Claims:

1. A method of treating breast cancer, the method comprising administering a Kidney associated antigen 1 inhibitor (KAAG1 inhibitor) to an individual having a breast cancer that has low expression of the estrogen receptor (ER), of the progesterone receptor (PgR) and/or of Her2.

2. The method of claim 1, wherein the KAAG1 inhibitor is an antibody or antigen binding fragment which is capable of specific binding to Kidney associated antigen 1 (KAAG1; SEQ ID N0..2).

3. The method of claim 1 or 2, 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 or basal-like breast cancer, the method comprising administering a Kidney associated antigen 1 inhibitor (KAAG1 inhibitor) to an individual in need.

5. The method of claim 4, wherein the KAAG1 inhibitor is an antibody or antigen binding fragment which is capable of binding to KAAG1 .

6. The method of any one of claims 2, 3 or 5, wherein the antibody or antigen binding fragment is conjugated with a therapeutic moiety.

7. The method of any one of claims 2, 3, 5 or 6, wherein the antibody or antigen binding fragment binds to the surface of cancer cells.

8. The method of any one of claims 2, 3, or 5 to 7, wherein the antibody or antigen binding fragment binds an epitope comprised between amino acids 30 to 84 of KAAG1 .

9. The method of any one of claims 2, 3, or 5 to 8, wherein the antibody is a monoclonal antibody, a chimeric antibody, a human antibody or a humanized antibody or an antigen binding fragment thereof.

10. The method of any one of claims 1 to 9, wherein the KAAG1 inhibitor is administered in combination with a chemotherapeutic or a cytotoxic agent.

11. The method of any one of claims 2, 3 or 5 to 10, wherein the antibody or antigen binding fragment comprises 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.

12. The method of any one of claims 2, 3 or 5 to 11, wherein the antibody or antigen binding fragment comprises 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.

13. The method of any one of claims 2, 3 or 5 to 11, wherein the antibody or antigen binding fragment comprises 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.

14. The method of any one of claims 2, 3, 5 to 11 or 13, wherein the light chain variable region is as set forth in SEQ ID NO.:187 and wherein the heavy chain variable region is as set forth in SEQ ID NO.:192.

15. The method of claim 2, 3, 5 to 11, 13 or 14, wherein the light chain variable region is as set forth in SEQ ID NO.:188 and wherein the heavy chain variable region is as set forth in SEQ ID NO.:193.

16. The method of any one of claims 2, 3, 5 to 11 or 13 to 15, wherein the antibody or antigen binding fragment comprises 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.

17. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

18. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

19. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

20. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

21. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

22. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

23. The method of any one of claims 2, 3, 5 to 11 or 13 to 16, wherein the antibody or antigen binding fragment comprises 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.

24. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO..202.

25. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:203.

26. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:204.

27. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:199 and a heavy chain as set forth in SEQ ID NO.:205.

28. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:202.

29. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ ID NO.:203.

30. The method of any one of claims 2, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:200 and a heavy chain as set forth in SEQ (D NO.:204.

31. The method of any one of claims 22, 3, 5 to 11 or 14 to 17, wherein the antibody or antigen binding fragment comprises a light chain as set forth in SEQ ID NO.:200 and a heavy *chain* as set forth in SEQ ID NO..205.

32. The method of any one of claims 2, 3 or 5 to 32, wherein the antibody or antigen binding fragment is conjugated with a therapeutic moiety.

33. The method of claim 33, wherein the therapeutic moiety is a cytotoxic agent.

34. The method of any one of claims 2, 3, 5 to 11, 14 to 17, or 32 to 34, wherein the antibody or antigen binding fragment thereof has a high affinity for KAAG1.

35. The method of any one of claims 22, 3, 5 to 11, 14 to 17, or 32 to 35, wherein the antibody or antigen binding fragment thereof has a high affinity for KAAG1.

36. The method of any one of claims 2, 3, 5 to 11, 14 to 17, or 32 to 36, wherein the antibody or antigen binding fragment thereof is internalized within a cell.

37. The method of any one of claims 1, 3 or 4, wherein the KAAG1 inhibitor comprises a nucleotide sequence complementary to SEQ ID NO.:1 or to a fragment thereof.

38. The method of claim 38, wherein the KAAG1 inhibitor comprises a nucleotide sequence complementary to nucleotides 738 to 992 (inclusively) of SEQ ID NO.:1 or to a fragment thereof.

39. The method of any one of claims 1 to 39, further comprising administering an anti-cancer agent.

Figure 1a

3A4-VL

murine	DVVMTQTPLSLAVSLGDQASISC**RSSQSLLHSNGNTYLE**WYLQKPGQSPKLLIH**TVSNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDLGVYYC**FQGSHVPLT**FGAGTRLELK	11/80 (86.3%)
Humanized1	DIVMTQTPLSLPVTPGEPASISC**RSSQSLLHSNGNTYLE**WYLQKPGQSPQLLIY**TVSNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**FQGSHVPLT**FGQGTKLEIK	0/80 (100%)
Humanized2	DVVMTQTPLSLPVTPGEPASISC**RSSQSLLHSNGNTYLE**WYLQKPGQSPKLLIY**TVSNRFS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**FQGSHVPLT**FGQGTKLEIK	2/80 (97.5%)
	CDR-L1 CDR-L2 CDR-L3	

Figure 1b

3A4-VH

mouse	QIQLVQSGPEMVKPGASVKMSCKAS**GYTFTDDYMS**WVKQSHGKSLEWIG**DINPYNGDTNYNQKFKG**KAILTVDKSSSTAYMQLNSLTSEDSAVYYCAR**DPGAMDY**WGQGTSVTVSS	21/82 (74.4%)
Humanized1	QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTDDYMS**WVRQAPGQGLEWMG**DINPYNGDTNYNQKFKG**RVTITADTSTSTAYMELSSLRSEDTAVYYCAR**DPGAMDY**WGQGTLVTVSS	0/82 (100%)
Humanized2	QIQLVQSGAEVKKPGASVKVSCKAS**GYTFTDDYMS**WVRQAPGQGLEWMG**DINPYNGDTNYNQKFKG**RVTITADKSTSTAYMELSSLRSEDTAVYYCAR**DPGAMDY**WGQGTLVTVSS	2/82 (97.5%)
Humanized3	QIQLVQSGAEVKKPGASVKVSCKAS**GYTFTDDYMS**WVRQAPGQGLEWIG**DINPYNGDTNYNQKFKG**RATLTVDKSTSTAYMELSSLRSEDTAVYYCAR**DPGAMDY**WGQGTLVTVSS	6/82 (92.7%)
Humanized4	QIQLVQSGAEVKKPGASVKVSCKAS**GYTFTDDYMS**WVKQAPGQGLEWIG**DINPYNGDTNYNQKFKG**KATLTVDKSTSTAYMELSSLRSEDTAVYYCAR**DPGAMDY**WGQGTLVTVSS	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
                ******:. :*.*.*:*****:*.** ***:******************** *****
```

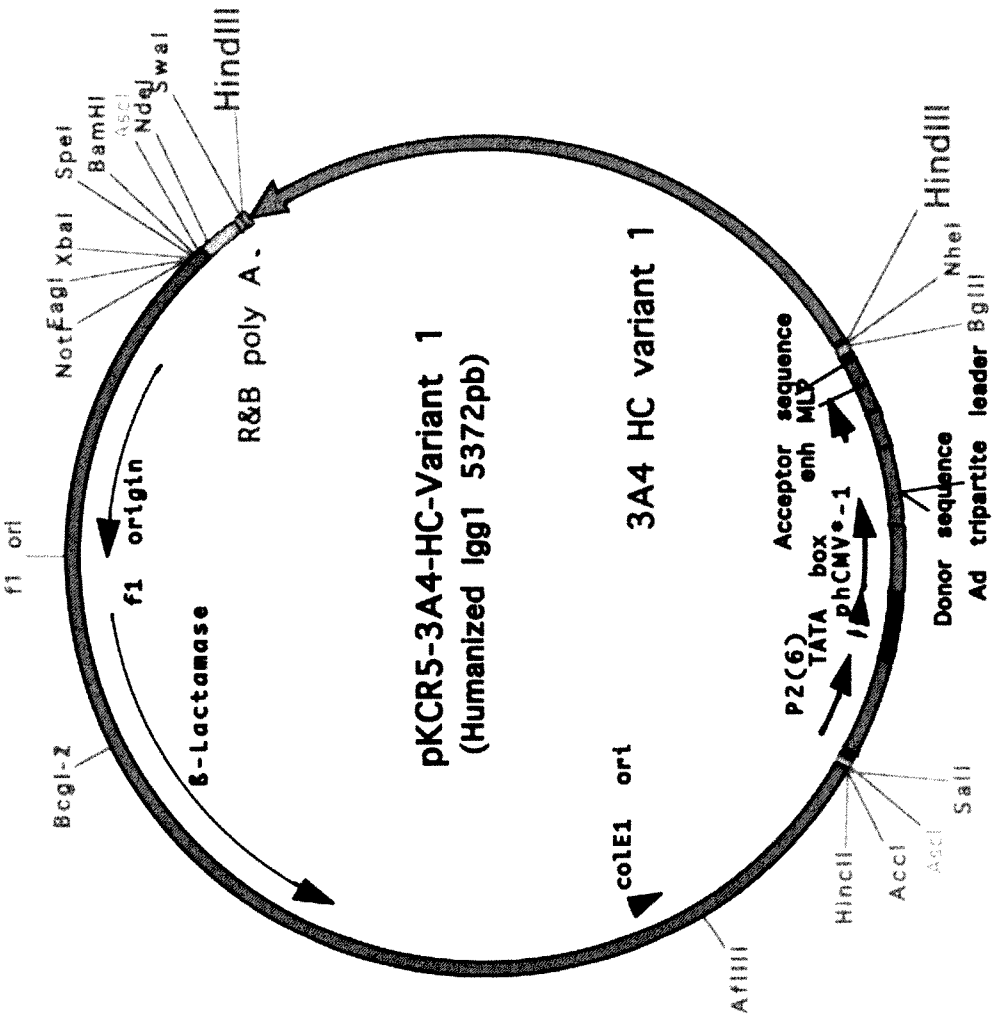

pKCR5-3A4-HC-Variant 1
(Humanized Igg1 5372pb)
3A4 HC variant 1
R&B poly A.
f1 origin
β-Lactamase
colE1 ori
f1 ori
P2(6)
TATA box
PhCMV*-1
Acceptor sequence
enh MLP
Donor sequence
Ad tripartite leader
HindIII
NheI
BglII
SalI
AscI
AccI
HincII
AflIII
Bcgl-2
NotI
EagI
XbaI
SpeI
BamHI
AscI
NdeI
SwaI
HindIII

Figure 3a

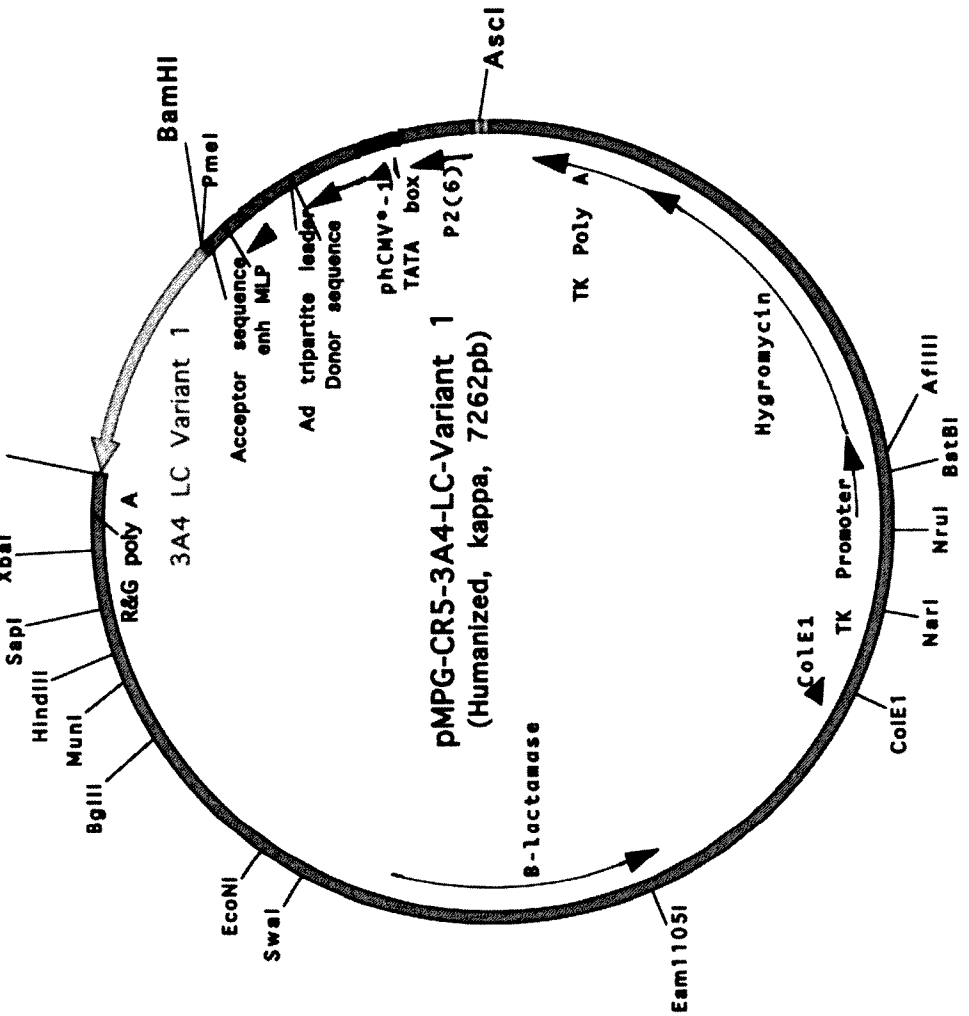

pMPG-CR5-3A4-LC-Variant 1
(Humanized, kappa, 7262pb)
3A4 LC Variant 1
BamHI
PmeI
AscI
Acceptor sequence
enh MLP
Ad tripartite leader
Donor sequence
phCMV*-1
TATA box
P2(6)
TK Poly A
Hygromycin
AflIII
BstBI
NruI
NarI
TK Promoter
ColE1
ColE1
Eam1105I
B-lactamase
EcoNI
SwaI
BglII
MunI
HindIII
SapI
XbaI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

Figure 3b

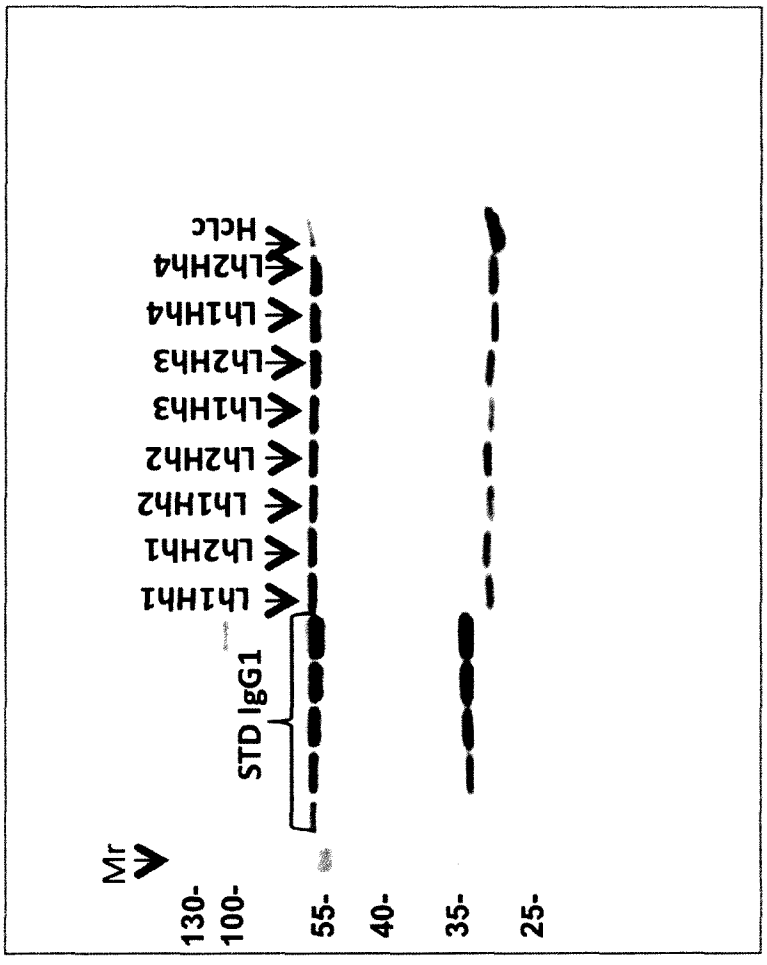
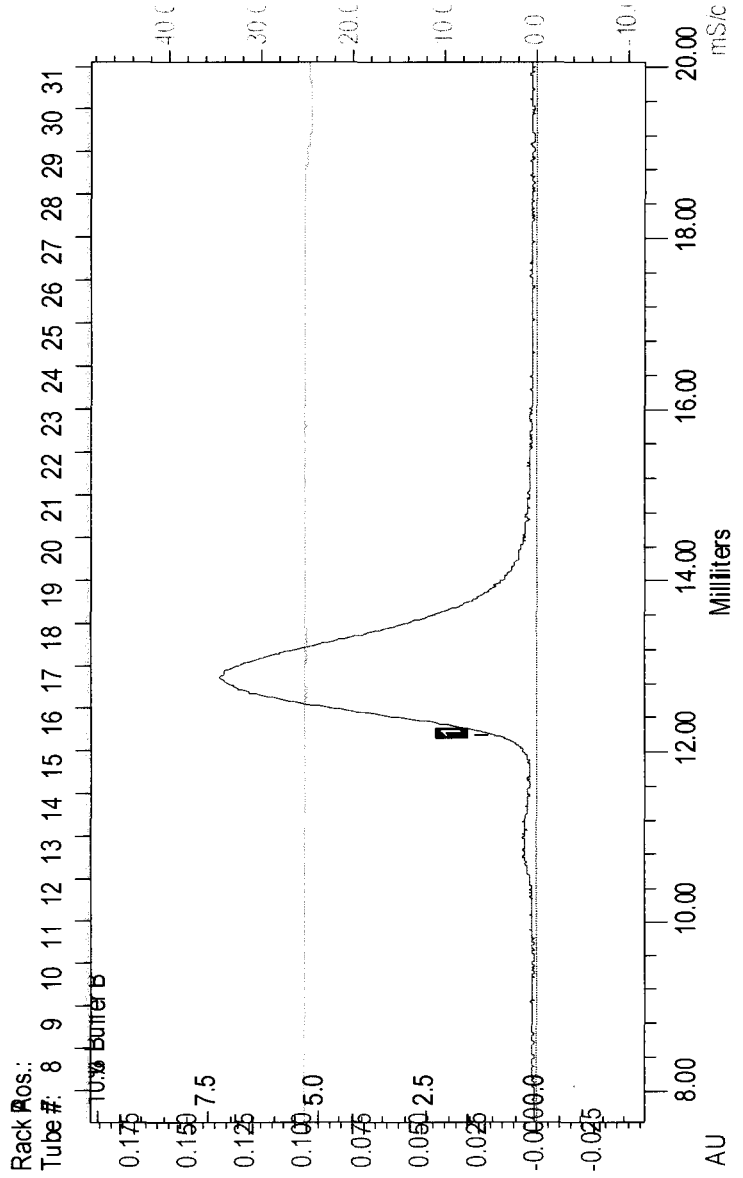

Mr
130-
100-
55-
40-
35-
25-
STD IgG1
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4
HcLc

Figure 4

Figure 5


A
B
Fractions
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

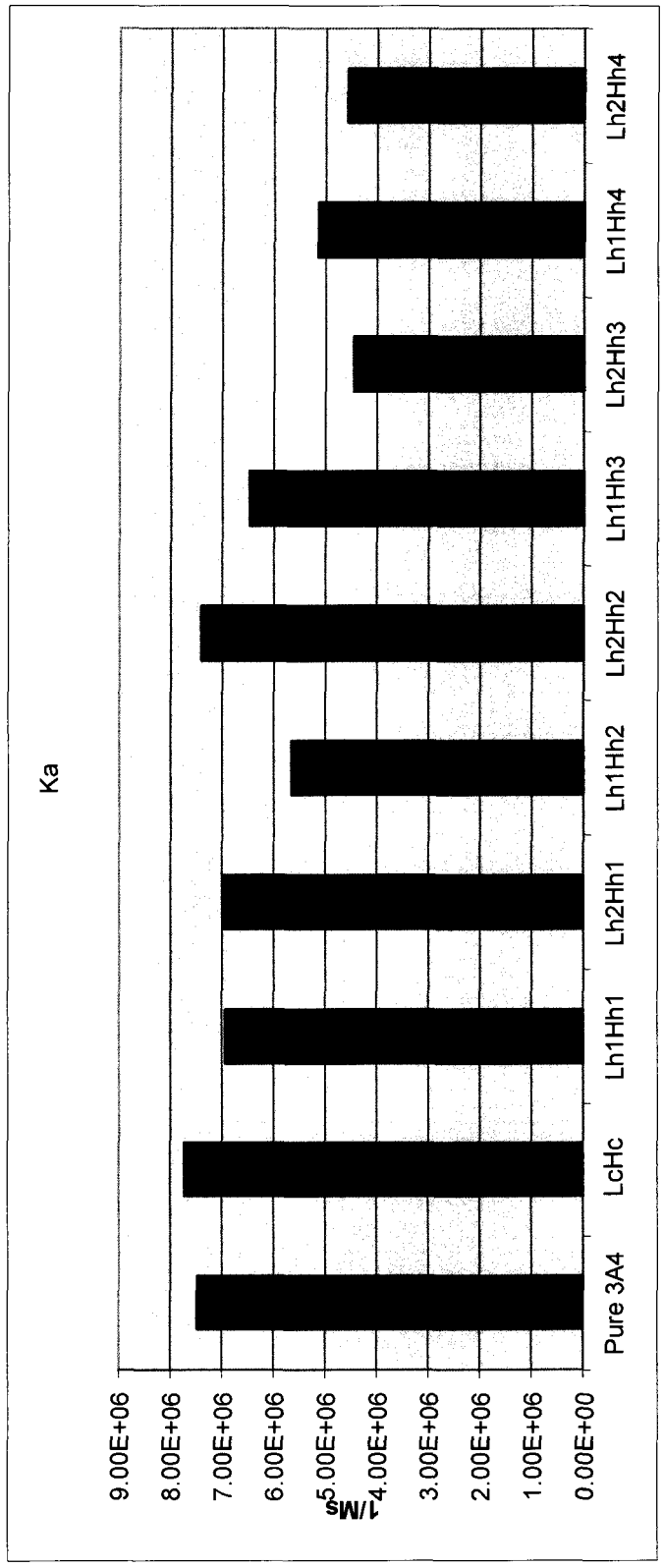

Ka
1/Ms
9.00E+06
8.00E+06
7.00E+06
6.00E+06
5.00E+06
4.00E+06
3.00E+06
2.00E+06
1.00E+06
0.00E+00
Pure 3A4
LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4

Figure 7b

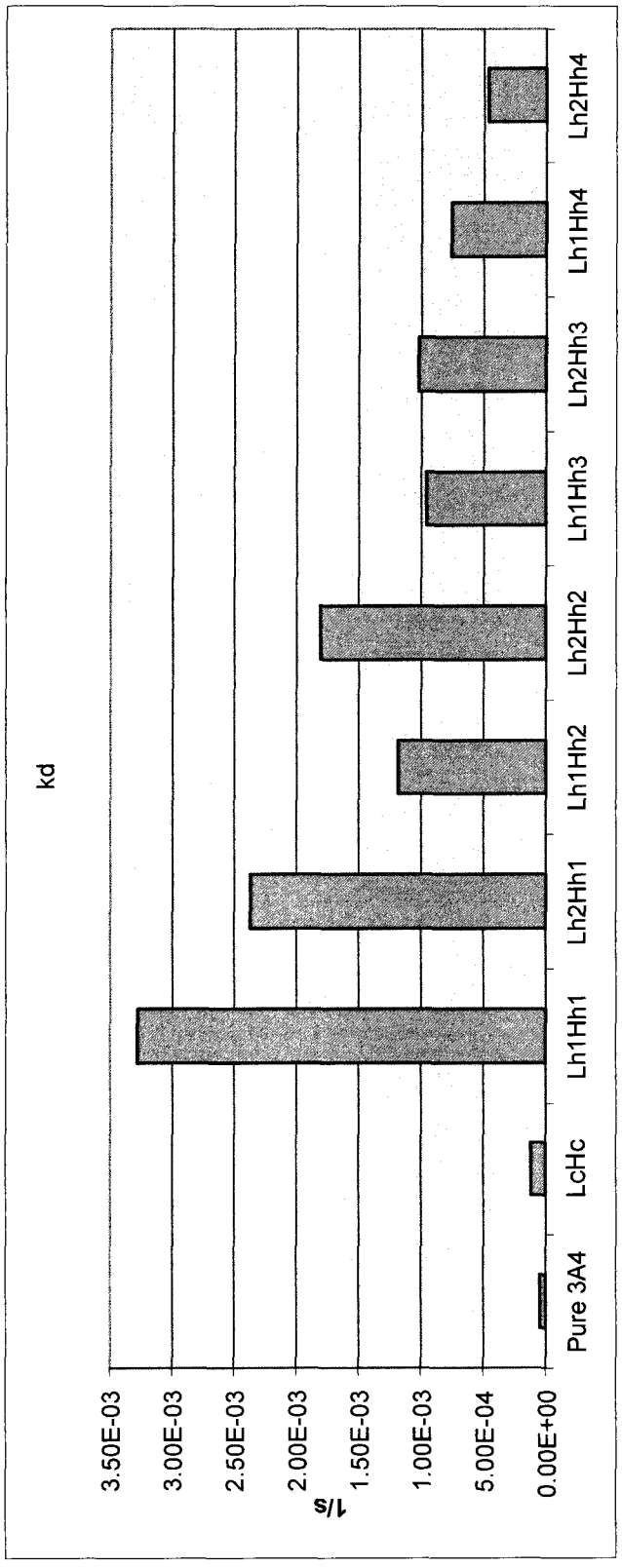
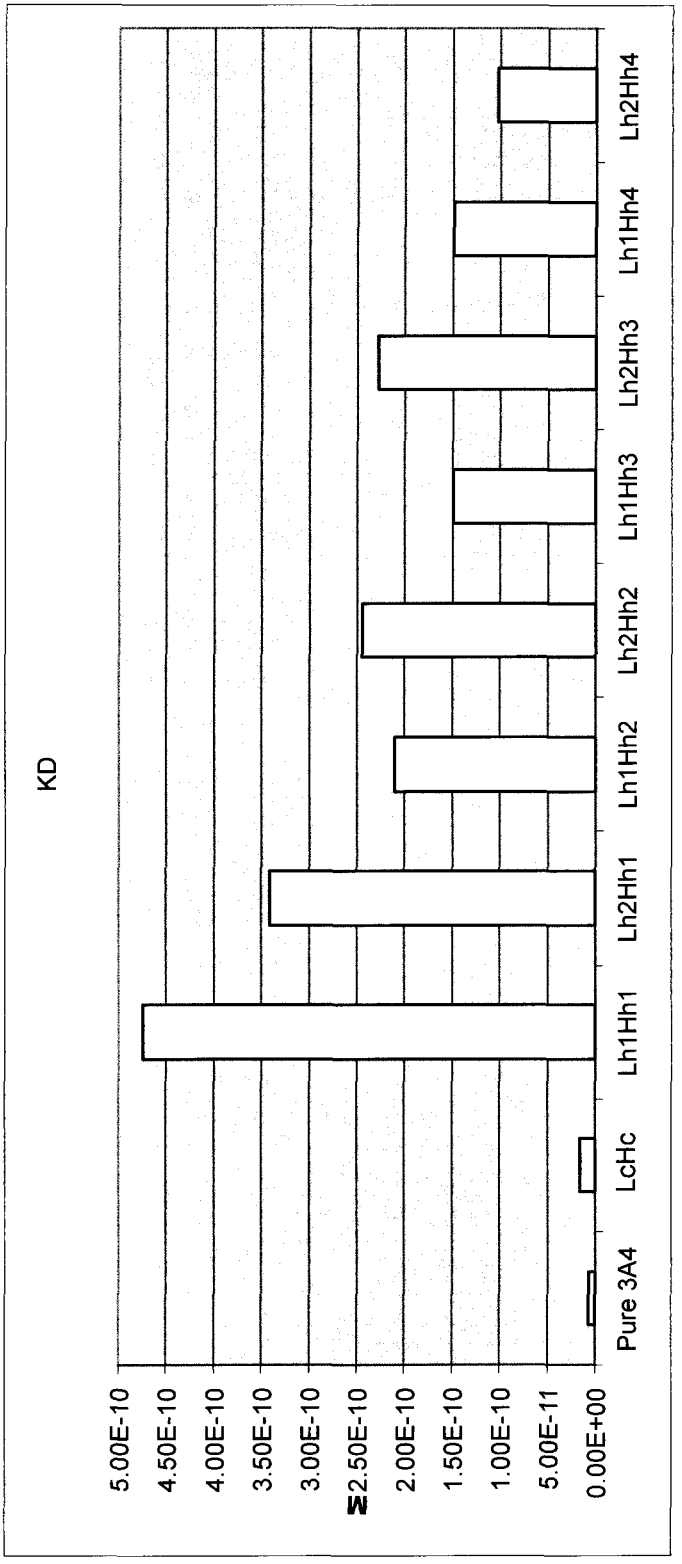

kd
1/s
3.50E-03
3.00E-03
2.50E-03
2.00E-03
1.50E-03
1.00E-03
5.00E-04
0.00E+00
Pure 3A4
LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4

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

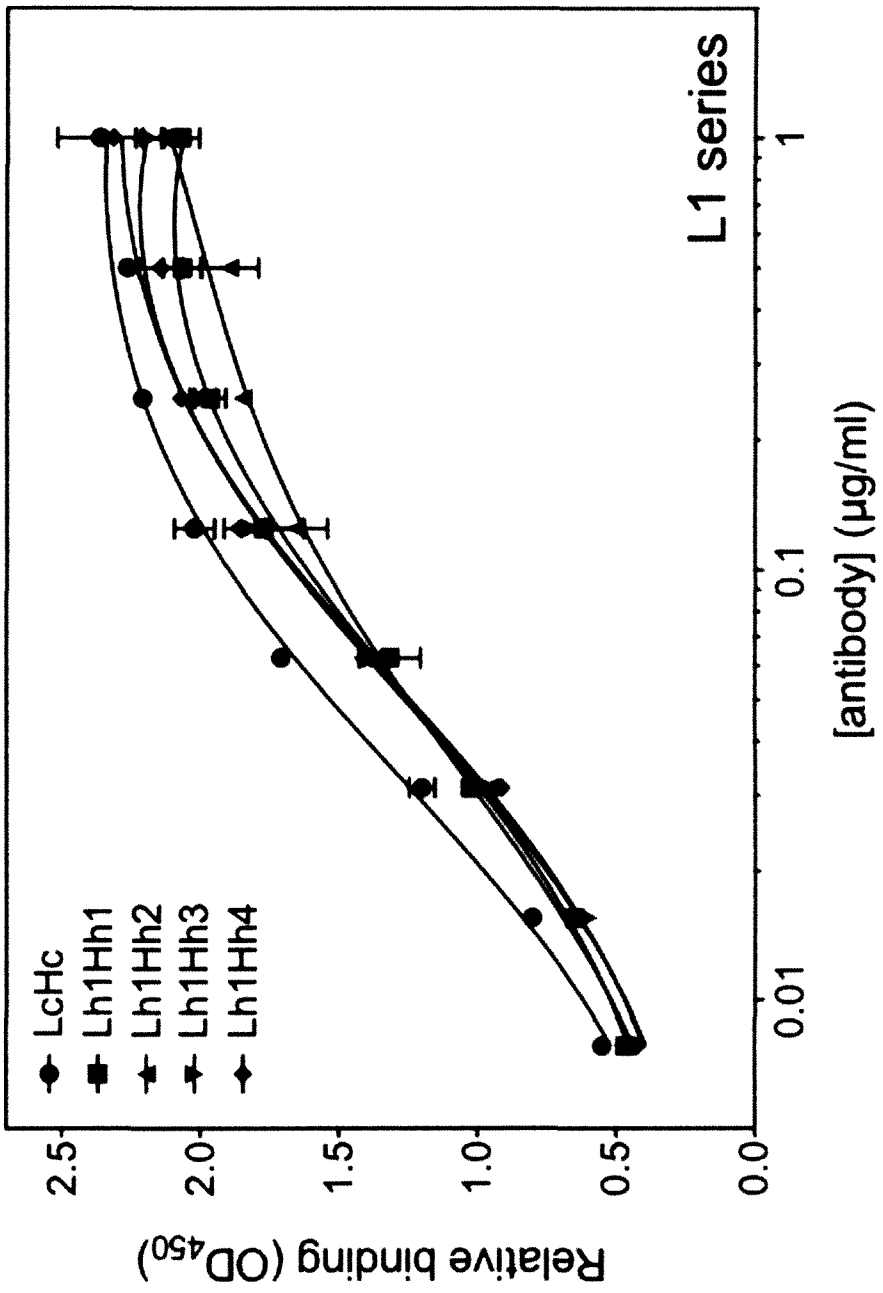

L1 series
LcHc
Lh1Hh1
Lh1Hh2
Lh1Hh3
Lh1Hh4
Relative binding (OD_{450})
0.0
0.5
1.0
1.5
2.0
2.5
0.01
0.1
1
[antibody] (µg/ml)

Figure 8a

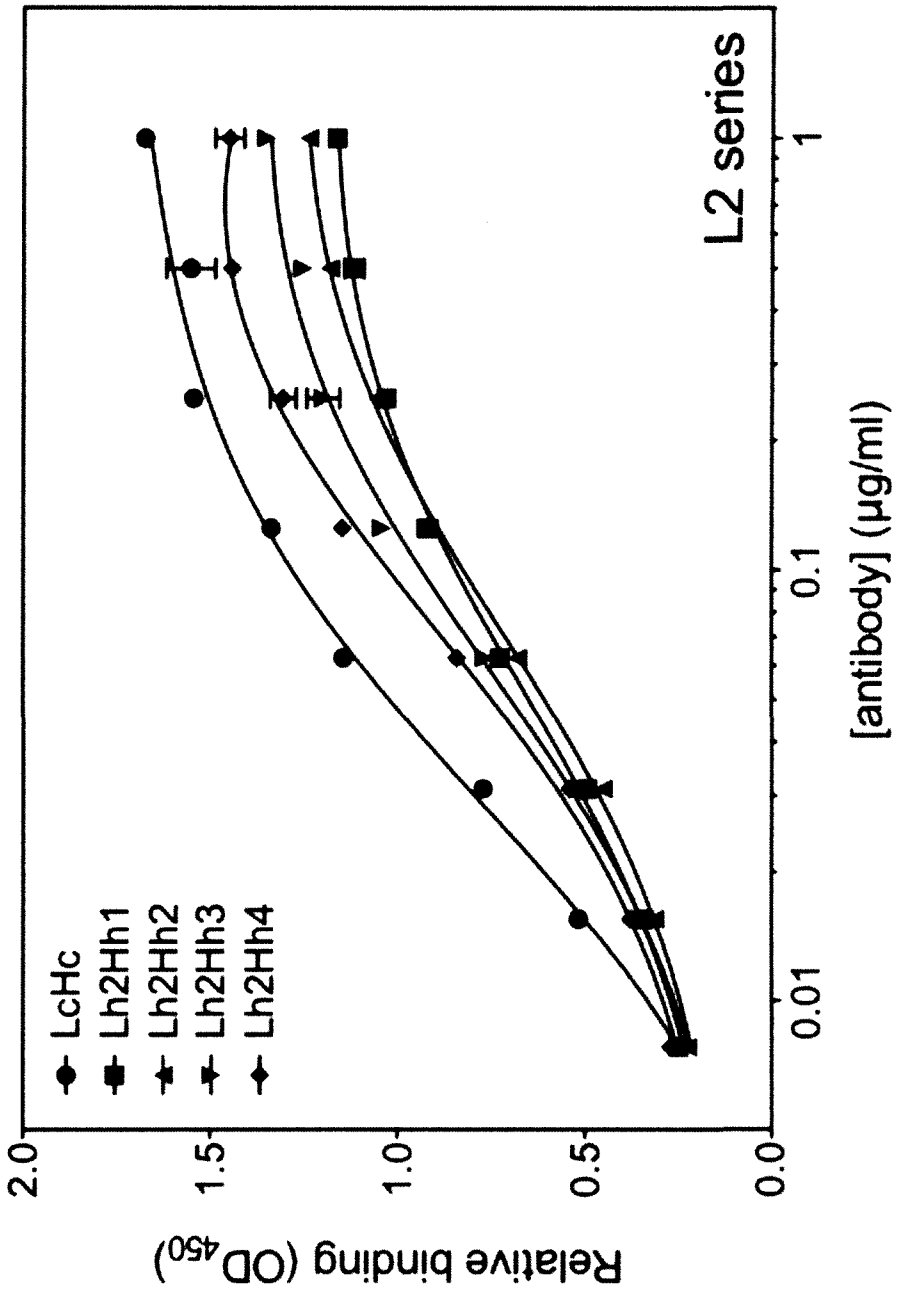

L2 series
LcHc
Lh2Hh1
Lh2Hh2
Lh2Hh3
Lh2Hh4
Relative binding (OD450)
[antibody] (µg/ml)
0.0
0.5
1.0
1.5
2.0
0.01
0.1
1

Figure 8b

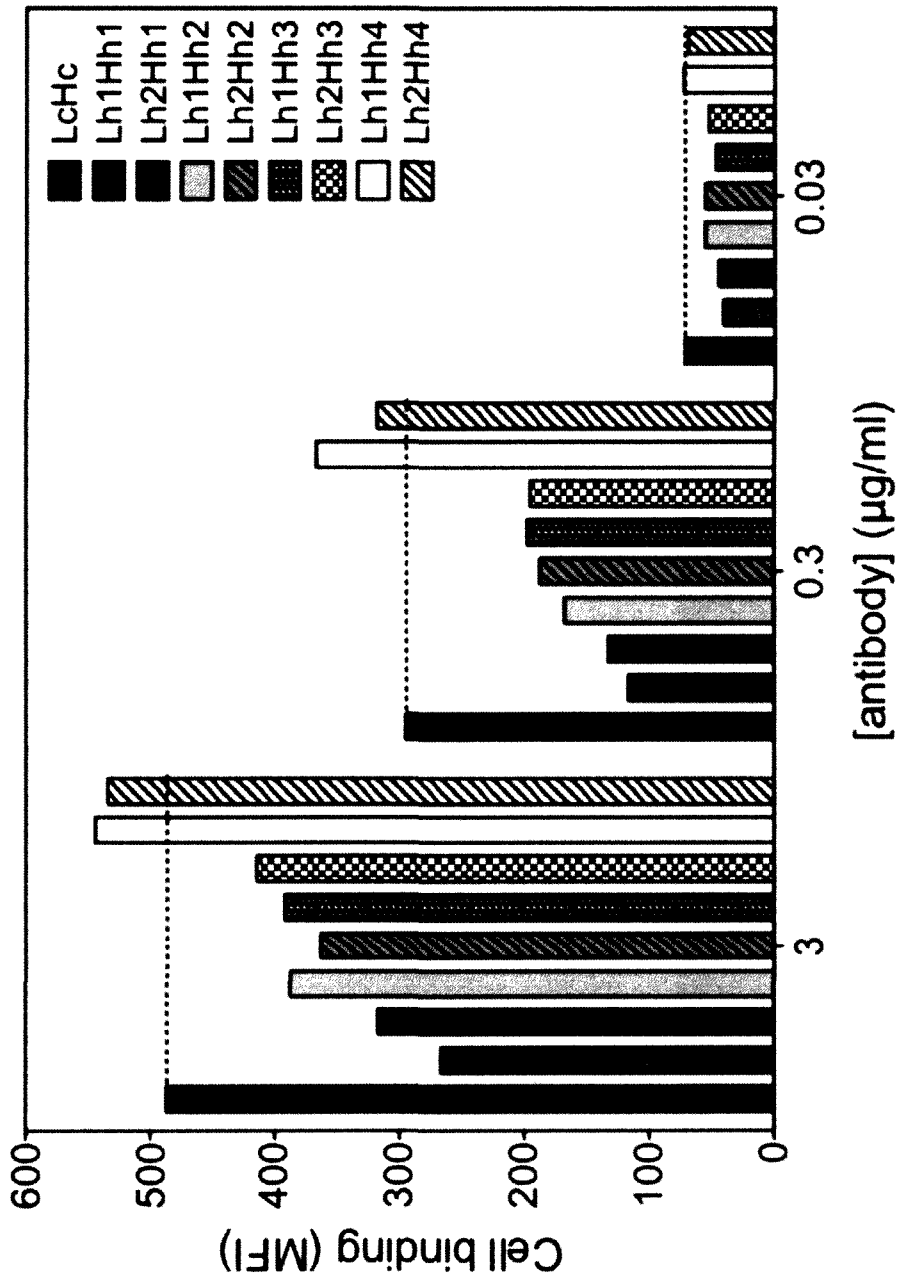
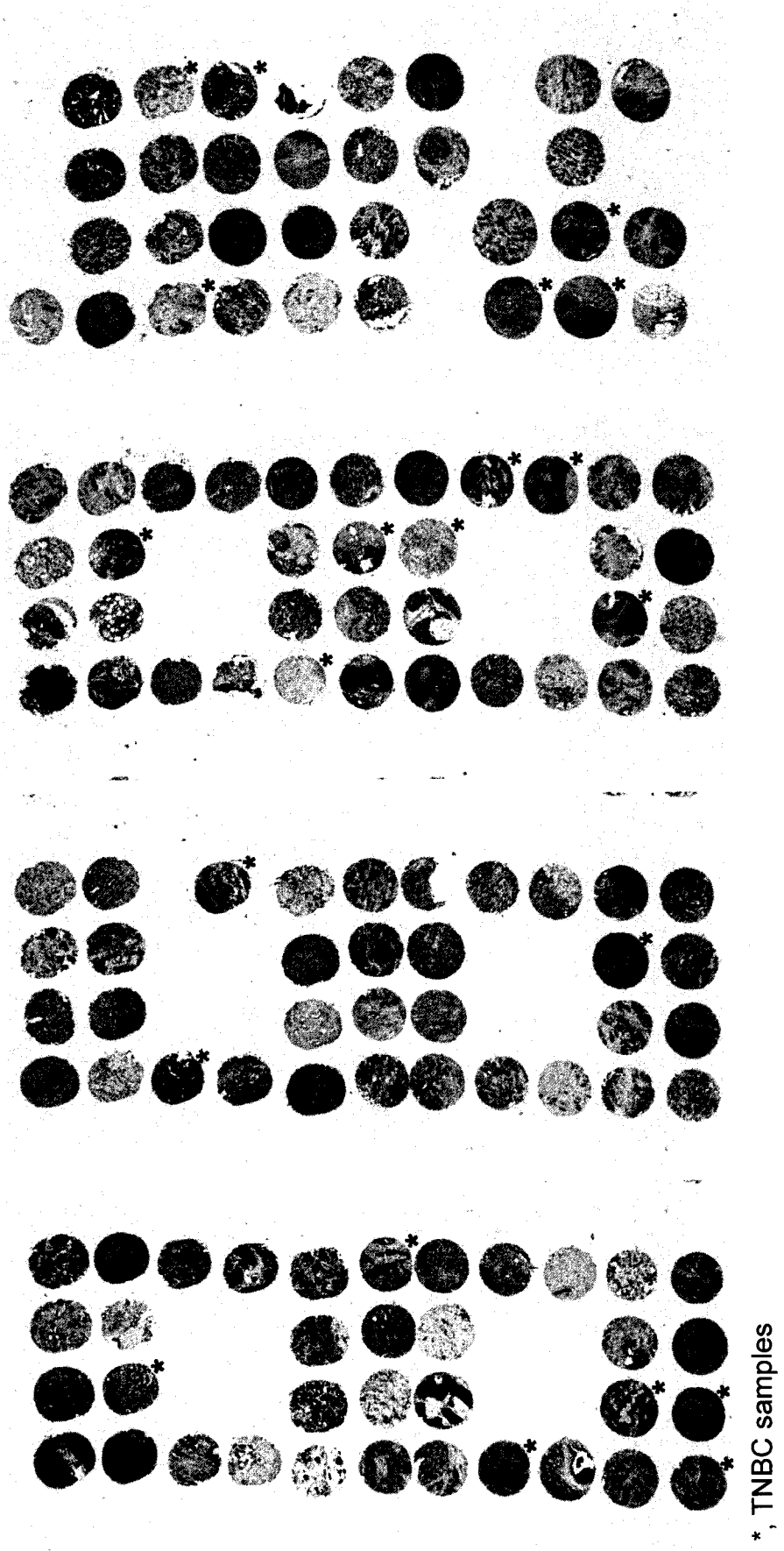

LcHc
Lh1Hh1
Lh2Hh1
Lh1Hh2
Lh2Hh2
Lh1Hh3
Lh2Hh3
Lh1Hh4
Lh2Hh4
Cell binding (MFI)
600
500
400
300
200
100
0
3
0.3
0.03
[antibody] (µg/ml)

Figure 9



*, TNBC samples

Figure 10

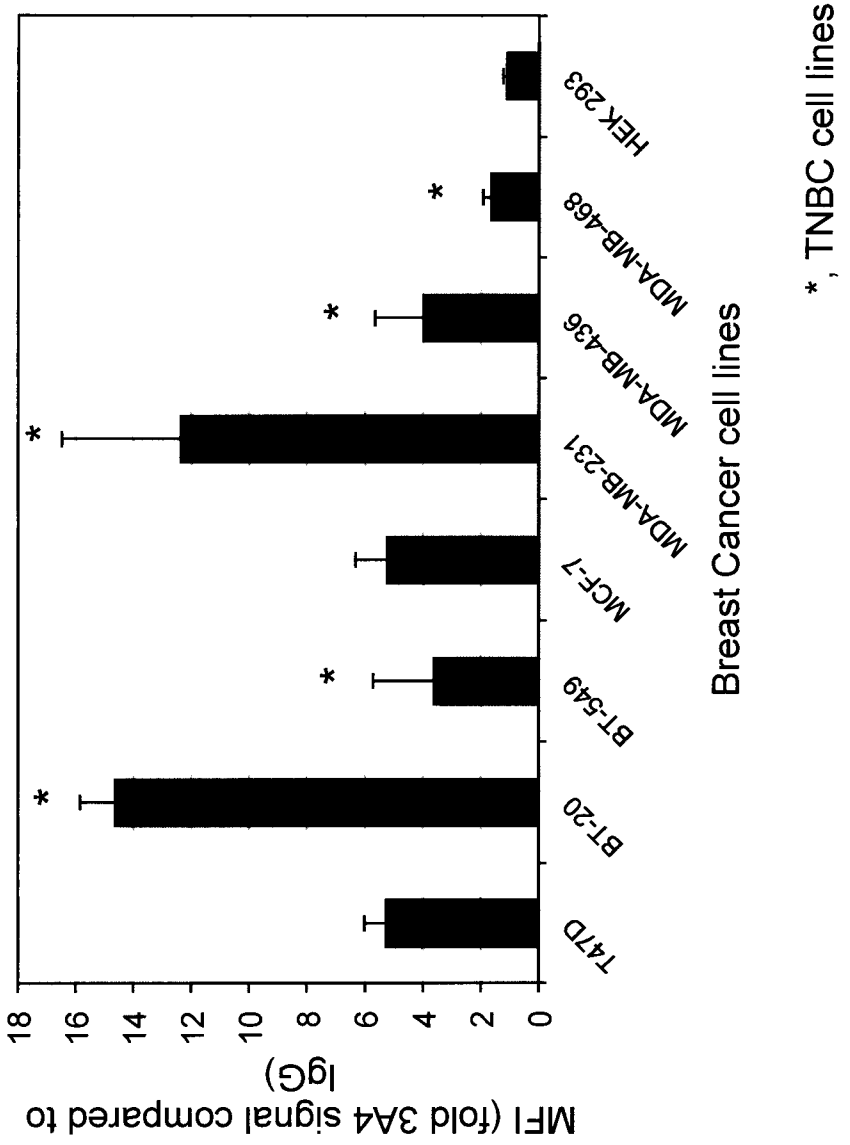

MFI (fold 3A4 signal compared to IgG)
18
16
14
12
10
8
6
4
2
0
T47D
BT-20
BT-549
MCF-7
MDA-MB-231
MDA-MB-436
MDA-MB-468
HEK 293
Breast Cancer cell lines
*, TNBC cell lines

Figure 11

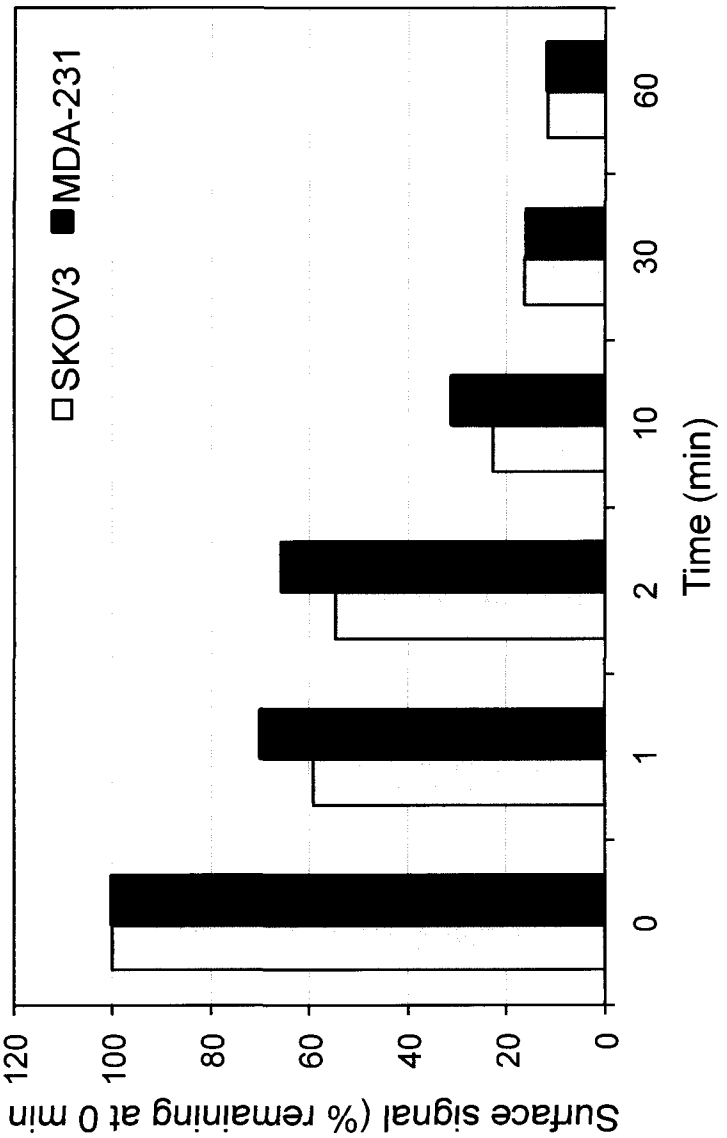

SKOV3
MDA-231
Surface signal (% remaining at 0 min
120
100
80
60
40
20
0
0
1
2
10
30
60
Time (min)

Figure 12

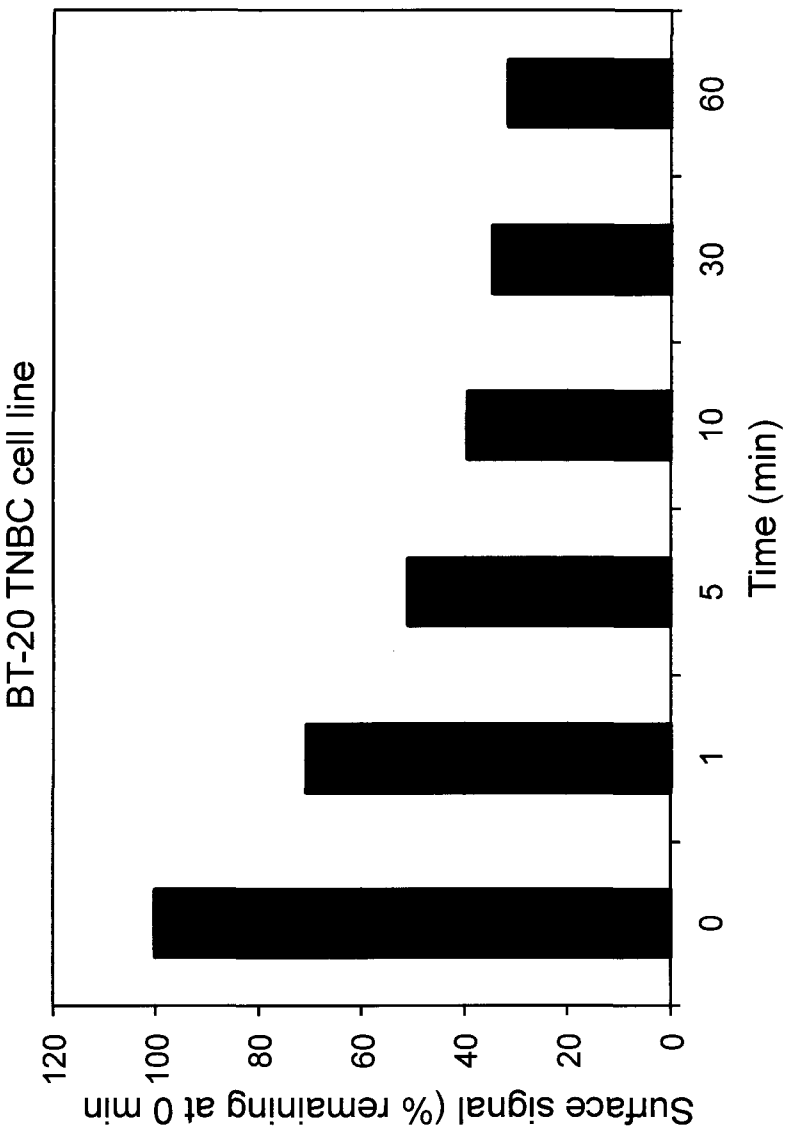

BT-20 TNBC cell line
Surface signal (% remaining at 0 min
120
100
80
60
40
20
0
0
1
5
10
30
60
Time (min)

Figure 13

Figure 14

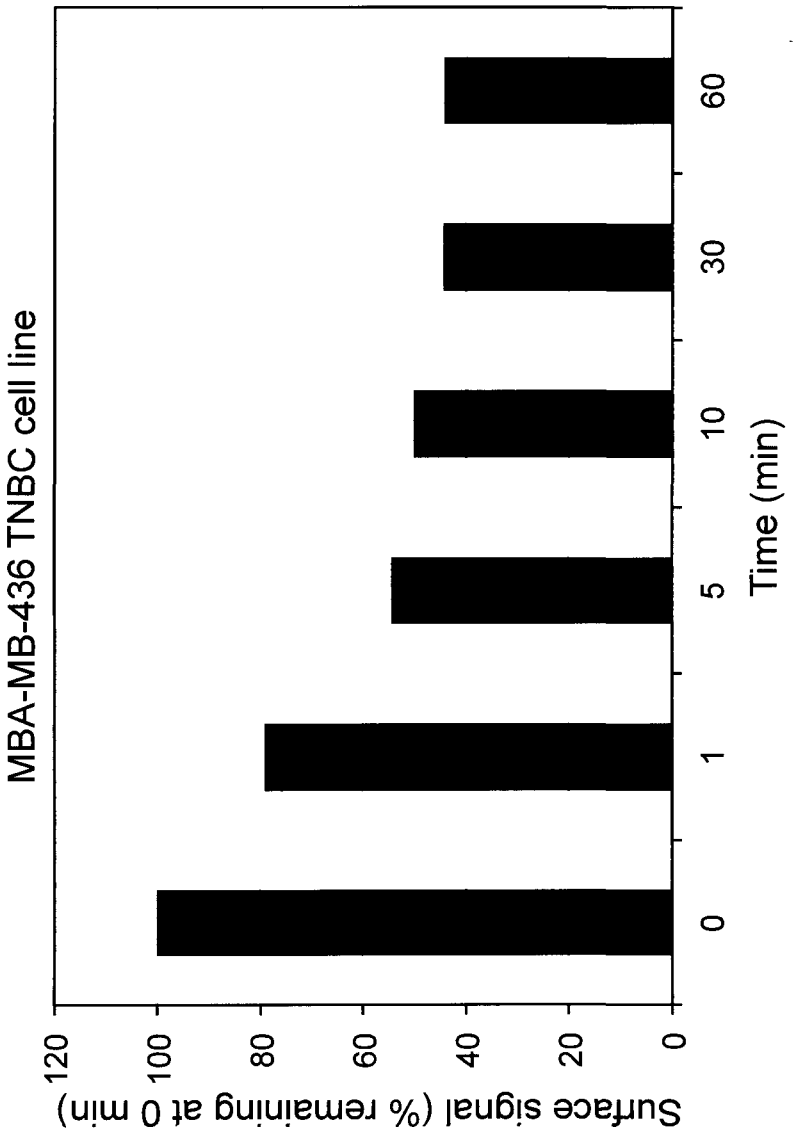

MBA-MB-436 TNBC cell line
Surface signal (% remaining at 0 min)
120
100
80
60
40
20
0
0
1
5
10
30
60
Time (min)

Figure 15

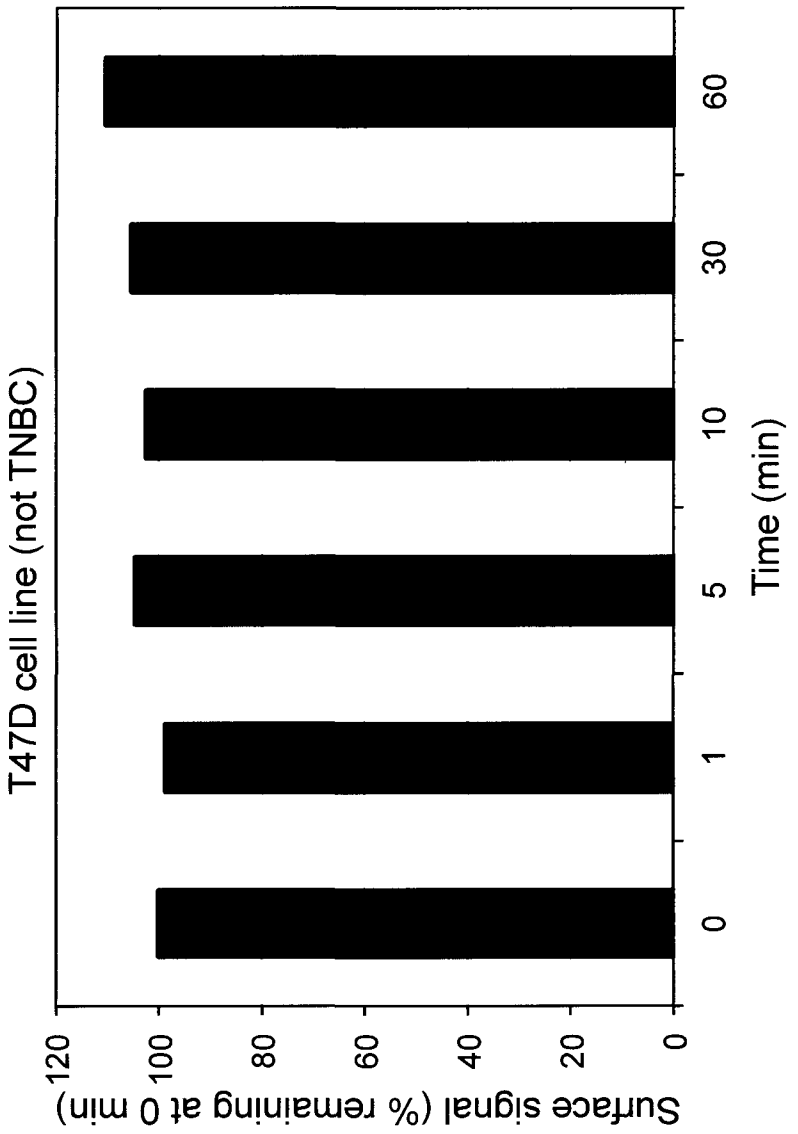
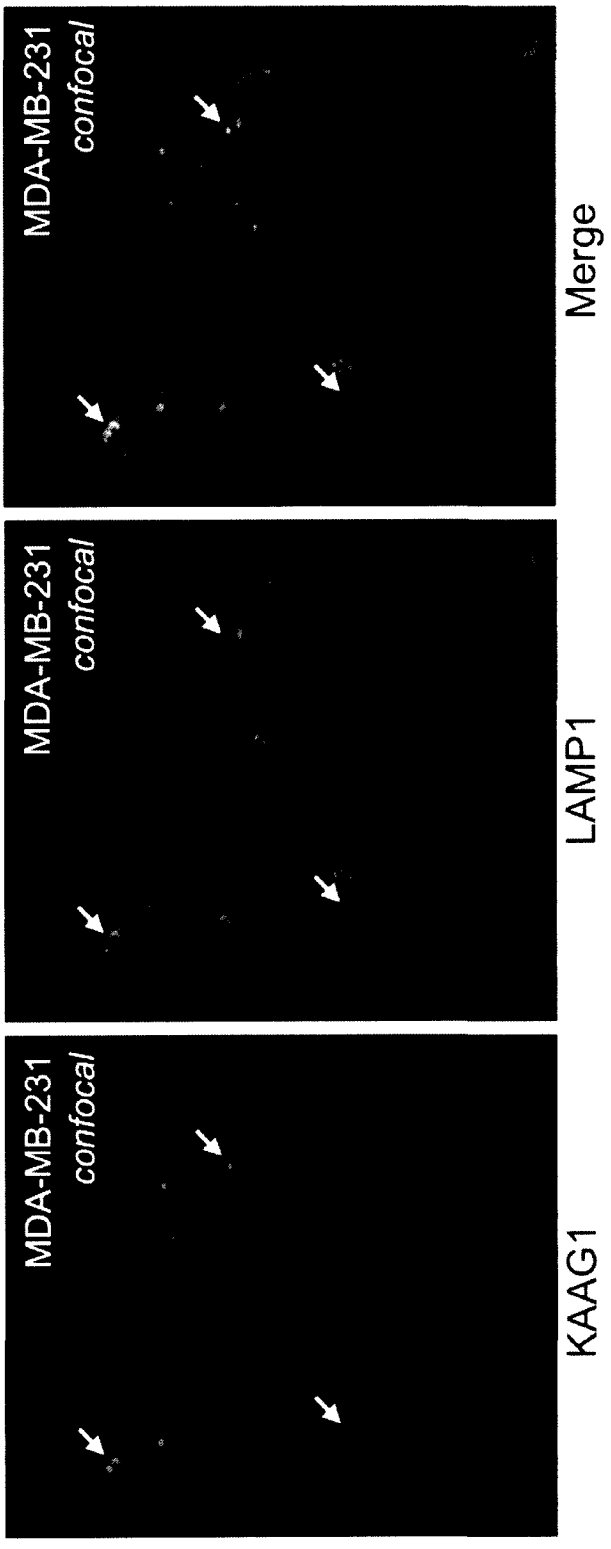

T47D cell line (not TNBC)
Surface signal (% remaining at 0 min)
120
100
80
60
40
20
0
0
1
5
10
30
60
Time (min)

Figure 16


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

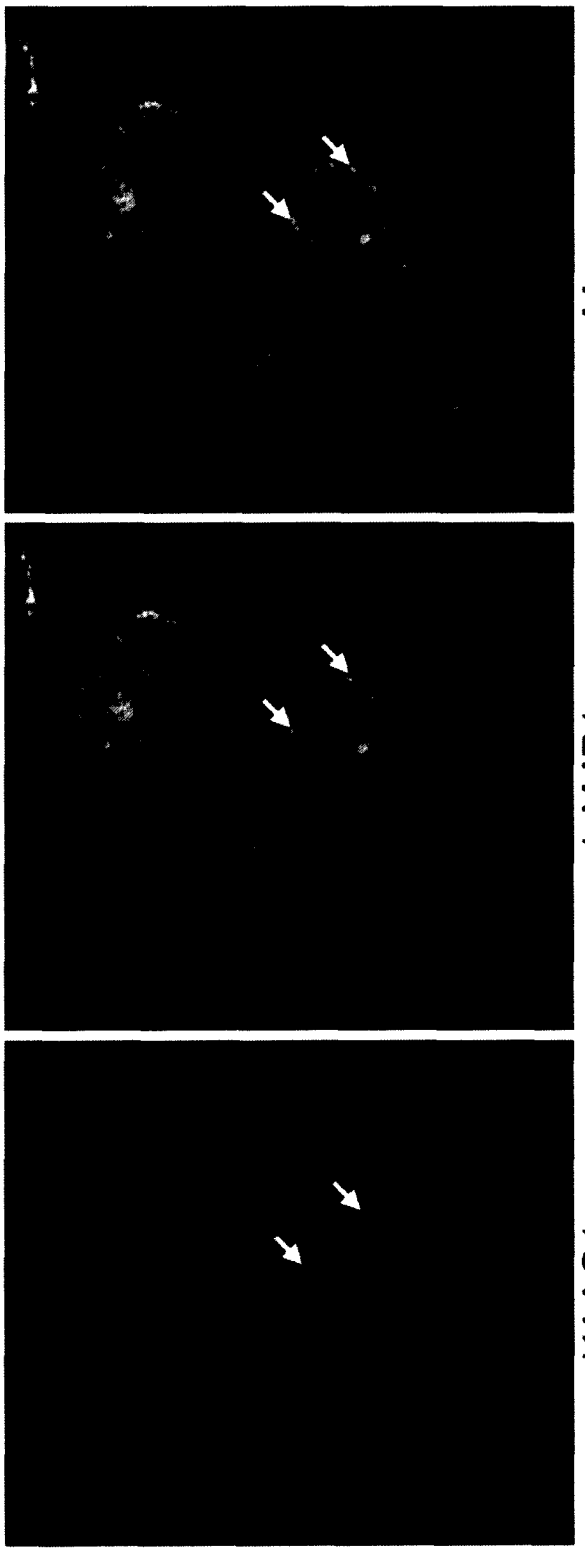


Figure 17

TITLE: METHOD FOR TREATING BREAST CANCER

BACKGROUND

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., 201 1), including tamoxifen, Arimidex™ (anastrozole), Aromasin™ (exemestane), Femara™ (letrozole), Faslodex™ (fulvestrant), Herceptin™ (trastuzumab) or Tykerb™ (lapatinib).

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.

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).

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., 201 1). 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.

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).