FIGURE 1

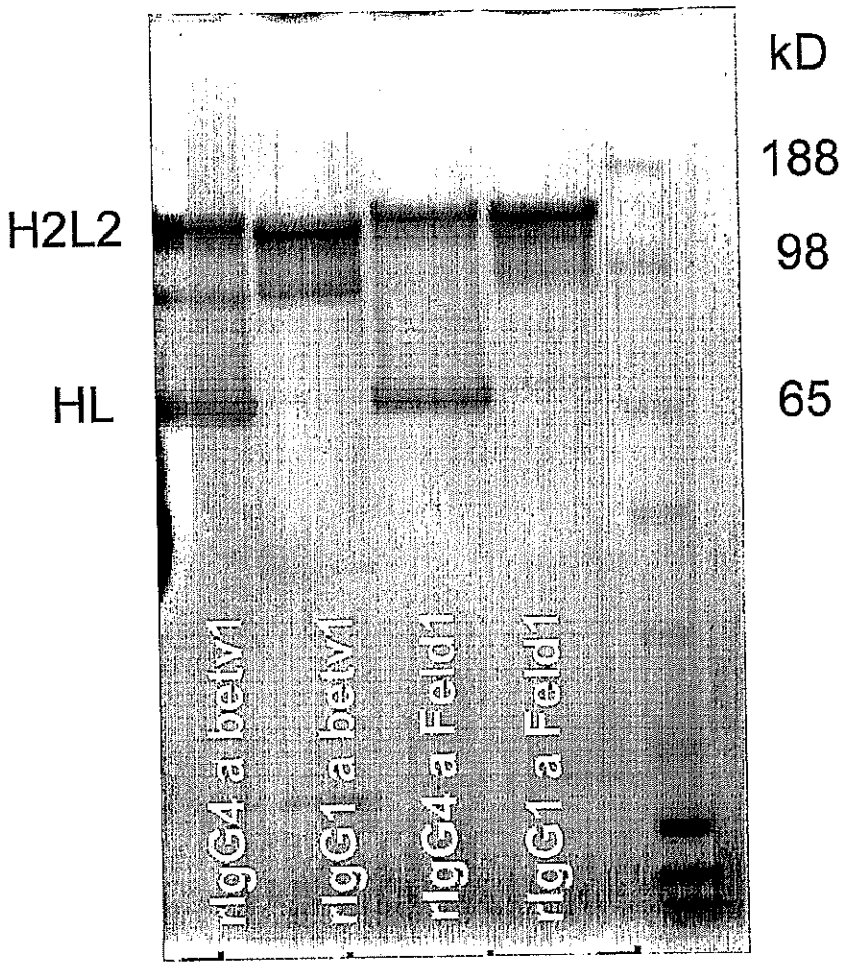

kD
188
98
65
H2L2
HL
hIgG4 beaV1
hIgG1 beaV1
hIgG4 Fab1
hIgG1 Fab1

FIGURE 2

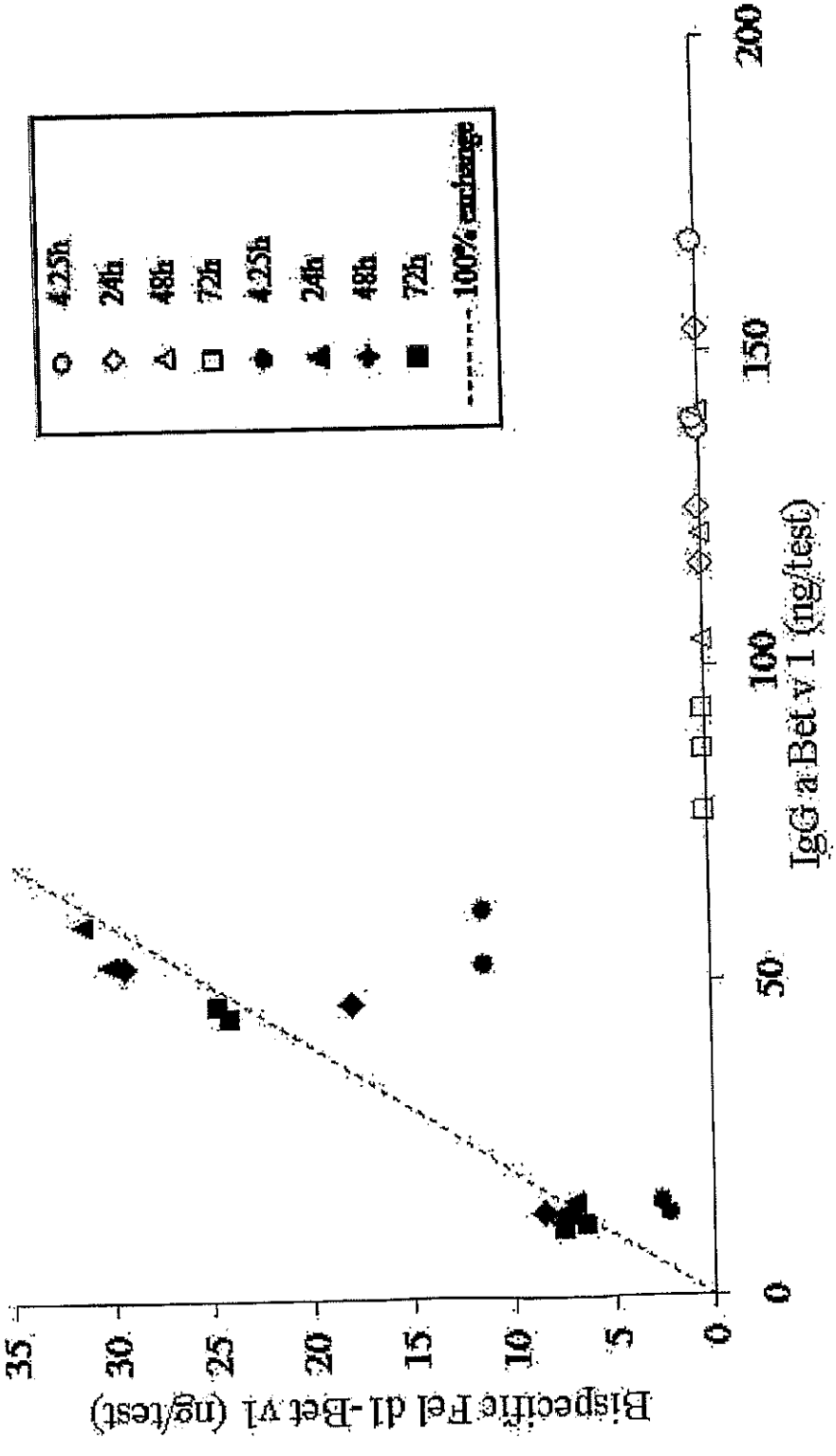

4.25h
24h
48h
72h
4.25h
24h
48h
72h
100% exchange
Bispecific Fel d1 -Bet v1 (ng/test)
IgG a Bet v 1 (ng/test)
0
5
10
15
20
25
30
35
0
50
100
150
200

FIGURE 3A

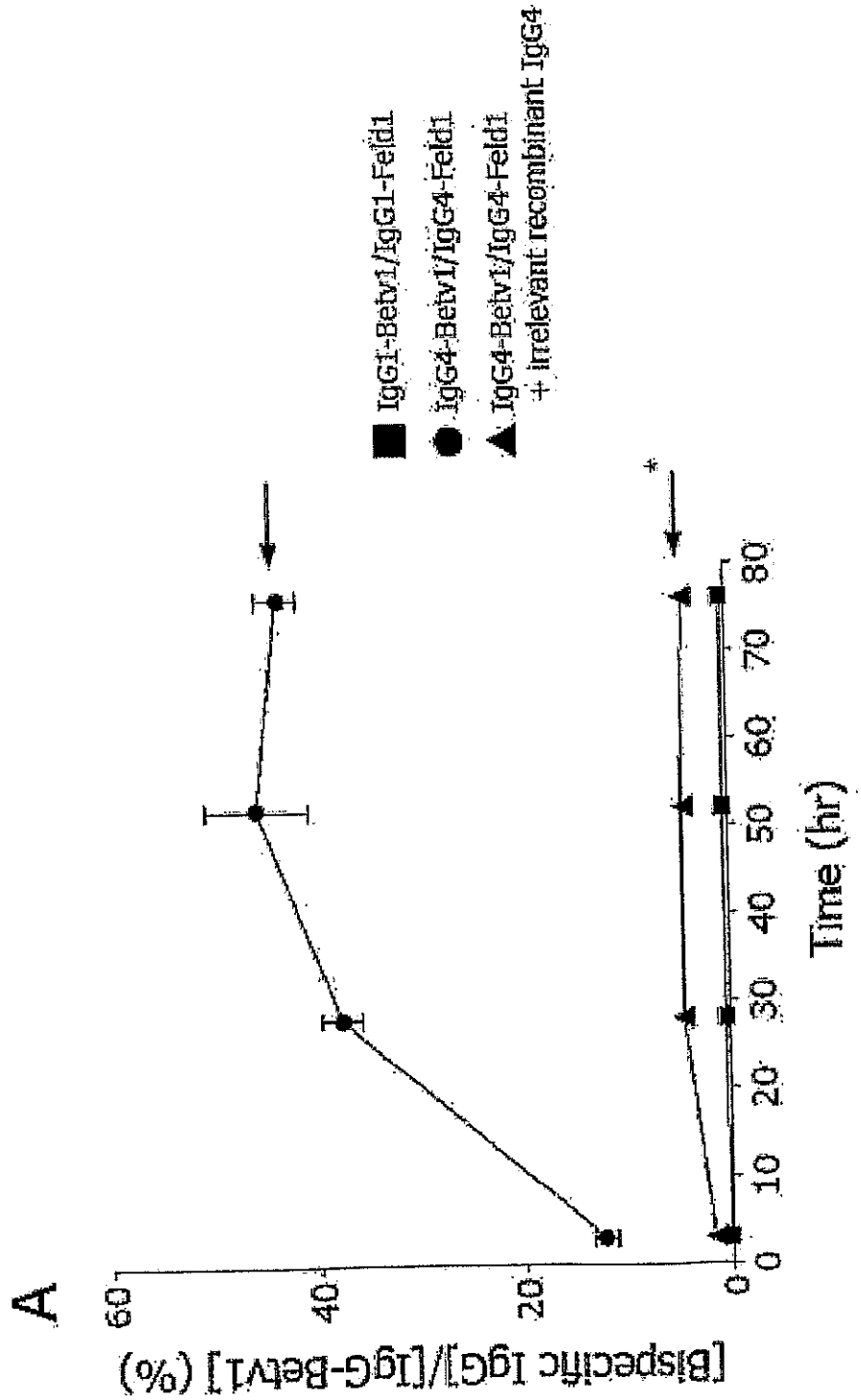

A
[Bispecific IgG]/[IgG-Betv1] (%)
60
40
20
0
0
10
20
30
40
50
60
70
80
Time (hr)
IgG1-Betv1/IgG1-Feld1
IgG4-Betv1/IgG4-Feld1
IgG4-Betv1/IgG4-Feld1
+ irrelevant recombinant IgG4

FIGURE 3B

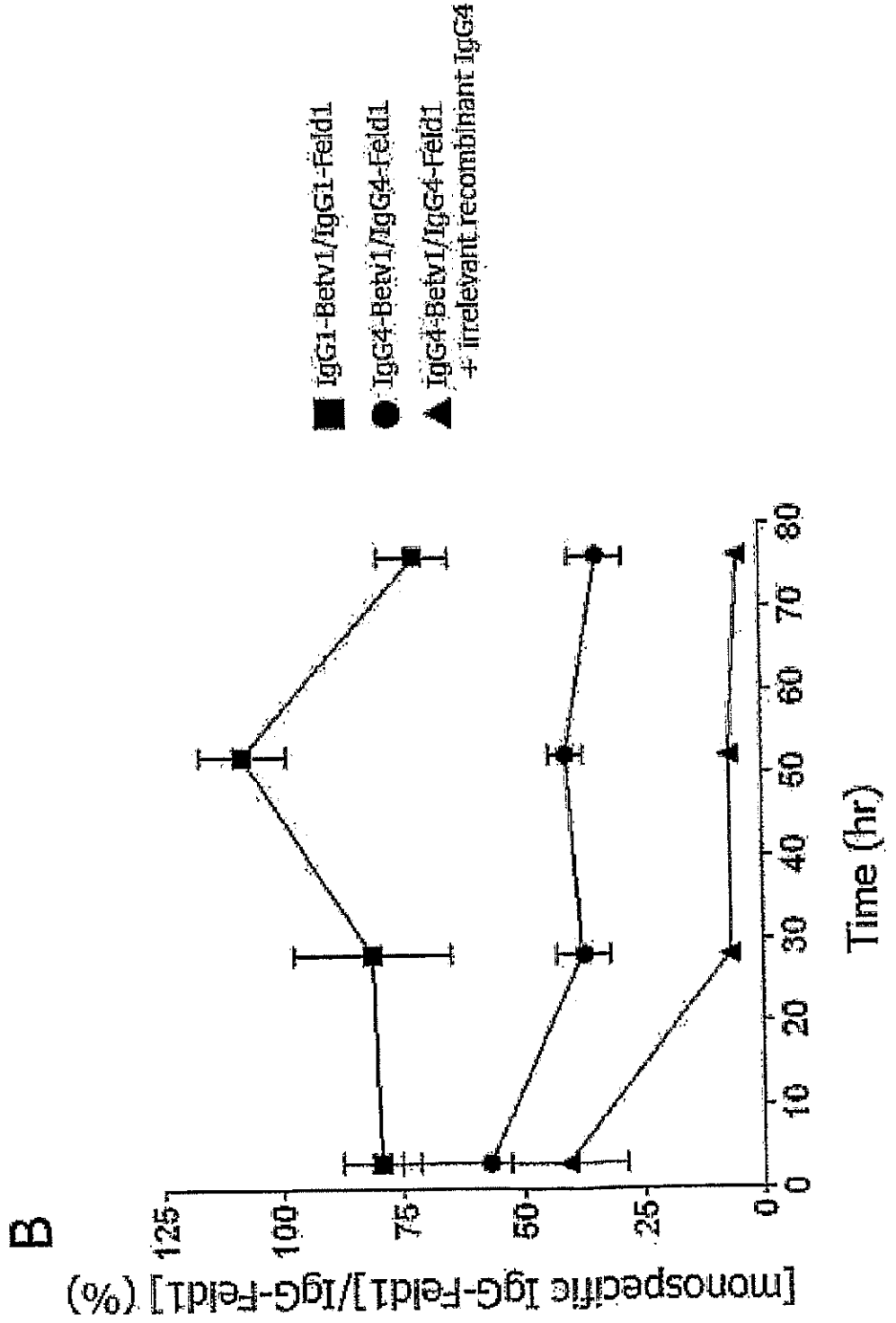

B
[monospecific IgG-Feld1]/IgG-Feld1] (%)
125
100
75
50
25
0
0
10
20
30
40
50
60
70
80
Time (hr)
IgG1-Betv1/IgG1-Feld1
IgG4-Betv1/IgG4-Feld1
IgG4-Betv1/IgG4-Feld1
+ irrelevant recombinant IgG4

FIGURE 4

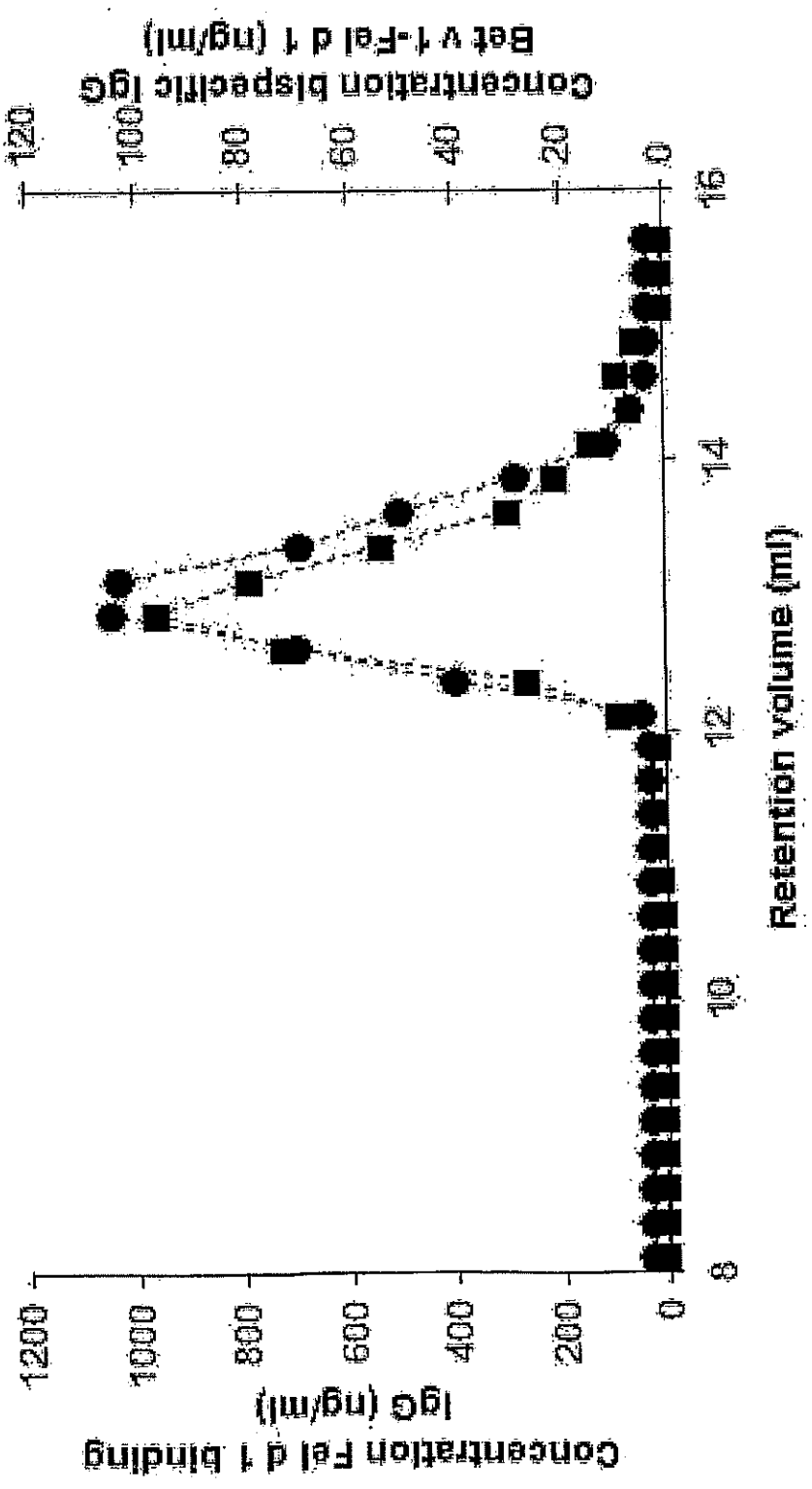

Concentration Fel d 1 binding
IgG (ng/ml)
1200
1000
800
600
400
200
0
8
10
12
14
16
Retention volume (ml)
Concentration bispecific IgG
Bet v 1-Fal d 1 (ng/ml)
120
100
80
60
40
20
0

FIGURE 5A

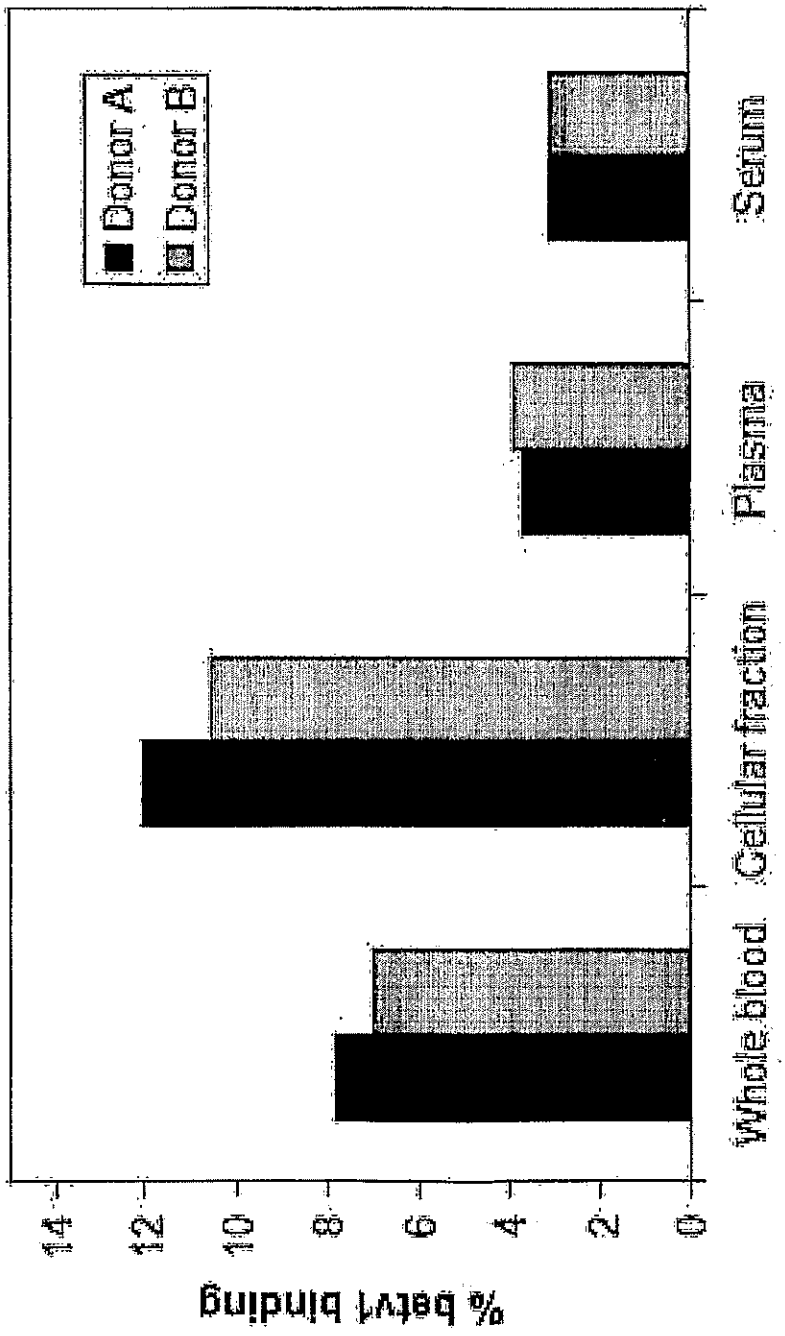

Donor A
Donor B
Serum
Plasma
Cellular fraction
Whole blood
% bound binding
0
2
4
6
8
10
12
14

FIGURE 5B

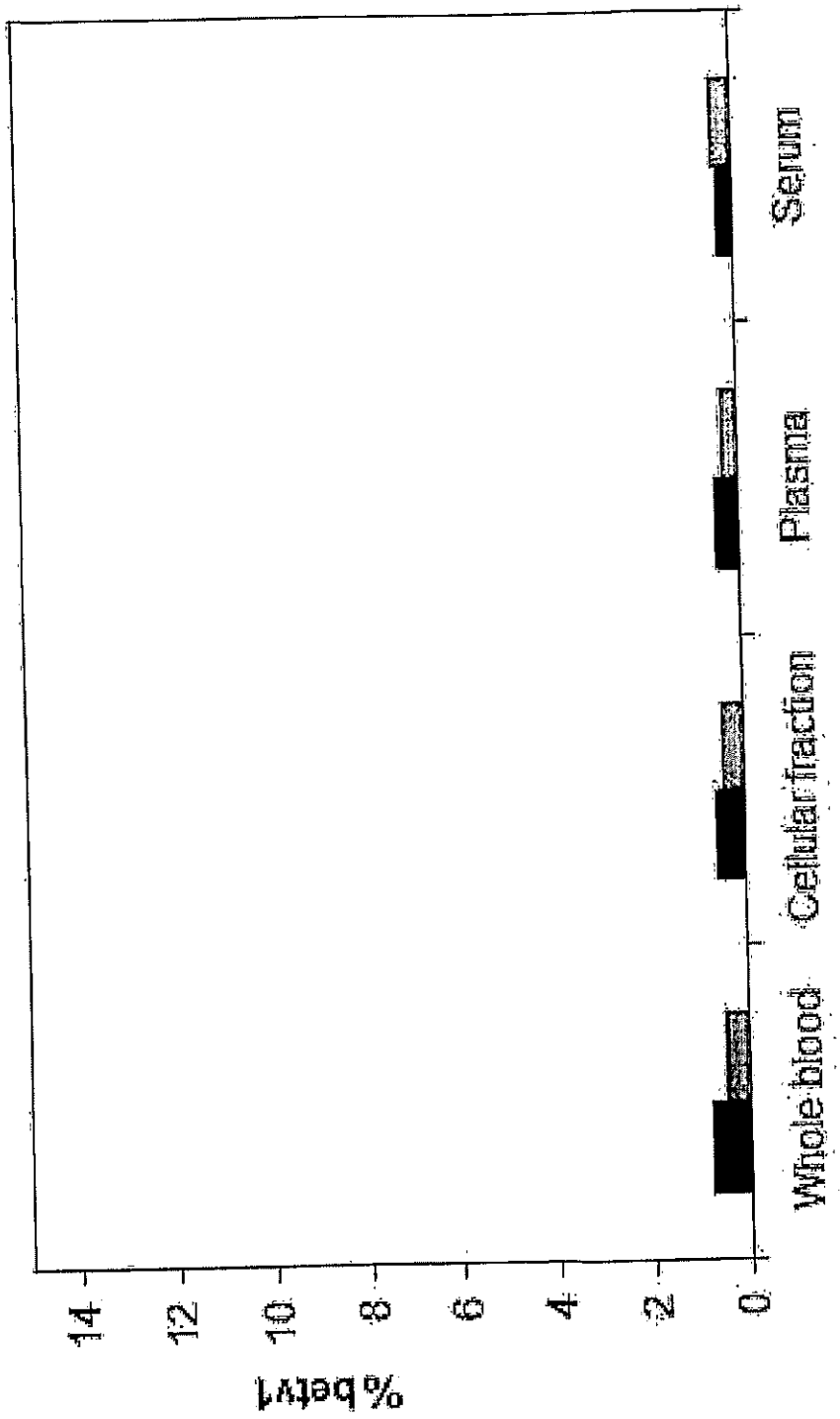

% beta1
0
2
4
6
8
10
12
14
Whole blood
Cellular fraction
Plasma
Serum

FIGURE 5C

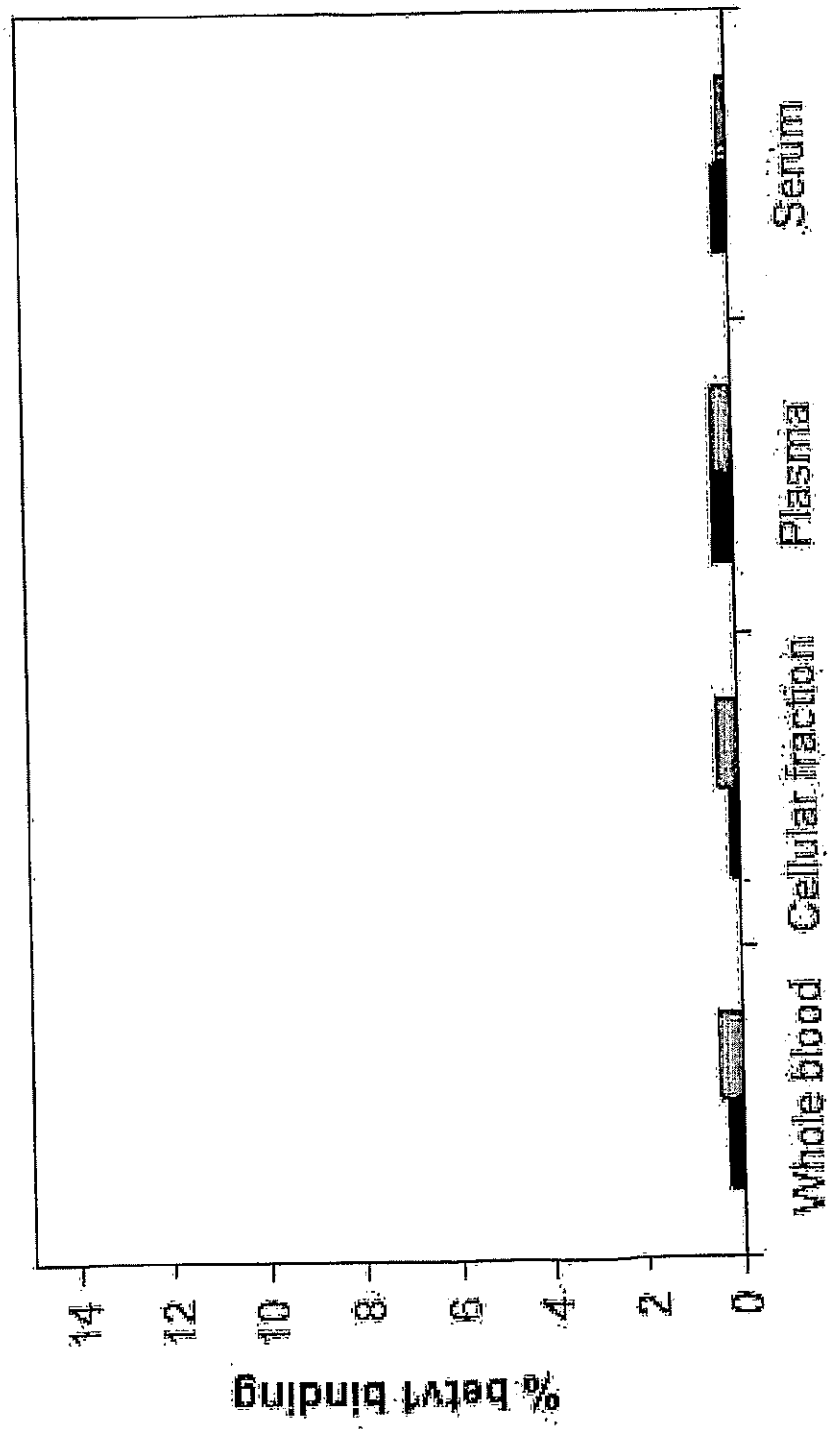

% beta1 binding
0
2
4
6
8
10
12
14
Whole blood
Cellular fraction
Plasma
Serum

FIGURE 6

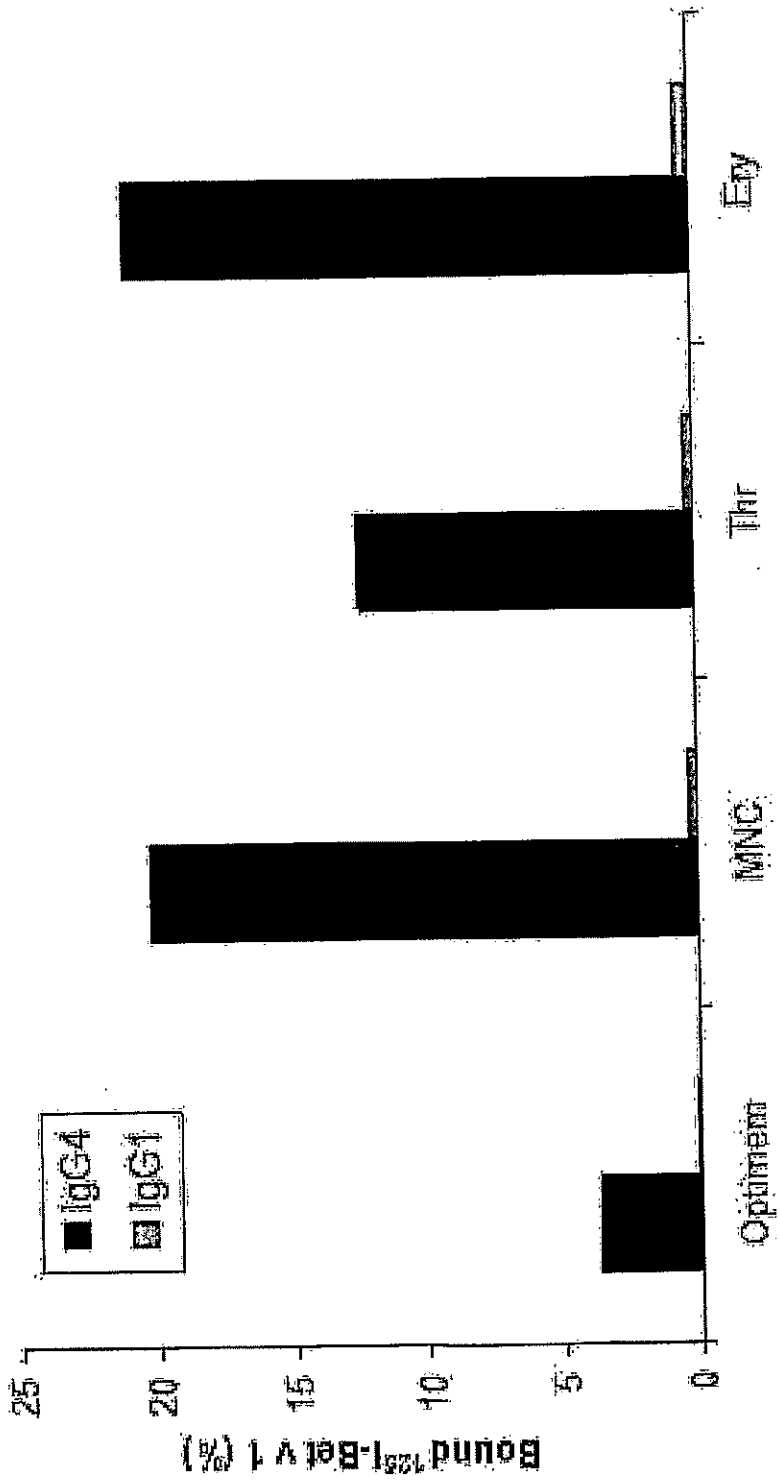


FIGURE 7

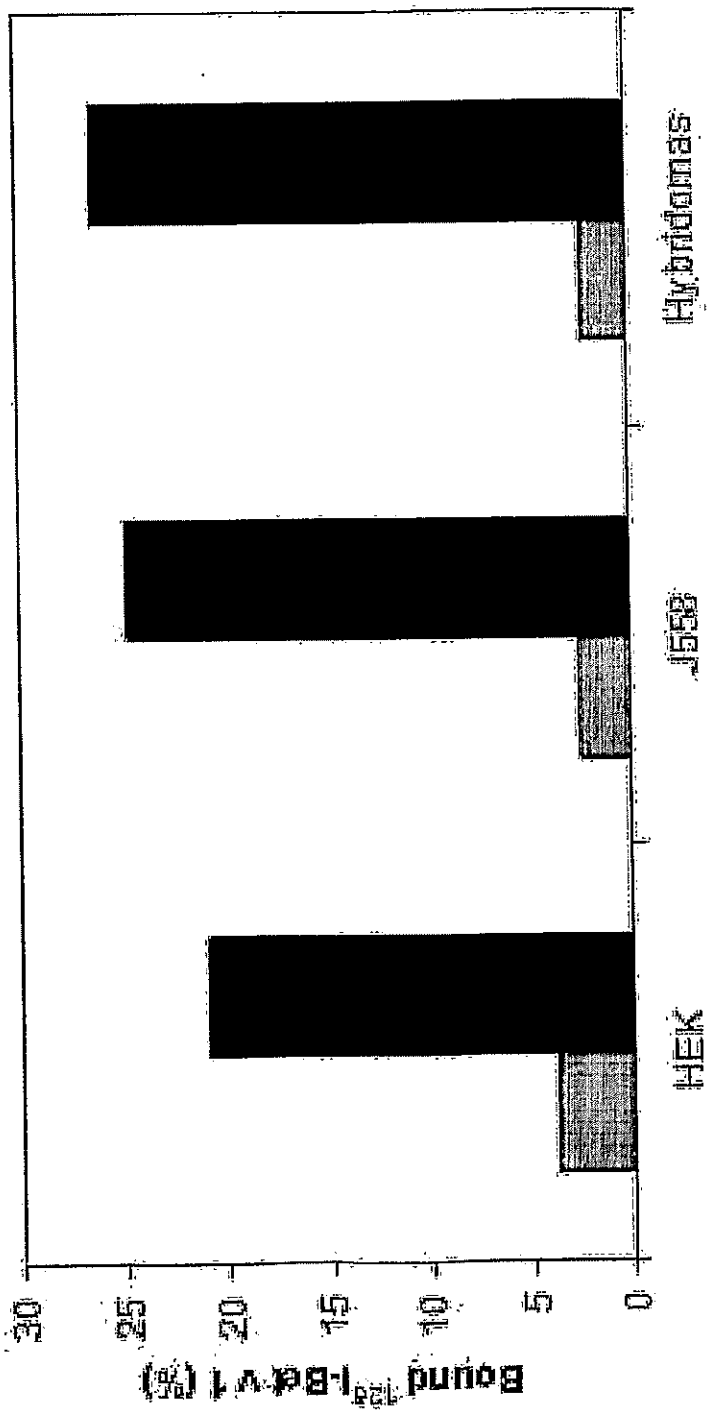


FIGURE 8

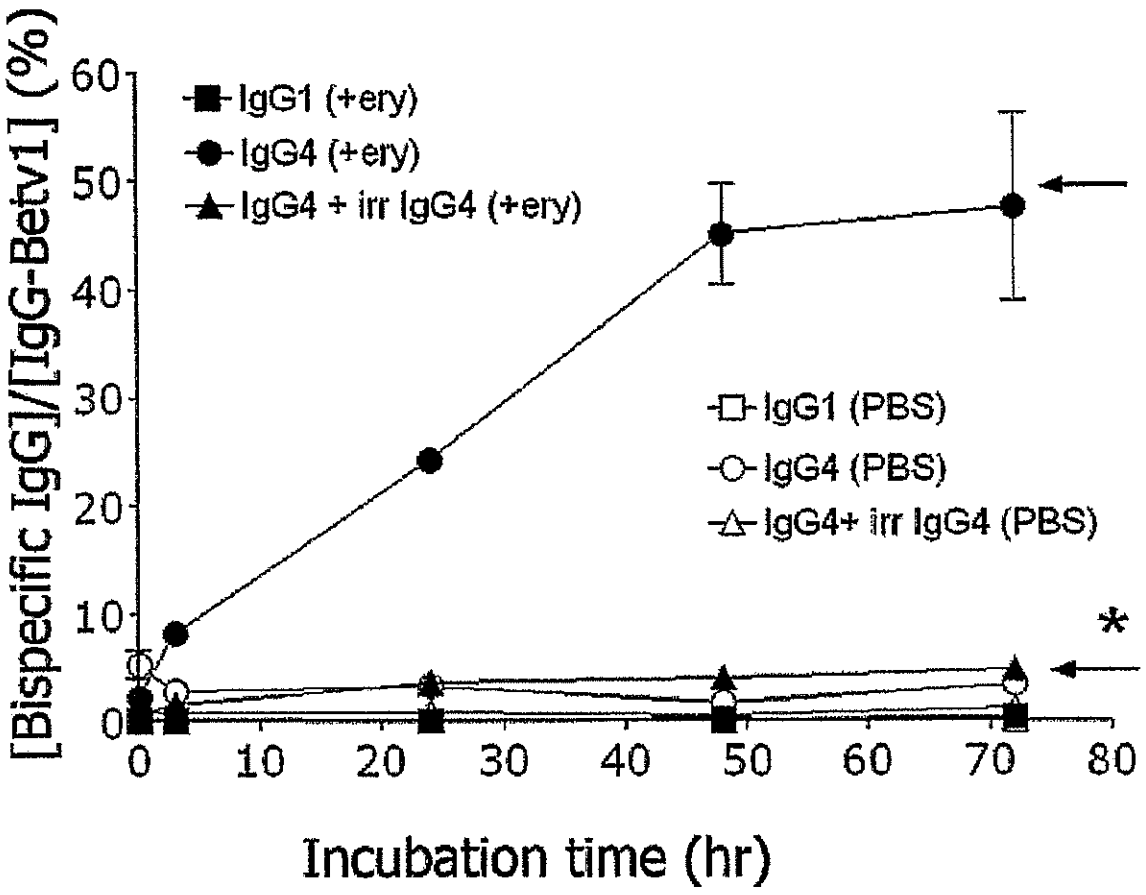

[Bispecific IgG]/[IgG-Betv1] (%)
60
50
40
30
20
10
0
IgG1 (+ery)
IgG4 (+ery)
IgG4 + irr IgG4 (+ery)
IgG1 (PBS)
IgG4 (PBS)
IgG4+ irr IgG4 (PBS)
*
0
10
20
30
40
50
60
70
80
Incubation time (hr)

FIGURE 9A

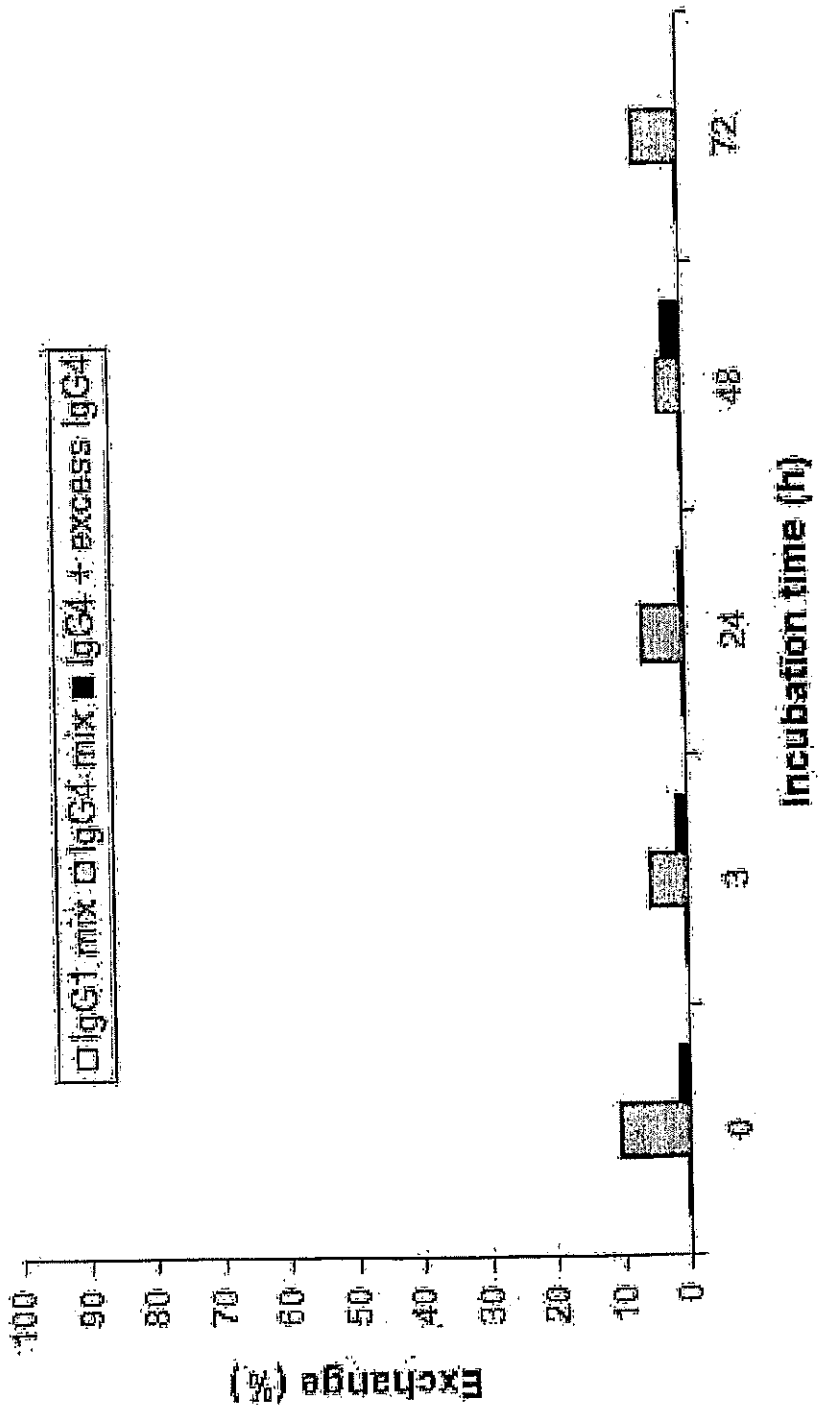

IgG1 mix IgG4 mix IgG4 + excess IgG4
Exchange (%)
100
90
80
70
60
50
40
30
20
10
0
0
3
24
48
72
Incubation time (h)

FIGURE 9B

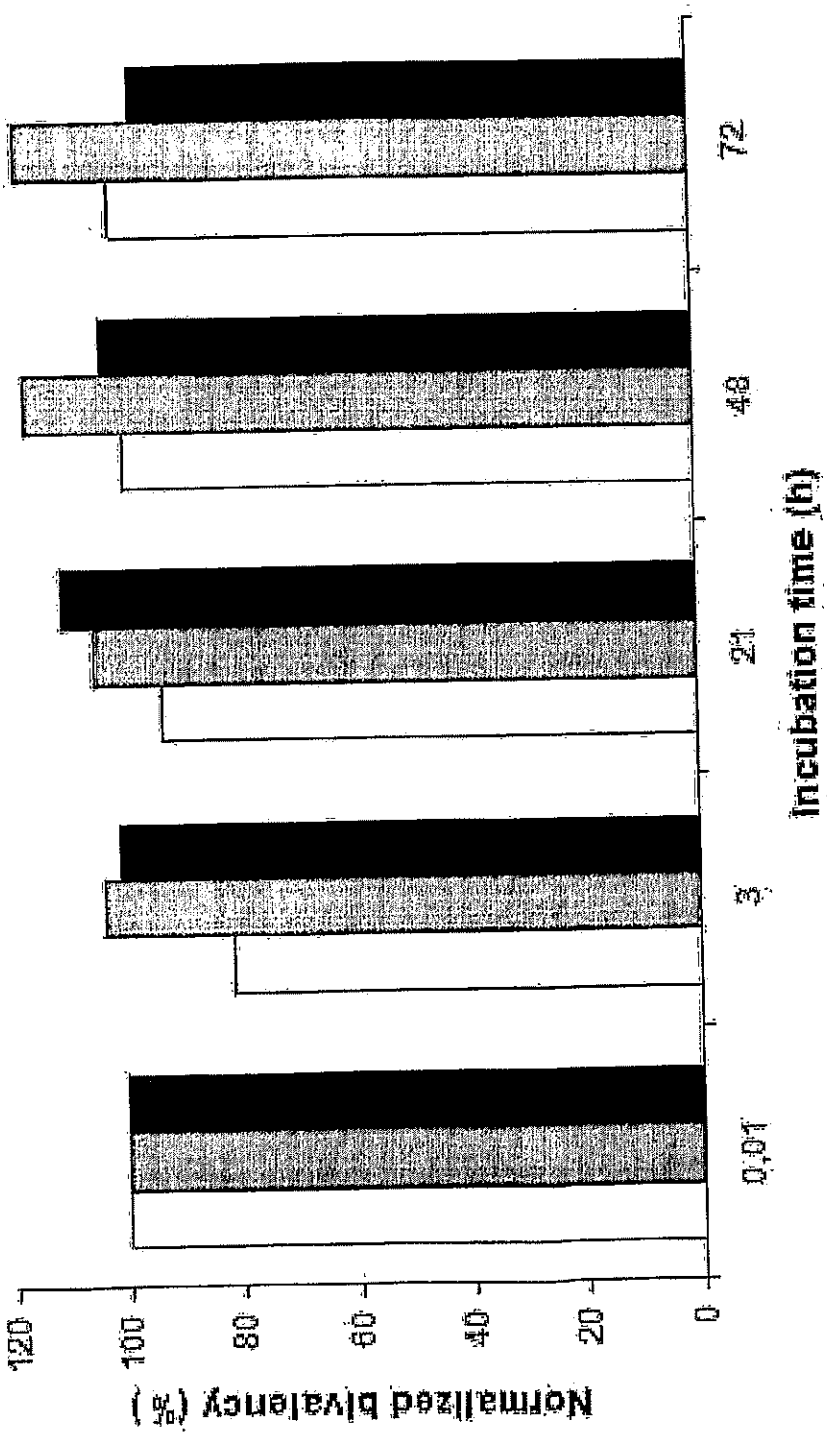

Normalized bivalency (%)
120
100
80
60
40
20
0
0,01
5
21
48
72
Incubation time (h)

FIGURE 10

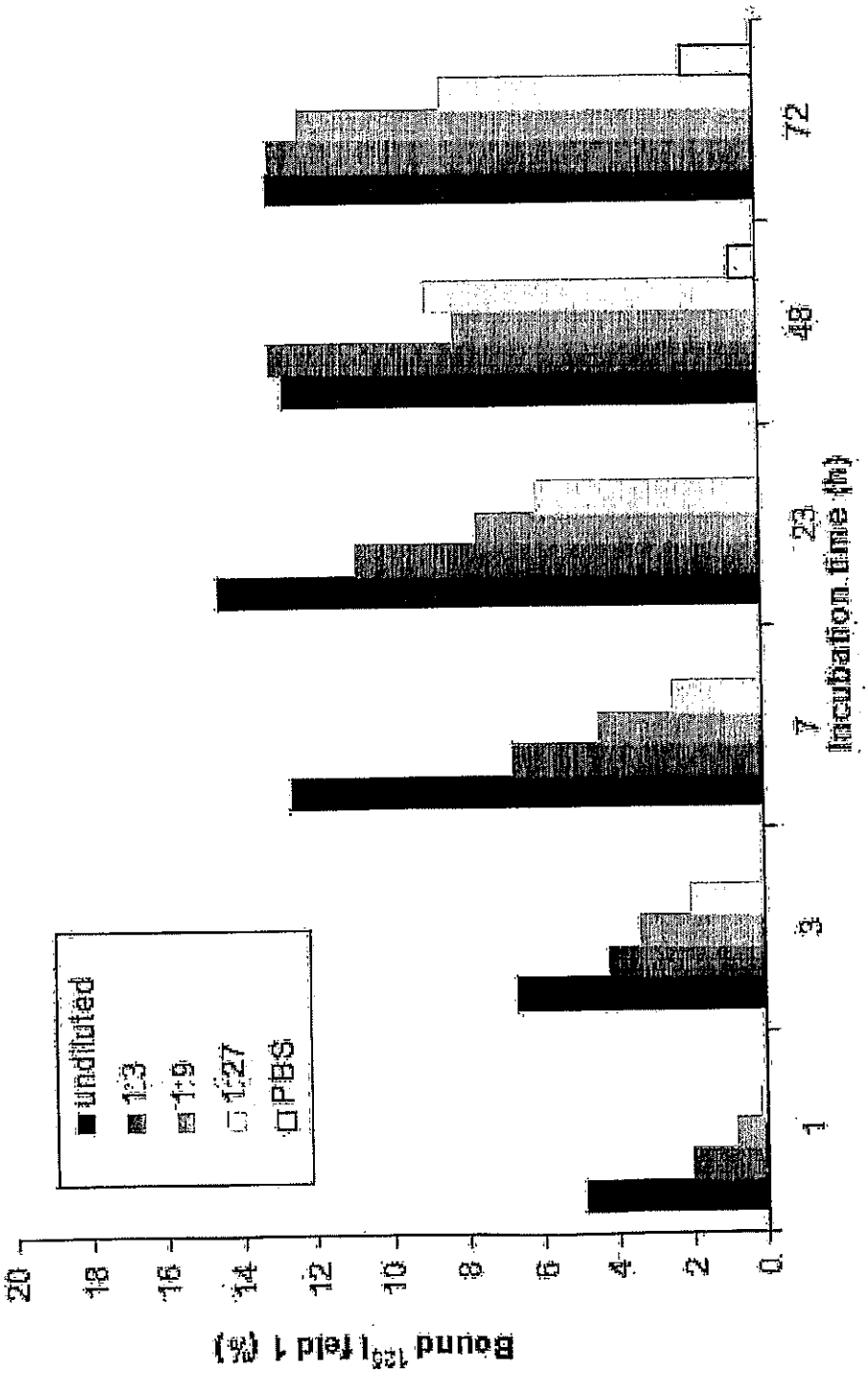

Bound 125I fold 1 (%)
0
2
4
6
8
10
12
14
16
18
20
1
3
7
23
48
72
incubation time (h)
undiluted
1:3
1:9
1:27
PBS

FIGURE 11

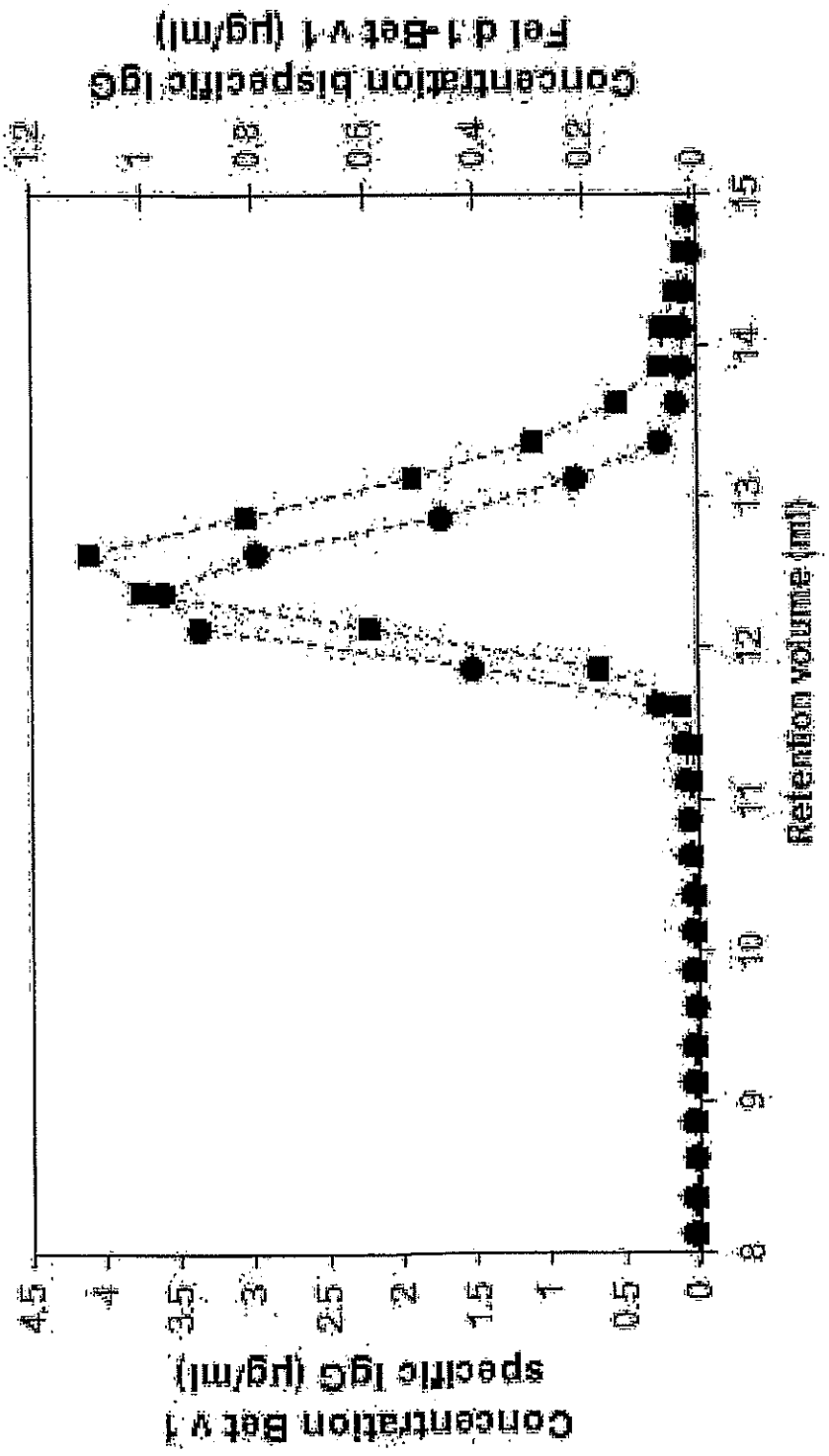

Concentration Bet v 1
specific IgG (µg/ml)
Retention volume (ml)
Concentration bispecific IgG
Fel d 1-Bet v 1 (µg/ml)

FIGURE 12

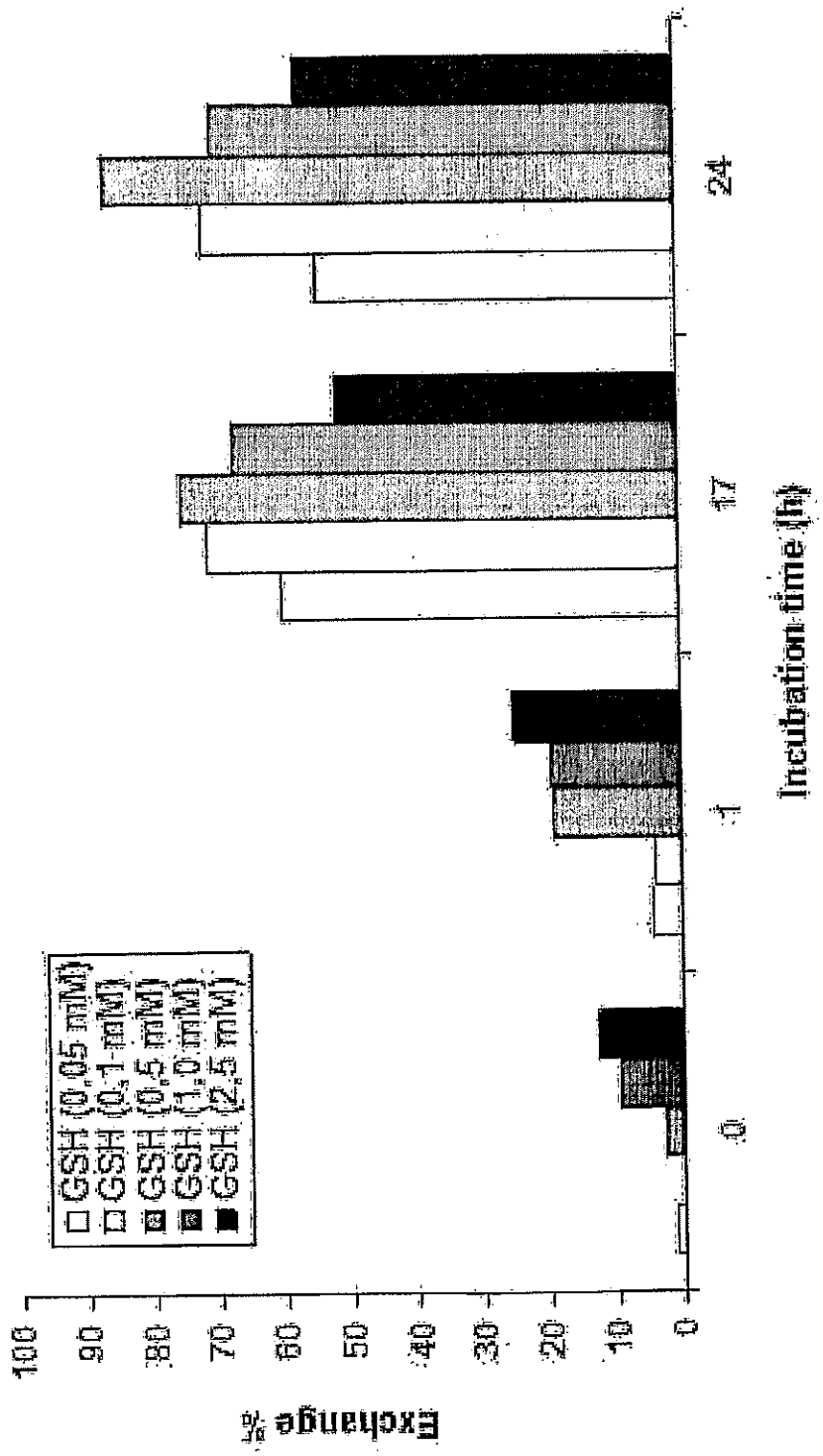

GSH (0,05 mM)
GSH (0,1 mM)
GSH (0,5 mM)
GSH (1,0 mM)
GSH (2,5 mM)
Exchange %
100
90
80
70
60
50
40
30
20
10
0
0
1
17
24
Incubation time (h)

FIGURE 13

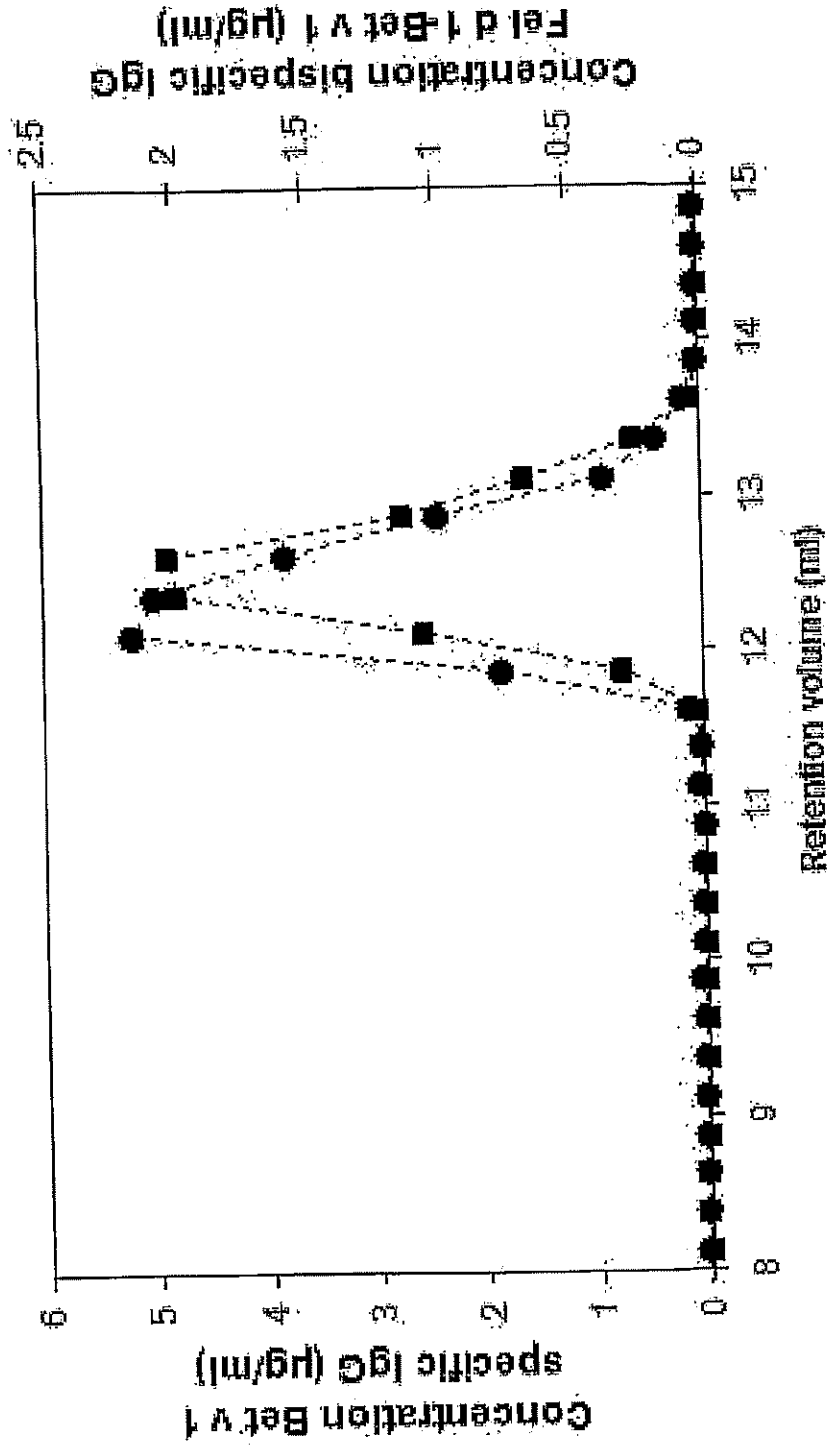

Concentration Bet v 1
specific IgG (µg/ml)
Concentration bispecific IgG
Fel d 1-Bet v 1 (µg/ml)
Retention volume (ml)

FIGURE 14

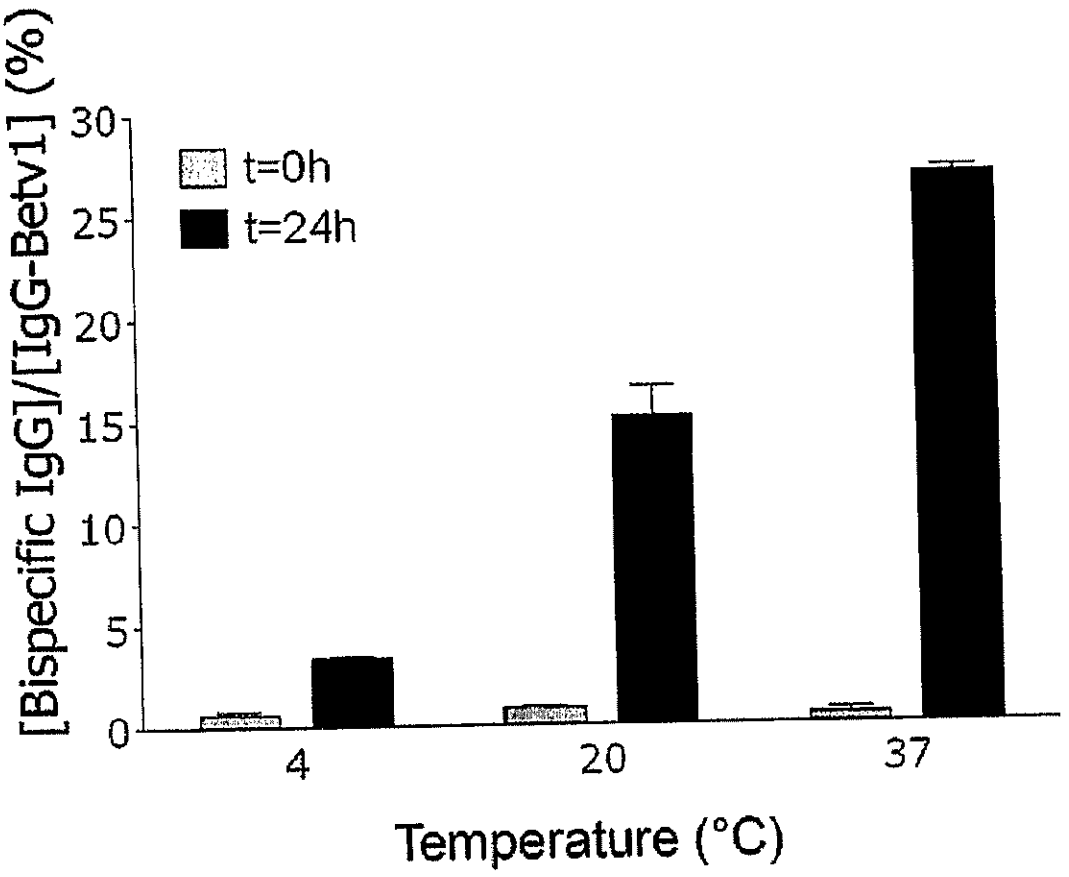
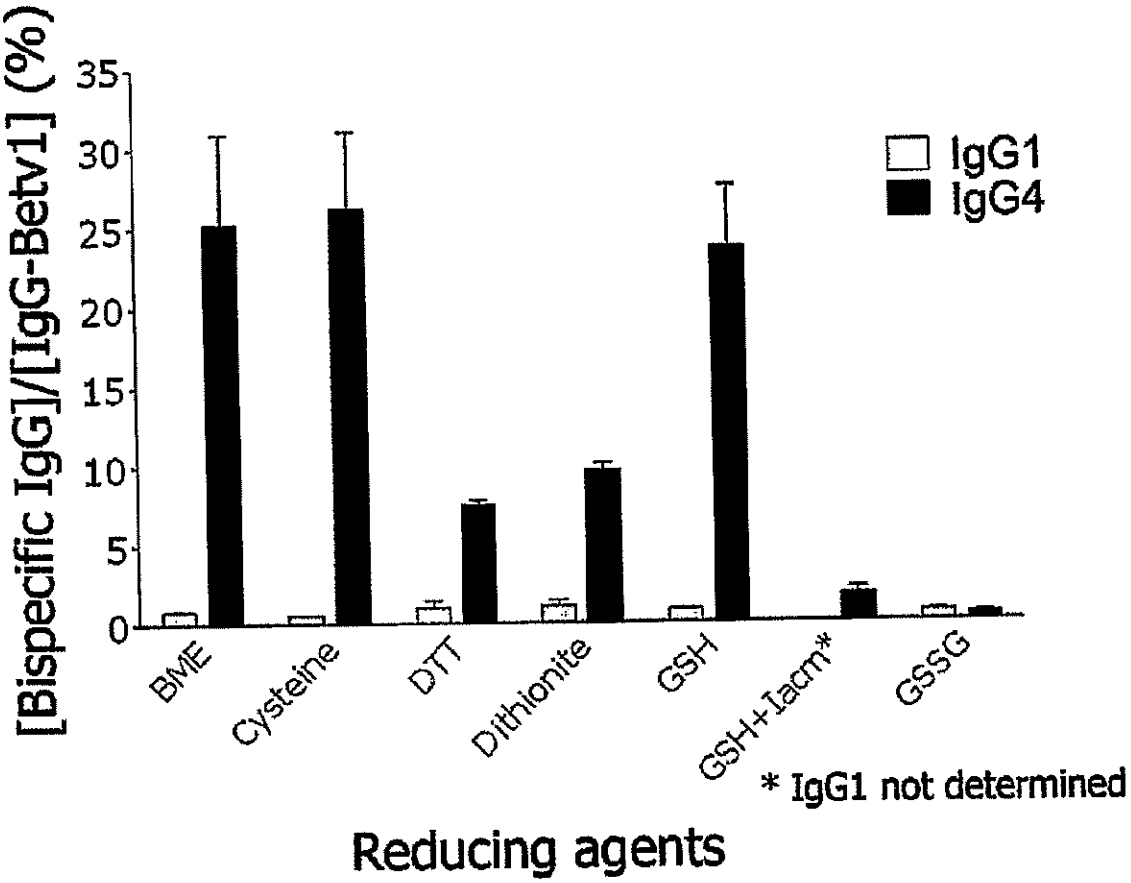

[Bispecific IgG]/[IgG-Betv1] (%)
30
25
20
15
10
5
0
t=0h
t=24h
4
20
37
Temperature (°C)

FIGURE 15


[Bispecific IgG]/[IgG-Betv1] (%)
35
30
25
20
15
10
5
0
IgG1
IgG4
BME
Cysteine
DTT
Dithionite
GSH
GSH+Iacm*
GSSG
* IgG1 not determined
Reducing agents

IGURE 16A

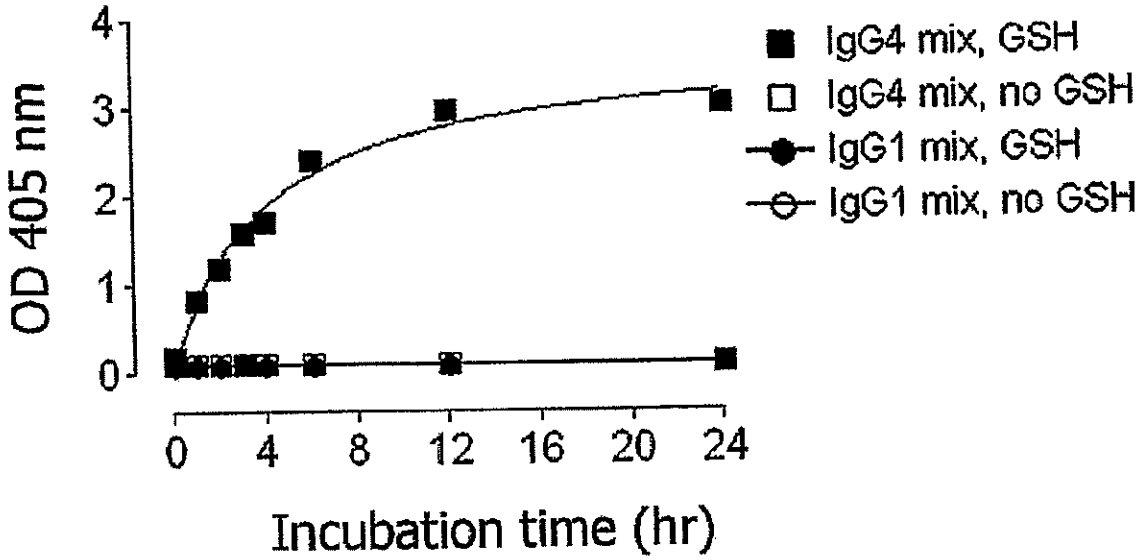


FIGURE 16B

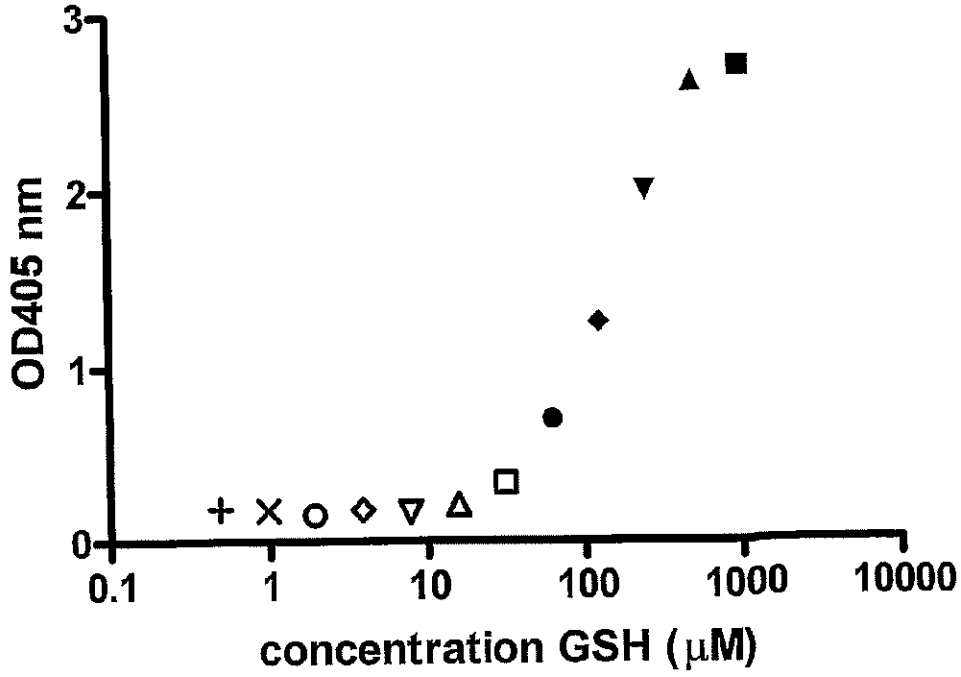


FIGURE 16C

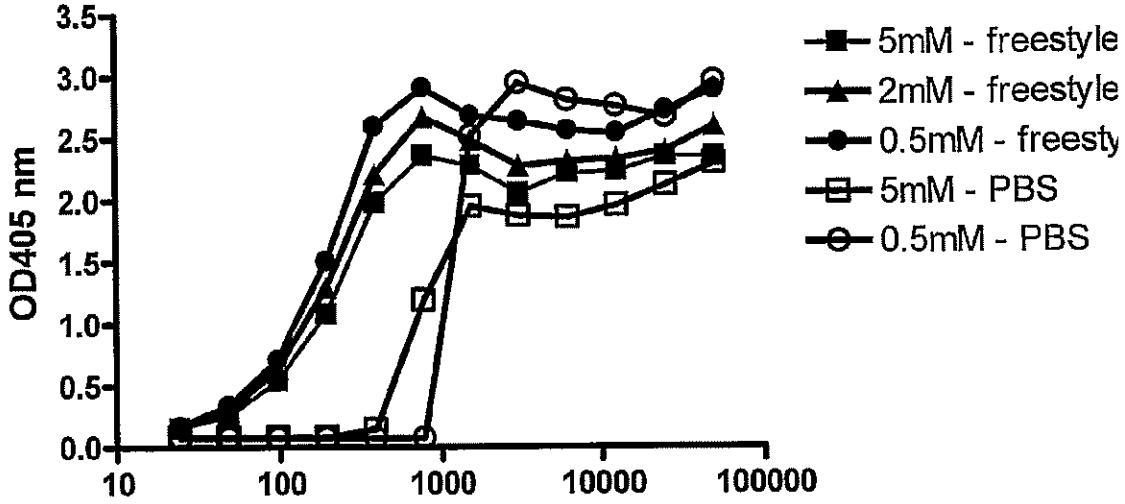


FIGURE 16D

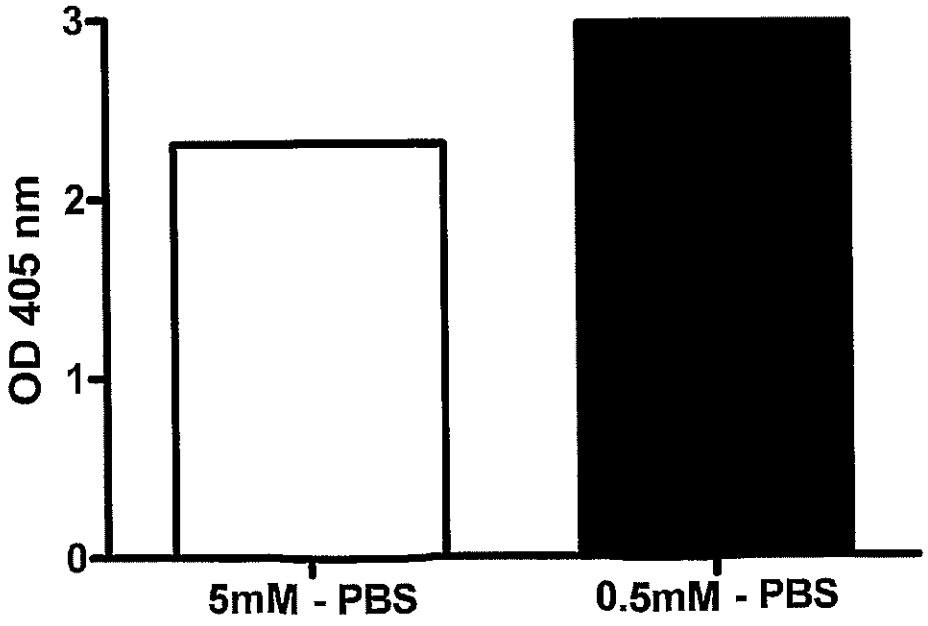


FIGURE 16E

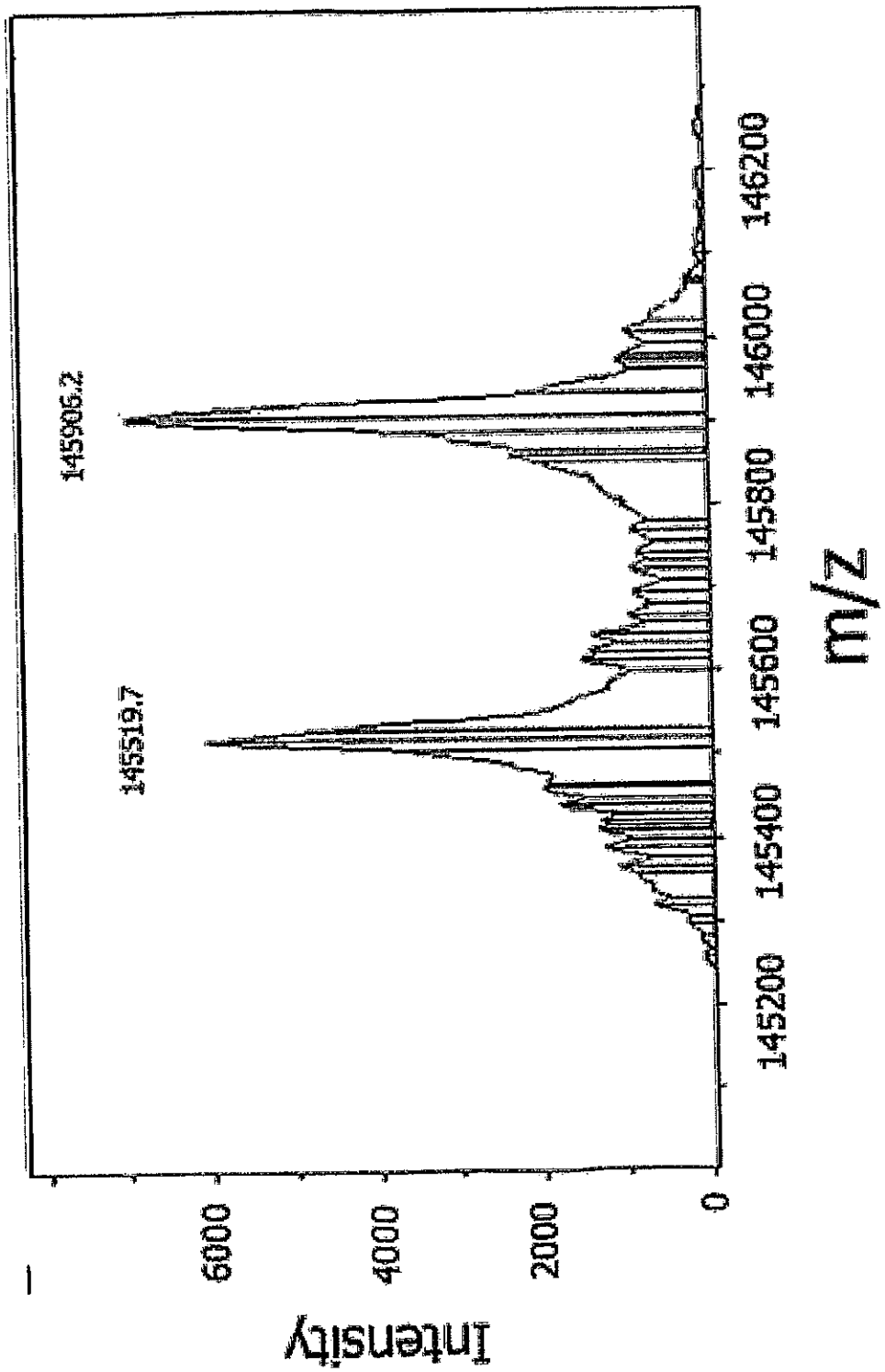

145906.2
145519.7
Intensity
6000
4000
2000
0
145200
145400
145600
145800
146000
146200
m/z

FIGURE 16F

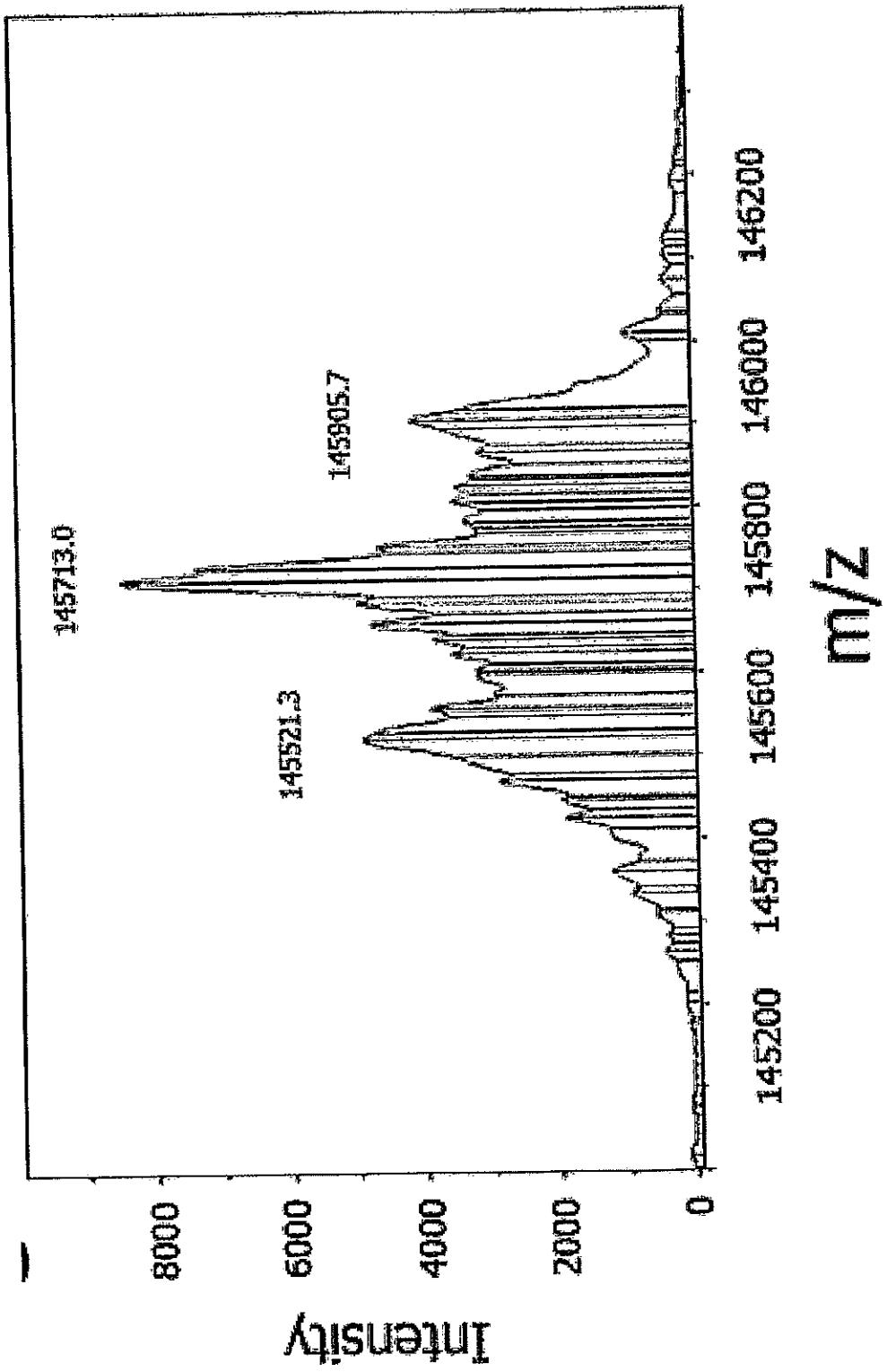

145713.0
145805.7
145521.3
Intensity
8000
6000
4000
2000
0
145200
145400
145600
145800
146000
146200
m/z

FIGURE 17A

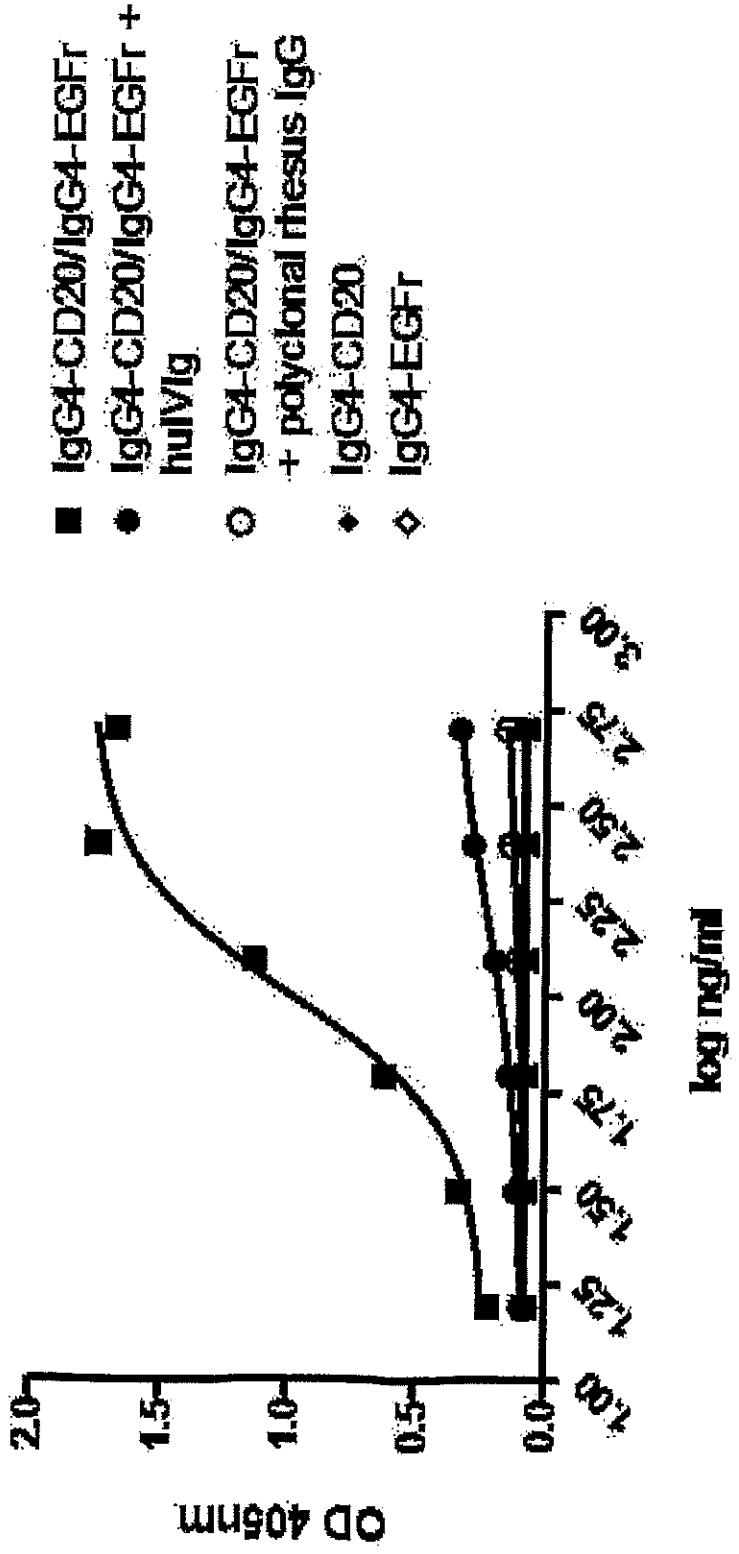

IgG4-CD20/IgG4-EGFr
IgG4-CD20/IgG4-EGFr + huIVIg
IgG4-CD20/IgG4-EGFr + polyclonal rhesus IgG
IgG4-CD20
IgG4-EGFr
OD 405nm
2.0
1.5
1.0
0.5
0.0
log ng/ml
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00

FIGURE 17B

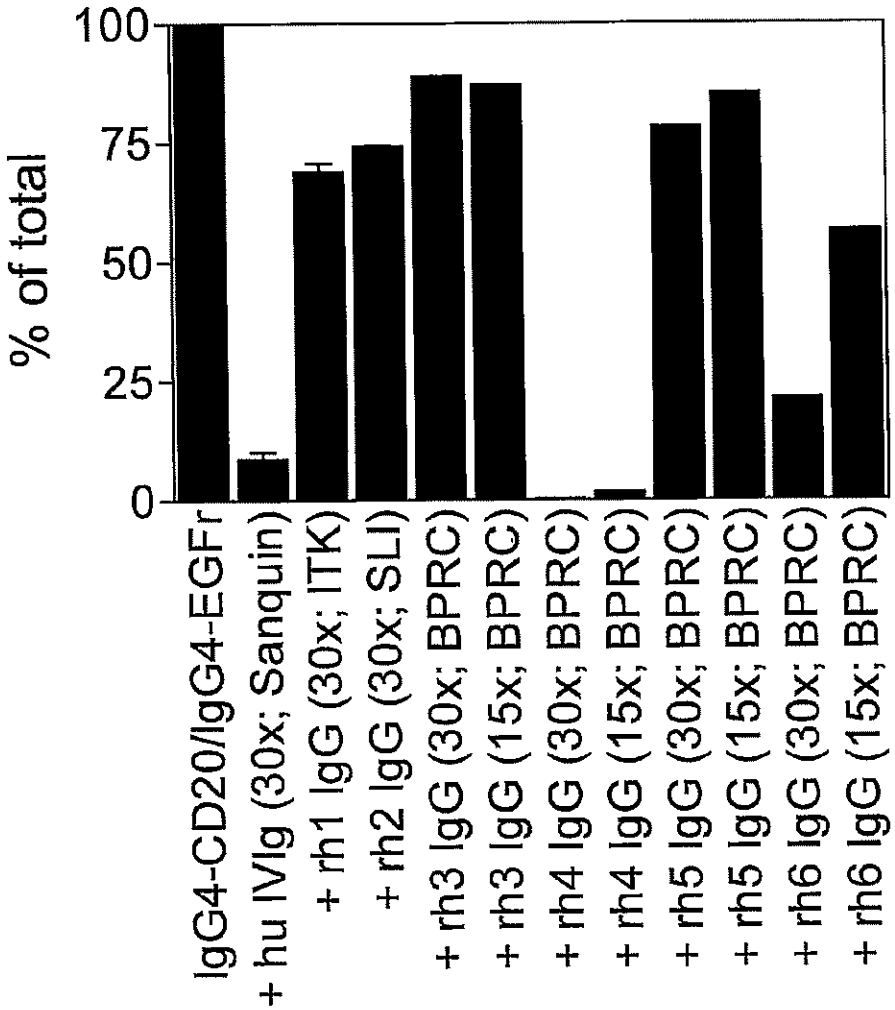

100
75
50
25
0
% of total
IgG4-CD20/IgG4-EGFr
+ hu IVIg (30x; Sanquin)
+ rh1 IgG (30x; ITK)
+ rh2 IgG (30x; SLI)
+ rh3 IgG (30x; BPRC)
+ rh3 IgG (15x; BPRC)
+ rh4 IgG (30x; BPRC)
+ rh4 IgG (15x; BPRC)
+ rh5 IgG (30x; BPRC)
+ rh5 IgG (15x; BPRC)
+ rh6 IgG (30x; BPRC)
+ rh6 IgG (15x; BPRC)

FIGURE 17C

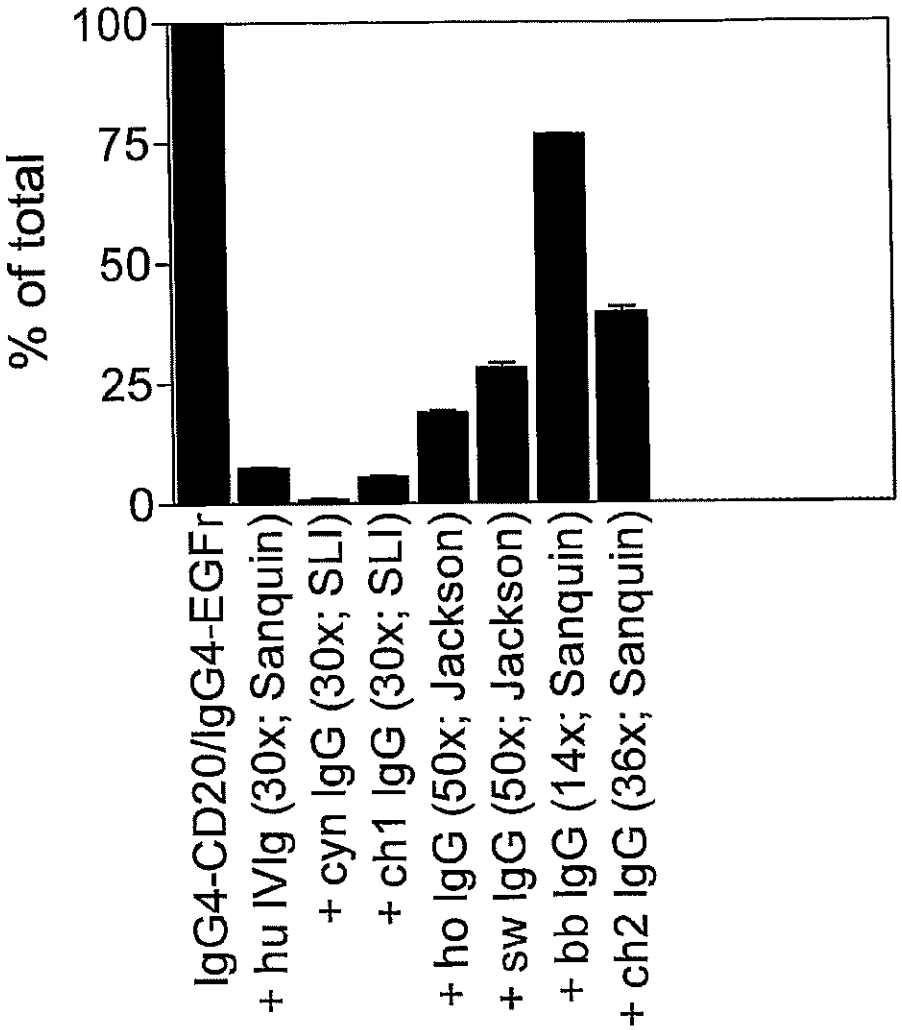

100
75
50
25
0
% of total
IgG4-CD20/IgG4-EGFr
+ hu IVIg (30x; Sanquin)
+ cyn IgG (30x; SLI)
+ ch1 IgG (30x; SLI)
+ ho IgG (50x; Jackson)
+ sw IgG (50x; Jackson)
+ bb IgG (14x; Sanquin)
+ ch2 IgG (36x; Sanquin)

FIGURE 18

SEQ ID NO: 19: aa sequence of IgG1 constant region (accession # P01857)

```
   1 astkgpsvfp lapSskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv
  51 htfpavlqss glyslssvvt vpssslgtqt yicnvnhkps ntkvdkkvep
 101 kscdkthtcp pcpapellgg psvflfppkp kdtlmisrtp evtcvvvdvs
 151 hedpevkfnw yvdgvevhna ktkpreeqyn styrvvsvlt vlhqdwlngk
 201 eykckvsnka lpapiektis kakgqprepq vytlppsRX4e X5tknqvsltc
 251 lvkgfypsdi avewesngqp ennykttppv ldsdgsffly sKltvdksrw
 301 qQgnvfscsv mhealhnhyt qkslslsPgk
```

wherein X_4 is D or E and X_5 is L or M

SEQ ID NO: 20: aa sequence of the IgG2 constant region (accession # P01859)

```
   1 astkgpsvfp lapcsrstse staalgclvk dyfpepvtvs wnsgaltsgv
  51 htfpavlqss glyslssvvt vpssnfgtqt ytcnvdhkps ntkvdktver
 101 kccvecppcp appvagpsvf lfppkpkdtl misrtpevtc vvvdvshedp
 151 evqfnwyvdg vevhnaktkp reeqfnstfr vvsvltvvhq dwlngkeykc
 201 kvsnkglpap iektisktkg qprepqvytl ppsReemtkn qvsltclvkg
 251 fypsdiavew esngqpenny kttppMldsd gsfflysKlt vdksrwqQgn
 301 vfscsvmhea lhnhytqksl slsPgk
```

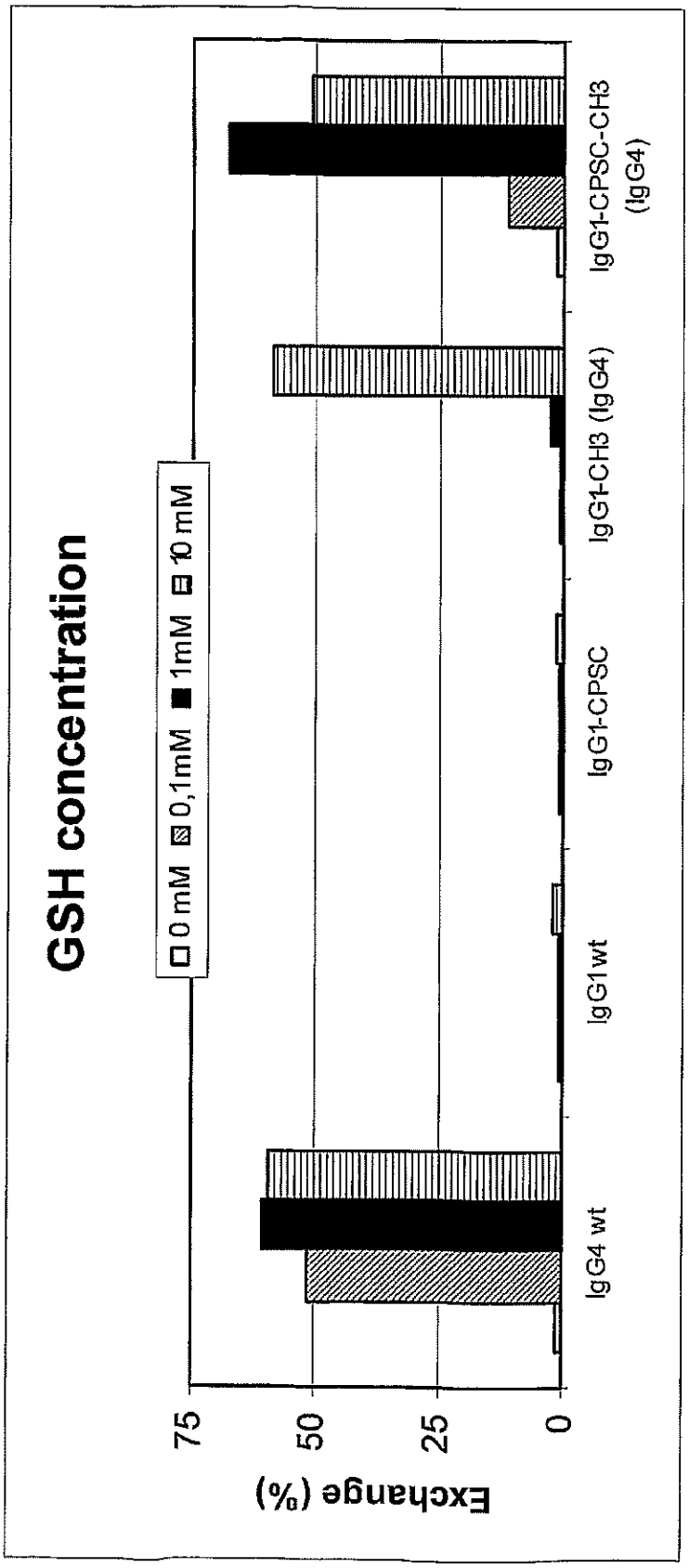
SEQ ID NO: 21: aa sequence of the IgG3 constant region (accession # A23511)

```
   1 astkgpsvfp lapcsrstsg gtaalgclvk dyfpepvtvs wnsgaltsgv
  51 htfpavlqss glyslssvvt vpssslgtqt ytcnvnhkps ntkvdkrvel
 101 ktplgdttht cprcpepksc dtpppcprcp epkscdtppp cprcpepksc
 151 dtpppcprcp apellggpsv flfppkpkdt lmisrtpevt cvvvdvshed
 201 pevqfkwyvd gvevhnaktk preeqynstf rvvsvltvlh qdwlngkeyk
 251 ckvsnkalpa piektisktk gqprepqvyt lppsReemtk nqvsltclvk
 301 gfypsdiave wesSgqpenn yNttppMlds dgsfflysKl tvdksrwqQg
 351 nIfscsvmhe alhnRFtqks lslsPgk
```

SEQ ID No: 22: aa sequence of the IgG4 constant region

```
   1 ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV
  51 HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES
 101 KYGPPCPSCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED
 151 PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK
 201 CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK
 251 GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG
 301 NVFSCSVMHE ALHNHYTQKS LSLSLGK
```

FIGURE 19A



SUBSTITUTE SHEET

FIGURE 19B

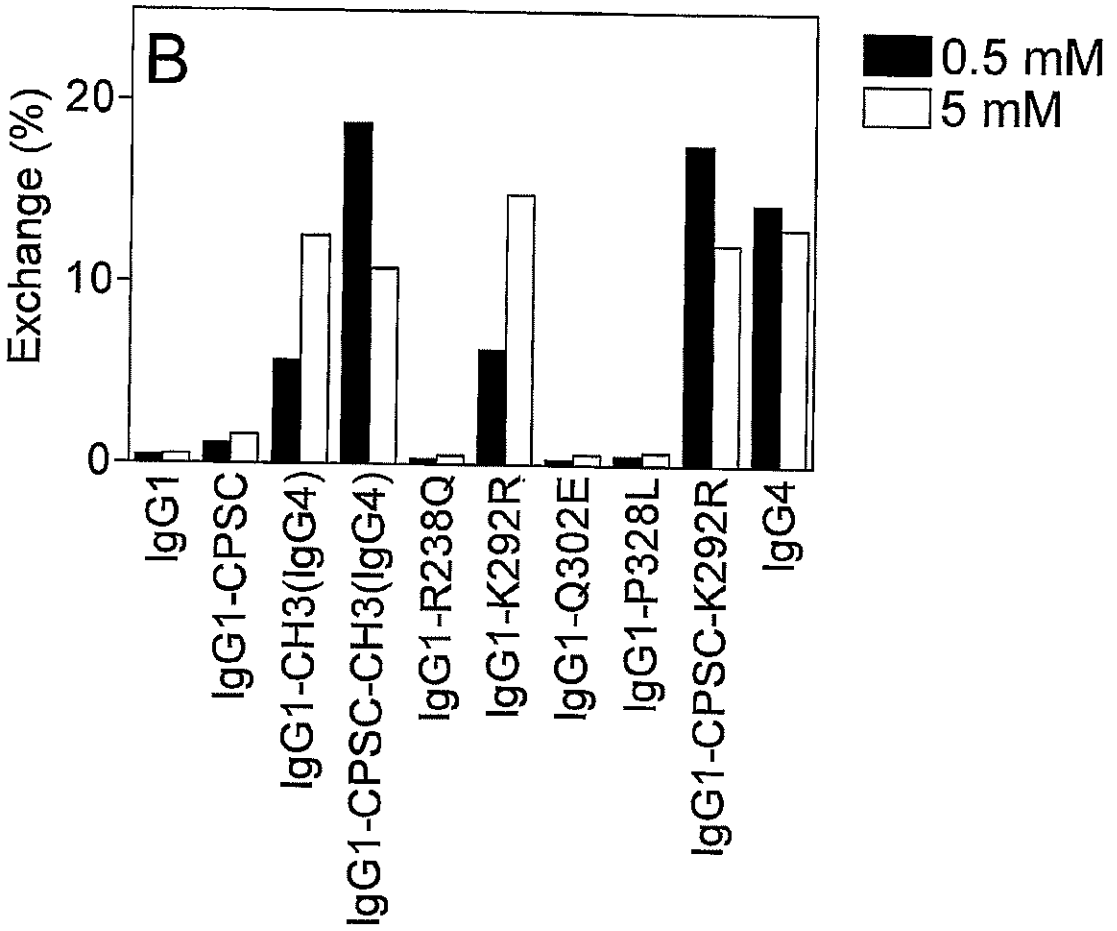

B
Exchange (%)
20
10
0
0.5 mM
5 mM
IgG1
IgG1-CPSC
IgG1-CH3(IgG4)
IgG1-CPSC-CH3(IgG4)
IgG1-R238Q
IgG1-K292R
IgG1-Q302E
IgG1-P328L
IgG1-CPSC-K292R
IgG4

FIGURE 19C

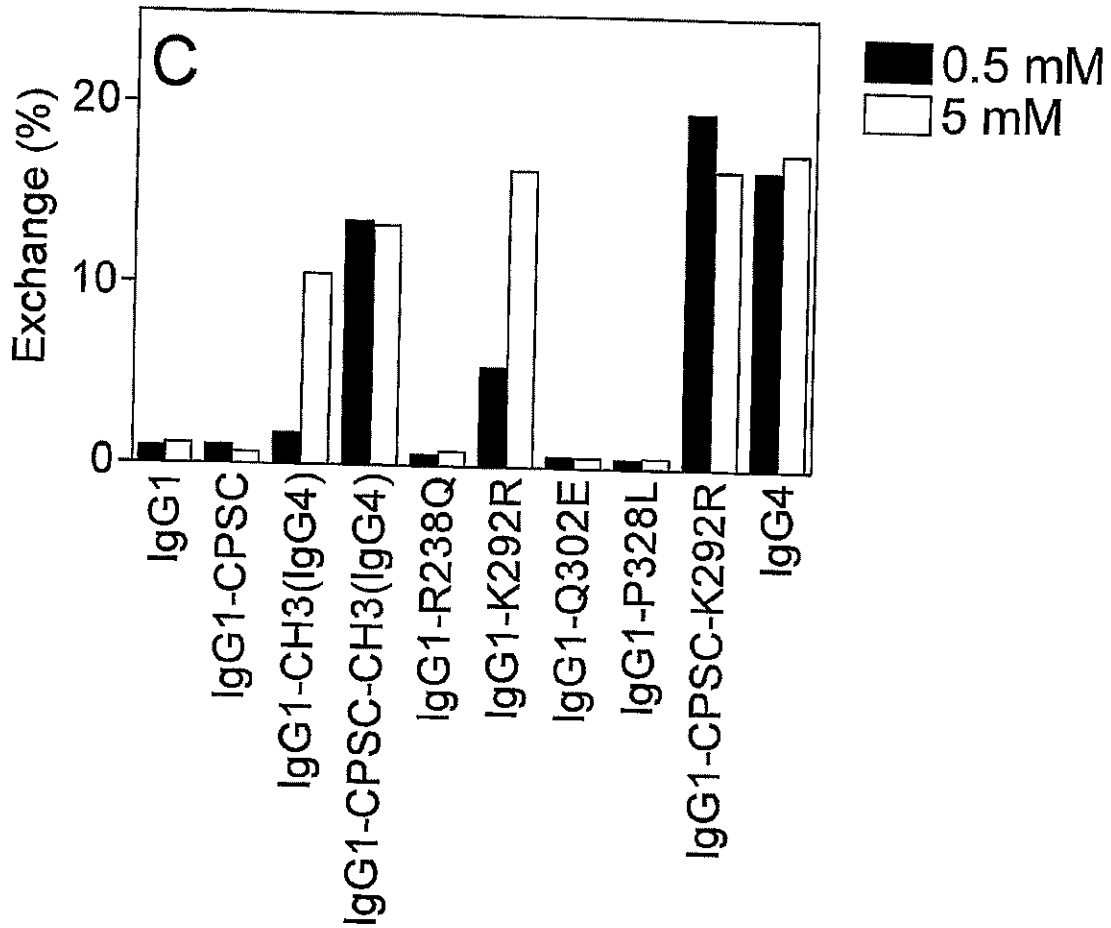

C
Exchange (%)
20
10
0
0.5 mM
5 mM
IgG1
IgG1-CPSC
IgG1-CH3(IgG4)
IgG1-CPSC-CH3(IgG4)
IgG1-R238Q
IgG1-K292R
IgG1-Q302E
IgG1-P328L
IgG1-CPSC-K292R
IgG4

FIGURE 20A

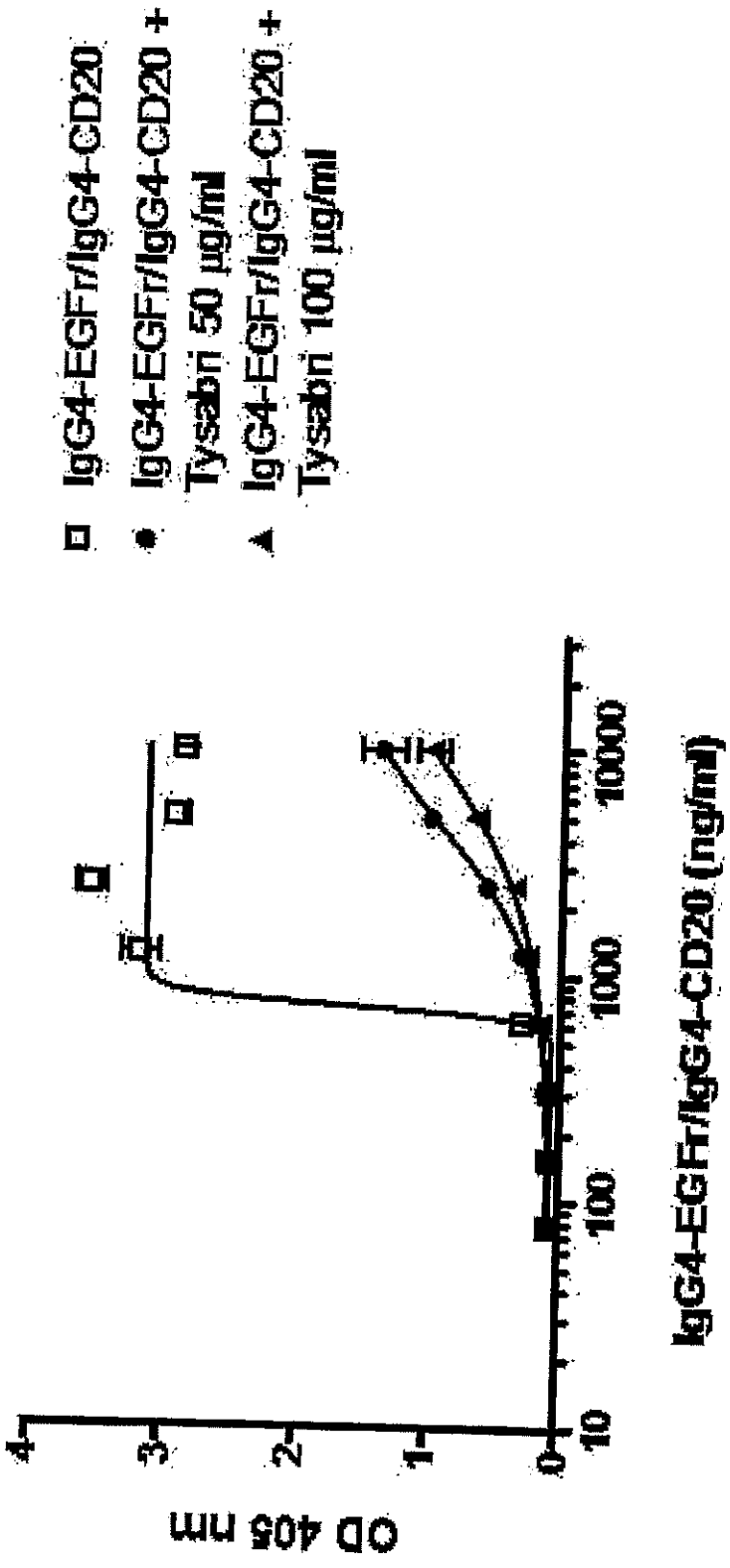

IgG4-EGFr/IgG4-CD20
IgG4-EGFr/IgG4-CD20 + Tysabri 50 µg/ml
IgG4-EGFr/IgG4-CD20 + Tysabri 100 µg/ml
OD 405 nm
0
1
2
3
4
10
100
1000
10000
IgG4-EGFr/IgG4-CD20 (ng/ml)

FIGURE 20B

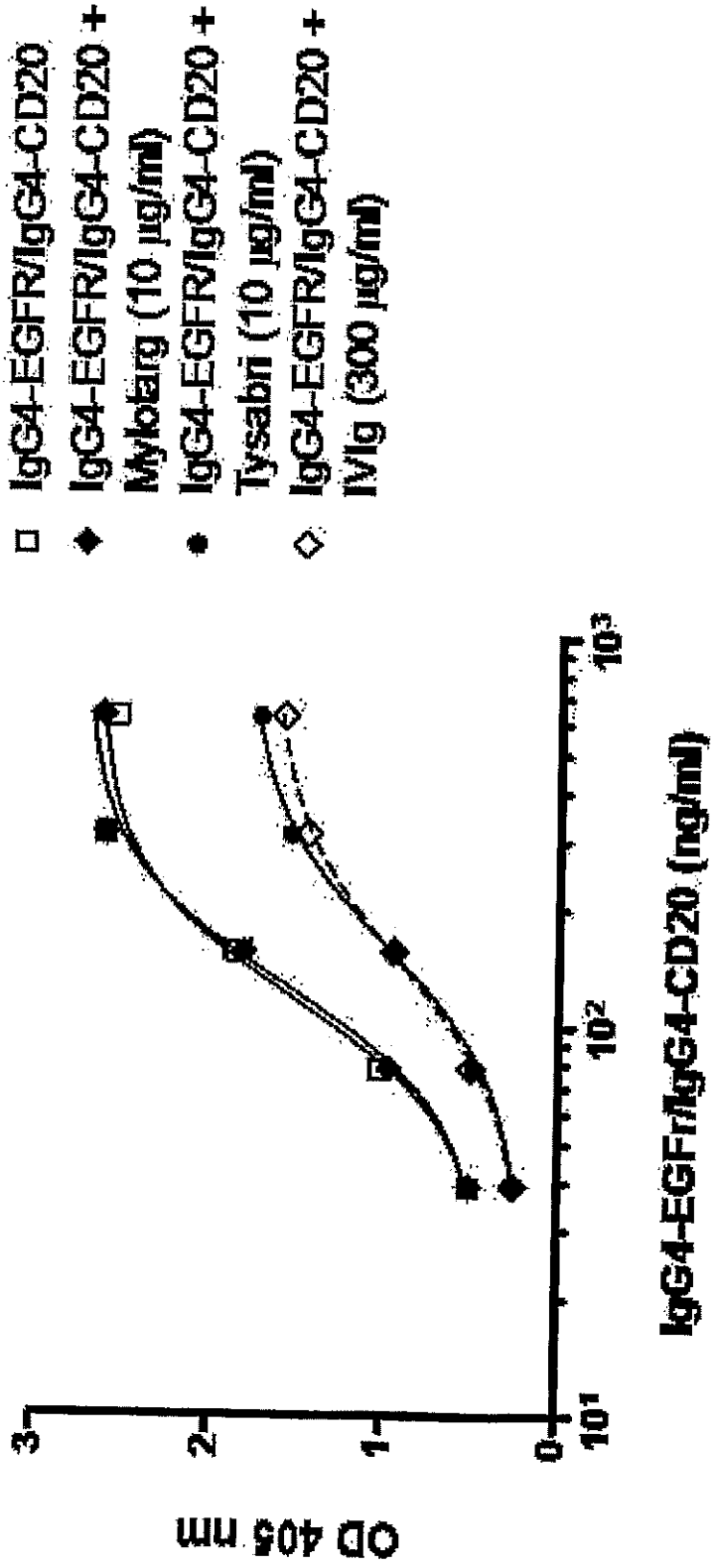

IgG4-EGFR/IgG4-CD20
IgG4-EGFR/IgG4-CD20 + Myobarg (10 µg/ml)
IgG4-EGFR/IgG4-CD20 + Tysabri (10 µg/ml)
IgG4-EGFR/IgG4-CD20 + IVIg (300 µg/ml)
OD 405 nm
0
1
2
3
10¹
10²
10³
IgG4-EGFr/IgG4-CD20 (ng/ml)

FIGURE 21

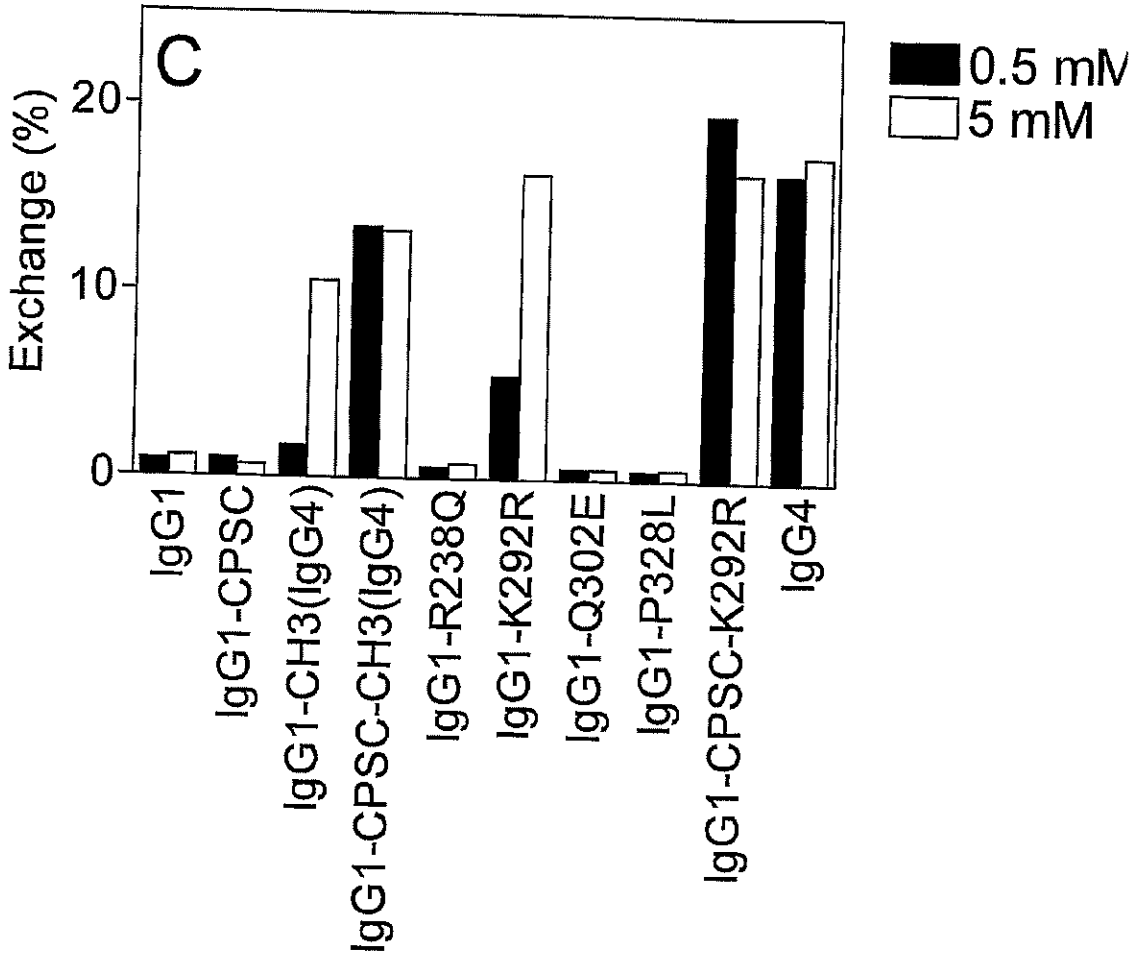

C
Exchange (%)
20
10
0
0.5 mM
5 mM
IgG1
IgG1-CPSC
IgG1-CH3(IgG4)
IgG1-CPSC-CH3(IgG4)
IgG1-R238Q
IgG1-K292R
IgG1-Q302E
IgG1-P328L
IgG1-CPSC-K292R
IgG4

FIGURE 22A

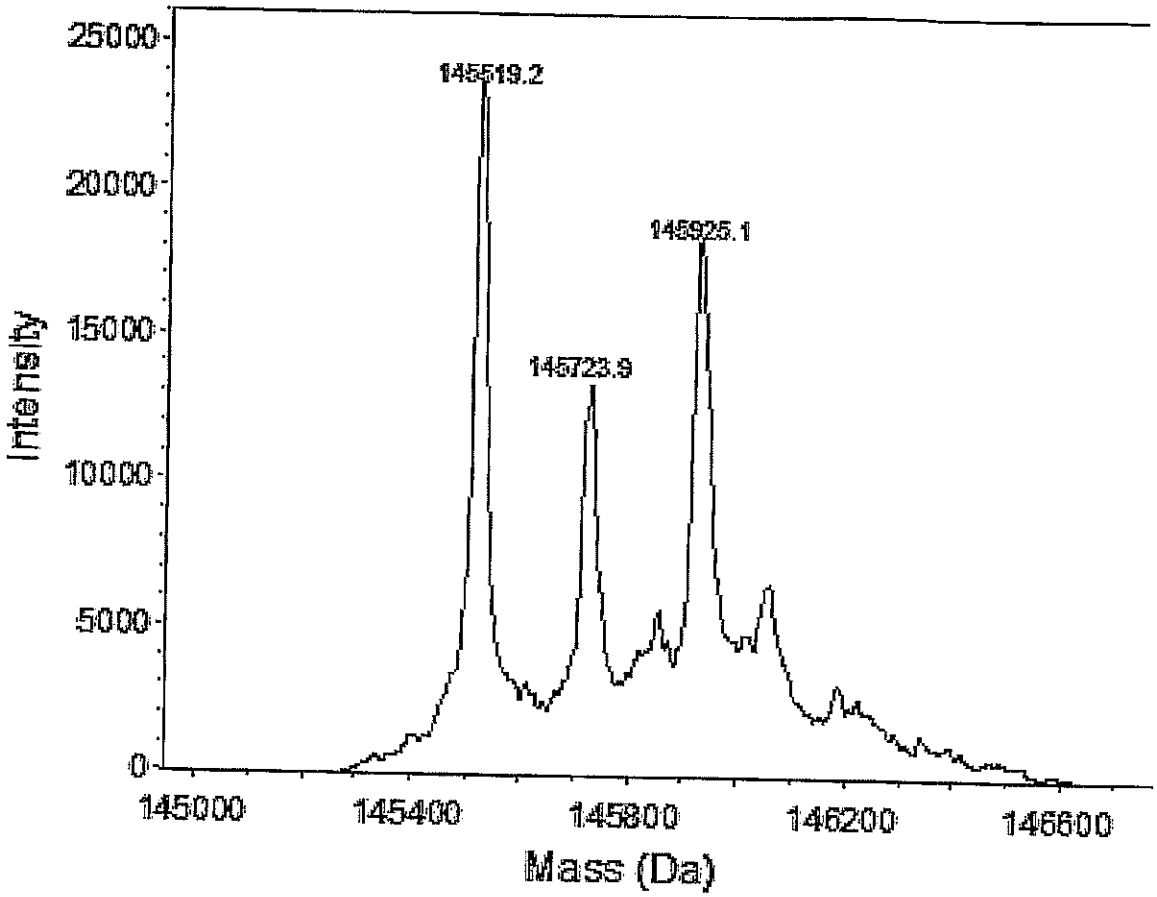

25000
20000
15000
10000
5000
0
Intensity
145619.2
145925.1
145723.9
145000
145400
145800
146200
146600
Mass (Da)

FIGURE 22B

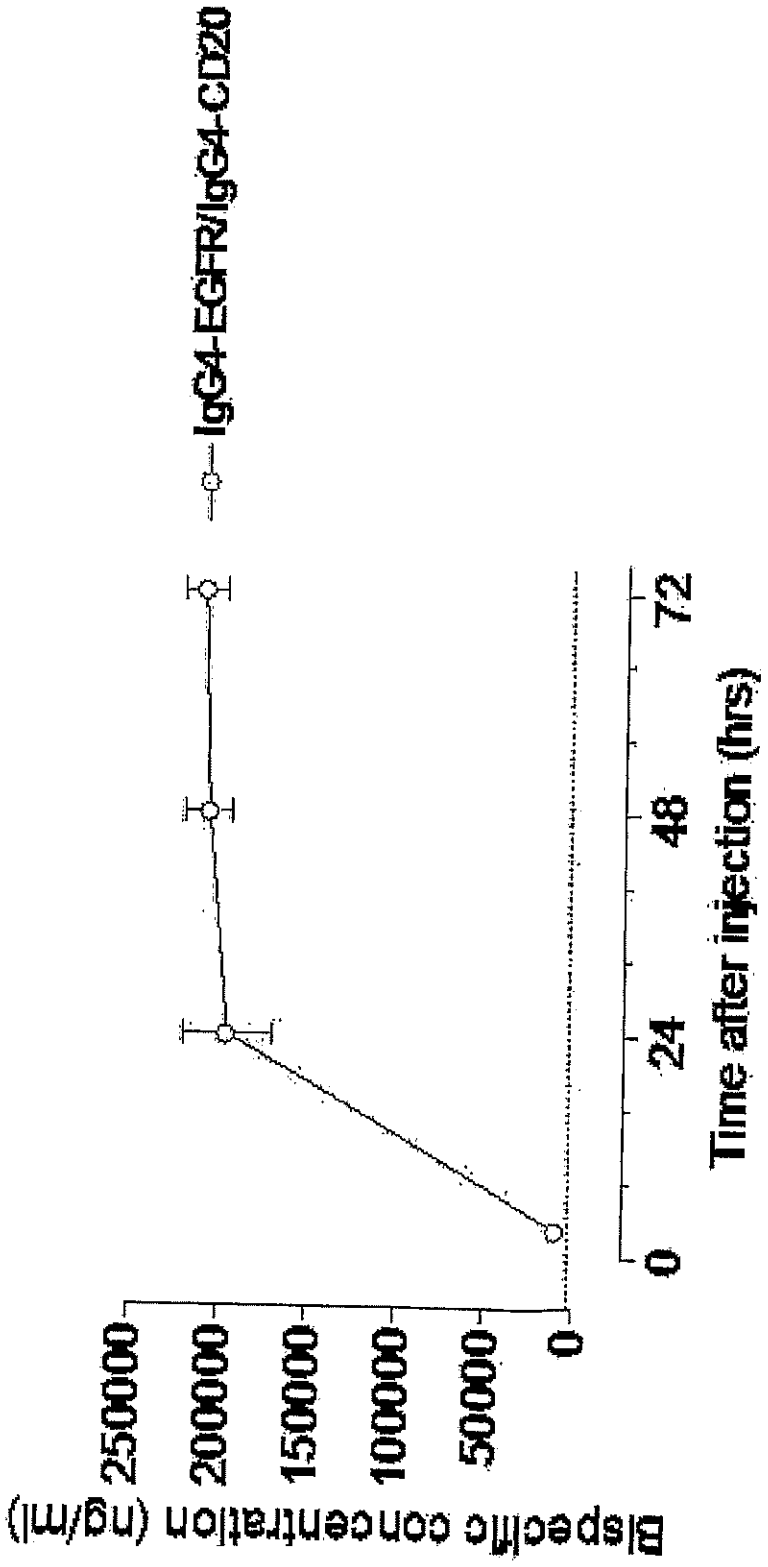

IgG4-EGFR/IgG4-CD20
Bispecific concentration (ng/ml)
250000
200000
150000
100000
50000
0
0
24
48
72
Time after injection (hrs)

FIGURE 23

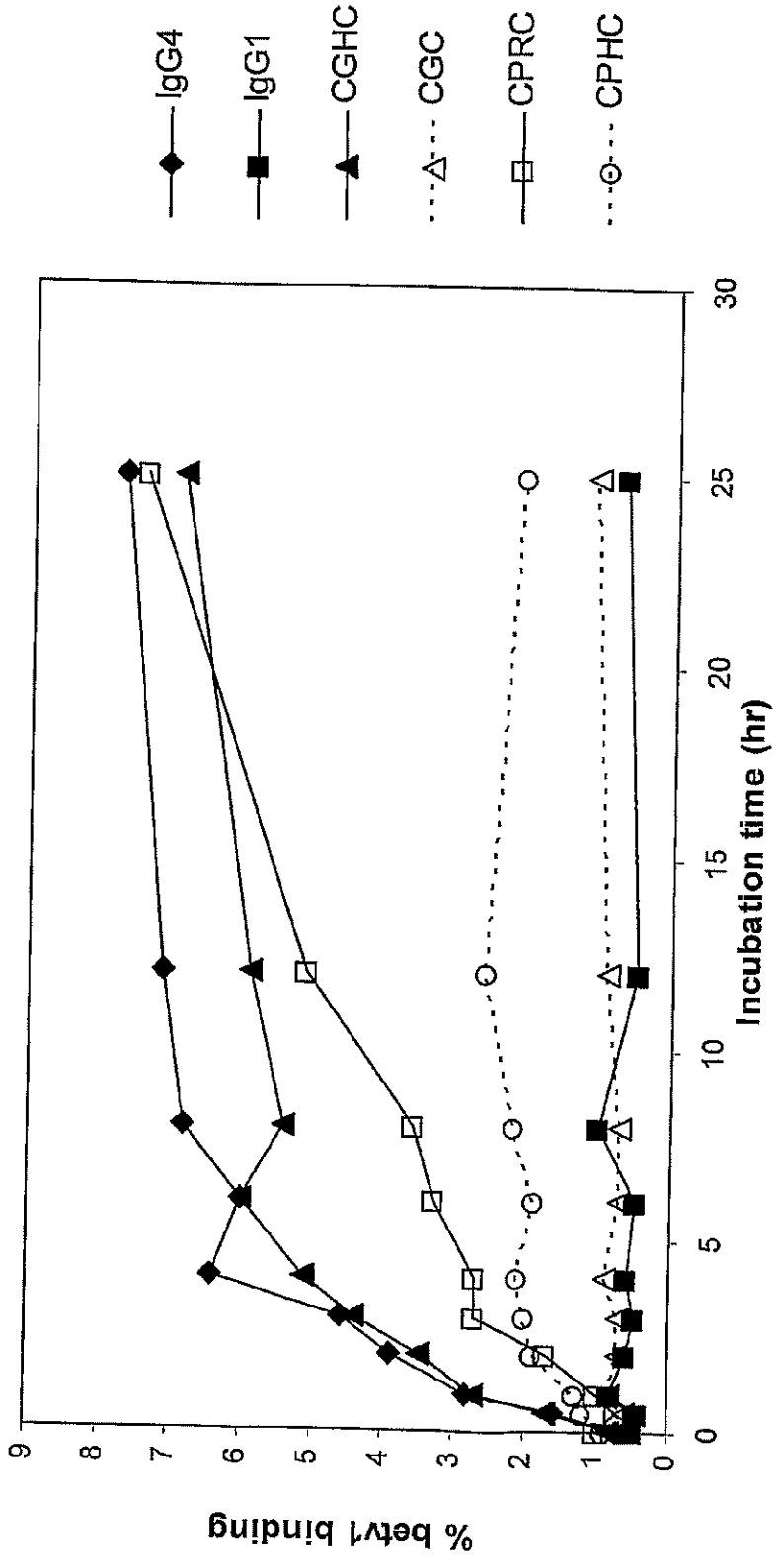
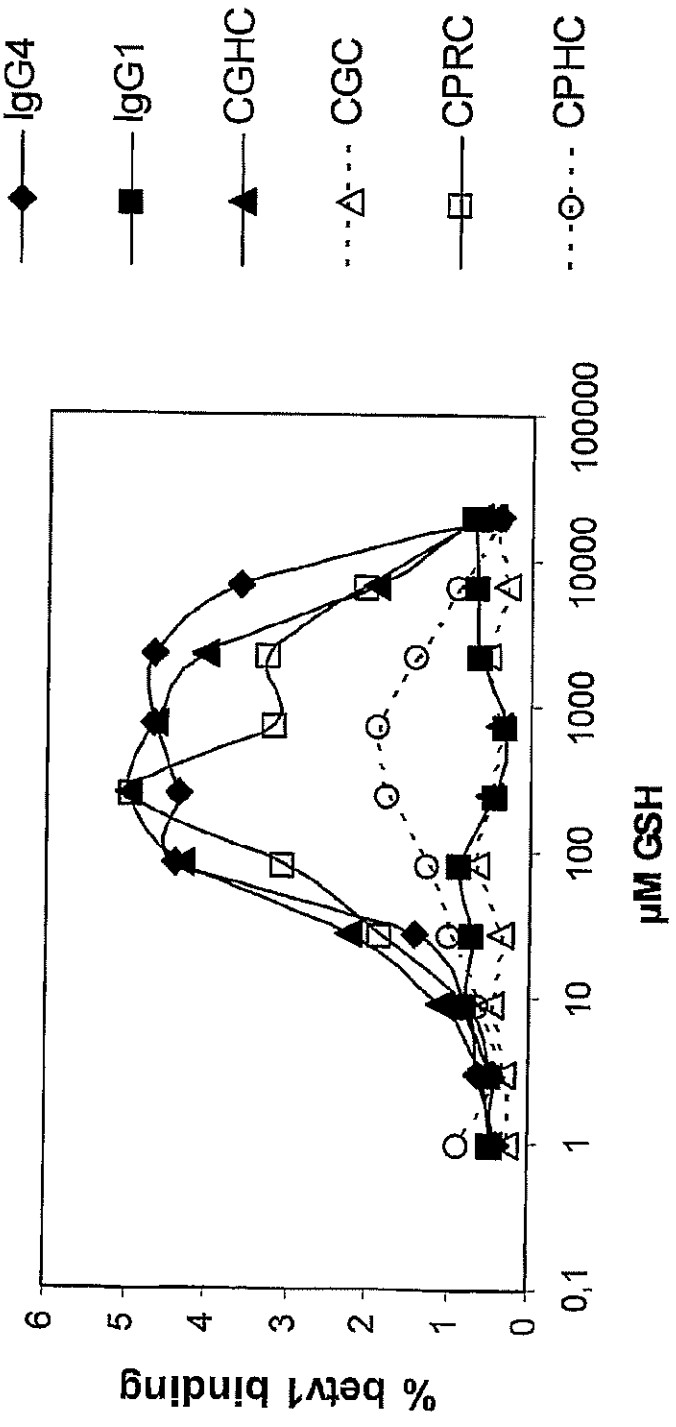

IgG4
IgG1
CGHC
CGC
CPRC
CPHC
% betv1 binding
Incubation time (hr)
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30

FIGURE 24


IgG4
IgG1
CGHC
CGC
CPRC
CPHC
% betv1 binding
0
1
2
3
4
5
6
0,1
1
10
100
1000
10000
100000
µM GSH