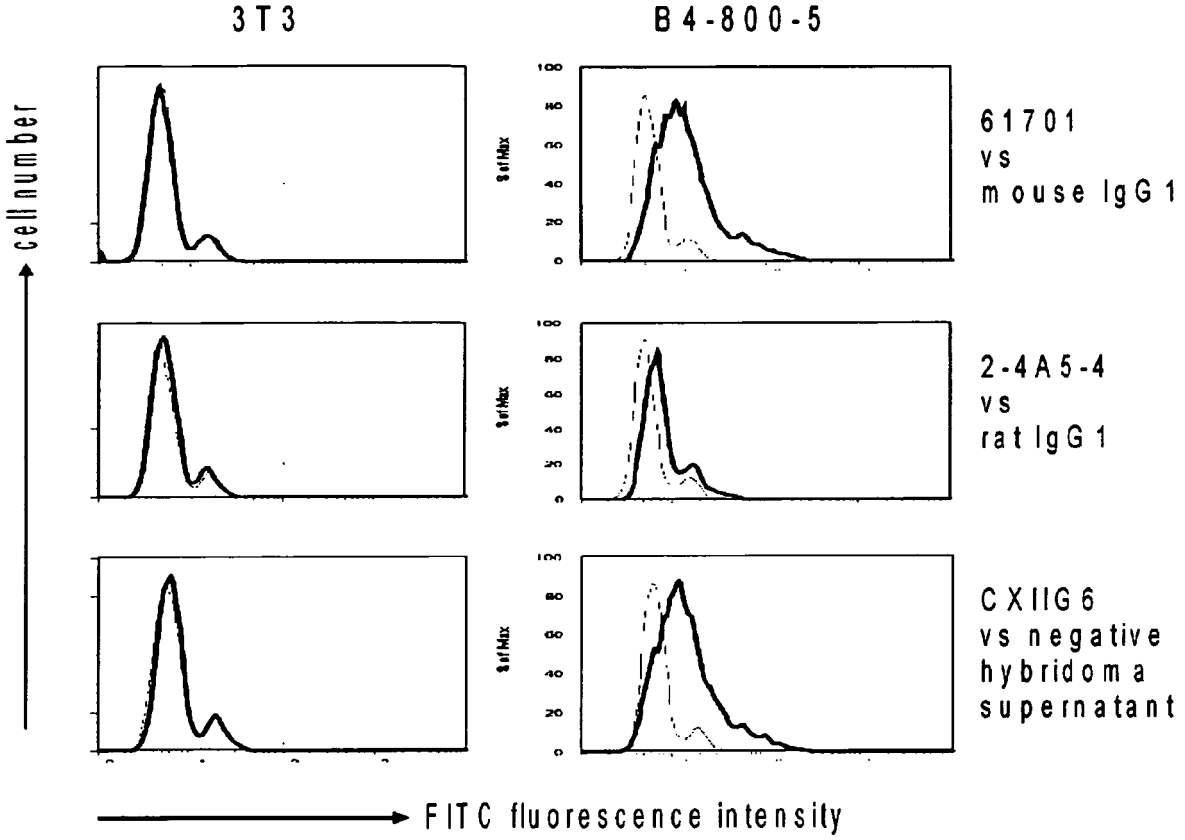

3T3
B4-800-5
cell number
61701
vs
mouse IgG1
2-4A5-4
vs
rat IgG1
CXIIG6
vs negative
hybridoma
supernatant
FITC fluorescence intensity

Fig. 1

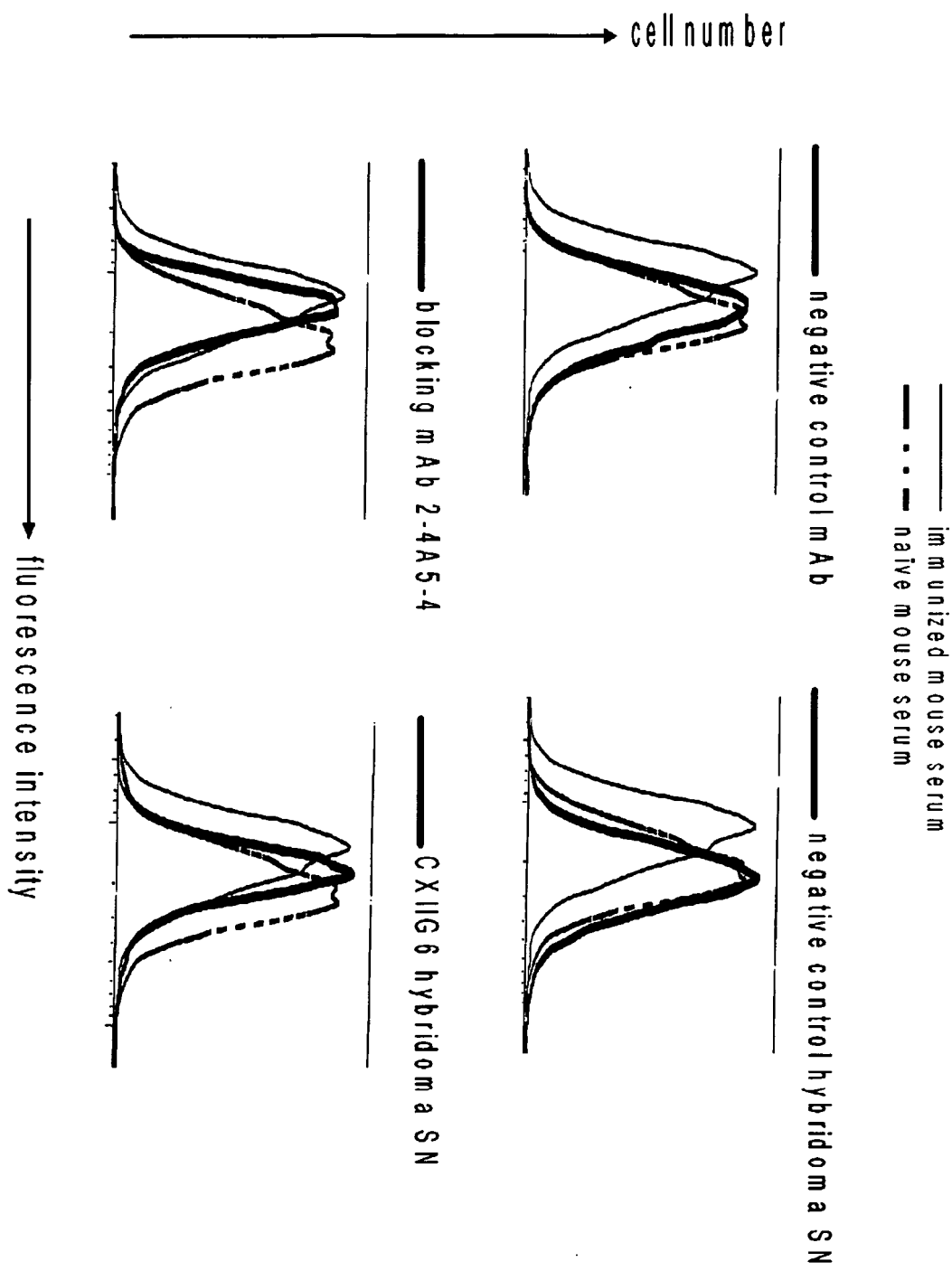

cell number
fluorescence intensity
immunized mouse serum
naive mouse serum
negative control mAb
blocking mAb 2-4A5-4
negative control hybridoma SN
CXIIG6 hybridoma SN

Fig. 2

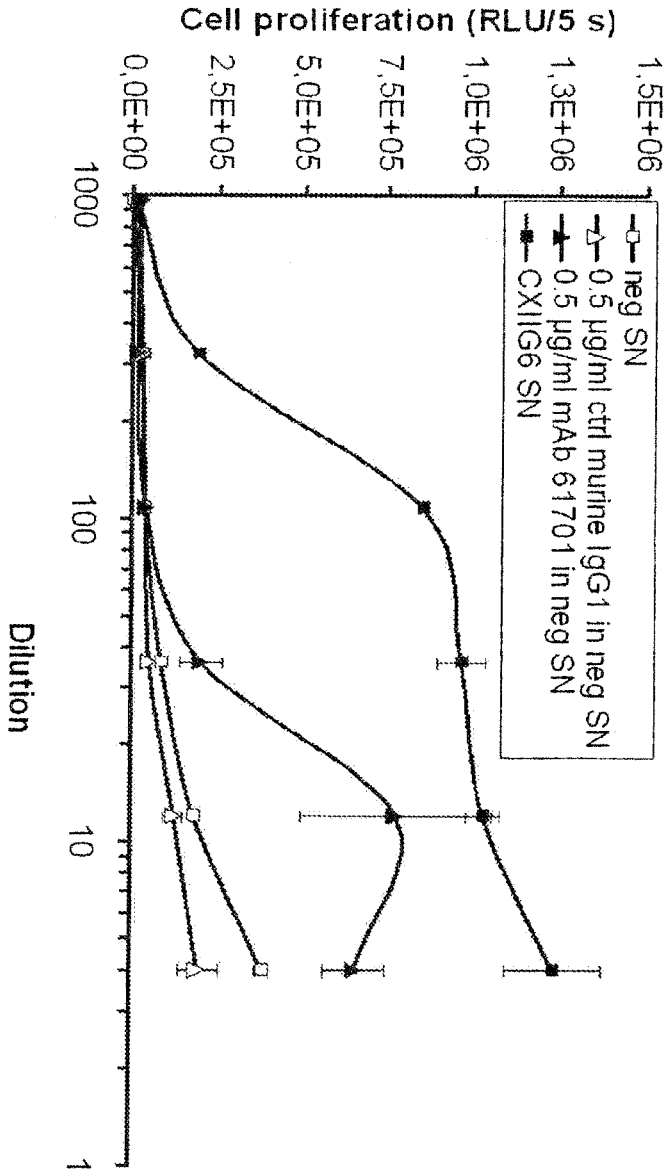

Cell proliferation (RLU/5 s)
0,0E+00
2,5E+05
5,0E+05
7,5E+05
1,0E+06
1,3E+06
1,5E+06
1000
100
10
1
Dilution
neg SN
0.5 µg/ml ctrl murine IgG1 in neg SN
0.5 µg/ml mAb 61701 in neg SN
CXIIG6 SN

Fig. 3

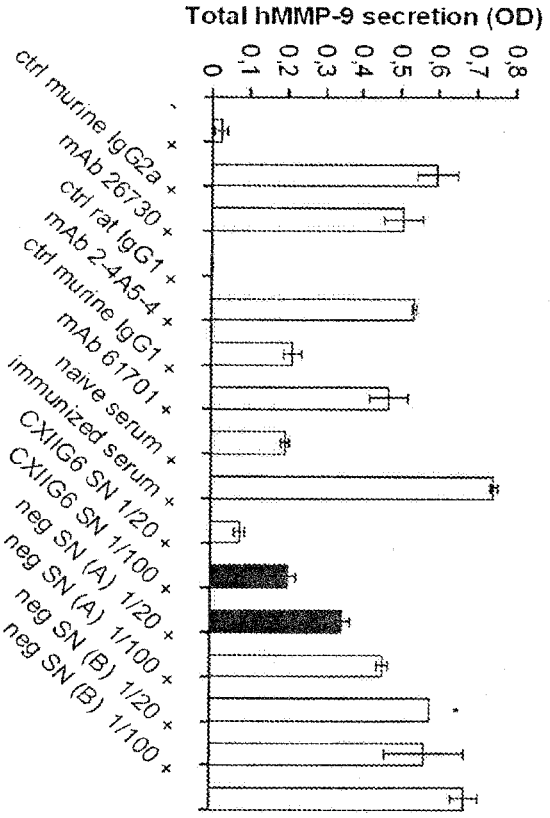

Total hMMP-9 secretion (OD)
0
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
ctrl murine IgG2a +
mAb 26730 +
ctrl rat IgG1 +
mAb 2-4A5-4 +
ctrl murine IgG1 +
mAb 61701 +
naive serum +
immunized serum +
CXIIG6 SN 1/20 +
CXIIG6 SN 1/100 +
neg SN (A) 1/20 +
neg SN (A) 1/100 +
neg SN (B) 1/20 +
neg SN (B) 1/100 +

Fig. 4

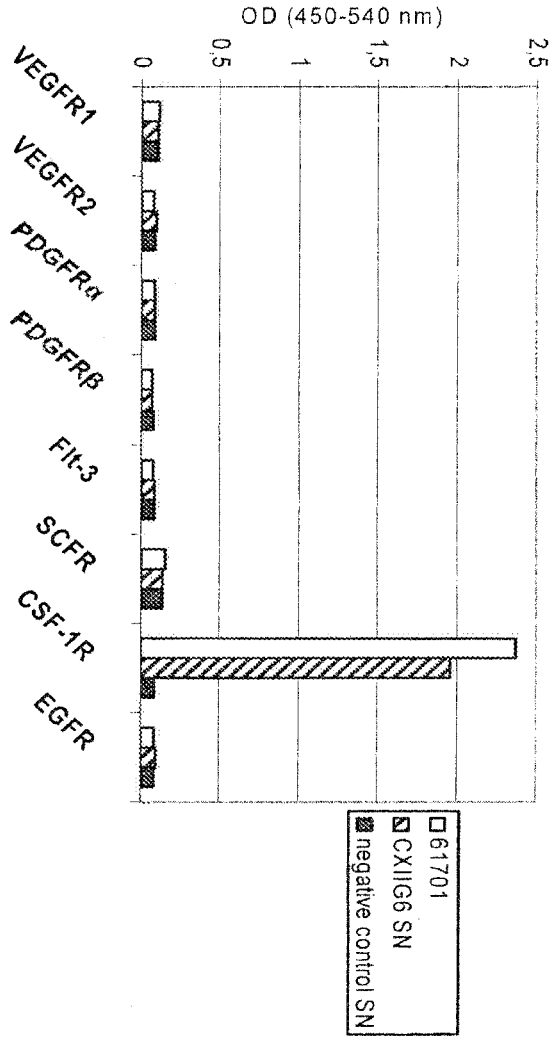

OD (450-540 nm)
0
0,5
1
1,5
2
2,5
VEGFR1
VEGFR2
PDGFRα
PDGFRβ
Flt-3
SCFR
CSF-1R
EGFR
61701
CXIIG6 SN
negative control SN

Fig. 5

```
     SfiI
GGCCCAGCCGGCCCAGTGACAGACACAGACATAGAACATTCACGATGTACTTGGGACTGA 60
                                                M  Y  L  G  L  N
ACTATGTATTCATAGTTTTTCTCCTAAATGGTGTCCAGAGTGAAGTGAAGCTTGAGGAGT 120
  Y  V  F  I  V  F  L  L  N  G  V  Q  S  E  V  K  L  E  E  S
CTGGAGGAGGCTTGGTGCAGCCTGGAGGATCCATGAAACTCTCTTGTGCTGCCTCTGGAT 180
  G  G  G  L  V  Q  P  G  G  S  M  K  L  S  C  A  A  S  G  F
TCACTTTTAGTGACGCCTGGATGGACTGGGTCCGCCAGTCTCCAGAGATGGGACTTGAGT 240
  T  F  S  D  A  W  M  D  W  V  R  Q  S  P  E  M  G  L  E  W
GGGTTGCTGAAATTAGAAGCAAAGCTAATAATCATGCAACATTCTATGCTGAGTCTGTGA 300
  V  A  E  I  R  S  K  A  N  N  N  H  A  T  F  Y  A  E  S  V  K
AAGGGAGGTTCACCATCTCAAGAGATGATTCCAAAAGTAGTGTCTACCTGCAAATGAACA 360
  G  R  F  T  I  S  R  D  D  S  K  S  S  V  Y  L  Q  M  N  S
GCTTAAGACCTGAAGACACTGGCATTTATTACTGTACCAGGGTAAAGGTAGGCTTTGACA 420
  L  R  P  E  D  T  G  I  Y  Y  C  T  R  V  K  V  G  F  D  N
ACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCAGCCAAAACAACAGCCCCATCGGTCT 480
  W  G  Q  G  T  T  L  T  V  S  S  A  K  T  T  A  P  S  V  Y
ATCCACTGGCCCCTGTGTGTGGAGATACAACTGGCTCCTCGGTGACTCTAGGATGCCTGG 540
  P  L  A  P  V  C  G  D  T  T  G  S  S  V  T  L  G  C  L  V
TCAAGGGTTATTTCCCTGAGCCAGTGACCTTGACCTGGAACTCTGGATCCCTGTCCAGTG 600
  K  G  Y  F  P  E  P  V  T  L  T  W  N  S  G  S  L  S  S  G
GTGTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACACCCTCAGCAGCTCAGTGA 660
  V  H  T  F  P  A  V  L  Q  S  D  L  Y  T  L  S  S  S  V  T
        XhoI
CTGTAACCTCGAGCACCTGGCCCAGCCAGTCCATCACCTGCAATGTGGCCCACCCGGCAA 720
  V  T  S  S  T  W  P  S  Q  S  I  T  C  N  V  A  H  P  A  S
GCAGCACCAAGGTGGACAAGAAAATTGAGCCCAGAGGGCCCACAATCAAGCCCTGTCCTC 780
  S  T  K  V  D  K  K  I  E  P  R  G  P  T  I  K  P  C  P  P
CATGCAAATGCCCAGCACCTAACCTCTTGGGTGGACCATCCGTCTTCATCTTCCCTCCAA 840
  C  K  C  P  A  P  N  L  L  G  G  P  S  V  F  I  F  P  P  K
AGATCAAGGATGTACTCATGATCTCCCTGAGCCCCATAGTCACATGTGTGGTGGTGGATG 900
  I  K  D  V  L  M  I  S  L  S  P  I  V  T  C  V  V  V  D  V
TGAGCGAGGATGACCCAGATGTCCAGATCAGCTGGTTTGTGAACAACGTGGAAGTACACA 960
  S  E  D  D  P  D  V  Q  I  S  W  F  V  N  N  V  E  V  H  T
CAGCTCAGACACAAACCCATAGAGAGGATTACAACAGTACTCTCCGGGTGGTCAGTGCCC 1020
  A  Q  T  Q  T  H  R  E  D  Y  N  S  T  L  R  V  V  S  A  L
TCCCCATCCAGCACCAGGACTGGATGAGTGGCAAGGAGTTCAAATGCAAGGTCAACAACA 1080
  P  I  Q  H  Q  D  W  M  S  G  K  E  F  K  C  K  V  N  N  K
AAGACCTCCCAGCGCCCATCGAGAGAACCATCTCAAAACCCAAAGGGTCAGTAAGAGCTC 1140
  D  L  P  A  P  I  E  R  T  I  S  K  P  K  G  S  V  R  A  P
CACAGGTATATGTCTTGCCTCCACCAGAAGAAGAGATGACTAAGAAACAGGTCACTCTGA 1200
  Q  V  Y  V  L  P  P  P  E  E  E  M  T  K  K  Q  V  T  L  T
CCTGCATGGTCACAGACTTCATGCCTGAAGACATTTACGTGGAGTGGACCAACAACGGGA 1260
  C  M  V  T  D  F  M  P  E  D  I  Y  V  E  W  T  N  N  G  K
AAACAGAGCTAAACTACAAGAACACTGAACCAGTCCTGGACTCTGATGGTTCTTACTTCA 1320
  T  E  L  N  Y  K  N  T  E  P  V  L  D  S  D  G  S  Y  F  M
TGTACAGCAAGCTGAGAGTGGAAAAGAAGAACTGGGTGGAAAGAAATAGCTACTCCTGTT 1380
  Y  S  K  L  R  V  E  K  K  N  W  V  E  R  N  S  Y  S  C  S
CAGTGGTCCACGAGGGTCTGCACAATCACCACACGACTAAGAGCTTCTCCCGGACTCCGG 1440
  V  V  H  E  G  L  H  N  H  H  T  T  K  S  F  S  R  T  P  G
                                                    NotI
GTAAATGAGCTCAGCACCCACAAAACTCTCAGGTCCAAAGAGACACCCACGCGGCCGC 1498
  K  *
```

Fig. 6

SfiI

*GGCCCAGCCGGCC*GGAGTCAGCCTCACACTGATCACACACAGACATGAGTGTGCCCACTC 60
M S V P T Q

AGGTCCTGGGGTTGCTGCTGCTGTGGCTTACAGATGCCAGATGTGACATCCAGATGACTC 120
V L G L L L L W L T D A R C **D I Q M T Q**

AGTCTCCAGCCTCCCTATCTGTATCTGTGGGAGAAACTGTCACCATCACATGTCGAGCAA 180
S P A S L S V S V G E T V T I T C R A S

GTGAGAATATTTACAGTAATTTAGCATGGTATCAGCAGAAACAGGGAAAATCTCCTCAGC 240
E N I Y S N L A W Y Q Q K Q G K S P Q L

TCCTGGTCCATGCTGCAACAAACTTAGCAGATGGTGTGCCATCAAGGTTCAGTGGCAGTG 300
L V H A A T N L A D G V P S R F S G S G

GATCAGGCACACAGTATTCCCTCAAGATCAACAGCCTGCAGTCTGAAGATTTTGGGAGTT 360
S G T Q Y S L K I N S L Q S E D F G S Y

ATTACTGTCAACATTTTTGGGGTACTCCTCGGACGTTCGGTGGAGGCACCAAGTTGGAAA 420
Y C Q H F W G T P R T F G G G T K L E I

TCAAACGGGCTGATGCTGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTAA 480
K R A D A A P T V S I F P P S S E Q L T

CATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAAAGACATCAATG 540
S G G A S V V C F L N N F Y P K D I N V

TCAAGTGGAAGATTGATGGCAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGATC 600
K W K I D G S E R Q N G V L N S W T D Q

AGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCTCACGTTGACCAAGGACGAGT 660
D S K D S T Y S M S S T L T L T K D E Y

ATGAACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTG 720
E R H N S Y T C E A T H K T S T S P I V

TCAAGAGCTTCAACAGGAATGAGTGTTAGAGACAAAGGTCCTGAGACGCCACCACCAGCT 788
K S F N R N E C *

NotI

GCGGCCGC 788

Fig. 7

pTG17753

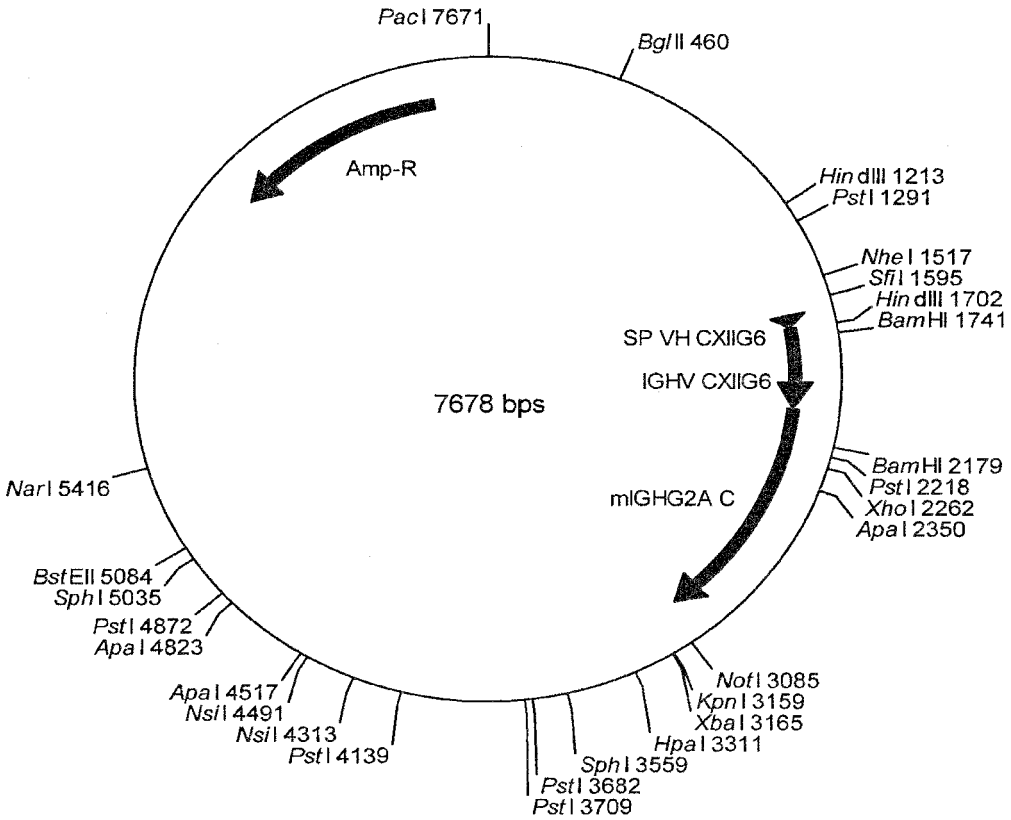


Fig. 8

pTG17727

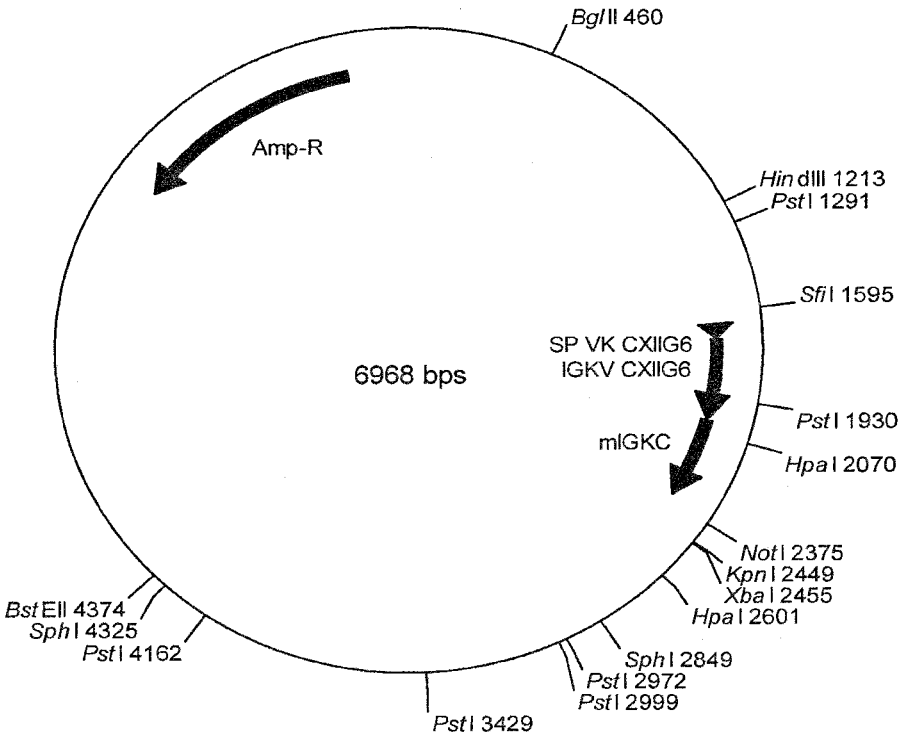


Fig. 9

pOptiVEC™

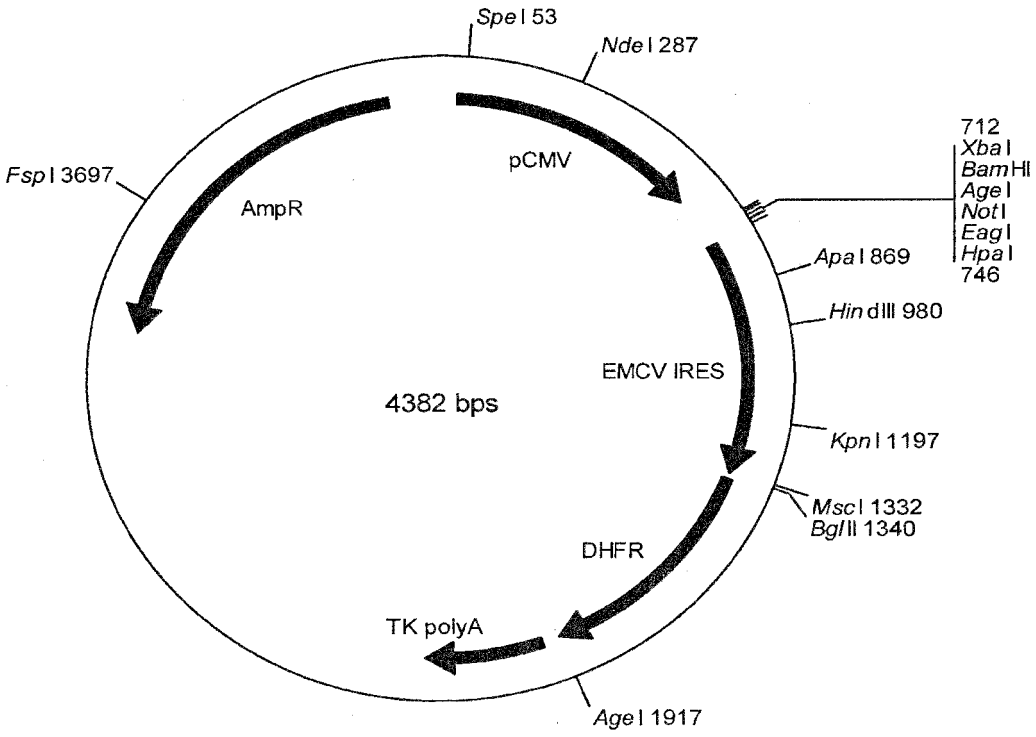


Fig. 10

pTG17895

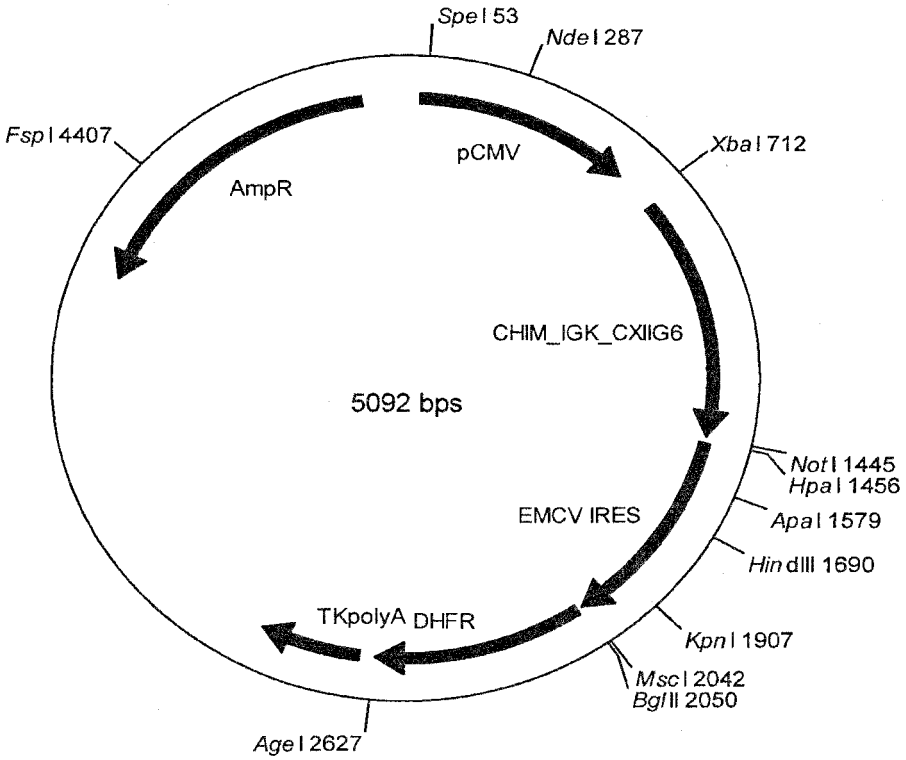


Fig. 11

pTG17812

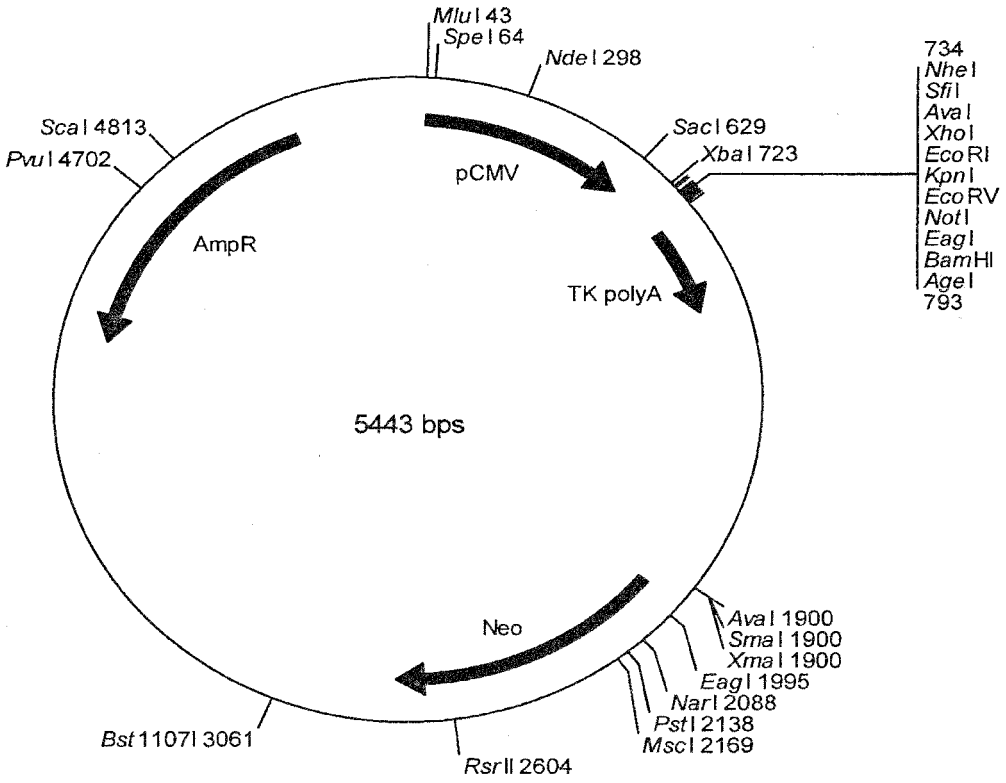


Fig. 12

pTG17868

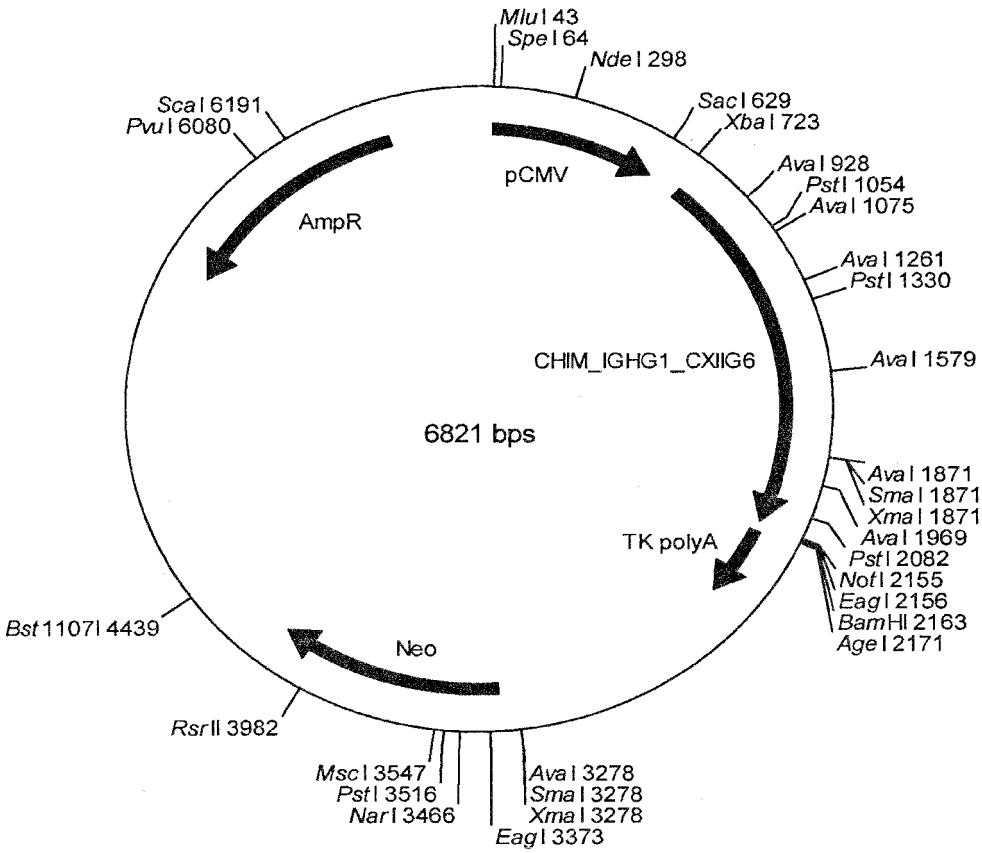


Fig. 13

pTG17869

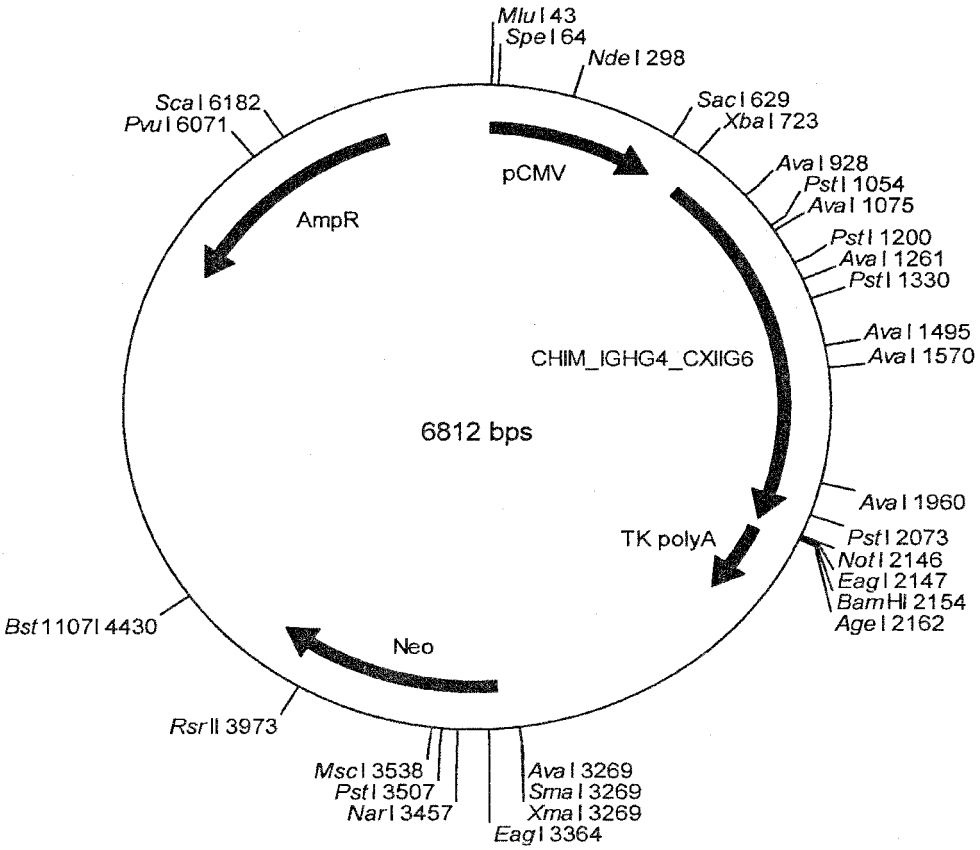


Fig. 14

		Substituted amino acids[a] in VL CXIIG																							
K1	pTG17896	A9S	V13A	E17D	T18R	Q40P	S43A	Q45K	V48L	H49Y	N53R	A55E	D56S	Q70D	S72T	K74T	N76S	S80P	G84A	S85T	G100Q
K2	pTG17897	A9S	V13A	E17D	T18R		S43A	Q45K	V48L	H49Y	N53R	A55E	D56S	Q70D	S72T	K74T	N76S		G84A	S85T	G100Q
K3	pTG17899	A9S	V13A	E17D	T18R		S43A	Q45K	V48L			A55E	D56S	Q70D	S72T	K74T	N76S		G84A	S85T	G100Q
K4	pTG17900	A9S		E17D	T18R		S43A	Q45K		H49Y	N53R	A55E	D56S	Q70D	S72T	K74T	N76S			S85T	G100Q
K5	pTG17901	A9S		E17D	T18R	Q40P	S43A	Q45K				A55E	D56S	Q70D	S72T	K74T	N76S	S80P		S85T	G100Q
K6	pTG17902	A9S		E17D	T18R		S43A	Q45K				A55E	D56S	Q70D	S72T	K74T	N76S			S85T	G100Q
K7	pTG17903	A9S		E17D	T18R		S43A	Q45K					D56S	Q70D			N76S				G100Q
K8	pTG17904			E17D																	G100Q
K9	pTG17905	A9S	V13A	E17D	T18R		S43A	Q45K	V48L				D56S	Q70D	S72T	K74T	N76S		G84A	S85T	G100Q
K10	pTG17906	A9S		E17D	T18R	Q40P	S43A	Q45K					D56S	Q70D	S72T	K74T	N76S	S80P		S85T	G100Q
K11	pTG17907	A9S		E17D	T18R		S43A	Q45K					D56S	Q70D	S72T	K74T	N76S			S85T	G100Q
K12	pTG17947	A9S	V13A	E17D	T18R	Q40D										K74T	N76S	S80P			G100Q
K13	pTG17948	A9S	V13A	E17D	T18R	Q40D	S43A	Q45K	V48L				D56S	Q70D	S72T	K74T	N76S	S80P	G84A	S85T	G100Q
K14	pTG17949	A9S	V13A	E17D	T18R	Q40P										K74T	N76S	S80P			
K15	pTG17950	A9S	V13A	E17D	T18R	Q40P	S43A	Q45K	V48L				D56S	Q70D	S72T	K74T	N76S	S80P	G84A	S85T	G100Q

[a]amino acids in bold have a relative side-chain solvent-accessibility above 50 %, underlined above 25%

Fig. 15

		Substituted amino acids[a] in VH CXIIG6																					
H1	**pTG17870**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**	**E50R**	**F61E**	**E64A**	**S79N**	**V81L**	**R89K**	**P90T**	**G94A**	**I95V**	**T113L**	**L114V**
H2	**pTG17871**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**	**E50R**	**F61E**	**E64A**	**S79N**	**V81L**	**R89K**	**P90T**	**G94A**	**I95V**	**T113L**	
H3	**pTG17872**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**	**E50R**	**F61E**	**E64A**	**S79N**	**V81L**	**R89K**	**P90T**	**G94A**	**I95V**		**L114V**
H4	**pTG17873**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**	**E50R**		**E64A**	**S79N**	**V81L**	**R89K**		**G94A**	**I95V**	**T113L**	**L114V**
H5	**PTG17874**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**	**E50R**		**E64A**	**S79N**	**V81L**	**R89K**		**G94A**	**I95V**	**T113L**	
H6	**pTG17875**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**	**E50R**		**E64A**	**S79N**	**V81L**	**R89K**		**G94A**	**I95V**		**L114V**
H7	**pTG17883**	**K3Q**	**E5V**		**K19R**	**S40A**	**E42G**	**M43K**				**E64A**	**S79N**		**R89K**			**I95V**	**T113L**	**L114V**
H8	**pTG17884**	**K3Q**	**E5V**		**K19R**	**S40A**	**E42G**	**M43K**				**E64A**	**S79N**		**R89K**			**I95V**	**T113L**	
H9	**pTG17885**	**K3Q**	**E5V**		**K19R**	**S40A**	**E42G**	**M43K**				**E64A**	**S79N**		**R89K**			**I95V**		**L114V**
H10	**pTG17886**	**K3Q**	**E5V**		**K19R**		**E42G**	**M43K**				**E64A**			**R89K**				**T113L**	**L114V**
H11	**pTG17887**	**K3Q**	**E5V**		**K19R**		**E42G**	**M43K**				**E64A**			**R89K**				**T113L**	
H12	**pTG17888**	**K3Q**	**E5V**		**K19R**		**E42G**	**M43K**				**E64A**			**R89K**					**L114V**
H13	**pTG17889**				**K19R**										**R89K**				**T113L**	**L114V**
H14	**pTG17890**				**K19R**										**R89K**				**T113L**	
H15	**pTG17891**				**K19R**										**R89K**					**L114V**
H16	**pTG17892**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**			**E64A**	**S79N**	**V81L**	**R89K**		**G94A**	**I95V**	**T113L**	**L114V**
H17	**pTG17893**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**			**E64A**	**S79N**	**V81L**	**R89K**		**G94A**	**I95V**	**T113L**	
H18	**pTG17894**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**	**A49G**			**E64A**	**S79N**	**V81L**	**R89K**		**G94A**	**I95V**		**L114V**
H19	**pTG17943**	**K3Q**	**E5V**	**M18L**												**P90A**				
H20	**pTG17944**	**K3Q**	**E5V**	**M18L**	**K19R**		**E42G**	**M43K**				**E64A**			**R89K**				**T113L**	**L114V**
H21	**pTG17945**	**K3Q**	**E5V**	**M18L**	**K19R**		**E42G**	**M43K**				**E64A**			**R89K**	**P90A**			**T113L**	**L114V**
H22	**pTG17946**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**				**E64A**			**R89K**	**P90A**		**I95V**	**T113L**	**L114V**
H23	**pTG17968**	**K3Q**	**E5V**	**M18L**	**K19R**		**E42G**	**M43K**							**R89K**				**T113L**	**L114V**
H24	**pTG17969**	**K3Q**	**E5V**	**M18L**	**K19R**		**E42G**	**M43K**							**R89K**	**P90A**			**T113L**	**L114V**
H25	**pTG17970**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**							**R89K**	**P90A**		**I95V**	**T113L**	**L114V**
H26	**pTG17985**	**K3Q**	**E5V**	**M18L**	**K19R**		**E42G**	**M43K**							**R89K**	**P90T**			**T113L**	**L114V**
H27	**pTG17986**	**K3Q**	**E5V**	**M18L**	**K19R**	**S40A**	**E42G**	**M43K**							**R89K**	**P90T**		**I95V**	**T113L**	**L114V**

[a]amino acids in bold have a relative side-chain solvent-accessibility above 50 %, underlined above 25%

Fig. 16

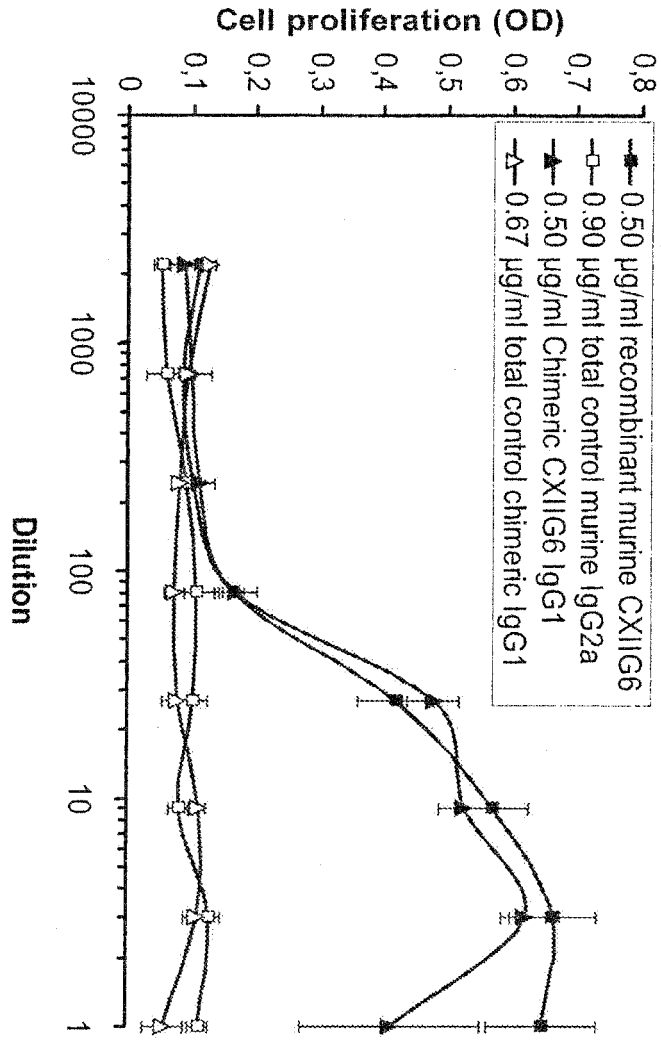

Cell proliferation (OD)
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
10000
1000
100
10
1
Dilution
0.50 µg/ml recombinant murine CXIIG6
0.90 µg/ml total control murine IgG2a
0.50 µg/ml Chimeric CXIIG6 IgG1
0.67 µg/ml total control chimeric IgG1

Fig. 17

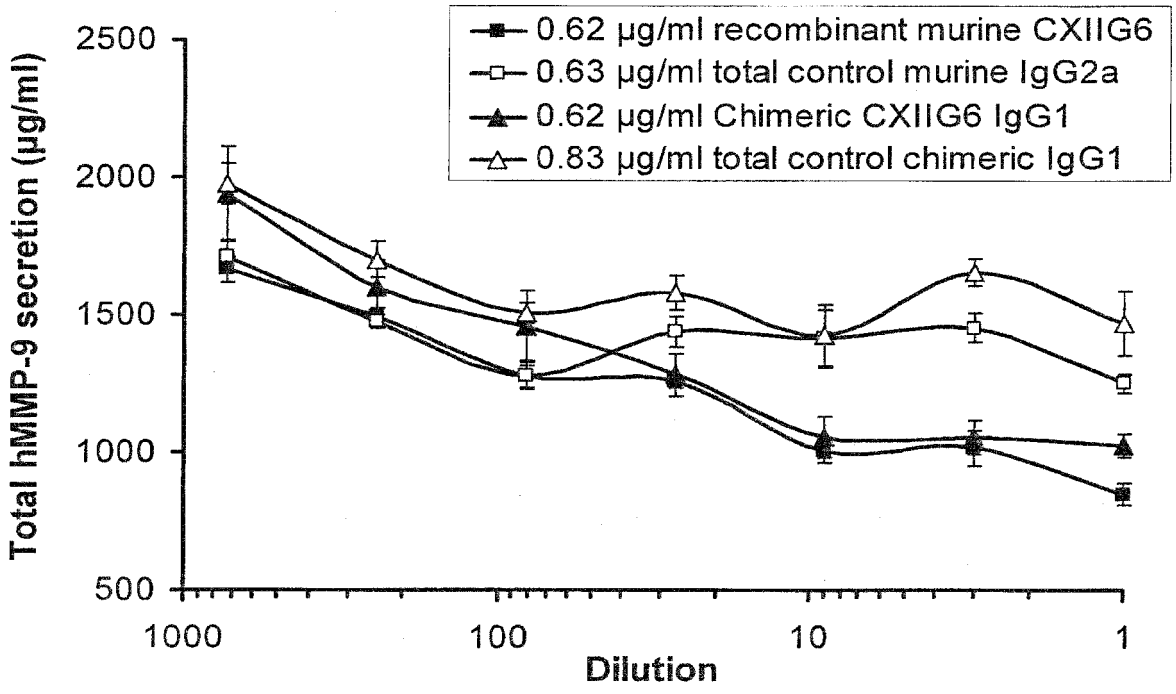

0.62 µg/ml recombinant murine CXIIG6
0.63 µg/ml total control murine IgG2a
0.62 µg/ml Chimeric CXIIG6 IgG1
0.83 µg/ml total control chimeric IgG1
Total hMMP-9 secretion (µg/ml)
2500
2000
1500
1000
500
1000
100
10
1
Dilution

Fig. 18

Fig. 19 : epitope mapping of ChCXIIG6, JF14 and 3291

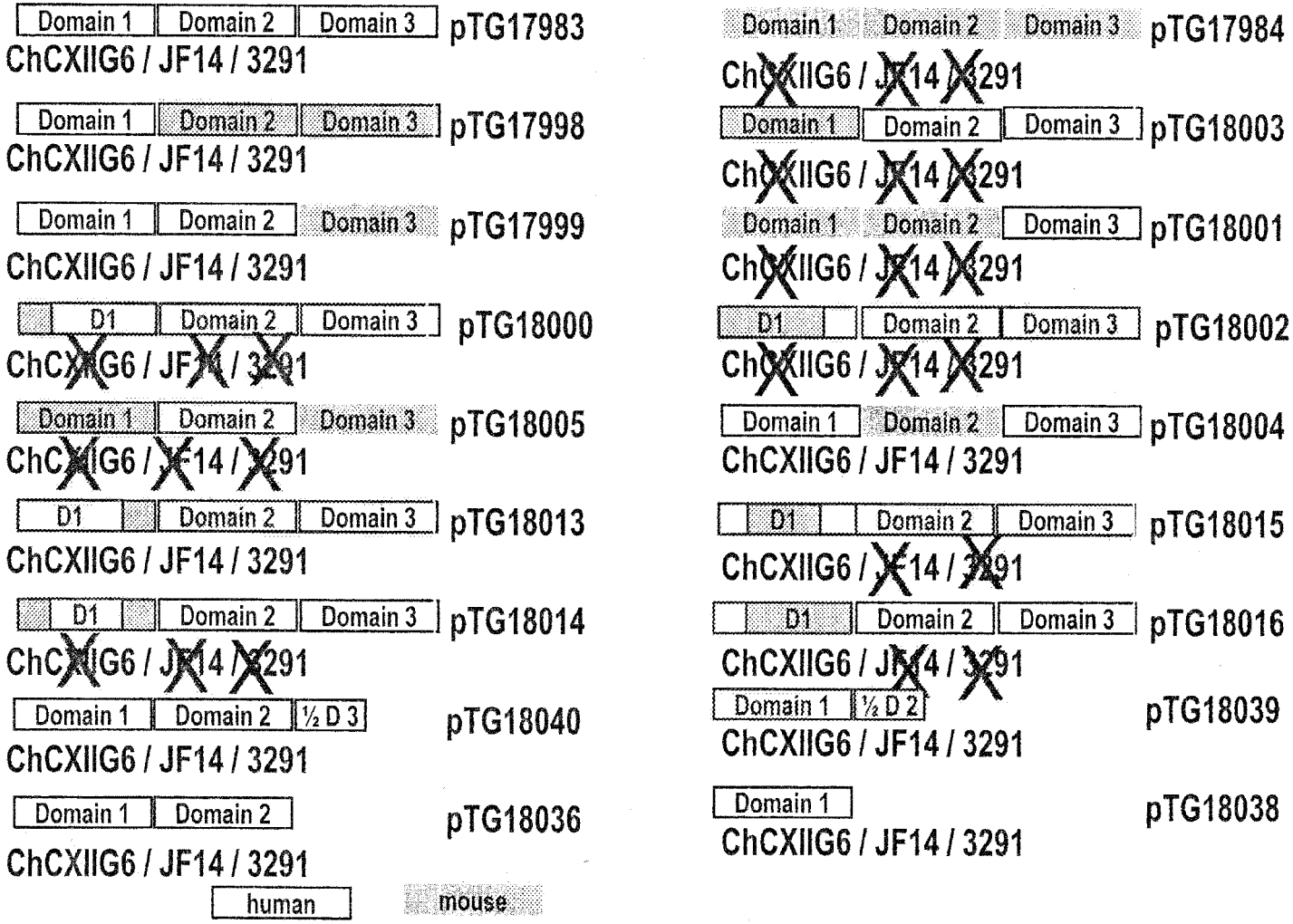


Fig. 20

Underlined in grey = CD115 mouse

Underlined in white = CD115 human

	Ig-like domain 1 (D1) aa 20 to 104	Ig-like domain 2 (D2) aa 105 to 199	Ig-like domain 3 (D3) aa 200 to 298
pTG17983	IPVIE...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG17984	APVIE...YVKDP	AHSWN...VNRVH	PEPPQ...QVVES
pTG17998	IPVIE...YVKDP	AHSWN...VNRVH	PEPPQ...QVVES
pTG17999	IPVIE...YVKDP	ARPWN...VQKVI	PEPPQ...QVVES
pTG18003	APVIE...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG18001	APVIE...YVKDP	AHSWN...VNRVH	PGPPA...RVVES
pTG18005	APVIE...YVKDP	ARPWN...VQKVI	PEPPQ...QVVES
pTG18004	IPVIE...YVKDP	AHSWN...VNRVH	PGPPA...RVVES

	Ig-like domain 1 (D1) aa 20 to 104			Ig-like domain 2 (D2) aa 105 to 199	Ig-like domain 3 (D3) aa 200 to 298
	aa20 to 41	aa42 to 90	aa91 to 104		
pTG18000	APVIE...TVTLR	CVGNG...EPGDP	LGGSA...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG18002	APVIE...TVTLR	CVSNG...ELEDP	LGGSA...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG18013	IPVIE...TVTLR	CVGNG...EPGDP	MAGST...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG18014	APVIE...TVTLR	CVGNG...EPGDP	MAGST...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG18015	IPVIE...TVTLR	CVSNG...ELEDP	LGGSA...YVKDP	ARPWN...VQKVI	PGPPA...RVVES
pTG18016	IPVIE...TVTLR	CVSNG...ELEDP	MAGST...YVKDP	ARPWN...VQKVI	PGPPA...RVVES

	Ig-like domain 1 (D1) aa 20 to 104	Ig-like domain 2 (D2) aa 105 to 199	½ Ig-like domain 3 (D3) aa 200 to 246
pTG18040	IPVIE...YVKDP	ARPWN...VQKVI	PGPPA...TKLAI
pTG18036	IPVIE...YVKDP	ARPWN...VQKVI	
	Ig-like domain 1 (D1) aa 20 to 104	½ Ig-like domain 2 (D2) aa 105 to 157	
pTG18039	IPVIE...YVKDP	ARPWN... NYSFS	
pTG18038	IPVIE...YVKDP		

Fig. 21: Competition curve
between ^{125}I-H27K15 antibody and unlabeled H27K15 on EL4-CD115

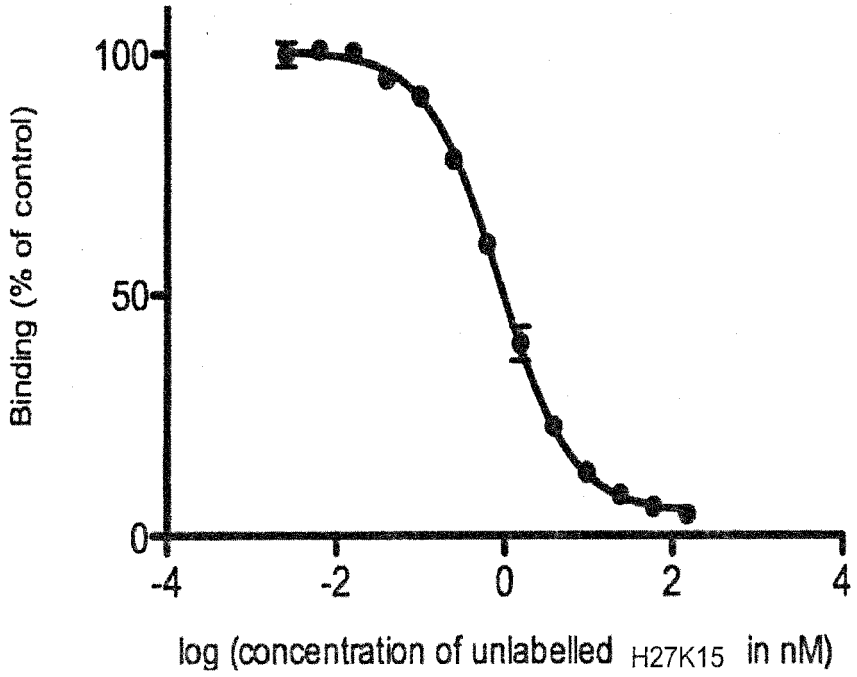


Fig. 22:

Competition curve between ^{125}I-H27K15 antibody and various antibodies on EL4-CD115

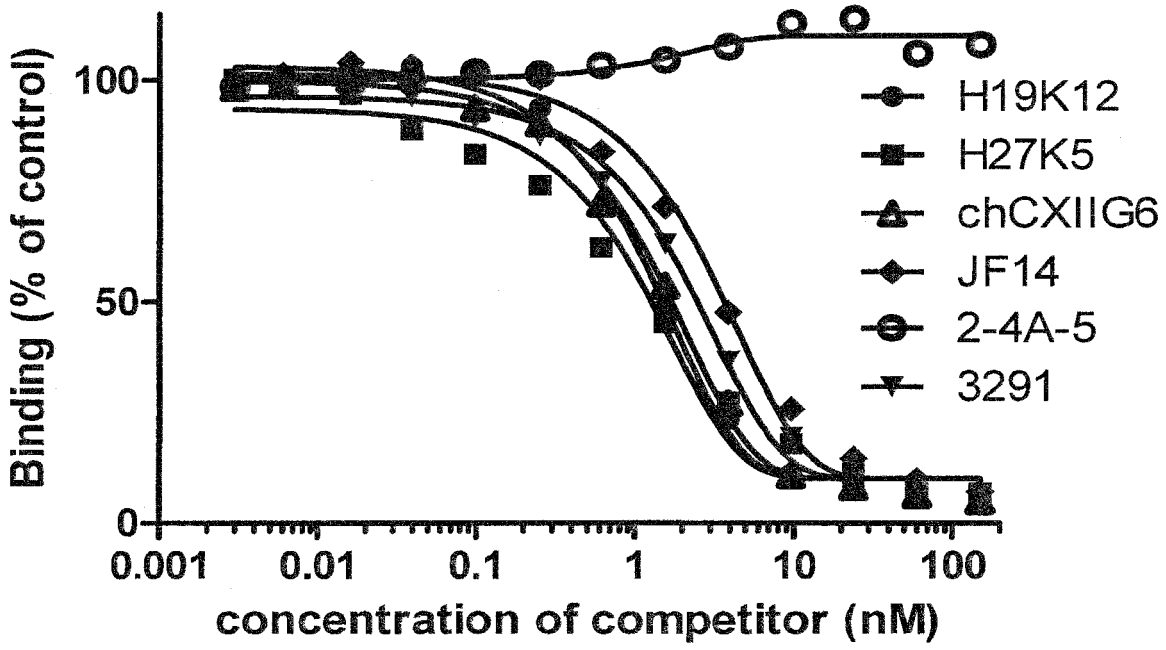


Fig.23 :Postincubation competition: CSF1 biot (1hour), then mAb (1hour)

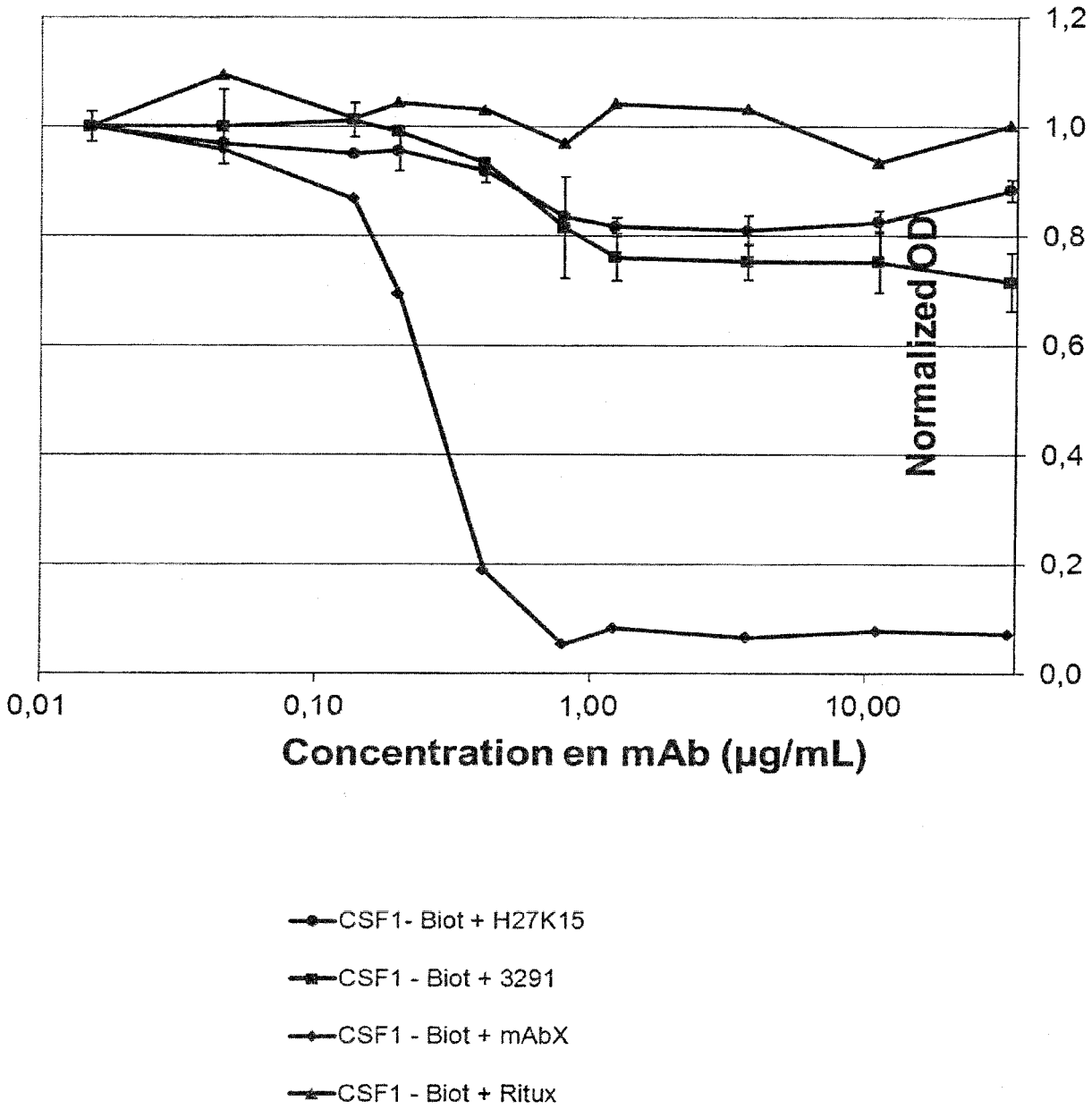
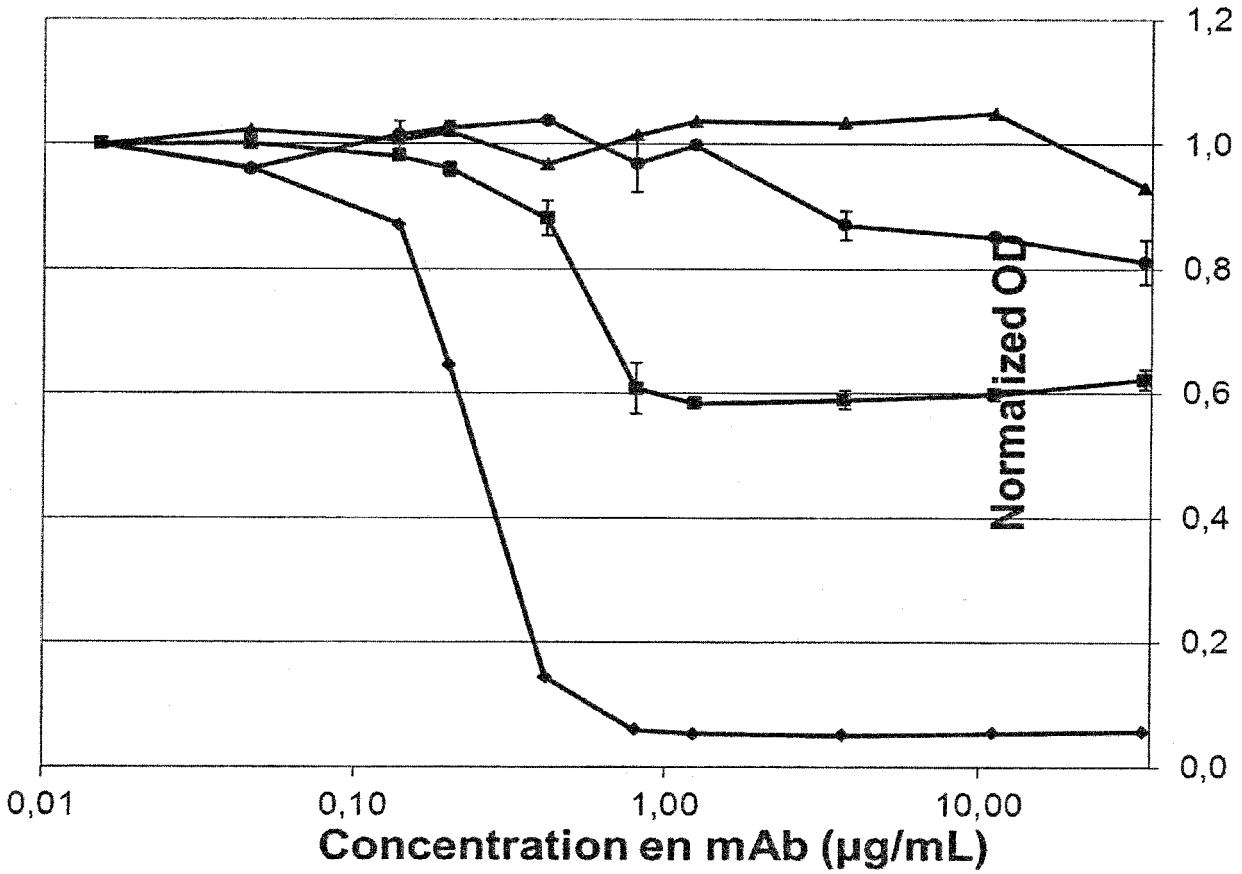


Fig. 24 :Preincubation competition:
mAb (1hour), then CSF1-biot (1hour)



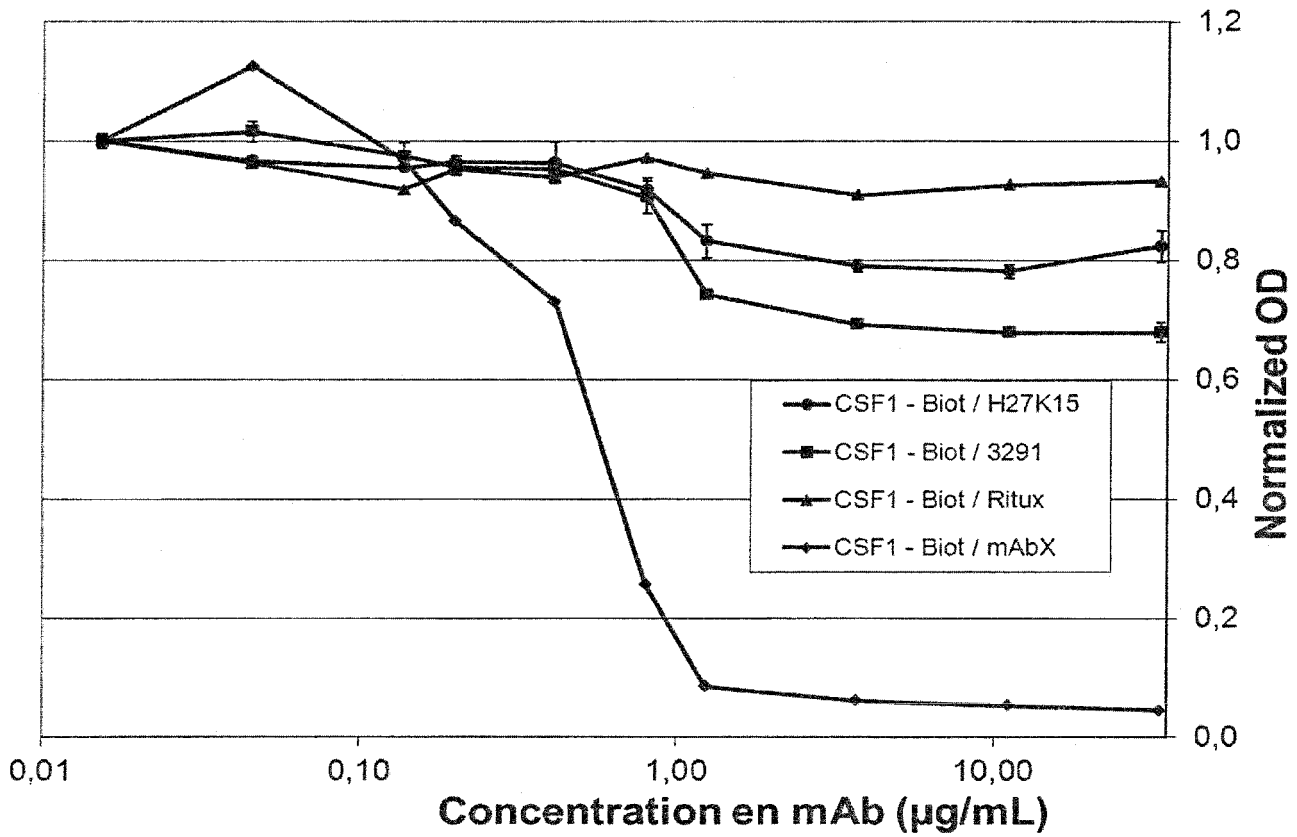
H27K15 + CSF1 - Biot

3291 + CSF1 - Biot

mAbX + CSF1 - Biot

Ritux + CSF1 - Biot

Fig.25 : Coincubation competition: mAb and CSF1-biot together (1hour)



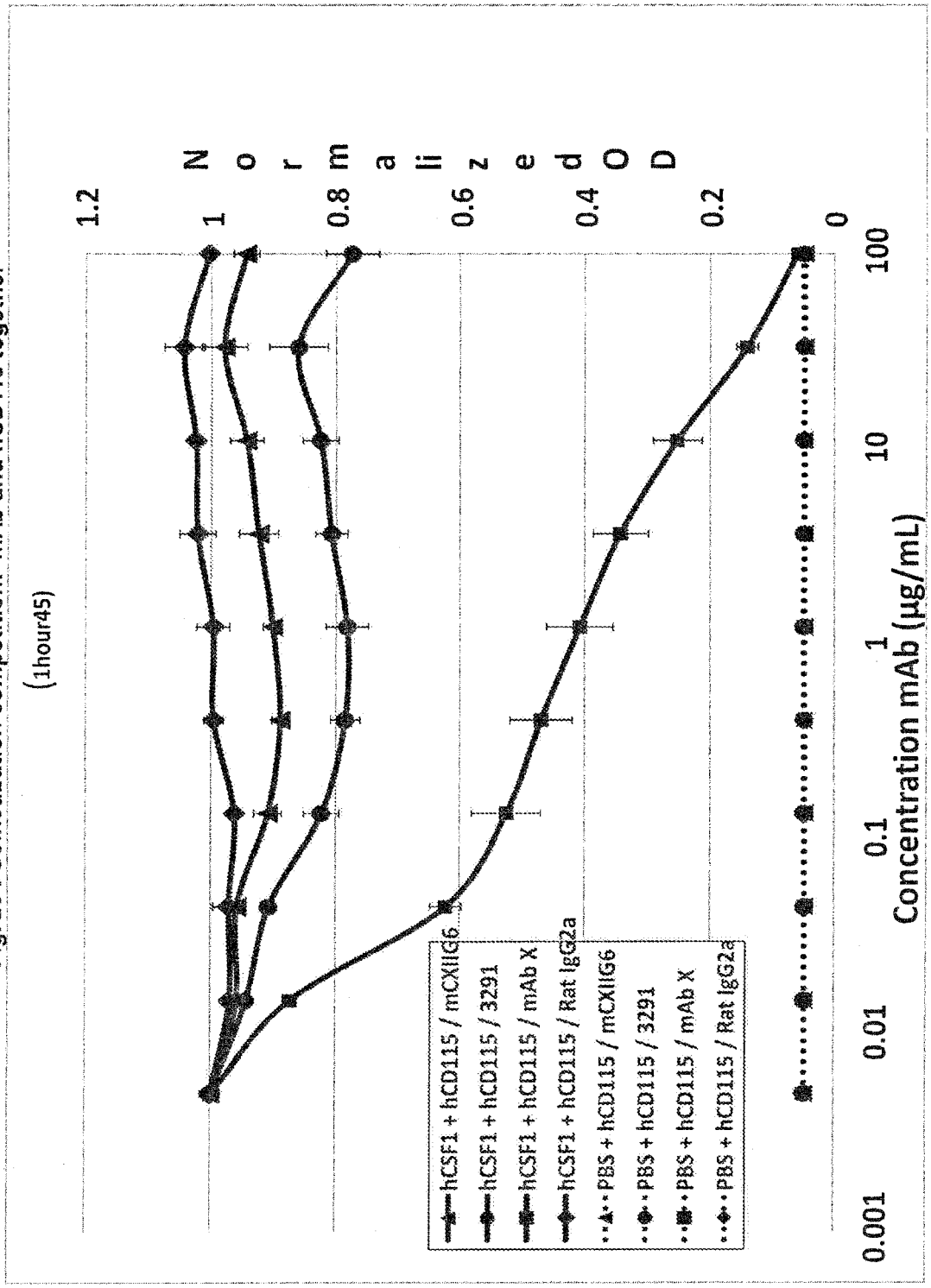
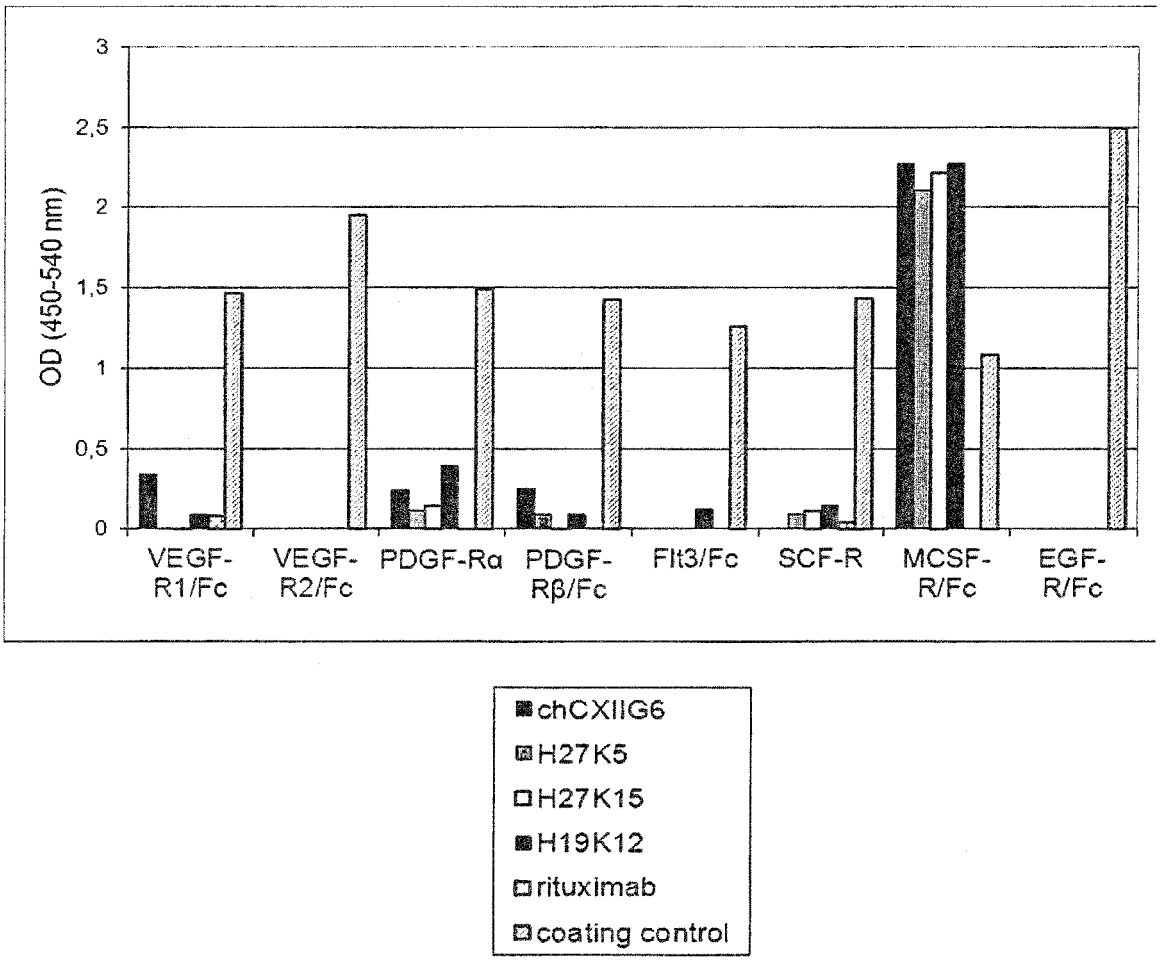


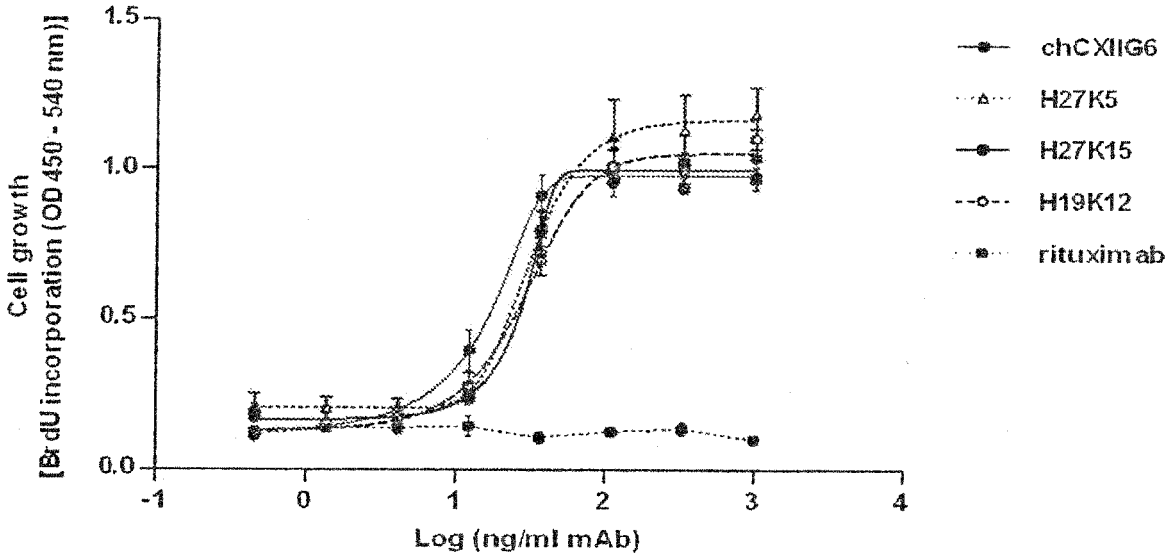
Fig. 26 : Coincubation competition: mAb and hCD115 together (1hour45)

Fig. 27 : Lack of cross-reactivity of hCXIIG6 variants with tyrosine kinase receptors from type III subfamily other than CD115



Bars correspond to values measured from single wells and are representative of 2 independent experiments.

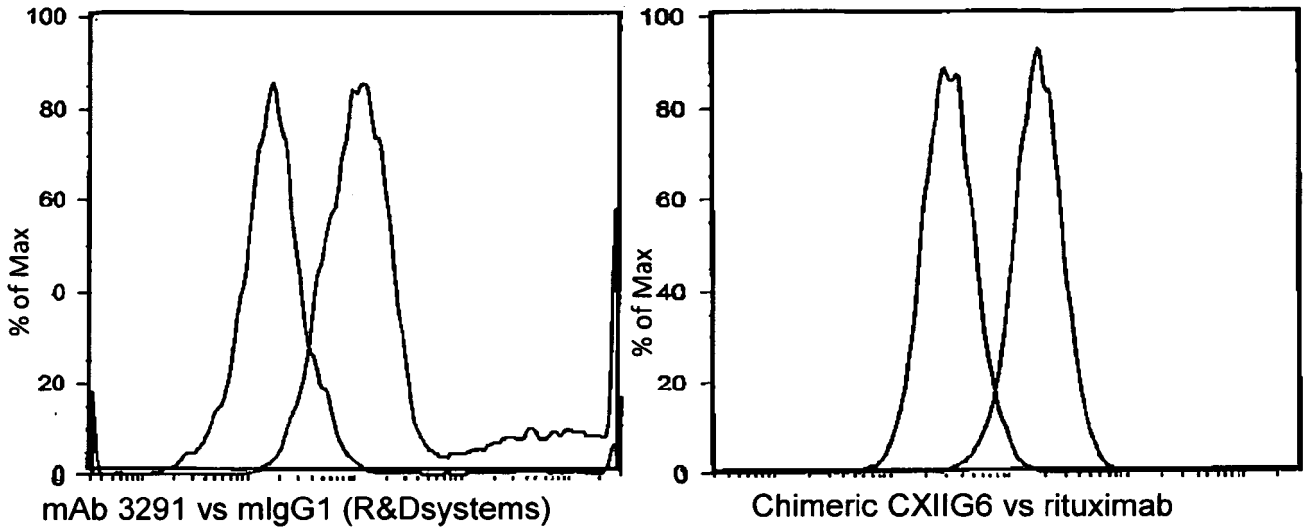
Fig. 28 : Blockade of soluble CD115 by hCXIIG6 variants and chCXIIG6 in the M-NFS-60-cell based assay



Neutralization Dose$_{50}$ (ND$_{50}$):
(five-parameter logistic equation)
H27K5 = 30.7 ng/ml
H27K15 = 29.1 ng/ml
H19K12 = 29.8 ng/ml
chCXIIG6 18.1 ng/ml

Fig. 29 : Inhibition of CSF-1-dependent proliferation of AML5 cells by hCXIIG6 variants

29A : AML5 cells express surface CD115



29B : AML5 cell growth is stimulated by CSF-1 in a dose-dependent fashion

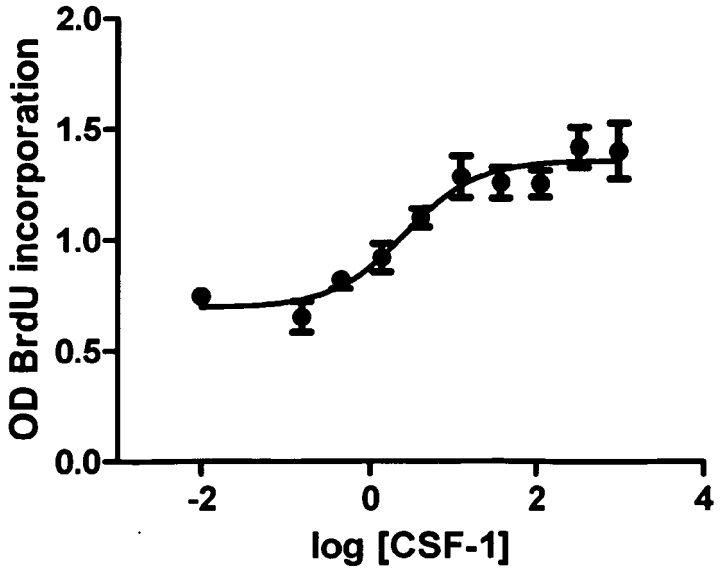
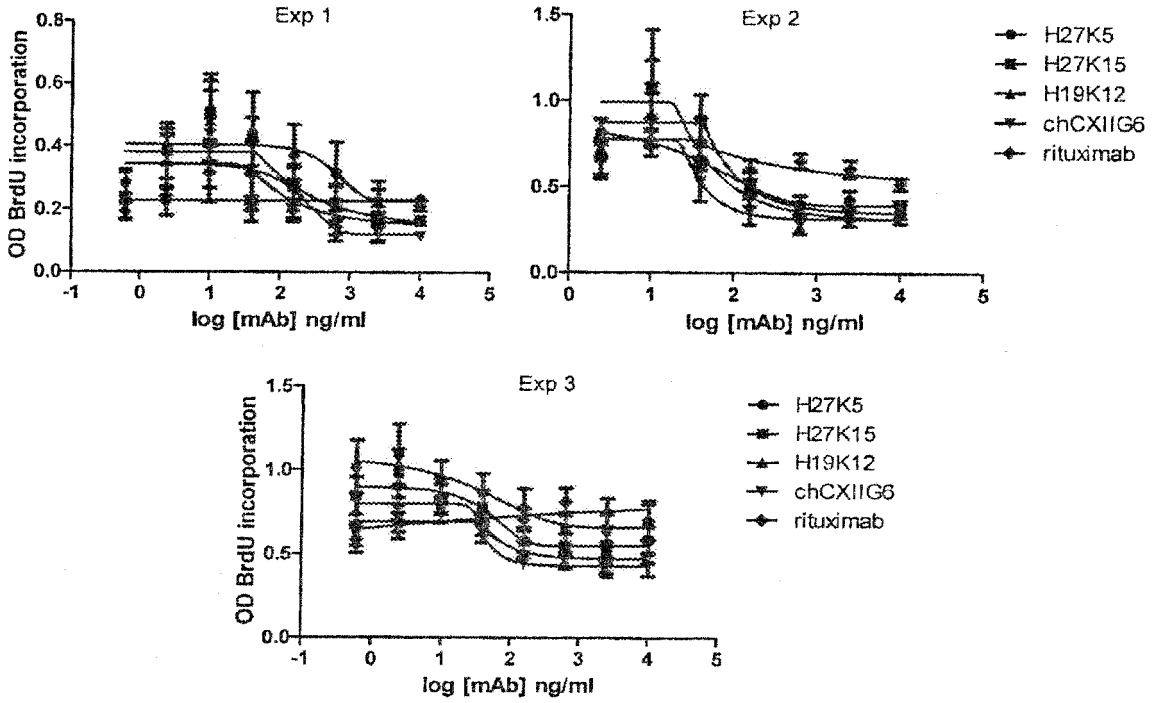


Fig. 29 : Inhibition of CSF-1-dependent proliferation of AML5 cells by hCXIIG6 variants

29C : hCXIIG6 variants and chCXIIG6 inhibit CSF-1-dependent proliferation of AML5 cells.

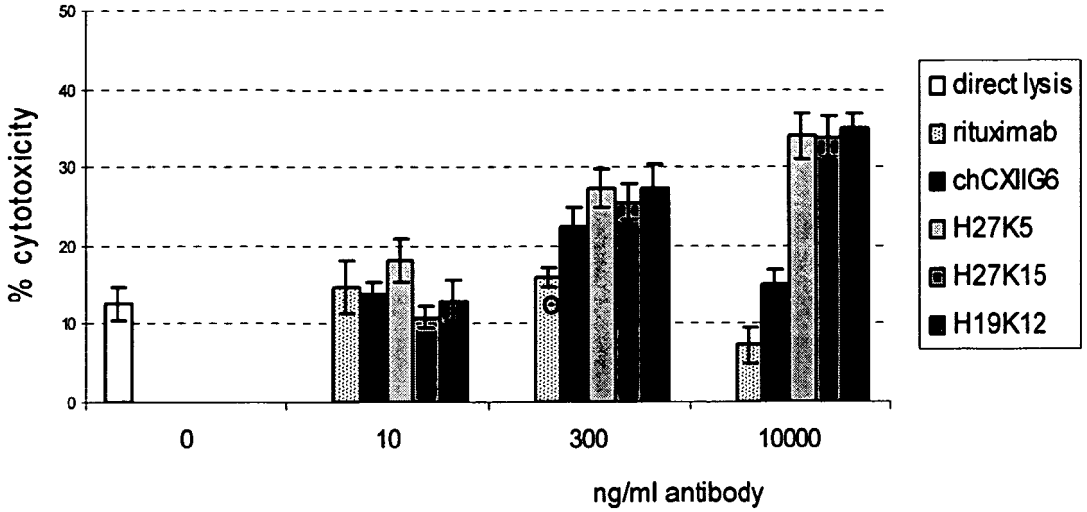


29 D : EC50 and R square values calculated by GraphPad Prism from the results shown in C

	EC50 / *R square*			
	H27K5	**H27K15**	**H19K12**	**chCXIIG6**
Exp 1	**608** / *0,19*	**188** / *0,36*	**105** / *0,23*	**217** / *0,27*
Exp 2	**50** / *0,74*	**86** / *0,56*	**46** / *0,62*	**37** / *0,57*
Exp 3	**40** / *0,22*	**54** / *0,34*	**48** / *0,41*	**49** / *0,44*

Fig. 30 : ADCC activity of hCXIIG6 variants on EL4-CD115 target cells

30A



30B

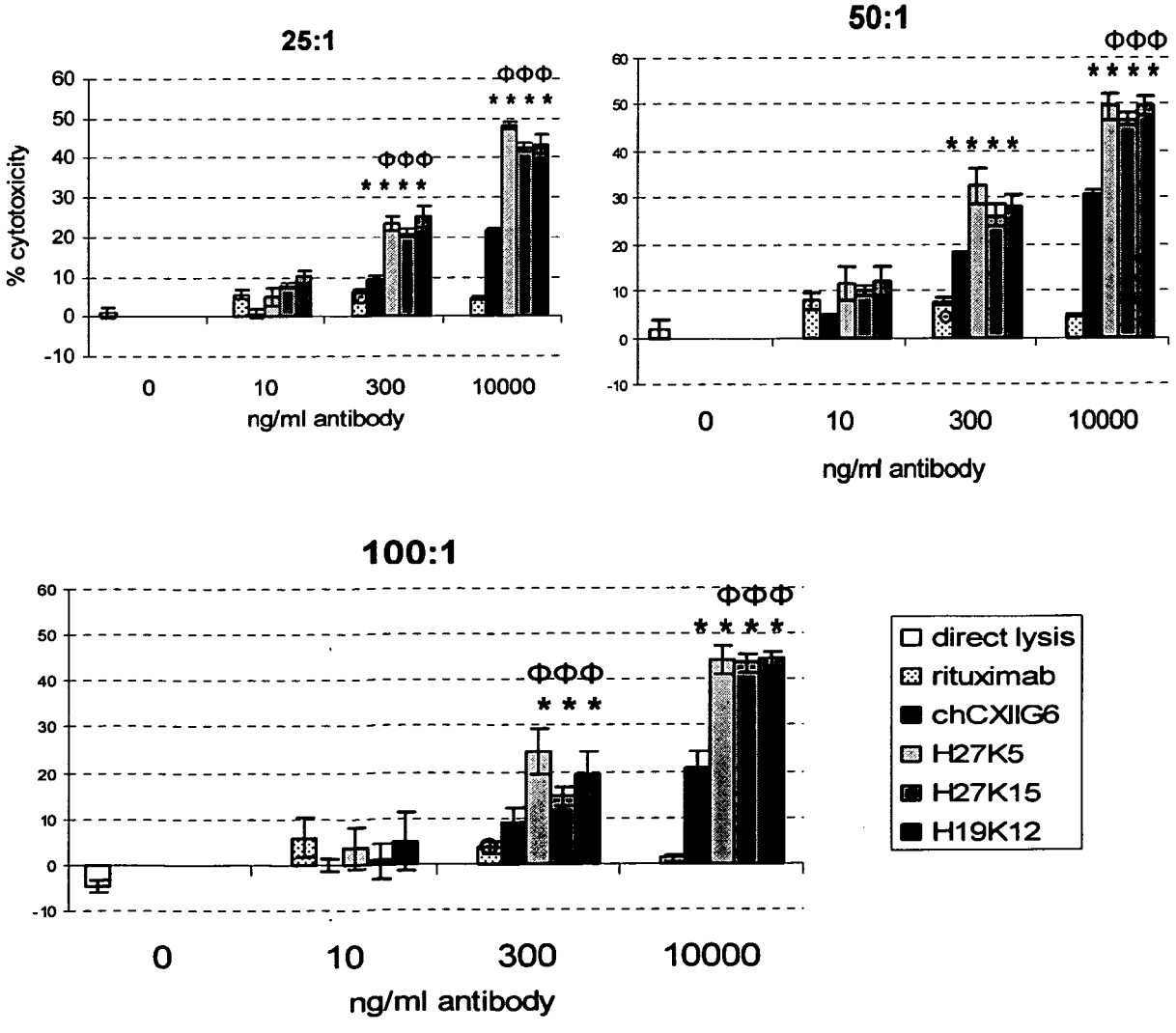
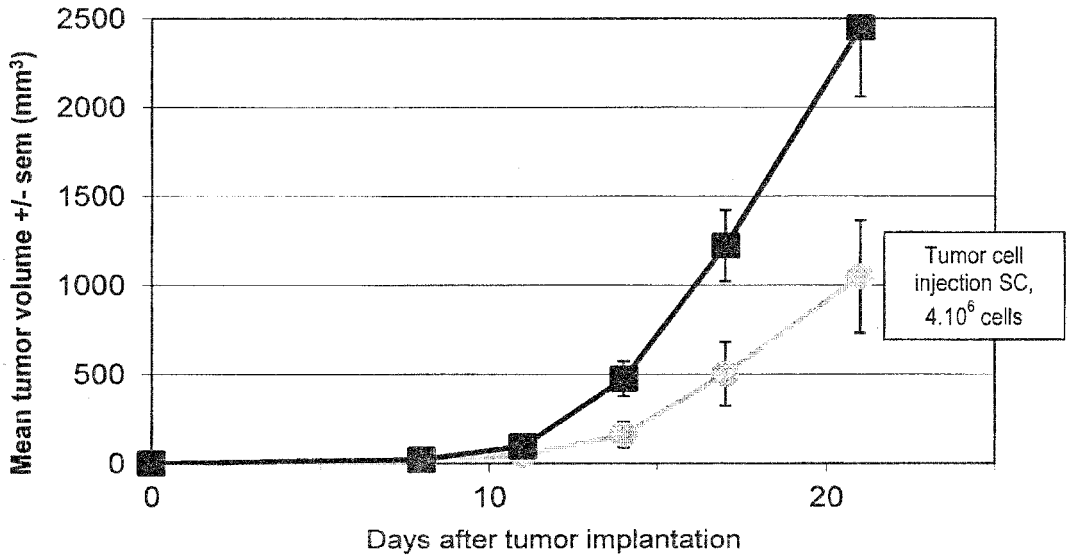


Fig. 31 : Therapeutic effect of chimeric CXIIG6 in the BeWo choriocarcinoma tumor model

31A



31B

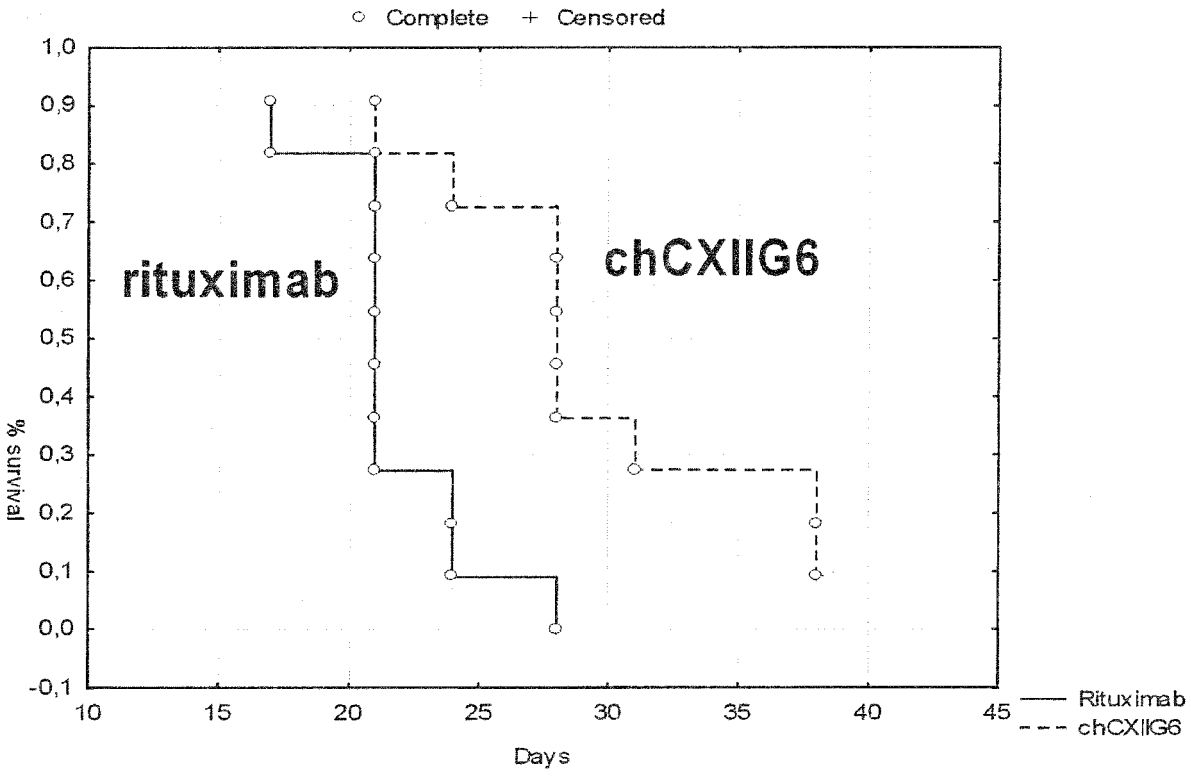


Fig. 32

sequence "H27" –the corresponding variable region is underlined (SEQ ID N0 :37)

Met Tyr Leu Gly Leu Asn Tyr Val Phe Ile Val Phe Leu Leu Asn Gly Val Gln Ser Glu

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala Trp Met Asp Trp Val Arg Gln Ala Pro

Gly Lys Gly Leu Glu Trp Val Ala Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Phe

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser Val

Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Gly Val Tyr Tyr Cys Thr Arg Val

Lys Val Gly Phe Asp Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

Leu Ser Leu Ser Pro Gly Lys

sequence "H19" –the corresponding variable region is underlined (SEQ ID N0 :38)

Met Tyr Leu Gly Leu Asn Tyr Val Phe Ile Val Phe Leu Leu Asn Gly Val Gln Ser Glu

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala Trp Met Asp Trp Val Arg Gln Ser Pro

Glu Met Gly Leu Glu Trp Val Ala Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Phe

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser Val

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Gly Ile Tyr Tyr Cys Thr Arg Val

Lys Val Gly Phe Asp Asn Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser

Leu Ser Leu Ser Pro Gly Lys

Sequence "K5" –the corresponding variable region is underlined (SEQ ID N0 :39)

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr Asp Ala Arg Cys

<u>Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Val Ser Val Gly Asp Arg Val Thr</u>

<u>Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro</u>

Gly Lys Ala Pro Lys Leu Leu Val His Ala Ala Thr Asn Leu Glu Ser Gly Val Pro Ser

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Arg Thr Phe Gly Gln

Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

Sequence "K12" –the corresponding variable region is underlined (SEQ ID N0 :40)

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr Asp Ala Arg Cys

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr

Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Asp

Gly Lys Ser Pro Gln Leu Leu Val His Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Arg Thr Phe Gly Gly

Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

Sequence "K15" –the corresponding variable region is underlined (SEQ ID N0 :41)

Met Ser Val Pro Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr Asp Ala Arg Cys

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr

Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Leu Leu Leu His Ala Ala Thr Asn Leu Ala Ser Gly Val Pro Ser

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Arg Thr Phe Gly Gln

Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

sequence "VH27" –variable region (SEQ ID N0 :42)

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala Trp Met Asp Trp Val Arg Gln Ala Pro

Gly Lys Gly Leu Glu Trp Val Ala Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Phe

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser Val

Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Gly Val Tyr Tyr Cys Thr Arg Val

Lys Val Gly Phe Asp Asn Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

sequence "VH19" –variable region (SEQ ID N0 :43)

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala Trp Met Asp Trp Val Arg Gln Ser Pro

Glu Met Gly Leu Glu Trp Val Ala Glu Ile Arg Ser Lys Ala Asn Asn His Ala Thr Phe

Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser Val

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Gly Ile Tyr Tyr Cys Thr Arg Val

Lys Val Gly Phe Asp Asn Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser

Sequence "VK5" –variable region (SEQ ID N0 :44)

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Val Ser Val Gly Asp Arg Val Thr

Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Leu Leu Val His Ala Ala Thr Asn Leu Glu Ser Gly Val Pro Ser

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Arg Thr Phe Gly Gln

Gly Thr Lys Leu Glu Ile Lys

Sequence "VK12" –variable region (SEQ ID N0 :45)

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr

Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Asp

Gly Lys Ser Pro Gln Leu Leu Val His Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Arg Thr Phe Gly Gly

Gly Thr Lys Leu Glu Ile Lys

Sequence "VK15" –variable region (SEQ ID N0 :46)

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr

Ile Thr Cys Arg Ala Ser Glu Asn Ile Tyr Ser Asn Leu Ala Trp Tyr Gln Gln Lys Pro

Gly Lys Ala Pro Lys Leu Leu Leu His Ala Ala Thr Asn Leu Ala Ser Gly Val Pro Ser

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Arg Thr Phe Gly Gln

Gly Thr Lys Leu Glu Ile Lys

Sequence of human CSF1, 1-444 (SEQ ID N0:47)

MetThrAlaProGlyAlaAlaGlyArgCysProProThrThrTrpLeuGlySerLeuLeu

LeuLeuValCysLeuLeuAlaSerArgSerIleThrGluGluValSerGluTyrCysSer

HisMetIleGlySerGlyHisLeuGlnSerLeuGlnArgLeuIleAspSerGlnMetGlu

ThrSerCysGlnIleThrPheGluPheValAspGlnGluGlnLeuLysAspProValCys

TyrLeuLysLysAlaPheLeuLeuValGlnAspIleMetGluAspThrMetArgPheArg

AspAsnThrProAsnAlaIleAlaIleValGlnLeuGlnGluLeuSerLeuArgLeuLys

SerCysPheThrLysAspTyrGluGluHisAspLysAlaCysValArgThrPheTyrGlu

ThrProLeuGlnLeuLeuGluLysValLysAsnValPheAsnGluThrLysAsnLeuLeu

AspLysAspTrpAsnIlePheSerLysAsnCysAsnAsnSerPheAlaGluCysSerSer

GlnAspValValThrLysProAspCysAsnCysLeuTyrProLysAlaIleProSerSer

AspProAlaSerValSerProHisGlnProLeuAlaProSerMetAlaProValAlaGly

LeuThrTrpGluAspSerGluGlyThrGluGlySerSerLeuLeuProGlyGluGlnPro

LeuHisThrValAspProGlySerAlaLysGlnAlaProProArgSerThrCysGlnSer

PheGluProProGluThrProValValLysAspSerThrIleGlyGlySerProGlnPro

ArgProSerValGlyAlaPheAsnProGlyMetGluAspIleLeuAspSerAlaMetGly

ThrAsnTrpValProGluGluAlaSerGlyGluAlaSerGluIleProValProGlnGly

ThrGluLeuSerProSerArgProGlyGlyGlySerMetGlnThrGluProAlaArgPro

SerAsnPheLeuSerAlaSerSerProLeuProAlaSerAlaLysGlyGlnGlnProAla

AspValThrGlyThrAlaLeuProArgValGlyProValArgProThrGlyGlnAspTrp

AsnHisThrProGlnLysThrAspHisProSerAlaLeuLeuArgAspProProGluPro

GlySerProArgIleSerSerLeuArgProGlnGlyLeuSerAsnProSerThrLeuSer

AlaGlnProGlnLeuSerArgSerHisSerSerGlySerValLeuProLeuGlyGluLeu

GluGlyArgArg