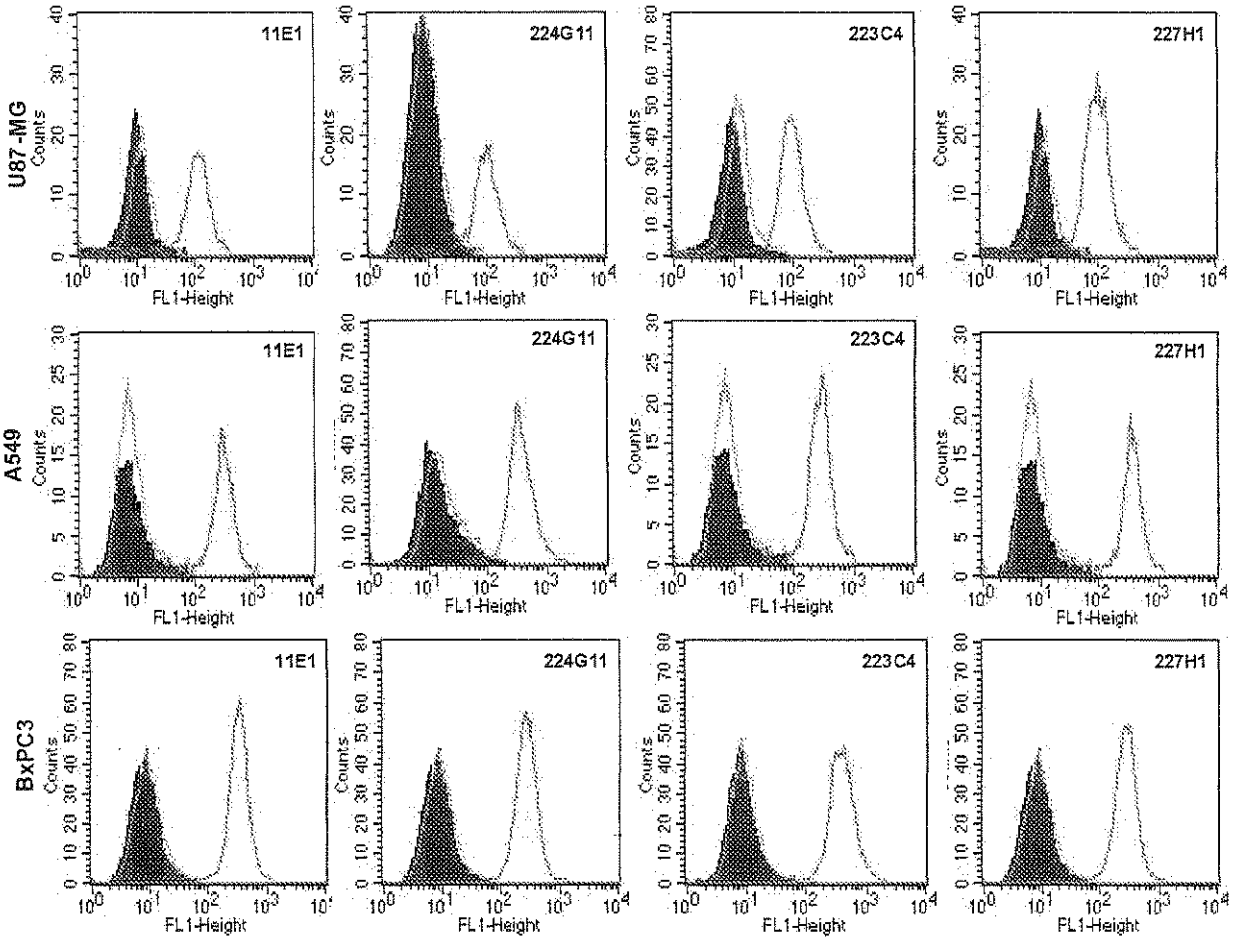


FIGURE 1

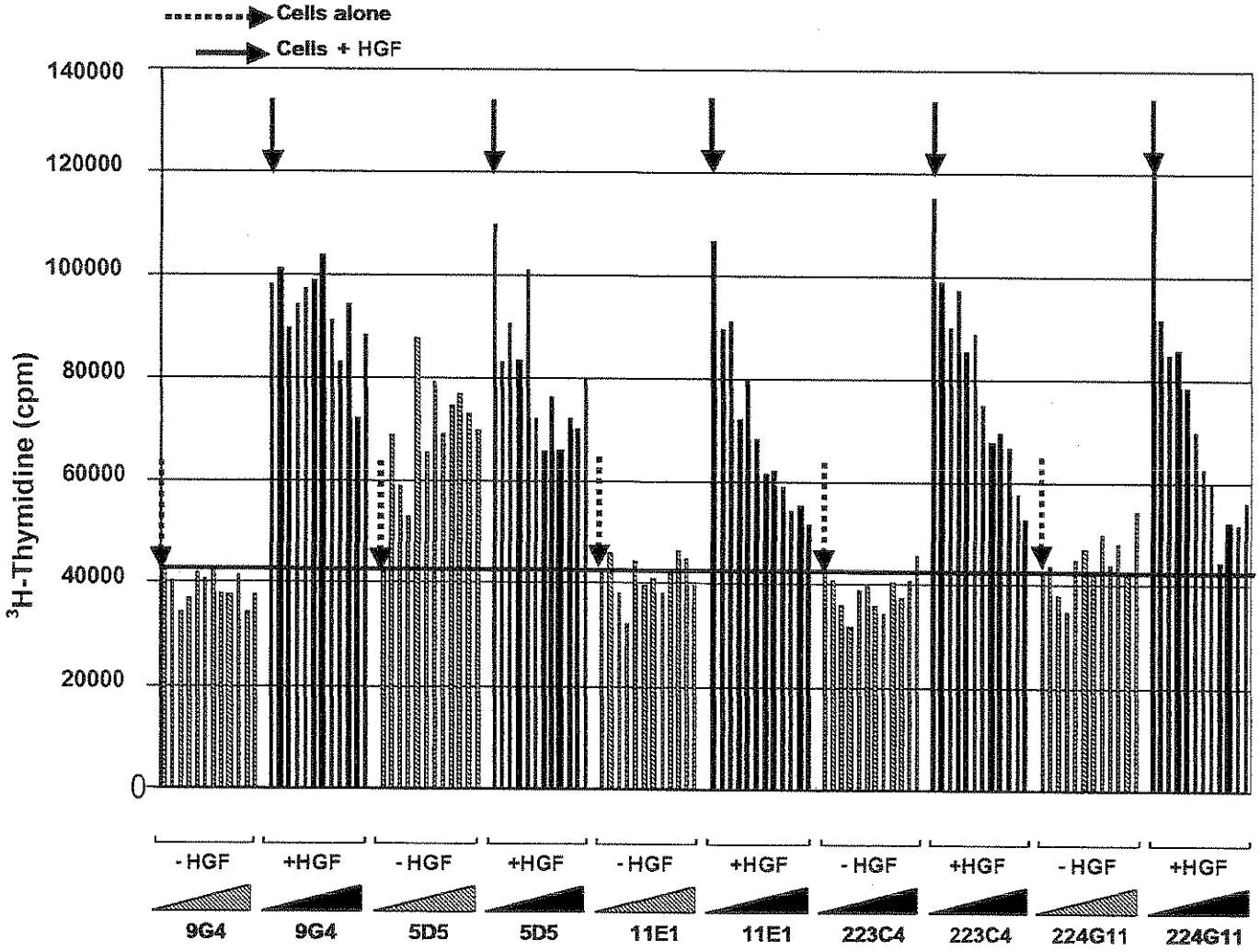

Cells alone
Cells + HGF
140000
120000
100000
80000
60000
40000
20000
0
^{3}H-Thymidine (cpm)
-HGF
+HGF
-HGF
+HGF
-HGF
+HGF
-HGF
+HGF
-HGF
+HGF
9G4
9G4
5D5
5D5
11E1
11E1
223C4
223C4
224G11
224G11

FIGURE 2A

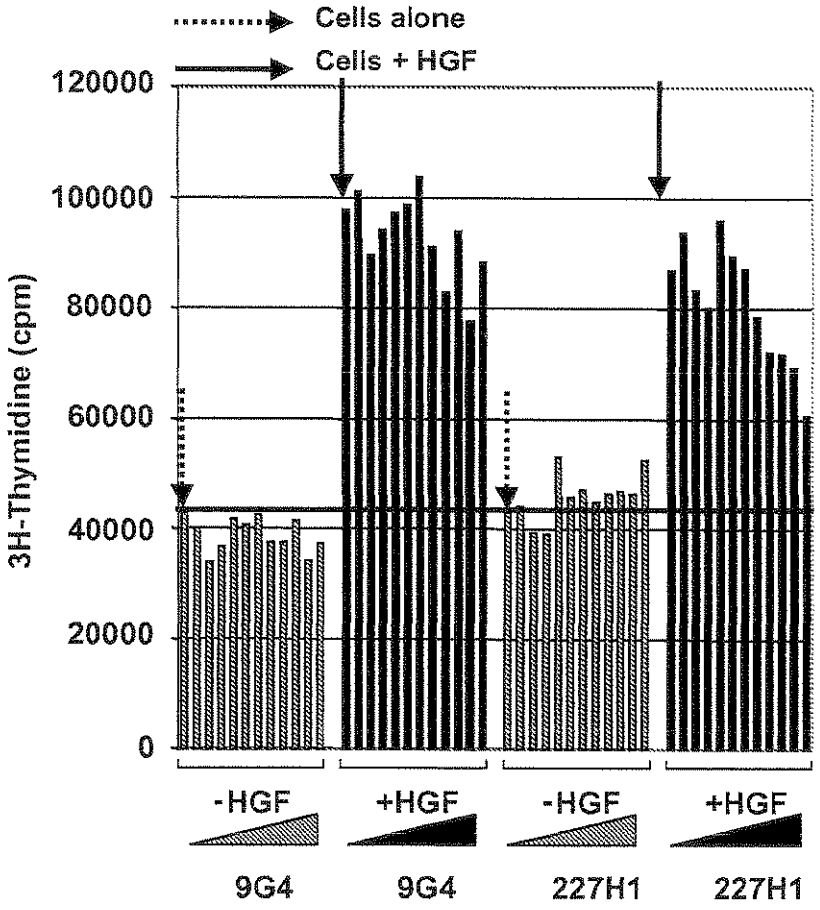

Cells alone
Cells + HGF
120000
100000
80000
60000
40000
20000
0
3H-Thymidine (cpm)
-HGF
+HGF
-HGF
+HGF
9G4
9G4
227H1
227H1

FIGURE 2B

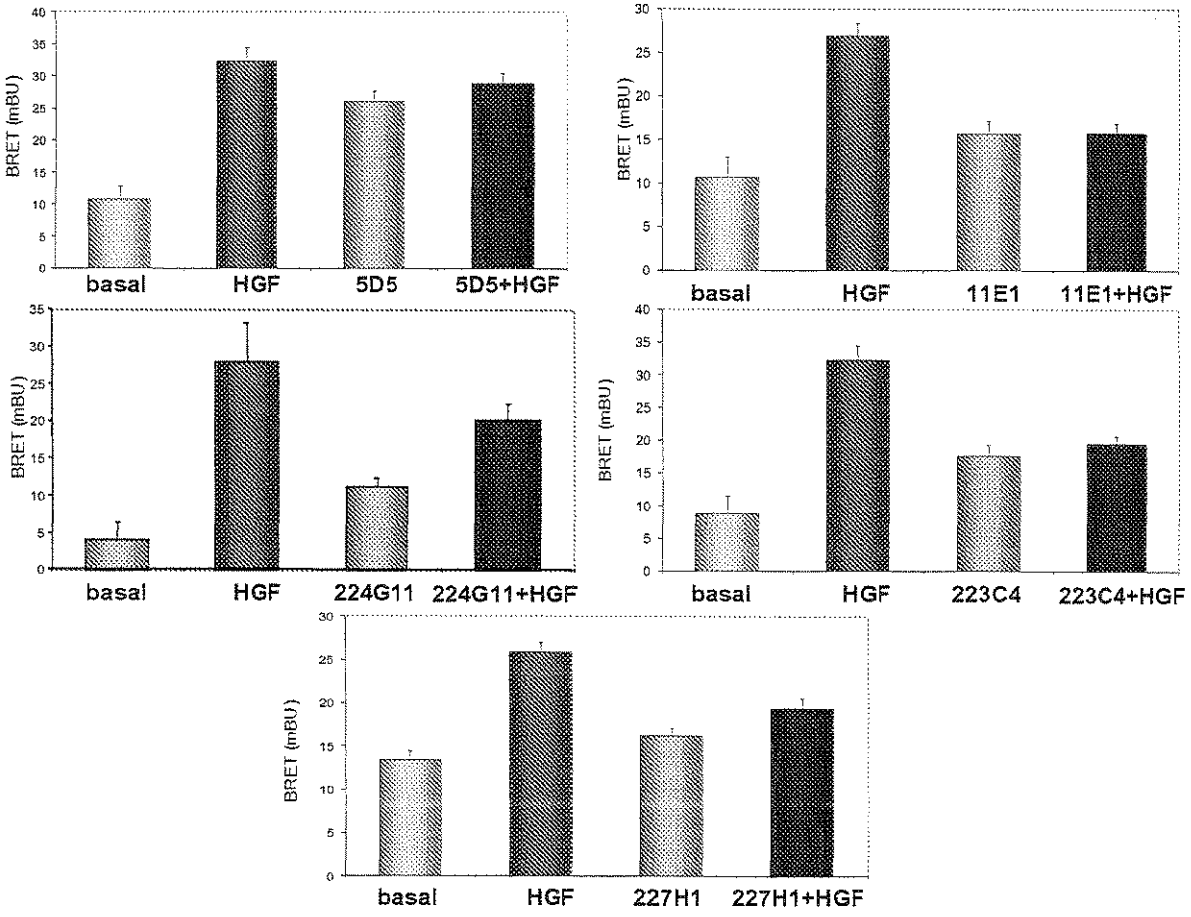
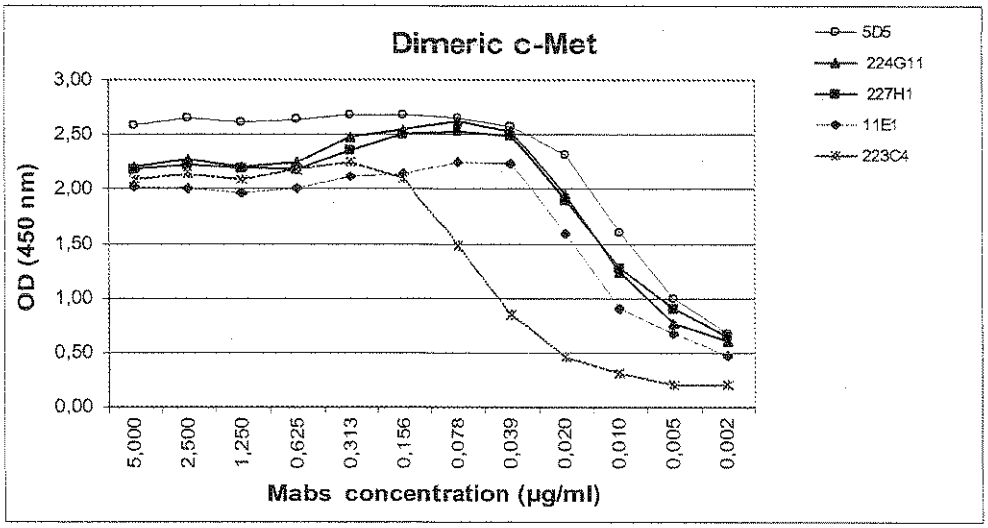
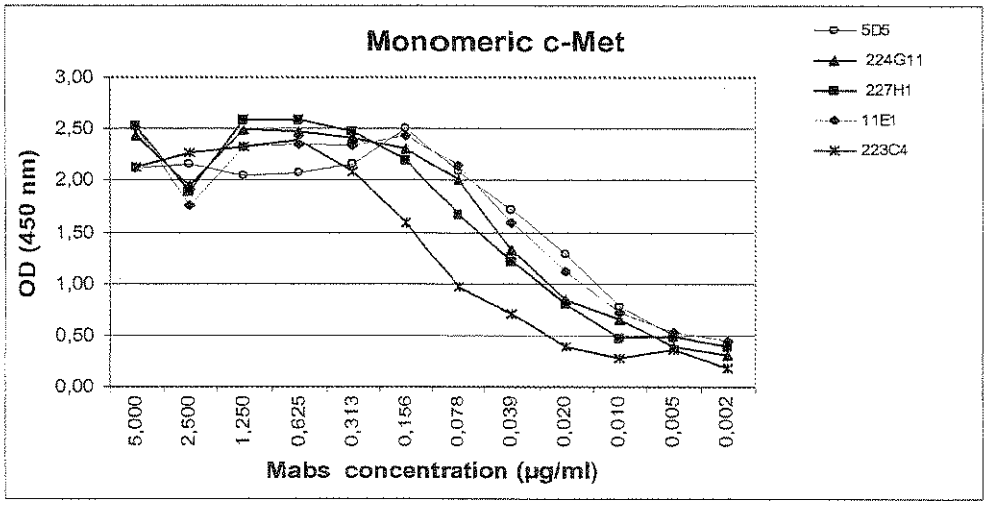

BRET (mBU)
basal
HGF
5D5
5D5+HGF
11E1
11E1+HGF
224G11
224G11+HGF
223C4
223C4+HGF
227H1
227H1+HGF

FIGURE 3


Dimeric c-Met
OD (450 nm)
3,00
2,50
2,00
1,50
1,00
0,50
0,00
5,000
2,500
1,250
0,625
0,313
0,156
0,078
0,039
0,020
0,010
0,005
0,002
Mabs concentration (µg/ml)
5D5
224G11
227H1
11E1
223C4


Monomeric c-Met
OD (450 nm)
3,00
2,50
2,00
1,50
1,00
0,50
0,00
5,000
2,500
1,250
0,625
0,313
0,156
0,078
0,039
0,020
0,010
0,005
0,002
Mabs concentration (µg/ml)
5D5
224G11
227H1
11E1
223C4

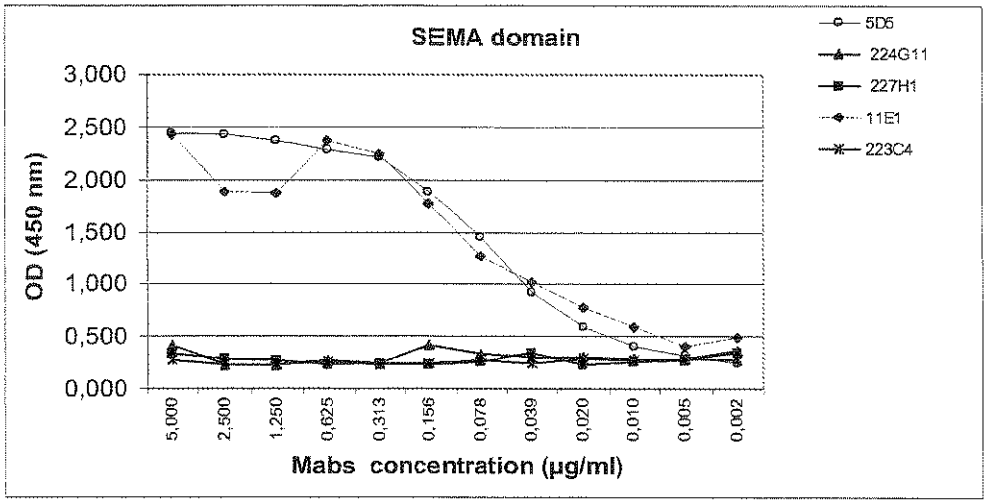

SEMA domain
OD (450 nm)
3,000
2,500
2,000
1,500
1,000
0,500
0,000
5,000
2,500
1,250
0,625
0,313
0,156
0,078
0,039
0,020
0,010
0,005
0,002
Mabs concentration (µg/ml)
5D5
224G11
227H1
11E1
223C4

FIGURE 4

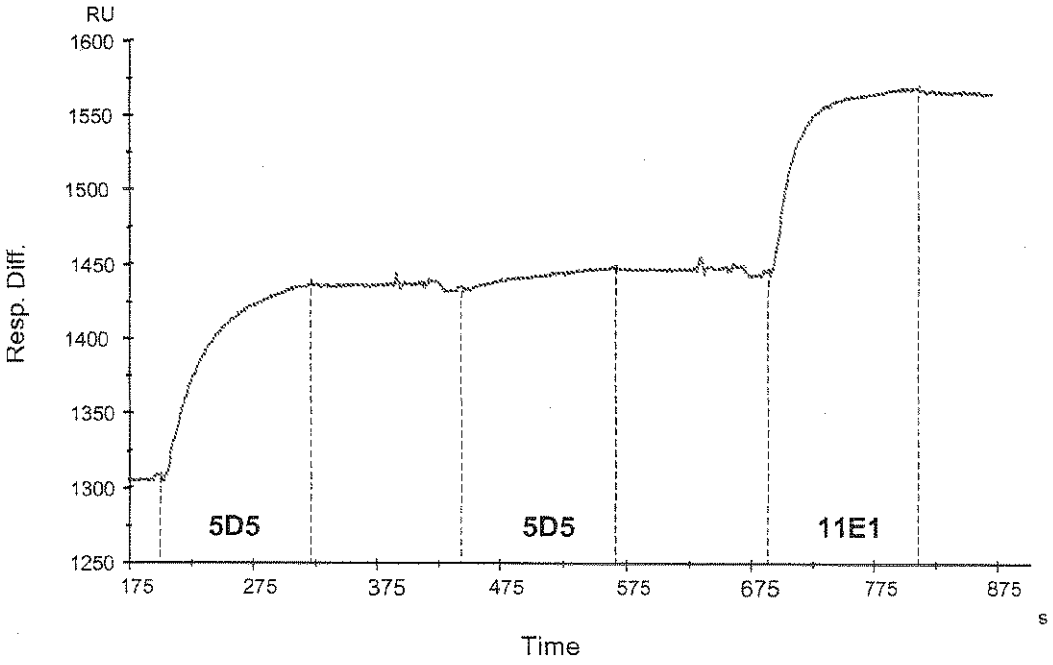


FIGURE 5A

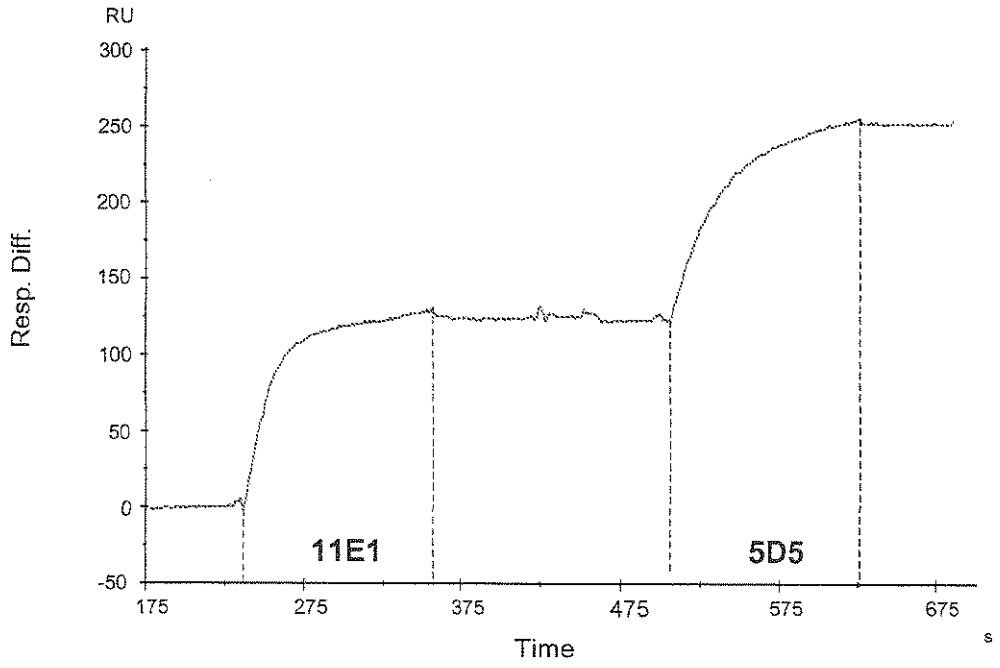


FIGURE 5B

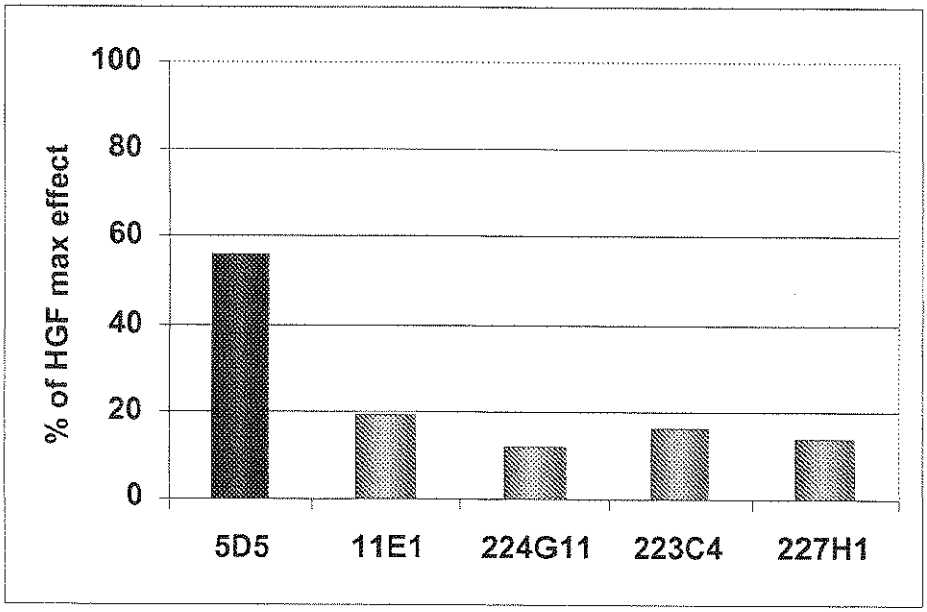


FIGURE 6A

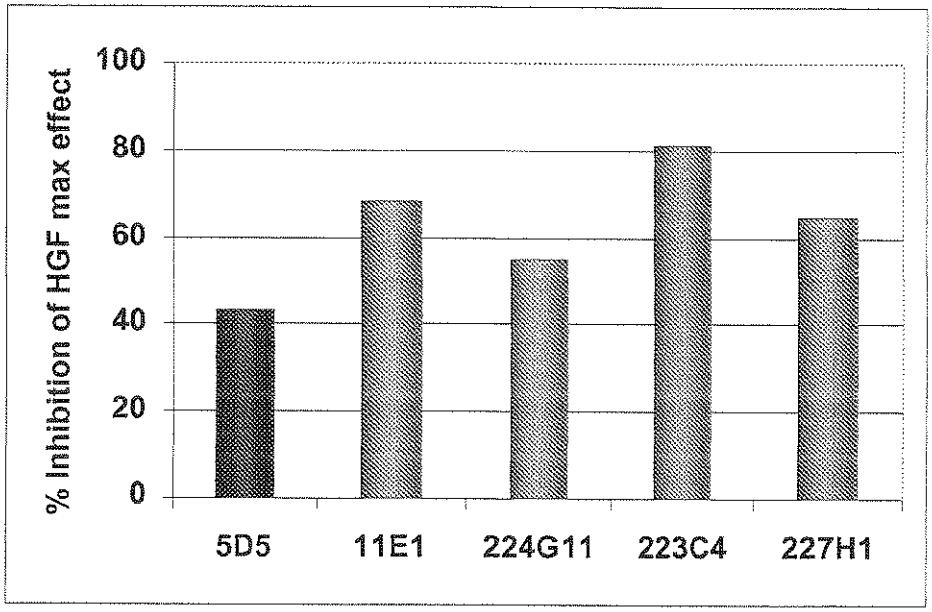


FIGURE 6B

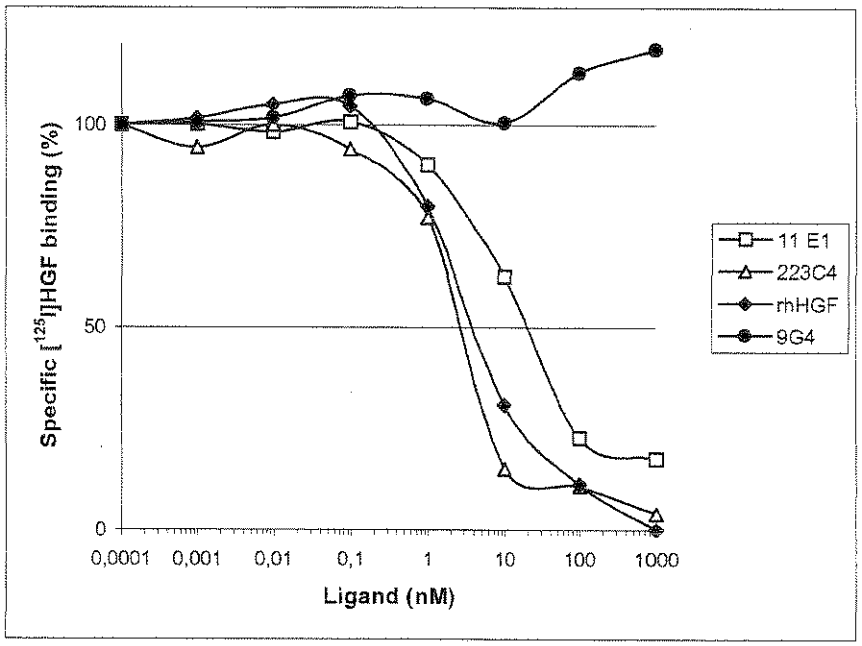


FIGURE 7A

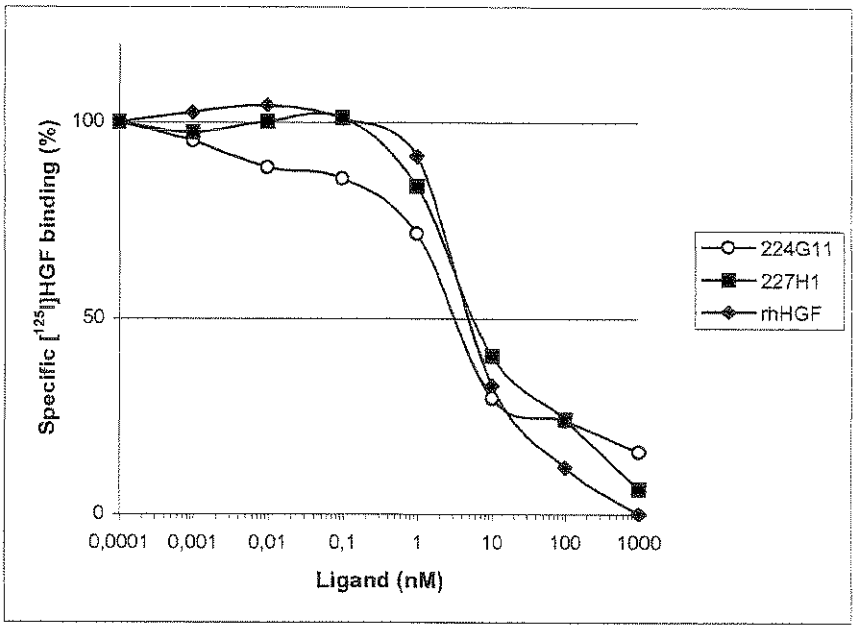


FIGURE 7B

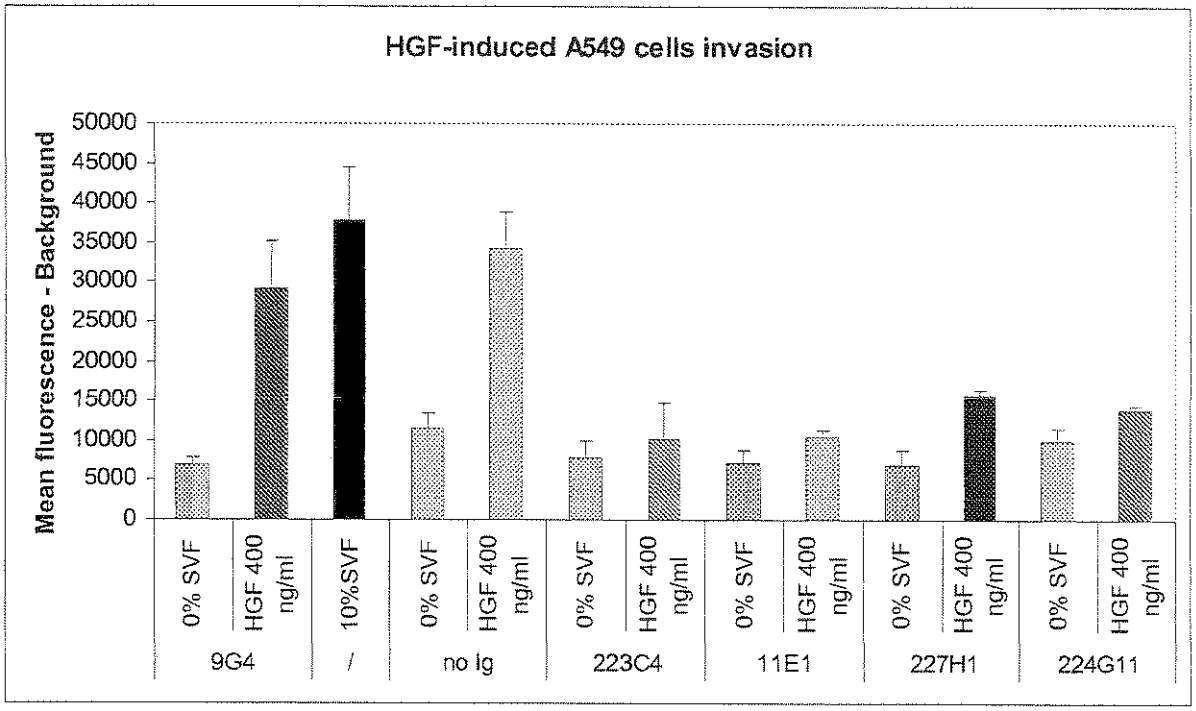

HGF-induced A549 cells invasion
Mean fluorescence - Background
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0% SVF
HGF 400 ng/ml
10%SVF
9G4
/
no Ig
223C4
11E1
227H1
224G11

FIGURE 8

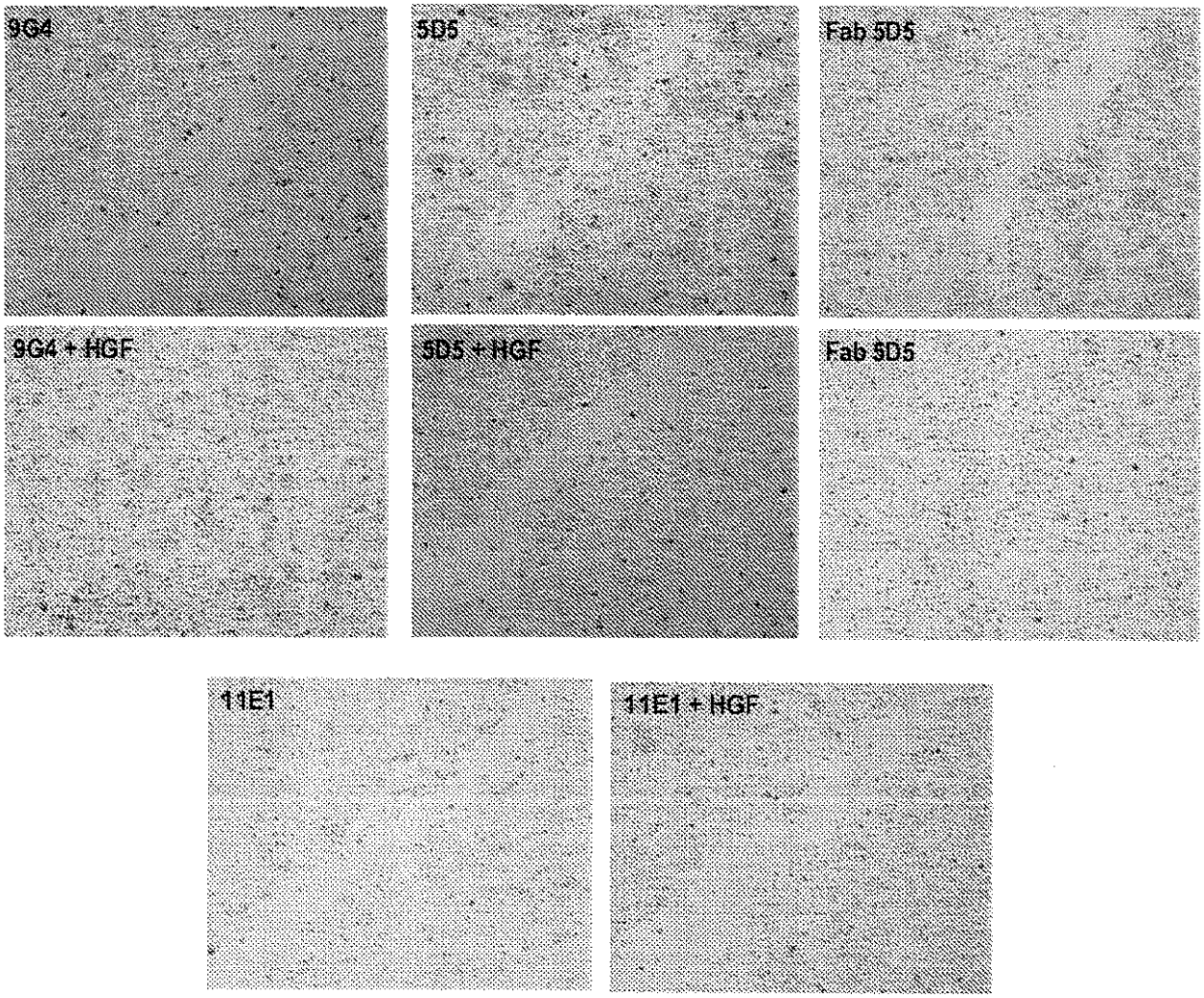


FIGURE 9

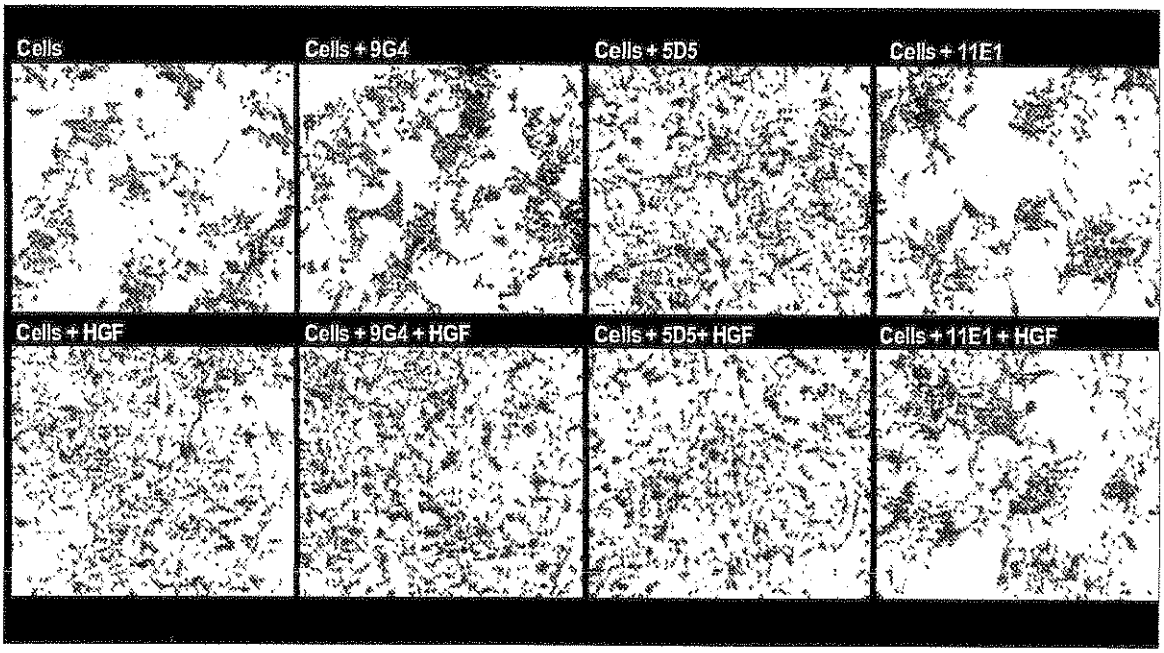


FIGURE 10A

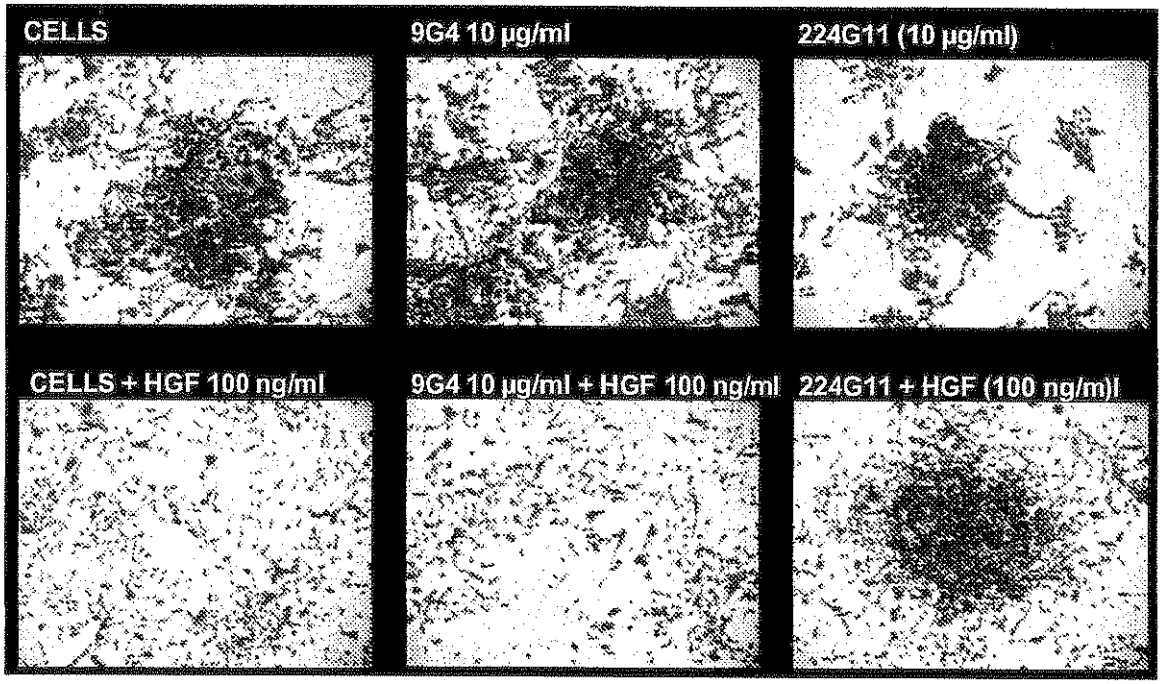


FIGURE 10B

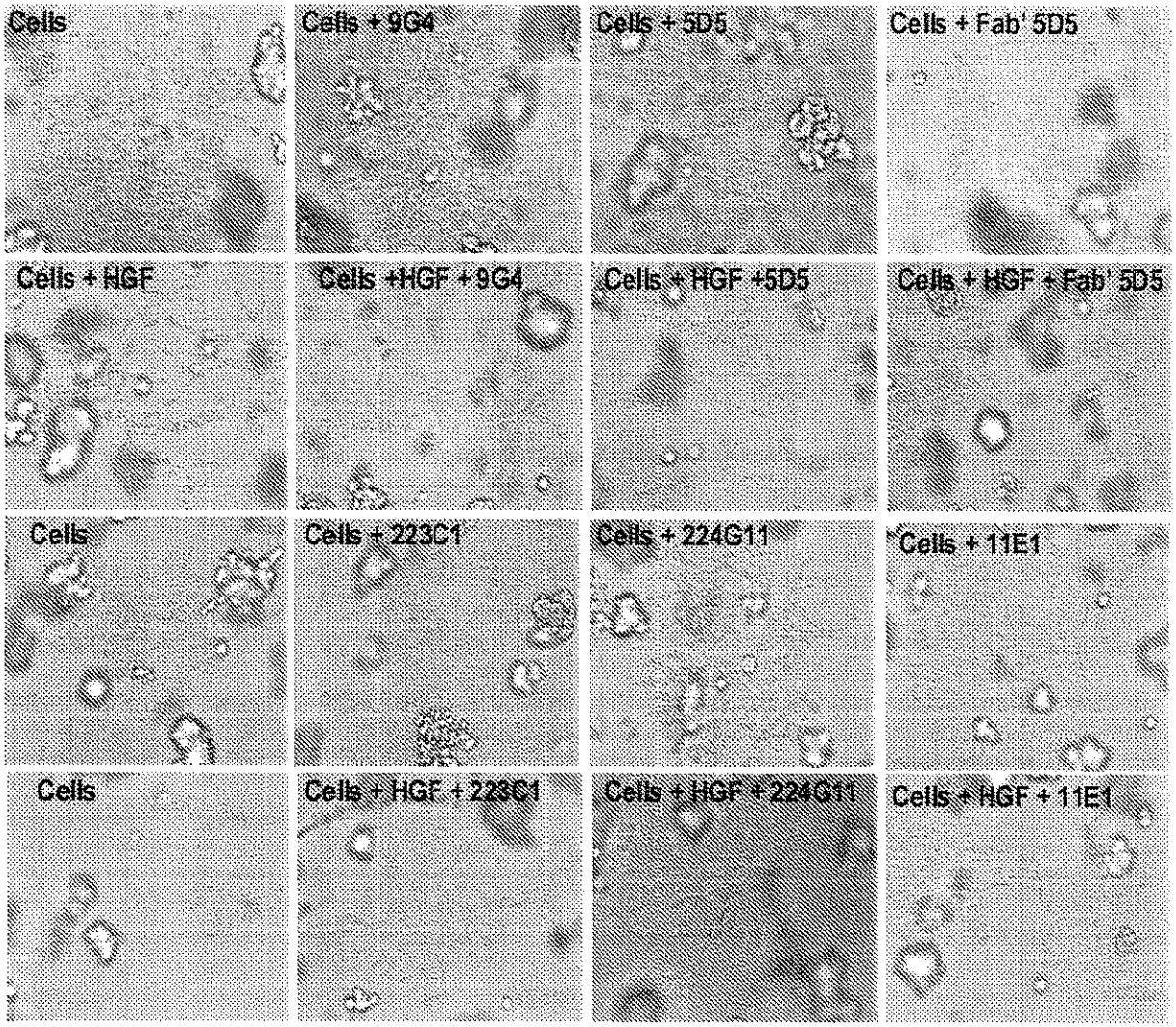

Cells
Cells + 9G4
Cells + 5D5
Cells + Fab' 5D5
Cells + HGF
Cells +HGF + 9G4
Cells + HGF +5D5
Cells + HGF + Fab' 5D5
Cells
Cells + 223C1
Cells + 224G11
Cells + 11E1
Cells
Cells + HGF + 223C1
Cells + HGF + 224G11
Cells + HGF + 11E1

FIGURE 11

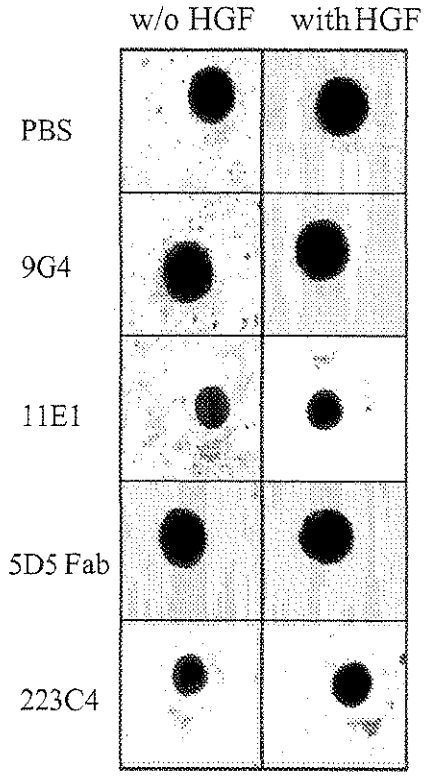


FIGURE 12A

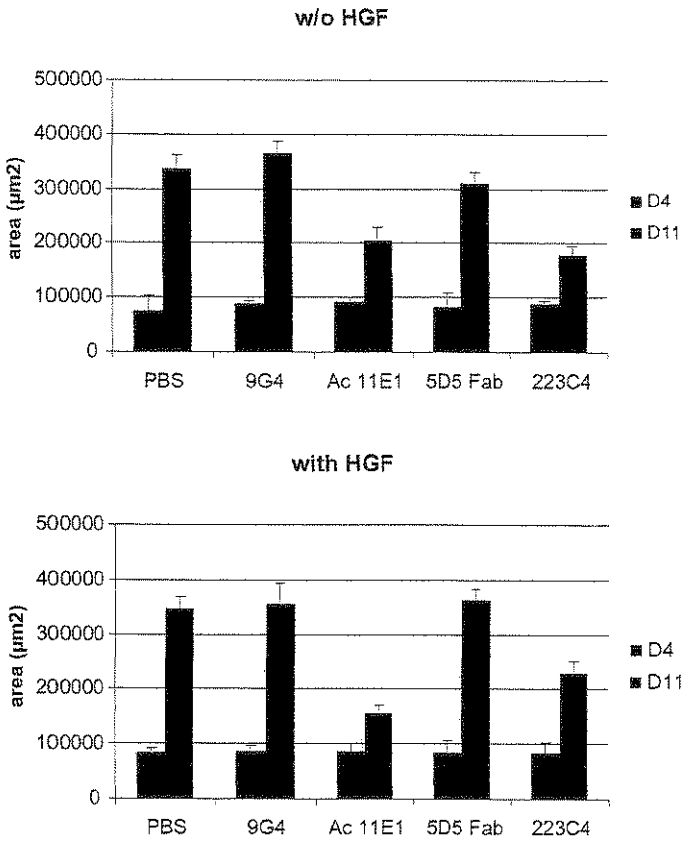


FIGURE 12B

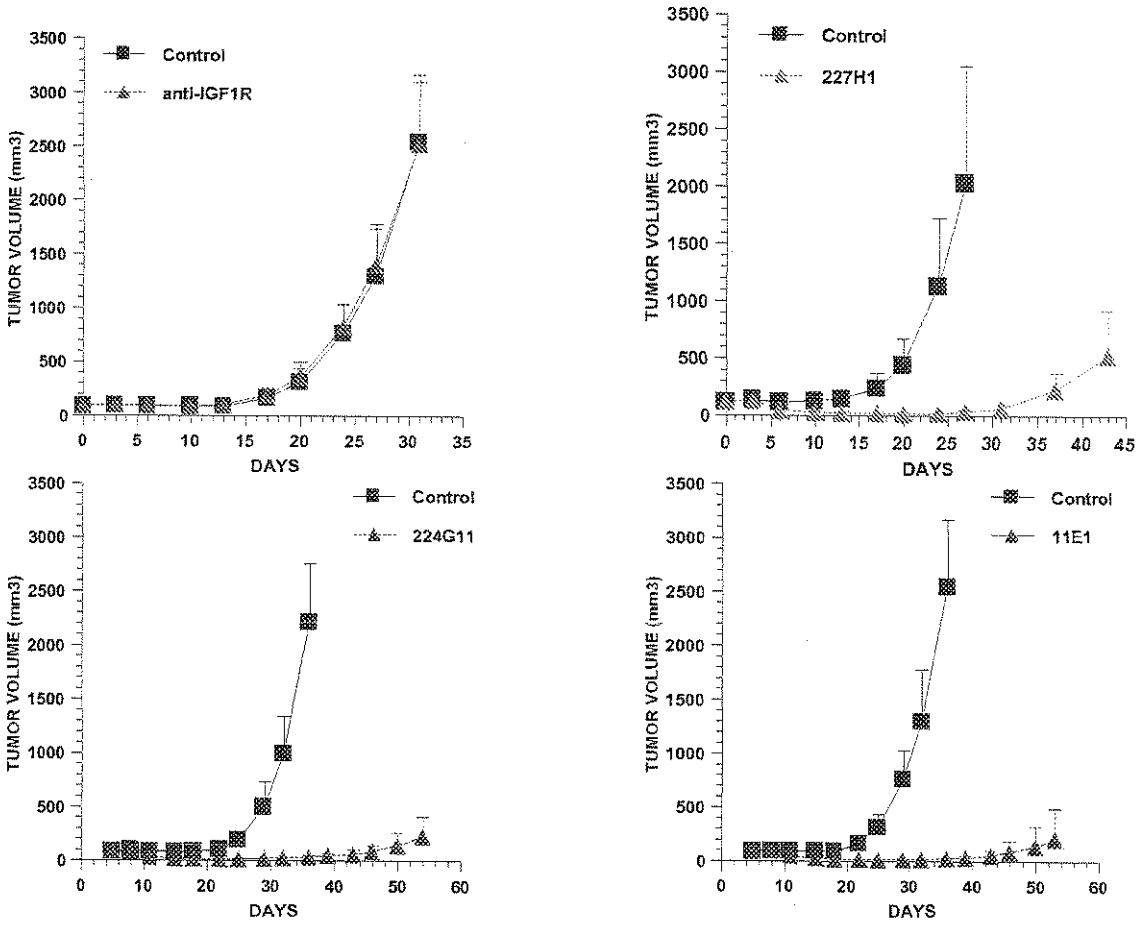


FIGURE 13

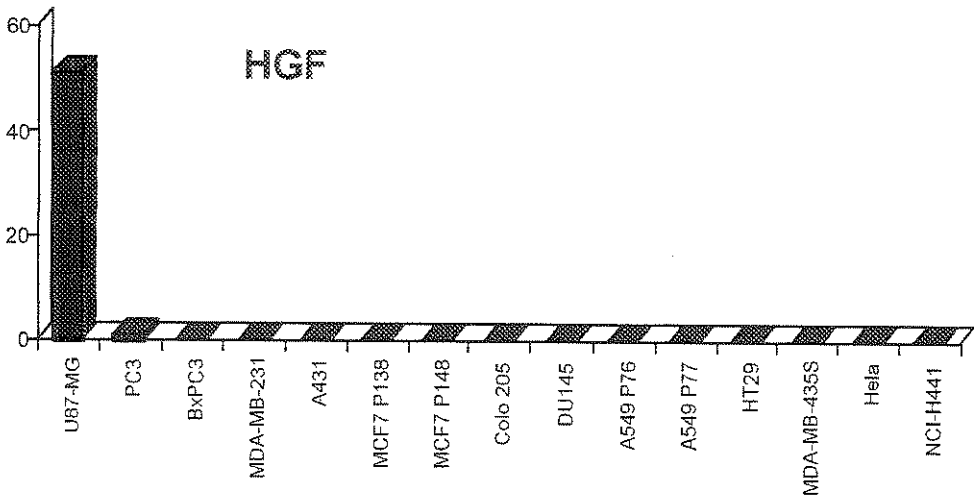


FIGURE 14

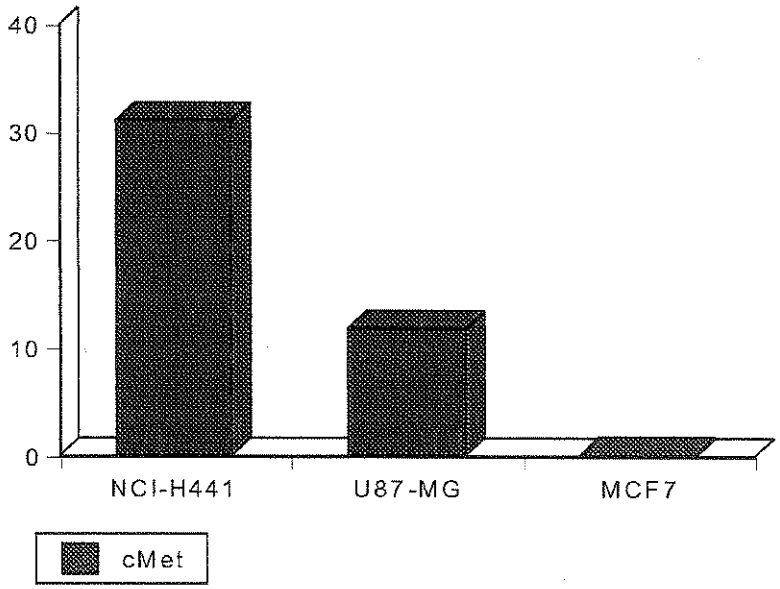


FIGURE 15A

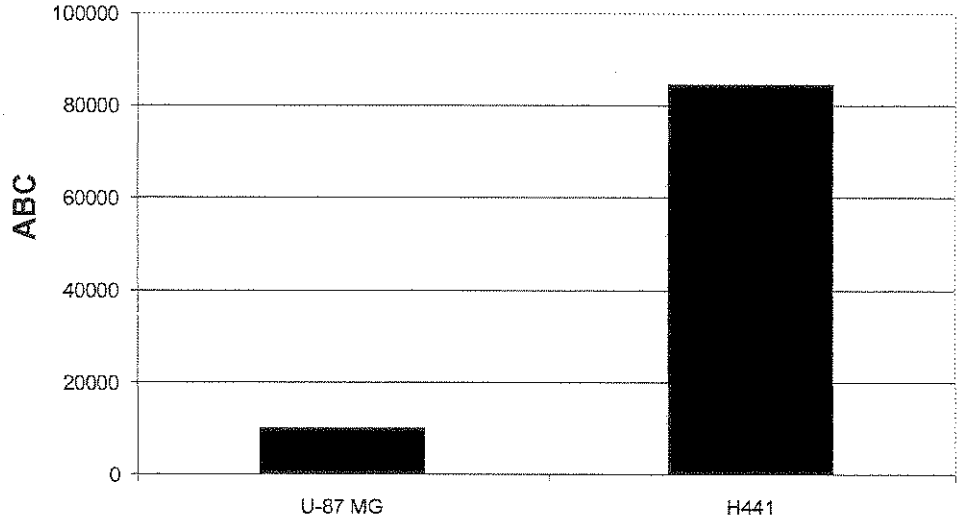


FIGURE 15B

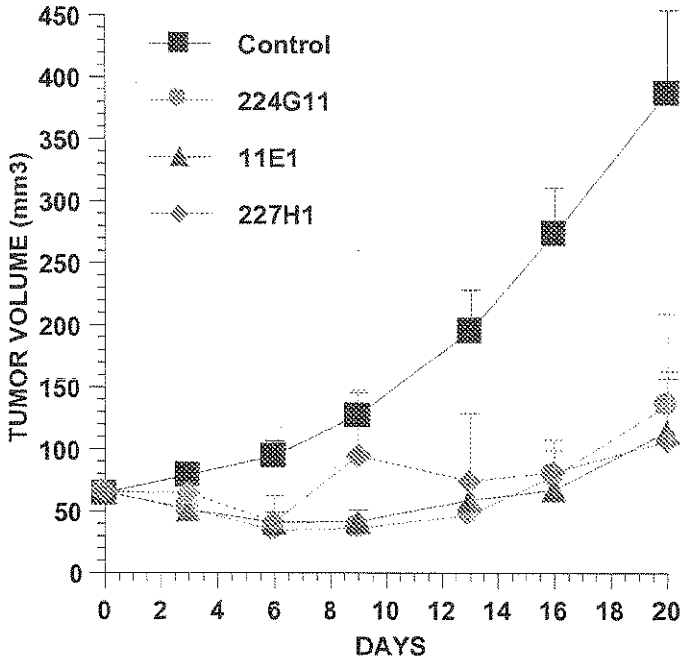

Control
224G11
11E1
227H1
TUMOR VOLUME (mm3)
DAYS
0
50
100
150
200
250
300
350
400
450
0
2
4
6
8
10
12
14
16
18
20

FIGURE 16

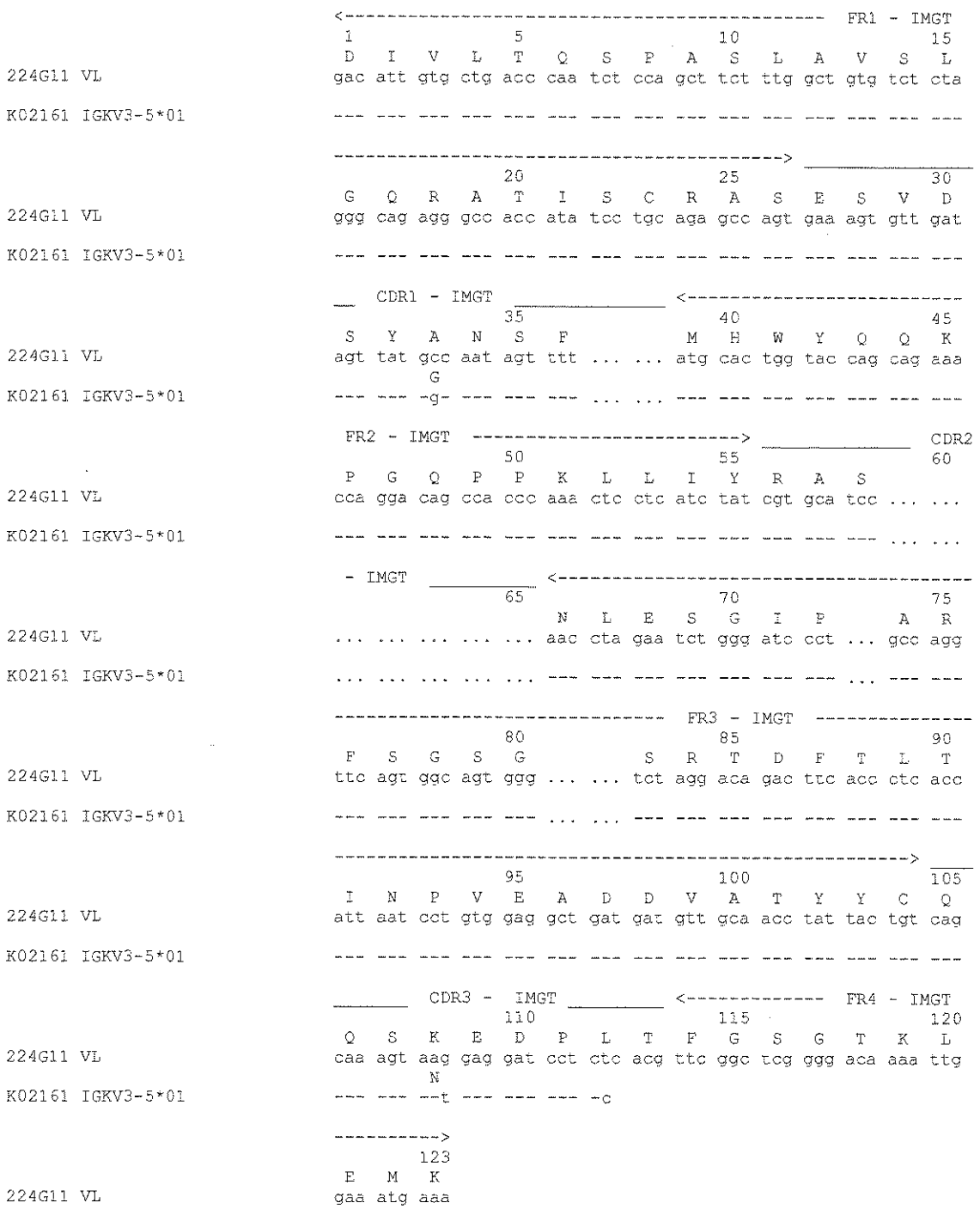

<---------- FR1 - IMGT
1 5 10 15
D I V L T Q S P A S L A V S L
224G11 VL gac att gtg ctg acc caa tct cca gct tct ttg gct gtg tct cta
K02161 IGKV3-5*01 --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
----------> _____
20 25 30
G Q R A T I S C R A S E S V D
224G11 VL ggg cag agg gcc acc ata tcc tgc aga gcc agt gaa agt gtt gat
K02161 IGKV3-5*01 --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
__ CDR1 - IMGT _____ <----------
35 40 45
S Y A N S F M H W Y Q Q K
224G11 VL agt tat gcc aat agt ttt ... ... atg cac tgg tac cag cag aaa
G
K02161 IGKV3-5*01 --- --- -g- --- --- --- ... ... --- --- --- --- --- --- ---
FR2 - IMGT ----------> _____ CDR2
50 55 60
P G Q P P K L L I Y R A S
224G11 VL cca gga cag cca ccc aaa ctc ctc atc tat cgt gca tcc ... ...
K02161 IGKV3-5*01 --- --- --- --- --- --- --- --- --- --- --- --- --- ... ...
- IMGT _____ <----------
65 70 75
N L E S G I P A R
224G11 VL ... ... aac cta gaa tct ggg atc cct ... gcc agg
K02161 IGKV3-5*01 ... ... --- --- --- --- --- --- --- ... --- ---
---------- FR3 - IMGT ----------
80 85 90
F S G S G S R T D F T L T
224G11 VL ttc agt ggc agt ggg ... ... tct agg aca gac ttc acc ctc acc
K02161 IGKV3-5*01 --- --- --- --- --- ... ... --- --- --- --- --- --- --- ---
----------> ____
95 100 105
I N P V E A D D V A T Y Y C Q
224G11 VL att aat cct gtg gag gct gat gat gtt gca acc tat tac tgt cag
K02161 IGKV3-5*01 --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
_____ CDR3 - IMGT _____ <---------- FR4 - IMGT
110 115 120
Q S K E D P L T F G S G T K L
224G11 VL caa agt aag gag gat cct ctc acg ttc ggc tcg ggg aca aaa ttg
N
K02161 IGKV3-5*01 --- --- --t --- --- --- -c
----------> 123
E M K
224G11 VL gaa atg aaa

FIGURE 17A

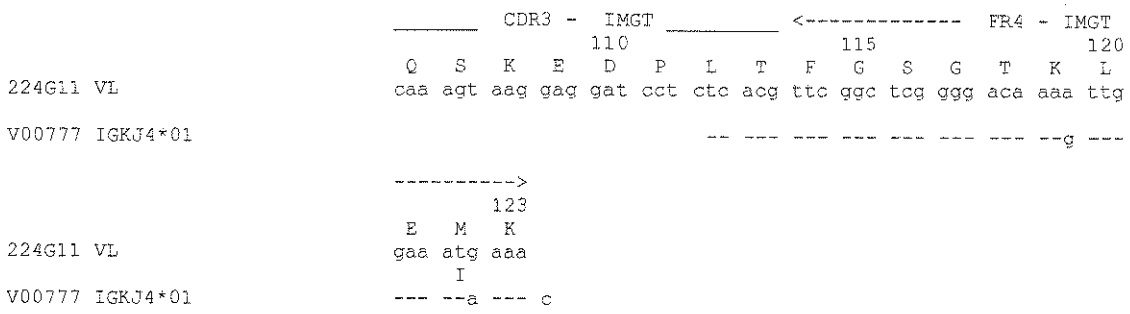

CDR3 - IMGT
<---------- FR4 - IMGT
110
115
120
Q S K E D P L T F G S G T K L
224G11 VL caa agt aag gag gat cct ctc acg ttc ggc tcg ggg aca aaa ttg
V00777 IGKJ4*01 -- --- --- --- --- --- --- --g ---
123
E M K
224G11 VL gaa atg aaa
I
V00777 IGKJ4*01 --- --a --- c

FIGURE 17B

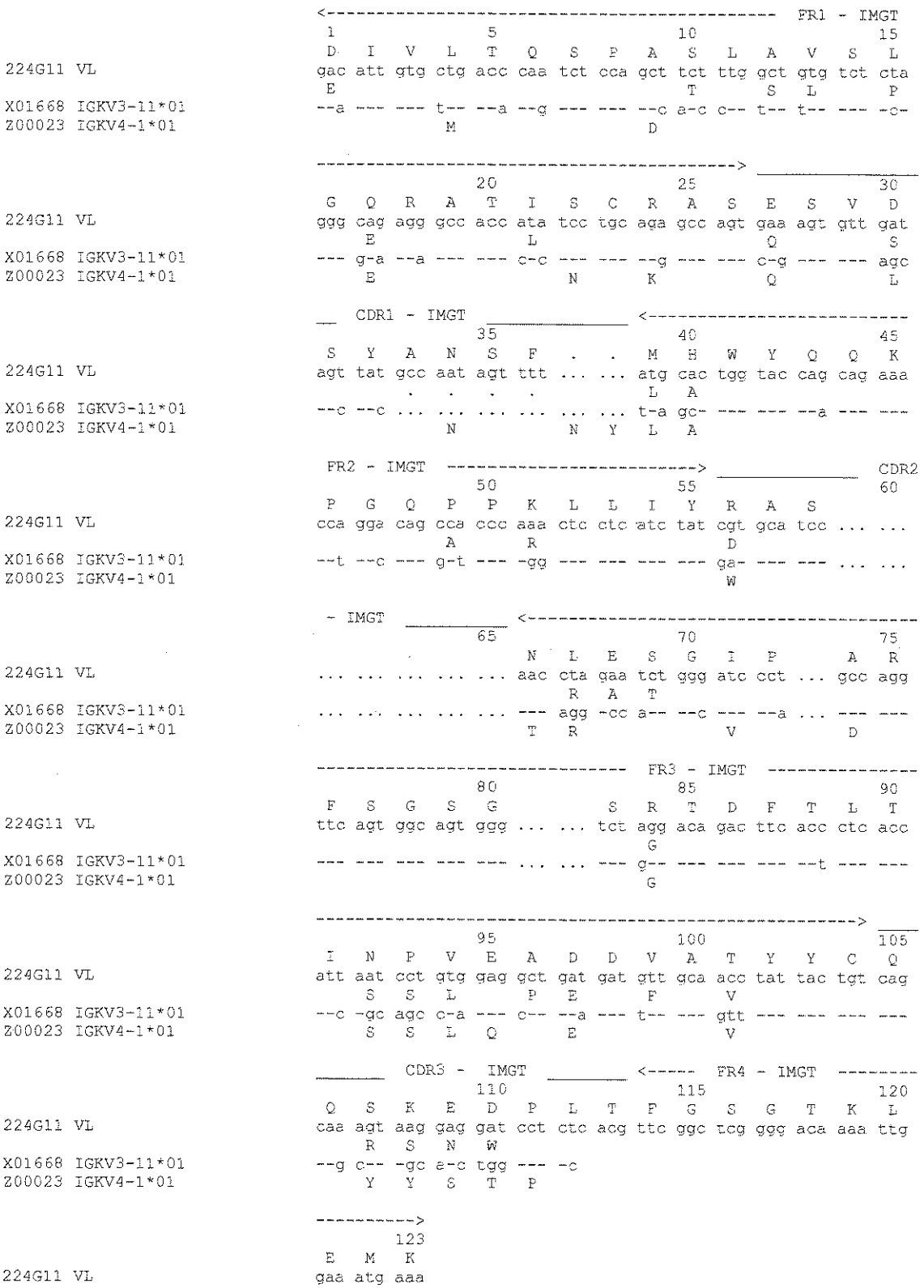

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
224G11 VL
X01668 IGKV3-11*01
Z00023 IGKV4-1*01

FIGURE 18A

```
                                 _______ CDR3 -  IMGT _________ <-----  FR4 - IMGT  --------
                                                110                 115                 120
                                  Q   S   K   E   D   P   L   T   F   G   S   G   T   K   L
224G11 VL                        caa agt aag gag gat cct ctc acg ttc ggc tcg ggg aca aaa ttg
                                                                         G                V
AF103571 IGKJ4*02                                       -- --- --- --- gga --- --c --g g--

                                 ---------->
                                         123
                                  E   M   K
224G11 VL                        gaa atg aaa
                                     I
AF103571 IGKJ4*02                --g --c --- c
```

FIGURE 18B

```
                          FR1-IMGT          CDR1-IMGT        FR2-IMGT      CDR2-IMGT
                           (1-26)            (27-38)         (39-55)       (56-65)
                 ____________________________ ____________ ____________________ ____________
                 1        10        20        30           40        50        60
                 .........|.........|...... ...|........ .|.........|..... ....|.....
224G11 VL        DIVLTQSPASLAVSLGQRATISCRAS ESVDSYANSF.. MHWYQQKPGQPPKLLIY RAS.......
                 3         3 33 2 3   3                  11        2 3
Human FR         E--------T-SL-P-E---L-----       ...... LA--------A-R----    .......
224G11 HZ1VL     EIVLTQSPATLSLSPGERATLSCRAS ESVDSYANSF.. MHWYQQKPGQAPRLLIY RAS.......

                                FR3-IMGT                      CDR3-IMGT   FR4-IMGT
                                (66-104)                      (105-113)   (114-123)
                 ____________________________________________ ___________ ___________
                    70        80        90        100          110         120
                 ....|.........|.........|.........|....   .....|...   ......|.....
224G11 VL        NLESGIP.ARFSGSG..SRTDFTLTINPVEADDVATYYC   QQSKEDPLT   FGSGTKLEMK
rank              223              1       323 33 2 3                     3   3 3
Human FR         -RAT---.-------..-G-------SSL-PE-F-V---                --G---V-I-
224G11 HZ1VL     NRATGIP.ARFSGSG..SRTDFTLTISSLEPEDFAVYYC   QQSKEDPLT   FGGGTKVEIK
```

FIGURE 19A

```
                          FR1-IMGT          CDR1-IMGT        FR2-IMGT      CDR2-IMGT
                           (1-26)            (27-38)         (39-55)       (56-65)
                 ____________________________ ____________ ____________________ ____________
                 1        10        20        30           40        50        60
                 .........|.........|...... ...|........ .|.........|..... ....|.....
224G11 VL        DIVLTQSPASLAVSLGQRATISCRAS ESVDSYANSF.. MHWYQQKPGQPPKLLIY RAS.......
                    1     3        3    3 32               11
Human FR         DIVMTQSPDSLAVSLGERATINCKSS               LAWYQQKPGQPPKLLIY    .......
224G11 HZ2VL     DIVLTQSPDSLAVSLGERATINCKSS ESVDSYANSF.. MHWYQQKPGQPPKLLIY RAS.......

                                FR3-IMGT                      CDR3-IMGT   FR4-IMGT
                                (66-104)                      (105-113)   (114-123)
                 ____________________________________________ ___________ ___________
                    70        80        90        100          110         120
                 ....|.........|.........|.........|....   .....|...   ......|.....
224G11 VL        NLESGIP.ARFSGSG..SRTDFTLTINPVEADDVATYYC   QQSKEDPLT   FGSGTKLEMK
                 22   3  3          1       3233 3   3                     3   3 3
Human FR         TRESGVP.DRFSGSG..SGTDFTLTISSLQAEDVAVYYC                FGGGTKVEIK
224G11 HZ2VL     TRESGVP.DRFSGSG..SRTDFTLTISSLQAEDVAVYYC   QQSKEDPLT   FGGGTKVEIK
```

FIGURE 19B

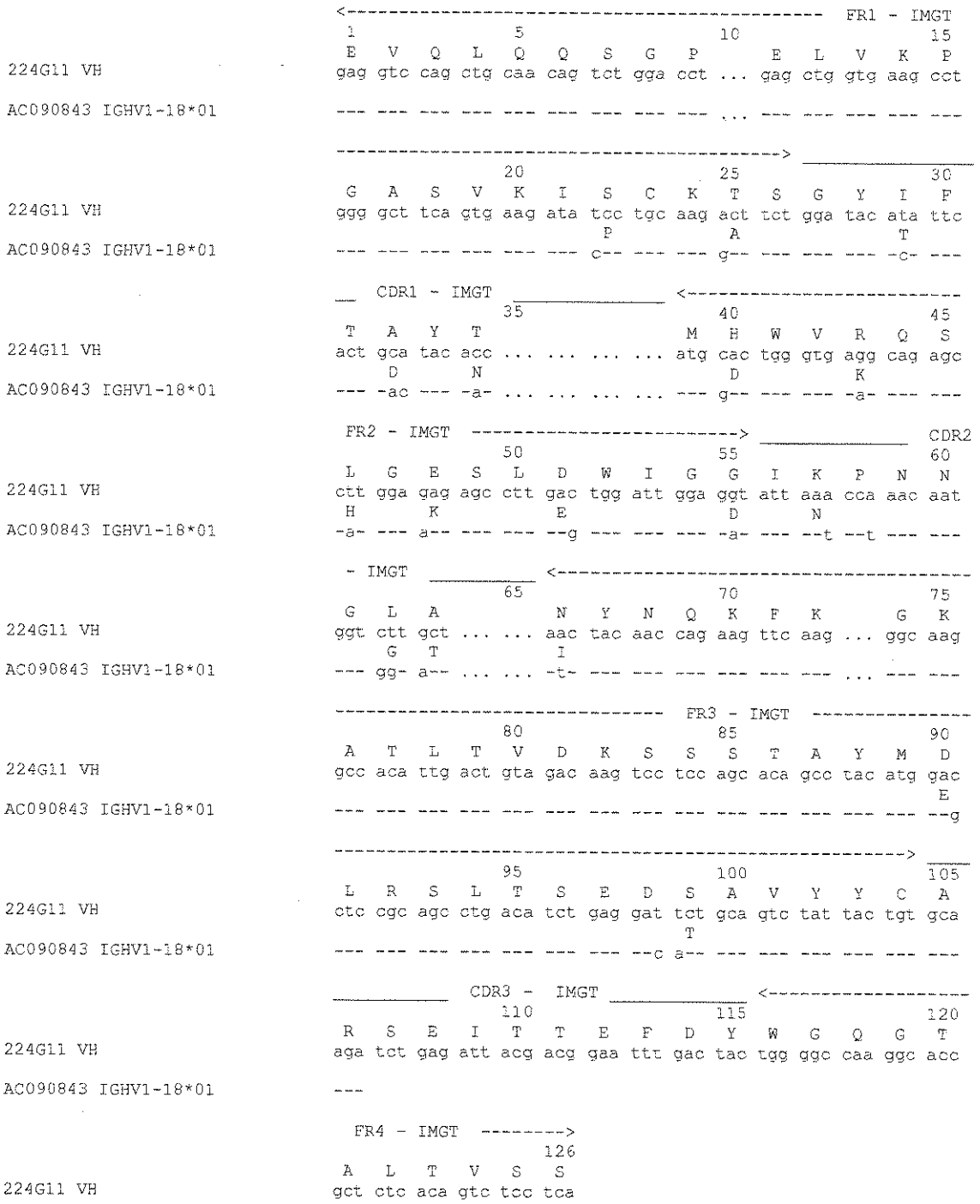

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
224G11 VH
AC090843 IGHV1-18*01

FIGURE 20A

```
                                 ______________ CDR3 -  IMGT ______________
                                 105                 110                 115
                                  A   R   S   E   I   T   T   E   F   D   Y
224G11 VH                        gca aga tct gag att acg acg gaa ttt gac tac
J00431 IGHD2-4*01                        a-- at- --- --- --
```

FIGURE 20B

```
                                 ___________ CDR3 -  IMGT ____________ <-------------------
                                                 110                 115                 120
                                  R   S   E   I   T   T   E   F   D   Y   W   G   Q   G   T
224G11 VH                        aga tct gag att acg acg gaa ttt gac tac tgg ggc caa ggc acc
                                                         Y
V00770 IGHJ2*01                  ... ... ... ... ... .ac t-c --- --- --- --- --- --- --- ---

                                   FR4 - IMGT  -------->
                                                     126
                                  A   L   T   V   S   S
224G11 VH                        gct ctc aca gtc tcc tca
                                  T
V00770 IGHJ2*01                  a-- --- --- --- --- --- g
```

FIGURE 20C

```
                          <-------------------------------------------- FR1 - IMGT
                           1               5                  10                  15
                           E   V   Q   L   Q   Q   S   G   P       E   L   V   K   P
224G11 VH                 gag gtc cag ctg caa cag tct gga cct ... gag ctg gtg aag cct
                           Q               V               A           V   K
X62106 IGHV1-2*02         c-- --g --- --- gtg --- --- --g g-- ... --- g-- aa- --- ---

                          ------------------------------------------> ______________
                                          20                  25                  30
                           G   A   S   V   K   I   S   C   K   T   S   G   Y   I   F
224G11 VH                 ggg gct tca gtg aag ata tcc tgc aag act tct gga tac ata ttc
                                                V               A               T
X62106 IGHV1-2*02         --- --c --- --- --- g-c --- --- --- g-- --- --- --- -cc ---

                          __  CDR1 - IMGT  _____________ <-------------------------
                                          35                  40                  45
                           T   A   Y   T                   M   H   W   V   R   Q   S
224G11 VH                 act gca tac acc ... ... ... ... atg cac tgg gtg agg cag agc
                               G       Y                                           A
X62106 IGHV1-2*02         --c -gc --- tat ... ... ... ... --- --- --- --- c-a --- gc-

                           FR2 - IMGT  ------------------------> _____________  CDR2
                                          50                  55                  60
                           L   G   E   S   L   D   W   I   G   G   I   K   P   N   N
224G11 VH                 ctt gga gag agc ctt gac tgg att gga ggt att aaa cca aac aat
                           P       Q   G       E       M       W       N           S
X62106 IGHV1-2*02         -c- --- c-a g-g --- --g --- --g --- t-g --c --c --t --- -g-

                           - IMGT  __________ <-------------------------------------
                                          65                  70                  75
                           G   L   A           N   Y   N   Q   K   F   K       G   K
224G11 VH                 ggt ctt gct ... ... aac tac aac cag aag ttc aag ... ggc aag
                               G   T                   A               Q           R
X62106 IGHV1-2*02         --- ggc a-a ... ... --- --t gca --- --- --t c-- ... --- -g-

                          ------------------------------ FR3 - IMGT ---------------
                                          80                  85                  90
                           A   T   L   T   V   D   K   S   S   S   T   A   Y   M   D
224G11 VH                 gcc aca ttg act gta gac aag tcc tcc agc aca gcc tac atg gac
                           V       M       R       T       I                       E
X62106 IGHV1-2*02         -t- --c a-- --c agg --- -c- --- at- --- --- --- --- --- --g

                          ------------------------------------------------------> ____
                                          95                  100                 105
                           L   R   S   L   T   S   E   D   S   A   V   Y   Y   C   A
224G11 VH                 ctc cgc agc ctg aca tct gag gat tct gca gtc tat tac tgt gca
                               S   R       R       D       T
X62106 IGHV1-2*02         --g a-- --g --- -g- --- --c --c a-g --c --g --- --- --- --g

                          _______  CDR3 -  IMGT  _______________ <-----  FR4 - IMGT
                                          110                 115                 120
                           R   S   E   I   T   T   E   F   D   Y   W   G   Q   G   T
224G11 VH                 aga tct gag att acg acg gaa ttt gac tac tgg ggc caa ggc acc

X62106 IGHV1-2*02         --- ga

                          ---------------------->
                                              126
                           A   L   T   V   S   S
224G11 VH                 gct ctc aca gtc tcc tca
```

FIGURE 21A

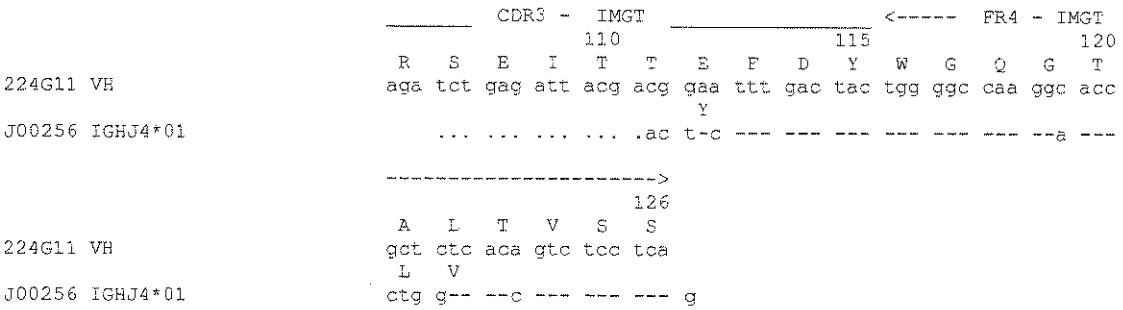

CDR3 - IMGT
110
115
<----- FR4 - IMGT
120
R S E I T T E F D Y W G Q G T
aga tct gag att acg acg gaa ttt gac tac tgg ggc caa ggc acc
Y
224G11 VH
J00256 IGHJ4*01
... ... .ac t-c --- --- --- --- --- --- --a ---
---------->
126
A L T V S S
gct ctc aca gtc tcc tca
L V
224G11 VH
ctg g-- --c --- --- --- g
J00256 IGHJ4*01

FIGURE 21B

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	CDR2-IMGT (56-65)
	1 10 20	30	40 50	60
224G11 VH	EVQLQQSGP.ELVKPGASVKISCKTS	GYIFTAYT....	MHWVRQSLGESLDWIGG	IKPNNGLA..
rank	3 3 3 33 3 2		33 22 1 2 1	
Human FR	Q---V---A.-VK-------V---A-		------AP-QG-E-M-W	
224G11 HZVH	QVQLVQSGA.EVKKPGASVKVSCKAS	GYIFTAYT....	MHWVRQAPGQGLDWMGG	IKPNNGLA..

	FR3-IMGT (66-104)	CDR3-IMGT (105-115)	FR4-IMGT (116-126)
	70 80 90 100	110	120
224G11 VH	NYNQKFK.GKATLTVDKSSSTAYMDLRSLTSEDSAVYYC	ARSEITTEFDY	WGQGTALTVSS
rank	3 3 32 2 1 1 3 2 33 3 3 3		33
Human FR	--A---Q.-RV-M-R-T-I-----E-SR-R-D-T-----		-----LV----
224G11 HZVH	NYAQKFQ.GRVTMTVDKSISTAYMELSRLRSDDTAVYYC	ARSEITTEFDY	WGQGTLVTVSS

FIGURE 22

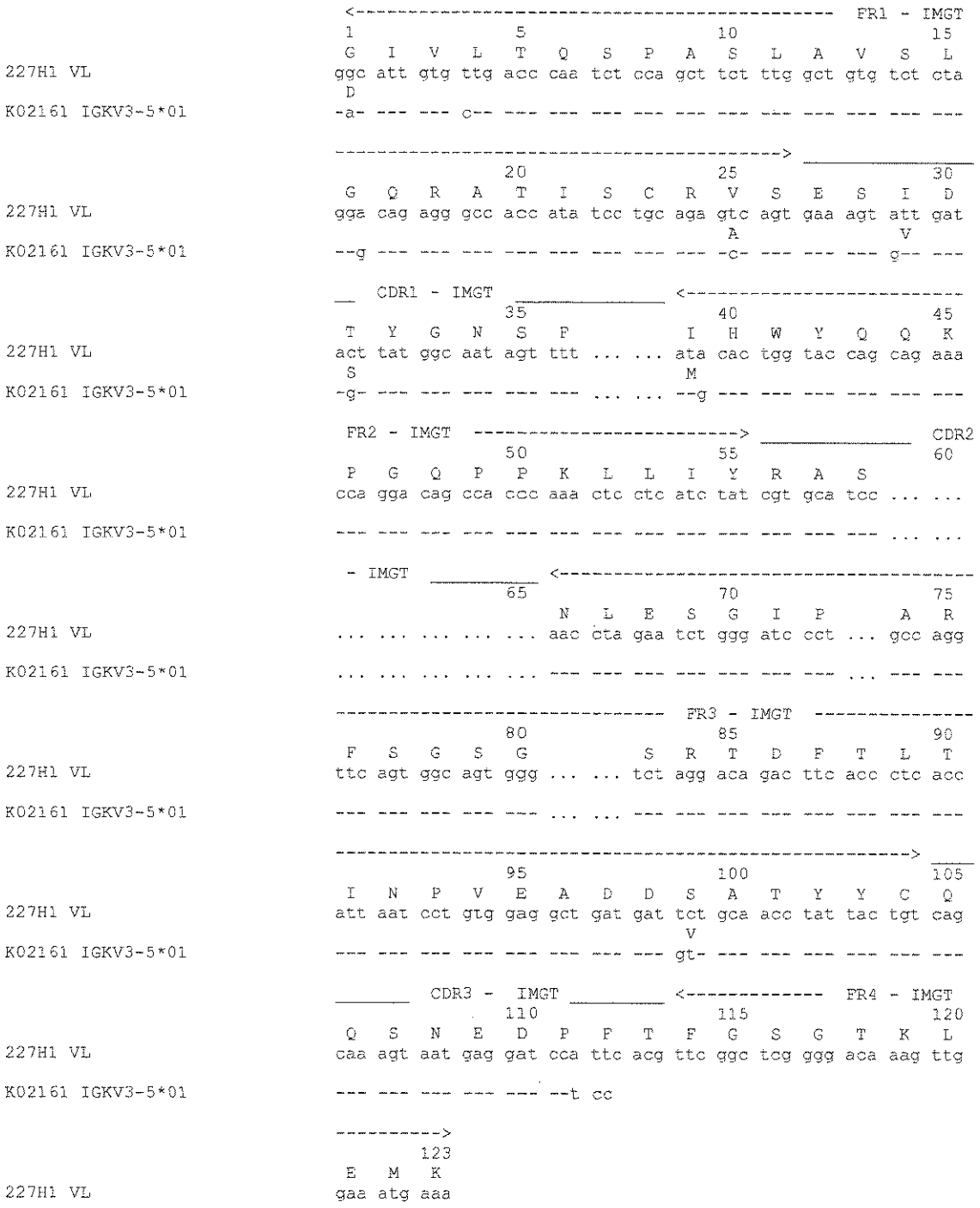

<---------- FR1 - IMGT
1 5 10 15
G I V L T Q S P A S L A V S L
227H1 VL ggc att gtg ttg acc caa tct cca gct tct ttg gct gtg tct cta
D
K02161 IGKV3-5*01 -a- --- --- c-- --- --- --- --- --- --- --- --- --- ---
----------> _____
20 25 30
G Q R A T I S C R V S E S I D
227H1 VL gga cag agg gcc acc ata tcc tgc aga gtc agt gaa agt att gat
A V
K02161 IGKV3-5*01 --g --- --- --- --- --- --- --- --- -c- --- --- --- g-- ---
__ CDR1 - IMGT _____ <----------
35 40 45
T Y G N S F I H W Y Q Q K
227H1 VL act tat ggc aat agt ttt ... ... ata cac tgg tac cag cag aaa
S M
K02161 IGKV3-5*01 -g- --- --- --- --- --- ... ... --g --- --- --- --- --- ---
FR2 - IMGT ----------> _____ CDR2
50 55 60
P G Q P P K L L I Y R A S
227H1 VL cca gga cag cca ccc aaa ctc ctc atc tat cgt gca tcc ... ...
K02161 IGKV3-5*01 --- --- --- --- --- --- --- --- --- --- --- --- --- ... ...
- IMGT _____ <----------
65 70 75
N L E S G I P A R
227H1 VL ... ... aac cta gaa tct ggg atc cct ... gcc agg
K02161 IGKV3-5*01 ... ... --- --- --- --- --- --- --- ... --- ---
---------- FR3 - IMGT ----------
80 85 90
F S G S G S R T D F T L T
227H1 VL ttc agt ggc agt ggg ... ... tct agg aca gac ttc acc ctc acc
K02161 IGKV3-5*01 --- --- --- --- --- ... ... --- --- --- --- --- --- --- ---
----------> ____
95 100 105
I N P V E A D D S A T Y Y C Q
227H1 VL att aat cct gtg gag gct gat gat tct gca acc tat tac tgt cag
V
K02161 IGKV3-5*01 --- --- --- --- --- --- --- --- gt- --- --- --- --- --- ---
_____ CDR3 - IMGT _____ <---------- FR4 - IMGT
110 115 120
Q S N E D P F T F G S G T K L
227H1 VL caa agt aat gag gat cca ttc acg ttc ggc tcg ggg aca aag ttg
K02161 IGKV3-5*01 --- --- --- --- --- --t cc
---------->
123
E M K
227H1 VL gaa atg aaa

FIGURE 23A

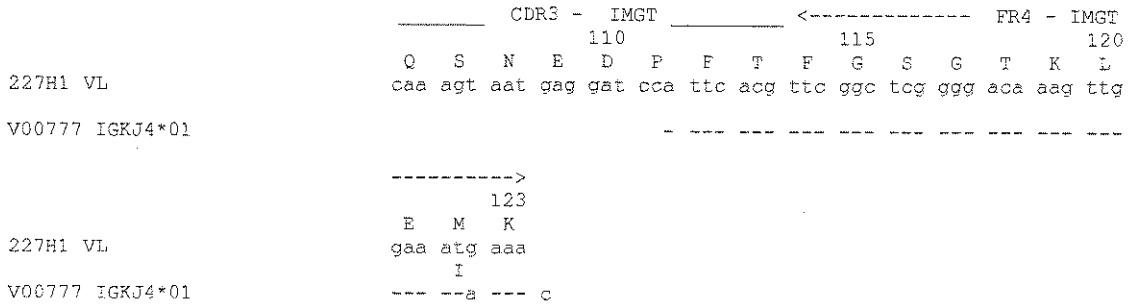

CDR3 - IMGT
FR4 - IMGT
110
115
120
Q S N E D P F T F G S G T K L
227H1 VL caa agt aat gag gat cca ttc acg ttc ggc tcg ggg aca aag ttg
V00777 IGKJ4*01 - --- --- --- --- --- --- --- --- ---
123
E M K
227H1 VL gaa atg aaa
I
V00777 IGKJ4*01 --- --a --- c

FIGURE 23B

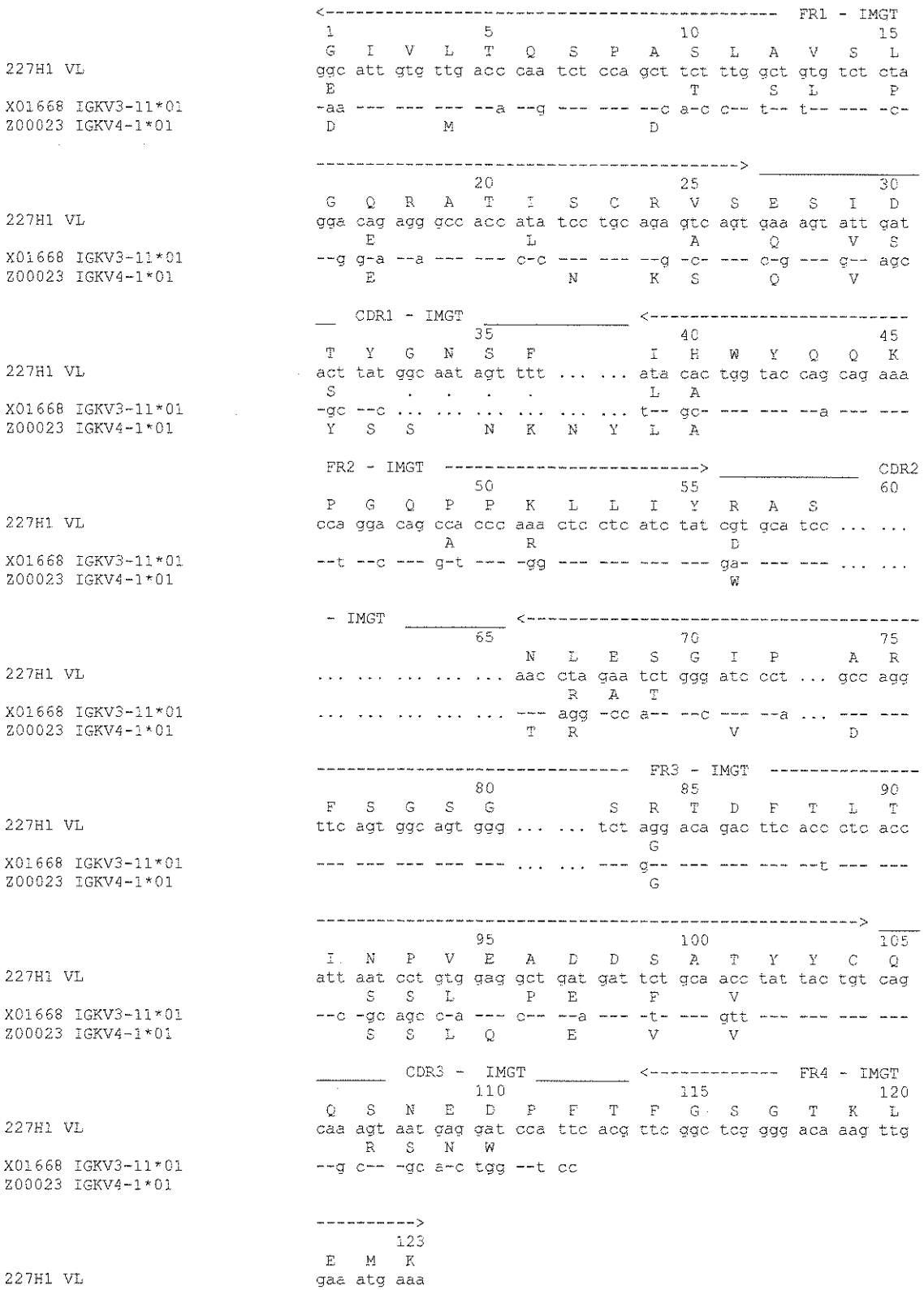

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
227H1 VL
X01668 IGKV3-11*01
Z00023 IGKV4-1*01

FIGURE 24A

```
                                 _______  CDR3 -  IMGT _________ <-------------  FR4 - IMGT
                                                 110                 115                 120
                                  Q   S   N   E   D   P   F   T   F   G   S   G   T   K   L
227H1 VL                         caa agt aat gag gat cca ttc acg ttc ggc tcg ggg aca aag ttg
                                                         L               G                V
AF103571 IGKJ4*02                                     g c-- --- --- --- gga --- --c --- g--

                                 ---------->
                                         123
                                  E   M   K
227H1 VL                         gaa atg aaa
                                     I
AF103571 IGKJ4*02                --g --c --- c
```

FIGURE 24B

```
                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT
                           (1-26)            (27-38)        (39-55)        (56-65)
                 ____________________________ ____________ ____________________ ____________
                 1       10        20         30          40        50         60
                 .........|.........|...... ...|........ .|.........|..... ....|.....
227H1 VL         GIVLTQSPASLAVSLGQRATISCRVS ESIDTYGNSF.. IHWYQQKPGQPPKLLIY RAS.......
                 3        3 33 2 3   3   2               11        2 3
Human FR         E--------T-SL-P-E---L---A-       ...... LA--------A-R----    .......
227H1 HZ1VL      EIVLTQSPATLSLSPGERATLSCRAS ESIDTYGNSF.. IHWYQQKPGQAPRLLIY RAS.......

                                FR3-IMGT                      CDR3-IMGT   FR4-IMGT
                                (66-104)                      (105-113)   (114-123)
                 ____________________________________________ ____________ ____________
                    70        80        90        100          110        120
                 ....|.........|.........|.........|....     .....|...   ......|.....
227H1 VL         NLESGIP.ARFSGSG..SRTDFTLTINPVEADDSATYYC     QQSNEDPFT   FGSGTKLEMK
                  223              1       323 33 2 3                      3   3 3
Human FR         -RAT---.-------..-G-------SSL-PE-F-V---                 --G---V-I-
227H1 HZ1VL      NRATGIP.ARFSGSG..SRTDFTLTISSLEPEDFAVYYC     QQSNEDPFT   FGGGTKVEIK
```

FIGURE 25 A

```
                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT
                           (1-26)            (27-38)        (39-55)        (56-65)
                 ____________________________ ____________ ____________________ ____________
                 1       10        20         30          40        50         60
                 .........|.........|...... ...|........ .|.........|..... ....|.....
227H1 VL         GIVLTQSPASLAVSLGQRATISCRVS ESIDTYGNSF.. IHWYQQKPGQPPKLLIY RAS.......
                 3  1    3        3    3 32               11
Human FR         DIVMTQSPDSLAVSLGERATINCKSS                LAWYQQKPGQPPKLLIY    .......
227H1 HZ2VL      DIVLTQSPDSLAVSLGERATINCKSS ESIDTYGNSF.. IHWYQQKPGQPPKLLIY RAS.......

                                FR3-IMGT                      CDR3-IMGT   FR4-IMGT
                                (66-104)                      (105-113)   (114-123)
                 ____________________________________________ ____________ ____________
                    70        80        90        100          110        120
                 ....|.........|.........|.........|....     .....|...   ......|.....
227H1 VL         NLESGIP.ARFSGSG..SRTDFTLTINPVEADDSATYYC     QQSNEDPFT   FGSGTKLEMK
                 22   3  3          1       3233 3 3 3                      3   3 3
Human FR         TRESGVP.DRFSGSG..SGTDFTLTISSLQAEDVAVYYC                 FGGGTKVEIK
227H1 HZ2VL      TRESGVP.DRFSGSG..SRTDFTLTISSLQAEDVAVYYC     QQSNEDPFT   FGGGTKVEIK
```

FIGURE 25 B

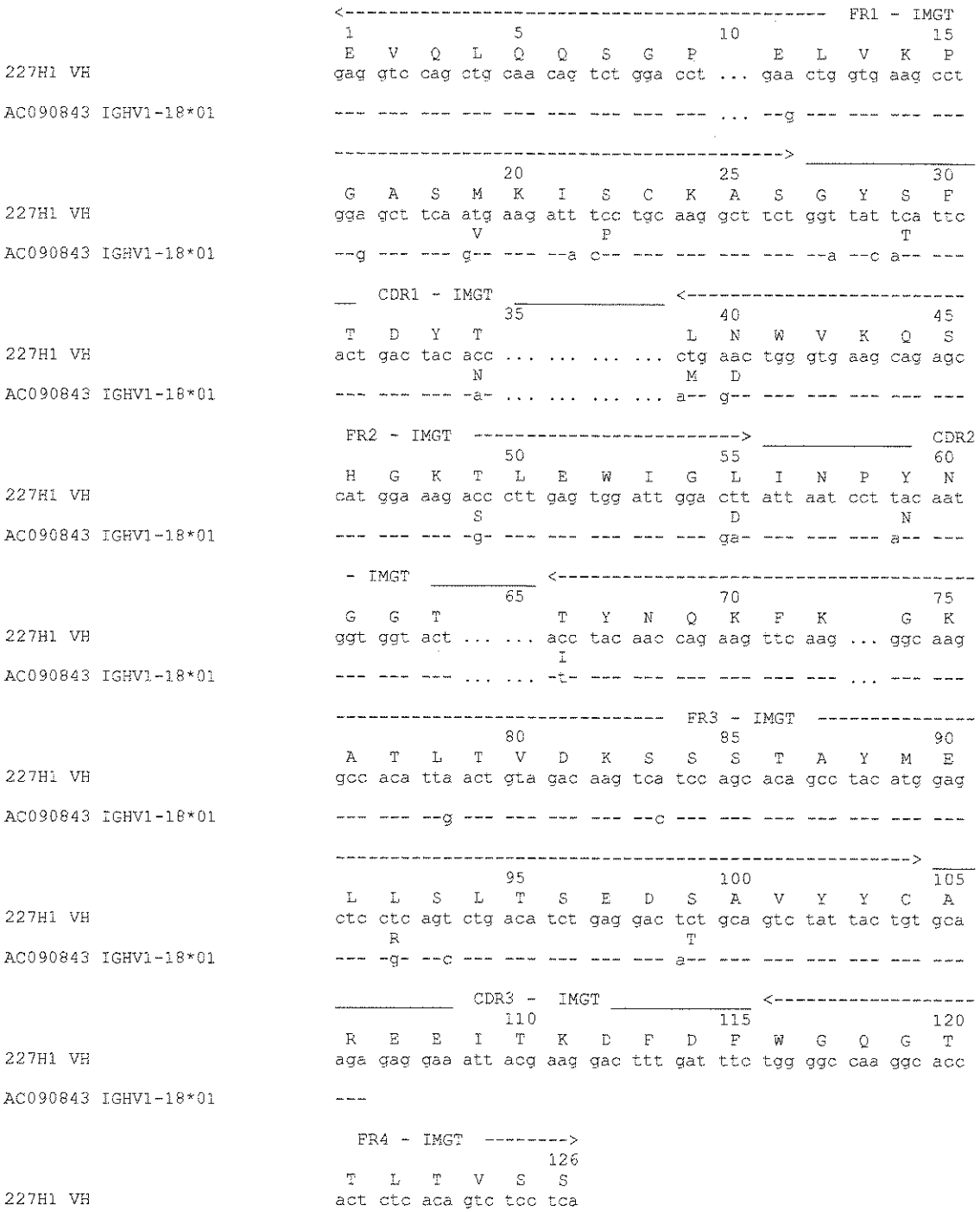

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
- IMGT
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
227H1 VH
AC090843 IGHV1-18*01

FIGURE 26A

```
                          ____________ CDR3 -  IMGT ____________
                          105                 110                 115
                           A   R   E   E   I   T   K   D   F   D   F
227H1 VH                  gca aga gag gaa att acg aag gac ttt gat ttc
IGHD1-1*02                        -t- -t- gc- --
```

FIGURE 26B

```
                          ___________ CDR3 -  IMGT ____________ <-------------------
                                          110                 115                 120
                           R   E   E   I   T   K   D   F   D   F   W   G   Q   G   T
227H1 VH                  aga gag gaa att acg aag gac ttt gat ttc tgg ggc caa ggc acc
                                                      Y           Y
V00770 IGHJ2*01                ... ... ... ... .-c t-- --- --c -a- --- --- --- --- ---

                            FR4 - IMGT  -------->
                                              126
                           T   L   T   V   S   S
227H1 VH                  act ctc aca gtc tcc tca

V00770 IGHJ2*01           --- --- --- --- --- --- g
```

FIGURE 26C

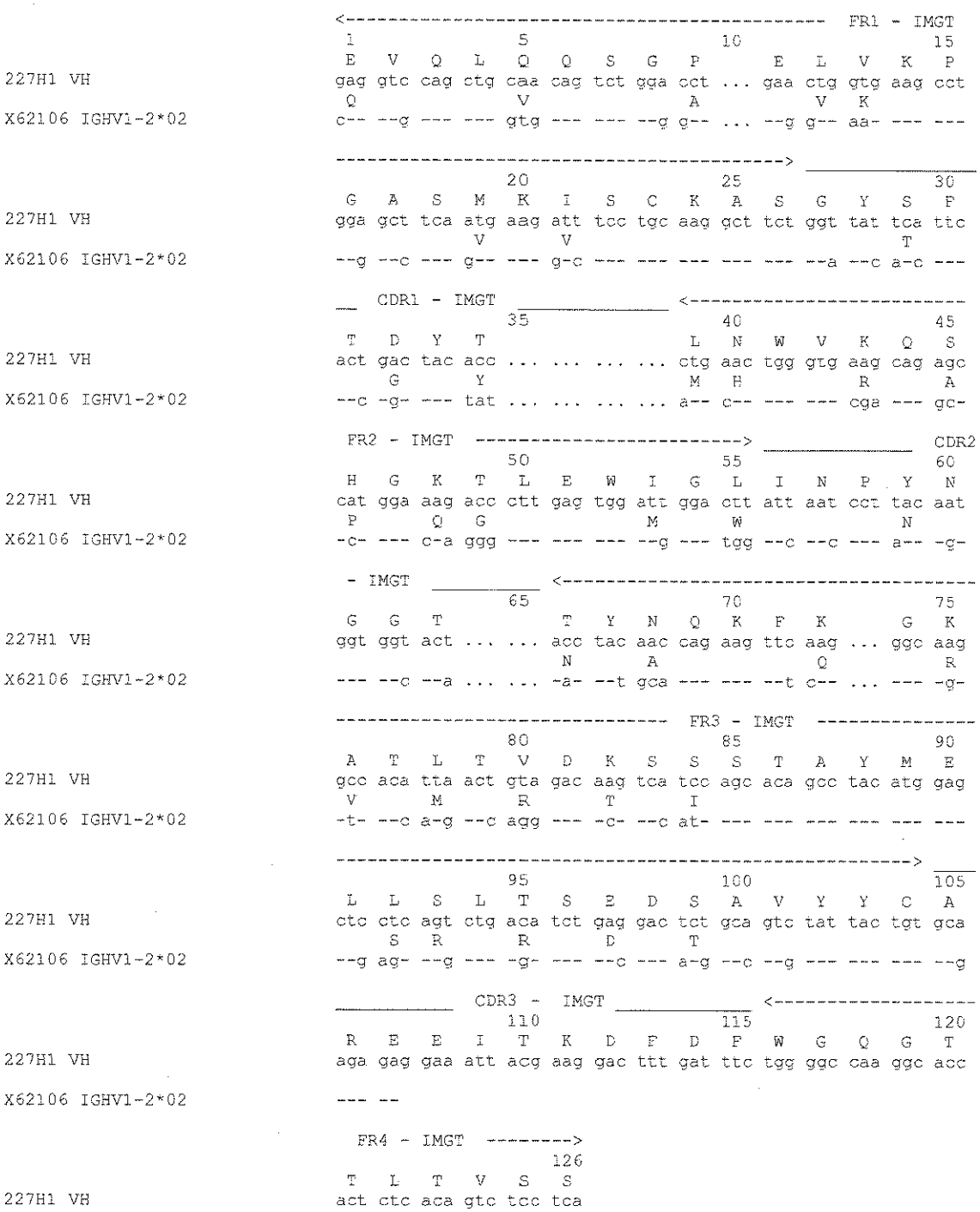

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
- IMGT
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
227H1 VH
X62106 IGHV1-2*02

FIGURE 27A

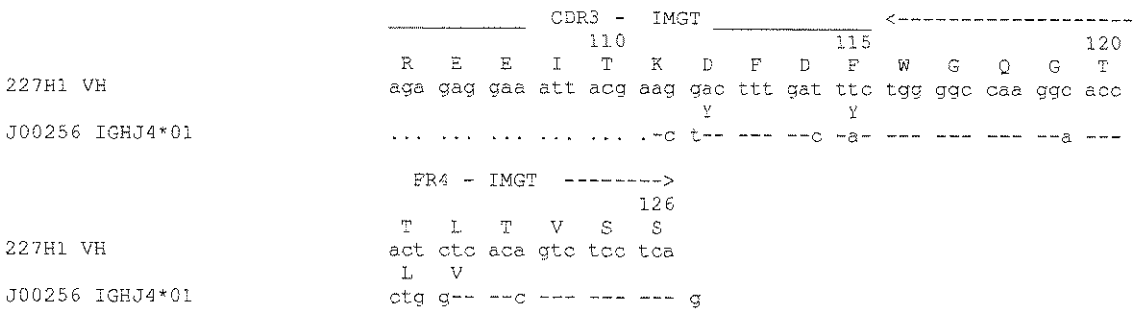


FIGURE 27B

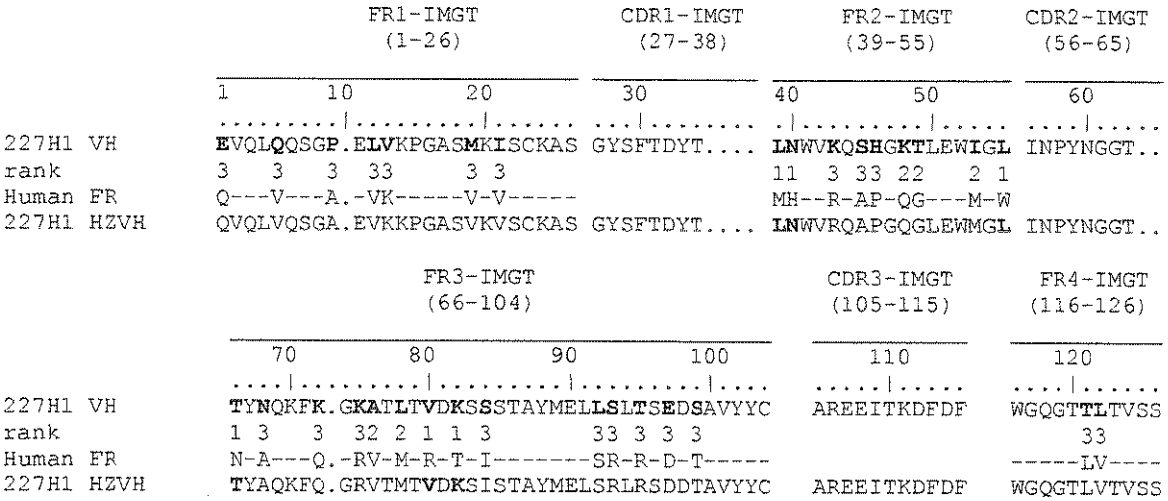


FIGURE 28

```
                                <-------------------------------------------- FR1 - IMGT
                                 1               5                  10                  15
                                 D   I   Q   M   T   Q   S   P   A   S   L   S   V   S   V
VL 223C4                        gac atc cag atg act cag tct cca gcc tcc cta tct gta tct gtg

AJ235956 IGKV12-46*01           --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

                                ------------------------------------------> ______________
                                                20                  25                  30
                                 G   E   T   V   T   I   T   C   R   A   S   E   N   I   Y
VL 223C4                        gga gaa act gtc acc atc aca tgt cga gca agt gag aat att tac

AJ235956 IGKV12-46*01           --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

                                __  CDR1 - IMGT  _____________ <-------------------------
                                                35                  40                  45
                                 S   N                           L   A   W   Y   Q   Q   K
VL 223C4                        agt aat ... ... ... ... ... ... tta gca tgg tat cag cag aaa

AJ235956 IGKV12-46*01           --- --- ... ... ... ... ... ... --- --- --- --- --- --- ---

                                 FR2 - IMGT  ------------------------> _____________  CDR2
                                                50                  55                  60
                                 Q   G   K   S   P   Q   L   L   V   Y   A   A   T
VL 223C4                        cag gga aaa tct cct cag ctc ctg gtc tat gct gca aca ... ...

AJ235956 IGKV12-46*01           --- --- --- --- --- --- --- --- --- --- --- --- --- ... ...

                                 - IMGT  __________ <-------------------------------------
                                                65                  70                  75
                                                     N   L   V   D   G   V   P       S   R
VL 223C4                        ... ... ... ... ... aac tta gta gat ggt gtg cca ... tca agg
                                                         A
AJ235956 IGKV12-46*01           ... ... ... ... ... --- --- -c- --- --- --- --- ... --- ---

                                ------------------------------- FR3 - IMGT ---------------
                                                80                  85                  90
                                 F   S   G   S   G           S   G   T   Q   Y   S   L   K
VL 223C4                        ttc agt ggc agt gga ... ... tca ggc aca cag tat tcc ctc aag

AJ235956 IGKV12-46*01           --- --- --- --- --- ... ... --- --- --- --- --- --- --- ---

                                ------------------------------------------------------> ____
                                                95                 100                 105
                                 I   N   S   L   Q   S   E   D   F   G   S   Y   Y   C   Q
VL 223C4                        atc aac agc ctg cag tct gaa gat ttt ggg agt tat tac tgt caa

AJ235956 IGKV12-46*01           --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---

                                _______  CDR3 -  IMGT _________ <---------------  FR4 - IMGT
                                               110                 115                 120
                                 H   F   W   G   P   P   Y   T   F   G   G   G   T   K   L
VL 223C4                        cat ttt tgg ggt cct ccg tac acg ttc gga ggg ggg acc aag ctg
                                                 T
AJ235956 IGKV12-46*01           --- --- --- --- a-- --t cc
```

FIGURE 29A

```
                                CDR3 -  IMGT ______ <---------------  FR4 - IMGT  -------->
                                   110                 115                 120         123
                                 G   P   P   Y   T   F   G   G   G   T   K   L   E   I   K
VL 223C4                        ggt cct ccg tac acg ttc gga ggg ggg acc aag ctg gag ata aag

VOO777 IGKJ2*01                          - --- --- --- --- --- --- --- --- --- --a --- --a
```

FIGURE 29B

```
                                <-------------------------------------------- FR1 - IMGT
                                1               5                   10                  15
                                 D   I   Q   M   T   Q   S   P   A   S   L   S   V   S   V
VL 223C4                        gac atc cag atg act cag tct cca gcc tcc cta tct gta tct gtg
                                                                S                   A
Y14865 IGKV1-NL1*01             --- --- --- --- --c --- --- --- t-- --- --g --- -c- --- --a

                                ------------------------------------------> ______________
                                                20                  25                  30
                                 G   E   T   V   T   I   T   C   R   A   S   E   N   I   Y
VL 223C4                        gga gaa act gtc acc atc aca tgt cga gca agt gag aat att tac
                                     D   R                                   Q   G       S
Y14865 IGKV1-NL1*01             --- --c -ga --- --- --- --t --c --g --g --- c-- ggc --- ag-

                                __  CDR1 - IMGT  _____________ <-------------------------
                                                35                  40                  45
                                 S   N                           L   A   W   Y   Q   Q   K
VL 223C4                        agt aat ... ... ... ... ... ... tta gca tgg tat cag cag aaa
                                 N   S
Y14865 IGKV1-NL1*01             -a- tc- ... ... ... ... ... ... --- --c --- --- --- --- ---

                                 FR2 - IMGT  -------------------------> _____________  CDR2
                                                50                  55                  60
                                 Q   G   K   S   P   Q   L   L   V   Y   A   A   T
VL 223C4                        cag gga aaa tct cct cag ctc ctg gtc tat gct gca aca ... ...
                                 P           A       K           L               S
Y14865 IGKV1-NL1*01             -ca --g --- g-c --- a-- --- --- c-- --- --- --- t-c ... ...

                                 - IMGT  __________ <-------------------------------------
                                                65                  70                  75
                                                     N   L   V   D   G   V   P       S   R
VL 223C4                        ... ... ... ... ... aac tta gta gat ggt gtg cca ... tca agg
                                                     R       E   S
Y14865 IGKV1-NL1*01             ... ... ... ... ... -ga --g -a- ag- --g --c --- ... --c ---

                                ------------------------------- FR3 - IMGT ---------------
                                                80                  85                  90
                                 F   S   G   S   G           S   G   T   Q   Y   S   L   K
VL 223C4                        ttc agt ggc agt gga ... ... tca ggc aca cag tat tcc ctc aag
                                                                        D       T       T
Y14865 IGKV1-NL1*01             --- --- --- --- --- ... ... --t --g --g g-t --c a-t --- -cc

                                ------------------------------------------------------> ____
                                                95                  100             104
                                 I   N   S   L   Q   S   E   D   F   G   S   Y   Y   C   Q
VL 223C4                        atc aac agc ctg cag tct gaa gat ttt ggg agt tat tac tgt caa
                                     S               P                   A   T
Y14865 IGKV1-NL1*01             --- -g- --- --- --- c-- --- --- --- -ca -c- --- --- --- ---

                                _______  CDR3 -  IMGT _________ <-------  FR4 - IMGT  -----
                                               110                 115                 120
                                 H   F   W   G   P   P   Y   T   F   G   G   G   T   K   L
VL 223C4                        cat ttt tgg ggt cct ccg tac acg ttc gga ggg ggg acc aag ctg
                                 Q   Y   Y   S   T
Y14865 IGKV1-NL1*01             --g -a- -at a-- a-c --t cc
```

FIGURE 30A

```
                                CDR3 -  IMGT ______ <--------------- FR4 - IMGT --------->
                                   110                 115                 120         123
                                 G   P   P   Y   T   F   G   G   G   T   K   L   E   I   K
VL 223C4                        ggt cct ccg tac acg ttc gga ggg ggg acc aag ctg gag ata aag
                                                            Q
J00242 IGKJ2*01                         - --- --t --t --c ca- --- --- --- --- --- --c --a
```

FIGURE 30B

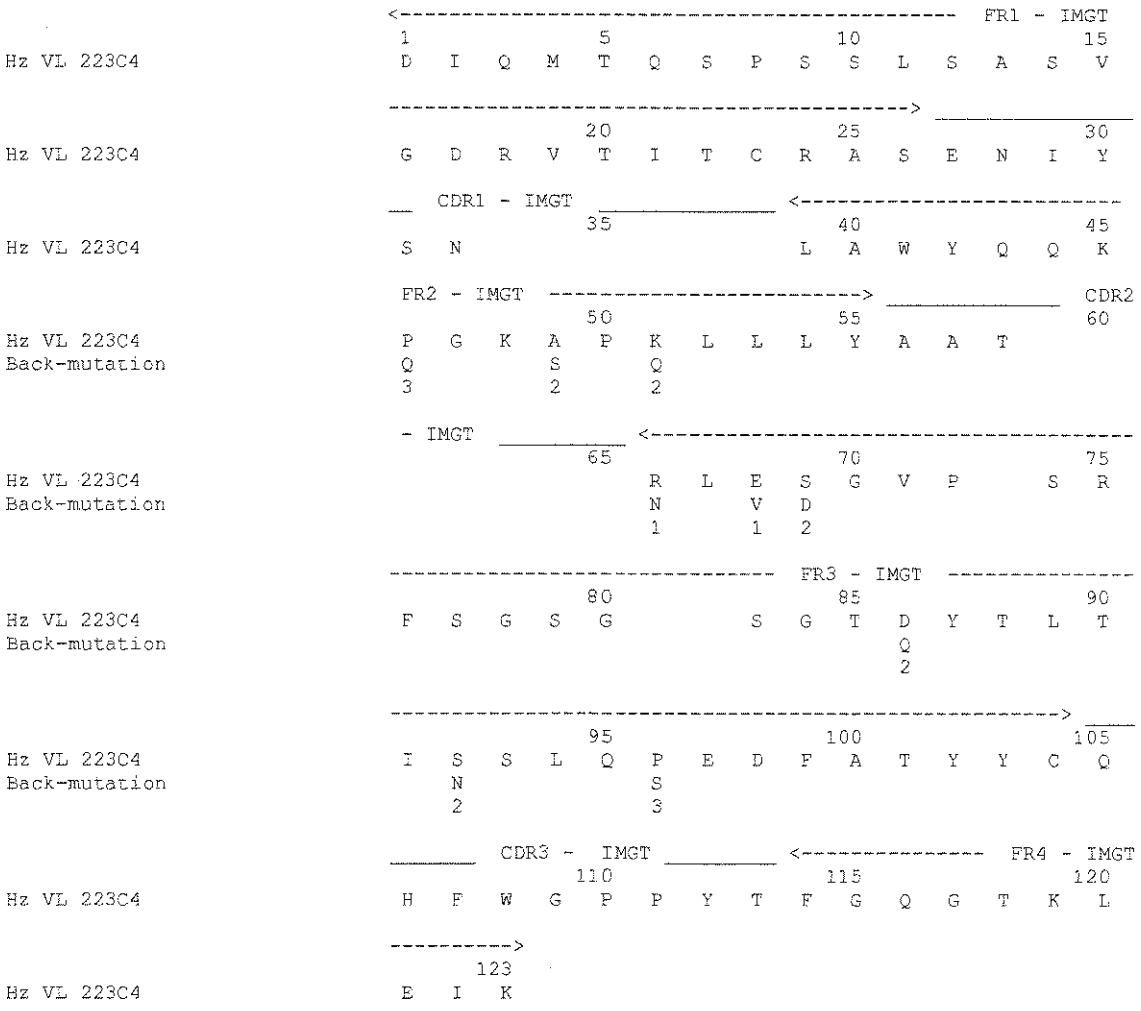

FR1 - IMGT
1 5 10 15
Hz VL 223C4 D I Q M T Q S P S S L S A S V
20 25 30
Hz VL 223C4 G D R V T I T C R A S E N I Y
CDR1 - IMGT
35 40 45
Hz VL 223C4 S N L A W Y Q Q K
FR2 - IMGT CDR2
50 55 60
Hz VL 223C4 P G K A P K L L L Y A A T
Back-mutation Q S Q
3 2 2
IMGT
65 70 75
Hz VL 223C4 R L E S G V P S R
Back-mutation N V D
1 1 2
FR3 - IMGT
80 85 90
Hz VL 223C4 F S G S G S G T D Y T L T
Back-mutation Q
2
95 100 105
Hz VL 223C4 I S S L Q P E D F A T Y Y C Q
Back-mutation N S
2 3
CDR3 - IMGT FR4 - IMGT
110 115 120
Hz VL 223C4 H F W G P P Y T F G Q G T K L
123
Hz VL 223C4 E I K

FIGURE 31

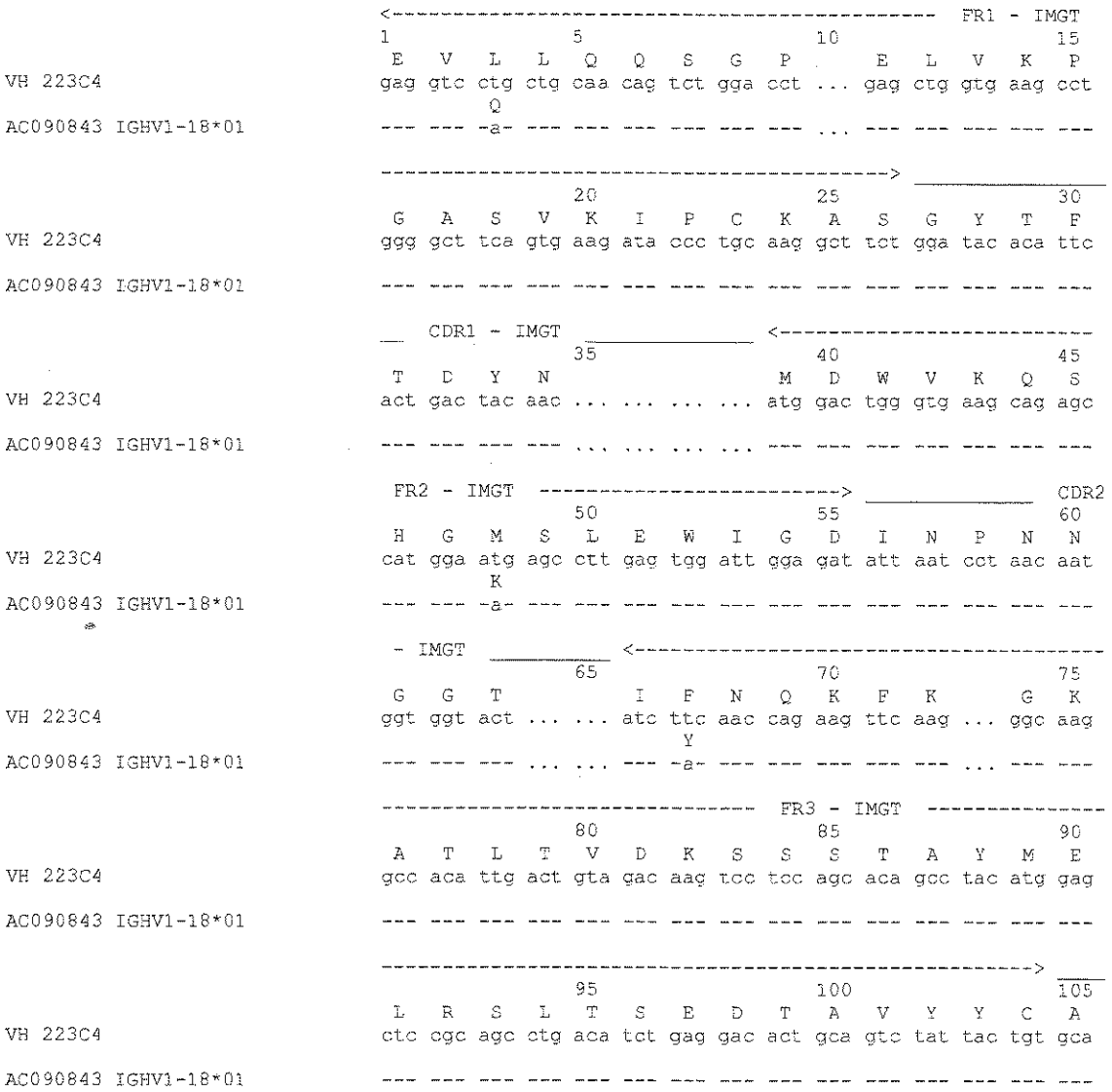


FIGURE 32A

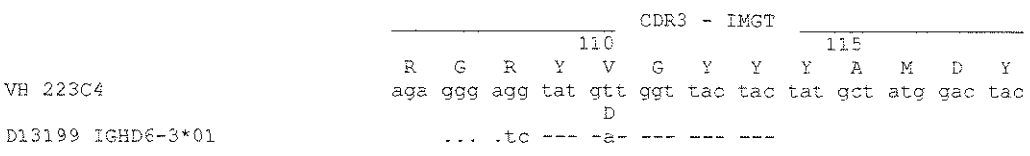


FIGURE 32B

```
                 ___ CDR3 - IMGT _____________ <--------------- FR4 - IMGT ------------->
                                 115                 120                 125             129
                  G   Y   Y   Y   A   M   D   Y   W   G   Q   G   T   S   V   T   V   S   S
VH 223C4         ggt tac tac tat gct atg gac tac tgg ggt caa gga acc tca gtc acc gtc tcc tca

V00770 IGHJ4*01       -t --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
```

FIGURE 32C

```
                                 <-------------------------------------------- FR1 - IMGT
                                 1               5                   10                  15
                                  E   V   L   L   Q   Q   S   G   P       E   L   V   K   P
VH 223C4                         gag gtc ctg ctg caa cag tct gga cct ... gag ctg gtg aag cct
                                  Q       Q       V               A           V   K
X62106 IGHV1-2*02                c-- --g -a- --- gtg --- --- --g g-- ... --- g-- aa- --- ---

                                 ------------------------------------------> ______________
                                                 20                  25                  30
                                  G   A   S   V   K   I   P   C   K   A   S   G   Y   T   F
VH 223C4                         ggg gct tca gtg aag ata ccc tgc aag gct tct gga tac aca ttc
                                                     V   S
X62106 IGHV1-2*02                --- --c --- --- --- g-c t-- --- --- --- --- --- --- --c ---

                                 __ CDR1 - IMGT _____________ <-------------------------
                                                 35                  40                  45
                                  T   D   Y   N                   M   D   W   V   K   Q   S
VH 223C4                         act gac tac aac ... ... ... ... atg gac tgg gtg aag cag agc
                                     G       Y                       H           R       A
X62106 IGHV1-2*02                --c -g- --- t-t ... ... ... ... --- c-- --- --- cga --- gc-

                                  FR2 - IMGT ------------------------> _____________ CDR2
                                                 50                  55                  60
                                  H   G   M   S   L   E   W   I   G   D   I   N   P   N   N
VH 223C4                         cat gga atg agc ctt gag tgg att gga gat att aat cct aac aat
                                  P       Q   G               M       W                   S
X62106 IGHV1-2*02                -c- --- caa g-g --- --- --- --g --- tgg --c --c --- --- -g-

                                  - IMGT _________ <-------------------------------------
                                                 65                  70                  75
                                  G   G   T           I   F   N   Q   K   F   K       G   K
VH 223C4                         ggt ggt act ... ... atc ttc aac cag aag ttc aag ... ggc aag
                                                     N   Y   A               Q           R
X62106 IGHV1-2*02                --- --c --a ... ... -a- -at gca --- --- --t c-- ... --- -g-

                                 ------------------------------ FR3 - IMGT ---------------
                                                 80                  85                  90
                                  A   T   L   T   V   D   K   S   S   S   T   A   Y   M   E
VH 223C4                         gcc aca ttg act gta gac aag tcc tcc agc aca gcc tac atg gag
                                  V       M       R       T       I
X62106 IGHV1-2*02                -t- --c a-- --c agg --- -c- --- at- --- --- --- --- --- ---

                                 ------------------------------------------------------> ____
                                                 95                  100                 105
                                  L   R   S   L   T   S   E   D   T   A   V   Y   Y   C   A
VH 223C4                         ctc cgc agc ctg aca tct gag gac act gca gtc tat tac tgt gca
                                     S   R       R       D
X62106 IGHV1-2*02                --g a-- --g --- -g- --- --c --- --g --c --g --- --- --- --g
```

FIGURE 33A

```
                                  ________________ CDR3 - IMGT ________________
                                                 110                 115
                                   R   G   R   Y   V   G   Y   Y   Y   A   M   D   Y
VH 223C4                          aga ggg agg tat gtt ggt tac tac tat gct atg gac tac

X97051 IGHD1-26*01                 -t --- --c --c tac
```

FIGURE 33B

```
                  ____________ CDR3 - IMGT ____________ <-------------- FR4 - IMGT
                        110                 115                 120                 125
                   R   Y   V   G   Y   Y   Y   A   M   D   Y   W   G   Q   G   T   S   V
VH 223C4          agg tat gtt ggt tac tac tat gct atg gac tac tgg ggt caa gga acc tca gtc
                          Y   Y               G           V                       T
J00256 IGHJ6*01       -- tac tac --- --- --c -g- --- --- gt- --- --g --- --g --- a-g ---

                   ------------->
                             129
                   T   V   S   S
VH 223C4          acc gtc tcc tca

J00256 IGHJ6*01   --- --- --- ---
```

FIGURE 33C

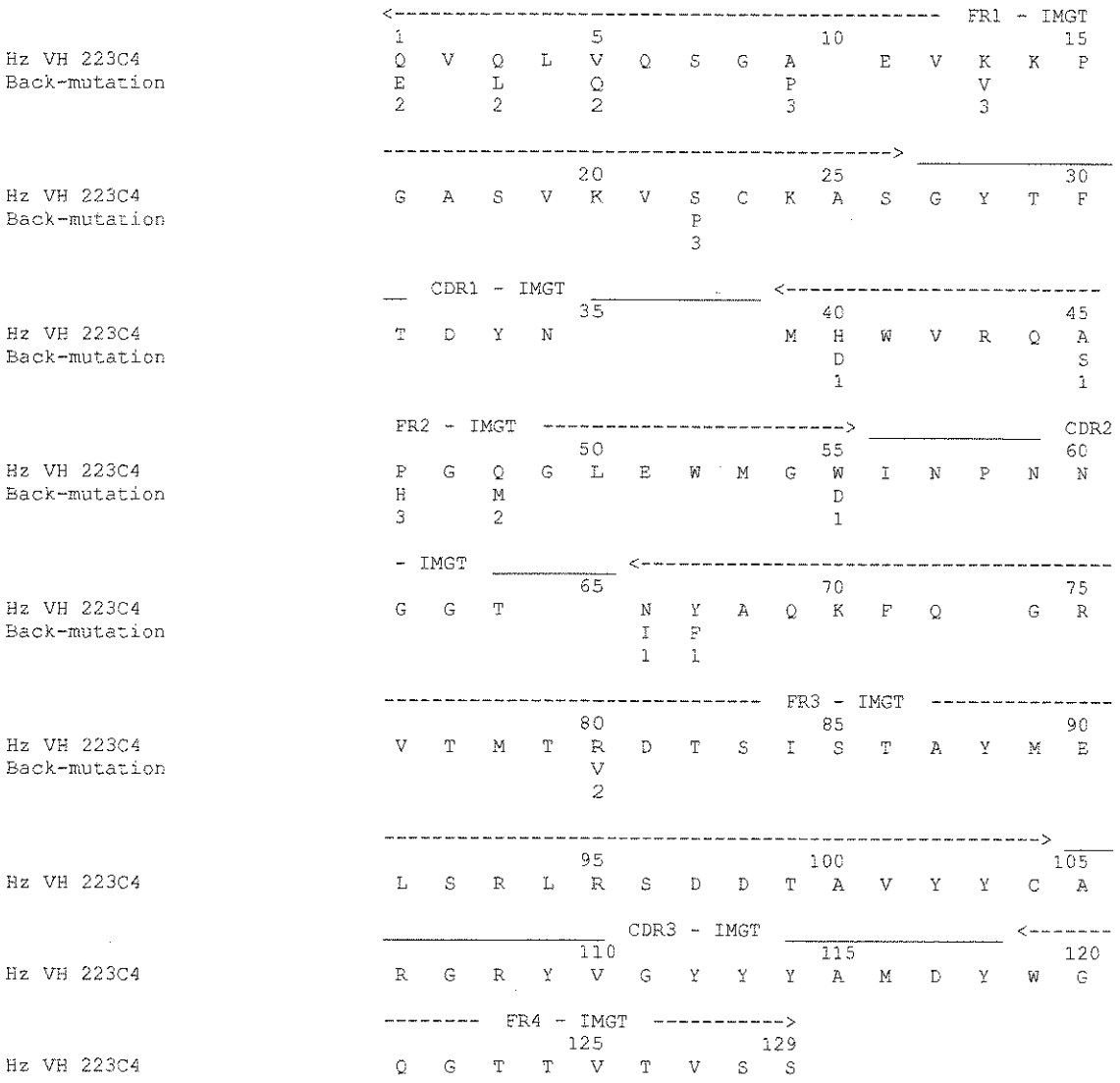

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
- IMGT
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
Hz VH 223C4
Back-mutation
Hz VH 223C4
Hz VH 223C4
Back-mutation
Hz VH 223C4
Back-mutation
Hz VH 223C4
Back-mutation
Hz VH 223C4
Hz VH 223C4
Hz VH 223C4

FIGURE 34

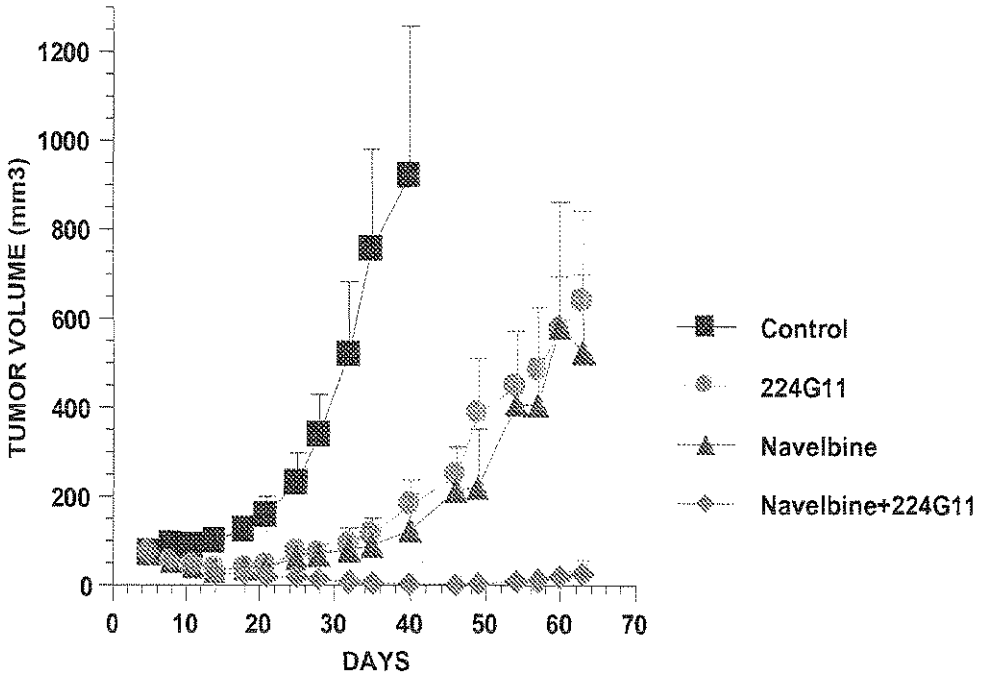

TUMOR VOLUME (mm3)
1200
1000
800
600
400
200
0
0
10
20
30
40
50
60
70
DAYS
Control
224G11
Navelbine
Navelbine+224G11

FIGURE 35

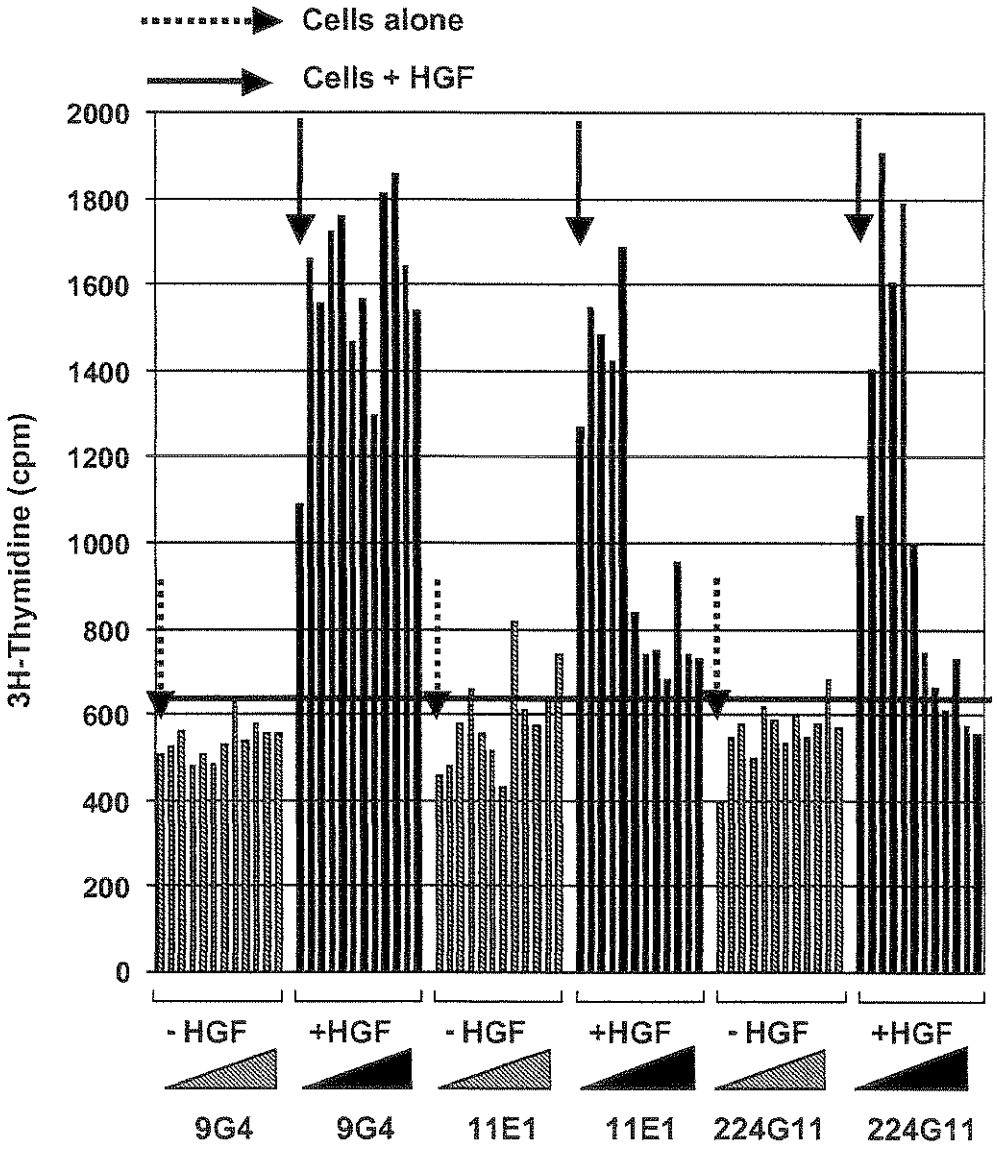

Cells alone
Cells + HGF
3H-Thymidine (cpm)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
- HGF
+HGF
- HGF
+HGF
- HGF
+HGF
9G4
9G4
11E1
11E1
224G11
224G11

FIGURE 36

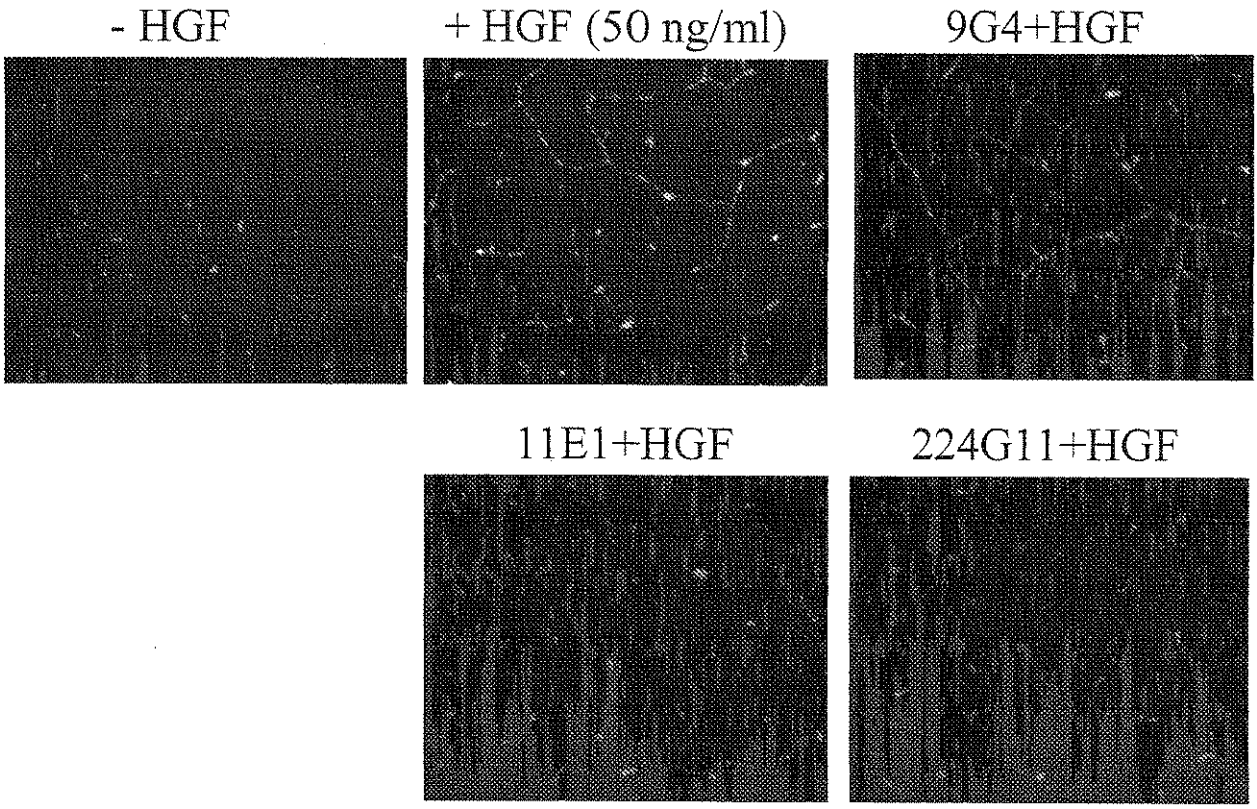


FIGURE 37

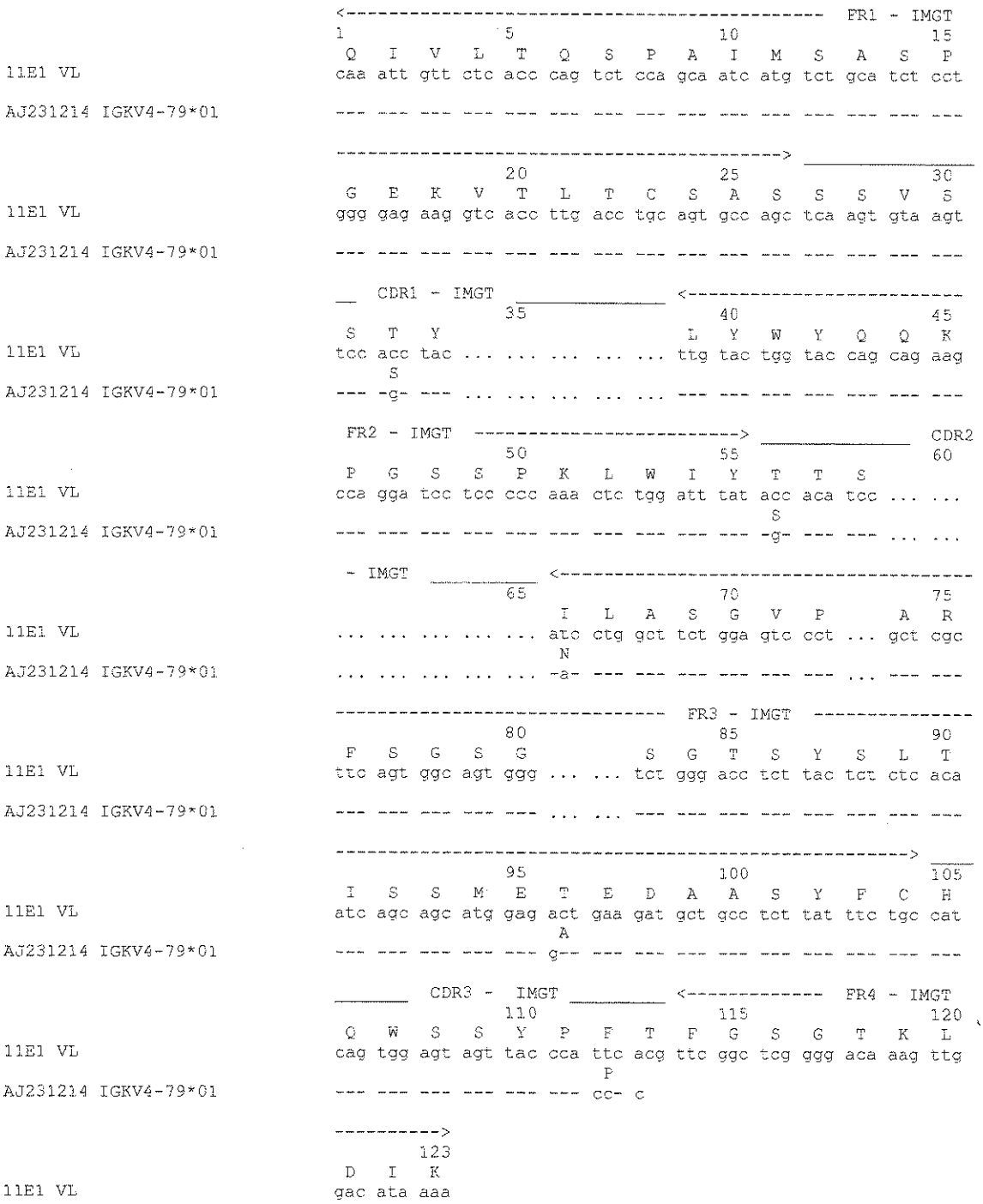

<---------- FR1 - IMGT
1 5 10 15
Q I V L T Q S P A I M S A S P
11E1 VL caa att gtt ctc acc cag tct cca gca atc atg tct gca tct cct
AJ231214 IGKV4-79*01 --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
----------> _____
20 25 30
G E K V T L T C S A S S S V S
11E1 VL ggg gag aag gtc acc ttg acc tgc agt gcc agc tca agt gta agt
AJ231214 IGKV4-79*01 --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
__ CDR1 - IMGT _____ <----------
35 40 45
S T Y L Y W Y Q Q K
11E1 VL tcc acc tac ... ... ttg tac tgg tac cag cag aag
S
AJ231214 IGKV4-79*01 --- -g- --- ... ... --- --- --- --- --- --- ---
FR2 - IMGT ----------> _____ CDR2
50 55 60
P G S S P K L W I Y T T S
11E1 VL cca gga tcc tcc ccc aaa ctc tgg att tat acc aca tcc ... ...
S
AJ231214 IGKV4-79*01 --- --- --- --- --- --- --- --- --- --- -g- --- --- ... ...
- IMGT _____ <----------
65 70 75
I L A S G V P A R
11E1 VL ... ... atc ctg gct tct gga gtc cct ... gct cgc
N
AJ231214 IGKV4-79*01 ... ... -a- --- --- --- --- --- --- ... --- ---
---------- FR3 - IMGT ----------
80 85 90
F S G S G S G T S Y S L T
11E1 VL ttc agt ggc agt ggg ... ... tct ggg acc tct tac tct ctc aca
AJ231214 IGKV4-79*01 --- --- --- --- --- ... ... --- --- --- --- --- --- --- ---
----------> ____
95 100 105
I S S M E T E D A A S Y F C H
11E1 VL atc agc agc atg gag act gaa gat gct gcc tct tat ttc tgc cat
A
AJ231214 IGKV4-79*01 --- --- --- --- --- g-- --- --- --- --- --- --- --- --- ---
_____ CDR3 - IMGT _____ <---------- FR4 - IMGT
110 115 120
Q W S S Y P F T F G S G T K L
11E1 VL cag tgg agt agt tac cca ttc acg ttc ggc tcg ggg aca aag ttg
P
AJ231214 IGKV4-79*01 --- --- --- --- --- --- cc- c
---------->
123
D I K
11E1 VL gac ata aaa

FIGURE 38A

```
                                 _______  CDR3 -  IMGT  _________  <-------------  FR4 - IMGT
                                                 110                  115                 120
                                  Q   W   S   S   Y   P   F   T   F   G   S   G   T   K   L
11E1 VL                          cag tgg agt agt tac cca ttc acg ttc ggc tcg ggg aca aag ttg

V00777 IGKJ4*01                                          --- --- --- --- --- --- --- --- ---

                                 ---------->
                                         123
                                  D   I   K
11E1 VL                          gac ata aaa
                                  E
V00777 IGKJ4*01                  --a --- --- c
```

FIGURE 38B

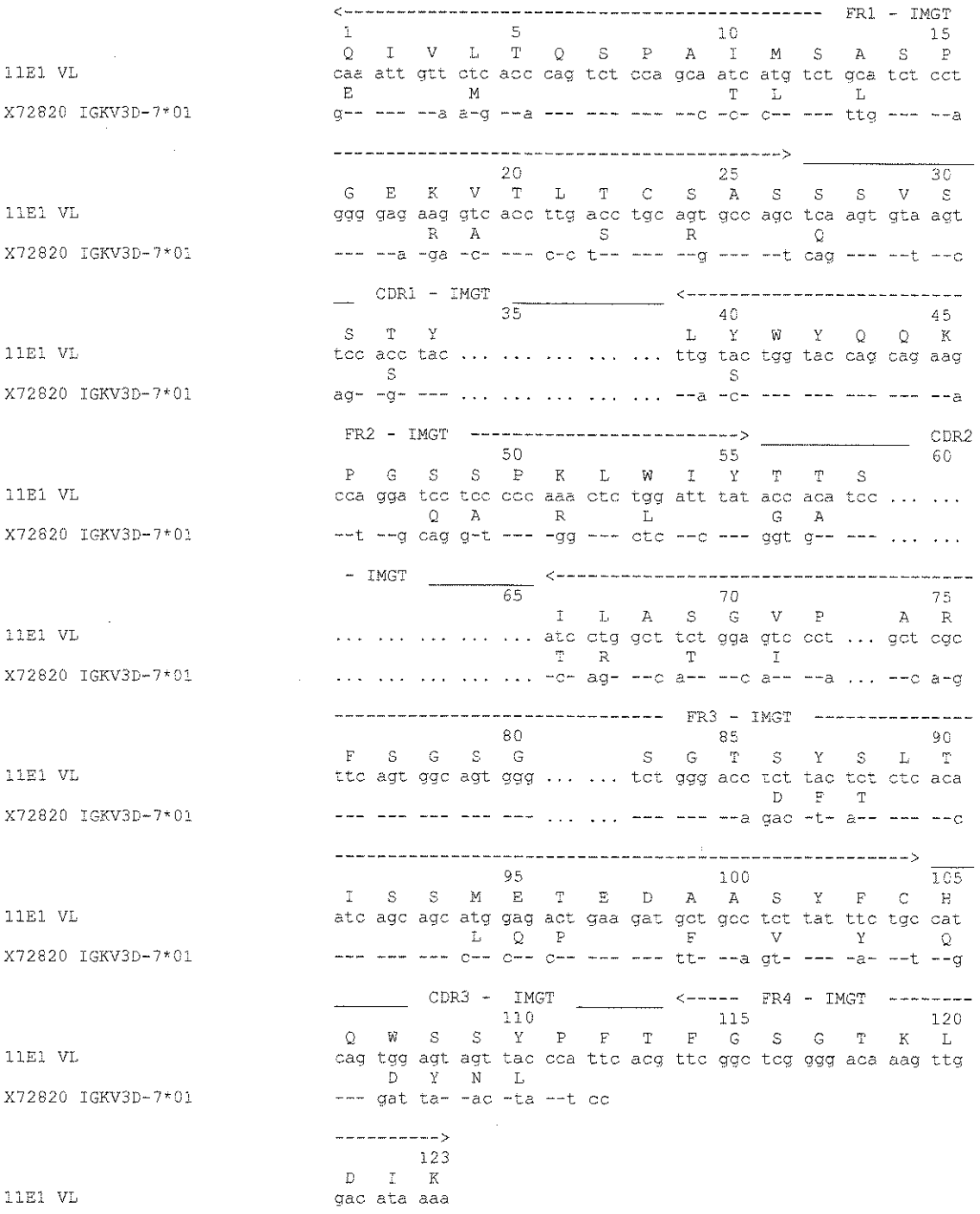

<---------- FR1 - IMGT
1 5 10 15
Q I V L T Q S P A I M S A S P
11E1 VL caa att gtt ctc acc cag tct cca gca atc atg tct gca tct cct
E M T L L
X72820 IGKV3D-7*01 g-- --- --a a-g --a --- --- --- --c -c- c-- --- ttg --- --a
----------> _____
20 25 30
G E K V T L T C S A S S S V S
11E1 VL ggg gag aag gtc acc ttg acc tgc agt gcc agc tca agt gta agt
R A S R Q
X72820 IGKV3D-7*01 --- --a -ga -c- --- c-c t-- --- --g --- --t cag --- --t --c
__ CDR1 - IMGT _____ <----------
35 40 45
S T Y L Y W Y Q Q K
11E1 VL tcc acc tac ... ... ttg tac tgg tac cag cag aag
S S
X72820 IGKV3D-7*01 ag- -g- --- ... ... --a -c- --- --- --- --- --a
FR2 - IMGT ----------> _____ CDR2
50 55 60
P G S S P K L W I Y T T S
11E1 VL cca gga tcc tcc ccc aaa ctc tgg att tat acc aca tcc ... ...
Q A R L G A
X72820 IGKV3D-7*01 --t --g cag g-t --- -gg --- ctc --c --- ggt g-- --- ... ...
- IMGT _____ <----------
65 70 75
I L A S G V P A R
11E1 VL ... ... atc ctg gct tct gga gtc cct ... gct cgc
T R T I
X72820 IGKV3D-7*01 ... ... -c- ag- --c a-- --c a-- --a ... --c a-g
---------- FR3 - IMGT ----------
80 85 90
F S G S G S G T S Y S L T
11E1 VL ttc agt ggc agt ggg ... ... tct ggg acc tct tac tct ctc aca
D F T
X72820 IGKV3D-7*01 --- --- --- --- --- ... ... --- --- --a gac -t- a-- --- --c
----------> ____
95 100 105
I S S M E T E D A A S Y F C H
11E1 VL atc agc agc atg gag act gaa gat gct gcc tct tat ttc tgc cat
L Q P F V Y Q
X72820 IGKV3D-7*01 --- --- --- c-- c-- c-- --- --- tt- --a gt- --- -a- --t --g
_____ CDR3 - IMGT _____ <----- FR4 - IMGT --------
110 115 120
Q W S S Y P F T F G S G T K L
11E1 VL cag tgg agt agt tac cca ttc acg ttc ggc tcg ggg aca aag ttg
D Y N L
X72820 IGKV3D-7*01 --- gat ta- -ac -ta --t cc
---------->
123
D I K
11E1 VL gac ata aaa

FIGURE 39A

```
                                CDR3 -  IMGT  __ <------------  FR4 - IMGT  ----------->
                                 110                 115                 120         123
                                  Y   P   F   T   F   G   S   G   T   K   L   D   I   K
11E1 VL                          tac cca ttc acg ttc ggc tcg ggg aca aag ttg gac ata aaa
                                                         G                 V   E
AF103571 IGKJ4*02                ......g c-- --- --- --- gga --- --c --- g-- --g --c --
```

FIGURE 39B

```
                                FR1-IMGT          CDR1-IMGT        FR2-IMGT      CDR2-IMGT
                                 (1-26)            (27-38)          (39-55)       (56-65)
                     ____________________________ ____________ ____________________ ____________
                     1        10        20        30          40        50         60
                     .........|.........|...... ...|........ .|.........|..... ....|.....
11E1 VL              QIVLTQSPAIMSASPGEKVTLTCSAS SSVSSTY..... LYWYQQKPGSSPKLWIY TTS.......
rank                 3  1      33 3     33  3 2                1       33 3 2
Human FR             E--M-----TL-L----RA--S-R--               -S-------QA-R-L--
11E1 HZVL            EIVLTQSPATLSLSPGERATLSCRAS SSVSSTY..... LYWYQQKPGQAPRLLIY TTS.......

                                  FR3-IMGT                        CDR3-IMGT     FR4-IMGT
                                  (66-104)                        (105-113)     (114-123)
                      ____________________________________________ ____________ ____________
                         70        80        90        100          110          120
                      ....|.........|.........|.........|....     .....|...     ......|...
11E1 VL               ILASGVP.ARFSGSG..SGTSYSLTISSMETEDAASYFC     HQWSSYPFT     FGSGTKLDIK
rank                  22 3 3              213     321  2 3 3                     3   32
Human FR              TR-T-I-.-------..---DFT-----LQP--F-V-Y-                   --G---VE--
11E1 HZVL             TRATGIP.ARFSGSG..SGTDYTLTISSLQTEDFAVYYC     HQWSSYPFT     FGGGTKVEIK
```

FIGURE 40

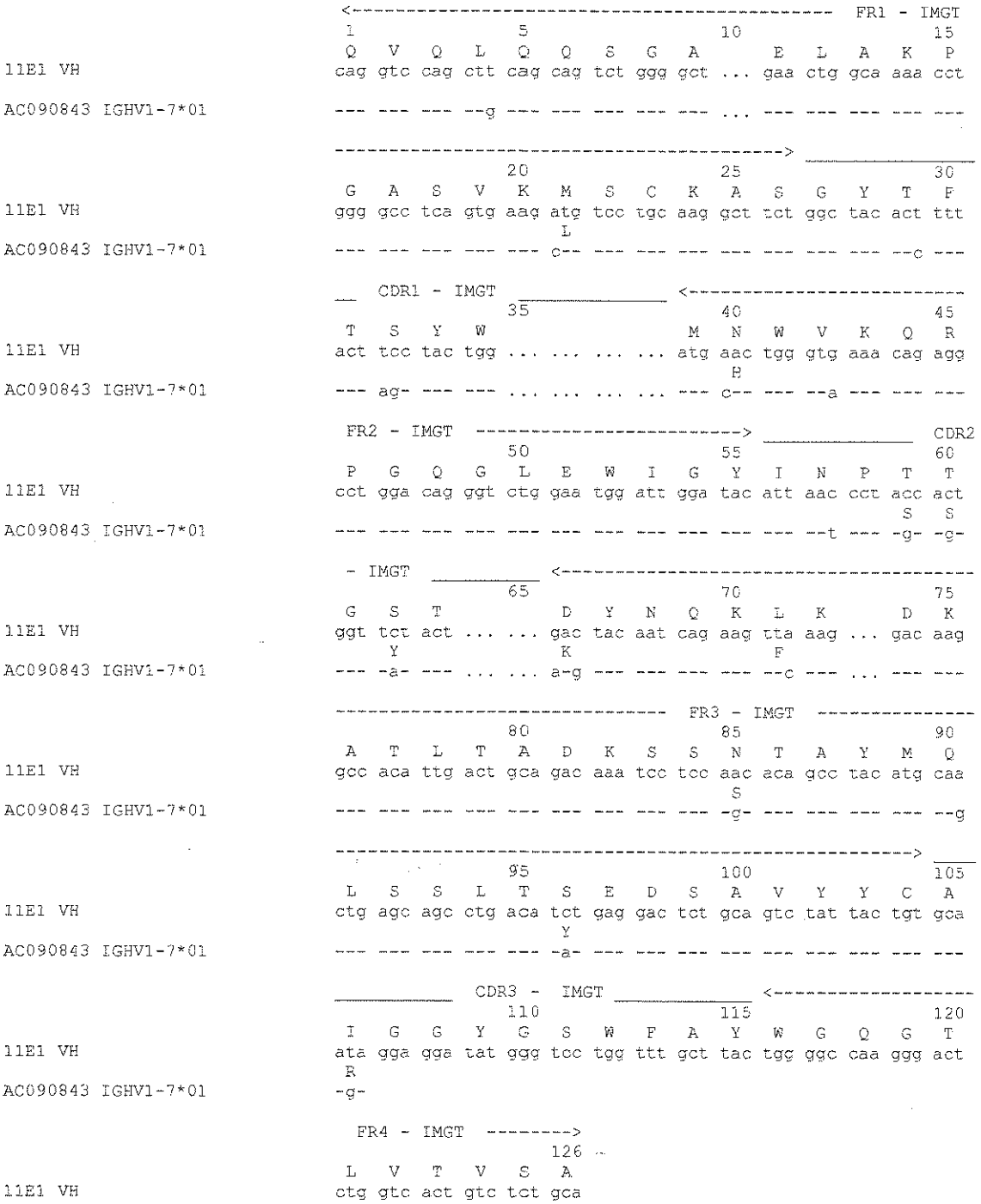

<---------- FR1 - IMGT
1 5 10 15
Q V Q L Q Q S G A E L A K P
11E1 VH cag gtc cag ctt cag cag tct ggg gct ... gaa ctg gca aaa cct
AC090843 IGHV1-7*01 --- --- --- --g --- --- --- --- --- ... --- --- --- --- ---
----------> _____
20 25 30
G A S V K M S C K A S G Y T F
11E1 VH ggg gcc tca gtg aag atg tcc tgc aag gct tct ggc tac act ttt
L
AC090843 IGHV1-7*01 --- --- --- --- --- c-- --- --- --- --- --- --- --- --c ---
__ CDR1 - IMGT _____ <----------
35 40 45
T S Y W M N W V K Q R
11E1 VH act tcc tac tgg ... ... atg aac tgg gtg aaa cag agg
R
AC090843 IGHV1-7*01 --- ag- --- --- ... ... --- c-- --- --a --- --- ---
FR2 - IMGT ----------> _____ CDR2
50 55 60
P G Q G L E W I G Y I N P T T
11E1 VH cct gga cag ggt ctg gaa tgg att gga tac att aac cct acc act
S S
AC090843 IGHV1-7*01 --- --- --- --- --- --- --- --- --- --- --- --t --- -g- -g-
- IMGT _____ <----------
65 70 75
G S T D Y N Q K L K D K
11E1 VH ggt tct act ... ... gac tac aat cag aag tta aag ... gac aag
Y K F
AC090843 IGHV1-7*01 --- -a- --- ... ... a-g --- --- --- --- --c --- ... --- ---
---------- FR3 - IMGT ----------
80 85 90
A T L T A D K S S N T A Y M Q
11E1 VH gcc aca ttg act gca gac aaa tcc tcc aac aca gcc tac atg caa
S
AC090843 IGHV1-7*01 --- --- --- --- --- --- --- --- --- -g- --- --- --- --- --g
----------> ____
95 100 105
L S S L T S E D S A V Y Y C A
11E1 VH ctg agc agc ctg aca tct gag gac tct gca gtc tat tac tgt gca
Y
AC090843 IGHV1-7*01 --- --- --- --- --- --a- --- --- --- --- --- --- --- --- ---
_____ CDR3 - IMGT _____ <----------
110 115 120
I G G Y G S W F A Y W G Q G T
11E1 VH ata gga gga tat ggg tcc tgg ttt gct tac tgg ggc caa ggg act
R
AC090843 IGHV1-7*01 -g-
FR4 - IMGT --------->
126
L V T V S A
11E1 VH ctg gtc act gtc tct gca

FIGURE 41A

```
                                 ____________ CDR3 -  IMGT ____________
                                105                 110                 115
                                 A   I   G   G   Y   G   S   W   F   A   Y
11E1 VH                         gca ata gga gga tat ggg tcc tgg ttt gct tac
L32868 IGHD4-1*01                    -g --- c
```

FIGURE 41B

```
                                 ___________ CDR3 -  IMGT ____________ <-------------------
                                                 110                 115                 120
                                 I   G   G   Y   G   S   W   F   A   Y   W   G   Q   G   T
11E1 VH                         ata gga gga tat ggg tcc tgg ttt gct tac tgg ggc caa ggg act

V00770 IGHJ3*01                  .. ... ... ... ... .-- --- --- --- --- --- --- --- --- ---

                                  FR4 - IMGT  -------->
                                                     126
                                 L   V   T   V   S   A
11E1 VH                         ctg gtc act gtc tct gca

V00770 IGHJ3*01                 --- --- --- --- --- --- g
```

FIGURE 41C

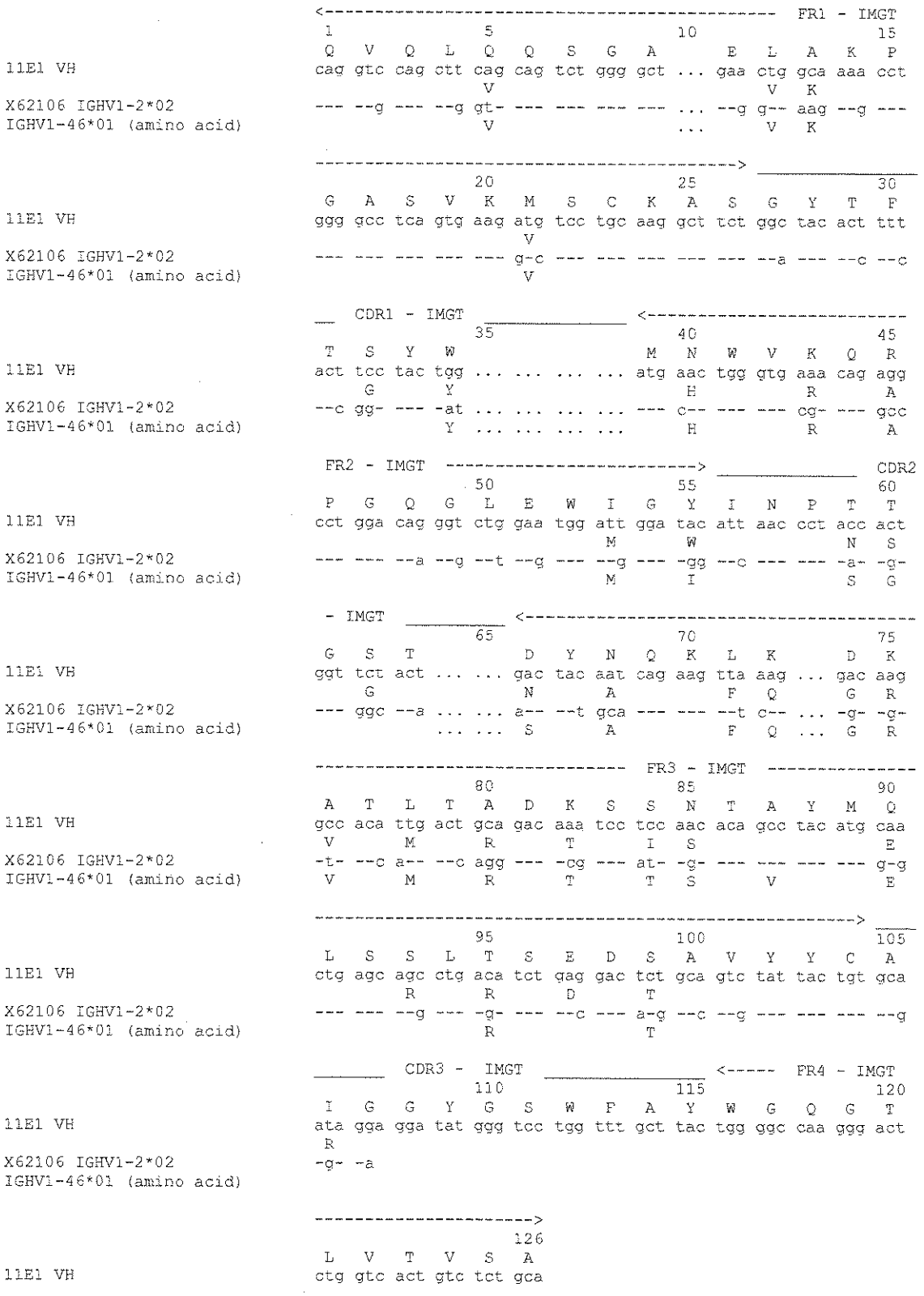

FR1 - IMGT
CDR1 - IMGT
FR2 - IMGT
CDR2
FR3 - IMGT
CDR3 - IMGT
FR4 - IMGT
11E1 VH
X62106 IGHV1-2*02
IGHV1-46*01 (amino acid)

FIGURE 42A

```
                    CDR3 -  IMGT  ___________ <-----  FR4 - IMGT  ---------------------->
                      110                 115                 120                     126
                       G   S   W   F   A   Y   W   G   Q   G   T   L   V   T   V   S   A
11E1 VH               ggg tcc tgg ttt gct tac tgg ggc caa ggg act ctg gtc act gtc tct gca
                                                                                       S
M25625 IGHJ4*03       ... .g- -ac --- -ac --- --- --- --- --- --c --- --- --c --- --c t-- g
```

FIGURE 42B

```
                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT
                           (1-26)            (27-38)        (39-55)       (56-65)
                 ____________________________ ____________ ____________________ ____________
                 1       10        20          30          40        50          60
                 .........|.........|......  ...|........  .|.........|.....  ....|.....
11E1 VH          QVQLQQSGA.ELAKPGASVKMSCKAS  GYTFTSYW....  MNWVKQRPGQGLEWIGY  INPTTGST..
rank                 3      33       3                     1  3 3       2 1
Human FR         ----V----.-VK-------V-----                -H--R-A-------M-I
11E1 HZVH        QVQLVQSGA.EVKKPGASVKVSCKAS  GYTFTSYW....  MNWVRQAPGQGLEWMGY  INPTTGST..

                                FR3-IMGT                      CDR3-IMGT      FR4-IMGT
                                (66-104)                      (105-115)     (116-126)
                 ____________________________________________ ____________ ____________
                    70        80        90        100          110          120
                 ....|.........|.........|.........|....    .....|.....    ....|......
11E1 VH          DYNQKLK.DKATLTADKSSNTAYMQLSSLTSEDSAVYYC    AIGGYGSWFAY    WGQGTLVTVSA
rank             1    23 332 2 1 1 33 2  3    3   3                                  3
Human FR         S-A--FQ.GRV-M-R-T-TS-V--E----R---T-----                   ----------S
11E1 HZVH        DYAQKFQ.GRVTMTADKSTSTVYMELSSLRSEDTAVYYC    AIGGYGSWFAY    WGQGTLVTVSS
```

FIGURE 43

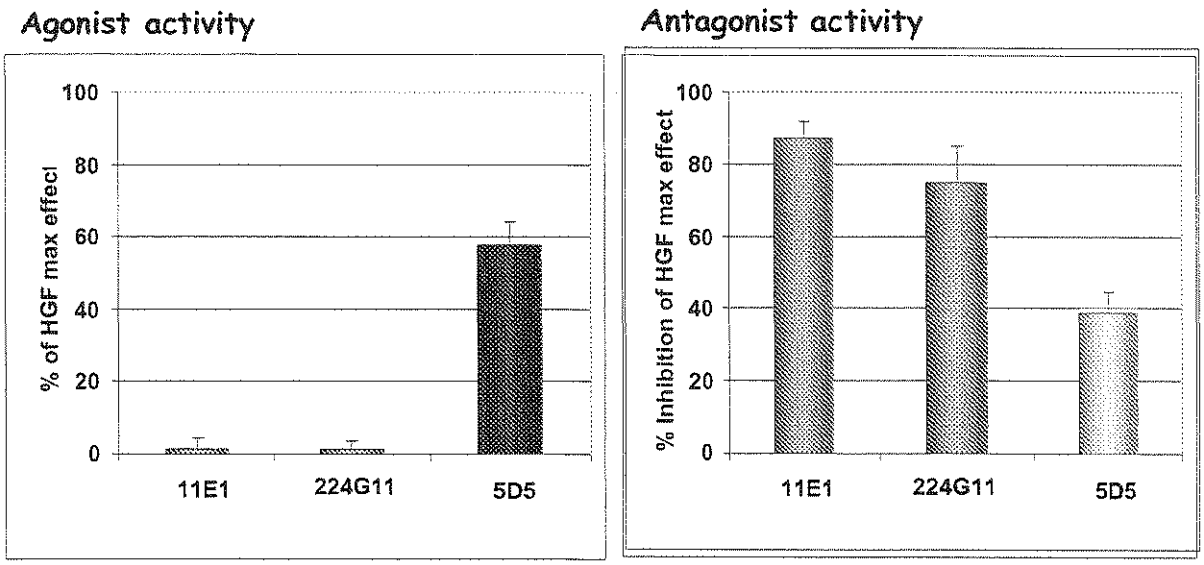


FIGURE 44A

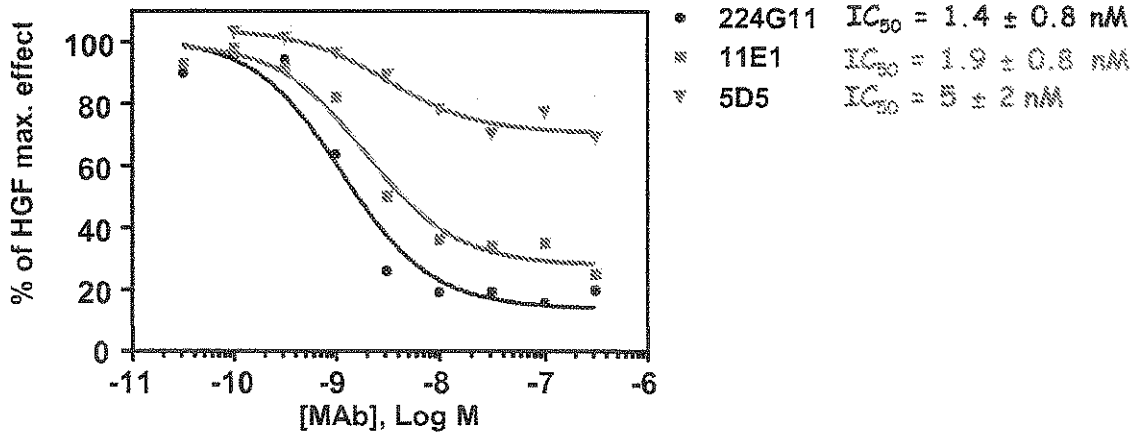


FIGURE 44B

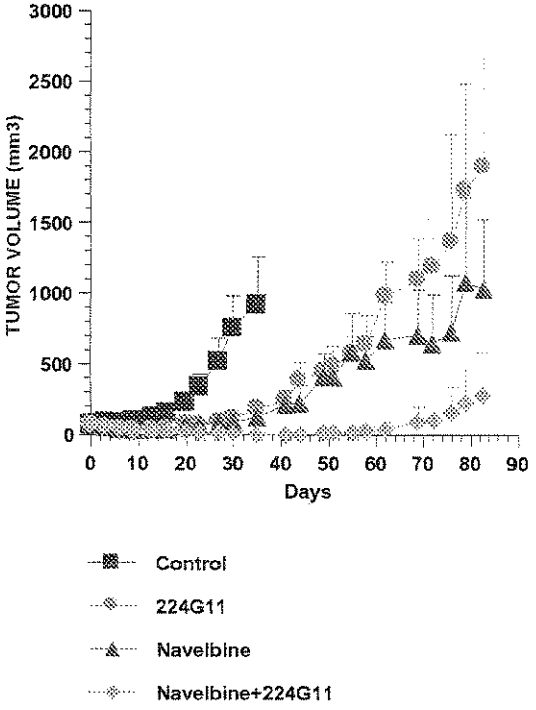


FIGURE 45

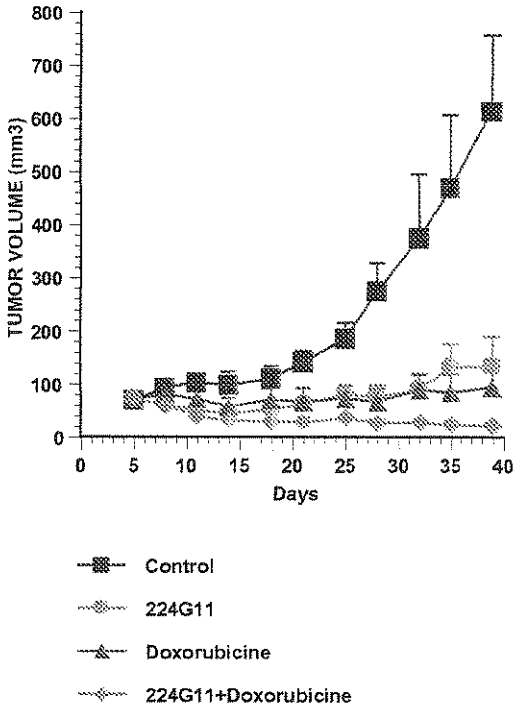


FIGURE 46

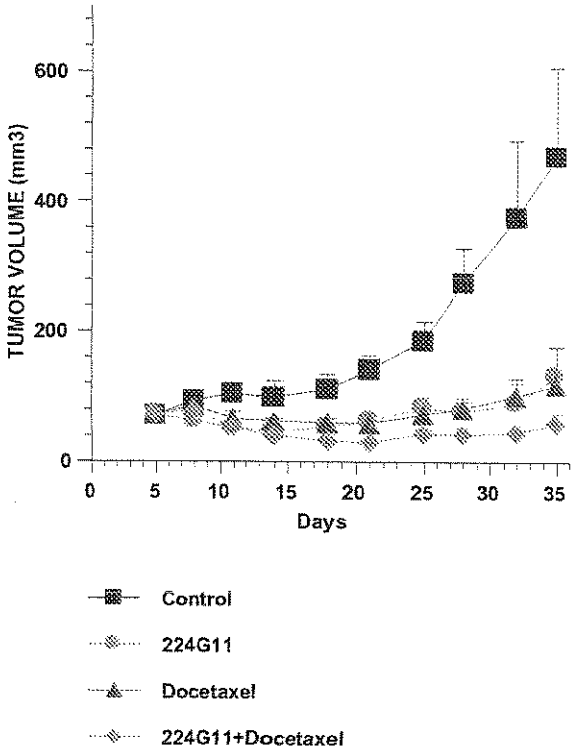


FIGURE 47

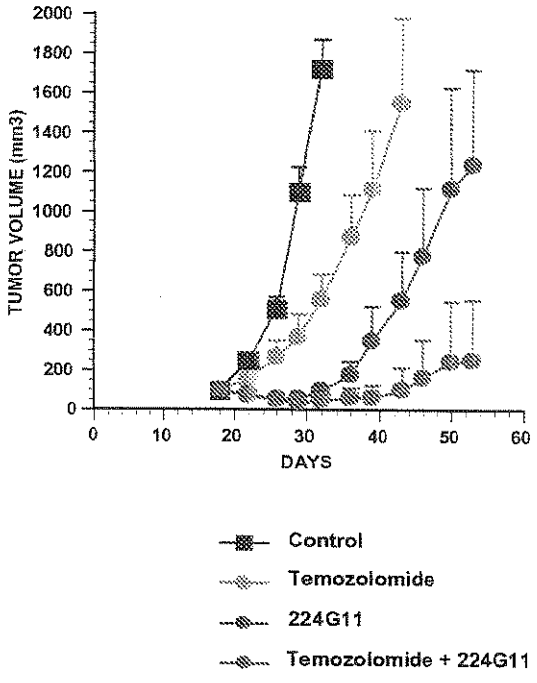


FIGURE 48

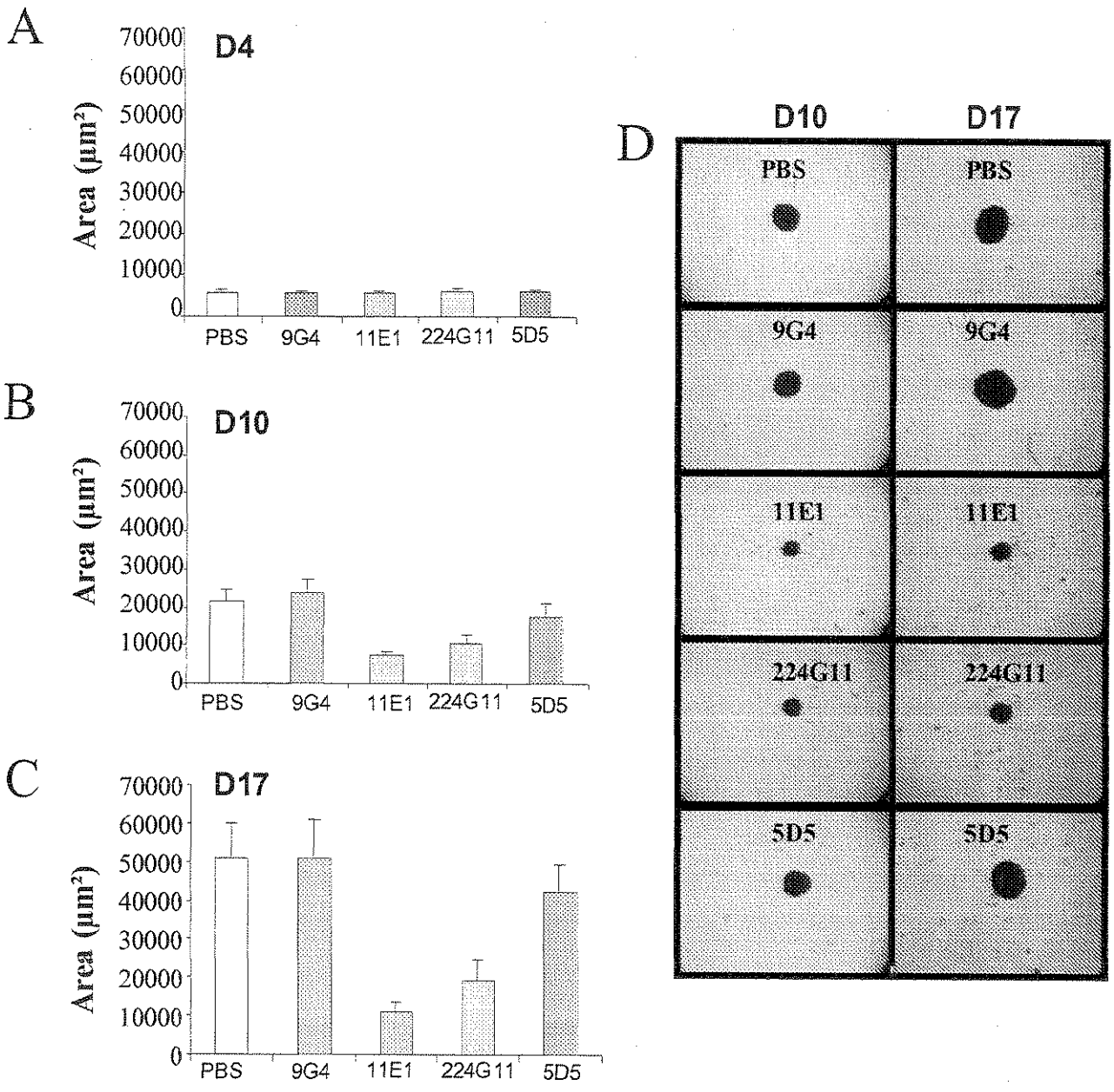


FIGURE 49A – FIGURE 49B – FIGURE 49C – FIGURE 49D

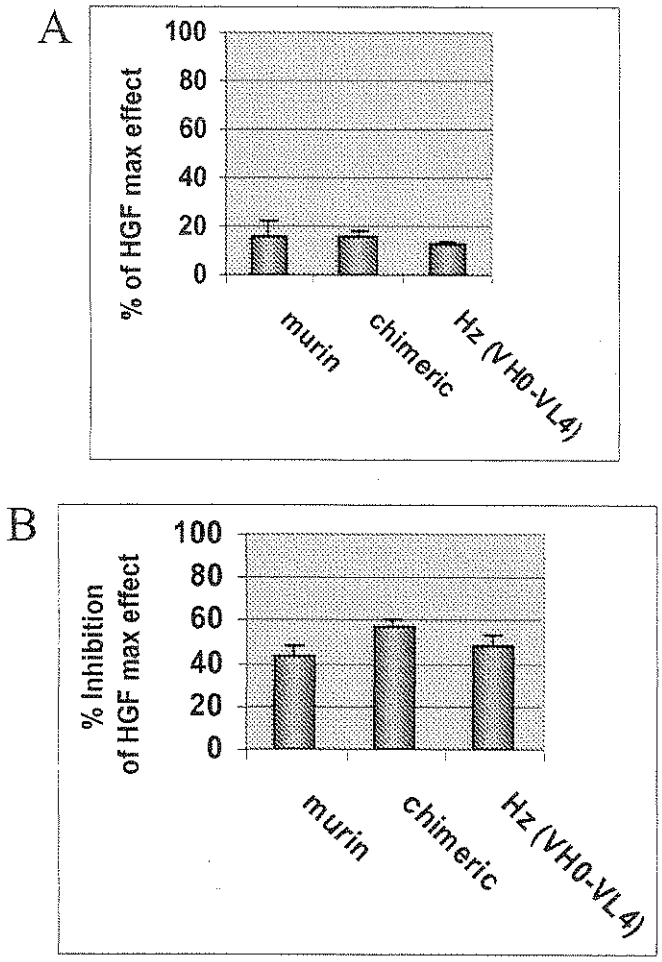


FIGURE 50A – FIGURE 50B

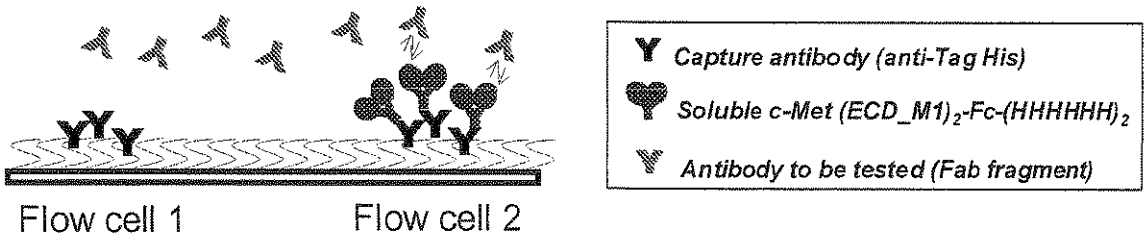


FIGURE 51

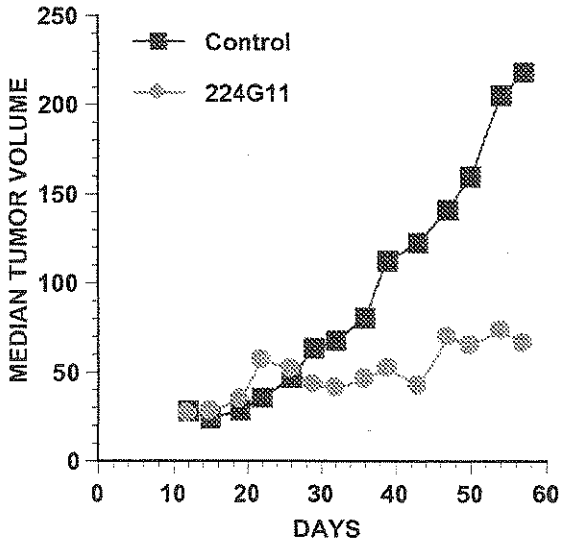


FIGURE 52

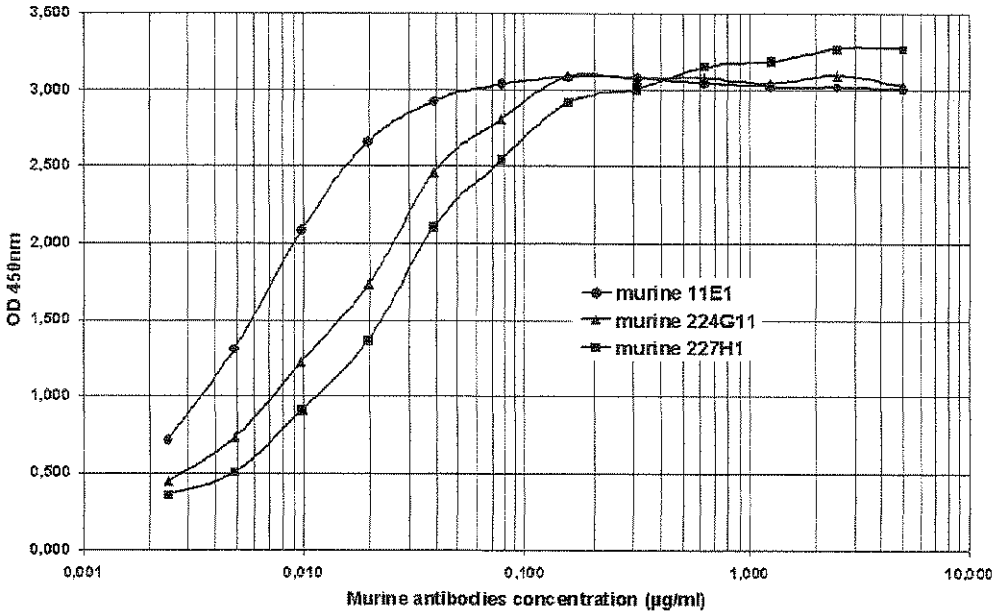


FIGURE 53

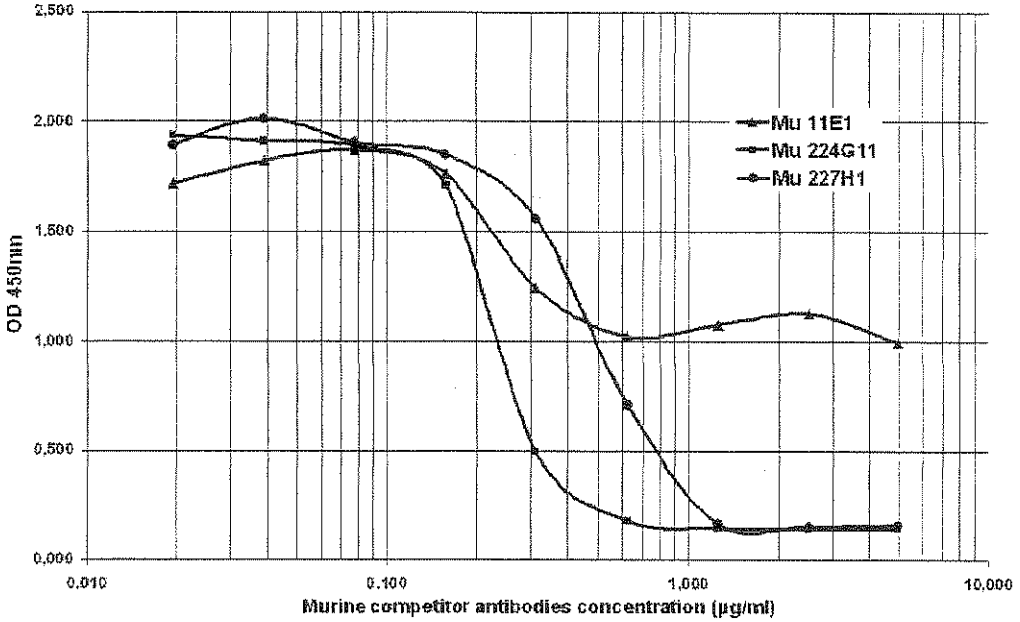


FIGURE 54

	FR1-IMGT (1-26)			CDR1-IMGT (27-38)	FR2-IMGT (39-55)		CDR2-IMGT (56-65)
	1	10	20	30	40	50	60
	.....|.....|.....			...|.....	.|.....|.....		....|.....
227H1 VH	EVQLQQSGP.ELVKPGASMKISCKAS			GYSFTDYT....	LNWVKQSHGKTLEWIGL		INPYNGGT..
Human FR	Q---V---A.-VK-----V-V-----				MH--R-AP-QG---M-W		
Changed in	* * 2 *2		3 *		11 * 33 22	2 1	
227H1 HZ3VH	QVQLVQSG**P**.EV**V**KPGAS**M**KVSCKAS			GYSFTDYT....	**LN**WVRQ**SH**G**KT**LEWI**GL**		INPYNGGT..
227H1 HZ2VH	QVQLVQSGA.EVKKPGASVKVSCKAS			GYSFTDYT....	**LN**WVRQAPG**KT**LEWI**GL**		INPYNGGT..
227H1 HZ1VH	QVQLVQSGA.EVKKPGASVKVSCKAS			GYSFTDYT....	**LN**WVRQAPGQGLEWM**GL**		INPYNGGT..

	FR3-IMGT (66-104)				CDR3-IMGT (105-115)	FR4-IMGT (116-126)
	70	80	90	100	110	120
	....|.....|.....|.....|....				.....|.....	....|.....
227H1 VH	TYNQKFK.GKATLTVDKSSSTAYMELLSLTSEDSAVYYC				AREEITKDFDF	WGQGTTLTVSS
Human FR	N-A---Q.-RV-M-R-T-I-------SR-R-D-T-----					-----LV----
Changed in	1 * 3 *2 2 1 1 3			** 3 3 *		22
227H1 HZ3VH	**T**YAQKF**K**.GRA**T**L**T**V**D**K**S**S**S**TAYMELSRL**T**S**E**DTAVYYC				AREEITKDFDF	WGQGT**TL**TVSS
227H1 HZ2VH	**T**YAQKFQ.GRA**T**L**T**V**D**KSISTAYMELSRLRSDDTAVYYC				AREEITKDFDF	WGQGT**TL**TVSS
227H1 HZ1VH	TYAQKFQ.GRVTMT**VDK**SISTAYMELSRLRSDDTAVYYC				AREEITKDFDF	WGQGTLVTVSS

FIGURE 55

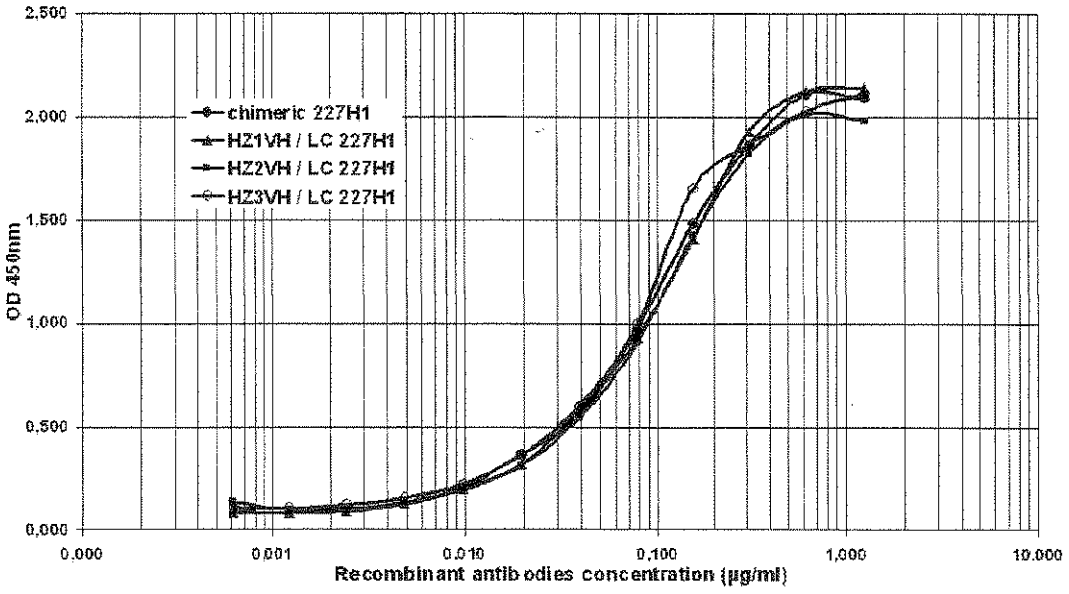


FIGURE 56

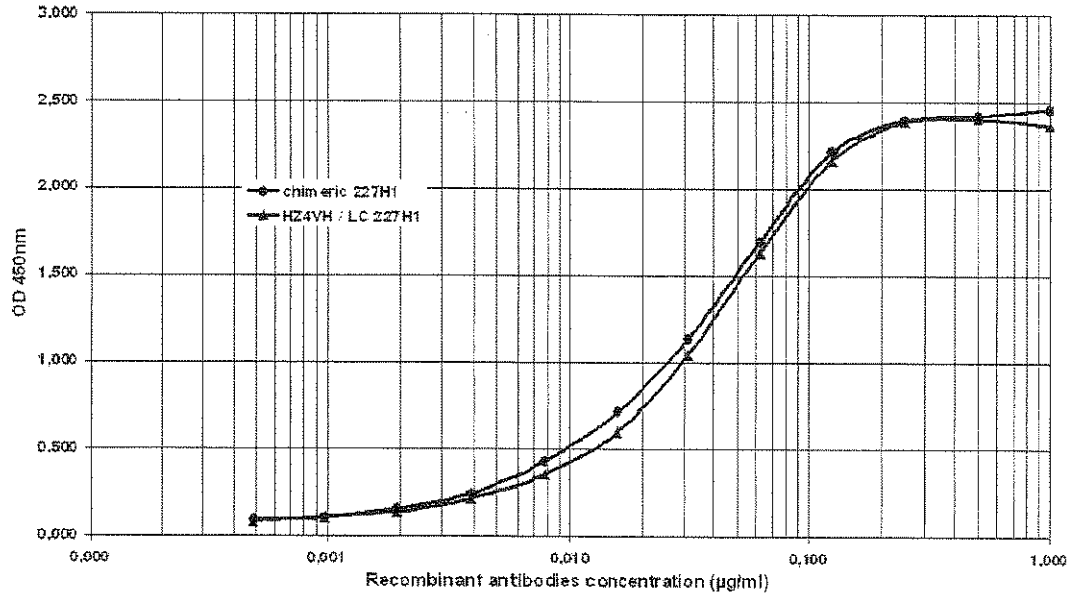


FIGURE 57

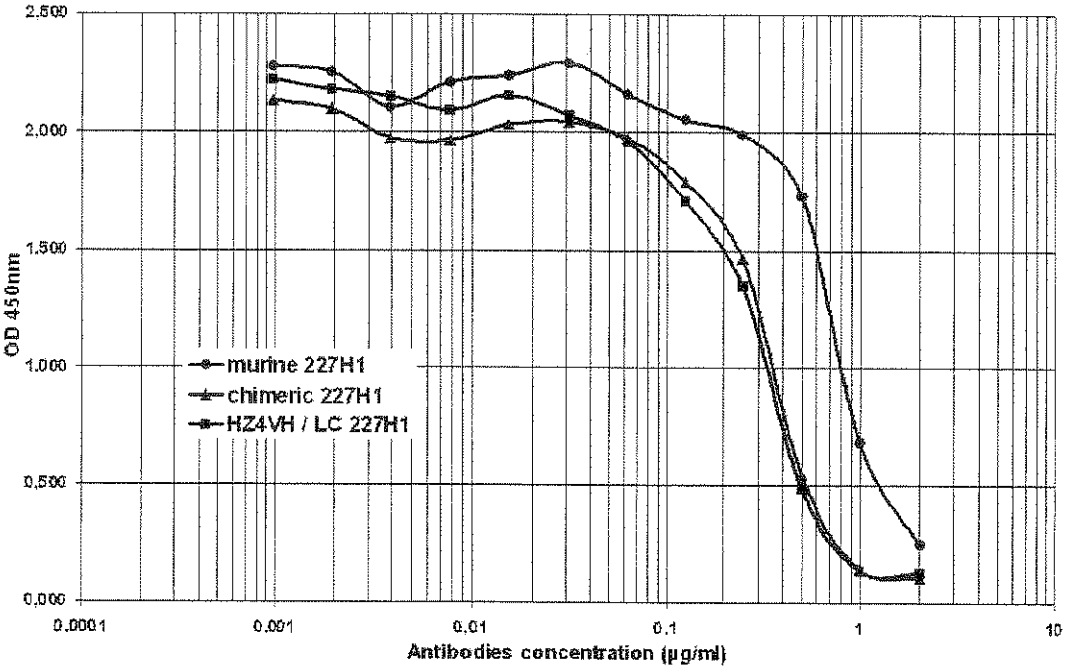


FIGURE 58

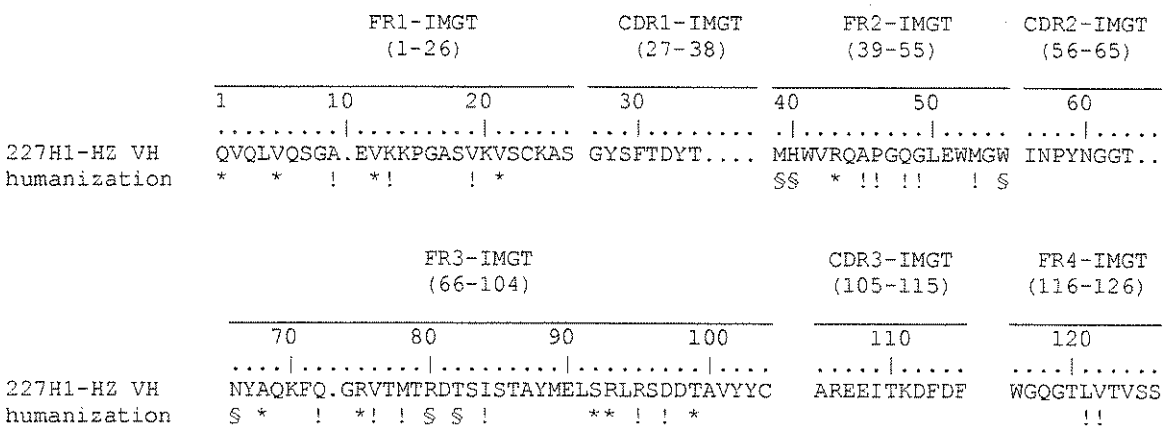


FIGURE 59

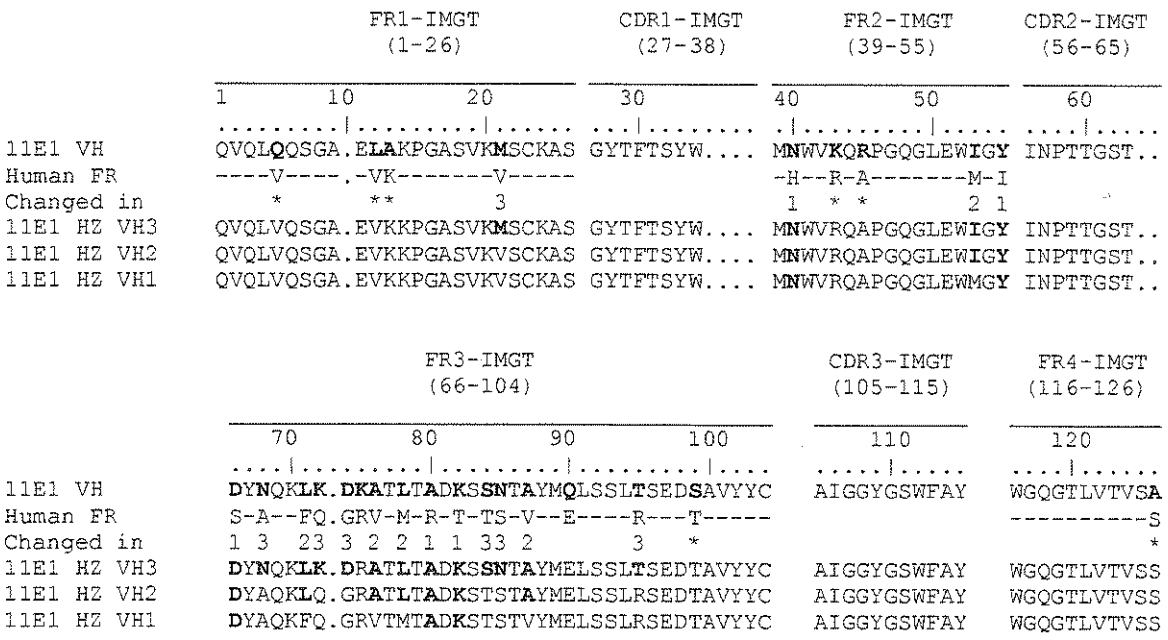


FIGURE 60

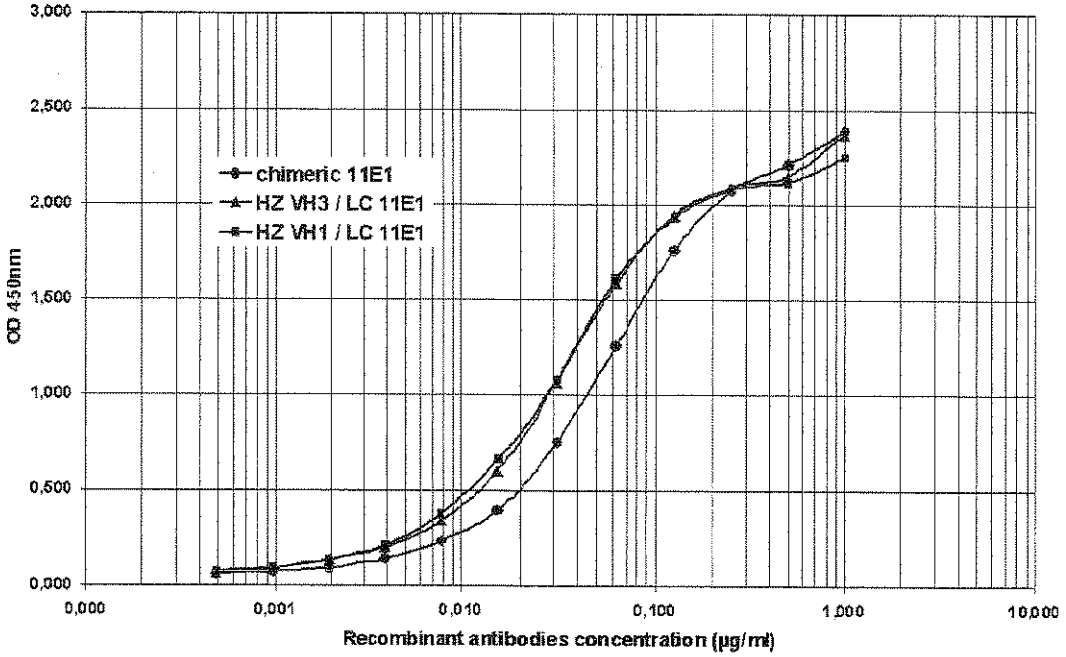


FIGURE 61

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	CDR2-IMGT (56-65)
	1 10 20	30	40 50	60
	.....|.....|.....	...|.....	.|.....|.....	....|.....
11E1 VL	QIVLTQSPAIMSASPGEKVTLTCSAS	SSVSSTY.....	LYWYQQKPGSSPKLWIY	TTS.....
Human FR	E--M-----TL-L----RA--S-R--		-S-------QA-R-L--	
Changed in	* 1 *3 * ** * 2		1 33 * 2	
11E1 HZ VL3	EIVLTQSPATMSLSPGERATLSCSAS	SSVSSTY.....	LYWYQQKPGSSPRLWIY	TTS.....
11E1 HZ VL2	EIVLTQSPATLSLSPGERATLSCSAS	SSVSSTY.....	LYWYQQKPGQAPRLWIY	TTS.....
11E1 HZ VL1	EIVLTQSPATLSLSPGERATLSCRAS	SSVSSTY.....	LYWYQQKPGQAPRLLIY	TTS.....

	FR3-IMGT (66-104)	CDR3-IMGT (105-113)	FR4-IMGT (114-123)
	70 80 90 100	110	120
	....|.....|.....|.....|....	.....|...	.....|...
11E1 VL	ILASGVP.ARFSGSG..SGTSYSLTISSMETEDAASYFC	HQWSSYPFT	FGSGTKLDIK
Human FR	TR-T-I-.-------..---DFT-----LQP--F-V-Y-		--G---VE--
Changed in	22 * * 213 321 2 3 3		3 *2
11E1 HZ VL3	ILATGIP.ARFSGSG..SGTSYSLTISSMETEDAASYFC	HQWSSYPFT	FGSGTKVDIK
11E1 HZ VL2	ILATGIP.ARFSGSG..SGTSYTLTISSLETEDAAVYYC	HQWSSYPFT	FGGGTKVDIK
11E1 HZ VL1	TRATGIP.ARFSGSG..SGTDYTLTISSLQTEDFAVYYC	HQWSSYPFT	FGGGTKVEIK

FIGURE 62

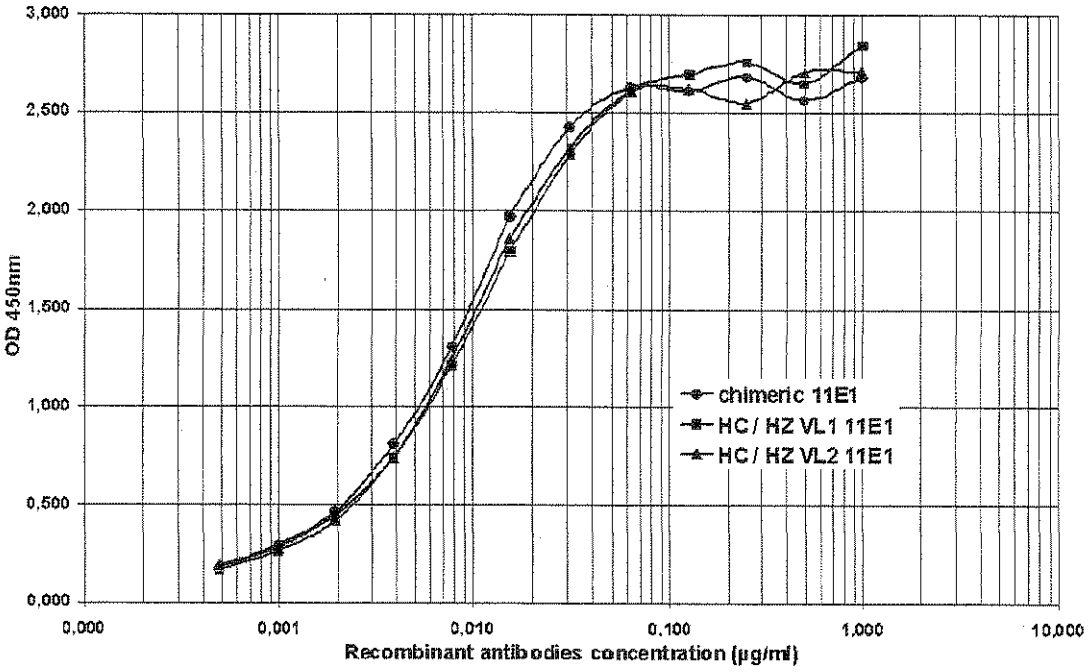


FIGURE 63

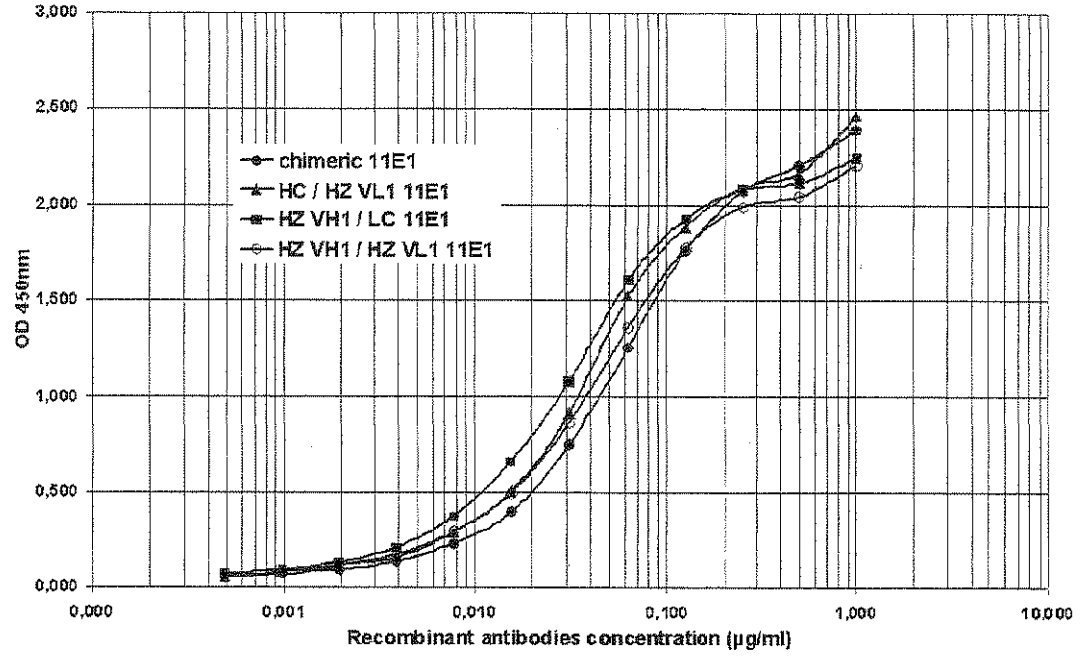


FIGURE 64

```
                          FR1-IMGT          CDR1-IMGT        FR2-IMGT      CDR2-IMGT
                            (1-26)            (27-38)         (39-55)       (56-65)
                 ____________________________ ____________ ____________________ ____________
                 1       10        20         30          40        50         60
                 .........|.........|.......  ...|........  .|.........|.....  ....|.....
224G11 VH        EVQLQQSGP.ELVKPGASVKISCKTS  GYIFTAYT....  MHWVRQSLGESLDWIGG  IKPNNGLA..
227H1 VH         EVQLQQSGP.ELVKPGASMKISCKAS  GYSFTDYT....  LNWVKQSHGKTLEWIGL  INPYNGGT..
Human FR         Q---V---A.-VK-------V---A-                ------AP-QG-E-M-W
224G11 HZ VH0    QVQLVQSGA.EVKKPGASVKVSCKAS  GYIFTAYT....  MHWVRQAPGQGLEWMGW  IKPNNGLA..

                                FR3-IMGT                      CDR3-IMGT      FR4-IMGT
                                (66-104)                      (105-115)     (116-126)
                 ____________________________________________ ____________ ____________
                    70        80        90        100          110          120
                 ....|.........|.........|.........|....  .....|.....  ....|......
224G11 VH        NYNQKFK.GKATLTVDKSSSTAYMDLRSLTSEDSAVYYC  ARSEITTEFDY  WGQGTALTVSS
227H1 VH         TYNQKFK.GKATLTVDKSSSTAYMELLSLTSEDSAVYYC  AREEITKDFDF  WGQGTTLTVSS
Human FR         --A---Q.-RV-M-R-T-I-----E-SR-R-D-T-----                -----LV----
224G11 HZ VH0    NYAQKFQ.GRVTMTRDTSISTAYMELSRLRSDDTAVYYC  ARSEITTEFDY  WGQGTLVTVSS
```

FIGURE 65

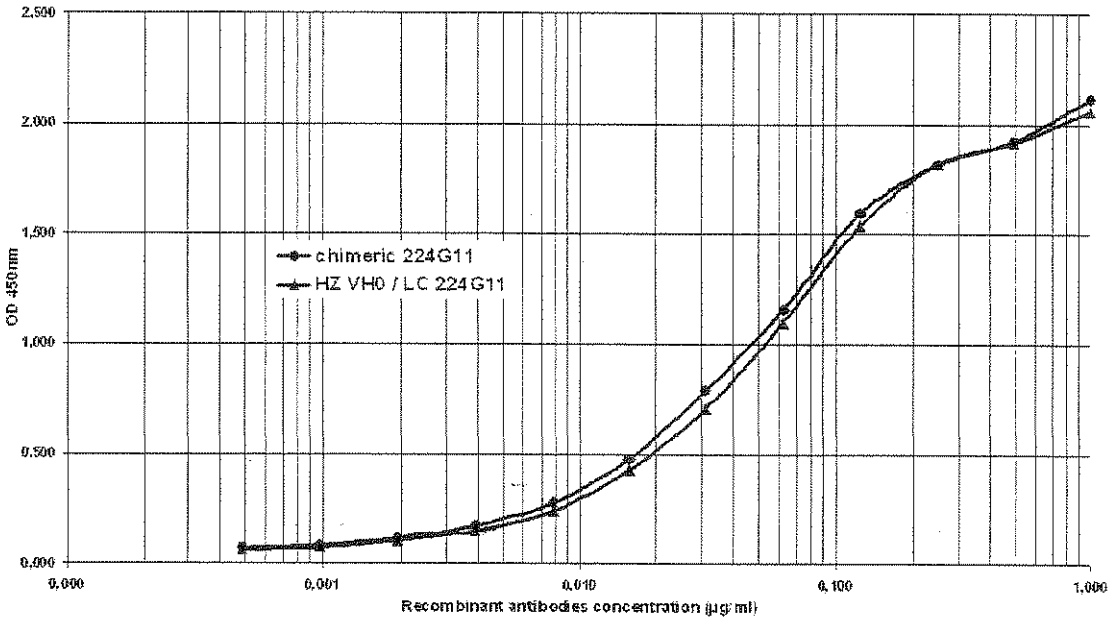


FIGURE 66

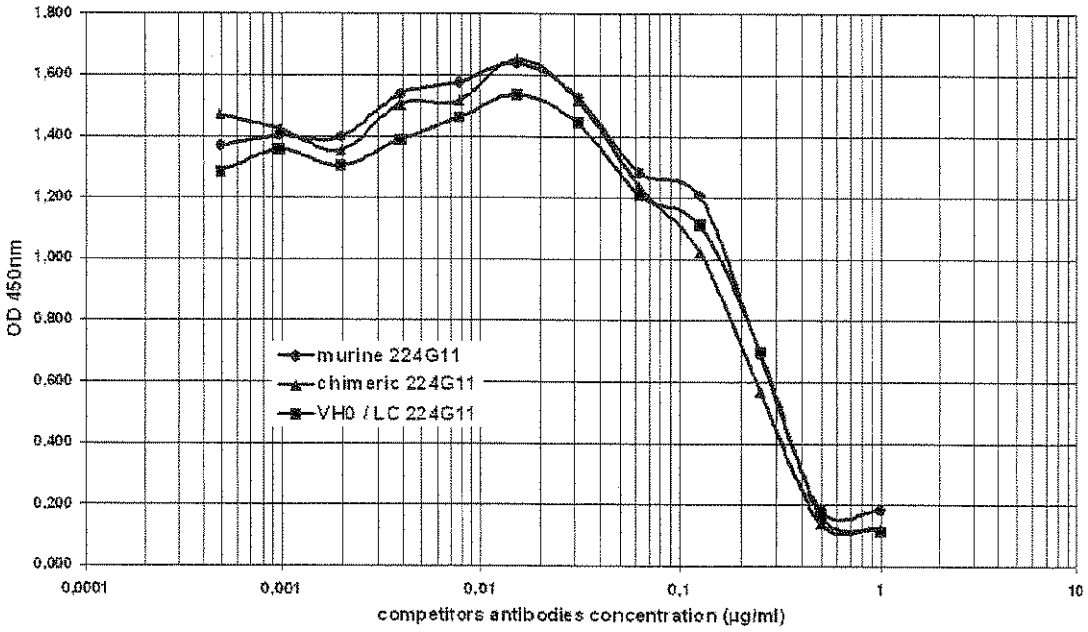


FIGURE 67

```
                                FR1-IMGT          CDR1-IMGT        FR2-IMGT        CDR2-IMGT
                                (1-26)            (27-38)          (39-55)         (56-65)

                    1       10        20        30          40        50        60
                    .........|.........|.....  ...|.......  .|.........|.....  ....|.....
224G11 VL           DIVLTQSPASLAVSLGQRATISCRAS ESVDSYANSF.. MHWYQQKPGQPPKLLIY RAS.......

Shorter Hu-FR       E--------T-SL-P-E---L-----         ..... LA--------A-R----     .......
Rank                *         * 3* 2 3   *                   11        2 3
224G11 HZ VL3       EIVLTQSPATLALSLGQRATLSCRAS ESVDSYANSF.. MHWYQQKPGQPPKLLIY RAS.......

Longer Hu-FR        ---M----D-------E----N-KS-                LA---------------     .......
Rank                   1    *        3    * 32                 11
224G11 HZ VL6       DIVLTQSPDSLAVSLGQRATINCRAS ESVDSYANSF.. MHWYQQKPGQPPKLLIY RAS.......

                                FR3-IMGT                                  CDR3-IMGT   FR4-IMGT
                                (66-104)                                  (105-113)   (114-123)

                      70        80        90        100                     110         120
                    ....|.....|.....|.....|.....|....                   .....|...  ......|.....
224G11 VL           NLESGIP.ARFSGSG..SRTDFTLTINPVEADDVATYYC              QQSKEDPLT   FGSGTKLEMK

Shorter Hu-FR       -RAT---.-------..-G-------SSL-PE-F-V---                         --G---V-I-
Rank                 22*               1        32* 33 2 3                           3   * *
224G11 HZ VL3       NLETGIP.ARFSGSG..SRTDFTLTINPLEADDVATYYC              QQSKEDPLT   FGSGTKVEIK

Longer Hu-FR        TR---V-.D-------..-G-------SSLQ-E---V---                        --G---V-I-
                    22    *  *          1        32*3 3   3                          3   * *
224G11 HZ VL6       NLESGVP.DRFSGSG..SRTDFTLTINPLEADDVATYYC              QQSKEDPLT   FGSGTKVEIK
```

FIGURE 68

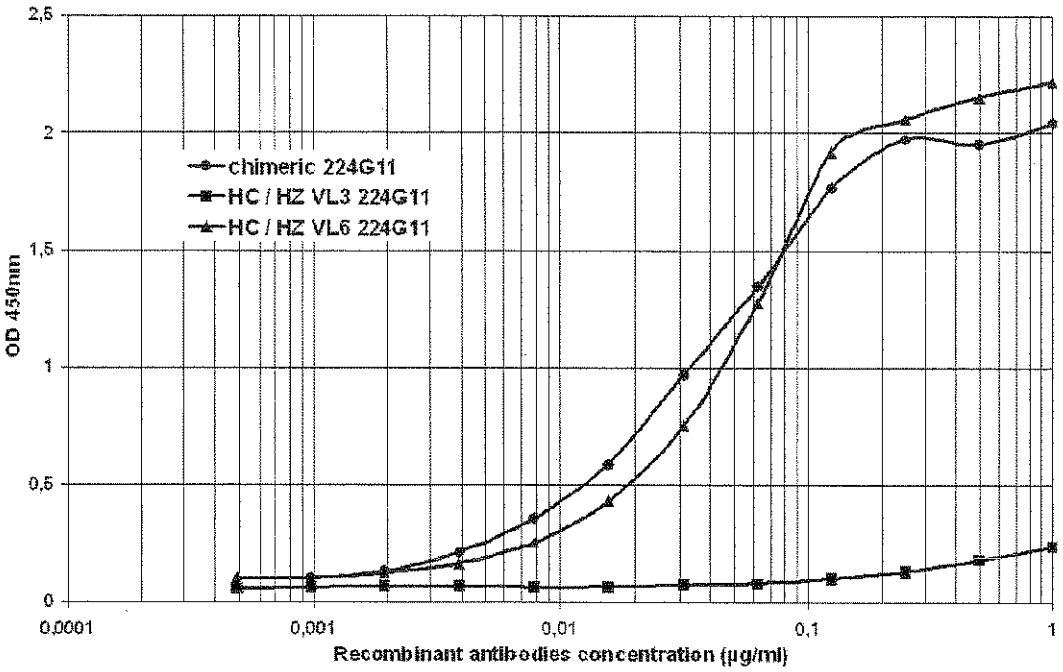


FIGURE 69

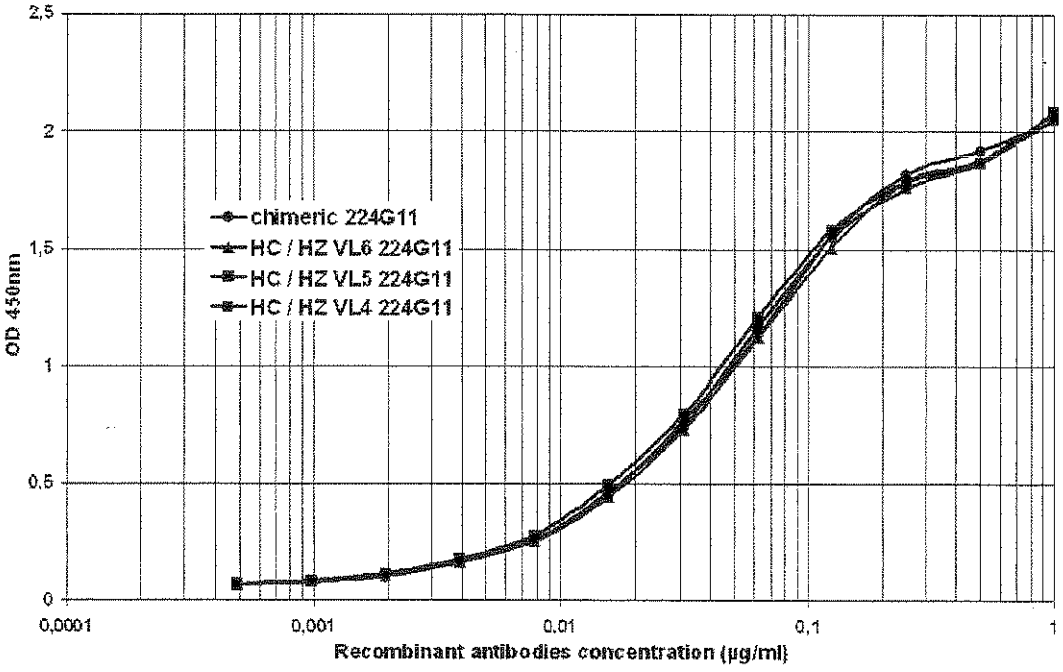


FIGURE 70

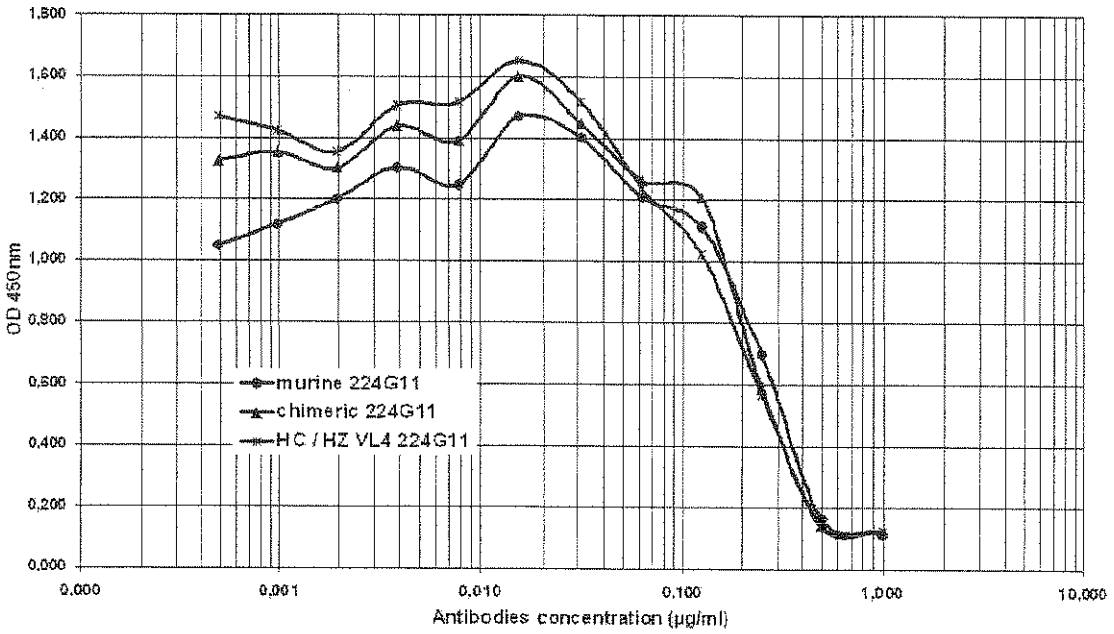


FIGURE 71

```
                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT
                           (1-26)            (27-38)         (39-55)       (56-65)
                 ________________________  ____________  ______________  ____________
                 1       10        20        30          40        50        60
                 .........|.........|......  ...|........  .|.........|.....  ....|.....
224G11 HZ VL4    DIVLTQSPDSLAVSLGERATINCKSS ESVDSYANSF..  MHWYQQKPGQPPKLLIY RAS.......
humanization       §    *       !    * !!                §§

                                FR3-IMGT                      CDR3-IMGT   FR4-IMGT
                                (66-104)                      (105-113)   (114-123)
                  ____________________________________________  ___________  ___________
                    70        80        90        100            110         120
                  ....|.........|.........|.........|....     .....|...    ......|.....
224G11 HZ VL4     TRESGVP.DRFSGSG..SRTDFTLTISSLQAEDVAVYYC     QQSKEDPLT    FGGGTKVEIK
humanization      !!   *  *          §       !!*! !   !                      !   * *
```

FIGURE 72

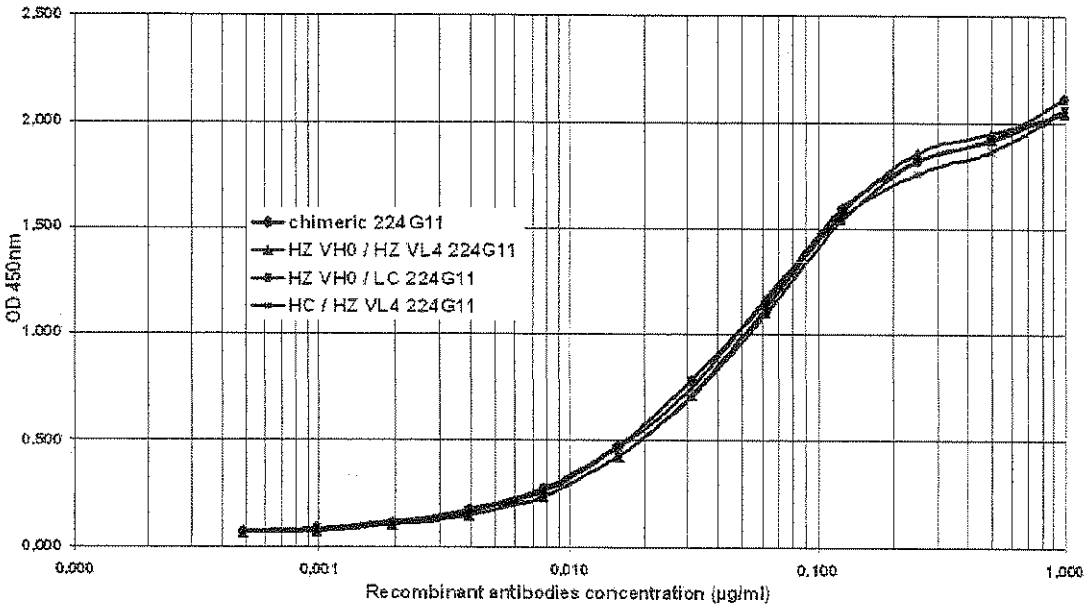


FIGURE 73

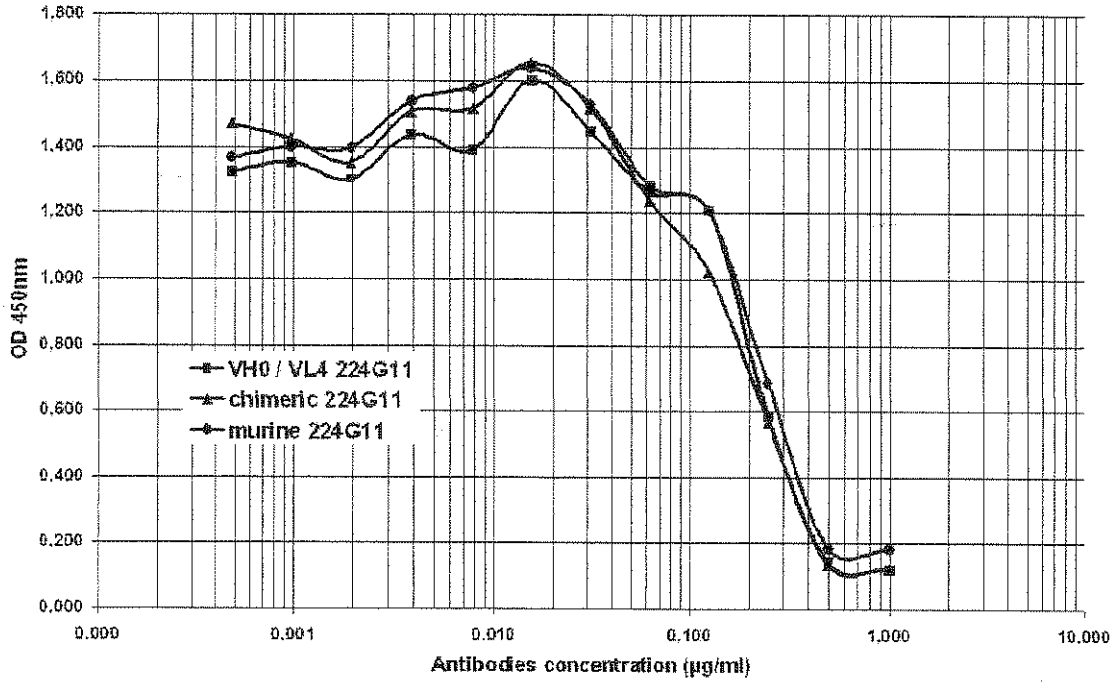


FIGURE 74

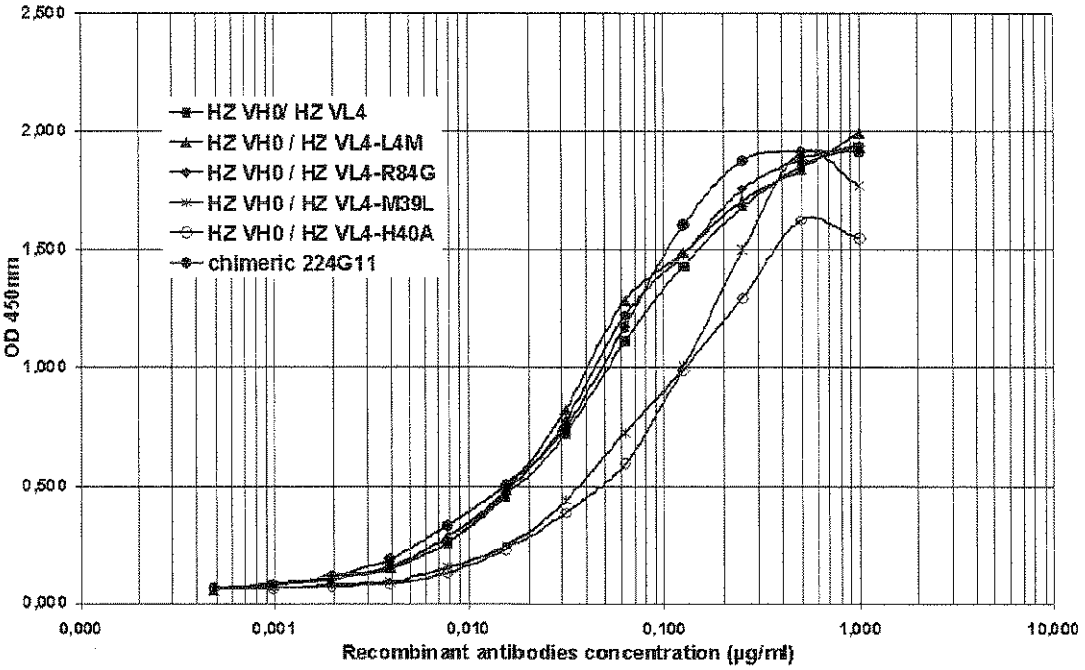


FIGURE 75

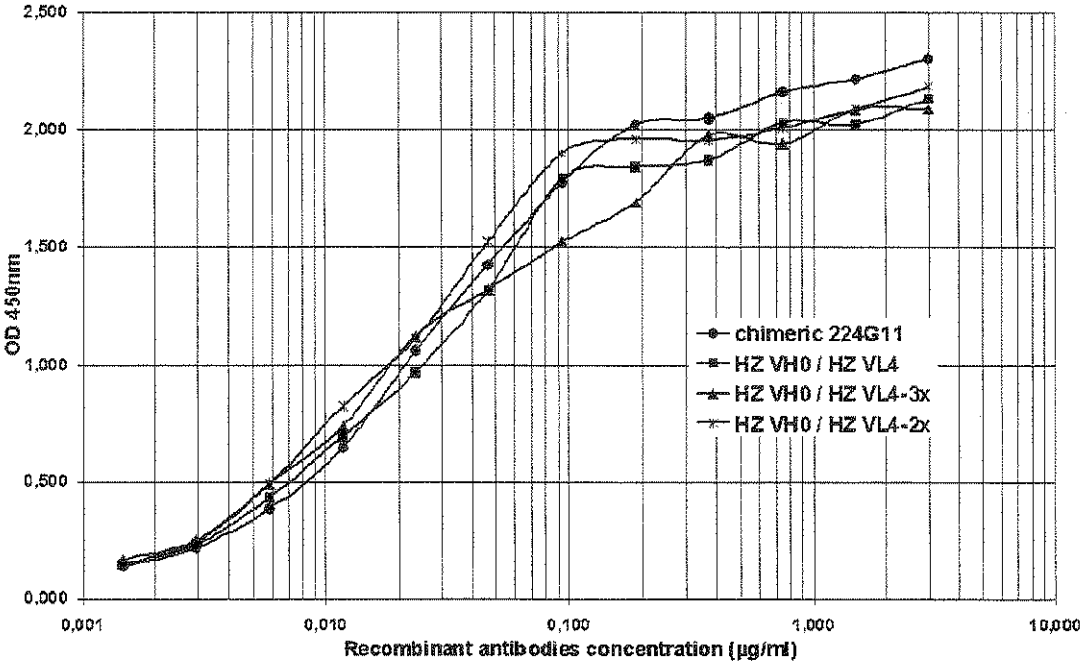


FIGURE 76

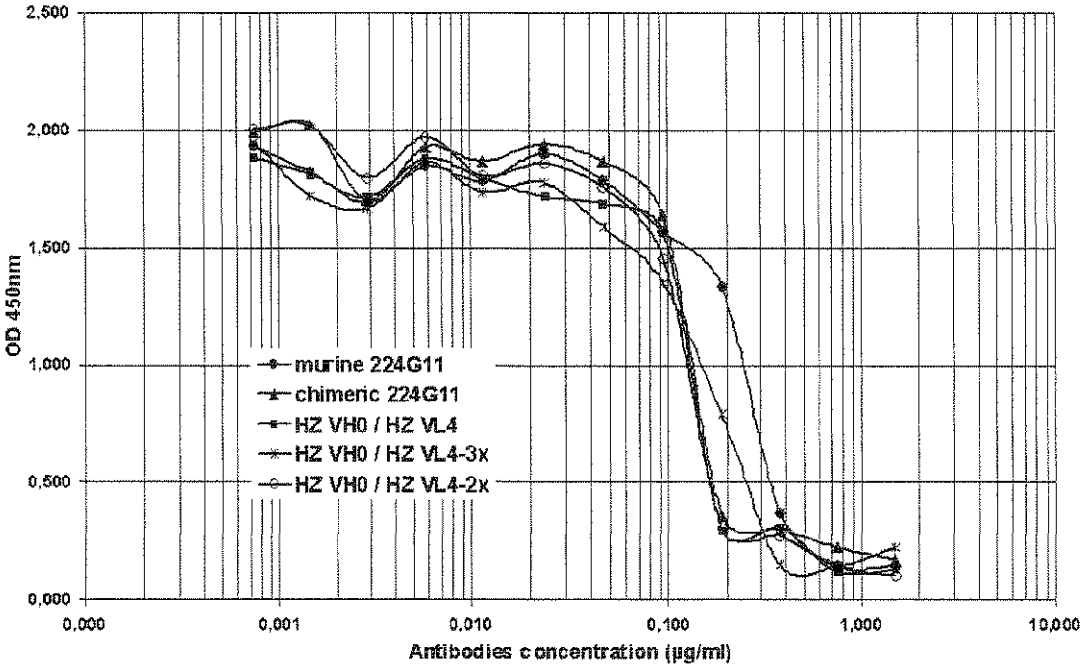

2,500
2,000
1,500
1,000
0,500
0,000
OD 450nm
murine 224G11
chimeric 224G11
HZ VH0 / HZ VL4
HZ VH0 / HZ VL4-3K
HZ VH0 / HZ VL4-2K
0,000
0,001
0,010
0,100
1,000
10,000
Antibodies concentration (µg/ml)

FIGURE 77