170                 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
            180                 185                 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
    210                 215                 220

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
225                 230                 235                 240

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445
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Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450 455 460

Gly Lys
465

<210> SEQ ID NO 172
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3C4 light chain variable region

<400> SEQUENCE: 172

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 173
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: humanized 3C4 heavy chain variable region

<400> SEQUENCE: 173

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Ser Gly
20 25 30

Tyr Gly Trp His Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Gln Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser
115

<210> SEQ ID NO 174
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3D3 light chain variable region
consensus 1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (64)..(64)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:16
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (112)..(112)

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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:16

<400> SEQUENCE: 174

Asp Ile Val Met Thr Gln Ser Pro Xaa Ser Leu Ala Val Ser Xaa Gly
1 5 10 15

Xaa Xaa Xaa Thr Xaa Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Xaa Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Xaa
50 55 60

Pro Asp Arg Phe Xaa Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Xaa Gln Ala Glu Asp Xaa Ala Xaa Tyr Xaa Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Xaa Gly Thr Lys Leu Glu Xaa
100 105 110

Lys

<210> SEQ ID NO 175
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3D3 light chain variable region consensus 2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be D or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be E or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa may be P or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (64)..(64)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be S or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa may be V or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: Xaa may be an aromatic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa may be Q or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (112)..(112)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid

<400> SEQUENCE: 175

Asp Ile Val Met Thr Gln Ser Pro Xaa Ser Leu Ala Val Ser Xaa Gly
1 5 10 15

Xaa Xaa Xaa Thr Xaa Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Xaa Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Xaa
50 55 60

Pro Asp Arg Phe Xaa Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Xaa Gln Ala Glu Asp Xaa Ala Xaa Tyr Xaa Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Xaa Gly Thr Lys Leu Glu Xaa
100 105 110

Lys

<210> SEQ ID NO 176
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3D3 light chain variable region
consensus 3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be D or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be L or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be E or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa may be R or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa may be A or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Xaa may be I or M
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa may be P or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (64)..(64)
<223> OTHER INFORMATION: Xaa may be V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be S or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be L or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: Xaa may be v or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa may be V or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: Xaa may be Y or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa may be Q or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (112)..(112)
<223> OTHER INFORMATION: Xaa may be I or L

<400> SEQUENCE: 176

Asp Ile Val Met Thr Gln Ser Pro Xaa Ser Leu Ala Val Ser Xaa Gly
1 5 10 15

Xaa Xaa Xaa Thr Xaa Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35 40 45

Xaa Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Xaa
    50 55 60

Pro Asp Arg Phe Xaa Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Xaa Gln Ala Glu Asp Xaa Ala Xaa Tyr Xaa Cys Gln Gln
                85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Xaa Gly Thr Lys Leu Glu Xaa
            100 105 110

Lys

<210> SEQ ID NO 177
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3D3 heavy chain variable region
      consensus 1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison

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with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (109)..(109)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:18

<400> SEQUENCE: 177

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

Ser Val Xaa Xaa Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Xaa Gln Xaa Pro Xaa Xaa Gly Leu Glu Trp Xaa
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Xaa Xaa Thr Xaa Thr Ala Asp Xaa Ser Xaa Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Xaa Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Xaa Xaa Thr Val Ser
100 105 110

Ser

<210> SEQ ID NO 178
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3D3 heavy chain variable region consensus 2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be V or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be G or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be K or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa may be K or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Xaa may be A or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Xaa may be G or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa may be Q or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: Xaa may be T or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa may be L or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (109)..(109)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid

<400> SEQUENCE: 178

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

Ser Val Xaa Xaa Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
            20 25 30

Glu Ile His Trp Val Xaa Gln Xaa Pro Xaa Xaa Gly Leu Glu Trp Xaa
        35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
    50 55 60

Lys Gly Xaa Xaa Thr Xaa Thr Ala Asp Xaa Ser Xaa Ser Thr Ala Tyr
65 70 75 80

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Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Xaa Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Xaa Xaa Thr Val Ser
100 105 110

Ser

<210> SEQ ID NO 179
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3D3 heavy chain variable region consensus 3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be V or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be G or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be V or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be K or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Xaa may be K or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa may be K or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa may be V or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa may be R or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Xaa may be A or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Xaa may be G or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa may be Q or H
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa may be M or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa may be R or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa may be V or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: Xaa may be I or L

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: Xaa may be T or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: Xaa may be T or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa may be T or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa may be L or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (109)..(109)
<223> OTHER INFORMATION: Xaa may be V or L

<400> SEQUENCE: 179

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

Ser Val Xaa Xaa Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Xaa Gln Xaa Pro Xaa Xaa Gly Leu Glu Trp Xaa
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Xaa Xaa Thr Xaa Thr Ala Asp Xaa Ser Xaa Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Xaa Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Xaa Xaa Thr Val Ser
100 105 110

Ser

<210> SEQ ID NO 180
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3C4 light chain variable region
consensus 1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (85)..(85)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:24
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 180

Asp Ile Val Met Xaa Gln Ser Pro Ser Ser Xaa Xaa Ala Ser Xaa Gly
1 5 10 15

Xaa Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
            20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Xaa Pro Lys Thr Leu Ile
        35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
    50 55 60

Ser Gly Ser Gly Xaa Asp Tyr Xaa Leu Thr Ile Ser Ser Leu Xaa Xaa
65 70 75 80

Glu Asp Xaa Xaa Xaa Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu

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               85                  90                  95

Thr Phe Gly Xaa Gly Thr Lys Leu Glu Xaa Xaa
            100                 105


<210> SEQ ID NO 181
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3C4 light chain variable region
      consensus 2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be S or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be an acidic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa may be A or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be T or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: Xaa may be Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: Xaa may be P or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: Xaa may be F or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be A or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (85)..(85)
<223> OTHER INFORMATION: Xaa may be T or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: Xaa may be Q or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (107)..(107)
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<223> OTHER INFORMATION: Xaa may be a basic amino acid

<400> SEQUENCE: 181

Asp Ile Val Met Xaa Gln Ser Pro Ser Ser Xaa Xaa Ala Ser Xaa Gly
1 5 10 15

Xaa Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Xaa Pro Lys Thr Leu Ile
35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Xaa Asp Tyr Xaa Leu Thr Ile Ser Ser Leu Xaa Xaa
65 70 75 80

Glu Asp Xaa Xaa Xaa Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
85 90 95

Thr Phe Gly Xaa Gly Thr Lys Leu Glu Xaa Xaa
100 105

<210> SEQ ID NO 182
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3C4 light chain variable region consensus 3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be T or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be L or M
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be S or Y
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be V or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be D or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa may be A or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be T or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: Xaa may be T or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (79)..(79)
<223> OTHER INFORMATION: Xaa may be Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: Xaa may be P or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (83)..(83)

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<223> OTHER INFORMATION: Xaa may be F or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be A or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (85)..(85)
<223> OTHER INFORMATION: Xaa may be T or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: Xaa may be Q or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa may be I or L
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: Xaa may be K or R

<400> SEQUENCE: 182

Asp Ile Val Met Xaa Gln Ser Pro Ser Ser Xaa Xaa Ala Ser Xaa Gly
1 5 10 15

Xaa Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
            20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Xaa Pro Lys Thr Leu Ile
        35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
    50 55 60

Ser Gly Ser Gly Xaa Asp Tyr Xaa Leu Thr Ile Ser Ser Leu Xaa Xaa
65 70 75 80

Glu Asp Xaa Xaa Xaa Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
            85 90 95

Thr Phe Gly Xaa Gly Thr Lys Leu Glu Xaa Xaa
            100 105

<210> SEQ ID NO 183
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3C4 heavy chain variable region
      consensus 1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
      with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
      with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
      with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison
      with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (44)..(44)

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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (117)..(117)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:26

<400> SEQUENCE: 183

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

Xaa Leu Ser Leu Thr Cys Thr Val Xaa Gly Phe Ser Ile Thr Ser Gly
            20 25 30

Tyr Gly Trp His Trp Ile Arg Gln Xaa Pro Gly Xaa Xaa Leu Glu Trp
        35 40 45

Xaa Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
    50 55 60

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Lys Ser Arg Xaa Xaa Ile Xaa Gln Asp Thr Ser Lys Asn Gln Phe Xaa
65                  70                  75                  80

Leu Xaa Leu Xaa Ser Val Thr Xaa Xaa Asp Thr Ala Xaa Tyr Tyr Cys
                85                  90                  95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Xaa
        115


<210> SEQ ID NO 184
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3C4 heavy chain variable region
      consensus 2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: xaa may be G or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa may be H or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Xaa may be K or N
<220> FEATURE:
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<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: Xaa may be G or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
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<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be S or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (88)..(88)
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<223> OTHER INFORMATION: Xaa may be A or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: Xaa may be A or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: Xaa may be V or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (117)..(117)
<223> OTHER INFORMATION: Xaa may be any amino acid, A or absent

<400> SEQUENCE: 184

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

Xaa Leu Ser Leu Thr Cys Thr Val Xaa Gly Phe Ser Ile Thr Ser Gly
            20 25 30

Tyr Gly Trp His Trp Ile Arg Gln Xaa Pro Gly Xaa Xaa Leu Glu Trp
        35 40 45

Xaa Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
    50 55 60

Lys Ser Arg Xaa Xaa Ile Xaa Gln Asp Thr Ser Lys Asn Gln Phe Xaa
65 70 75 80

Leu Xaa Leu Xaa Ser Val Thr Xaa Xaa Asp Thr Ala Xaa Tyr Tyr Cys
                85 90 95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100 105 110

Val Thr Val Ser Xaa
        115

<210> SEQ ID NO 185
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Humanized 3C4 heavy chain variable region
      consensus 3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa may be G or D
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be T or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Xaa may be S or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa may be H or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Xaa may be K or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (45)..(45)
<223> OTHER INFORMATION: Xaa may be G or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa may be I or M

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa may be V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be T or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: Xaa may be S or T
<220> FEATURE:
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<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: Xaa may be S or F
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: Xaa may be K or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be S or N
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: Xaa may be A or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (89)..(89)
<223> OTHER INFORMATION: Xaa may be A or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: Xaa may be V or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (117)..(117)
<223> OTHER INFORMATION: Xaa may be A or absent

<400> SEQUENCE: 185

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

Xaa Leu Ser Leu Thr Cys Thr Val Xaa Gly Phe Ser Ile Thr Ser Gly
20 25 30

Tyr Gly Trp His Trp Ile Arg Gln Xaa Pro Gly Xaa Xaa Leu Glu Trp
35 40 45

Xaa Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Xaa Xaa Ile Xaa Gln Asp Thr Ser Lys Asn Gln Phe Xaa
65 70 75 80

Leu Xaa Leu Xaa Ser Val Thr Xaa Xaa Asp Thr Ala Xaa Tyr Tyr Cys
85 90 95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Xaa
115

<210> SEQ ID NO 186
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant light chain variable region
consensus 1
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (50)..(50)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:48

<400> SEQUENCE: 186

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Asp Xaa Val Met Thr Gln Thr Pro Leu Ser Leu Xaa Val Xaa Xaa Gly
1               5                   10                  15

Xaa Xaa Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Xaa Leu Leu Ile His Thr Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Xaa Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser His Val Pro Leu Thr Phe Gly Xaa Gly Thr Xaa Leu Glu Xaa Lys
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100 105 110

<210> SEQ ID NO 187
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant light chain variable region consensus 2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be A or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be L or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be an acidic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa may be Q or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (50)..(50)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: Xaa may be A or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid

<400> SEQUENCE: 187

Asp Xaa Val Met Thr Gln Thr Pro Leu Ser Leu Xaa Val Xaa Xaa Gly
1 5 10 15

Xaa Xaa Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Xaa Leu Leu Ile His Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Xaa Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Xaa Gly Thr Xaa Leu Glu Xaa Lys

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100 105 110

<210> SEQ ID NO 188
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant light chain variable region consensus 3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be V or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be A or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Xaa may be S or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa may be L or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa may be D or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa may be Q or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (50)..(50)
<223> OTHER INFORMATION: Xaa may be K or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: Xaa may be L or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: Xaa may be A or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa may be R or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa may be L or I

<400> SEQUENCE: 188

Asp Xaa Val Met Thr Gln Thr Pro Leu Ser Leu Xaa Val Xaa Xaa Gly
1 5 10 15

Xaa Xaa Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Xaa Leu Leu Ile His Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Xaa Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Xaa Gly Thr Xaa Leu Glu Xaa Lys

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            100                 105                 110


<210> SEQ ID NO 189
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant-1 light chain variable region: Lvh1

<400> SEQUENCE: 189

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35                  40                  45

Pro Gln Leu Leu Ile Tyr Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
        85                  90                  95

Ser His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
    100                 105                 110


<210> SEQ ID NO 190
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant-2 light chain variable region: Lvh2

<400> SEQUENCE: 190

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1                   5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
                20                  25                  30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Thr Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> SEQ ID NO 191
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant heavy chain variable region
      consensus 1
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in
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comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (87)..(87)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa is an amino acid substitution in comparison with SEQ ID NO.:46

<400> SEQUENCE: 191

Gln Xaa Gln Leu Val Gln Ser Gly Xaa Glu Xaa Xaa Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Xaa Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Xaa Gln Xaa Xaa Gly Xaa Xaa Leu Glu Trp Xaa
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Xaa Xaa Xaa Xaa Thr Xaa Asp Xaa Ser Xaa Ser Thr Ala Tyr
65 70 75 80

Met Xaa Leu Xaa Ser Leu Xaa Ser Glu Asp Xaa Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Xaa Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 192
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant heavy chain variable region consensus 2
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be P or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be V or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Xaa may be S or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa may be H or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Xaa may be S or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa may be a basic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be I or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: Xaa may be an hydrophobic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: Xaa may be K or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: Xaa may be Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be N or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (87)..(87)
<223> OTHER INFORMATION: Xaa may be T or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa may be a neutral hydrophilic amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa may be S or L

<400> SEQUENCE: 192

Gln Xaa Gln Leu Val Gln Ser Gly Xaa Glu Xaa Xaa Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Xaa Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Xaa Gln Xaa Xaa Gly Xaa Xaa Leu Glu Trp Xaa
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Xaa Xaa Xaa Xaa Thr Xaa Asp Xaa Ser Xaa Ser Thr Ala Tyr
65 70 75 80

Met Xaa Leu Xaa Ser Leu Xaa Ser Glu Asp Xaa Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Xaa Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 193
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant heavy chain variable region
consensus 3
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be I or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa may be P or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa may be M or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa may be V or K
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Xaa may be M or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa may be K or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Xaa may be S or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (41)..(41)

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<223> OTHER INFORMATION: Xaa may be H or P
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa may be K or Q
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (44)..(44)
<223> OTHER INFORMATION: Xaa may be S or G
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa may be I or M
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa may be K or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (68)..(68)
<223> OTHER INFORMATION: Xaa may be A or V
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa may be I or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (70)..(70)
<223> OTHER INFORMATION: Xaa may be L or I
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (72)..(72)
<223> OTHER INFORMATION: Xaa may be V or A
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (74)..(74)
<223> OTHER INFORMATION: Xaa may be K or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (76)..(76)
<223> OTHER INFORMATION: Xaa may be S or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: Xaa may be Q or E
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Xaa may be N or S
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (87)..(87)
<223> OTHER INFORMATION: Xaa may be T or R
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (91)..(91)
<223> OTHER INFORMATION: Xaa may be S or T
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa may be S or L

<400> SEQUENCE: 193

Gln Xaa Gln Leu Val Gln Ser Gly Xaa Glu Xaa Xaa Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Xaa Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
            20 25 30

Tyr Met Ser Trp Val Xaa Gln Xaa Xaa Gly Xaa Xaa Leu Glu Trp Xaa
        35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
    50 55 60

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Lys Gly Xaa Xaa Xaa Xaa Thr Xaa Asp Xaa Ser Xaa Ser Thr Ala Tyr
65 70 75 80

Met Xaa Leu Xaa Ser Leu Xaa Ser Glu Asp Xaa Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Xaa Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 194
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant-1 heavy chain variable region: Hvh1

<400> SEQUENCE: 194

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 195
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant-2 heavy chain variable region: Hvh2

<400> SEQUENCE: 195

Gln Ile Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

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Thr Val Ser Ser
115

<210> SEQ ID NO 196
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant-3 heavy chain variable region: Hvh3

<400> SEQUENCE: 196

Gln Ile Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 197
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 variant-4 heavy chain variable region: Hvh4

<400> SEQUENCE: 197

Gln Ile Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 198
<211> LENGTH: 219
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 murine light (kappa) chain

<400> SEQUENCE: 198

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile His Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Arg Leu Glu Leu Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 199
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 humanized ligh (kappa) chain variant 1: Lh1

<400> SEQUENCE: 199

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Thr Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

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Ser His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210> SEQ ID NO 200
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 humanized ligh (kappa) chain variant 2: Lh2

<400> SEQUENCE: 200

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Thr Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> SEQ ID NO 201
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 murine heavy (IgG1) chain

<400> SEQUENCE: 201

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Met Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
20 25 30

Tyr Met Ser Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

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Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 202
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 humanized heavy (Igg1) chain variant 1: Hh1

<400> SEQUENCE: 202

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255
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Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 203
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 humanized heavy (Igg1) chain variant 2: Hh2

<400> SEQUENCE: 203

Gln Ile Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160
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Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 204
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 humanized heavy (Igg1) chain variant 3: Hh3

<400> SEQUENCE: 204

Gln Ile Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60
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Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 205
<211> LENGTH: 446
<212> TYPE: PRT
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 3A4 humanized heavy (Igg1) chain variant 4: Hh4

<400> SEQUENCE: 205

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Gln Ile Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asp
            20                  25                  30

Tyr Met Ser Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Asp Ile Asn Pro Tyr Asn Gly Asp Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Pro Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
```

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    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

<210> SEQ ID NO 206
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 206

atacccaagc ttgccaccat ggagacagac acac 34

<210> SEQ ID NO 207
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 207

atacccaagc ttcatttccc gggagacagg gag 33

<210> SEQ ID NO 208
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 208

atacccaagc ttgggccacc atgaactttc tgctgtcttg g 41

<210> SEQ ID NO 209
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: primer

<400> SEQUENCE: 209

atacccaagc ttctaacact ctcccctgtt gaag 34

<210> SEQ ID NO 210
<211> LENGTH: 3962
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: plasmid pK-CR5

<400> SEQUENCE: 210

ctaaattgta agcgttaata ttttgttaaa attcgcgtta aatttttgtt aaatcagctc 60

atttttttaac caataggccg aaatcggcaa aatcccttat aaatcaaaag aatagaccga 120

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gatagggttg agtgttgttc cagtttggaa caagagtcca ctattaaaga acgtggactc 180

caacgtcaaa gggcgaaaaa ccgtctatca gggcgatggc ccactacgtg aaccatcacc 240

ctaatcaagt tttttggggt cgaggtgccg taaagcacta aatcggaacc ctaaagggag 300

cccccgattt agagcttgac ggggaaagcc ggcgaacgtg gcgagaaagg aagggaagaa 360

agcgaaagga gcgggcgcta gggcgctggc aagtgtagcg gtcacgctgc gcgtaaccac 420

cacacccgcc gcgcttaatg cgccgctaca gggcgcgtcc cattcgccat tcaggctgcg 480

caactgttgg gaagggcgat cggtgcgggc ctcttcgcta ttacgccagc tggcgaaagg 540

gggatgtgct gcaaggcgat taagttgggt aacgccaggg ttttcccagt cacgacgttg 600

taaaacgacg gccagtgagc gcgcgtaata cgactcacta tagggcgaat tggagctcca 660

ccgcggtggc ggccgctcta gaactagtgg atccacatcg gcgcgccaaa tgatttgccc 720

tcccatatgt ccttccgagt gagagacaca aaaaattcca acacactatt gcaatgaaaa 780

taaatttcct ttattagcca gaggtcgaga tttaaataag cttgctagca gatctttgga 840

cctgggagtg gacacctgtg gagagaaagg caaagtggat gtcattgtca ctcaagtgta 900

tggccagatc gggccaggtg aatatcaaat cctcctcgtt tttggaaact gacaatctta 960

gcgcagaagt aatgcccgct tttgagaggg agtactcacc ccaacagctg gatctcaagc 1020

ctgccacacc tcacctcgac catccgccgt ctcaagaccg cctactttaa ttacatcatc 1080

agcagcacct ccgccagaaa caaccccgac cgccacccgc tgccgcccgc cacggtgctc 1140

agcctacctt gcgactgtga ctggttagac gcctttctcg agaggttttc cgatccggtc 1200

gatgcggact cgctcaggtc cctcggtggc ggagtaccgt tcggaggccg acgggtttcc 1260

gatccaagag tactggaaag accgcgaaga gtttgtcctc aaccgcgagc ccaacagctg 1320

gccctcgcag acagcgatgc ggaagagagt gaccgcggag gctggatcgg tcccggtgtc 1380

ttctatggag gtcaaaacag cgtggatggc gtctccaggc gatctgacgg ttcactaaac 1440

gagctctgct tatataggcc tcccaccgta cacgcctacc tcgacccggg taccaatctt 1500

ataatacaaa cagaccagat tgtctgtttg ttataataca aacagaccag attgtctgtt 1560

tgttataata caaacagacc agattgtctg tttgttataa tacaaacaga ccagattgtc 1620

tgtttgttat aatacaaaca gaccagattg tctgtttgtt ataatacaaa cagaccagat 1680

tgtctgtttg ttaaggttgt cgagtgaaga cgaaagggtt cattaaggcg cgccgtcgac 1740

ctcgaggggg ggcccggtac ccagcttttg ttccctttag tgagggttaa ttgcgcgctt 1800

ggcgtaatca tggtcatagc tgtttcctgt gtgaaattgt tatccgctca caattccaca 1860

caacatacga gccggaagca taaagtgtaa agcctggggt gcctaatgag tgagctaact 1920

cacattaatt gcgttgcgct cactgcccgc tttccagtcg ggaaacctgt cgtgccagct 1980

gcattaatga atcggccaac gcgcggggag aggcggtttg cgtattgggc gctcttccgc 2040

ttcctcgctc actgactcgc tgcgctcggt cgttcggctg cggcgagcgg tatcagctca 2100

ctcaaaggcg gtaatacggt tatccacaga atcaggggat aacgcaggaa agaacatgtg 2160

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gctttctcat agctcacgct gtaggtatct cagttcggtg taggtcgttc gctccaagct 2460

gggctgtgtg cacgaacccc ccgttcagcc cgaccgctgc gccttatccg gtaactatcg 2520

tcttgagtcc aacccggtaa gacacgactt atcgccactg gcagcagcca ctggtaacag 2580

gattagcaga gcgaggtatg taggcggtgc tacagagttc ttgaagtggt ggcctaacta 2640

cggctacact agaaggacag tatttggtat ctgcgctctg ctgaagccag ttaccttcgg 2700

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acgctcaccg gctccagatt tatcagcaat aaaccagcca gccggaaggg ccgagcgcag 3180

aagtggtcct gcaactttat ccgcctccat ccagtctatt aattgttgcc gggaagctag 3240

agtaagtagt tcgccagtta atagtttgcg caacgttgtt gccattgcta caggcatcgt 3300

ggtgtcacgc tcgtcgtttg gtatggcttc attcagctcc ggttcccaac gatcaaggcg 3360

agttacatga tcccccatgt tgtgcaaaaa agcggttagc tccttcggtc ctccgatcgt 3420

tgtcagaagt aagttggccg cagtgttatc actcatggtt atggcagcac tgcataattc 3480

tcttactgtc atgccatccg taagatgctt ttctgtgact ggtgagtact caaccaagtc 3540

attctgagaa tagtgtatgc ggcgaccgag ttgctcttgc ccggcgtcaa tacgggataa 3600

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aaaactctca aggatcttac cgctgttgag atccagttcg atgtaaccca ctcgtgcacc 3720

caactgatct tcagcatctt ttactttcac cagcgtttct gggtgagcaa aaacaggaag 3780

gcaaaatgcc gcaaaaaagg gaataagggc gacacggaaa tgttgaatac tcatactctt 3840

cctttttcaa tattattgaa gcatttatca gggttattgt ctcatgagcg gatacatatt 3900

tgaatgtatt tagaaaaata aacaaatagg ggttccgcgc acatttcccc gaaaagtgcc 3960

ac 3962

<210> SEQ ID NO 211
<211> LENGTH: 6530
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: plasmid pMPG-CR5

<400> SEQUENCE: 211

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tccttccgag tgagagacac aaaaaattcc aacacactat tgcaatgaaa ataaatttcc 120

tttattagcc agaggtcgag gtcgggggat ccgtttaaac ttggacctgg gagtggacac 180

ctgtggagag aaaggcaaag tggatgtcat tgtcactcaa gtgtatggcc agatcgggcc 240

aggtgaatat caaatcctcc tcgtttttgg aaactgacaa tcttagcgca gaagtaatgc 300

ccgcttttga gagggagtac tcaccccaac agctggatct caagcctgcc acacctcacc 360

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agaaacaacc ccgaccgcca cccgctgccg cccgccacgg tgctcagcct accttgcgac 480

tgtgactggt tagacgcctt tctcgagagg ttttccgatc cggtcgatgc ggactcgctc 540

aggtccctcg gtggcggagt accgttcgga ggccgacggg tttccgatcc aagagtactg 600

gaaagaccgc gaagagtttg tcctcaaccg cgagcccaac agctggccct cgcagacagc 660

gatgcggaag agagtgaccg cggaggctgg atcggtcccg gtgtcttcta tggaggtcaa 720

aacagcgtgg atggcgtctc caggcgatct gacggttcac taaacgagct ctgcttatat 780

aggcctccca ccgtacacgc ctacctcgac ccgggtacca atcttataat acaaacagac 840

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aaacagacca gattgtctgt ttgttataat acaaacagac cagattgtct gtttgttaag 1020

gttgtcgagt gaagacgaaa gggttaatta aggcgcgccg tcgactagct tggcacgcca 1080

gaaatccgcg cggtggtttt tgggggtcgg gggtgtttgg cagccacaga cgcccggtgt 1140

tcgtgtcgcg ccagtacatg cggtccatgc ccaggccatc caaaaaccat gggtctgtct 1200

gctcagtcca gtcgtggacc agaccccacg caacgcccaa aataataacc cccacgaacc 1260

ataaaccatt ccccatgggg gaccccgtcc ctaacccacg gggccagtgg ctatggcagg 1320

gcctgccgcc ccgacgttgg ctgcgagccc tgggccttca cccgaacttg gggggtgggg 1380

tggggaaaag gaagaaacgc gggcgtattg gccccaatgg ggtctcggtg gggtatcgac 1440

agagtgccag ccctgggacc gaaccccgcg tttatgaaca aacgacccaa cacccgtgcg 1500

ttttattctg tctttttatt gccgtcatag cgcgggttcc ttccggtatt gtctccttcc 1560

gtgtttcagt tagcctcccc catctccccc attcctttgc cctcggacga gtgctggggc 1620

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agatgcaata ggtcaggctc tcgctgaatt ccccaatgtc aagcacttcc ggaatcggga 2400

gcgcggccga tgcaaagtgc cgataaacat aacgatcttt gtagaaacca tcggcgcagc 2460

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gtgaatgcgc aaaccaaccc ttggcagaac atatccatcg cgtccgccat ctccagcagc 3360

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ataggctccg ccccccctgac gagcatcaca aaaatcgacg ctcaagtcag aggtggcgaa 3480

acccgacagg actataaaga taccaggcgt ttcccccctgg aagctccctc gtgcgctctc 3540

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cgctttctca tagctcacgc tgtaggtatc tcagttcggt gtaggtcgtt cgctccaagc 3660

tgggctgtgt gcacgaaccc cccgttcagc ccgaccgctg cgccttatcc ggtaactatc 3720

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ggattagcag agcgaggtat gtaggcggtg ctacagagtt cttgaagtgg tggcctaact 3840

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gaaaaagagt tggtagctct tgatccggca aacaaaccac cgctggtagc ggtggttttt 3960

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tttctacggg gtctgacgct cagtggaacg aaaactcacg ttaagggatt ttggtcatga 4080

gattatcaaa aaggatcttc acctagatcc ttttaaatta aaaatgaagt tttaaatcaa 4140

tctaaagtat atatgagtaa acttggtctg acagttacca atgcttaatc agtgaggcac 4200

ctatctcagc gatctgtcta tttcgttcat ccatagttgc ctgactcccc gtcgtgtaga 4260

taactacgat acgggagggc ttaccatctg gccccagtgc tgcaatgata ccgcgagacc 4320

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cattctgaga atagtgtatg cggcgaccga gttgctcttg cccggcgtca acacgggata 4800

ataccgcgcc acatagcaga actttaaaag tgctcatcat tggaaaacgt tcttcggggc 4860

gaaaactctc aaggatctta ccgctgttga gatccagttc gatgtaaccc actcgtgcac 4920

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1. A method of treating breast cancer, the method comprising administering an antibody or an antigen binding fragment thereof, capable of specific binding to Kidney associated antigen 1 (KAAG1) to an individual having a breast cancer that has low expression of the estrogen receptor (ER), of the progesterone receptor (PgR) and/or of human epidermal growth factor receptor 2 (Her2).

2. (canceled)

3. The method of claim **1**, wherein the individual has a breast cancer that is characterized as being negative for estrogen receptor (ER) expression, progesterone receptor (PgR) expression and/or for Her2 overexpression.

4. A method of treating triple negative breast cancer, the method comprising administering an antibody or an antigen binding fragment thereof capable of specific binding to Kidney associated antigen 1 (KAAG1) to an individual in need.

5. (canceled)

6. The method of claim **4**, wherein the antibody or antigen binding fragment thereof is conjugated with a therapeutic moiety.

7. (canceled)

8. The method of claim **4**, wherein the antibody or antigen binding fragment thereof binds an epitope comprised between amino acids 30 to 84 of KAAG1.

9. The method of claim **4**, wherein the antibody or antigen binding fragment thereof is a monoclonal antibody, a chimeric antibody, a human antibody or a humanized antibody or an antigen binding fragment thereof.

10. The method of claim **4**, wherein the antibody or antigen binding fragment thereof is administered in combination with an anti-cancer agent.

11. The method of claim **4**, wherein the antibody or antigen binding fragment thereof comprises:

a. a CDRH1 as set forth in SEQ ID NO.:49, a CDRH2 as set forth in SEQ ID NO.:50 or in SEQ ID NO.:212, a CDRH3 as set forth in SEQ ID NO.:51, a CDRL1 as set forth in SEQ ID NO.: 52, a CDRL2 as set forth in SEQ ID NO.:53 and a CDRL3 as set forth in SEQ ID NO.: 54;

b. a light chain variable region as set forth in SEQ ID NO.:48 and a heavy chain variable region as set forth in SEQ ID NO.:46;

c. a light chain variable region as set forth in SEQ ID NO.:186 wherein at least one of the amino acid identified by X is an amino acid substitution in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48 and a heavy chain variable region as set forth in SEQ ID NO.:191 wherein at least one of the amino acid identified by X is an amino acid substitution in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46;

d. a light chain variable region as set forth in SEQ ID NO.:187 and a heavy chain variable region as set forth in SEQ ID NO.:192;

e. a light chain variable region as set forth in SEQ ID NO.:188 and a heavy chain variable region as set forth in SEQ ID NO.:193;
f. a light chain variable region as set forth in SEQ ID NO.: 189 or SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197;
g. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:194;
h. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:195;
i. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:196;
j. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:197;
k. a light chain variable region as set forth in SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:194;
l. a light chain variable region as set forth in SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:195;
m. a light chain as set forth in SEQ ID NO.: 199 or SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202, SEQ ID NO.:203, SEQ ID NO.:204 or SEQ ID NO.:205;
n. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:202;
o. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:203;
p. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:204;
q. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:205;
r. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202;
s. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:203;
t. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:204 or;
u. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:205.

12-31. (canceled)

32. The method of claim **11**, wherein the antibody or antigen binding fragment thereof is conjugated with a therapeutic moiety.

33. The method of claim **32**, wherein the therapeutic moiety is a cytotoxic agent.

34. The method of claim **6**, wherein the antibody or antigen binding fragment thereof has a high affinity for KAAG1.

35-39. (canceled)

40. The method of claim **1**, wherein the antibody or antigen binding fragment thereof is conjugated with a therapeutic moiety.

41. The method of claim **40**, wherein the antibody or antigen binding fragment thereof has a high affinity for KAAG1.

42. The method of claim **1**, wherein the antibody or antigen binding fragment thereof comprises:

a. a CDRH1 as set forth in SEQ ID NO.:49, a CDRH2 as set forth in SEQ ID NO.:50 or in SEQ ID NO.:212, a CDRH3 as set forth in SEQ ID NO.:51, a CDRL1 as set forth in SEQ ID NO.: 52, a CDRL2 as set forth in SEQ ID NO.:53 and a CDRL3 as set forth in SEQ ID NO.: 54;
b. a light chain variable region as set forth in SEQ ID NO.:48 and a heavy chain variable region as set forth in SEQ ID NO.:46;
c. a light chain variable region as set forth in SEQ ID NO.:186 wherein at least one of the amino acid identified by X is an amino acid substitution in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48 and a heavy chain variable region as set forth in SEQ ID NO.:191 wherein at least one of the amino acid identified by X is an amino acid substitution in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46;
d. a light chain variable region as set forth in SEQ ID NO.:187 and a heavy chain variable region as set forth in SEQ ID NO.:192;
e. a light chain variable region as set forth in SEQ ID NO.:188 and a heavy chain variable region as set forth in SEQ ID NO.:193;
f. a light chain variable region as set forth in SEQ ID NO.: 189 or SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197;
g. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:194;
h. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:195;
i. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:196;
j. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:197;
k. a light chain variable region as set forth in SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:194;
l. a light chain variable region as set forth in SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:195;
m. a light chain as set forth in SEQ ID NO.: 199 or SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202, SEQ ID NO.:203, SEQ ID NO.:204 or SEQ ID NO.:205;
n. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:202;
o. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:203;
p. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:204;
q. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:205;
r. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202;
s. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:203;
t. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:204 or;

u. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:205.

43. The method of claim **42**, wherein the antibody or antigen binding fragment thereof is conjugated with a therapeutic moiety.

44. A method of treating basal-like breast cancer, the method comprising administering an antibody or an antigen binding fragment thereof capable of specific binding to Kidney associated antigen 1 (KAAG1) to an individual in need.

45. The method of claim **44**, wherein the antibody or antigen binding fragment thereof is conjugated with a therapeutic moiety.

46. The method of claim **45**, wherein the antibody or antigen binding fragment thereof has a high affinity for KAAG1.

47. The method of claim **44**, wherein the antibody or antigen binding fragment thereof comprises:

a. a CDRH1 as set forth in SEQ ID NO.:49, a CDRH2 as set forth in SEQ ID NO.:50 or in SEQ ID NO.:212, a CDRH3 as set forth in SEQ ID NO.:51, a CDRL1 as set forth in SEQ ID NO.: 52, a CDRL2 as set forth in SEQ ID NO.:53 and a CDRL3 as set forth in SEQ ID NO.: 54;

b. a light chain variable region as set forth in SEQ ID NO.:48 and a heavy chain variable region as set forth in SEQ ID NO.:46;

c. a light chain variable region as set forth in SEQ ID NO.:186 wherein at least one of the amino acid identified by X is an amino acid substitution in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:48 and a heavy chain variable region as set forth in SEQ ID NO.:191 wherein at least one of the amino acid identified by X is an amino acid substitution in comparison with a corresponding amino acid in the polypeptide set forth in SEQ ID NO.:46;

d. a light chain variable region as set forth in SEQ ID NO.:187 and a heavy chain variable region as set forth in SEQ ID NO.:192;

e. a light chain variable region as set forth in SEQ ID NO.:188 and a heavy chain variable region as set forth in SEQ ID NO.:193;

f. a light chain variable region as set forth in SEQ ID NO.: 189 or SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:194, SEQ ID NO.:195, SEQ ID NO.:196 or SEQ ID NO.:197;

g. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:194;

h. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:195;

i. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:196;

j. a light chain variable region as set forth in SEQ ID NO.:189 and a heavy chain variable region as set forth in SEQ ID NO.:197;

k. a light chain variable region as set forth in SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:194;

l. a light chain variable region as set forth in SEQ ID NO.:190 and a heavy chain variable region as set forth in SEQ ID NO.:195;

m. a light chain as set forth in SEQ ID NO.: 199 or SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202, SEQ ID NO.:203, SEQ ID NO.:204 or SEQ ID NO.:205;

n. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:202;

o. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:203;

p. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:204;

q. a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:205;

r. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202;

s. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:203;

t. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:204 or;

u. a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:205.

48. The method of claim **47**, wherein the antibody or antigen binding fragment thereof is conjugated with a therapeutic moiety.

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