US 20180142005A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2018/0142005 A1**

LOGTENBERG et al. (43) **Pub. Date: May 24, 2018**

(54) **ANTIBODY PRODUCING NON-HUMAN ANIMALS**

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(73) Assignee: **Merus N.V.**, Utrecht (NL)

(21) Appl. No.: **15/870,647**

(22) Filed: **Jan. 12, 2018**

Related U.S. Application Data

(60) Division of application No. 12/589,181, filed on Oct. 19, 2009, which is a continuation of application No. 12/459,285, filed on Jun. 29, 2009, now abandoned.

(60) Provisional application No. 61/133,274, filed on Jun. 27, 2008.

Publication Classification

(51) **Int. Cl.**

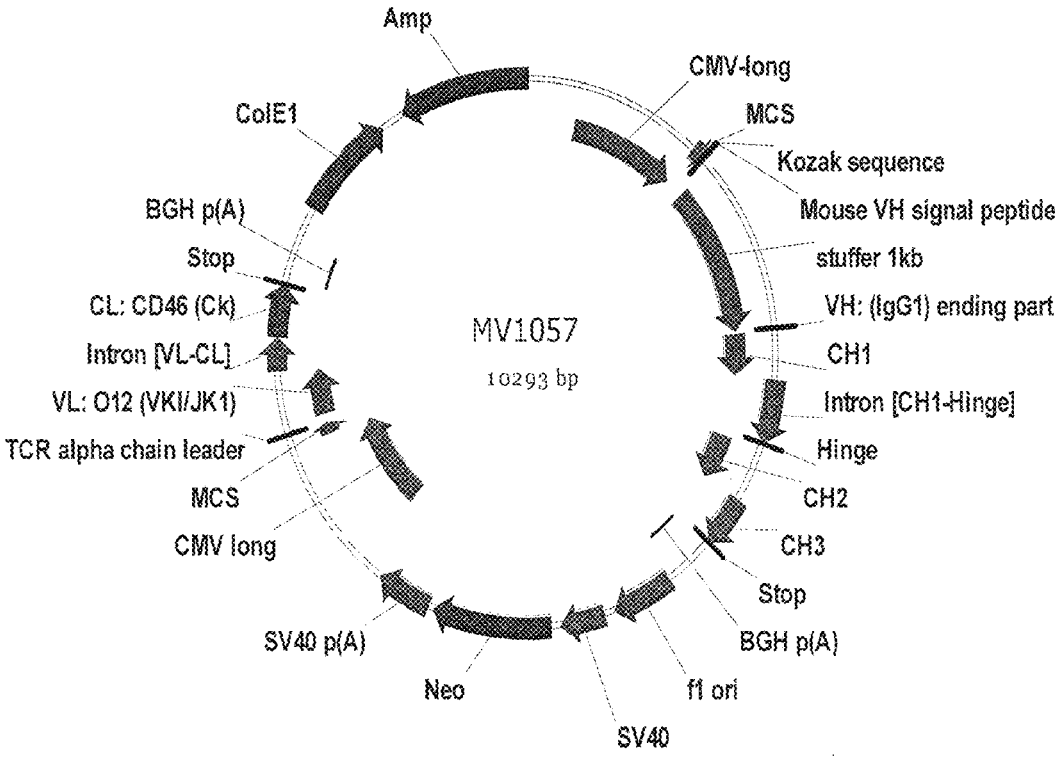
C07K 16/12	(2006.01)
C12P 21/00	(2006.01)
A01K 67/027	(2006.01)
C12N 15/85	(2006.01)
C07K 16/24	(2006.01)
C07K 14/47	(2006.01)

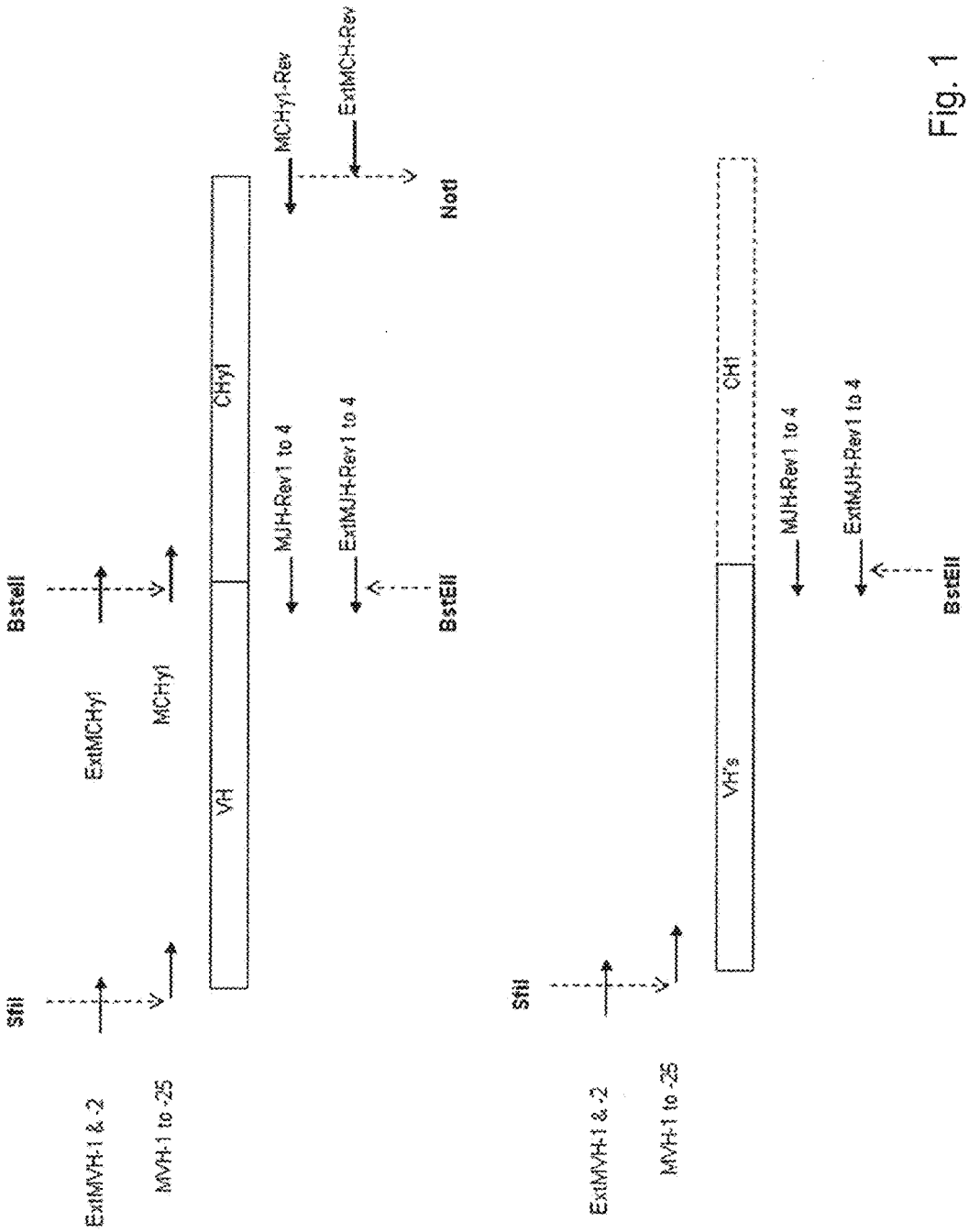
(52) **U.S. Cl.**

CPC ***C07K 16/1282*** (2013.01); ***C12P 21/00*** (2013.01); ***A01K 67/027*** (2013.01); ***C12N 15/8509*** (2013.01); *C07K 2317/24* (2013.01); ***C07K 16/248*** (2013.01); ***C07K 14/47*** (2013.01); *A01K 2267/01* (2013.01); *A01K 2227/105* (2013.01); *A01K 2217/206* (2013.01); *A01K 2217/15* (2013.01); *A01K 2217/075* (2013.01); *A01K 2217/052* (2013.01); *A01K 2207/15* (2013.01); ***A01K 67/0278*** (2013.01)

(57) **ABSTRACT**

Described are transgenic, non-human animals comprising a nucleic acid encoding an immunoglobulin light chain, whereby the immunoglobulin light chain is human, human-like, or humanized. The nucleic acid is provided with a means that renders it resistant to DNA rearrangements and/or somatic hypermutations. In one embodiment, the nucleic acid comprises an expression cassette for the expression of a desired molecule in cells during a certain stage of development in cells developing into mature B cells. Further provided is methods for producing an immunoglobulin from the transgenic, non-human animal.

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MVH-1 to -25
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VH
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BstEII
MCHγ1-Rev
ExtMCH-Rev
NotI
SfiI
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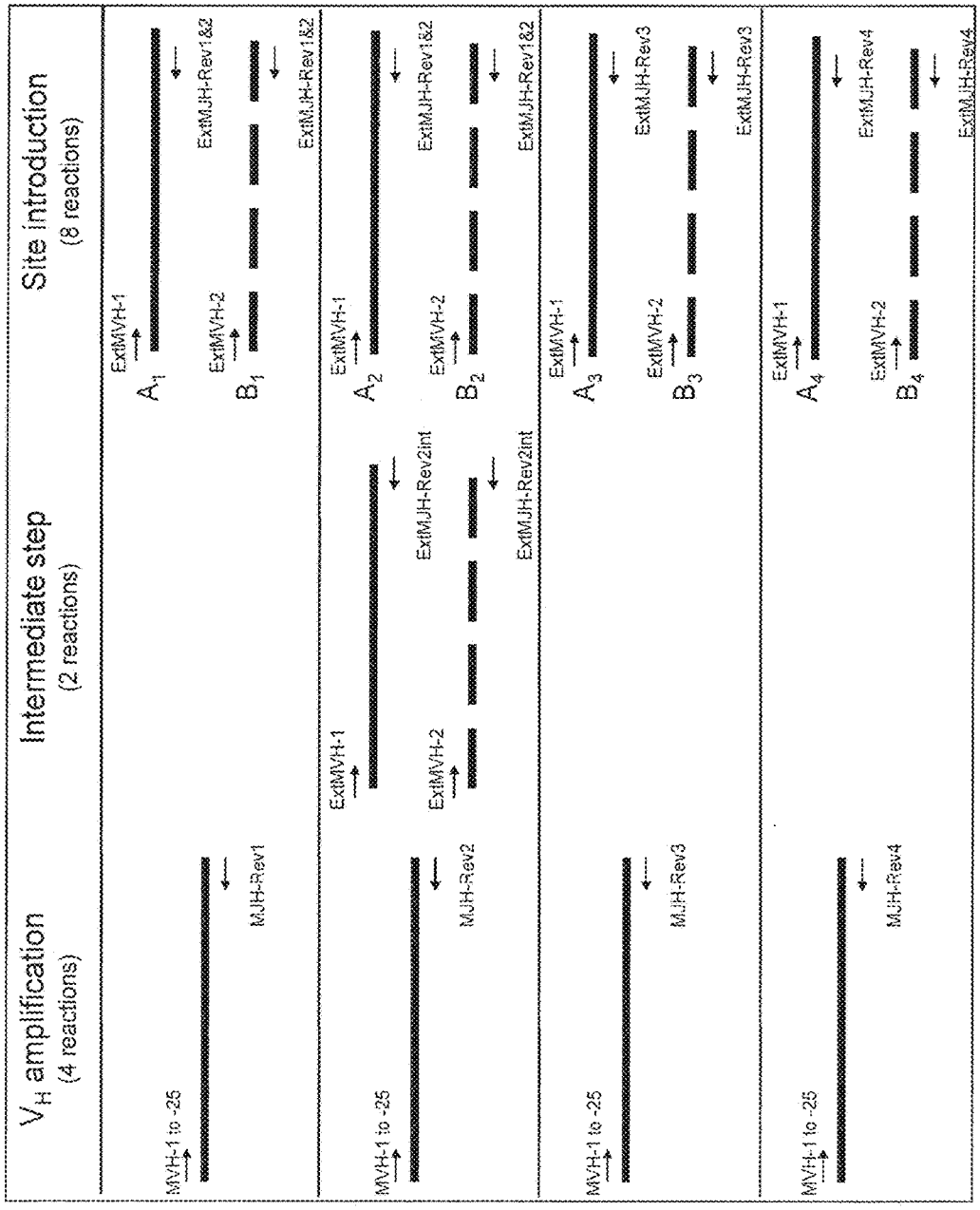
Fig. 1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(4 reactions)
Intermediate step
(2 reactions)
Site introduction
(8 reactions)
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MJH-Rev1
ExtMVH-1
ExtMVH-2
A_1
B_1
ExtMJH-Rev1&2
MJH-Rev2
ExtMJH-Rev2int
A_2
B_2
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A_4
B_4
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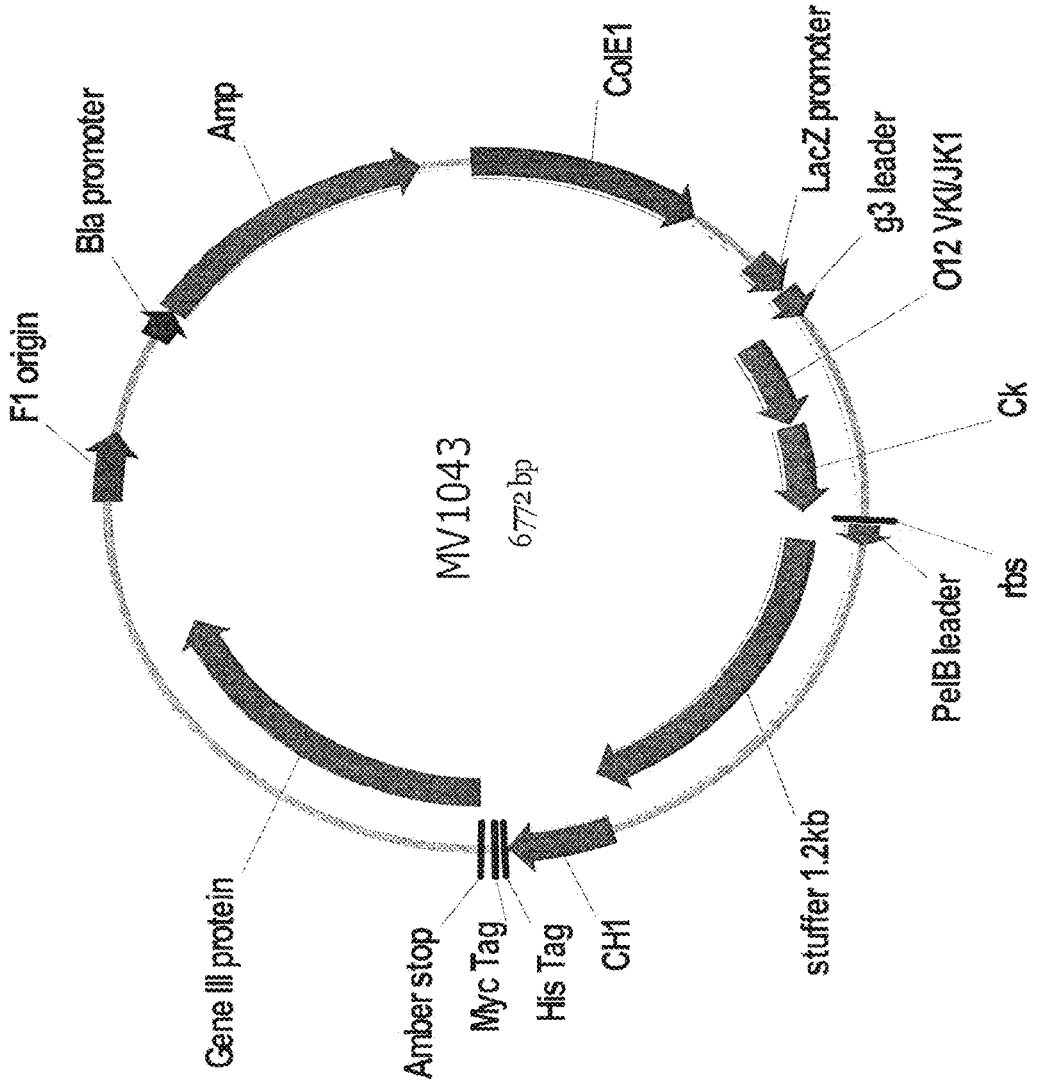
Fig. 2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Bla promoter
Amp
ColE1
LacZ promoter
g3 leader
O12 VK/JK1
Ck
rbs
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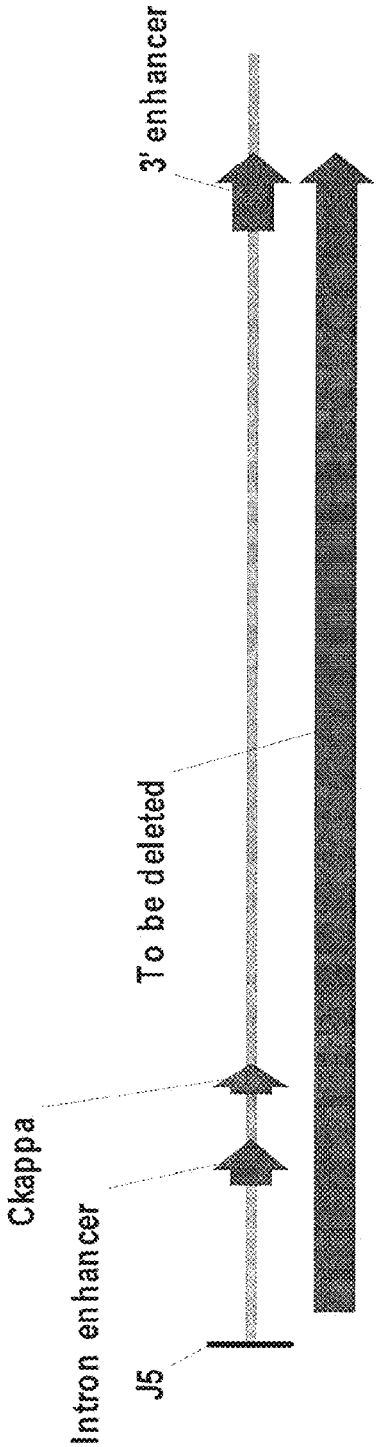
stuffer 1.2kb
CH1
His Tag
Myc Tag
Amber stop
Gene III protein

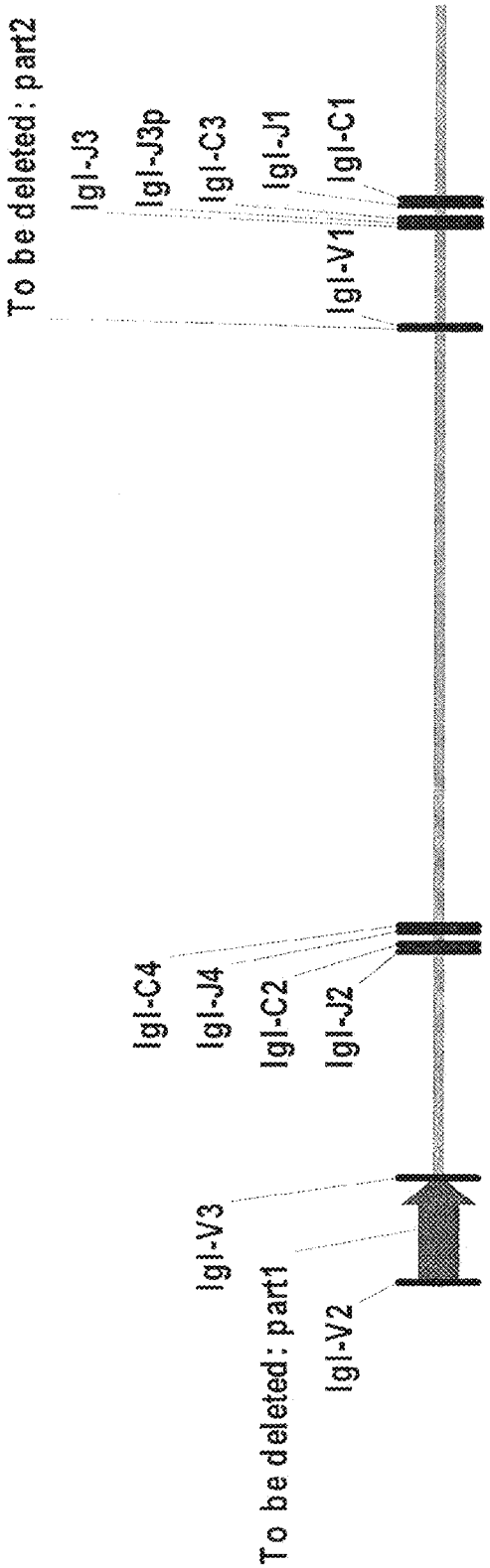
Fig. 3



Mouse kappa silencing strategy Merus

13181 bp

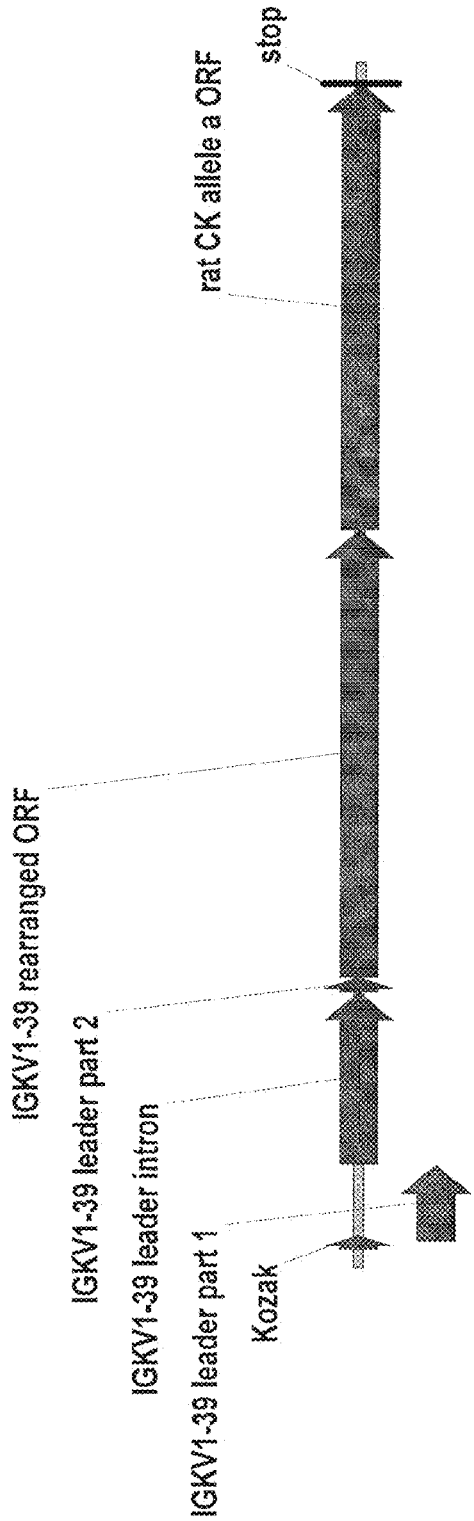
Fig. 4



Mouse lambda silencing strategy Merus

234987 bp

Fig. 5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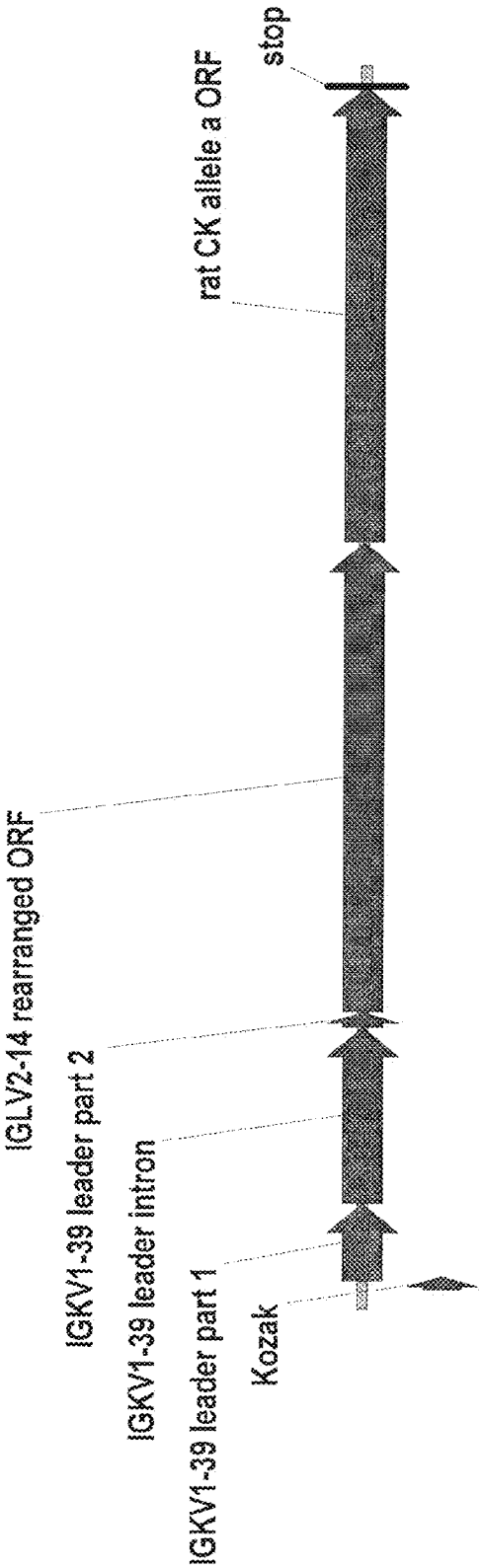
IGKV1-39 leader part 2
IGKV1-39 leader intron
IGKV1-39 leader part 1
Kozak

Fig. 6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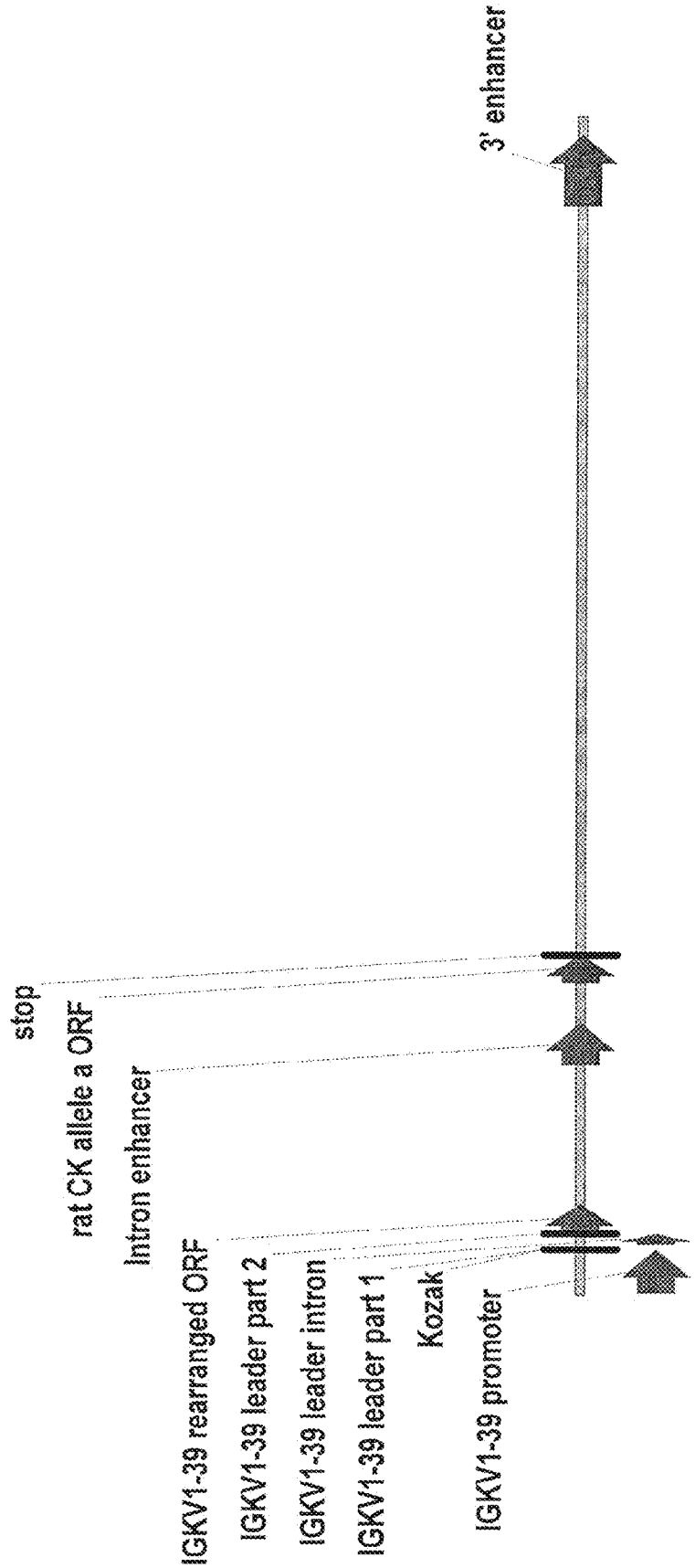
IGKV1-39 leader part 2
IGKV1-39 leader intron
IGKV1-39 leader part 1
Kozak

Fig. 7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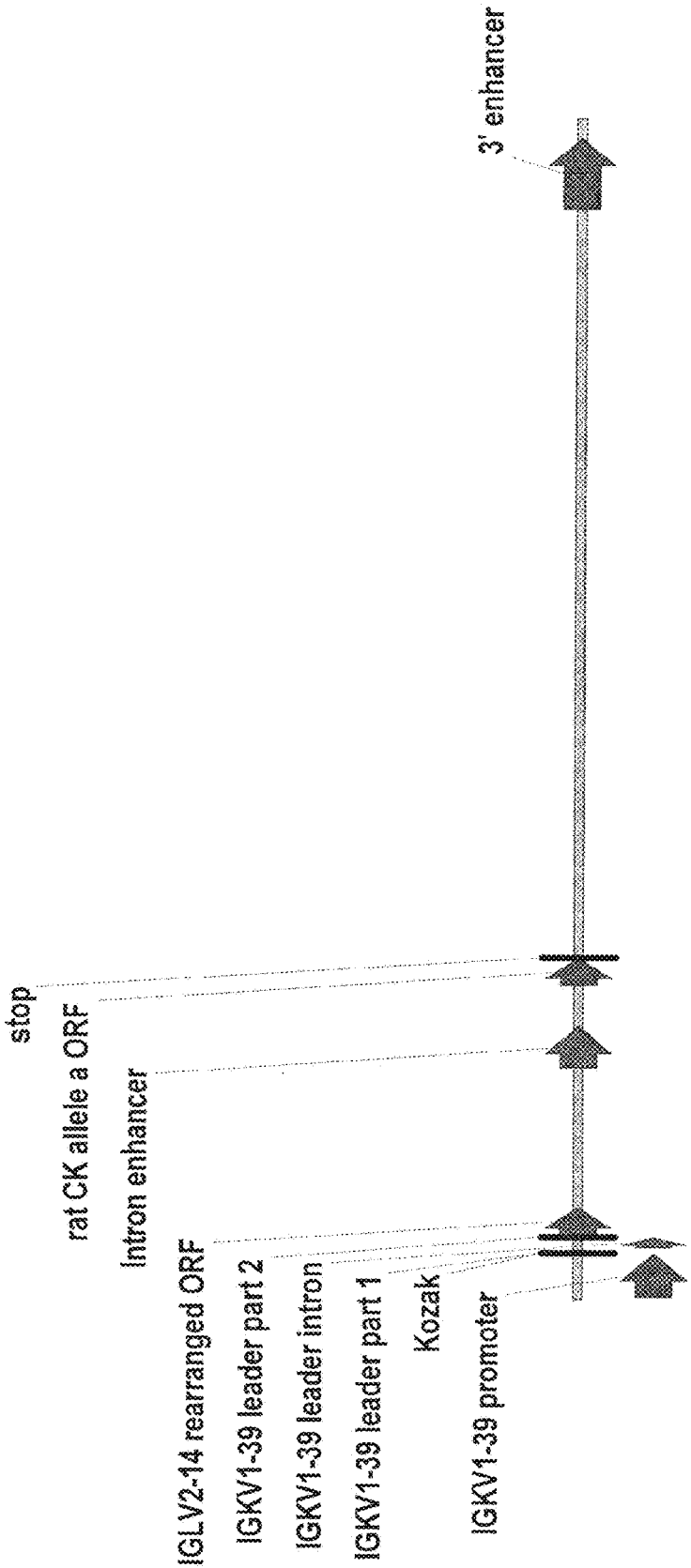
stop
rat CK allele a ORF
Intron enhancer
IGKV1-39 rearranged ORF
IGKV1-39 leader part 2
IGKV1-39 leader intron
IGKV1-39 leader part 1
Kozak
IGKV1-39 promoter

Fig. 8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Intron enhancer
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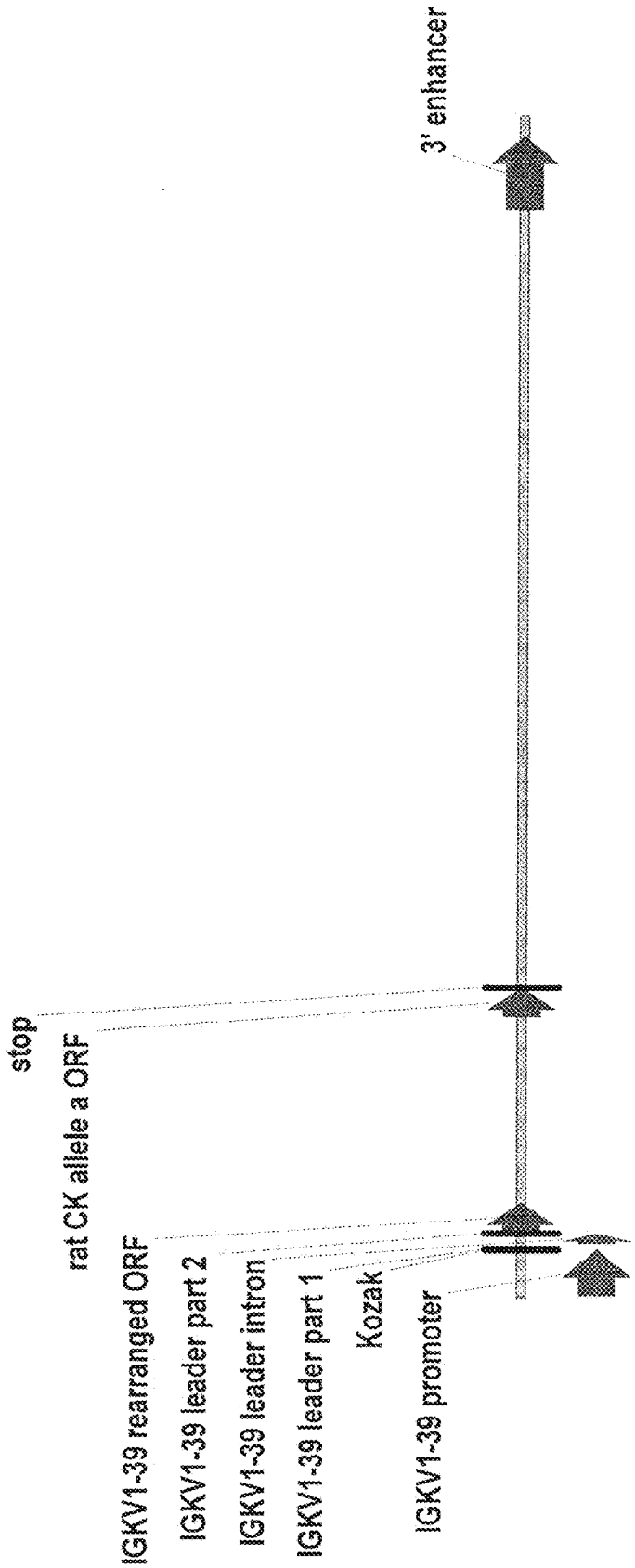
IGKV1-39 leader intron
IGKV1-39 leader part 1
Kozak
IGKV1-39 promoter

Fig. 9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stop
rat CK allele a ORF
IGKV1-39 rearranged ORF
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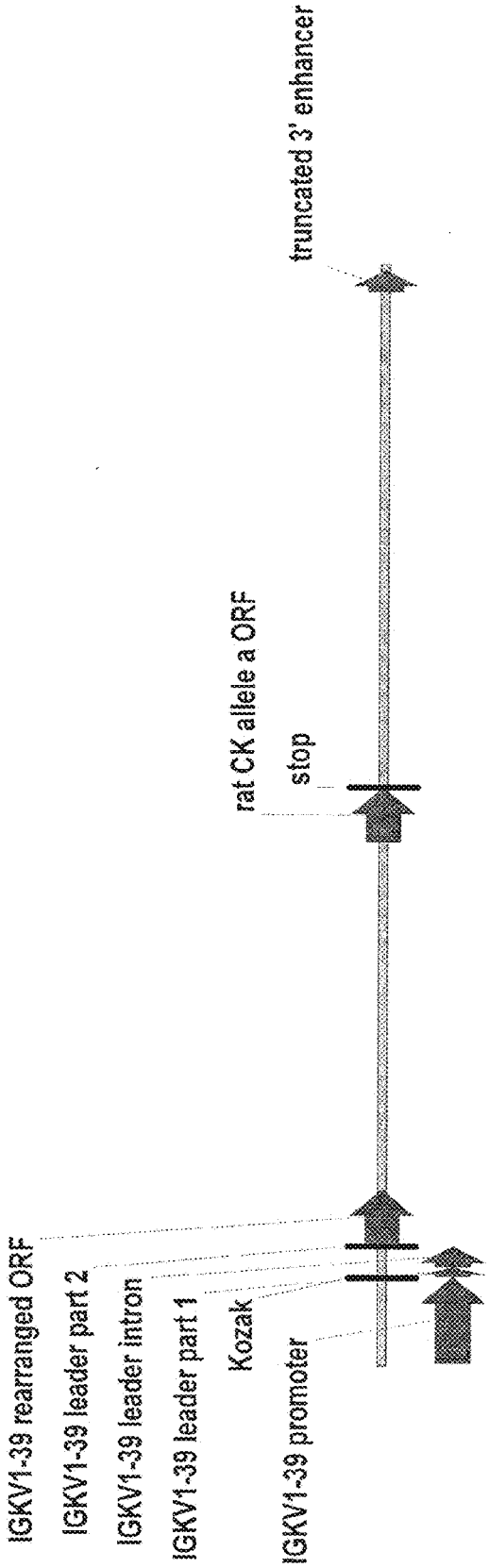
IGKV1-39 leader part 1
Kozak
IGKV1-39 promoter

Fig. 10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IGKV1-39 leader part 2
IGKV1-39 leader intron
IGKV1-39 leader part 1
Kozak
IGKV1-39 promoter
stop
rat CK allele a ORF
truncated 3' enhancer

Fig. 11

Fig. 12

human germline IGKV1-39/J DNA

```
  1   GAC ATC CAG ATG ACC CAG AGC CCC AGC AGC CTG AGC GCC AGC GTG GGC GAC AGA GTG ACC ATC ACC TGC AGA GCC AGC
 79   CAG AGC ATC AGC AGC TAC CTG AAC TGG TAT CAG CAG AAG CCC GGC AAG GCC CCC AAG CTG CTG ATC TAC GCC GCC AGC
157   TCC CTG CAG AGC GGC GTG CCC AGC AGA TTC AGC GGC AGC GGC TCC GGC ACC GAC TTC ACC CTG ACC ATC AGC AGC CTG
235   CAG CCC GAG GAC TTC GCC ACC TAC TAC TGC CAG CAG AGC TAC AGC ACC CCC CCC ACC TTC GGC CAG GGC ACC AAG GTG
313   GAG ATC AAG
```

human germline IGKV1-39/J Protein

```
  1   DIQMTQSPSS LSASVGDRVT ITCRASQSIS SYLNWYQQKP GKAPKLLIYA
 51   ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SYSTPPTFGQ
101   GTKVEIK
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human germline IGLV2-14/J DNA

```
  1   CAG TCT GCC CTG ACC CAG CCC GCC TCT GTG TCT GGC AGC CCT GGC CAG AGC ATC ACC ATC AGC TGC ACC GGC ACC AGC
 79   AGC GAC GTG GGC GGC TAC AAC TAC GTG TCC TGG TAT CAG CAG CAC CCC GGC AAG GCC CCC AAG CTG ATG ATC TAC GAG
157   GTG TCC AAC AGA CCC AGC GGC GTG AGC AAC AGA TTC AGC GGC AGC AAG AGC GGC AAC ACC GCC AGC CTG ACC ATC AGC
235   GGC CTC CAG GCT GAG GAC GAG GCC GAC TAC TAC TGC AGC AGC TAC ACC AGC AGC TCC ACC CTG GTG TTT GGC GGC GGA
313   ACA AAG CTG ACC GTG CTG
```

human germline IGLV2-14/J Protein

```
  1   QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI
 51   YEVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTLV
101   FGGGTKLTVL
```

Rat IGCK allele a DNA

```
  1   AGA GCC GAC GCC GCT CCC ACC GTG TCC ATC TTC CCC CCC AGC ATG GAA CAG CTG ACC TCT GGC GGA GCC ACC GTG GTC
 79   TGC TTC GTG AAC AAC TTC TAC CCC AGA GAC ATC AGC GTG AAG TGG AAG ATC GAC GGC AGC GAG CAG AGG GAC GGC GTG
157   CTG GAC AGC GTG ACC GAC CAG GAC AGC AAG GAC TCC ACC TAC AGC ATG AGC AGC ACC CTG AGC CTG ACC AAG GTG GAG
235   TAC GAG AGG CAC AAC CTG TAC ACC TGC GAG GTG GTG CAC AAG ACC AGC TCC AGC CCC GTG GTC AAG TCC TTC AAC CGG
313   AAC GAG TGT
```

Fig. 12, contd.

Rat IGCK allele a protein

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   1   RADAAPTVSI FPPSMEQLTS GGATVVCFVN NFYPRDISVK WKIDGSEQRD
  51   GVLDSVTDQD SKDSTYSMSS TLSLTKVEYE RHNLYTCEVV HKTSSSPVVK
 101   SFNRNEC
```

IGKV1-39/J-Ck

```
   1   GGT ACC GCG GCC GCC ACC ATG GAC ATG AGA GTG CCC GCC CAG CTC CTG GGG CTC CTG CTA CTC TGG CTC CGA GGT AAG
  79   GAT GGA GAA CAC TAG GAA TTT ACT CAG CCA GTG TGC TCA GTA CTG ACT GGA ACT TCA GGG AAG TTC TCT GAT AAC ATG
 157   ATT AAT AGT AAG AAT ATT TGT TTT TAT GTT TCC AAT CTC AGG TGC CAG ATG TGA CAT CCA GAT GAC CCA GAG CCC CAG
 235   CAG CCT GAG CGC CAG CGT GGG CGA CAG AGT GAC CAT CAC CTG CAG AGC CAG CCA GAG CAT CAG CAG CTA CCT GAA CTG
 313   GTA TCA GCA GAA GCC CGG CAA GGC CCC CAA GCT GCT GAT CTA CGC CGC CAG CTC CCT GCA GAG CGG CGT GCC CAG CAG
 391   ATT CAG CGG CAG CGG CTC CGG CAC CGA CTT CAC CCT GAC CAT CAG CAG CCT GCA GCC CGA GGA CTT CGC CAC CTA CTA
 469   CTG CCA GCA GAG CTA CAG CAC CCC CCC CAC CTT CGG CCA GGG CAC CAA GGT GGA GAT CAA GAG AGC CGA CGC CGC TCC
 547   CAC CGT GTC CAT CTT CCC CCC CAG CAT GGA ACA GCT GAC CTC TGG CGG AGC CAC CGT GGT CTG CTT CGT GAA CAA CTT
 625   CTA CCC CAG AGA CAT CAG CGT GAA GTG GAA GAT CGA CGG CAG CGA GCA GAG GGA CGG CGT GCT GGA CAG CGT GAC CGA
 703   CCA GGA CAG CAA GGA CTC CAC CTA CAG CAT GAG CAG CAC CCT GAG CCT GAC CAA GGT GGA GTA CGA GAG GCA CAA CCT
 781   GTA CAC CTG CGA GGT GGT GCA CAA GAC CAG CTC CAG CCC CGT GGT CAA GTC CTT CAA CCG GAA CGA GTG TTG AGC TAG
 859   CGA GCT C
```

IGLV2-14/J-Ck

```
   1   GGT ACC GCG GCC GCC ACC ATG GAC ATG AGA GTG CCC GCC CAG CTC CTG GGG CTC CTG CTA CTC TGG CTC CGA GGT AAG
  79   GAT GGA GAA CAC TAG GAA TTT ACT CAG CCA GTG TGC TCA GTA CTG ACT GGA ACT TCA GGG AAG TTC TCT GAT AAC ATG
 157   ATT AAT AGT AAG AAT ATT TGT TTT TAT GTT TCC AAT CTC AGG TGC CAG ATG TCA GTC TGC CCT GAC CCA GCC CGC CTC
 235   TGT GTC TGG CAG CCC TGG CCA GAG CAT CAC CAT CAG CTG CAC CGG CAC CAG CAG CGA CGT GGG CGG CTA CAA CTA CGT
 313   GTC CTG GTA TCA GCA GCA CCC CGG CAA GGC CCC CAA GCT GAT GAT CTA CGA GGT GTC CAA CAG ACC CAG CGG CGT GAG
 391   CAA CAG ATT CAG CGG CAG CAA GAG CGG CAA CAC CGC CAG CCT GAC CAT CAG CGG CCT CCA GGC TGA GGA CGA GGC CGA
 469   CTA CTA CTG CAG CAG CTA CAC CAG CAG CTC CAC CCT GGT GTT TGG CGG CGG AAC AAA GCT GAC CGT GCT GAG AGC CGA
 547   CGC CGC TCC CAC CGT GTC CAT CTT CCC CCC CAG CAT GGA ACA GCT GAC CTC TGG CGG AGC CAC CGT GGT CTG CTT CGT
 625   GAA CAA CTT CTA CCC CAG AGA CAT CAG CGT GAA GTG GAA GAT CGA CGG CAG CGA GCA GAG GGA CGG CGT GCT GGA CAG
 703   CGT GAC CGA CCA GGA CAG CAA GGA CTC CAC CTA CAG CAT GAG CAG CAC CCT GAG CCT GAC CAA GGT GGA GTA CGA GAG
 781   GCA CAA CCT GTA CAC CTG CGA GGT GGT GCA CAA GAC CAG CTC CAG CCC CGT GGT CAA GTC CTT CAA CCG GAA CGA GTG
 859   TTG AGC TAG CGA GCT C
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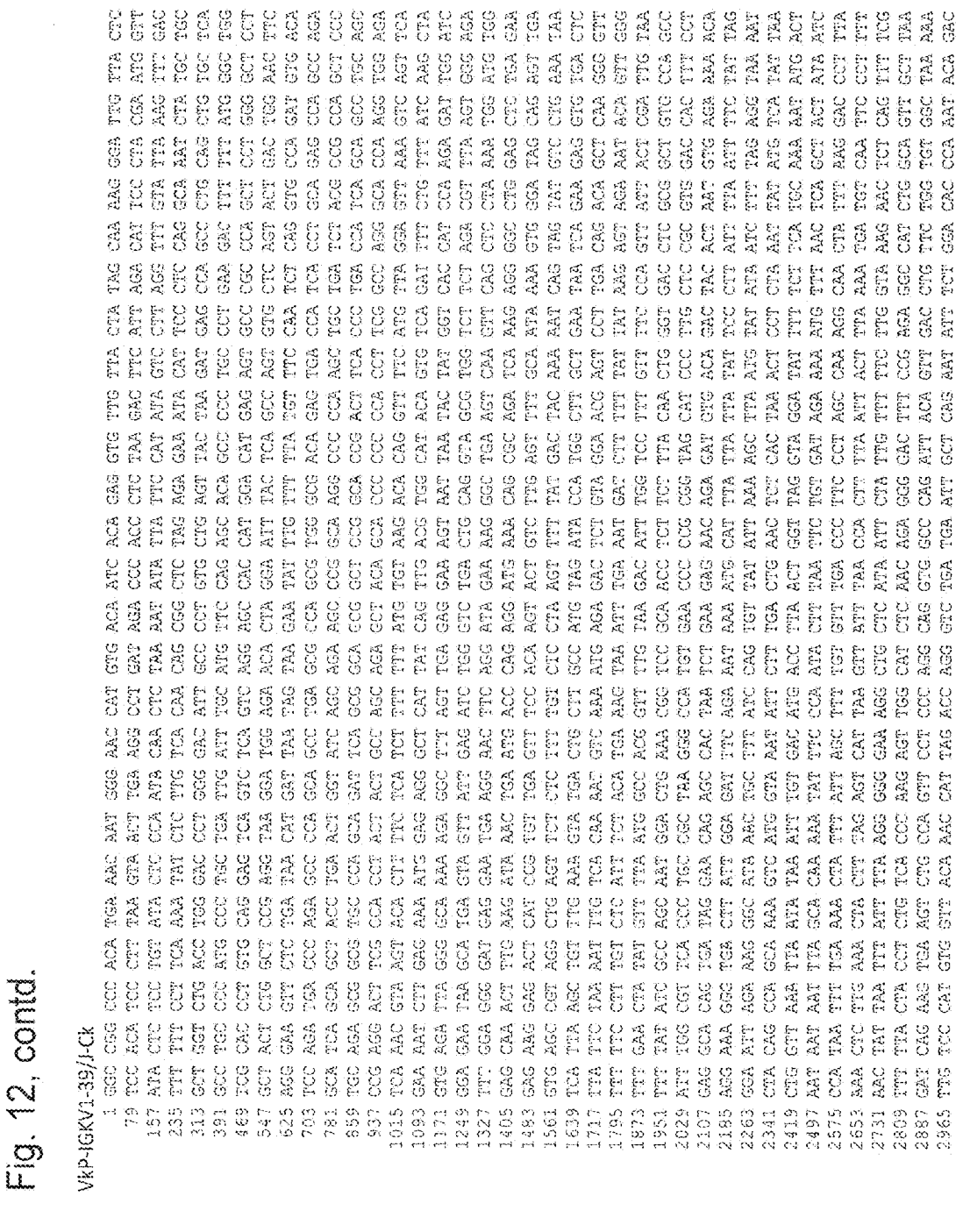
Fig. 12, contd.



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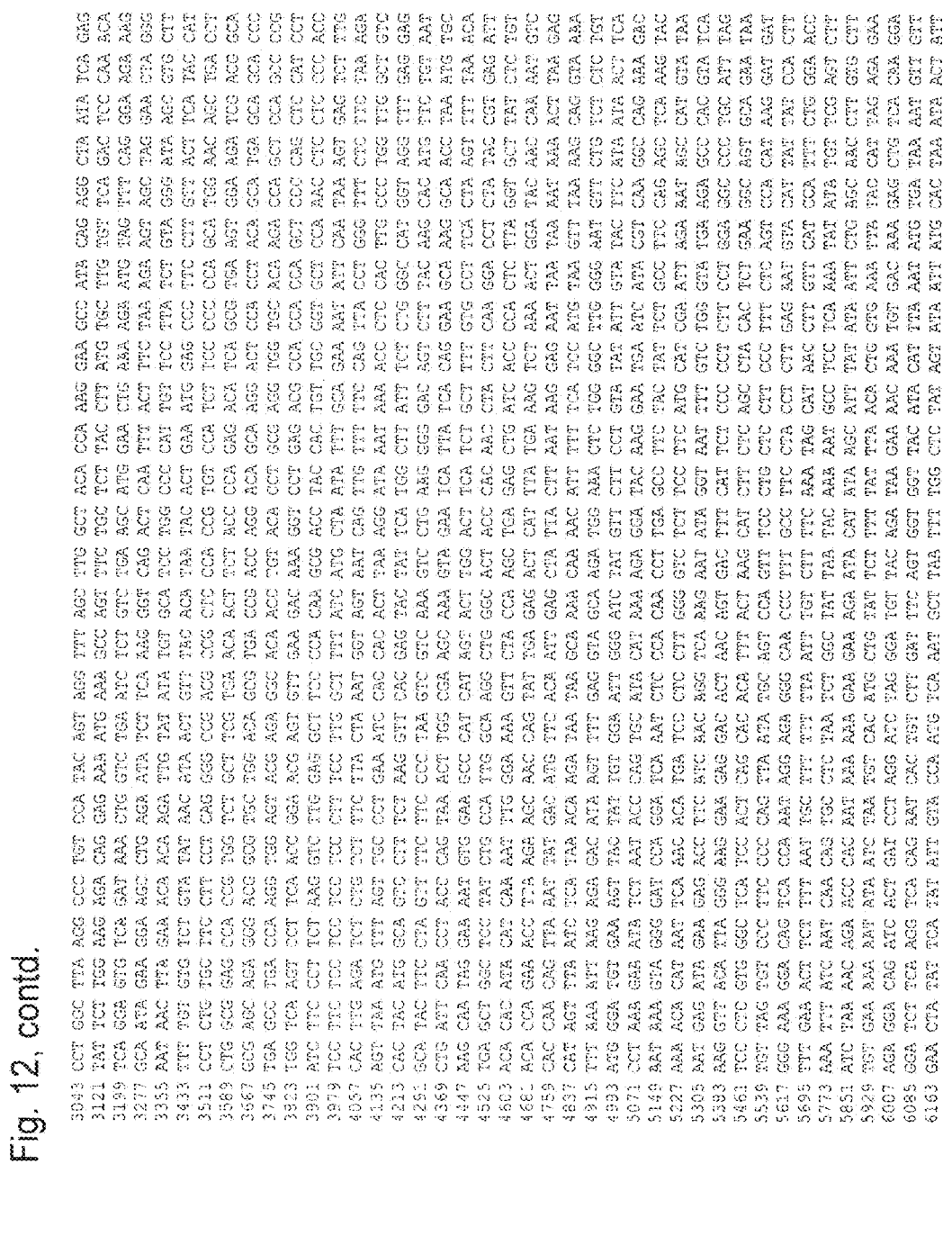

Fig. 12, contd.

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6475 CTA GCT TCA AGC TGC TGT TGC TGA CCT AGT GAA CCA GCC CCA AGC TGT GAG CCC CAA TAG CAC AAA GCT ACT GCC CAA
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Fig. 12, contd.

Fig. 12, contd.

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13261 GGA TAG TTG TCA GTA AAC ACC CCA CAA CCC ATA ACA GAA GTA TTC TCT TCT TTC TAT ATC CCT TTT CCA TCC ATG TAG
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VkP-IGKV1-39/J-Ck-Δ1

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    1 GGC CGG CCC ACA TGA AAC AAT GGG AAC CAT GTG ACA ATC ACA GAG GTG TTG TTA CTA TAG CAA AAG GGA TTG TTA CTC
   79 TCC ACA TCC CTT TAA GTA ACT TGA AGG CCT GAT AGA CCC ACC CTC TAA GAC CTC ATT AGA CAT TCC CTA CGA ATG GTT
  157 ATA CTC TCC TGT ATA CTC CCA ATA CAA CTC TAA AAT ATA TTA TTC CAT ATA GTC CTT AGG TTT GTA TTA AAG TTT GAC
  235 TTT TTT CCT TCA AAA TAT CTC TTG TCA CAA CAG CGG CTC TAG AGA GAA ATA CAC TCC CTC CAG GCA AAT CTA TGC TGC
  313 GCT GGT CTG ACC TGG GAC CCT GGG GAC ATT GCC CCT GTG CTG AGT TAC TAA GAT GAG CCA GCC CTG CAG CTG TGC TCA
  391 GCC TGC CCC ATG CCC TGC TGA TTG ATT TGC ATG TTC CAG AGC ACA GCC CCC TGC CCT GAA GAC TTT TTT ATG GGC TGG
  469 TCG CAC CCT GTG CAG GAG TCA GTC TCA GTC AGG AGC CAC CAT GGA CAT GAG AGT GCC CGC CCA GCT CCT GGG GCT CCT
  547 GCT ACT CTG GCT CCG AGG TAA GGA TGG AGA ACA CTA GGA ATT TAC TCA GCC AGT GTG CTC AGT ACT GAC TGG AAC TTC
  625 AGG GAA GTT CTC TGA TAA CAT GAT TAA TAG TAA GAA TAT TTG TTT TTA TGT TTC CAA TCT CAG GTG CCA GAT GTG ACA
  703 TCC AGA TGA CCC AGA GCC CCA GCA GCC TGA GCG CCA GCG TGG GCG ACA GAG TGA CCA TCA CCT GCA GAG CCA GCC AGA
  781 GCA TCA GCA GCT ACC TGA ACT GGT ATC AGC AGA AGC CCG GCA AGG CCC CCA AGC TGC TGA TCT ACG CCG CCA GCT CCC
  859 TGC AGA GCG GCG TGC CCA GCA GAT TCA GCG GCA GCG GCT CCG GCA CCG ACT TCA CCC TGA CCA TCA GCA GCC TGC AGC
  937 CCG AGG ACT TCG CCA CCT ACT ACT GCC AGC AGA GCT ACA GCA CCC CCC CCA CCT TCG GCC AGG GCA CCA AGG TGG AGA
 1015 TCA AAC GTA AGT ACA CTT TTC TCA TCT TTT TTT ATG TGT AAG ACA CAG GTT TTC ATG TTA GGA GTT AAA GTC AGT TCA
 1093 GAA AAT CTT GAG AAA ATG GAG AGG GCT CAT TAT CAG TTG ACG TGG CAT ACA GTG TCA GAT TTT CTG TTT ATC AAG CTA
 1171 GTG AGA TTA GGG GCA AAA AGA GGC TTT AGT TGA GAG GAA AGT AAT TAA TAC TAT GCT CAC CAT CCA AGA GAT TGG ATC
 1249 GGA GAA TAA GCA TGA GTA GTT ATT GAG ATC TGG GTC TGA CTG CAG GTA GCG TGG TCT TCT AGA CGT TTA AGT GGG AGA
 1327 TTT GGA GGG GAT GAG GAA TGA AGG AAC TTC AGG ATA GAA AAG GGC TGA AGT CAA GTT CAG CTC CTA AAA TGG ATG TGG
 1405 GAG CAA ACT TTG AAG ATA AAC TGA ATG ACC CAG AGG ATG AAA CAG CGC AGA TCA AAG AGG GGC CTG GAG CTC TGA GAA
 1483 GAG AAG GAG ACT CAT CCG TGT TGA GTT TCC ACA AGT ACT GTC TTG AGT TTT GCA ATA AAA GTG GGA TAG CAG AGT TGA
 1561 GTG AGC CGT AGG CTG AGT TCT CTC TTT TGT CTC CTA AGT TTT TAT GAC TAC AAA AAT CAG TAG TAT GTC CTG AAA TAA
 1638 TCA TTA AGC TGT TTG AAA GTA TGA CTG CTT GCC ATG TAG ATA CCA TGG CTT GCT GAA TAA TCA GAA GAG GTG TGA CTC
 1717 TTA TTC TAA AAT TTG TCA CAA AAT GTC AAA ATG AGA GAC TCT GTA GGA ACG AGT CCT TGA CAG ACA GCT CAA GGG GTT
 1795 TTT TTC CTT TGT CTC ATT TCT ACA TGA AAG TAA ATT TGA AAT GAT CTT TTT TAT TAT AAG AGT AGA AAT ACA GTT GGG
 1873 TTT GAA CTA TAT GTT TTA ATG GCC ACG GTT TTG TAA GAC ATT TGG TCC TTT GTT TTC CCA GTT ATT ACT CGA TTG TAA
 1951 TTT TAT ATC GCC AGC AAT GGA CTG AAA CGG TCC GCA ACC TCT TCT TTA CAA CTG GGT GAC CTC GCG GCT GTG CCA GCC
 2029 ATT TGG CGT TCA CCC TGC CGC TAA GGG CCA TGT GAA CCC CCG CGG TAG CAT CCC TTG CTC CGC GTG GAC CAC TTT CCT
 2107 GAG GCA CAG TGA TAG GAA CAG AGC CAC TAA TCT GAA GAG AAC AGA GAT GTG ACA GAC TAC ACT AAT GTG AGA AAA ACA
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Fig. 12, contd.

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2185 AGG AAA GGG TGA CTT ATT GGA GAT TTC AGA AAT AAA ATG CAT TTA TTA TTA TAT TCC CTT ATT TTA ATT TTC TAT TAG
2263 GGA ATT AGA AAG GGC ATA AAC TGC TTT ATC CAG TGT TAT ATT AAA AGC TTA ATC TAT ATA ATC TTT TAG AGG TAA AAT
2341 CTA CAG CCA GCA AAA GTC ATG GTA AAT ATT CTT TGA CTG AAC TCT CAC TAA ACT CCT CTA AAT TAT ATG TCA TAT TAA
2419 CTG CTT AAA TTA ATA TAA ATT TGT GAC ATG ACC TTA ACT GGT TAG GTA GGA TAT TTT TCT TCA TGC AAA AAT ATG ACT
2497 AAT AAT AAT TTA GCA CAA AAA TAT TTC CCA ATA CTT TAA TTC TGT GAT AGA AAA ATG TTT AAC TCA GCT ACT ATA ATC
2575 CCA TAA TTT TGA AAA CTA TTT ATT TGT CTA CAC CAA AGG AAG CCA TAC AGA GGC TAA TAT CAG AGT ATT CTT GGA AGA
2653 GAC AGG AGA AAA TGA AAG CCA GTT TCT GCT CTT ACC TTA TGT GCT TGT GTT CAG ACT CCC AAA CAT CAG GAG TGT CAG
2731 ATA AAC TGC TCT GAA TCT CTG TGT GAA GCA TGG AAC TGA AAA GAA TGT AGT TTC AGG GAA GAA AGG CAA TAG AAG GAA
2809 GCC TGA GAA TAT CTT CAA AGG GTC AGA CTC AAT TTA CTT TCT AAA GAA GTA GCT AGG AAC TAG GGA ATA ACT TAG AAA
2887 CAA CAA GAA TGT ATA TAT GTG CAT CCT GGC CCC ATT GTT CCT TAT CTG TAG GGA TAA GCG TGC TTT TTT GTG CTG
2965 TAT ATA ACA TAA CTG TTT ACA CAT AAT ACA CTG AAA TGG AGC CCT TCC TTG TTA CTT CAT ACC ATC CTC TGT GCT TCG
3043 TTC CTC ASG GGC CGA CGC CGC TCC CAC CGT GTC CAT CTT CCC CCC CAG CAT CTA TAC CAC ACA GCT GAC CTC TGG CGG AGC CAC
3121 CGT GGT CTG CTT CGT GAA CAA CTT CTA CCC CAG AGA CAT CAG CGT GAA GTG GAA CAT CGA CGA CGA CCA GAG GCA GAG GGA
3199 CGG CGT GCT GGA CAG CGT GAC CGA CCA GGA CAG CAA GGA CTC CAC CTA CAG CAT GAG CAG CAC CCT GAG CCT GAC CAA
3277 GGT GGA GTA CGA GAG GCA CAA CCT GTA CAC CTG CGA GGT GGT GCA CAA GAC CAG CTC CAG CCC CGT GGT CAA GTC CTT
3355 CAA CCG GAA CGA GTG TTG AAG ACA AAG GTC CTG AGA CGC CAC CAC CAG CTC CCC AGC TCC ATC CTA TCT TCC CTT CTA
3433 AGG TCT TGG AGC CTT CCC CAC AAG CGA CCT ACC ACT GTT GCG GTG CTC CAA ACC TCC TCC CCA CCT CCT TCT CCT CCT
3511 CCT CCC TTT CCT TGG CTT TTA TCA TGC TAA TAT TTG CAG AAA ATA TTC AAT AAA GTG AGT CTT TGC ACT TGA GAT CTC
3589 TGT CTT TCT TAC TAA ATG GTA GTA ATC AGT TGT TTT TCC AGT TAC CTG GGT TTC TCT TCT TCT AAA GAA GTT AAA TGT TTA
3667 GTT GCC CTG AAA TCC ACC ACA CTT AAA GGA TAA ATA AAA CCC TCC ACT TGC CCT GGT TGG CTG TCC ACT ACA TGG CAG
3745 TCC TTT CTA AGG TTC AGG AGT ACT ATT CAT GGC TTA TTT CTC TGG GCC ATG GTA GGT TTG AGG AGG CAT ACT TCC TAG
3823 TTT TCT TCC CCT AAG TCG TCA AAG TCC TGA AGG GGG ACA GTC TTT ACA AGC ACA TGT TCT GTA ATC TGA TTC AAC CTA
3901 CCC AGT AAA CTT GGC GAA GCA AAG TAG AAT CAT TAT CAC AGG AAG CAA AGC CAA CCT AAA TGT GCA AGC AAT AGG AAA
3979 ATG TGG AAG CCC ATC ATA GTA CTT GGA CTT CAT CTG CTT TTG TGC CTT CAC TAA GTT TTT AAA CAT GAG CTC GCT CCT
4057 ATC TGC CAT TGG CAA GGC TGG GCA CTA CCC ACA ACC TAC TTC AAG GAC CTC TAT ACC GTG CTT ATC TCT GTA CAC ACA TAC ATC
4135 AAA ATT TGC GAA AAG TTC TAC CAA GCT GAG AGC TGA TCA CCC CAC TCT TAG GTG CTT ATC TCC ACC AAC AGT TAA
4213 TAA GAA GCA ACC AGT ATT GAG AGA CTC ATT TAT GAA AGT CTA AAA CTG GAT ACA ACC AAA ATG TCC AAC AGT TAA
4291 ATT ATG ACA TGT TCA CAA TTG AGC TAT TAC TTA ATA AGG AGA ATT AAT AAA ATA AAA CTT AAG AGC ATA GTT TAA TCT
4369 CAT AAA CAA GAT AAT AAG CAA AAC AAA ACA TTT TTT CAT CCA TGT AAG TTT AAA AGC AGG TAA AAT TTA AAA TTA AGA
4447 GAG ACA TAA GTT TTG AGG TAG CAA GAT GGA AAC TCT GGG GCT TGG GGA ATG TTC TGT CTC TCT GTA TGG GAT GTG AAA
4525 GTT ACT ATT GTG GAA TTG GGA TCT ATG TTC TTC CTG TAT ATA TTG TAT ACT TCA TAA TAA CTT CAC CTA AAG AAA TAT
4603 CTA ATA CCC AGT GCA TAC ATA AAA GAG GAT ACA AGG AAT GAA TCA TAC GTC AAG GCC AGA AAG ACA ATA AAG TAG GGG
4681 ATC CAG GAA ATC TCC CAC AAC CTT GAG CCT TCT ACT ATT CTG CCT TCC AGA GCT CAA AGT ACA AAA CAC ATA ATT
4759 CAA ACA CAT GAT CCC TCC TTG GGG TCT CTT CCT TCA TGC ATC GAA TTA GAA ATA GCC ATG TAT AAA ATG AGA TAG AAG
4837 AGA CCT TCA TCA ACA GCT CAA AGA ATA TAG GTA ATT TTG TCT GGG TAT GAA GAG CCC ACG TAT CAA AGG TTA CAT TAG
4915 GGA AGG AAG AGG ACA CTA ACA GTG ACT TTC ATT CTC CCC CTC TTC CTG GAG GTC CCT GCA TTT AGT CCC TCG TGG GCT
4993 CAT CCA CTC AGC ACA CAT CTA CTA AGC ATC TTC TCA GCC TAC ACT CTG AAG GCA GTG CAG AAT AAT GTT AGT GTC CCT
5071 TCC CCC AGT TAA TAT GCA GTC CAG TTT CCC TGC TCC TTC CCT TTC TCA GTC CAC ATA AGG ATG ATG GGA AAG GAC AGT
5149 CAC CAA ATA GGA GAG GGC AAC CCT TTG CCT TCC TAC CTC TTG AGA ATG TAC ATT ATT ATC CAC TTT TTG AAA CTT CTT
5227 TTA ATT GCT TTT TTT TAA TTT GTC TTT TCA AAT AGC ATA ACC TTG TTC ATC CAT TTC TGG GAA CCA AAT TTA TCA ATC
5305 AAC AGT GGC TCT AAT CTG GCT ATT AAT ACA AAA ATG CCT CCT CAA AAT ATA TAT GTT CGA GTC TTA TCT AAA ACA GAA
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Fig. 12, contd.

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5383 CCC ACA ATA AAA AAG AAG AAA GAA TAC ATA TAA GCA TTT ATA TAA TTC TGA GCA ACC TTG TGC TTT GTG AAA AAA ATA
5461 TAA TCT AAT GTC ACA TGC TGT ATT CTT TTT ATT TAA CAC TGG TGA AAT TAT ACC ATT AGA GAG AAA GAG GAC AGA TCA
5539 CTG ATC CTA GGA TCT AGG GAT GTT ACA GAT AAG AAA ACA AAT GTG ACA AAG AGC TGT CAC AAG GAG GAT CTT CAA GCT
5617 CAC AGA ATC ACT GTC TTG ATT TCA GTG GTG GTT ACA TAC ATT TAA ATA TGT GAT AAA ATG CTG TTG AAC TAT ATT CAT
5695 ATA TTG TAC CAA TGT CAA ATG CTT AAT TTT GGC TCT ATA GTA TAA TTA TGC ACT AAA TAA CTA TTT GGA CAA AGA AAA
5773 TGA TGT TTA CAT CAA AGG TGA GGC CAT ATT TGT TAG GAA CAT AAC TTA AAA ACC ATT TTG GAT AAC TAA TGA AAA GCC
5851 ATT TTG TGT GCC TTG GCA TAT CAT GCC TAA GCT GTC ACC AGA TAG ATC TAA TAA GAC CTA AGC CTC AGA AGC AAG CCC
5929 CTG CCC AGC AAG CAG GCA GCA CAG ATA AGA GCT AAA CCC AGG ACA GGC CAT GAT ATG CTA ATG AAC TAC CTT CAA GGT
6007 GGT GTT GCT GAC CTA GTG AAC CAG CCC CAA GCT GTG AGC CCC AAT AGC ACA AAG CTA CTG CCC AAA GAA ATT ATA CAA
6085 AAA TTG GAA CTT TGG GAA TGG TGT GCA GGA TCG CTC TGC TGT ATG CCT GGA ACA CAG CTT CTC TAT GTT TTG TAT TGA
6163 TAC CAG TCT AGA AGC TTC CAA AAC TTT CTC ACT GAA GAA GAT TCC CCA TGT GGG ACC CCT ACA GAC TCT TTT GCC CAA
6241 ACA ACT GCT TCC CTC CTG GTG TGA TAT CTG TTT TGC TTT CAT GTT AGC ATA ATA TTA TAA GGA ATG TTT GTG TGA ATA
6319 AAC CAA ACA TAT TTT AAA AGC AAA TAT TGT ATG CAC ATC CTA ATT GCT AAA AAG TTT ACA GCT AAT AGT CCC ATG CTC
6397 TCC ACA ATA CTG GAT CCA AAT AAG TCC TAA TTT CAA TGT TGG GCA TCT TTA CAG AGA GAA AGA CAT TAA AAA TGA AGA
6475 GAC ATG CAG AGA GTG CAC CAT GCC ATC GTG GAG ACA GAC TGA AGT GAC ACA ACT GTT AGT CAA AGA GGA TTA AGG ACT
6553 TCC AGA AGC CAC CAA AGG AAG GAG GTA TGA AGT GGT TTC TCC CTC AGA GTA TCC AGA GGA GAC TAA ACC AAC CAA CAC
6631 CTT TTT GCT TAA GAC TTC TTG CCT TCA GGA CTG TGA GAA GGT AGC TTC CTA TTG TTC TAA GCC CCA GTA TGT GGC ATT
6709 TTG TTA AGG TAG AGT CAA GAA ACC AAT AAA ATG CAG ACA GAC AAA AGG ATA GCT GAG TTT TCC AGG CCC TTC CTT CTT
6787 ATT TTT GGT TTT GTT GGT GGT GGT GGT GGT GGT GGT GAT GGT GGT GGT TTT GTT TAT GTT TTG TTT GGG GAG TTT TTT
6865 GGG GTT TTT TTG GGT TTT GTT TTT GTT GTT GTT TTG GGG GTT TTT GTT GTT GTT GTT GTT TGC TTT TTT GTT TTT TGT
6943 TTT TTG TTT TTT TGA GAC AGT GTT TCT CTG TAT AGC CCT GGC TGT CCT GGA GTT CCT TCT ATC TCT AAT GTC TAC ATC
7021 TCA GAG GGG ATC CTC TAA TTT CAA ATG AGC AGT AGC TCT CCA TTT TTA GCT CTT ATT TAT TCA TTT ATT TAC TTA CTT
7099 ACT TAT TGT CTG TAG ATG AAA GAA TTT TGG AGT GGG AAA GGG TTC ATG AGC CCC CAG CAA CTA ATG AGG AGC TAC AGA
7177 CAA TTG ATG TTT CTG GGG AAA GGA GAC TCA GTT TCT TTG AGA GTA TAG CTT CTG ATG GGT CAA CCA TGT TCC TGT GGC
7255 TGA TGT CAC ACC CAG GAG TAT GCA GAC AAC AGA AAC TGG AGT TAA TGA GTT GTT TTA AAA ATA AAA AAG GGC ATG AAG
7333 CTT GGG ATA GAA ATT AAG GAT AAA TAC AAT TAA ATA CAG GAA ATT CTG AAA GAA TTA ATA AAA ACA TTT CTT TTT TTA
7411 AAA AAA AAT CCA GAA TTA GCT ATG CTT CTT CAA AAT TGC TTC TGG AGA ACT TTA CAA GTT AAA TAA GTT ATA TTG TAG
7489 AAA AGG TAG AGA GGA GAA CAG TGG AAG AGA GAC ATA AGG AGA CTT CAA AAG GAG TGG AGG GAG ATA GAG GAG GAG AAA
7567 GCA GAA GCA ATG GCT GAT AGA CAC AGG ATA AGA GGG AAC AGA AAG GAG AAA GAG GAA GCC AGG ATG GGT ATT TCT TTG
7645 CCT ATC TGT GAC TTG CAC ATG GTC TTG GCA ATT ATT GAT GAG TTC AAG GCT TAA TTC TTC ACT TGT GCC AAC TCA ACA
7723 GAG TCT TTC TTT CTT ATA ACC AGG CCC CCA GTA TGC TCA TGT ATG TAT CAG GTC CTC TTA TCT CCT TAT AGC AAT CCT
7801 GTT TAT AAC TGG GTA ACT TTG TGA AGG GAA GGA AGT GCA CAC TGA GAT GTG CTA CAA CTT TTT AAT ACA AAA TTT TGA
7879 ACA GTT TGT ACA ATG TAT GTA TAA TTA ATA ATT AAT ATT ATG CAC TTT AGA TTT TGA TTT CAA CTC AAG ATA CTA ATT
7957 CTA TAT ATA TGG GTT AAA TCA ATA TAT TAA TAA GTT TAA TTT CAC ATG CTT ATT TTT ATT GTG GTT TTC GAG ACA GGG
8035 TTT CTC TGT ATA GCC CTG GCT GTC CTG GAA CCC ACT TTG TAG ACC AGG CTG GCC TCA AAC TCA GAA ACC TAC CTG CCT
8113 CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT
8191 CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT CTG CCT
8269 CTG CCT CTG CCT CTG CCT AGT GCT GGA ATT AAA GGT TTG CGC CAC CAC GCC CGG TGA AAT TTT TAA ACT TTA TAT ATG
8347 TCT CAT TCT ATT TCT ATC AGA TAG GAC TGT GTA GAC TGT GCT AAA CTA ATA AAT GTG CCC TCA AAA GTA ATC GCA AGT
8425 TGT ATT GTT GTT GTT TTG CTT TGC TTT GCT TTG CTT TGC TTT GCT TTG CTT TGC TTT GCT TTG CTT TGC TTT GCT TTG
8503 CTT TGC TTT GCT TTG CTT TGC TTT GCT TTG CTT TGC TTT GCT TTT TTG TTT TGG GTT TTT TTC CGG GGG AGG GAG GGT
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Fig. 12, contd.

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 8581 GGA GAA AGA ATC TTA CTA TGA AGC TGT GAC TGT CCT GGG AAC TCA CTA TAT AGA TCA GGC TTG ATT CAA CTC ATA GAG
 8659 ATC TGC CTT CTT CTG CCT CCC AAG TGC TGG GAA TAA AGG CAT ACA CCT CCA TGC CCA GAT AGT GAT CCC AAG TTT TAG
 8737 CAA AAG TTT CTA GAC TTG ACA TTA ATC GAT GGA GAT AGA CAT GAA TTA CAC AAA GAA CTA ATG TGG AGT TTA CCT CAA
 8815 TCA TAC TCT ATA CTT TAT CAG AGA TTA AAT TAA CAT TTA ATA ATC CAG TGC CAG GCT AGA GCC ACC ATT CAA TGG CAG
 8893 TGT TTG CCA TCA TGC ATA GCC TTA GTC TTC AGT GCT GAA AGG CAT TGG GGC CAA TAT TAC TCA TTA TAC AGA TGA GAA
 8971 ACT GGG AAA GAC TTG CCT CAG ATT CTC TAC TGA AAG GCT GAG TTT GTG GCT TCT AGA AAA TCT TTT ACT TTC AAT AAT ACT
 9049 TTT AAT GTA TAA TTT TTT TAT TTC CAC TGA TTT TAT TTA ATT TTT TTA ACA AGA AAT AAA TGC AAT AAA CCA
 9127 AAT ACA TGG ACA AAA AAA TAC AAG AAT CAT ATG ATC ACC TCA ATG GAA GGA AAA AAA AAG AAA GAA AAA GTC TTT GAT
 9205 AAG ATT CAA CAT TCA TTC TTT TAT TAC ATA TTT TCT TCA TTT ACA TTT CAA ATG CTA TCC CCA AAG CCC CCT ATA
 9283 CCT TCC CCT GCC CTG CTC CCC AAC CCA CCT ACT CCT GCT TTC TGG CCC TGG CAC TCC TCT GTA CTG AGG CAT ATG ATC
 9361 TTC AAA AAA CCA AGG GCC TCT CCT CTC ATT GGT GGC CGA CTA TTA GGC CAT CTT TTG CTA CAT ATG CAA CTA GAG ACA
 9439 CAG CTC TGG GGG TTA CTG GTT AGT TCA TAT TGT TAG TCC TCC TAT AGA GTT GCA GAC CCC TTT AGC TCC TTG GAT ACT
 9517 TTC TCT AGT TCC TTC ATT AGG GGC CCT GTG TCC CAT CCA ATA GAT GAC TGT GAG CAT CCA CTT CTG TAT TTG CCA GGC
 9595 ACT GGC ATA GCC TCA CGA GAA AGA GAG AGC TAT GTC AGG ATC CTG GAG GAC TCT CTG AAA CTT TTC TGG CAT ATG CAA TAG TAT
 9673 CTG GGT TTG GTG GTA TAT GGG ATG GAT CCC CAA GTG GAG CAG TCT CTG AAT GGT CCT TCC TTC CAT CTC AGC TCC AAT
 9751 AAA CTT TGT CTC TAT AAC TCC TTC CAT GGG TAT TTT GTT CCC CAT TCT AAG AAG GAG TGA AGA ATC CAC ACT TTG GTC
 9829 TTC CTT CTT CTT GAG TTT CAT ATG TTG CAT CTT GGA TAT TCT AAG TTT CTG GGT TAA TAT CCA CGT ATC AGT GAG TGC
 9907 ATA TCA TGC GTG TTA TTT TGT GAT TAG TTT ACC TCA CTC AGG ATG ATA TCC TCC AGA TGC ATC CAT TTG CCT AAG AAT
 9985 TTC ATT AAT TCA CTG TTT TTA ATT GCT GAA TAG TAC TCC ATT GTG TAA ATG TAC CAC ATT TTC TGT ATC CAT TCC TCT
10063 GTT GAG GGG CAT CTG GGT TCT TTC CAG CTT CTG GCT ATT ATA AAT AAG GCT GCT GCT ATG AGC ATA GCG GAG CAT GTG TCC
10141 TTA TCA AGT TGG AAC ATC TTC TAG GTA TAT GCC CAG GAG AGG AAT TGC TGG ATC TTC CGG TAG TAC CAT CAA CAT GCA
10219 TTC TTA ATA AAA GCC CTA GAA CAA GGA GGA CTG TAG GAA ACA TAT TCC AAC ATA ATA AAG GTT ATG TAT GAC AAA CTC
10297 ATG ACC AAT ATC CTA AAT GAA TGA AAC CAT TAA TAA GCT CCA TTA AAA TCA GAG GAC TGC CCA CTA TCC CTA CTT
10375 CTC ATC CAT AAT GAG ATT GAA GCA TTA GCT GGA GCA ATA AGG CAA GAG AAG GGA TAC AAA TGG GAA AAT ATT AAG TCA
10453 AAT TGT TTT CAA TTG AAG ATT ATA TTA TCT TAT ACC CAA TGA CCT CAA ATT TTG ACT AGA AAA ATT GTA GAA ATT ATC
10531 AAT AAT TTC AGC AAA GTG TTA TGA TGC ACC ACA TCC TTA TTC TTC TCC CCA GCT TCT GCT TGC AGC GTG TAA CTC TCC TGT GAC TGA
10609 CTT CAT CCT TTC TGT CCT TCC ATC TGC CTG CAC TCT TGT CTC AAG ACT GAG TTT GTC TTT CTG AAG CTA TGA GGC TCT CTA CAT AGA
10687 GTA TCT CAC AAA ACG TTC TAC CTG CCA AAC CTG GAT GAG GGG GAA GGC TGA CAT TAG CAT TGC TCC TGT GTG GCT CCT
10765 CTC AAG AAG GAA ATG ACA GGG AGG AGG TAA TAA TCA AGT GGG GAA GGC TGA CAT TAG CAT TGC TCC TGT GTG GCT CCT
10843 TAA TTT CTC ATA CTT CAC ACT GAG ATG TTA TTA ACT GTG ACT CAT AGG TGA AGA AGC CAG AGC TAA GGT TCT CAT ATT
10921 TGA GTG TTA TAG AAT GAG TAG AGC AGT AGT TCT CAA ACT ATG GGT CAT GAC TCC TTT ATG GGT CAA ACT ACC CTT TCA
10999 CAC AGG TTG CAT ATC AGA TAT CCT AAT TTT ATA TAC ATA TAT ATA TGT ATA TAT ATA TAT TTC ACA ACA GTA
11077 GGA AAA TTA TTT AGT AAT CAT TTT ATA CTT GTG GGT CAT GGC AAC ATG AGG AAC TGT ACT AAA GGG TTG CAG CAT TAG
11155 GAA TGT TGA GAC CCA CTG TAA TAG AGA ATG AGG CTT AAG GCA GGG CTA TAA AGC CCA ACG GAC CAT GTG CCT TTT CCA
11233 ACA TTT GCC ACA TGG TAA GCT CTG TAT AGA CTT TTT AAA GAA CAT TGG TTT GTA ATT TCA AAT GCA AAA ATC CTC AAC CTA
11311 CTG TCT ATC ACC CAT TAT AAT AAA TAC ATA AGC TTT GAT TCC ACC ATG GAT TCA AAT GCA AAA ATC CTC AAC CTA
11389 AGA CAT AGC AGT GAA ACA TTG ATG ACC AAA TAG GAA ATC CAT GTA GAG ACC TTC TAT CTT CTG ATG GCT CCA CAG GCA
11467 CCA TCT TGC AAC AGA GCT CTA CTT TGC TAC CAG TAA TGA ATA CAG TGT CTC AAC TCC TGC CAT TGA ATC TTC AGG AAG
11545 CCC CTG AAA TGA GTT GTA CTA CAC CAT TTC TTA AAG ACA GAA AAG CTA AGA CTT AGA GGG AAT AAA TGT CAT GCC TGA
11623 GAT CAT GCA ACC AAT TAA GTC CAA CTT GGC CTG ATC AAG AGG CAC AAT TCA AAA GCA ATG TTG TTC CTT CAC TAG CTC
11701 TTG TGT ATG GTT GCT GAT TCC GGA AGC AAA GTA TCA GTG AAT ATC CCT AGT GGG AAA AGA CTT GGA AAT CAA ATG TCT
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Fig. 12, contd.

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11779 CAT TTA ACA GAT TAG GAG ATG AAA CGG TAG ACT CTG TGT AGT TGT ACA CCC CTG TGA TCC CAT CGC TAG GAA GAC TGA
11857 GGC AGG AAG TCC TCG AGC TCA AAC CAG CTT AGG CTA CAC AGA GAA ACT ATC TAA AAA ATA ATT ACT AAC TAC TTA ATA
11935 GGA GAT TGG ATG TTA AGA TCT GGT CAC TAA GAG GCA GAA TTG AGA TTC GAA GCC AGT ATT TTC TAC CTG GTA TGT TTT
12013 AAA TTG CAG TAA GGA TCT AAG TGT AGA TAT ATA ATA ATA AGA TTC TAT TGA TCT CTG CAA CAA CAG AGA GTG TTA GAT
12091 TTG TTT GGA AAA AAA TAT TAT CAG CCA ACA TCT TCT ACC ATT TCA GTA TAG CAC AGA GTA CCC ACC CAT ATC TCC CCA
12169 CCC ATC CCC CAT ACC AGA CTG GTT ATT GAT TTT CAT GGT GAC TGG CCT GAG AAG ATT AAA AAA AGT AAT GCT ACC TTA
12247 TTG GGA GTG TCC CAT GGA CCA AGA TAG CAA CTG TCA TAG CTA CCG TCA CAC TGC TTT GAT CAA GAA GAC CCT TTG AGG
12325 AAC TGA AAA CAG AAC CTT AGG CAC ATC TGT TGC TTT CGC TCC CAT CCT CCT CCA ACA GCC TGG GTG GTG CAC TCC ACA
12403 CCC TTT CAA GTT TCC AAA GCC TCA TAC ACC TGC TCC CTA CCC CAG CAC CTG GCC AAG GCT GTA TCC AGC ACT GGG ATG
12481 AAA ATG ATA CCC CAC CTC CAT CTT GTT TGA TAT TAC TCT ATC TCA AGC CCC AGG TTA GTC CCC AGT CCC AAT GCT TTT
12559 GCA CAG TCA AAA CTC AAC TTG GAA TAA TCA GTA TCC TTG AAG AGT TCT GAT ATG GTC ACT GGG CCC ATA TAC CAT GTA
12637 AGA CAT GTG GAA AAG ATG TTT CAT GGG GCC CAG ACA CGT TCT AGA AGT ACC TGA GAG TGG CAA AAA ATA GTT GTG CTA
12715 AAT AGT TTG GCC ATC TTT AGG CTG AGA GAC TAG GAA ATA CAG CGA TGG ACT ATA TCA GCA TTG CAG GAT AGT TGT CAG
12793 TAA ACA CCC CAC AAC CCA TAA CAG AAG TAT TCT CTT CTT TCT ATA TCC CTT TTC CAT CCA TGT AGA TGG CTG TCT TCA
12871 TAT TTG TTC TAG ACG GCC GGC C
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VkP-IGKV1-39/J-Ck-Δ2

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    1 GGC CGG CCC ACA TGA AAC AAT GGG AAC CAT GTG ACA ATC ACA GAG GTG TTG TTA CTA TAG CAA AAG GGA TTG TTA CTC
   79 TCC ACA TCC CTT TAA GTA ACT TGA AGG CCT GAT AGA CCC ACC CTC TAA GAC TTC ATT AGA CAT TCC CTA CGA ATG GTT
  157 ATA CTC TCC TGT ATA CTC CCA ATA CAA CTC TAA AAT ATA TTA TTC CAT ATA GTC CTT AGG TTT GTA TTA AAG TTT GAC
  235 TTT TTT CCT TCA AAA TAT CTC TTG TCA CAA CAG CGG CTC TAG AGA GAA ATA CAT TCC CTC CAG GCA AAT CTA TGC TGC
  313 GCT GGT CTG ACC TGG GAC CCT GGG GAC ATT GCC CCT GTG CTG AGT TAC TAA GAT GAG CCA GCC CTG CAG CTG TGC TCA
  391 GCC TGC CCC ATG CCC TGC TGA TTG ATT TGC ATG TTC CAG AGC ACA GCC CCC TGC CCT GAA GAC TTT TTT ATG GGC TGG
  469 TCG CAC CCT GTG CAG GAG TCA GTC TCA GTC AGG AGC CAC CAT GGA CAT GAG AGT GCC CGC CCA GCT CCT GGG GCT CCT
  547 GCT ACT CTG GCT CCG AGG TAA GGA TGG AGA ACA CTA GGA ATT TAC TCA GCC AGT GTG CTC AGT ACT GAC TGG AAC TTC
  625 AGG GAA GTT CTC TGA TAA CAT GAT TAA TAG TAA GAA TAT TTG TTT TTA TGT TTC CAA TCT CAG GTG CCA GAT GTG ACA
  703 TCC AGA TGA CCC AGA GCC CCA GCA GCC TGA GCG CCA GCG TGG GCG ACA GAG TGA CCA TCA CCT GCA GAG CCA GCC AGA
  781 GCA TCA GCA GCT ACC TGA ACT GGT ATC AGC AGA AGC CCG GCA AGG CCC CCA AGC TGC TGA TCT ACG CCG CCA GCT CCC
  859 TGC AGA GCG GCG TGC CCA GCA GAT TCA GCG GCA GCG GCT CCG GCA CCG ACT TCA CCC TGA CCA TCA GCA GCC TGC AGC
  937 CCG AGG ACT TCG CCA CCT ACT ACT GCC AGC AGA GCT ACA GCA CCC CCC CCA CCT TCG GCC AGG GCA CCA AGG TGG AGA
 1015 TCA AAC GTA AGT ACA CTT TTC TCA TCT TTT TTT ATG TGT AAG ACA CAG GTT TTC ATG TTA GGA GTT AAA GTC AGT TCA
 1093 GAA AAT CTT GAG AAA ATG GAG AGG GCT CAT TAT CAG TTG ACG TGG CAT ACA GTG TCA GAT TTT CTG TTT ATC AAG CTA
 1171 GTG AGA TTA GGG GCA AAA AGA GGC TTT AGT TGA GAG GAA AGT AAT TAA TAC TAT GCT CAC CAT CCA AGA GAT TGG ATC
 1249 GGA GAA TAA GCA TGA GTA GTT ATT GAG ATC TGG GTC TGA CTG CAG GTA GCG TGG TCT TCT AGA CGT TTA AGT GGG AGA
 1327 TTT GGA GGG GAT GAG GAA TGA AGG AAC TTC AGG ATA GAA AAG GGC TGA AGT CAA GTT CAG CTC CTA AAA TGG ATG TGG
 1405 GAG CAA ACT TTG AAG ATA AAC TGA ATG ACC CAG AGG ATG AAA CAG CGC AGA TCA AAG AGG GGC CTG GAG CTC TGA GAA
 1483 GAG AAG GAG ACT CAT CCG TGT TGA GTT TCC ACA AGT ACT GTC TTG AGT TTT GCA ATA AAA GTG GGA TAG CAG AGT TGA
 1561 GTG AGC CGT AGG CTG AGT TCT CTC TTT TGT CTC CTA AGT TTT TAT GAC TAC AAA AAT CAG TAG TAT GTC CTG AAA TAA
 1639 TCA TTA AGC TGT TTG AAA GTA TGA CTG CTT GCC ATG TAG ATA CCA TGG CTT GCT GAA TAA TCA GAA GAG GTG TGA CTC
 1717 TTA TTC TAA AAT TTG TCA CAA AAT GTC AAA ATG AGA GAC TCT GTA GGA ACG AGT CCT TGA CAG ACA GCT CAA GGG GTT
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Fig. 12, contd.

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1735 TTT TTC CTT TGT CTC ATT TCT ACA TGA AAG CAA ATT TGA AAT GAT CTT TTT TAT TAT AAG AGT AGA AAT ACA GTT GGG
1873 TTT GAA CTA TAT GTT TTA ATG GCC ACG GTT CTG TAA GAC ATT TGG TCC TTT GTT TTC CCA GTT ATT ACT CGA TTG TAA
1951 TTT TAT ATC GCC AGC AAT GGA CTG AAA CGG TCC GCA ACC TCT TCT TTA CAA CTG GGT GAC CTC GCG GCT GTG CCA GCC
2029 ATT TGG CGT TCA CCC TGC CGC TAA GGG CCA TGT GAA CCC CCG CGG TAG CAT CCC TTG CTC CGC GTG GAC CAC TTT CCT
2107 GAG GCA CAG TGA TAG GAA CAG AGC CAC TAA TCT GAA GAG AAC AGA GAT GTG ACA GAC TAC ACT AAT GTG AGA AAA ACA
2185 AGC AAA GGG TGA CTT ATT GGA GAT TTC AGA AAT AAA ATG CAT TTA TTA TAT TCC CTT ATT TTA ATT TTC TAT TAG
2263 GGA ATT AGA AAG GGC ATA AAC TGC TTT ATC CAG TGT TAT ATT AAA AGC TTA ATG TAT ATA ATC TTT TAG AGG TAA AAT
2341 CTA CAG CCA GCA AAA GTC ATG GTA AAT ATT CTT TGA CTG AAC TCT CAC TAA ACT CCT CTA AAT TAT ATG TCA TAT TAA
2419 CTG GTT AAA ATA TAA ATT TGT GAC ATG ACC TTA ACT GGT TAG GTA GGA TAT TTT TCT TCA TGC AAA AAT ATG ACT
2497 AAT AAT AAT TTA GCA CAA AAA TAT TTC CCA ATA CTT TAA TTC TGT GAT AGA AAA ATG TTT AAC TCA GCT ACT ATA ATC
2575 CCA TAA TTT TGA AAA CTA TTT AAT TGG CTA CAC CAA AGG AAG CCA TAC AGA GGC TAA TAT CAG AGT ATT CTT GGA AGA
2653 GAC AGG AGA AAA TGA AAG CCA GTT TCT GCT CTT ACC TTA TGT GCT TGT GTT CAG ACT CCC AAA CAT CAG GAG TGT CAG
2731 ATA AAC TGC TCT CTG TCT GAA GCA TGG AAC TGA AAA GAA TGT AGT TTC AGG GAA GAA AGG CAA TAG GGA ATA ACT TAG AAA
2809 GCC TGA GAA TAT CAT CAA AGG GTC AGA CTC AAT TTA CTT TCT AAA GAA GTA GCT AGG AAC TAG GGA ATA ACT TAG AAA
2887 CAA CAA GAT TGT ATA TAT GTG CAT CCT GGC CCC ATT GTT CCT TAT CTG TAG GGA TAA GTT TTT AAA CAT GAG CTG GCT GTG
2965 TAT ATA ACA TAA CTG TTT ACA CAT AAT AAA TGG AGC CCT TCC TTG TTA CTT CAT ACC ATC AGA TTA CAC ACA TAC ACC ATC
3043 TTC CTC AGG GGC CGA CGC CGC TCC CAC CGT GTC CAT CTT CCC CCC CAG CAT GGA CAT GGA ACA GCT GAC CTC TGG AGC CAC
3121 CGT GGT CTG CTT CGT GAA CAA CTT CTA CCC CAG AGA CAT CAG CGT GAA GTG GAA GAT CGA CGT CAG CAG CGA GCA GAG GCA
3199 CGG CGT GCT GGA CAG CGT GAC CGA CCA GGA CAG CAA GGA CTC CAC CTA CAG CAT GAG CAG CAC CCT GAG CCT GAC CAA
3277 GGT GGA GTA CGA GAG GCA CAA CCT GTA CAC CTG CGA GGT GGT GCA CAA GAC CAG CTC CAG CCC CGT GGT CAA GTC CTT
3355 CAA CCG GAB CGA GTG TTG AAG ACA AAG GTC CTG AGA CGC CAC CAC CAG CTC CCC ATC TCT TCC CTT CTA
3433 AGG TCT TGG AGC CTT CCC CAC AAG CGA CCT ACC ACT GTT GCG GTG CTC CAA ACC TCC TCC CCA CCT CCT TCT CCT CCT
3511 CCT CCC TTT CCT TGG CTT TTA TCA TGC TAA TAT TTG CAG AAA ATA TTC AAT AAA GTG AGT CTT TGC ACT TGA GAT CTC
3589 TGT CTT TCT TAC TAA ATG GTA GTA ATC AGT TGT TTT TCC AGT TAC CTG GGT TTC TCT TCT AAA GTT AAA TGT TTA
3667 GTT GCC CTG AAA TCC ACC ACA CTT AAA GGA TAA ATA AAA CCC TCC ACT TGC CCT GGT TGG CTG CTG TCC ACT ACA TGG CAG
3745 TCC TTC CTA AGG TTC ACG AGT ACT AGT CAT GGC TTA ITT CTC TGG GCC ATG GTA GGT TTG AGG AGG CAT ACT TCC TAG
3823 TTT TGT TCC CCT AAG TTG TCA AAG TCC TGA AGG GGG ACA GTC TTT ACA AGC ACA TGT TCT GTA ATC TGA TTC AAC CTA
3901 CCC AGT AAA CTT GGC GAA GCA AAG TAG AAT CAT TAT CAC AGG AAG CAA AGG CAA CCT AAA TGT GCA AGC AAT AGG AAA
3979 ATG TGG AAG CCC ATC ATA GTA CTT GGA CAT CAT CTG CTT TTG TGC CTT CAC TAA GTT TTT AAA CAT GAG CTG GCT CCT
4057 ATC TGC CAT TGG CAA GGC TGG GCA CTA CCC ACA ACC TAC TTC AAG GAC CTC TAT ACC GTG AGA TTA CAC ACA TAC ACC
4135 AAA ATT TGG GAA AAG TTC TAC CAA GCT GAG AGC TGA TCA CCC CAC TCT TAG GTG CTT ATC TCT GTA CAC CAG AAA CCT
4213 TAA GAA GCA ACC AGT ATT GAG AGA CTC ACT TAT GAA AGT CTA AAA ACC AAA ATG TCC AAC AGT TAA
4291 ATT ATG ACA TGT TCA CAA TTG AGC TAT TAC TTA ATA AGG AGA ATT AAT AAA ATA AAA CTT AAG AGC ATA GTT TAA TCT
4369 CAT AAA CAA GAT AAT AAG CAA AAC AAA ACA TTT TTT CAT CCA TGT AAG TTT AAA AGC AGG TAA AAT TTA AAA TTA AGA
4447 GAG ACA TAA GTT TTG AGG TAG CAA GAT GGA AAC TCT GGG GCT TGG GGA ATG TTC TGT CTC TCT GTA TCG GAT GTG AAA
4525 GTT ACT ACT GTG GAA TTG GGA TCT ATG TTC TTC CTG TAT ATA TTG TAT ACT TCA TAA TTA CTT CAC CTA AAG AAA TAT
4603 CTA ATA CCC AGT GCA TAC ATA AAA GAG GAT ACA AGG AAT GAA TCA TAC GTC AAG GCC AGA AAG ACA ATA AAG TAG GGG
4681 ATC CAG GAT CAA ATC TCC CAC AAC CTT GAG CCT TCT ACT ATT CTG CCT TCC AGA GCT CAA AGT ACA AAA CAC ATA ATT
4759 CAA ACA CAT GAT CCC TCC TTG GGG TCT CTT CCT TCA TGC ATC GAA TTA GAA ATA GCC ATG TAT AAA ATG AGA TAG ATT
4837 AGA CCT TCA TCA ACA GGT CAA AGA ATA TAG GTA ATT TTG TCT GGG TAT GAA GAG GCC ACG TAT CAA AGG TTA CAT TAG
4915 GGA AGG AAG AGG ACA CTA ACA GTG ACT TTC ATT CTC CCC CTG TTC CTG GAG GCC CCT GCA TTT AGT CCC TCG TGG GCT
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Fig. 12, contd.

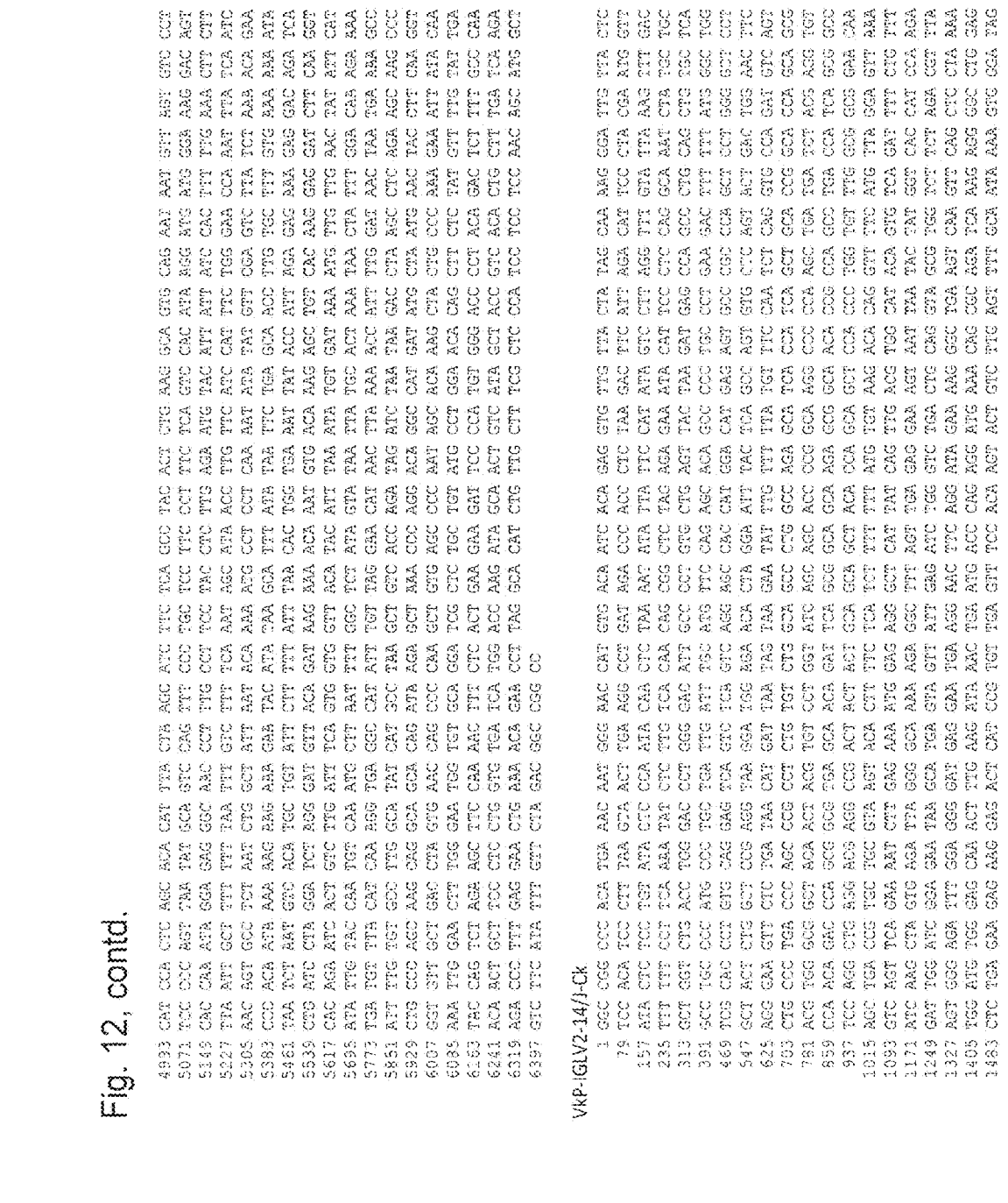

Fig. 12, contd.

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1561 CAG AGT TGA GTG AGC CGT AGG CTG AGT TCT CTC TTT TGT CTC CTA AGT TTT TAT GAC TAC AAA AAT CAG TAG TAT GTC
1639 CTG AAA TAA TCA TTA AGC TGT TTG AAA GTA TGA CTG CTT GCC ATG TAG ATA CCA TGG CTT GCT GAA TAA TCA GAA GAG
1717 GTG TGA CTC TTA TTC TAA AAT TTG TCA CAA AAT GTC AAA ATG AGA GAC TCT GTA GGA ACG AGT CCT TGA CAG ACA GCT
1795 CAA GGG GTT TTT TTC CTT TGT CTC ATT TCT ACA TGA AAG TAA ATT TGA AAT GAT CTT TTT TAT TAT AAG AGT AGA AAT
1873 ACA GTT GGG TTT GAA CTA TAT GTT TTA ATG GCC ACG GTT TTG TAA GAC ATT TGG TCC TTT GTT TTC CCA GTT ATT ACT
1951 CGA TTG TAA TTT TAT ATC GCC AGC AAT GGA CTG AAA CGG TCC GCA ACC TCT TCT TTA CAA CTG GGT GAC CTC GCG GCT
2029 GTG CCA GCC ATT TGG CGT TCA CCC TGC CGC TAA GGG CCA TGT GAA CCC CCG CGG TAG CAT CCC TTG CTC CGC GTG GAC
2107 CAC TTT CCT GAG TCA CAG TGA TAG GAA CAG AGC CAC TAA TCT GAA GAG AAC AGA GAT GTG ACA GAC TAC ACT AAT GTG
2185 ACA AAA ACA AGG AAA GGG TGA CTT ATT GGA GAT TTC ATC AGA AAT AAA ATG CAT TTA TTA TAT TCC CTT ATT TTA ATT
2263 TTC TAT TAG GGA ATT AGA AAG GGC ATA AAC TGC TTT ATC CAG TGT TAT ATT AAA AGC TTA ATG TAT ATA ATC TTT TAG
2341 AGG TAA AAT CTA CAG CCA GCA AAA GTC ATG GAC ATT CTT TGA CTG AAC TCT CAC TAA ACT CCT CTA AAT TAT TAT ATG
2419 TCA TAT TAA CTG GTT AAA TTA ATA TAA ATT TGT GAC ATG ACC TTA ACT GGT TAG GTA GGA TAT TTT TCT TCA TSC AAA
2497 AAT ATG ACT AAT AAT TTA GCA CAA AAA TAT TTC CCA ATA CTT TAA TTC TGT GAT AGA AAA ATG TTT AAC TCA GCT
2575 ACT ATA ATC CCA TAA TTT ATT AGC TTT TGT GTT TGA CCC TTC CCT AGC CAA AAG CAA AGG ACT CCA CCT ACA CCA TGA
2653 GAC CCT TTA AAA CTC TTG AAA CTA CTT TAG AGT CAT TAA GTT ATT TAA CCA CTT TTA AAT ACT TTA AAA TGA TGT CAA
2731 TTC CCT TTT AAC TAT TAA TTT ATT TTA AGG GCG GAA AGG CTG CTC ATA ATT CTA TTG TTT TTC TTG GTA AAG AAC TCT
2809 CAG TTT TCG TTT TTA CTA CCT CTG TCA CCC AAG AGT TGG CAT CTC AAC AGA GGG GAC TTT CCG AGA ATG TTT AAC TCA GCA
2887 GTT GCT TAA GAT CAG AAG TGA AGT CTG GTT CCA GTT CCT CCC AGG CAG GTG GCC CAG ATT ACA GTT GAC CTG TTC TGG TGT
2965 GGC TAA AAA TTG TCC CAT GTG GTT ACA AAC CAT TAG ACC AGG GTC TGA TGA ATT CAT TTA ACT TTA AAA TGA TGT CAC CCA
3043 AAT ACA GAC CCT GGC TTA AAG CCC TGT CCA TAC AGT AGG TTT AGC TTG GCT ACA CCA AAG AAG CAA GAC CCC CAT GAA ATG GAG CCC TTC CTT GTT ACT
3121 ATA TCA GAG TAT TCT TGG AAG AGA CAG GAG AAA ATG AAA GCC AGT TTC TGC TCT TAC CAT TTC TGT TCA GAC
3199 TCC CAA ACA TCA GGA GTG TCA GAT AAA CTG GTC TGA ATC TCT GTC TGA AGC ATG GAA CTG AAA AGA ATG TAG TTT CAG
3277 GGA AGA AAG GCA ATA GAA GGA AGC CTG AGA ATA TCT TCA AAG GCT CAG ACT CAA TTT ACT TTC TAA AGA AGT AGC TAG
3355 GAA CTA CGG AAT AAC TTA GAA ACA ACA AGA TTG TAT ATA TGT GCA TCC TGG CCC CAT TGT TCC TTA TCT GTA GGG ATA
3433 AGC GTG CTT TTT TGT GTG TCT GTA TAT AAC ATA ACT GTT TAC ACA TAA TAC ACT GAA ATG GAG CCC TTC CTT GTT ACT
3511 TCA TAC CAT CCT CTG TGC TTC CTT CCT CAG GGG CCG ACG CCG CTC CCA CCG TGT CCA TCT TCC CCC CCA GCA TGG AAC
3589 AGC TCA CCT CTG GCG GAG CCA CGC TGG TCT GCT TCG TGA ACA ACT TCT GGT AGT AAT ACC CAA TAA AGT
3667 TCG ACG CCA GCG AGC AGA GGG ACG GCG TGC TGG ACA GCG TGA CCG ACC AGG AGG TGG TGC ACA AGA CCA GCT
3745 GCA GCA CCC TGA GCC TGA CCA AGG TGG AGT ACG AGA GGC ACA ACC TGT ACA CCT GCG AGG TGG TGC ACA AGA CCA GCT
3823 CCA GCC CCG TGG TCA AGT CCT TCA ACC GGA ADG AGT GTT GAA GAC AAA GGT CCT GAG ACG CCA CCA CCA GCT CCC CAG
3901 CTC CAT CCT ATC TTC CCT TCT AAG GTC TTG GAG GCT TCC CCA CAA GCG ACC TAC TGT TGC GGT GCT CCA AAC CTC
3979 CTC CCC ACC TCC TCC TCC TCC CTT TCC TTG GCT TTT ATC ATG CTA ATA TTT TTC CAG TTT TTC GCA GAA AAT AAT CAA TAA AGT
4057 GAG TCT TTG CAC TTG AGA TCT CTG TCT TTC TTA CTA AAT GGT AGT AAT CAG TTG TTT TTC CAG TTA CCT GGG TTT CTC
4135 TTC TAA AGA AGT TAA ATG TTT AGT TGC CCT GAA ATC CAC CAC ACT TAA AGG ATA AAT AAA ACC CTC CAC TTG CCC TGG
4213 TTG GCT GTC CAC TAC ATG GCA GTC CTT TCT AAG GTT CAC GAG TAC TAT TCA TGG CTT AGT TCT CTG GGC CAT GGT AGG
4291 TTT GAG GAG GCA TAC TTC CTA GTT TTC CCC TAA ACT TGG CGA AGC AAA GTC AAA GTC CTG AAG GGG GAC AGT CTT TAC AAG CAC ATG
4369 TTC TGT AAT CTG ATT CAA CCT ACC CAG TAA ACT TGG CGA AGC AAA GTA CAA TCA TTA TCA CAG GAA GCA AAG GCA ACC
4447 TAA ATG TGC AAG CAA TAG GAA AAT GTG GAA GCC CAT CAT CAT AGT ACT TGG ACT TCA TCA GCT TTT GTG CCT TCA CTA AGT
4525 TTT TAA ACA TGA GCT GGC TCC TAT CTG GCA AGG CTG GGC ACT ACC CAC AAC CTA CTT CAA GGA CCT CTA TAC
4603 CGT GAG ATT ACA CAC ATA CAT CAA AAT TTG GGA AAA GTT CTA CCA AGC TGA GAG CTG ATC ACC CCA CTC TTA GGT GCT
4681 TAT CTC TGT ACA CCA GAA ACC TTA AGA AGC AAC CAG TAT TGA GAG ACT CAT TTA TGA AAG TCT AAA ACT GGA TAC AAC
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Fig. 12, contd.

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4759 CAA AAT GTC CAC CAA CAG TTA AAT TAT GAC ATG TTC ACA ATT GAG CTA TTA CTT AAT AAG GAG AAT TAA TAA AAT AAA
4837 ACT TAA GAG CAT AGT TTA ATC TCA TAA ACA AGA TAA TAA GCA AAA CAA AAC ATT TTT TCA TCC ATG TAA GTT TAA AAG
4915 CAG GCA AAA TTT AAA ATT AAG AGA GAC ATA AGT TTT GAG GTA GCA AGA TGG AAA CTC TGG GGC TTG GGG AAT GTT CTG
4993 TCC CTC TGT ATC GGA TGT GAA AGT TAC TAT TCT GGA ATT GGG ATC TAT GTT CTT CCT GTA TAT ATT GTA TAC TTC ATA
5071 ATA ACT TCA CCT AAA GAA ATA TCT AAT ACC CAG TGC ATA CAT AAA AGA GGA TAC AAG GAA TGA ATC ATA CGT CAA GGC
5149 CAG AAA GAC AAT AAA GTA GGG GAT CCA TCA AAT CTC CCA CAA CCT TGA GCC TTC TAC TAT TCT GCC TTC CAG AGC
5227 TCA AAG TAC AAA ACA CAT AAT TCA AAC ACA TGA TCC CTC CTT GGG GTC TCT TCC TTC ATG CAT CGA ATT AGA AAT AGC
5305 CAT GTA TAA AAT GAG ATA GAA GAG ACC TTC ATC AAC AGG TCA AAG AAT ATA GGT AAT TTT GTC TGG GTA TGA AGA GCC
5383 CAC GTA TCA AAG GTT ACA TTA GGG AAG GAG GAC ACT AAC AGT GAC TTT CAT TCT CCC CCT CTT CCT GGA GGC CCC
5461 TGC ATT TAC TCC CTC GTG GGC TCA TCC ACT CAG CAC ACA TTT ACT AAG CAT CTT CTC AGC CTA CAC TCT GAA GGC AGT
5539 GCA GAA TAA TGT TAG TGT CCC TTC CCC CAG TTA ATA TGC AGT CCA GTT TCC CTG CTC CTT CCC TTT CTC AGT GCA CAT
5617 AAG GAT GAT GGG AAA GGA CAG TCA CCA AAT AGG AGA GGG CAA CCC TTT GCC TTC CAC TGA AGA AGA TTC CCC ATG TGG GAC
5695 TAT CCA CTT TTT GAA ACT TCT TTT AAT TGC TTT ATT TTA ATT TGT CTT TTC AAA TAG CAT AAC CTT GTT TTG TAG CAT AAT ATT
5773 CTG GGA ACC AAA TTT ATC AAT CAA CAG TGC CTC TAA TCT GGC TAT TAA TAC AAA AAT GCC TCC TCA AAA TAT ATA TGT
5851 TCG AGT CTT ATC TAA AAC AGA ACC CAC AAT AAA AAA GAA GAA AGA ATA CAT ATA AGC ATT TAT ATA ATT CTG AGC AAC
5929 CTT GTG CTT TGT GAA AAA AAT ATA ATC TAA TGT CAC ATG CTG TAT TCT TTT TAT TTA ACA CTG GTG AAA TTA TAC CAT
6007 TAG AGA GAA AGA GGA CAG ATC ACT GAT CCT AGG ATC TAG GGA TGT TAC AGA TAA GAA AAC AAA TGT GAC AAA GAG CTG
6085 TCA CAA GGA GGA TCT TCA AGG TCA CAG AAT CAC TGT CTT GAT TTC AGT GGT GGT TAC ATA CAT TTA AAT ATG TGA TAA
6163 AAT GTT GTT GTT GAA CTA TAT TCA TAT ATT GTA CCA ATG TCA AAT GCT TAA TTT TGG CTC TAT AGT ATA ATT ATC CAC TAA
6241 ATA ACT ACT ATT TGG ACA AAG AAA ATG ATG TTT ACA TCA AAG GTG AGG CCA TAT TTG TTA GGA ACA TAA CTT AAA AAC CAT
6319 TTT GGA TAA CTA ATG AAA AGC CAT TTT GTG TGC CTT GGC ATA TCA TGC CTA AGC TGT CAC CAG ATA GAT CTA ATA AGA
6397 CCT AAG CCT CAG AAC CAA GCC CCT GCC CAG GCA GGC AGC ACA GAT AAG CAA TAA AGC CAG GAC AGG CCA TGA TAT
6475 GCT AAT GAA CTA CCT TCA AGG TGG TGT TGC TGA CCT AGT GAA CCA GCC CCA AGC TGT GAG CCC CAA TAG CAC AAA GCT
6553 ACT GCC CAA AGA AAT TAT ACA AAA ATT GGA ACT TTG GGA ATG GTG TGC AGG ATC GGT CTG CTG TAT GCC TGG AAC ACA
6631 GCT TCT CTA TGT TTT GTA TTG ATA CCA GTC TAG AAG CTT CCA AAA CTT TCT CAC TGA AGA AGG TAC CTT CAT AAT ATT
6709 CCC TAC AGA CTC TTT TGC CCA AAC TGC TTC CCT CCT GGT GTG ATA TCT GTT TTG TAT GCA ATA TTG CTT TTA TGT TAA AAA GTT
6787 ATA AGG AAT GTT TGT GTG AAT AAA CCA AAC ATA TTT TAA AAG CAA ATA TTG TAT GCA CAT CCT AAT TCA ATG TTC GGC ATC TTT ACA GAG
6865 TAC AGC TAA TAG TCC CAT GCT CTC CAC AAT ACT GGA TCC AAA TAA GTC CTA ATT TCA ATG TTC GGC ATC TTT ACA GAG
6943 AGA AAG ACA TTA AAA ATG AAG AGA CAT GCA GAG AGT GCA CCA TGC CAT CGT GSA GAC AGA CTG AAG TGA CAC AAC TGT
7021 TAG TCA AAG AGG ATT AAG GAC TTC CAG AAG CCA CCA AAG GAA GGA GGT ATG AAG TGG TTT CTC CCT CAG AGT ATG CAG
7099 AGG AGA CTA AAC CAA CCA ACA CCT TTT TGC TTA AGA CTT CTT GCC TTC AGG ACT GTG AGA AGG TAG CTT CCT ATT GTT
7177 CTA AGC CCC AGT ATG TGG CAT TTT GTT AAG GTA GAG TCA AGA AAC CAA TAA AAT GCA GAC AGA CAA AAG GAT AGC TGA
7255 GTT TTC CAG GCC CTT CCT TCT TAT TTT TGG TTT TGT TGG TGG TGG TGG TGG TGA TGG TGC TGG TTT TGT TGT TGA TTA
7333 TGT TTT GTT TGG GGA GTT TTT TTT GGG GGT TTT TGT TTT GTT TGT TGT TGT TTT GGG GGT TTT TGT TGT TGT TGT TGC
7411 TGT TTG CTT TTT TGT TCT TTG TTT TTT GTT TTT TTG AGA CAG TCT TTC TTC TCT GTA TAG CCC TGG CTG TCC TGG AGT TCC
7489 TTC TAT CTC TAA TGT CCA CAT CTC AGA GGG GAT CCC CTA ATT TCA AAT GAG CAG TAG CTC TCC ATT TTT AGC TCT TAT
7567 TTA TTC ATT TAT TTA CTT ACT TAC TTA TTG TCT GTA GAT GAA AGA ATT TTG GAG TGG GAA AGG GTT CAT GAG CCC CCA
7645 GCA ACT AAT GAG GAG CTA CAG CAG ACA ATT GAT GTT TCT GGG GAA AGG AGA CTC AGT TTC TTT GAG AGT ATA GCT TCT GAT
7723 GGG TCA ACC ATG TTC CTG TGG CTG ATG TCA CAC CCA GGA GTA TGC AGA CAA CAG AAA CTG GAG TTA ATG AGT TGT TTT
7801 AAA AAT AAA AAA GGG CAT GAA GCT TGG GAT AGA AAT TAA GGA TAA ATA CAA TTA AAT ACA GGA AAT TCT GAA AGA ATT
7879 AAT AAA AAC ATT TCT TTT TTT AAA AAA AAA TCC AGA ATT AGC TAT GCT TCT TCA AAA TTG CTT CTG GAG AAC TTT AGA
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Fig. 12, contd.



Fig. 12, contd.

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11155 CGT GTA ACT CTC CTG TGA CTG AGT ATC TCA CAA AAC GTT CTA CCT GCC AAA CCT GGA TGA GCC CTT TGT CTT TCT GAA
11233 GCT ATG AGG CTC TCT ACA TAG ACT CAA GAA GGA AAT GAC AGG GAG GAG GTA ATA ATG AAG TGG GGA AGG CTG ACA TTA
11311 GCA TTG CTC CTG TGT GGC TCC TTA ATT TCT CAT ACT TCA CAC TGA GAT GTT ATT AAC TGT GAC TCA TAG GTG AAG AAG
11389 CCA GAG CTA AGG TTC TCA TAT TTG AGT GTT ATA GAA TGA GTA GAG CAG TAG TTC TCA AAC TAT GGG TCA TGA CTC CTT
11467 TAT GGG TCA AAC TAC CCT TTC ACA CAG GTT GCA TAT CAG ATA TCC TAA TTT TAT ATA CAT ATA TAT ATG CAT ATG TAC
11545 ATA TAT ATA TTT CAC AAC AGT AGG AAA ATT ATT TAG TAA TCA TTT TAT AGT TGT GGG TCA TGG CAA CAT GAG GAA CTG
11623 TAT TAA AGG GTT GCA GCA TTA GGA ATG TTG AGA CCC ACT GTA ATA GAG AAT GAG GCT TAA GGC AGG GCT ATA AAG CCC
11701 AAT GGA CCA TGT GCC TTT TCC AAC ATT TGC CAC ATG GTA AGC TCT GTA TAG ACT TTT TAA AGA ACA TTG GTT TGT AAT
11779 TTT AAA TGG ATA AGG GTC TTC ACT GTC TAT CAC CCA TCT ATA TAA TAA ATA CAT AAG TTT TGA TTC CAC CAT GGA TTC
11857 AAA TGC AAA AAT CCT CAA CCT AAG ACA TAG CAG TGA AAC ATT GAT GAC CAA ATA GGA AAT CCA TGT AGA GAC CTT CTA
11935 TCT TCT GAT GGC TCC ACA GGC ACC ATC TTG CAA CAG AGT TCT ACT TTG CTA CCA GTA ATG AAT ACA GTG TCT CAA CTC
12013 CTG CCA TTG AAT CTT CAG GAA GCC CCT GAA ATG ACT TGT ACT ACA CCA TTT CTT AAA GAC AGA AAA GCT AAG ACT TAG
12091 AGG GAA TAA ATG TCA TGC CTG AGA TCA TGC AAC CAA TTA AGT CCA ACT TGG CCT GAT CAA GAG GCA CAA TTC AAA AGC
12169 AAT GTT GTT CCT TCA CTA GCT CTT GTG TAT GGT TGC TGA TTC CGG AAG CAA AGT ATC AGT GAA TAT CCC TAG TGG GAA
12247 AAG ACT TGG AAA TCA AAT GTC TCA TTT AAC AGA TTA GGA GAT GAA ACG GTA GAC TCT GTG TAG TTG TAC ACC CCT GTG
12325 ATC CCA TCG CTA GGA AGA CTG AGG CAG GAA GTC CTC GAG CTC AAA CCA GCT TAG GCT ACA CAG AGA AAC TAT CTA AAA
12403 AAT AAT TAC TAA CTA CTT AAT AGG AGA TTG GAT GTT AAG ATC TGG TCA CTA AGA GGC AGA ATT GAG ATT CGA AGC CAG
12481 TAT TTT CTA CCT GGT ATG TTT TAA ATT GCA GTA AGG ATC TAA GTG TAG ATA TAT AAT AAT AAG ATT CTA TTG ATC TCT
12559 GCA ACA ACA GAG AGT GTT AGA TTT GTT TGG AAA AAA ATA TTA TCA GCC AAC ATC TTC TAC CAT TTC AGT ATA GCA CAG
12637 AGT ACC CAC CCA TAT CTC CCC ACC CAT CCC CCA TAC CAG ACT GGT TAT TGA TTT TCA TGG TGA CTG GCC TGA GAA GAT
12715 TAA AAA AAG TAA TGC TAC CTT ATT GGG AGT GTC CCA TGG ACC AAG ATA GCA ACT GTC ATA GCT ACC GTC ACA CTG CTT
12793 TGA TCA AGA AGA CCC TTT GAG GAA CTG AAA ACA GAA CCT TAG GCA CAT CTG TTG CTT TCG CTC CCA TCC TCC TCC AAC
12871 AGC CTG GGT GGT GCA CTC CAC ACC CTT TCA AGT TTC CAA AGC CTC ATA CAC CTG CTC CCT ACC CCA GCA CCT GGC CAA
12949 GGC TGT ATC CAG CAC TGG GAT GAA AAT GAT ACC CCA CCT CCA TCT TGT TTG ATA TTA CTC TAT CTC AAG CCC CAG GTT
13027 AGT CCC CAG TCC CAA TGC TTT TGC ACA GTC AAA ACT CAA CTT GGA ATA ATC AGT ATC CTT GAA GAG TTC TGA TAT GGT
13105 CAC TGG GCC CAT ATA CCA TGT AAG ACA TGT GGA AAA GAT GTT TCA TGG GGC CCA GAC ACG TTC TAG AAG TAC CTG AGA
13183 GTG GCA AAA AAT AGT TGT GCT AAA TAG TTT GGC CAT CTT TAG GCT GAG AGA CTA GGA AAT ACA GCG ATG GAC TAT AIC
13261 AGC ATT GCA GGA TAG TTG TCA GTA AAC ACC CCA CAA CCC ATA ACA GAA GTA TTC TCT TCT TTC TAT ATC CCT TTT CCA
13339 TCC ATG TAG ATG GCT GTC TTC ATA TTT GTT CTA GAC GGC CGG CC
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pSELECT-IGKV1-39/J-Ck

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   1 GCG GCC GCA ATA AAA TAT CTT TAT TTT CAT TAC ATC TGT GTG TTG GTT TTT TGT GTG AAT CGT AAC TAA CAT ACG CTC
  79 TCC ATC AAA ACA AAA CGA AAC AAA ACA AAC TAG CAA AAT AGG CTG TCC CCA GTG CAA GTG CAG GTG CCA GAA CAT TTC
 157 TCT ATC GAA GGA TCT GCG ATC GCT CCG GTG CCC GTC AGT GGG CAG AGC GCA CAT CGC CCA CAG TCC CCG AGA AGT TGG
 235 GGG GAG GGG TCG GCA ATT GAA CGG GTG CCT AGA GAA GGT GGC GCG GGG TAA ACT GGG AAA GTG ATG TCG TGT ACT GGC
 313 TCC GCC TTT TTC CCG AGG GTG GGG GAG AAC CGT ATA TAA GTG CAG TAG TCG CCG TGA ACG TTC TTT TTC GCA ACG GGT
 391 TTG CCG CCA GAA CAC AGC TGA AGC TTC GAG GGG CTC GCA TCT CTC CTT CAC GCG CCC GCC GCC CTA CCT GAG GCC GCC
 469 ATC CAC GCC GGT TGA GTC GCG TTC TGC CGC CTC CCG CCT GTG GTG CCT CCT GAA CTG CGT CCG CCG TCT AGG TAA GTT
 547 TAA AGC TCA GGT CGA GAC CGG GCC TTT GTC CGG CGC TCC CTT GGA GCC TAC CTA GAC TCA GCC GGC TCT CCA CGC TTT
 625 GCC TGA CCC TGC TTG CTC AAC TCT ACG TCT TTG TTT CGT TTT CTG TTC TGC GCC GTT ACA GAT CCA AGC TGT GAC CGG
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Fig. 12, contd.

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 703  CGC CTA CCT GAG ATC ACC GGC GTG TCG ACG CCA CCA TGG ACA TGA GAG TGC CCG CCC AGC TCC TGG GGC TCC TGC TAC
 781  TCT GGC TCC GAG GTA AGG ATG GAG AAC ACT AGG AAT TTA CTC AGC CAG TGT GCT CAG TAC TGA CTG GAA CTT CAG GGA
 859  AGT TCT CTG ATA ACA TGA TTA ATA GTA AGA ATA TTT GTT TTT ATG TTT CCA ATC TCA GCT GCC AGA TGT GAC ATC CAG
 937  ATG ACC CAG AGC CCC AGC AGC CTG AGC GCC AGC GTG GGC GAC AGA GTG ACC ATC ACC TGC AGA GCC AGC CAG AGC ATC
1015  AGC AGC TAC CTG AAC TGG TAT CAG CAG AAG CCC GGC AAG GCC CCC AAG CTG CTG ATC TAC GCC GCC AGC TCC CTG CAG
1093  AGC GGC GTG CCC AGC AGA TTC AGC GGC AGC GGC TCC GGC ACC GAC TTC ACC CTG ACC ATC AGC AGC CTG CAG CCC GAG
1171  GAC TTC GCC ACC TAC TAC TGC CAG CAG AGC TAC AGC ACC CCC CCC ACC TTC GGC CAG GGC ACC AAG GTG GAG ATC AAG
1249  AGA GCC GAC GCC GCT CCC ACC GTG TCC ATC TTC CCC CCC AGC ATG GAA CAG CTG ACC TCT GGC GGA GCC ACC GTG GTC
1327  TGC TTC GTG AAC AAC TTC TAC CCC AGA GAC ATC AGC GTG AAG TGG AAG ATC GAC GGC AGC GAG CAG AGG GAC GGC GTG
1405  CTG GAC AGC GTG ACC GAC CAG GAC AGC AAG GAC TCC ACC TAC AGC ATG AGC AGC ACC CTG ACC CTG ACC AAG GTG GAG
1483  TAC GAG AGG CAC AAC CTG TAC ACC TGC GAG GTG GTG CAC AAG ACC AGC TCC AGC CCC GTG GTC AAG TCC TTC AAC CGG
1561  AAC GAG TGT TGA GCT AGC TGG CCA GAC ATG ATA AGA TAC ATT GAT GAG TTT GGA CAA ACC ACA ACT AGA ATG CAG TGA
1639  AAA AAA TGC TTT ATT TGT GAA ATT TGT GAT GCT ATT GCT TTA TTT GTA ACC ATT ATA AGC TGC AAT AAA CAA GTT AAC
1717  AAC AAC AAT TGC ATT CAT TTT ATG TTT CAG GTT CAG GGG GAG GTG TGG GAG GTT TTT TAA AGC AAG TAA AAC CTC TAC
1795  AAA TGT GGT ATG GAA TTC TAA AAT ACA GCA TAG CAA AAC TTT AAC CTC CAA ATC AAG CCT CTA CTT GAA TCC TTT TCT
1873  GAG GGA TGA ATA AGG CAT AGG CAT CAG GGG CTG TTG CCA ATG TGC ATT AGC TGT TTG CAG CCT CAC CTT CTT TCA TGG
1951  AGT TTA AGA TAT AGT GTA TTT TCC CAA GGT TTG AAC TAG CTC TTC ATT TCT TTA TGT TTT AAA TGC ACT GAC CTC CCA
2029  CAT TCC CTT TTT AGT AAA ATA TTC AGA AAT AAT TTA AAT ACA TCA TTG CAA TGA AAA TAA ATG TTT TTT ATT AGG CAG
2107  AAT CCA GAT GCT CAA GGC CCT TCA TAA TAT CCC CCA GTT TAG TAG TTG GAC TTA GGG AAC AAA GGA ACC TTT AAT AGA
2185  AAT TGG ACA GCA AGA AAG CGA GCT TCT AGC GAA TTC TCG ACT CAT TCC TTT GCC CTC GGA CGA GTG CTG GGG CGT CGG
2263  TTT CCA CTA TCG GCG AGT ACT TCT ACA CAG CCA TCG GTC CAG ACG GCC GCG CTT CTG CGG GCG ATT TGT GTA CGC CCG
2341  ACA GTC CCG GCT CCG GAT CGG ACG ATT GCG TCG CAT CGA CCC TGC GCC CAA GCT GCA TCA TCG AAA TTG CCG TCA ACC
2419  AAG CTC TGA TAG AGT TGG TCA AGA CCA ATG CGG AGC ATA TAC GCC CGG AGC CGC GGC GAT CCT GCA AGC TCC GGA TGC
2497  CTC CGC TCG AAG TAG CGC GTC TGC TGC TCC ATA CAA GCC AAC CAC GGC CTC CAG AAG AAG ATG TTG GCG ACC TCG TAT
2575  TGG GAA TCC CGG AAC ATC GCC TCG CTC CAG TCA ATG ACC GCT GTT ATG CGG CCA TTG TCC GTC AGG ACA TTG TTG GAG
2653  CCG AAA TCC GCG TGC ACG AGG TGC CGG ACT TCG GGG CAG TCC TCG GCC CAA AGC ATC AGC TCA TCG AGA GCC TGC GCG
2731  ACG GAC GCA CTG ACG GTG TCG TCC ATC ACA GTT TGC CAG TGA TAC ACA TGG GGA TCA GCA ATC GCG CAT ATG AAA TCA
2809  CGC CAT GTA GTG TAT TGA CCG ATT CCT TGC GGT CCG AAT GGG CCG AAC CCG CTC GTC TGG CTA AGA TCG GCC GCA GCG
2887  ATC GCA TCC ATG AGC TCC GCG ACG GGT TGC AGA ACA GCG GGC AGT TCG GTT TCA GGC AGG TCT TGC AAC GTG ACA CCC
2965  TGT GCA CGG CGG GAG ATG CAA TAG GTC AGG CTC TCG CTG AAT TCC CCA ATG TCA AGC ACT TCC GGA ATC GGG AGC GCG
3043  GCC GAT GCA AAG TGC CGA TAA ACA TAA CGA TCT TTG TAG AAA CCA TCG GCG CAG CTA TTT ACC CGC AGG ACA TAT CCA
3121  CGC CCT CCT ACA TCG AAG CTG AAA GCA CGA GAT TCT TCG CCC TCC GAG AGC TGC ATC AGG TCG GAG ACG CTG TCG AAC
3199  TTT TCG ATC AGA AAC TTC TCG ACA GAC GTC GCG GTG AGT TCA GGC TTT TTC ATG ATG GCC CTC CTA TAG TGA GTC GTA
3277  TTA TAC TAT GCC GAT ATA CTA TGC CGA TGA TTA ATT GTC AAA ACA GCG TGG ATG GCG TCT CCA GCT TAT CTG ACG GTT
3355  CAC TAA ACG AGC TCT GCT TAT ATA GAC CTC CCA CCG TAC ACG CCT ACC GCC CAT CTG CGT CAA TGG GGC GGA GTT GTT
3433  ACG ACA TTT TGG AAA GTC CCG TTG ATT TAC TAG TCA AAA CAA ACT CCC ATT GAC GTC AAT GGG GTG GAG ACT TGG AAA
3511  TCC CCG TGA GTC AAA CCG CTA TCC ACG CCC ATT GAT GTA CTG CCA AAA CCG CAT CAT CAT GGT AAT AGC GAT GAC TAA
3589  TAC GTA GAT GTA CTG CCA AGT AGG AAA GTC CCA TAA GGT CAT GTA CTG GGC ATA ATG CCA GGC GGG CCA TTT ACC GTC
3667  ATT GAC GTC AAT AGG GGG CGT ACT TGG CAT ATG ATA CAC TTG ATG TAC TGC CAA GTG GGC AGT TTA CCG TAA ATA CTC
3745  CAC CCA TTG ACG TCA ATG GAA AGT CCC TAT TGG CGT TAC TAT GGG AAC ATA CGT CAT TAT TGA CGT CAA TGG GCG GGG
3823  GTC GTT GGG CGG TCA GCC AGG CGG GCC ATT TAC CGT AAG TTA TGT AAC GCC TGC AGG TTA ATT AAG AAC ATG TGA GCA
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Fig. 12, contd.

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3901    AAA GGC CAG CAA AAG GCC AGG AAC CGT AAA AAG GCC GCG TTG CTG GCG TTT TTC CAT AGG CTC CGC CCC CCT GAC GAG
3973    CAT CAC AAA AAT CGA CGC TCA AGT CAG AGG TGG CGA AAC CCG ACA GGA CTA TAA AGA TAC CAG GCG TTT CCC CCT GGA
4057    AGC TCC CTC GTG CGC TCT CCT GTT CCG ACC CTG CCG CTT ACC GGA TAC CTG TCC GCC TTT CTC CCT TCG GGA AGC GTG
4135    GCG CTT TCT CAT AGC TCA CGC TGT AGG TAT CTC AGT TCG GTG TAG GTC GTT CGC TCC AAG CTG GGC TGT GTG CAC GAA
4213    CCC CCC GTT CAG CCC GAC CGC TGC GCC TTA TCC GGT AAC TAT CGT CTT GAG TCC AAC CCG GTA AGA CAC GAC TTA TCG
4291    CCA CTG GCA GCA GCC ACT GGT AAC AGG ATT AGC AGA GCG AGG TAT GTA GGC GGT GCT ACA GAG TTC TTG AAG TGG TGG
4369    CCT AAC TAC GGC TAC ACT AGA AGA ACA GTA TTT GGT ATC TGC GCT CTG CTG AAG CCA GTT ACC TTC GGA AAA AGA GTT
4447    GGT AGC TCT TGA TCC GGC AAA CAA ACC ACC GCT GGT AGC GGT GGT TTT TTT GTT TGC AAG CAG CAG ATT ACG CGC AGA
4525    AAA AAA GGA TCT CAA GAA GAT CCT TTG ATC TTT TCT ACG GGG TCT GAC GCT CAG TGG AAC GAA AAC TCA CGT TAA GGG
4603    ATT TTG GTC ATG GCT AGT TAA TTA ACA TTT AAA TCA
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pSelect-iGLV2-14/J-Ck

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   1    GCG GCC GCA ATA AAA TAT CTT TAT TTT CAT TAC ATC TGT GTG TTG GTT TTT TGT GTG AAT CGT AAC TAA CAT ACG CTC
  79    TCC ATC AAA ACA AAA CGA AAC AAA ACA AAC TAG CAA AAT AGG CTG TCC CCA GTG CAA GTG CAG GTG CCA GAA CAT TTC
 157    TCT ATC GAA GGA TCT GCG ATC GCT CCG GTG CCC GTC AGT GGG CAG AGC GCA CAT CGC CCA CAG TCC CCG AGA AGT TGG
 235    GGG GAG GGG TCG GCA ATT GAA CGG GTG CCT AGA GAA GGT GGC GCG GGG TAA ACT GGG AAA GTG ATG TCG TGT ACT GGC
 313    TCC GCC TTT TTC CCG AGG GTG GGG GAG AAC CGT ATA TAA GTG CAG TAG TCG CCG TGA ACG TTC TTT TTC GCA ACG GGT
 391    TTG CCG CCA GAA CAC AGC TGA AGC TTC GAG GGG CTC GCA TCT CTC CTT CAC GCG CCC GCC GCC CTA CCT GAG GCC GCC
 469    ATC CAC GCC GGT TGA GTC GCG TTC TGC CGC CTC CCG CCT GTG GTG CCT CCT GAA CTG CGT CCG CCG TCT AGG TAA GTT
 547    TAA AGC TCA GGT CGA GAC CGG GCC TTT GTC CGG CGC TCC CTT GGA GCC TAC CTA GAC TCA GCC GGC TCT CCA CGC TTT
 625    GCC TGA CCC TGC TTG CTC AAC TCT ACG TCT TTG TTT CGT TTT CTG TTC TGC GCC GTT ACA GAT CCA AGC TGT GAC CGG
 703    CGC CTA CCT GAG ATC ACC GGC GTG TCG ACG CCA CCA TGG ACA TGA GAG TGC CCG CCC AGC TCC TGG GGC TCC TGC TAC
 781    TCT GGC TCC GAG GTA AGG ATG GAG AAC ACT AGG AAT TTA CTC AGC CAG TGT GCT CAG TAC TGA CTG GAA CTT CAG GGA
 859    AGT TCT CTG AIA ACA TGA TTA ATA GTA AGA ATA TTT GTT TTT ATG TTT CCA ATC TCA GGT GCC AGA TGT CAG TCT GCC
 937    CTG ACC CAG CCC GCC TCT GTG TCT GGC AGC CCT GGC CAG AGC ATC ACC ATC AGC TGC ACC GGC ACC AGC AGC GAC GTG
1015    GGC GGC TAC AAC TAC GTG TCC TGG TAT CAG CAG CAC CCC GGC AAG GCC CCC AAG CTG ATG ATC TAC GAG GTG TCC AAC
1093    AGA CCC AGC GGC GTG AGC AAC AGA TTC AGC GGC AGC AAG AGC GGC AAC ACC GCC AGC CTG ACC ATC AGC GGC CTC CAG
1171    GCT GAG GAC GAG GCC GAC TAC TAC TGC AGC AGC TAC ACC AGC AGC TCC ACC CTG GTG TTT GGC GGC GGA ACA AAG CTG
1249    ACC GTG CTG AGA GCC GAC GCC GCT CCC ACC GTG TCC ATC TTC CCC CCC AGC ATG GAA CAG CTG ACC TCT GGC GGA GCC
1327    ACC GTG GTC TGC TTC GTG AAC AAC TTC TAC CCC AGA GAC ATC AGC GTG AAG TGG AAG ATC GAC GGC AGC GAG CAG AGG
1405    GAC GGC GTG CTG GAC AGC GTG ACC GAC CAG GAC AGC AAG GAC TCC ACC TAC AGC ATG AGC AGC ACC CTG ACC CTG ACC
1483    AAG GTG GAG TAC GAG AGG CAC AAC CTG TAC ACC TGC GAG GTG GTG CAC AAG ACC AGC TCC AGC CCC GTG GTC AAG TCC
1561    TTC AAC CGG AAC GAG TGT TGA GCT AGC TGG CCA GAC ATG ATA AGA TAC ATT GAT GAG TTT GGA CAA ACC ACA ACT AGA
 937    CTG ACT CAG CCT GCC TCC GTG TCT GGG TCT CCT GGA CAG TCG ATC ACC ATC TCC TGC ACT GGA ACC AGC AGT GAC GTT
1015    GGT GGT TAT AAC TAT GTC TCC TGG TAC CAA CAG CAC CCA GGC AAA GCC CCC AAA CTC ATG ATT TAT GAG GTC AGT AAT
1093    CGG CCC TCA GGG GTT TCT AAT CGC TTC TCT GGC TCC AAG TCT GGC AAC ACG GCC TCC CTG ACC ATC TCT GGG CTC CAG
1171    GCT GAG GAC GAG GCT GAT TAT TAC TGC AGC TCA TAT ACA AGC AGC AGC ACT CTC GTA TTC GGC GGA GGG ACC AAG CTG
1249    ACC GTC CTA CGG GCT GAT GCT GCA CCA ACT GTA TCC ATC TTC CCA CCA TCC ATG GAA CAG TTA ACA TCT GGA GGT GCC
1327    ACA GTC GTG TGC TTC GTG AAC AAC TTC TAT CCC AGA GAC ATC AGT GTC AAG TGG AAG ATT GAT GGC AGT GAA CAA CGA
1405    GAT GGT GTC CTG GAC AGT GTT ACT GAT CAG GAC AGC AAA GAC AGC ACG TAC AGC ATG AGC AGC ACC CTC TCG TTG ACC
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Fig. 12, contd.

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1483  AAG GTT GAA TAT GAA AGG CAT AAC CTC TAT ACC TGT GAG GTT GTT CAT AAG ACA TCA TCC TCA CCC GTC GTC AAG AGC
1561  TTC AAC AGC AAT GAG TGT TAG GCT AGC TGG CCA GAC ATG ATA AGA TAC ATT GAT GAG TTT GGA CAA ACC ACA ACT AGA
1639  ATG CAG TGA AAA AAA TGC TTT ATT TGT GAA ATT TGT GAT GCT ATT GCT TTA TTT GTA ACC ATT ATA AGC TGC AAT AAA
1717  CAA GTT AAC AAC AAC AAT TGC ATT CAT TTT ATG TTT CAG GTT CAG GGG GAG GTG TGG GAG GTT TTT TAA AGC AAG TAA
1795  AAC CTC TAC AAA TGT GGT ATG GAA TTC TAA AAT ACA GCA TAC CAA AAC TTT AAC CTC CAA ATC AAG CCT CTA CTT GAA
1873  TCC TTT TCT GAG GGA TGA ATA AGG CAT AGG CAT CAG GGG CTG TTG CCA ATG TGC ATT AGC TGT TTG CAG CCT CAC CTT
1951  CTT TCA TGG AGT TTA AGA TAT AGT GTA TTT TCC CAA GGT TTG AAC TAG CTC TTC ATT TCT TTA TGT TTT AAA TGC ACT
2029  GAC CTC CCA CAT TCC CTT TTT AGT AAA ATA TTC AGA AAT AAT TTA AAT ACA TCA TTG CAA TGA AAA TAA ATG TTT TTT
2107  ATT AGG CAG AAT CCA GAT GCT CAA GGC CCT TCA TAA TAT CCC CCA GTT TAG TAG TTG GAC TTA GGG AAC AAA GGA ACC
2185  TTT AAT AGA AAT TGG ACA GCA AGA AAG CGA GCT TCT AGC GAA TTC TCG ACT CAT TCC TTT GCC CTC GGA CGA GTG CTG
2263  GGG CGT CGG TTT CCA CTA TGG GCG AGT ACT TCT ACA CAG CCA TCG GTC CAG ACG GCC GCG CTT CTG CGG GCG ATT TGT
2341  GTA CGC CCG ACA GTC CCG GCT CCG GAT CGG ACG ATT GCG TCG CAT CGA CCC TGC GCC CAA GCT GCA TCA TCG AAA TTG
2419  CCG TCA ACC AAG CTC TGA TAG AGT TGG TCA AGA CCA ATG CGG AGC ATA TAC GCC CGG AGC CGC GGC GAT CCT GCA AGC
2497  TCC GGA TGC CTC CGC TCG AAG TAG CGC GTC TGC TGC TCC ATA CAA GCC AAC CAC GGC CTC CAG AAG AAG ATG TTG GCG
2575  ACC TCG TAT TGG GAA TCC CCG AAC ATC GCC TCG CTC CAG TCA ATG ACC GCT GTT ATG CGG CCA TTG TCC GTC AGG ACA
2653  TTG TTG GAG CCG AAA TCC GCG TGC ACG AGG TGC CGG ACT TCG GGG CAG TCC TCG GCC CAA AGC ATC AGC TCA TCG AGA
2731  GCC TGC GCG ACG GAC GCA CTG ACG GTG TCG TCC ATC ACA GTT TGC CAG TGA TAC ACA TGG GGA TCA GCA ATC GCG CAT
2809  ATG AAA TCA CGC CAT GTA GTG TAT TGA CCG ATT CCT TGC GGT CCG AAT GGG CCG AAC CCG CTC GTC TGG CTA AGA TCG
2887  GCC GCA GCG ATC GCA TCC ATG AGC TCC GCG ACG GGT TGC AGA ACA GCG GGC AGT TCG GTT TCA GGC AGG TCT TGC AAC
2965  GTG ACA CCC TGT GCA CGG CGG GAG ATG CAA TAG GTC AGG CTC TCG CTG AAT TCC CCA ATG TCA AGC ACT TCC GGA ATC
3043  GCG AGC GCG GCC GAT GCA AAG TGC CGA TAA ACA TAA CGA TCT TTG TAG AAA CCA TCG GCG CAG CTA TTT ACC CGC AGG
3121  ACA TAT CCA CGC CCT CCT ACA TCG AAG CTG AAA GCA CGA GAT TCT TCG CCC TCC GAG AGC TGC ATC AGG TCG GAG ACG
3199  CTG TCG AAC TTT TCG ATC AGA AAC TTC TCG ACA GAC GTC GCG GTG AGT TCA GGC TTT TTC ATG ATG GCC CTC CTA TAG
3277  TGA GTC GTA TTA TAC TAT GCC GAT ATA CTA TGC CGA TGA TTA ATT GTC AAA ACA GCG TGG ATG GCG TCT CCA GCT TAT
3355  CTG ACG GTT CAC TAA ACG AGC TCT GCT TAT ATA GAC CTC CCA CCG TAC ACG CCT ACC GCC CAT TTG CGT CAA TGG GGC
3433  GGA GTT GTT ACG ACA TTT TGG AAA GTC CCG TTG ATT TAC TAG TCA AAA CAA ACT CCC ATT GAC GTC AAT GGG GTG GAG
3511  ACT TGG AAA TCC CCG TGA GTC AAA CCG CTA TCC ACG CCC ATT GAT GTA CTG CCA AAA CCG CAT CAT CAT GGT AAT AGC
3589  GAT GAC TAA TAC GTA GAT GTA CTG CCA AGT AGG AAA GTC CCA TAA GGT CAT GTA CTG GGC ATA ATG CCA GGC GGG CCA
3667  TTT ACC GTC ATT GAC GTC AAT AGG GGG CGT ACT TGG CAT ATG ATA CAC TTG ATG TAC TGC CAA GTG GGC AGT TTA CCG
3745  TAA ATA CTC CAC CCA TTG ACG TCA ATG GAA AGT CCC TAT TGG CGT TAC TAT GGG AAC ATA CGT CAT TAT TGA CGT CAA
3823  TGG GCG GGG GTC GTT GGG CGG TCA GCC AGG CGG GCC ATT TAC CGT AAG TTA TGT AAC GCC TGC AGG TTA ATT AAG AAC
3901  ATG TGA GCA AAA GGC CAG CAA AAG GCC AGG AAC CGT AAA AAG GCC GCG TTG CTG GCG TTT TTC CAT AGG CTC CGC CCC
3979  CCT GAC GAG CAT CAC AAA AAT CGA CGC TCA AGT CAG AGG TGG CGA AAC CCG ACA GGA CTA TAA AGA TAC CAG GCG TTT
4057  CCC CCT GGA AGC TCC CTC GTG CGC TCT CCT GTT CCG ACC CTG CCG CTT ACC GGA TAC CTG TCC GCC TTT CTC CCT TCG
4135  GGA AGC GTG GCG CTT TCT CAT AGC TCA CGC TGT AGG TAT CTC AGT TCG GTG TAG GTC GTT CGC TCC AAG CTG GGC TGT
4213  GTG CAC GAA CCC CCG GTT CAG CCC GAC CGC CGC GCC TTA TCC GGT AAC TAT CGT CTT GAG TCC AAC CCG GTA AGA CAC
4291  GAC TTA TCG CCA CTG GCA GCA GCC ACT GGT AAC AGG ATT AGC AGA GCG AGG TAT GTA GGC GGT GCT ACA GAG TTC TTG
4369  AAG TGG TGG CCT AAC TAC GGC TAC ACT AGA AGA ACA GTA TTT GGT ATC TGC GCT CTG CTG AAG CCA GTT ACC TTC GGA
4447  AAA AGA GTT GGT AGC TCT TGA TCC GGC AAA CAA ACC ACC GCT GGT AGC GGT GGT TTT TTT GTT TGC AAG CAG CAG ATT
4525  ACG CGC AGA AAA AAA GGA TCT CAA GAA GAT CCT TTG ATC TTT TCT ACG GGG TCT GAC GCT CAG TGG AAC GAA AAC TCA
4603  CGT TAA GGG ATT TTG GTC ATG GCT AGT TAA CTA ACA TTT AAA TCA
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Fig. 12, contd.

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   1 CTT GAT TTG GGT GAT GGT TCA CGT AGT GGG CCA TCG CCC TGA TAG ACG GTT TTT CGC CCT TTG ACG TTG GAG TCC ACG
  79 TTC TTT AAT AGT GGA CTC TTG TTC CAA ACT GGA ACA ACA CTC AAC TCT ATC TCG GGC TAT TCT TTT GAT TTA TAA GGG
 157 ATT TTG CCG ATT TCG GTC TAT TGG TTA AAA AAT GAG CTG ATT TAA CAA AAA TTT AAC GCG AAT TTT AAC AAA ATA TTA
 235 ACG TTT ACA ATT TTA TGG TGC AGT CTC AGT ACA ATC TGC TCT GAT GCC GCA TAG TTA AGC CAG CCC CGA CAC CCG CCA
 313 ACA CCC GCT GAC GCG CCC TGA CGG GCT TGT CTG CTC CCG GCA TCC GCT TAC AGA CAA GCT GTG ACC GTC TCC GGG AGC
 391 TGC ATG TGT CAG AGG TTT TCA CCG TCA TCA CCG AAA CGC GCG AGA CGA AAG GGC CTC GTG ATA CGC CTA TTT TTA TAG
 469 GTT AAT GTC ATG ATA ATA ATG GTT TCT TAG ACG TCA GGT GGC ACT TTT CGG GGA AAT GTG CGC GGA ACC CCT ATT TGT
 547 TTA TTT TTC TAA ATA CAT TCA AAT ATG TAT CCG CTC ATG AGA CAA TAA CCC TGA TAA ATG CTT CAA TAA TAT TGA AAA
 625 AGG AAG AGT ATG AGT ATT CAA CAT TTC CGT GTC GCC CTT ATT CCC TTT TTT GCG GCA TTT TGC CTT CCT GTT TTT GCT
 703 CAC CCA GAA ACG CTG GTG AAA GTA AAA GAT GCT GAA GAT CAG TTG GGT GCC GGA GTG GGT TAC ATC GAA CTG GAT CTC
 781 AAC AGC GGT AAG ATC CTT GAG AGT TTT CGC CCC GAA GAA CGT TTT CCA ATG ATG AGC ACT TTT AAA GTT CTG CTA TGT
 859 GGC GCG GTA TTA TCC CGT ATT GAC GCC GGG CAA GAG CAA CTC GGT CGC CGC ATA CAC TAT TCT CAG AAT GAC TTG GTT
 937 GAG TAC TCA CCA GTC ACA GAA AAG CAT CTT ACG GAT GGC ATG ACA GTA AGA GAA TTA TGC AGT GCT GCC ATA ACC ATG
1015 AGT GAT AAC ACT GCG GCC AAC TTA CTT CTG ACA ACG ATC GGA GGA CCG AAG GAG CTA ACC GCT TTT TTG CAC AAC ATG
1093 GGG GAT CAT GTA ACT CGC CTT GAT CGT TGG GAA CCG GAG CTG AAT GAA GCC ATA CCA AAC GAC GAG CGT GAC ACC ACG
1171 ATG CCT GTA GCA ATG GCA ACA ACG TTG CGC AAA CTA TTA ACT GGC GAA CTA CTT ACT CTA GCT TCC CGG CAA CAA TTA
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1717 CCG CTA CCA GCG GTG GTT TGT TTG CCG GAT CAA GAG CTA CCA ACT CTT TTT CCG AAG GTA ACT GGC TTC AGC AGA GCG
1795 CAG ATA CCA AAT ACT GTT CTT CTA GTG TAG CCG TAG TTA GGC CAC CAC TTC AAG AAC TCT GTA GCA CCG CCT ACA TAC
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1951 TAG TTA CCG GAT AAG GCG CAG CGG TCG GGC TGA ACG GGG GGT TCG TGC ATA CAG CCC AGC TTG GAG CGA ACG ACC TAC
2029 ACC GAA CTG AGA TAC CTA CAG CGT GAG CTA TGA GAA AGC GCC ACG CTT CCC GAA GGG AGA AAG GCG GAC AGG TAT CCG
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2341 GTG GAT AAC CGT ATT ACC GCC TTT GAG TGA GCT GAT ACC GCT CGC CGC AGC CGA ACG ACC GAG CGC AGC GAG TCA GTG
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2497 GAC AGG TTT CCC GAC TGG AAA GCG GGC AGT GAG CGC AAC GCA ATT AAT GTG AGT TAG CTC ACT CAT TAG GCA CCC CAG
2575 GCT TTA CAC TTT ATG CTT CCG GCT CGT ATG TTG TGT GGA ATT GTG AGC GGA TAA CAA TTT CAC ACA GGA AAC AGC TAT
2653 GAC CAT GAT TAC GCC AAG CTT TGG AGC CTT TTT TTT GGA GAT TTT CAA CGT GAA AAA ATT ATT ATT CGC AAT TCC TTT
2731 AGT TGT TCC TTT CTA TTC TCA CAG TGC ACA GAT CCA AAT GAC CCA GTC TCC ATC CTC CCT GTC TGC ATC TGT AGG AGA
2809 CAG AGT CAC CAT CAC TTG CCG GGC AAG TCA GAG CAT TAG CAG CTA CTT AAA TTG GTA TCA GCA GAA ACC AGG GAA AGC
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2965 AGA TTT CAC TCT CAC CAT CAG CAG TCT GCA ACC TGA AGA TTT TGC AAC TTA CTA CTG TCA ACA GAG TTA CAG TAC CCC
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Fig. 12, contd.

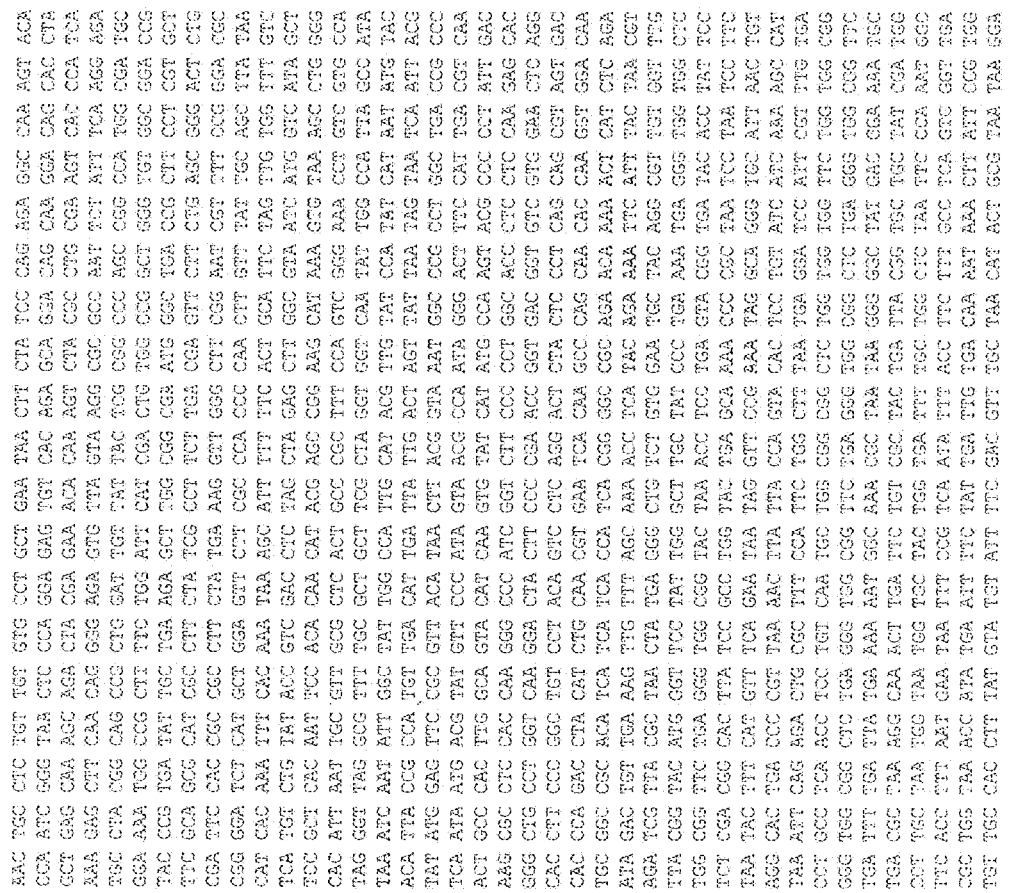

Fig. 12, contd.

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6475 GCC TGA ATG GCG AAT GGC GCC TGA TGC GGT ATT TTC TCC TTA CGC ATC TGT GCG GTA TTT CAC ACC GCA TAC GTC AAA
6553 GCA ACC ATA GTA CGC GCC CTG TAG CGG CGC ATT AAG CGC GGC GGG TGT GGT GGT TAC GCG CAG CGT GAC CGC TAC ACT
6631 TGC CAG CGC CCT AGC GCC CGC TCC TTT CGC TTT CTT CCC TTC CTT TCT CGC CAC GTT CGC CGG CTT TCC CCG TCA AGC
6709 TCT AAA TCG GGG GCT CCC TTT AGG GTT CCG ATT TAG TGC TTT ACG GCA CCT CGA CCC CAA AAA A
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 157 CGA TCC CCT ATG GTG CAC TCT CAG TAC AAT CTG CTC TGA TGC CGC ATA GTT AAG CCA GTA TCT GCT CCC TGC TTG TGT
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 313 TCT GCT TAG GGT TAG GCG TTT TGC GCT GCT TCG CTA GGT GGT CAA TAT TGG CCA TTA GCC ATA TTA TTC ATT GGT TAT
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 469 TGT CCA ACA TTA CCG CCA TGT TGA CAT TGA TTA TTG ACT AGT TAT TAA TAG TAA TCA ATT ACG GGG TCA TTA GTT CAT
 547 AGC CCA TAT ATG GAG TTC CGC GTT ACA TAA CTT ACG GTA AAT GGC CCG CCT GGC TGA CCG CCC AAC GAC CCC GCC CCA
 625 TTG ACG TCA ATA ATG ACG TAT GTT CCC ATA GTA ACG CCA ATA GGG ACT TTC CAT TGA CGT CAA TGG GTG GAG TAT TTA
 703 CGG TAA ACT GCC CAC TTG GCA GTA CAT CAA GTG TAT CAT ATG CCA AGT ACG CCC CCT ATT GAC GTC AAT GAC GGT AAA
 781 TGG CCC GCC TGG CAT TAT GCC CAG TAC ATG ACC TTA TGG GAC TTT CCT ACT TGG CAG TAC ATC TAC GTA TTA GTC ATC
 859 GCT ATT ACC ATG GTG ATG CGG TTT TGG CAG TAC ATC AAT GGG CGT GGA TAG CGG TTT GAC TCA CGG GGA TTT CCA AGT
 937 CTC CAC CCC ATT GAC GTC AAT GGG AGT TTG TTT TGG CAC CAA AAT CAA CGG GAC TTT CCA AAA TGT CGT AAC AAC TCC
1015 GCC CCA TTG ACG CAA ATG GGC GGT AGG CGT GTA CGG TGG GAG GTC TAT ATA AGC AGA GCT CGT TTA GTG AAC CGT CAG
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1171 CGG TGC ATT GGA ACG TTG GTA CCG GTG AAT TGG CCG GCC CGC GCC GTC GAG GTT ATC GAT CCG ACC GAC GCG TTC GCG
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1327 ATG GGG CGG AGA ATG GGC GGA AGT GGG CGG AGT TAG GGG CGG GAT GGG CGG AGT TAG GGG CGG GAC TAT GGT TGC TGA
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1717 CCC AGA ATA GAA TGA CAC CTA CTC AGA CAA TGC GAT GCA ATT TCC TCA TTT TAT TAG GAA AGG ACA GTG GGA GTG GCA
1795 CCT TCC AGG GTC AAG GAA GGC ACG GGG GAG GGG CAA ACA ACA GAT GGC TGG CAA CTA GAA GGC ACA GTC GAG GCT GAT
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1951 GGC ACC GGG CTT GCG GGT CAT GCA CCA GGT GCG CGG TCC TTC GGG CAC CTC GAC GTC GGC GGT GAC GGT GAA GCC GAG
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```

Fig. 12, contd.

Fig. 12, contd.

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5773 TGA GCG GGA CTC TGG GGT TCG GTG CTA CGA GAT TTC GAT TCC ACC GCC GCC TTC TAT GAA AGG TTG GGC TTC GGA ATC
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6319 GGC CAT TAG CCA TAT TAT TCA TTG GTT ATA TAG CAT AAA TCA ATA TTG GCT ATT GGC CAT TGC ATA CGT TGT ATC CAT
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7333 GGA GAC AGA GTC ACC ATC ACT TGC CGG GCA AGT CAG AGC ATT AGC AGC TAC TTA AAT TGG TAT CAG CAG AAA CCA GGG
7411 AAA GCC CCT AAG CTC CTG ATC TAT GCT GCA TCC AGT TTG CAA AGT GGG GTC CCA TCA AGG TTC AGT GGC AGT GGA TCT
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8581 TAT CCA CAG AAT CAG GGG ATA ACG CAG GAA AGA ACA TGT GAG CAA AAG GCC AGC AAA AGG CCA GGA ACC GTA AAA AGG
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Fig. 12, contd.

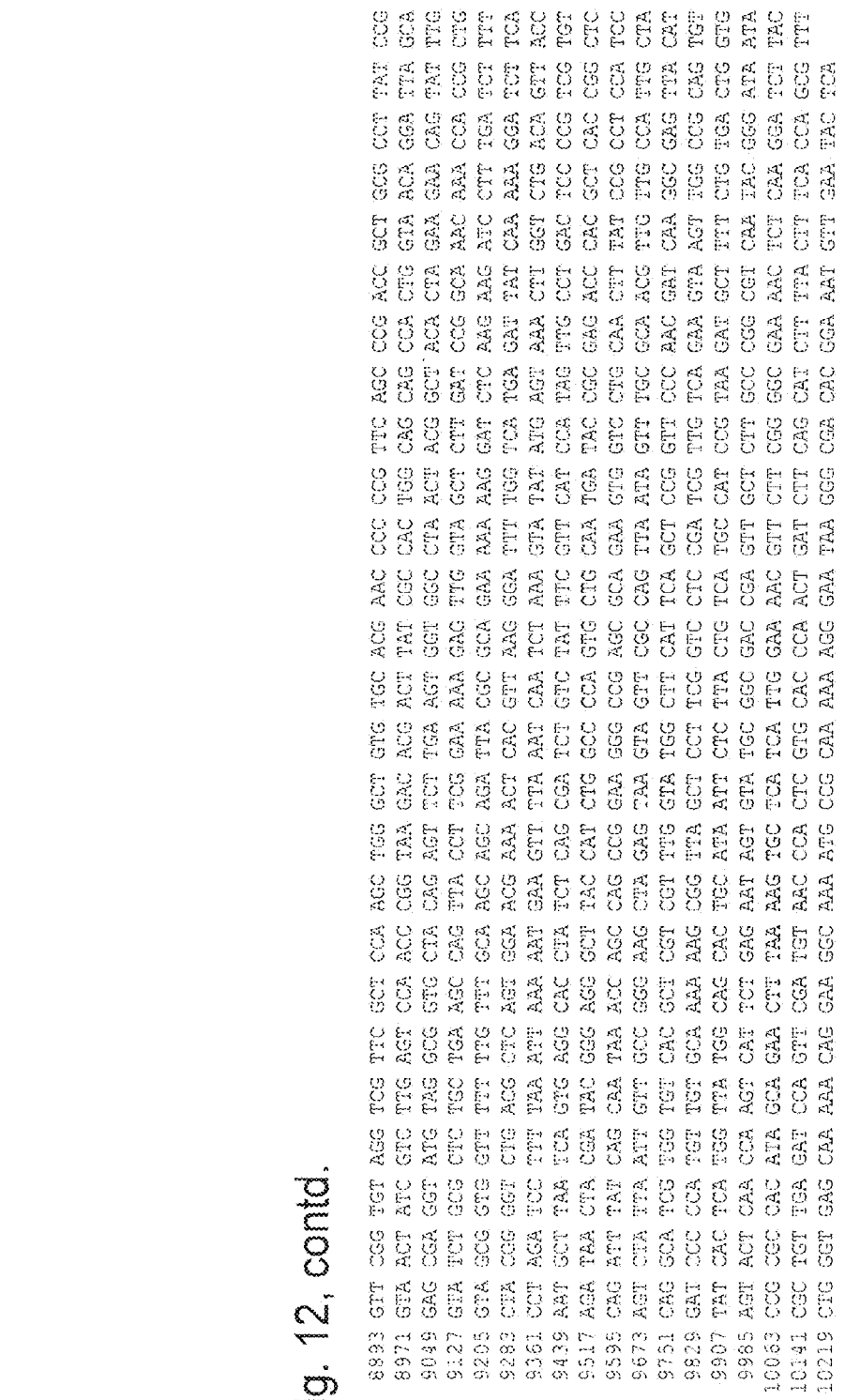
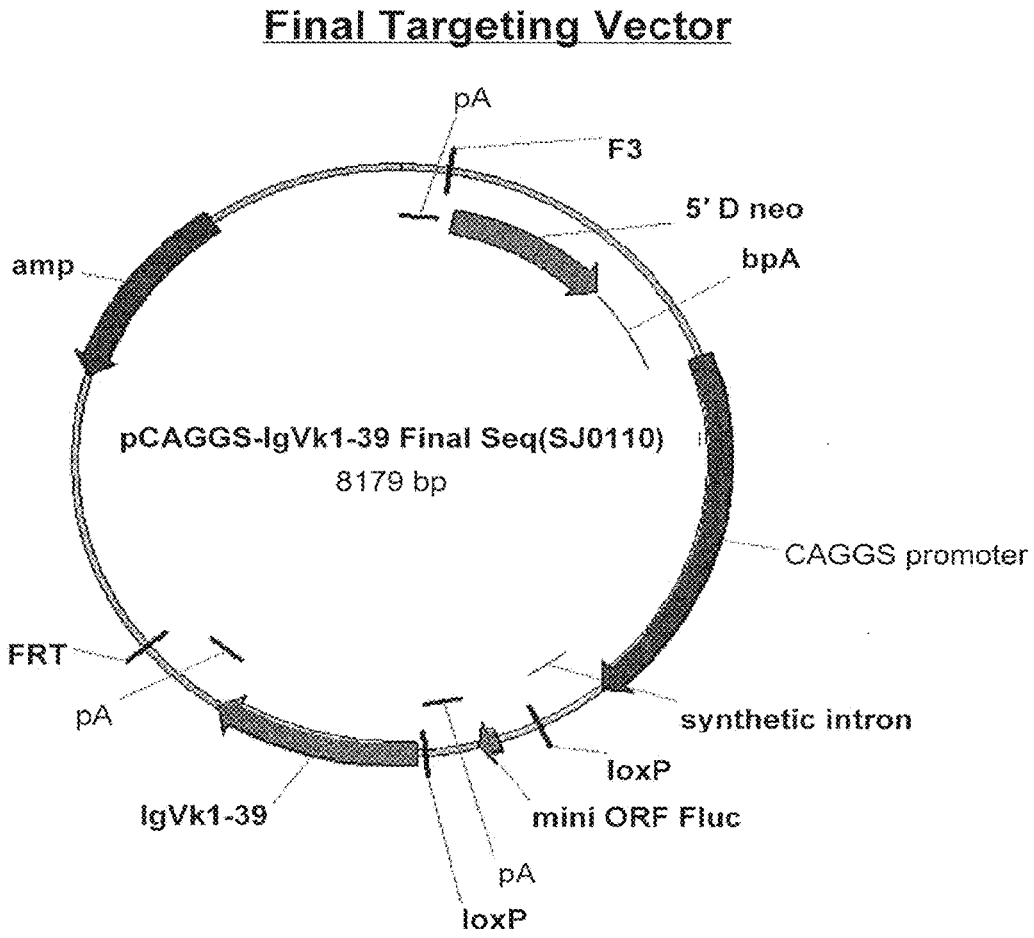


Fig. 13A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loxP
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mini ORF Fluc
pA
loxP

Fig. 13B

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Fig. 13B, contd.

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Fig. 13B, contd.

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Fig. 13B, contd.

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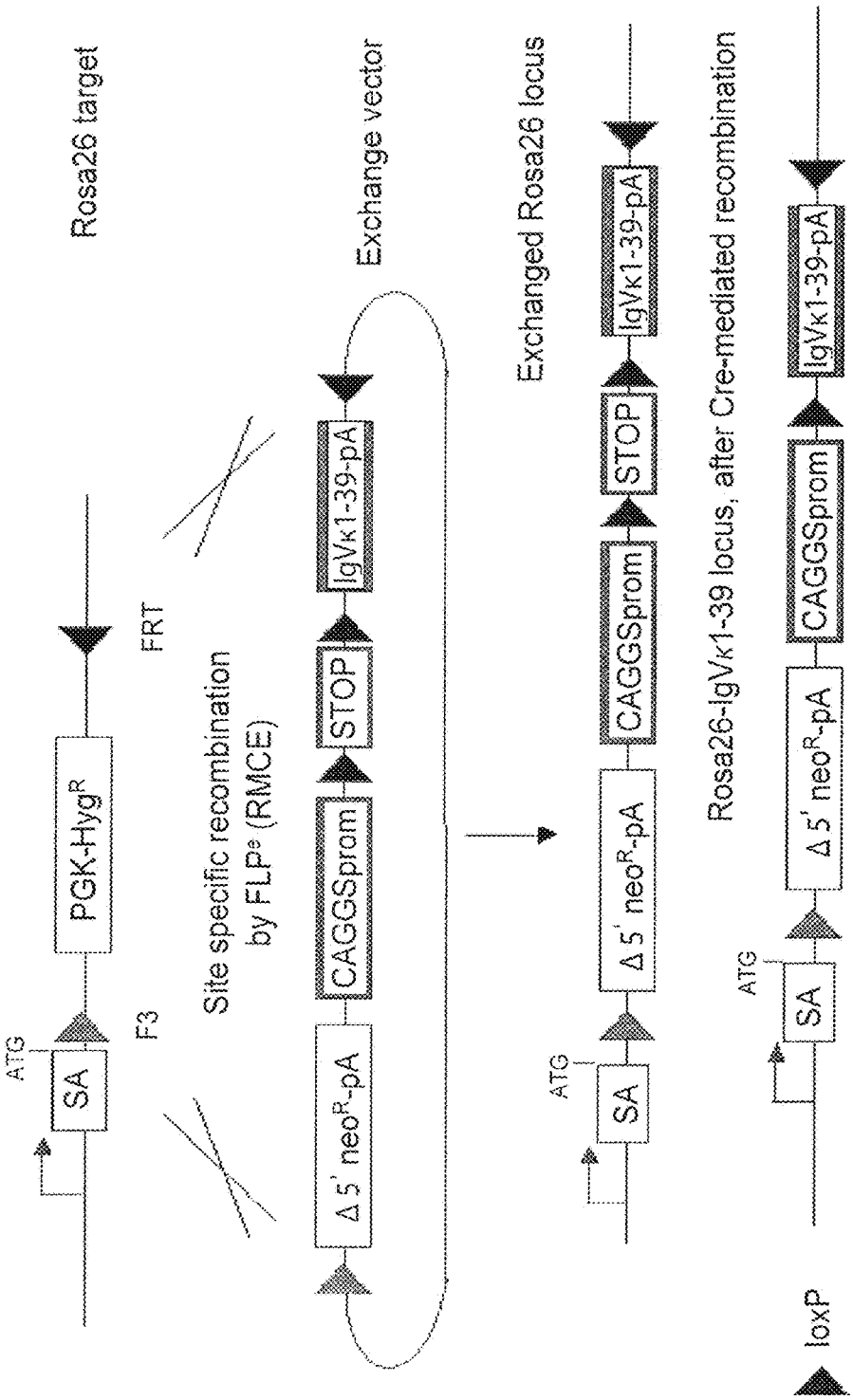
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ATG
SA
F3
FRT
Site specific recombination
by FLPᵉ (RMCE)
Δ 5' neoᴿ-pA
CAGGSprom
STOP
IgVκ1-39-pA
Exchange vector
Exchanged Rosa26 locus
Rosa26-IgVκ1-39 locus, after Cre-mediated recombination
loxP

Fig. 13C

Fig. 14A

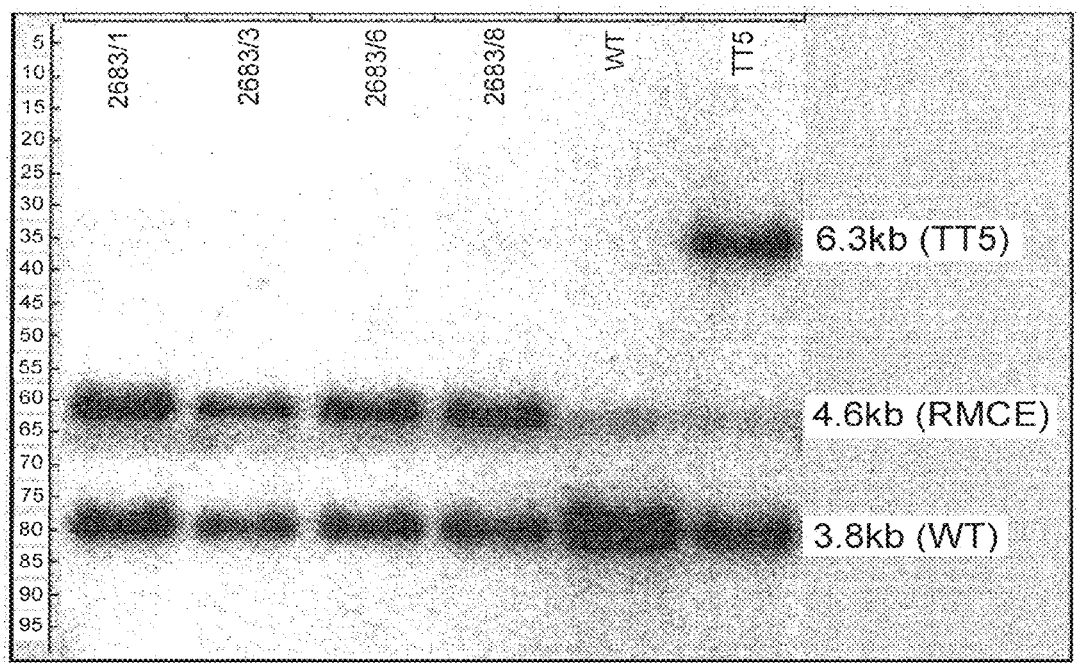


Fig. 14B

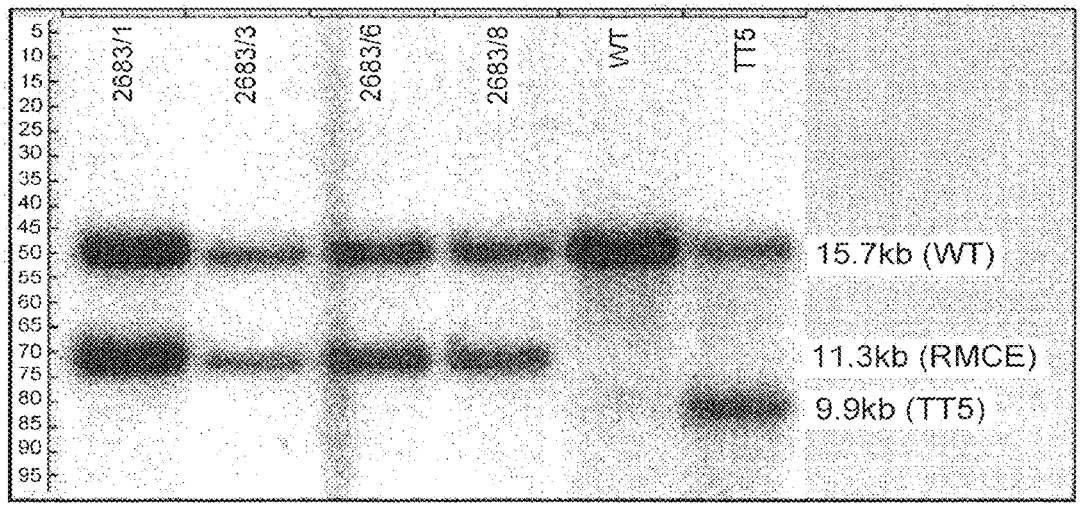
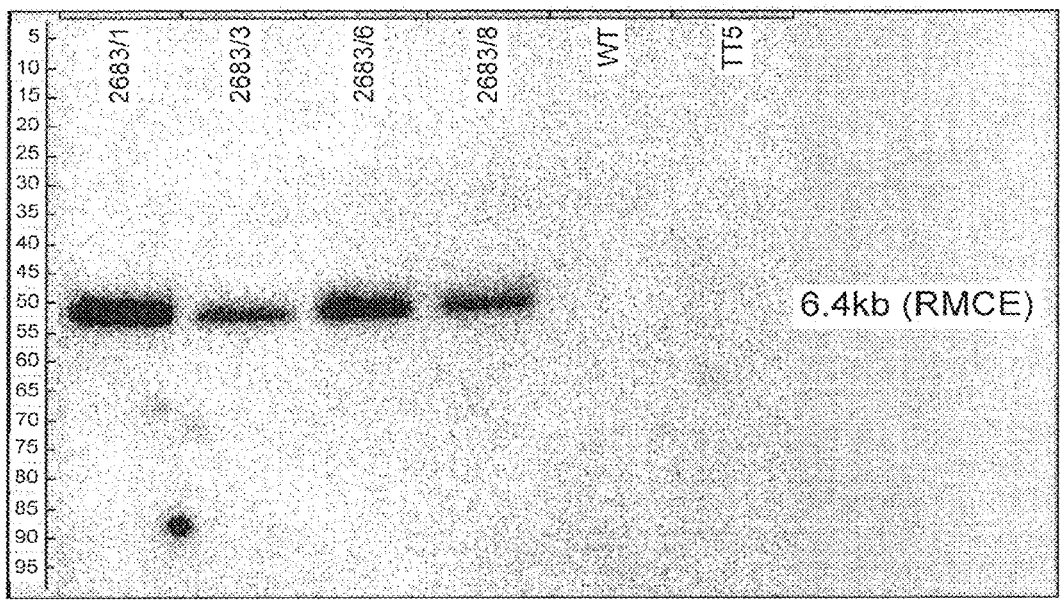


Fig. 14C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TT5
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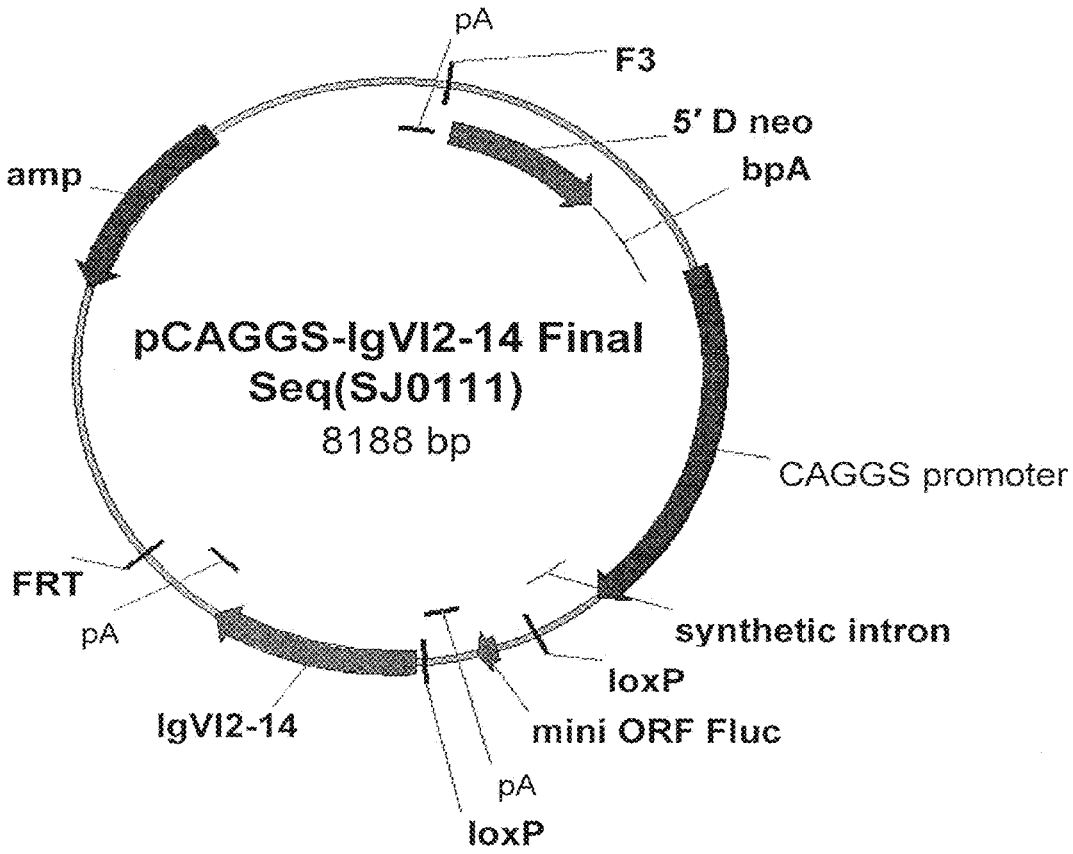
Fig. 15A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F3
5' D neo
bpA
amp
pCAGGS-IgVI2-14 Final Seq(SJ0111)
8188 bp
CAGGS promoter
FRT
pA
synthetic intron
loxP
IgVI2-14
mini ORF Fluc
pA
loxP

Fig. 15B

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```

Fig. 15B, contd.

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Fig. 15B, contd.

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Fig. 15B, contd.

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6721 gccgagcgca gaagtggtcc tgcaacttta tccgcctcca tccagtctat taattgttgc
6781 cgggaagcta gagtaagtag ttcgccagtt aatagtttgc gcaacgttgt tgccattgct
6841 acaggcatcg tggtgtcacg ctcgtcgttt ggtatggctt cattcagctc cggttcccaa
6901 cgatcaaggc gagttacatg atcccccatg ttgtgcaaaa aagcggttag ctccttcggt
6961 cctccgatcg ttgtcagaag taagttggcc gcagtgttat cactcatggt tatggcagca
7021 ctgcataatt ctcttactgt catgccatcc gtaagatgct tttctgtgac tggtgagtac
7081 tcaaccaagt cattctgaga atagtgtatg cggcgaccga gttgctcttg cccggcgtca
7141 atacgggata ataccgcgcc acatagcaga actttaaaag tgctcatcat tggaaaacgt
7201 tcttcggggc gaaaactctc aaggatctta ccgctgttga gatccagttc gatgtaaccc
7261 actcgtgcac ccaactgatc ttcagcatct tttactttca ccagcgtttc tgggtgagca
7321 aaaacaggaa ggcaaaatgc cgcaaaaaag ggaataaggg cgacacggaa atgttgaata
7381 ctcatactct tccttttttca atattattgm agcatttatc agggttattg tctcatgagc
7441 ggatacatat ttgaatgtat ttagaaaaat aaacaaatag gggttccgcg cacatttccc
7501 cgaaaagtgc cacctaaatt gtaagcgtta atattttgtt aaaattcgcg ttaaattttt
7561 gttaaatcag ctcatttttt aaccaatagg ccgaaatcgg caaaatccct tataaatcaa
7621 aagaatagac cgagataggg ttgagtgttg ttccagtttg gaacaagagt ccactattaa
7681 agaacgtgga ctccaacgtc aaagggcgaa aaaccgtcta tcagggcgat ggcccactac
7741 gtgaaccatc accctaatca agtttttttgg ggtcgaggtg ccgtaaagca ctaaatcgga
7801 accctaaagg gagcccccga tttagagctt gacggggaaa gccggcgaac gtggcgagaa
7861 aggaagggaa gaaagcgaaa ggagcgggcg ctagggcgct ggcaagtgta gcggtcacgc
7921 tgcgcgtaac caccacaccc gccgcgctta atgcgccgct acagggcgcg tcccattcgc
7981 cattcaggct gcgcaactgt tgggaagggc gatcggtgcg ggcctcttcg ctattacgcc
8041 agctggcgaa aggggatgt gctgcaaggc gattaagttg ggtaacgcca gggttttccc
8101 agtcacgacg ttgtaaaacg acggccagtg agcgcgcgta atacgactca ctatagggcg
8161 aattgggggt aactaagtaa ggatcgag
```

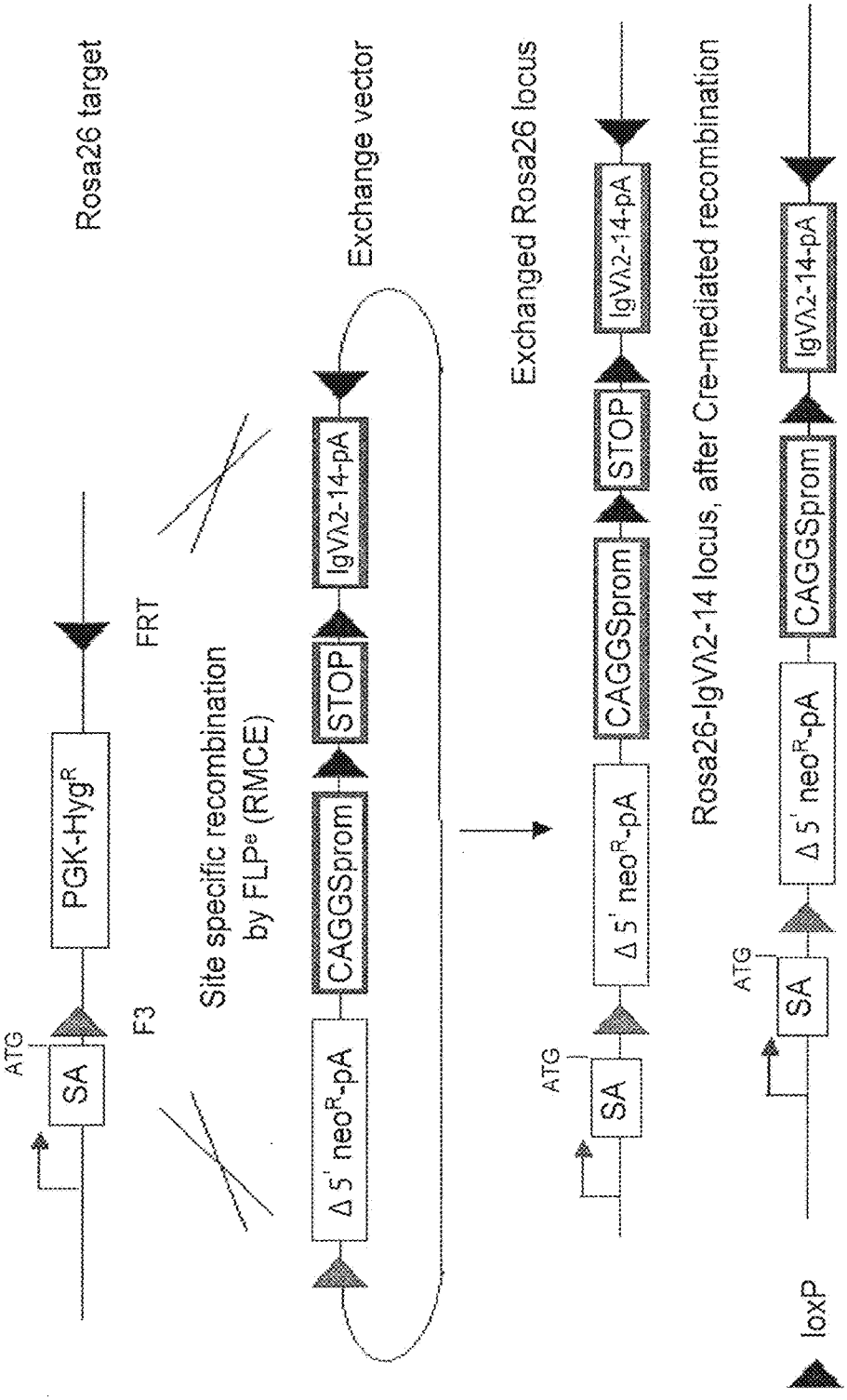

Rosa26 target
ATG
SA
PGK-Hyg^R
F3
FRT
Site specific recombination
by FLP^e (RMCE)
Δ 5' neo^R-pA
CAGGSprom
STOP
IgVλ2-14-pA
Exchange vector
Exchanged Rosa26 locus
Rosa26-IgVλ2-14 locus, after Cre-mediated recombination
loxP

Fig. 15C

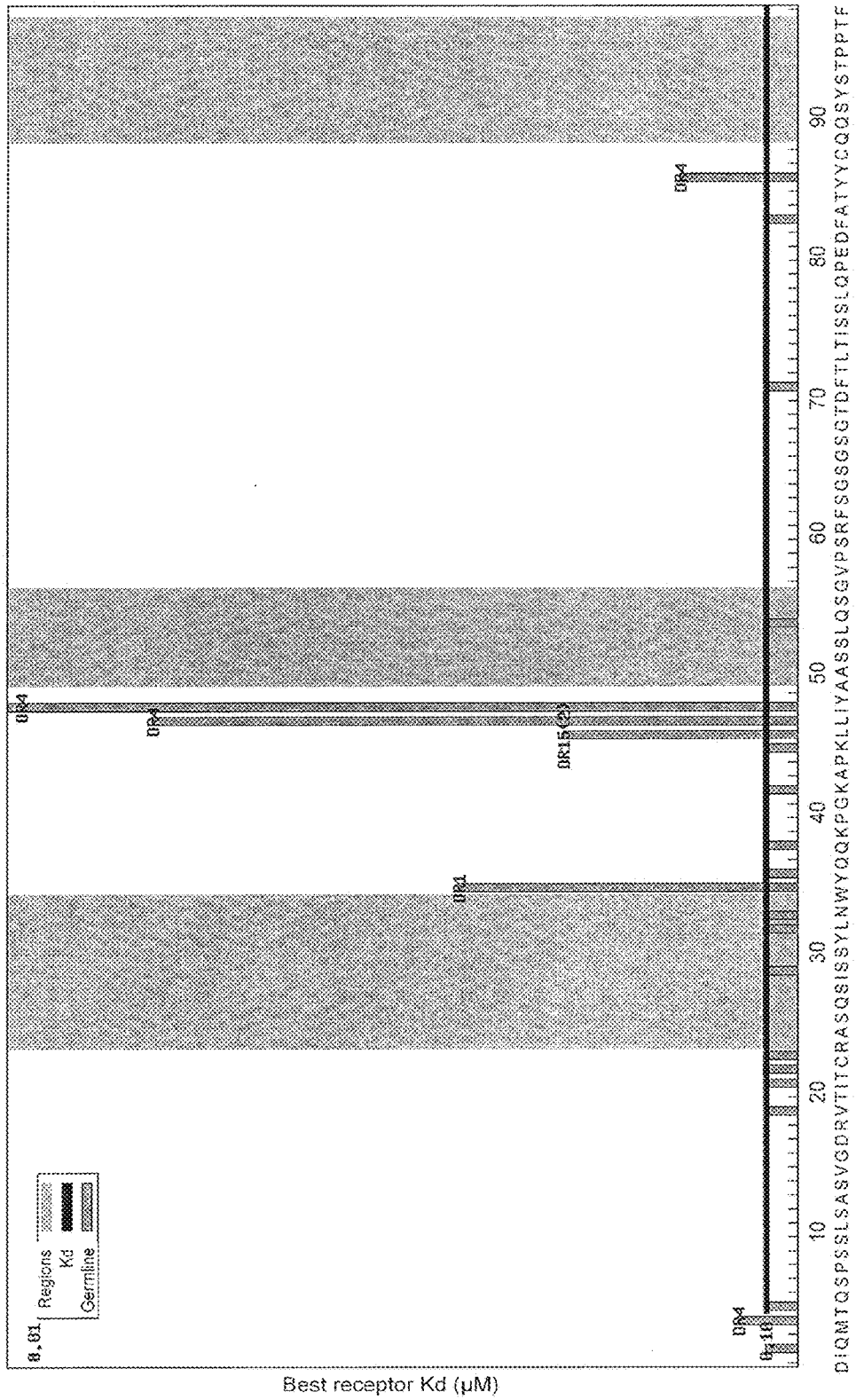

Regions
Kd
Germline
Best receptor Kd (μM)
DR4
DR1
DR15(2)
10
20
30
40
50
60
70
80
90

Fig. 16A

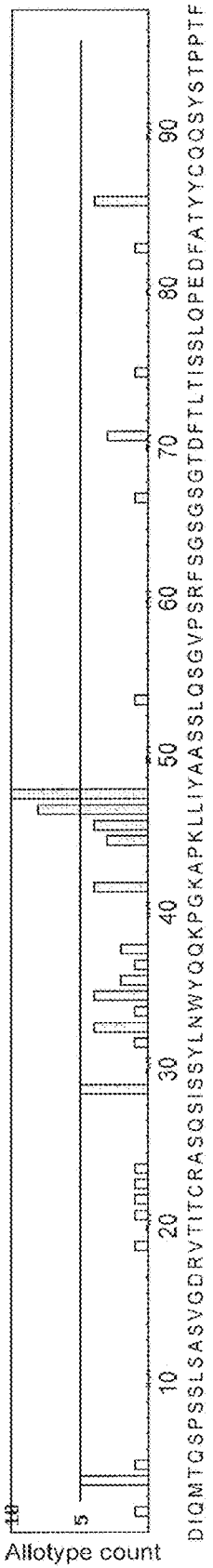

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPTF
10
20
30
40
50
60
70
80
90
Allotype count
10
5

Fig. 16B

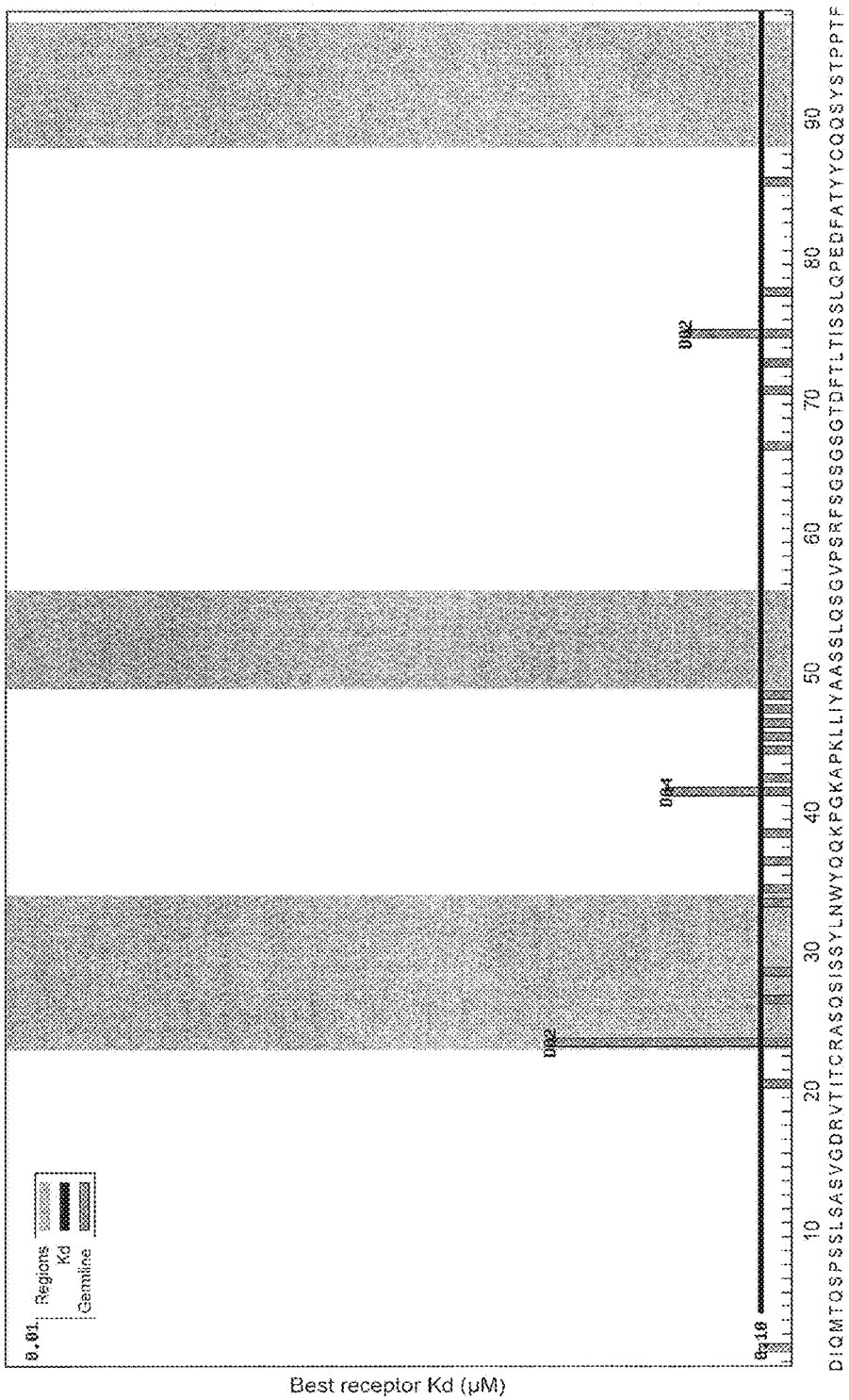

0.01
Regions
Kd
Germline
Best receptor Kd (μM)
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPTF

Fig. 16C

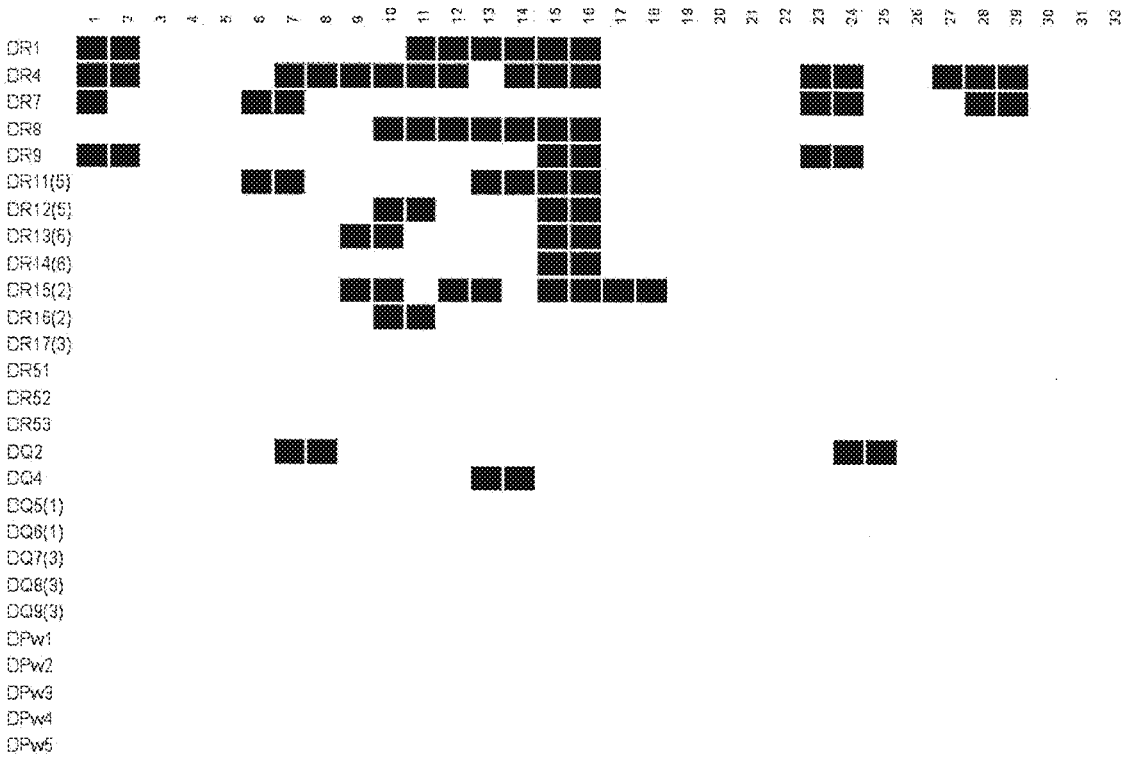

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
DR1
DR4
DR7
DR8
DR9
DR11(5)
DR12(5)
DR13(6)
DR14(6)
DR15(2)
DR16(2)
DR17(3)
DR51
DR52
DR53
DQ2
DQ4
DQ5(1)
DQ6(1)
DQ7(3)
DQ8(3)
DQ9(3)
DPw1
DPw2
DPw3
DPw4
DPw5

Fig. 17

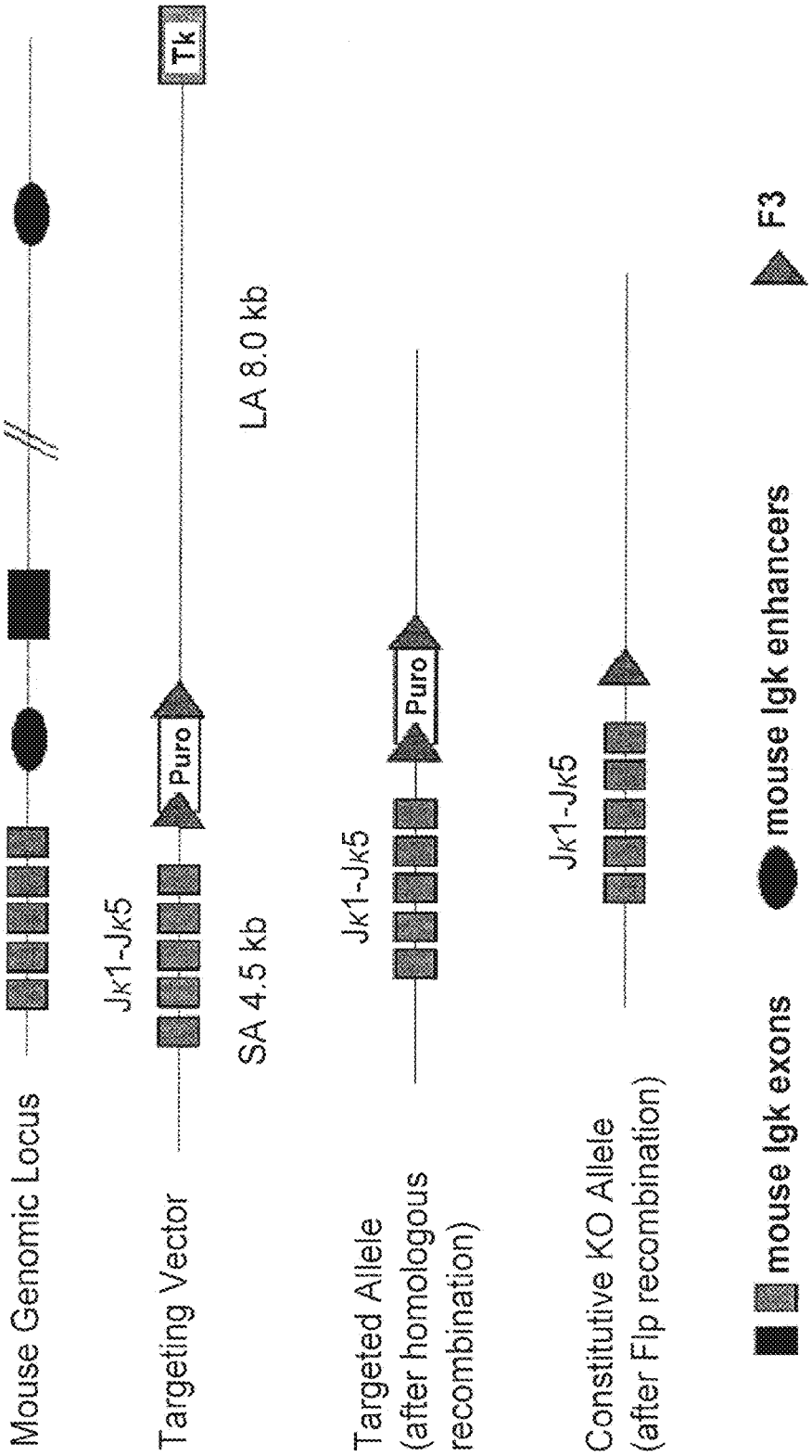
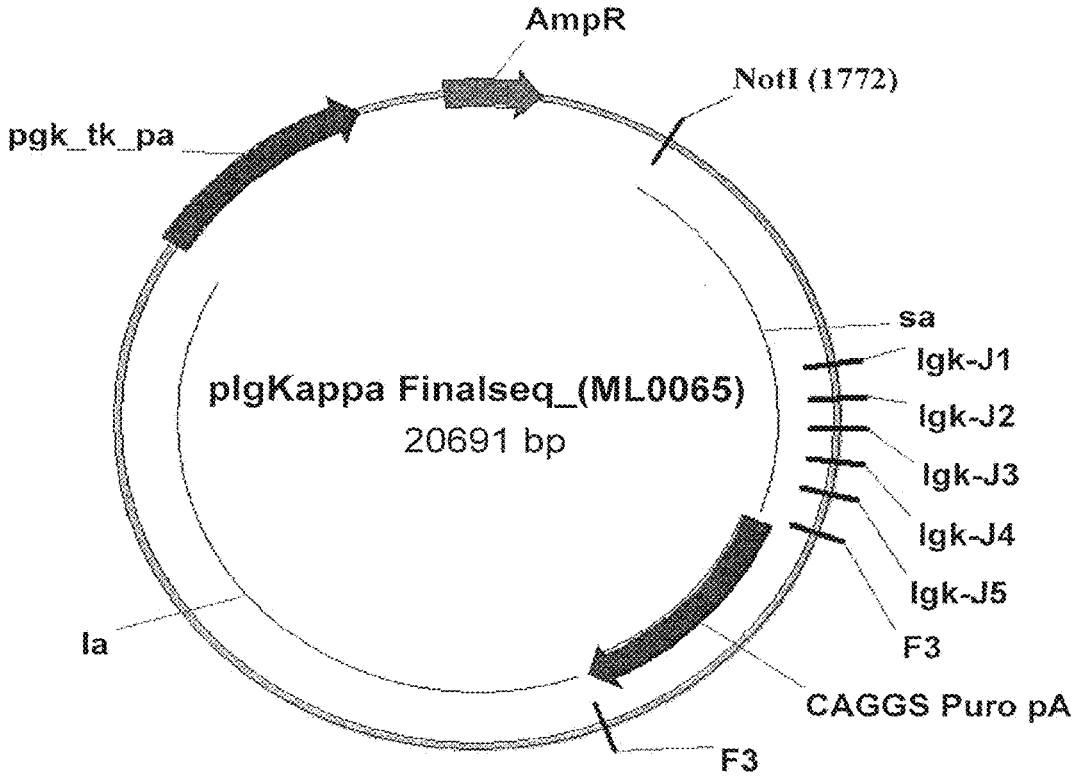

Mouse Genomic Locus
Jκ1-Jκ5
MiEκ
Cκ
3'Eκ
Targeting Vector
Jκ1-Jκ5
Puro
Tk
SA 4.5 kb
LA 8.0 kb
Targeted Allele
(after homologous
recombination)
Jκ1-Jκ5
Puro
Constitutive KO Allele
(after Flp recombination)
Jκ1-Jκ5
mouse Igk exons
mouse Igk enhancers
F3

Fig. 18A

Fig. 18B


AmpR
NotI (1772)
pgk_tk_pa
sa
Igk-J1
Igk-J2
Igk-J3
Igk-J4
Igk-J5
F3
pIgKappa Finalseq_(ML0065)
20691 bp
Ia
CAGGS Puro pA
F3

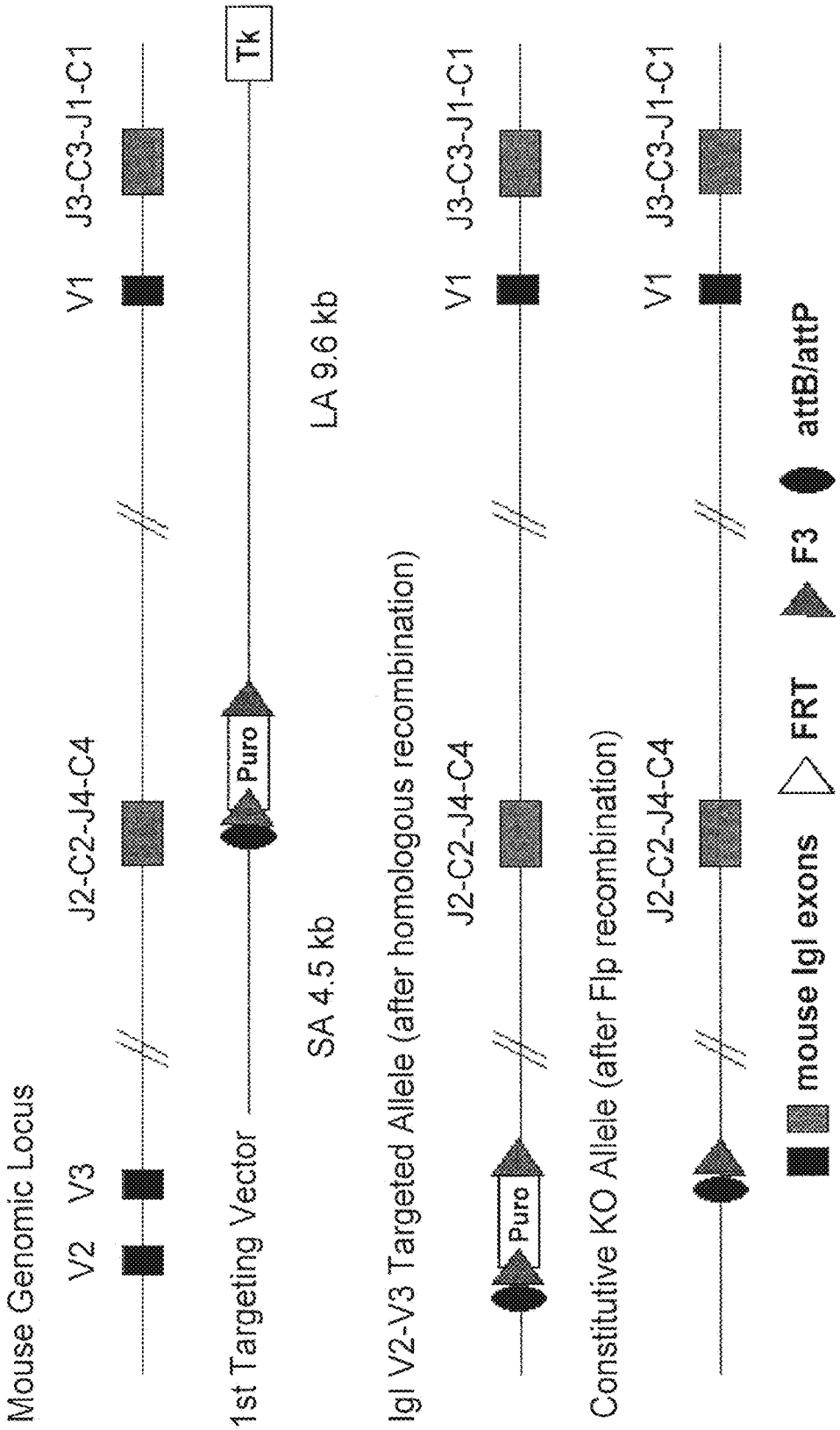

Mouse Genomic Locus
V2
V3
J2-C2-J4-C4
V1
J3-C3-J1-C1
1st Targeting Vector
Puro
Tk
SA 4.5 kb
LA 9.6 kb
Igl V2-V3 Targeted Allele (after homologous recombination)
Puro
J2-C2-J4-C4
V1
J3-C3-J1-C1
Constitutive KO Allele (after Flp recombination)
J2-C2-J4-C4
V1
J3-C3-J1-C1
mouse Igl exons
FRT
F3
attB/attP

Fig. 19A

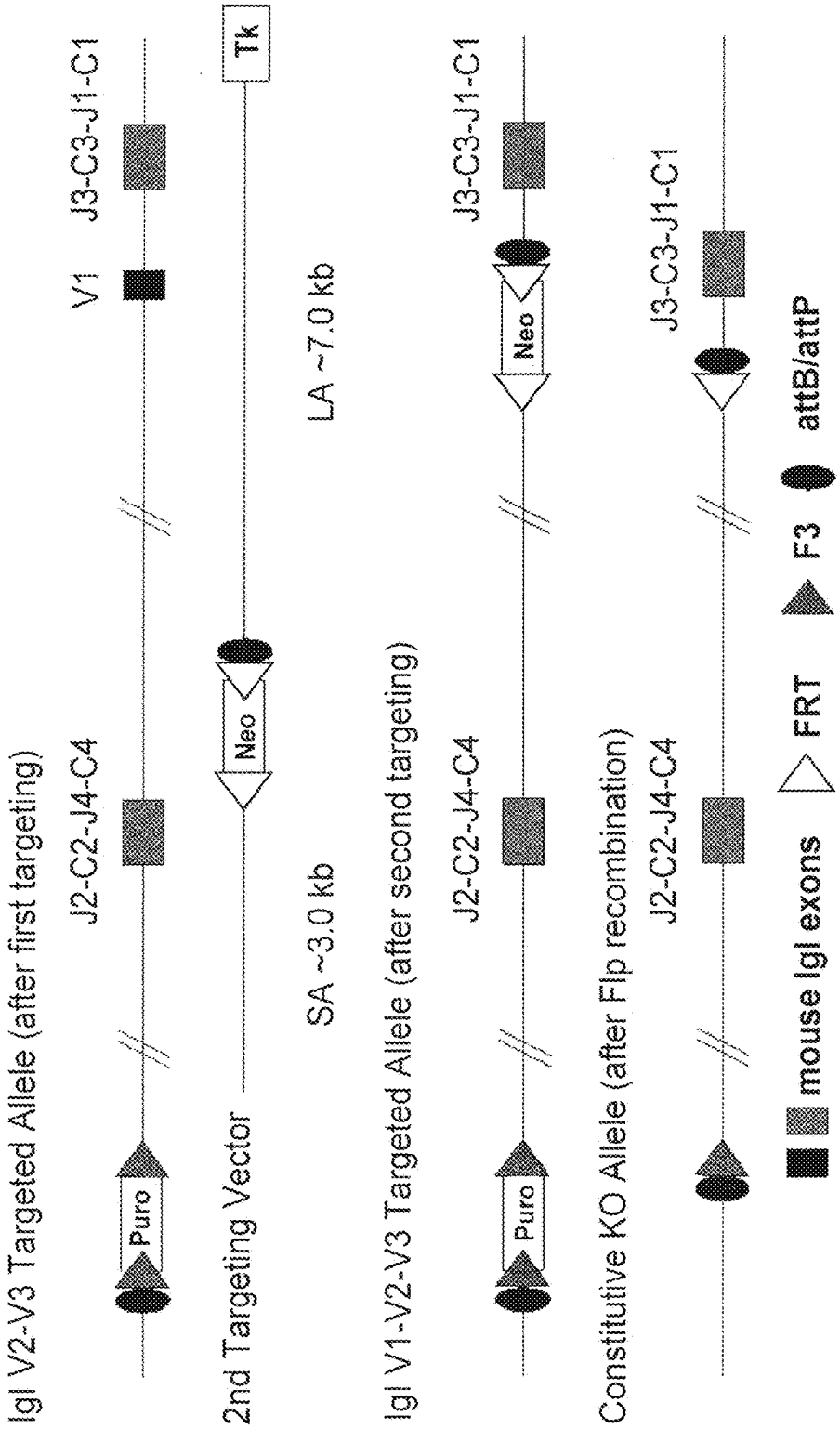

Igl V2-V3 Targeted Allele (after first targeting)
J2-C2-J4-C4
V1
J3-C3-J1-C1
Puro
2nd Targeting Vector
Neo
Tk
SA ~3.0 kb
LA ~7.0 kb
Igl V1-V2-V3 Targeted Allele (after second targeting)
J2-C2-J4-C4
J3-C3-J1-C1
Puro
Neo
Constitutive KO Allele (after Flp recombination)
J2-C2-J4-C4
J3-C3-J1-C1
mouse Igl exons
FRT
F3
attB/attP

Fig. 19B

Fig. 20A

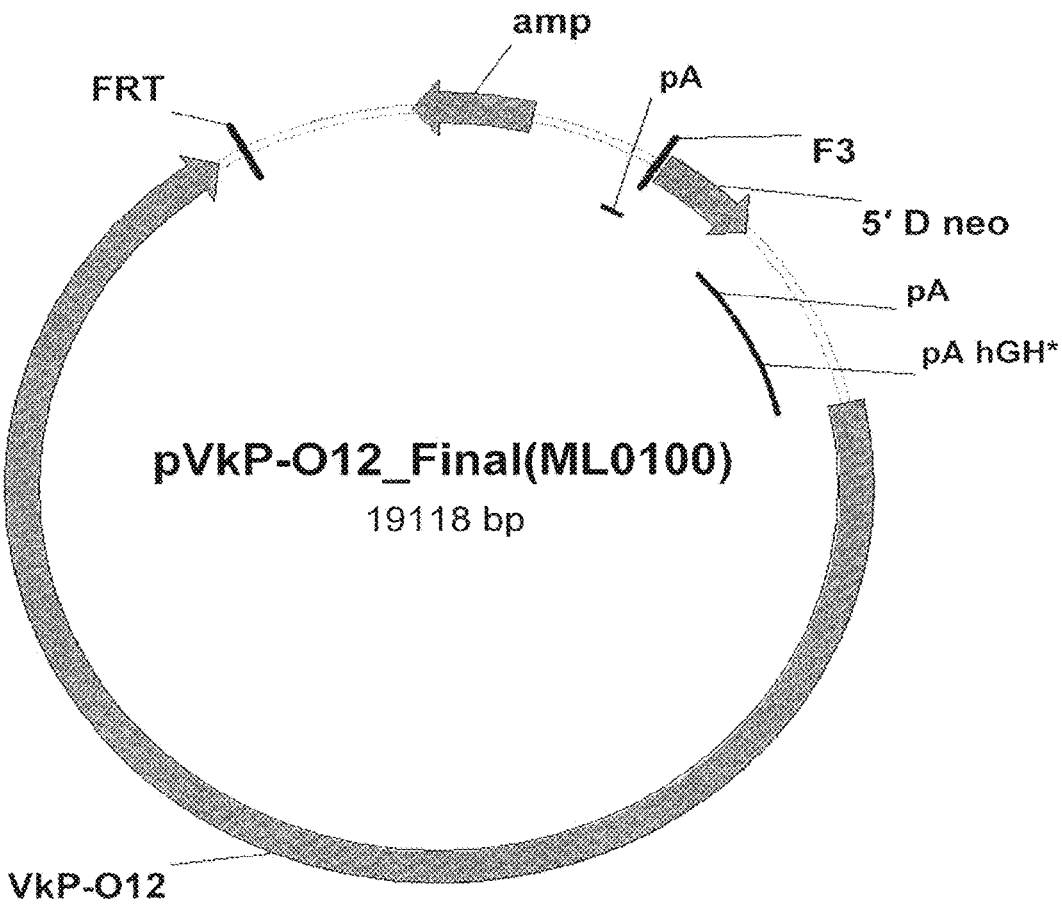

amp
FRT
pA
F3
5' D neo
pA
pA hGH*
pVkP-O12_Final(ML0100)
19118 bp
VkP-O12

Fig. 20B

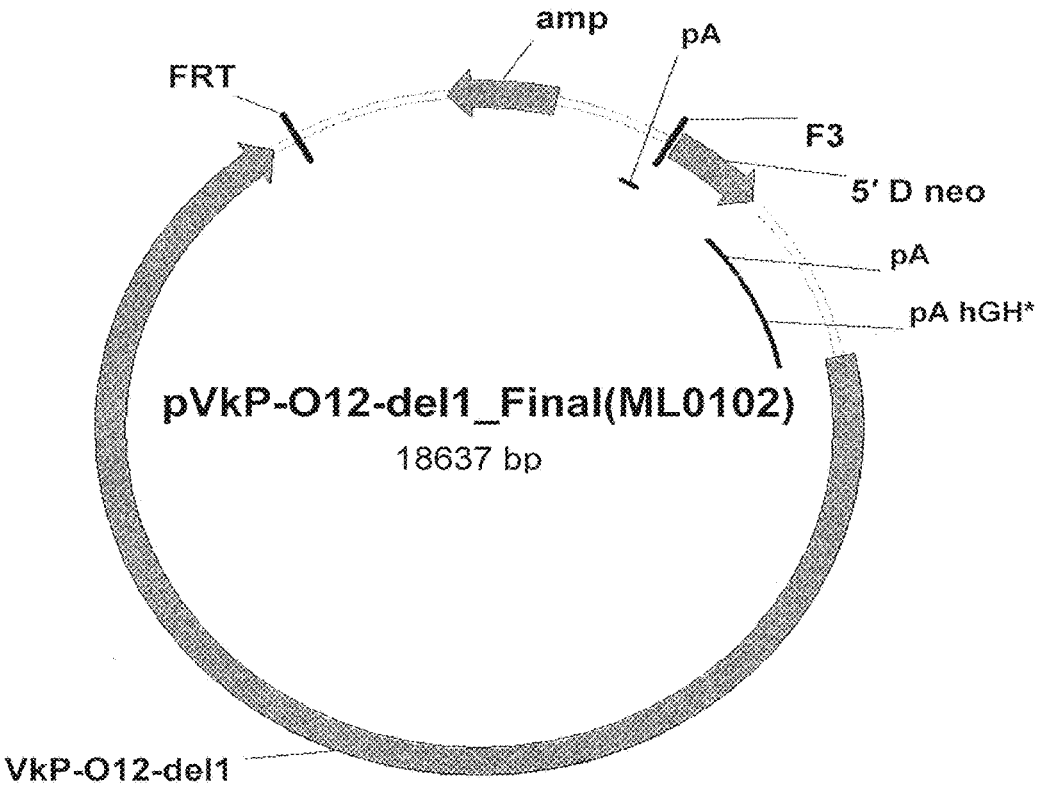
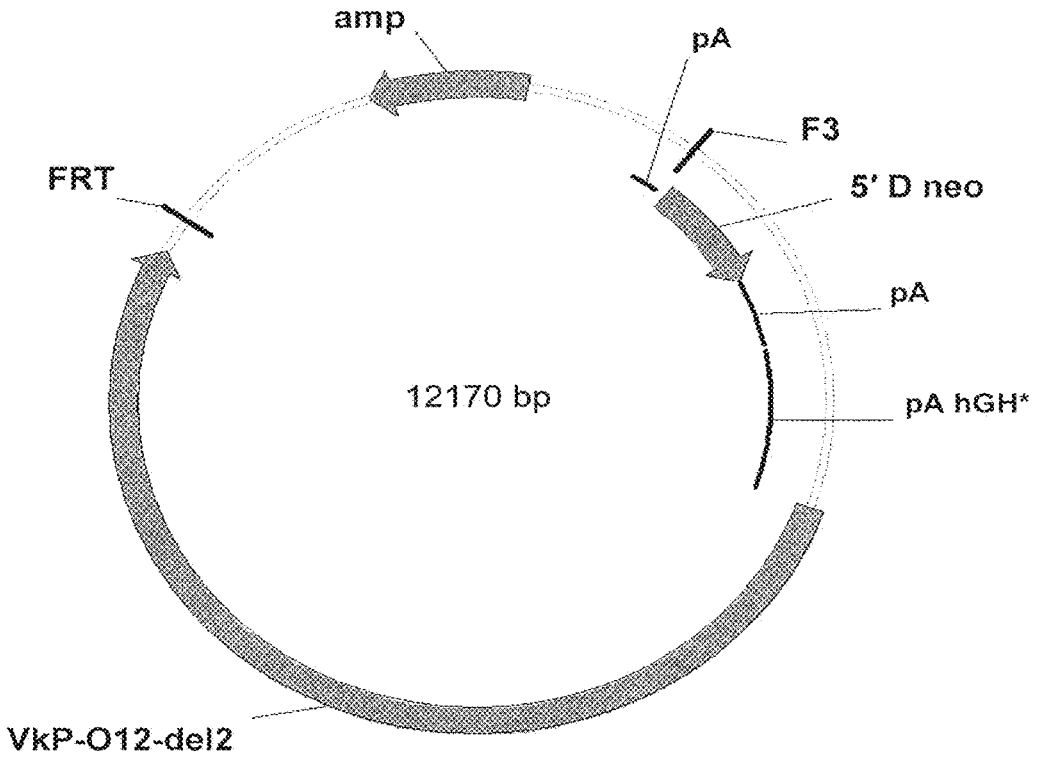

amp
pA
FRT
F3
5' D neo
pA
pA hGH*
pVkP-O12-del1_Final(ML0102)
18637 bp
VkP-O12-del1

Fig. 20C



pVkP-O12-del2_Final(ML104)

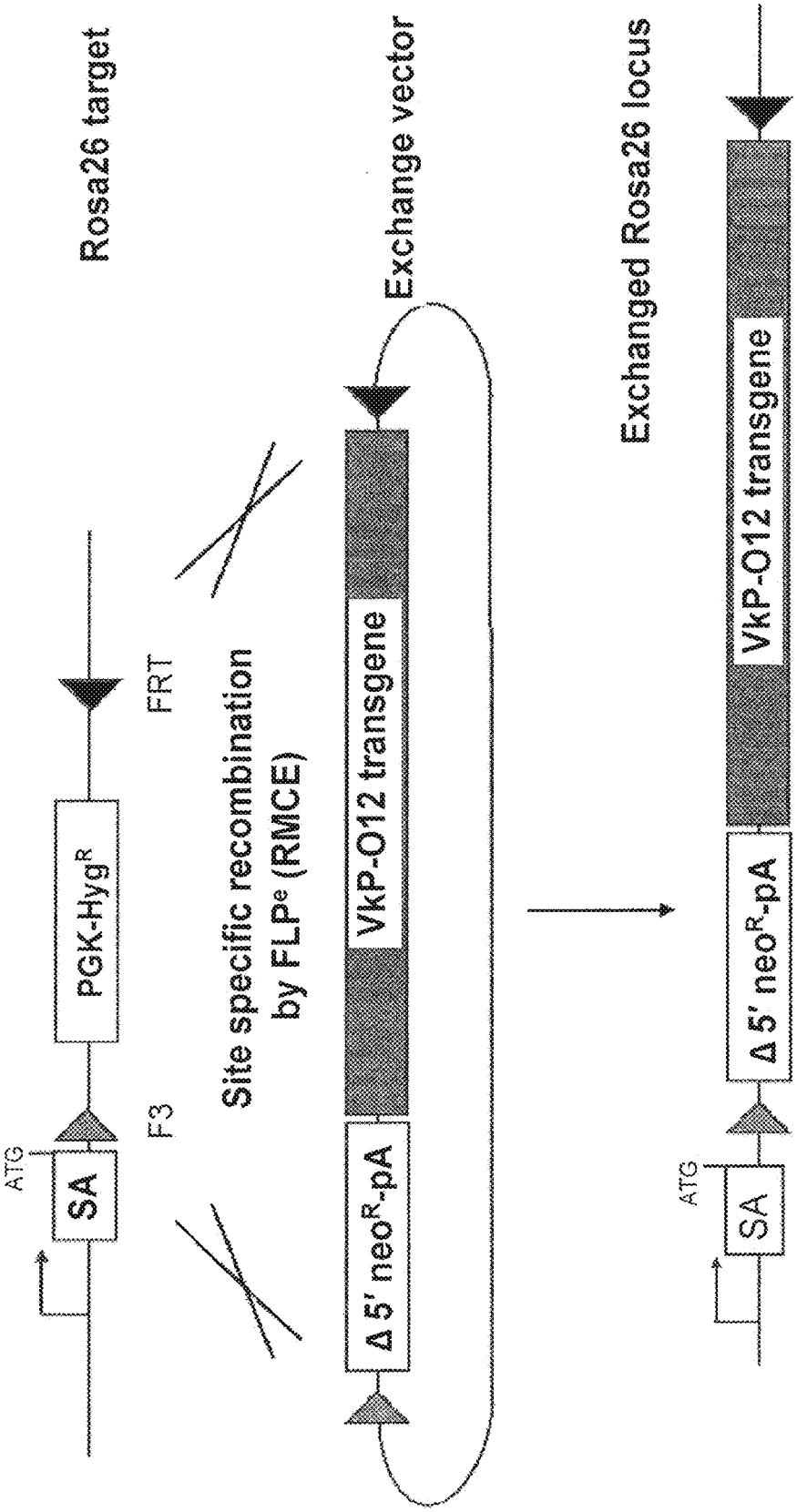

Rosa26 target
Exchange vector
Exchanged Rosa26 locus
ATG
SA
PGK-Hyg^R
F3
FRT
Site specific recombination
by FLP^e (RMCE)
Δ 5' neo^R-pA
VkP-O12 transgene
ATG
SA
Δ 5' neo^R-pA
VkP-O12 transgene

Fig. 21A

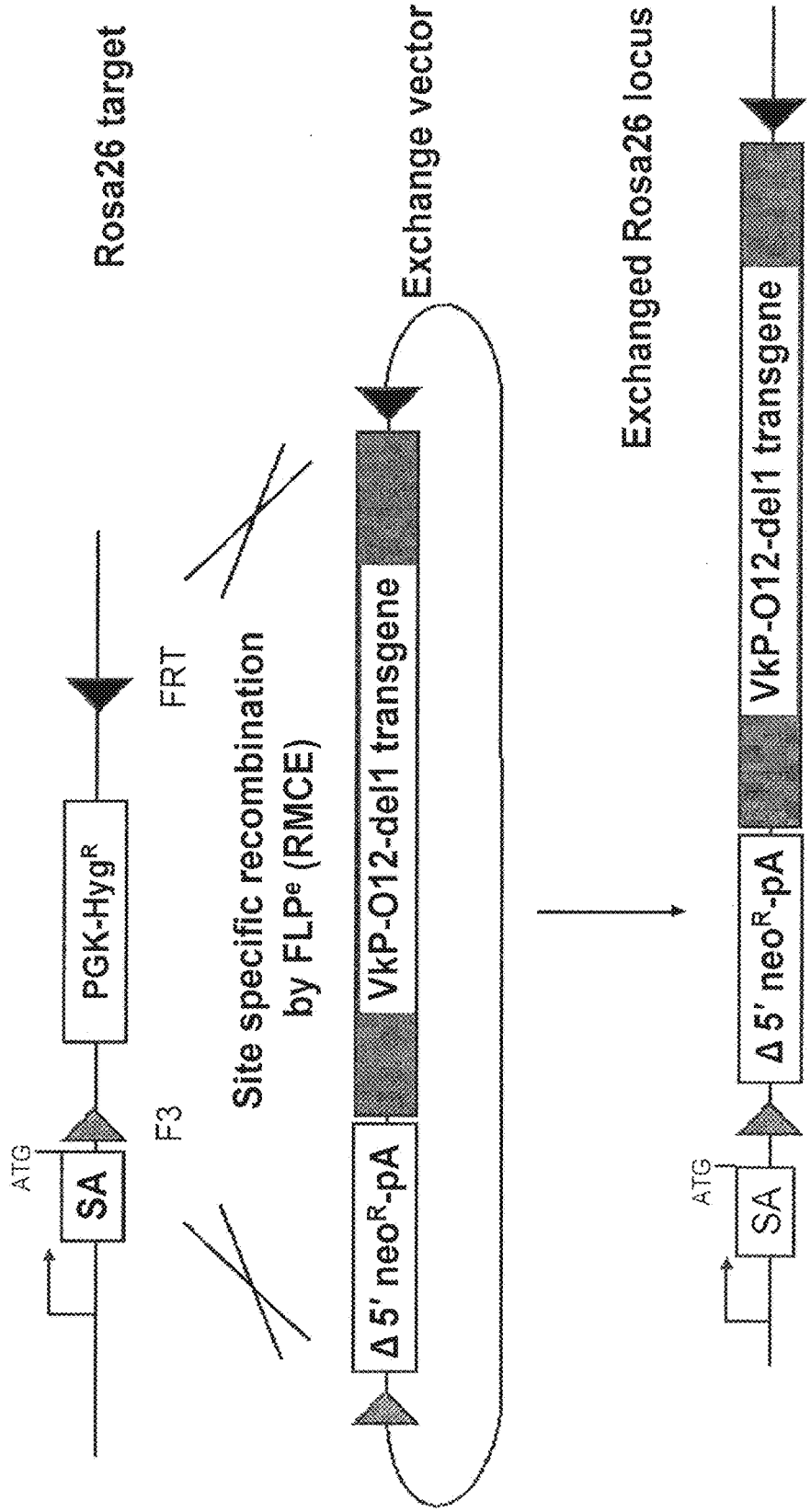

Rosa26 target
Exchange vector
Exchanged Rosa26 locus
ATG
SA
F3
PGK-Hyg^R
FRT
Site specific recombination
by FLP^e (RMCE)
Δ 5' neo^R-pA
VkP-O12-del1 transgene
ATG
SA
Δ 5' neo^R-pA
VkP-O12-del1 transgene

Fig 21B

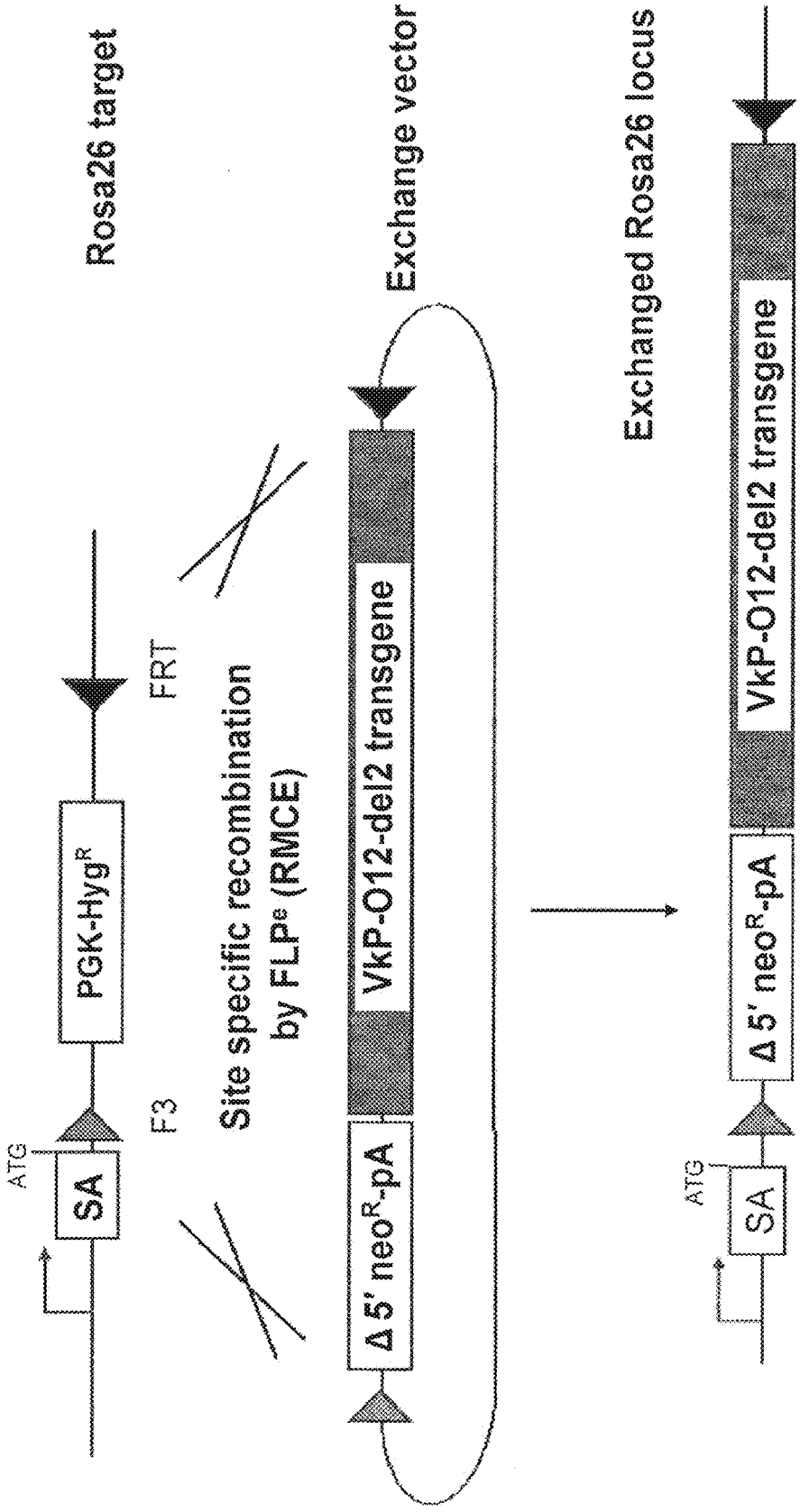

Rosa26 target
Exchange vector
Exchanged Rosa26 locus
ATG
SA
PGK-Hyg^R
FRT
F3
Site specific recombination
by FLPe (RMCE)
Δ 5' neo^R-pA
VkP-O12-del2 transgene
ATG
SA
Δ 5' neo^R-pA
VkP-O12-del2 transgene

Fig 21C

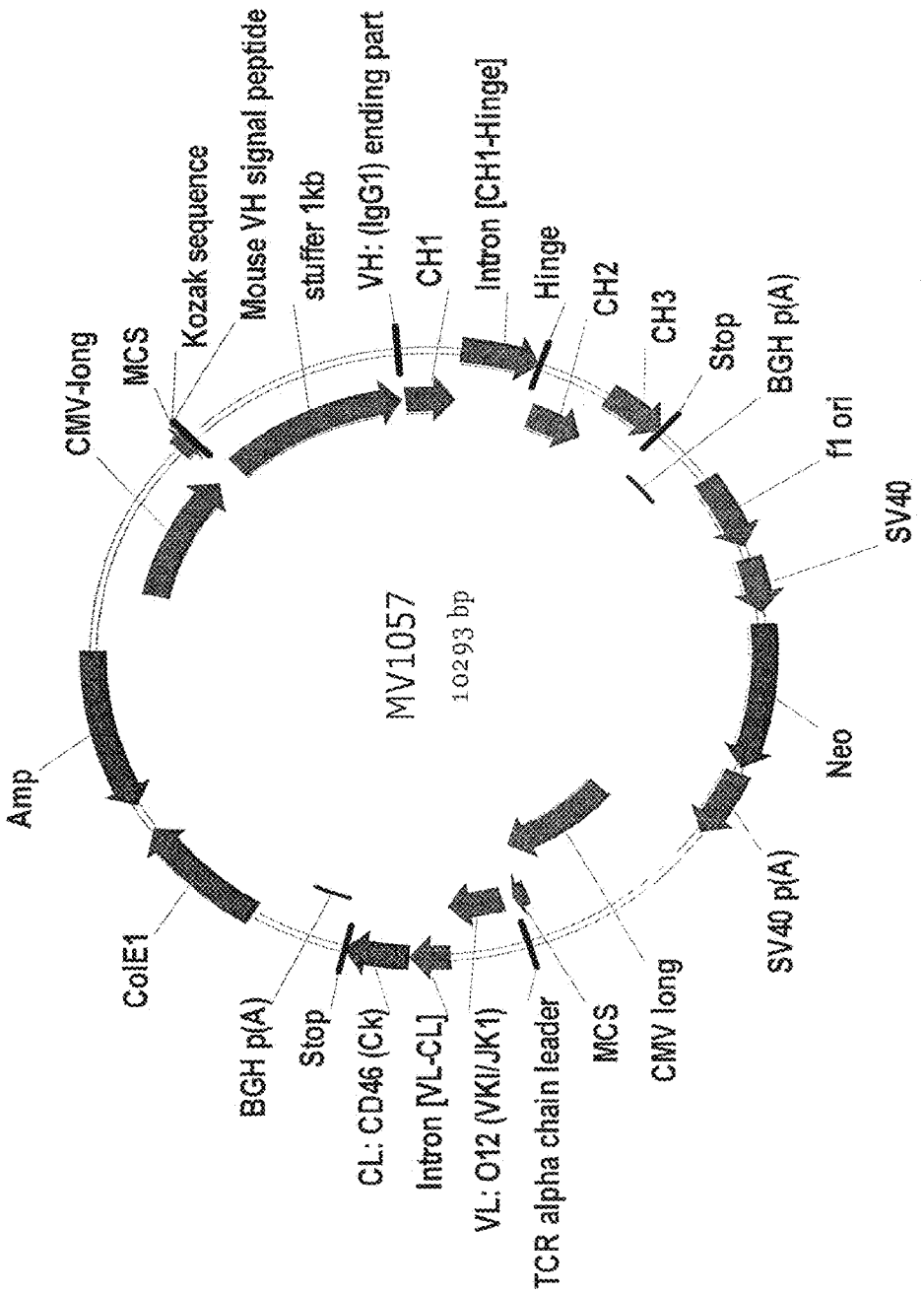

MV1057
10293 bp
CMV-long
MCS
Kozak sequence
Mouse VH signal peptide
stuffer 1kb
VH: (IgG1) ending part
CH1
Intron [CH1-Hinge]
Hinge
CH2
CH3
Stop
BGH p(A)
f1 ori
SV40
Neo
SV40 p(A)
CMV long
MCS
TCR alpha chain leader
VL: O12 (VKI/JK1)
Intron [VL-CL]
CL: CD46 (Ck)
Stop
BGH p(A)
ColE1
Amp

Fig 22

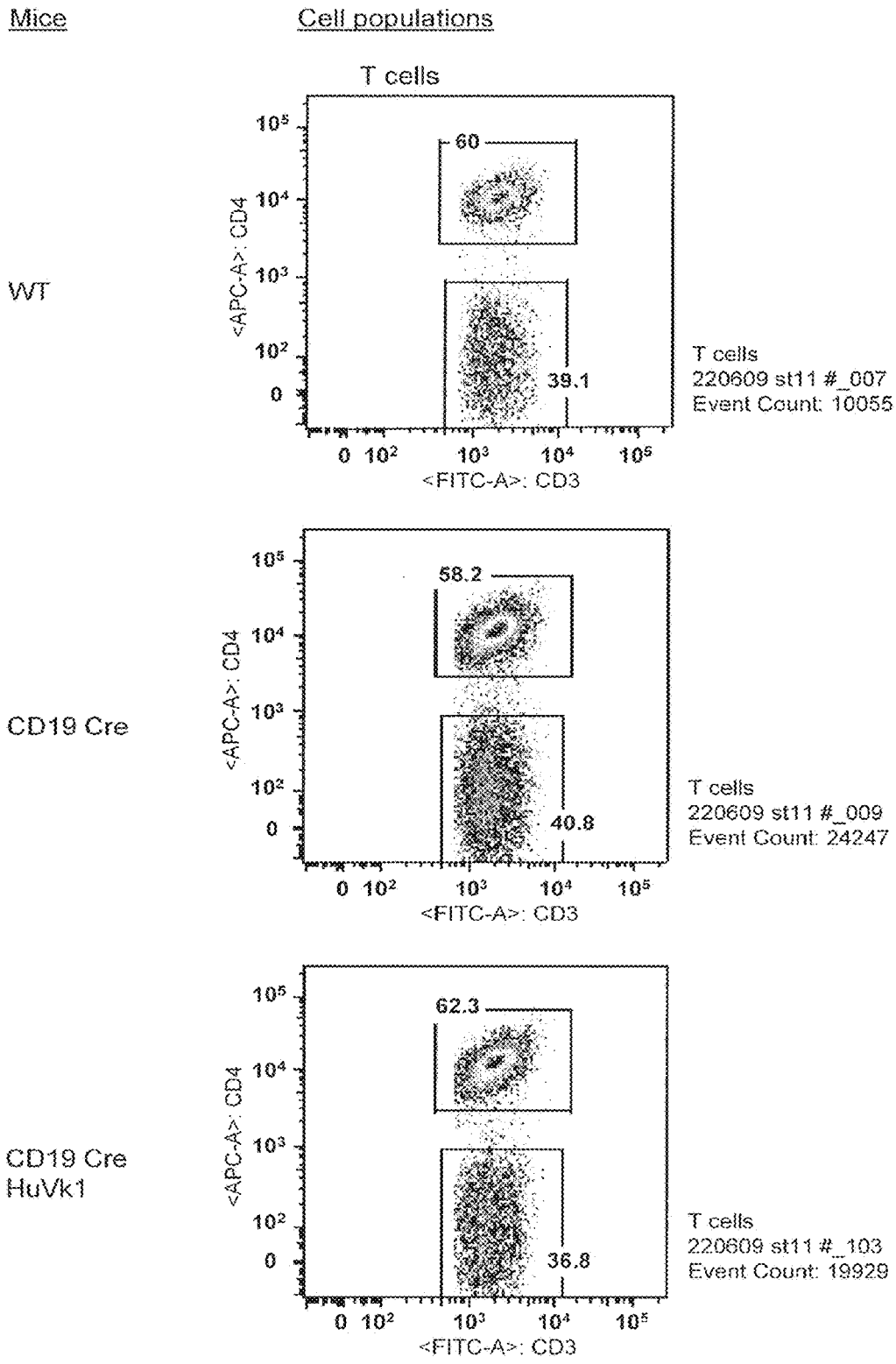

Mice
Cell populations
T cells
WT
CD19 Cre
CD19 Cre
HuVk1
<APC-A>: CD4
<FITC-A>: CD3
60
39.1
58.2
40.8
62.3
36.8
T cells
220609 st11 #_007
Event Count: 10055
T cells
220609 st11 #_009
Event Count: 24247
T cells
220609 st11 #_103
Event Count: 19929

Fig. 23

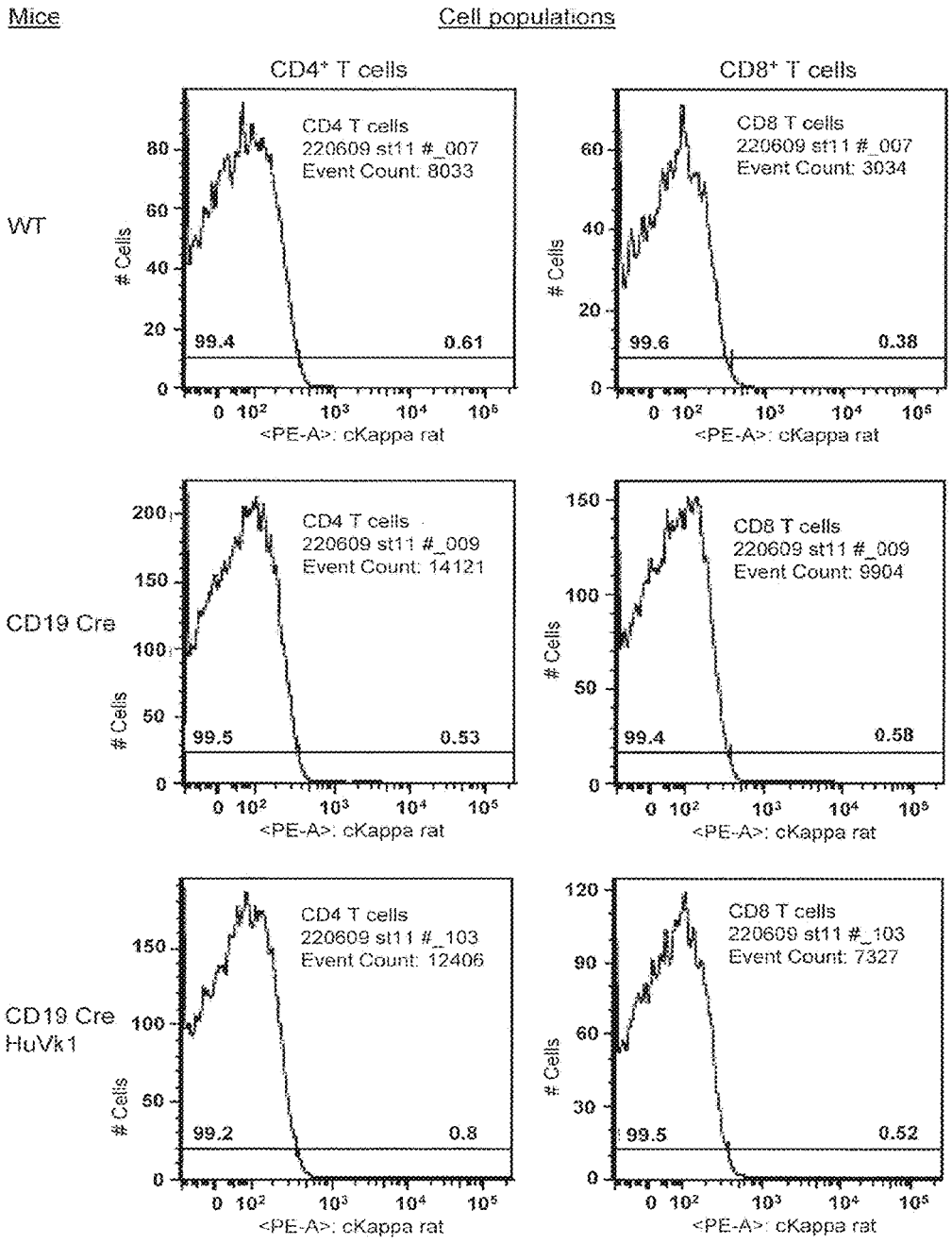

Mice
Cell populations
CD4+ T cells
CD8+ T cells
WT
CD19 Cre
CD19 Cre HuVk1
CD4 T cells 220609 st11 #_007 Event Count: 8033
CD8 T cells 220609 st11 #_007 Event Count: 3034
CD4 T cells 220609 st11 #_009 Event Count: 14121
CD8 T cells 220609 st11 #_009 Event Count: 9904
CD4 T cells 220609 st11 #_103 Event Count: 12406
CD8 T cells 220609 st11 #_103 Event Count: 7327
99.4
0.61
99.6
0.38
99.5
0.53
99.4
0.58
99.2
0.8
99.5
0.52
Cells
<PE-A>: cKappa rat

Fig. 23, contd.

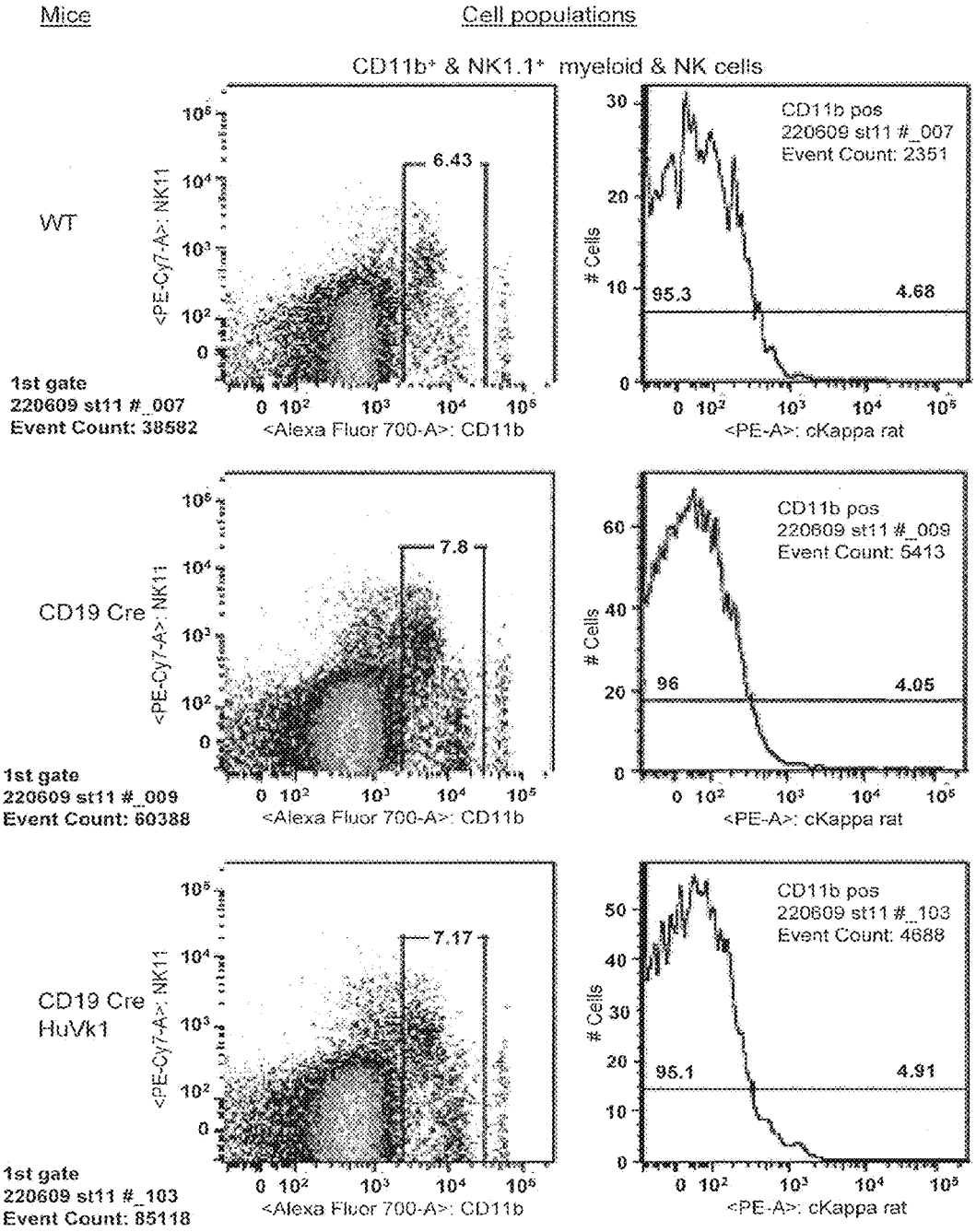

Mice
Cell populations
CD11b+ & NK1.1+ myeloid & NK cells
WT
1st gate
220609 st11 #_007
Event Count: 38582
6.43
<PE-Cy7-A>: NK11
<Alexa Fluor 700-A>: CD11b
CD11b pos
220609 st11 #_007
Event Count: 2351
95.3
4.68
Cells
<PE-A>: cKappa rat
CD19 Cre
1st gate
220609 st11 #_009
Event Count: 60388
7.8
CD11b pos
220609 st11 #_009
Event Count: 5413
96
4.05
CD19 Cre
HuVk1
1st gate
220609 st11 #_103
Event Count: 85118
7.17
CD11b pos
220609 st11 #_103
Event Count: 4688
95.1
4.91

Fig. 23, contd.

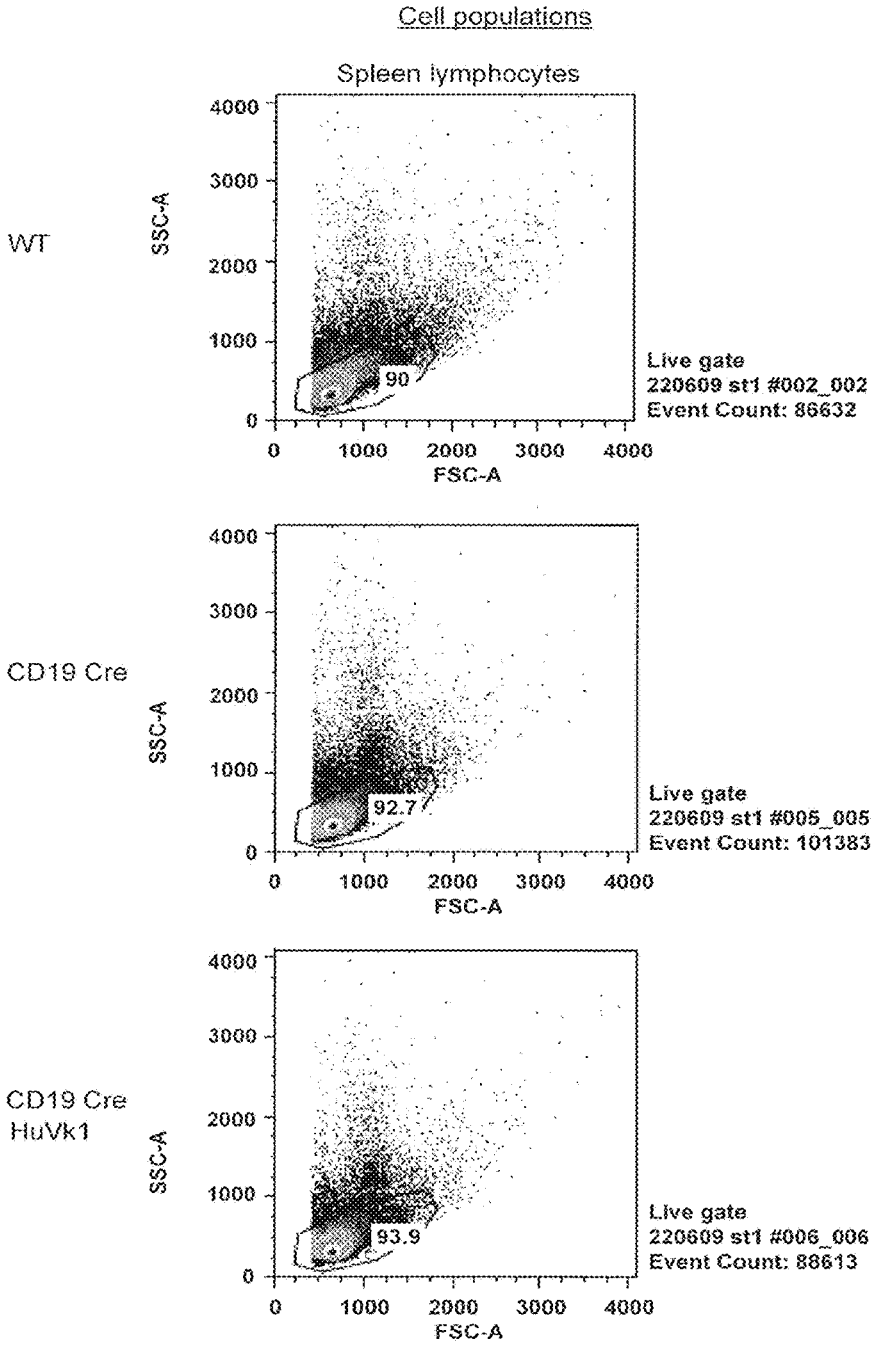

Mice
Cell populations
Spleen lymphocytes
WT
CD19 Cre
CD19 Cre
HuVk1
SSC-A
FSC-A
0
1000
2000
3000
4000
90
92.7
93.9
Live gate
220609 st1 #002_002
Event Count: 86632
Live gate
220609 st1 #005_005
Event Count: 101383
Live gate
220609 st1 #006_006
Event Count: 88613

Fig. 24

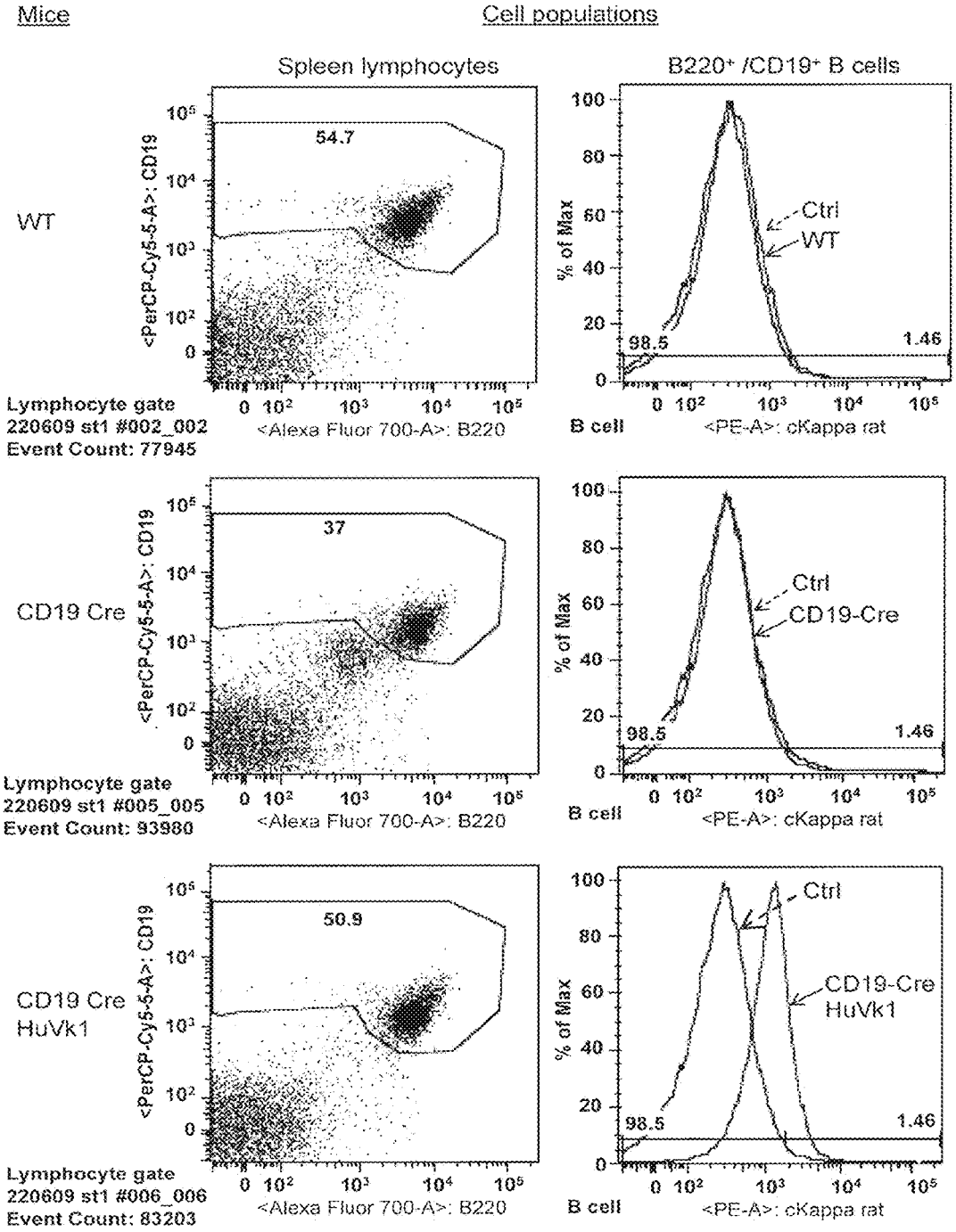

Mice
Cell populations
Spleen lymphocytes
B220+ /CD19+ B cells
WT
CD19 Cre
CD19 Cre HuVk1
54.7
37
50.9
<PerCP-Cy5-5-A>: CD19
<Alexa Fluor 700-A>: B220
% of Max
<PE-A>: cKappa rat
B cell
Ctrl
WT
CD19-Cre
HuVk1
98.5
1.46
Lymphocyte gate
220609 st1 #002_002
Event Count: 77945
Lymphocyte gate
220609 st1 #005_005
Event Count: 93980
Lymphocyte gate
220609 st1 #006_006
Event Count: 83203

Fig. 24, contd.

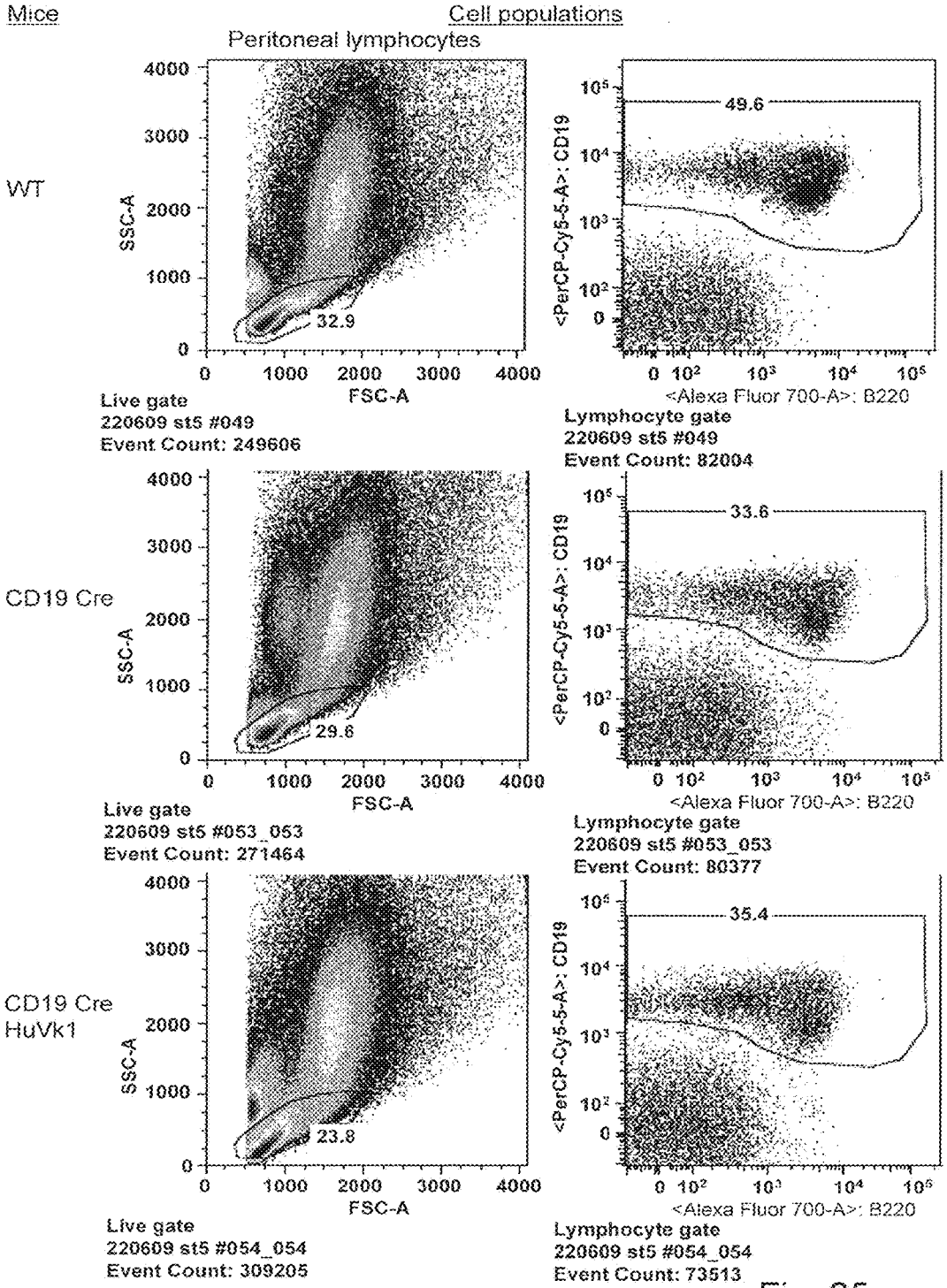

Mice
Cell populations
Peritoneal lymphocytes
WT
CD19 Cre
CD19 Cre HuVk1
SSC-A
FSC-A
32.9
Live gate
220609 st5 #049
Event Count: 249606
<PerCP-Cy5-5-A>: CD19
<Alexa Fluor 700-A>: B220
49.6
Lymphocyte gate
220609 st5 #049
Event Count: 82004
29.6
Live gate
220609 st5 #053_053
Event Count: 271464
33.6
Lymphocyte gate
220609 st5 #053_053
Event Count: 80377
23.8
Live gate
220609 st5 #054_054
Event Count: 309205
35.4
Lymphocyte gate
220609 st5 #054_054
Event Count: 73513

Fig. 25

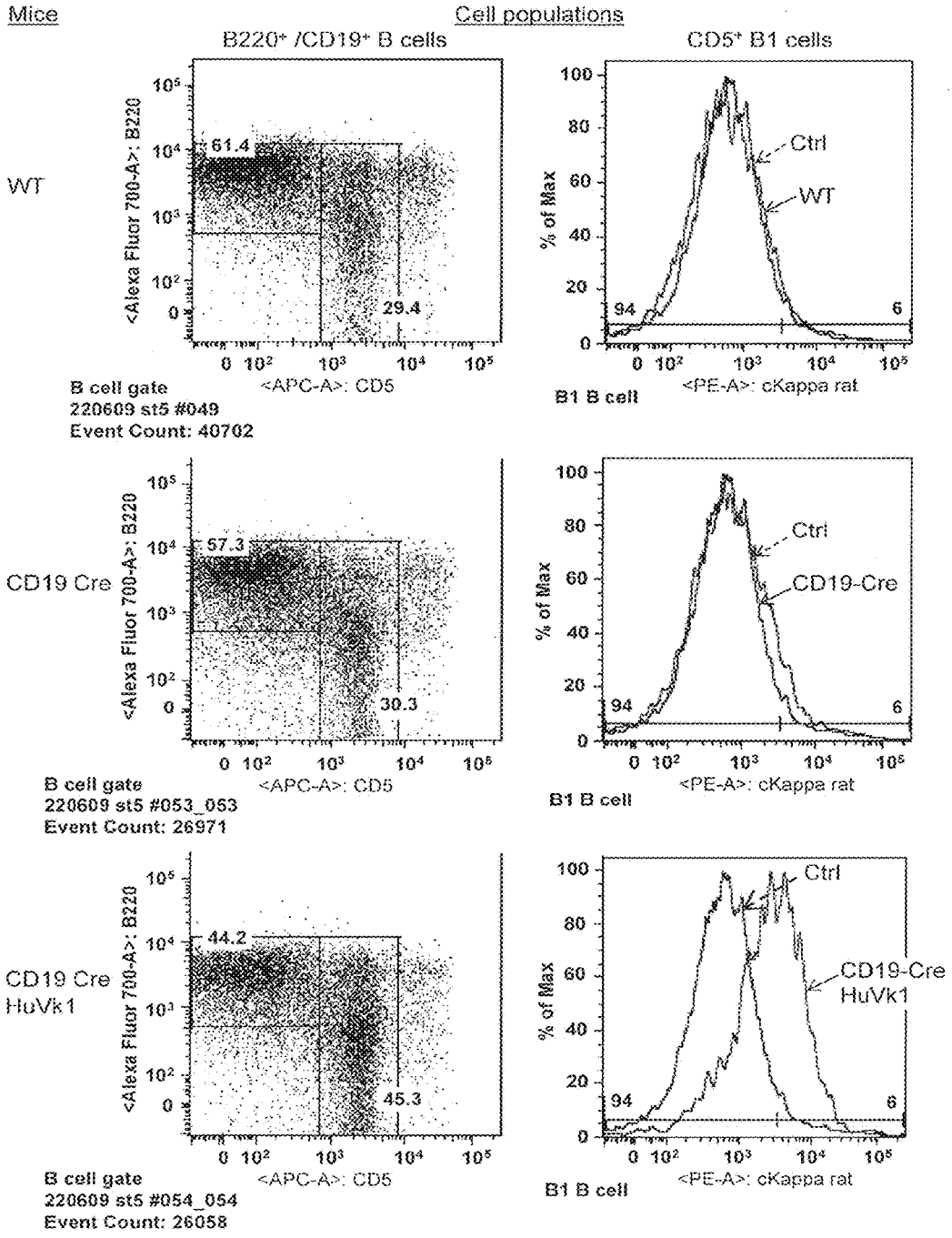

Mice
Cell populations
B220+ /CD19+ B cells
CD5+ B1 cells
WT
CD19 Cre
CD19 Cre HuVk1
<Alexa Fluor 700-A>: B220
<APC-A>: CD5
<PE-A>: cKappa rat
% of Max
61.4
29.4
57.3
30.3
44.2
45.3
Ctrl
WT
CD19-Cre
CD19-Cre HuVk1
94
6
B cell gate
220609 st5 #049
Event Count: 40702
220609 st5 #053_053
Event Count: 26971
220609 st5 #054_054
Event Count: 26058
B1 B cell

Fig. 25, contd.

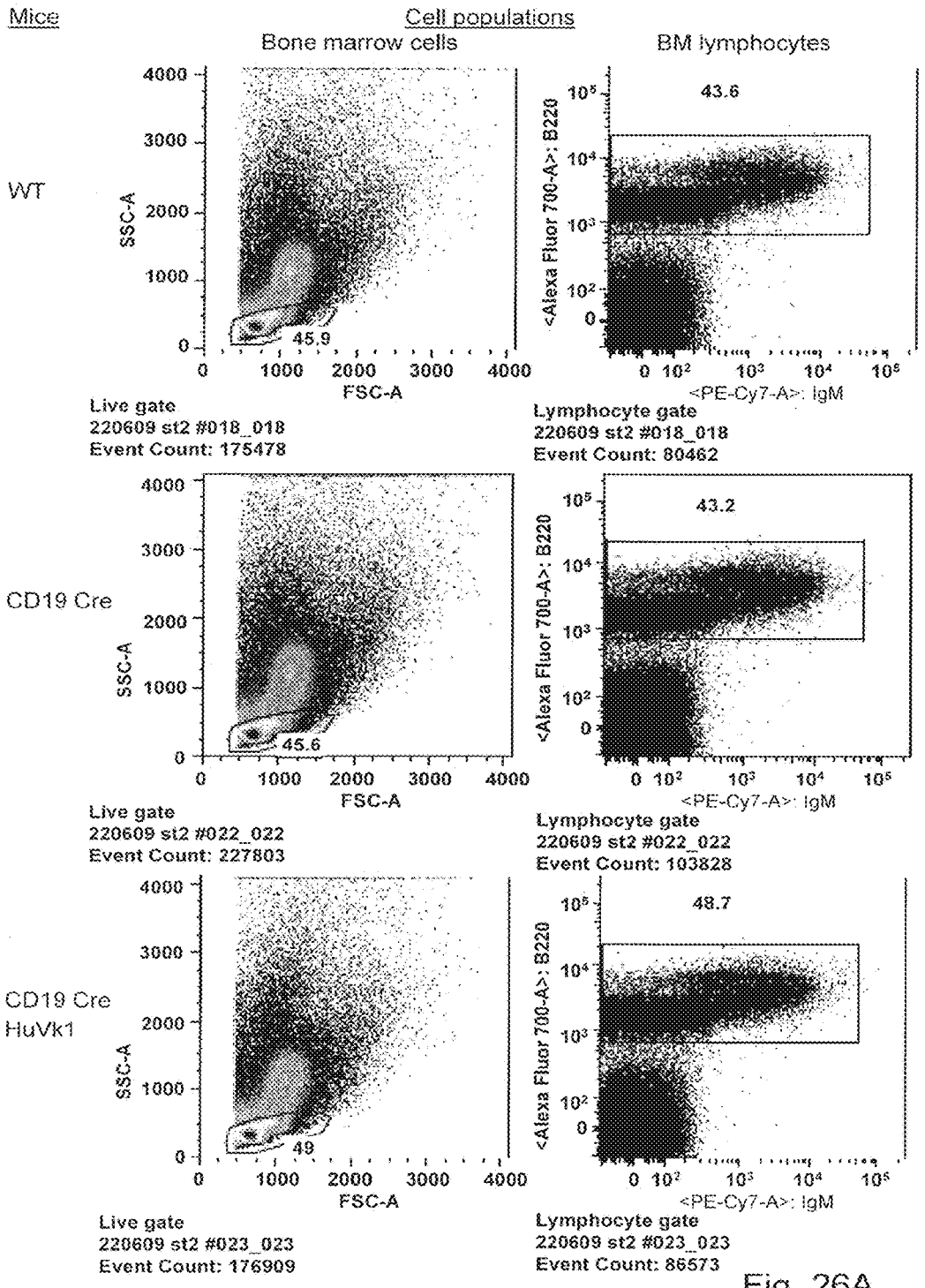

Mice
Cell populations
Bone marrow cells
BM lymphocytes
WT
CD19 Cre
CD19 Cre HuVk1
SSC-A
FSC-A
<Alexa Fluor 700-A>: B220
<PE-Cy7-A>: IgM
45.9
43.6
45.6
43.2
49
48.7
Live gate
220609 st2 #018_018
Event Count: 175478
Lymphocyte gate
220609 st2 #018_018
Event Count: 80462
Live gate
220609 st2 #022_022
Event Count: 227803
Lymphocyte gate
220609 st2 #022_022
Event Count: 103828
Live gate
220609 st2 #023_023
Event Count: 176909
Lymphocyte gate
220609 st2 #023_023
Event Count: 86573

Fig. 26A

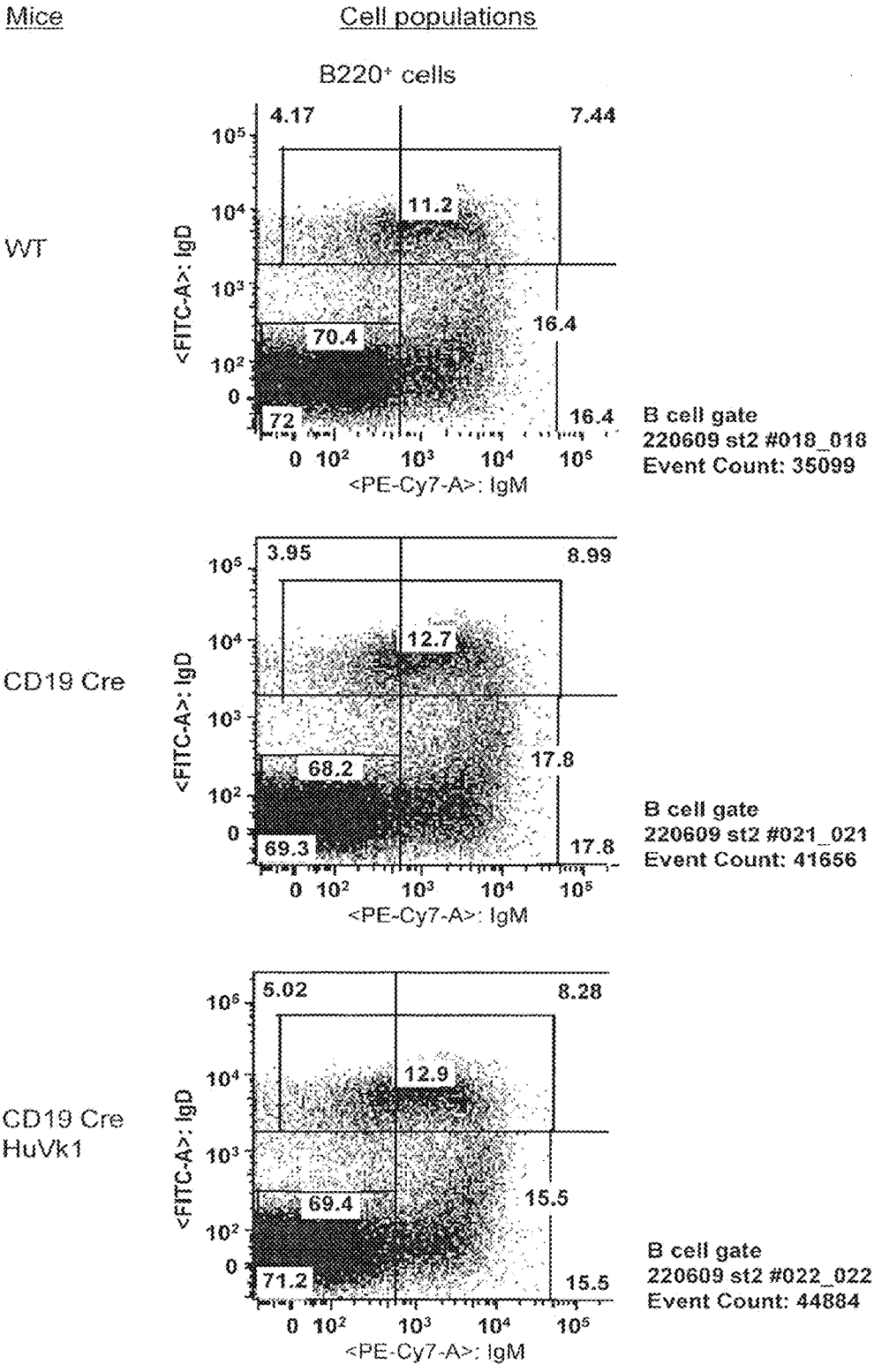


Fig. 26A, contd.

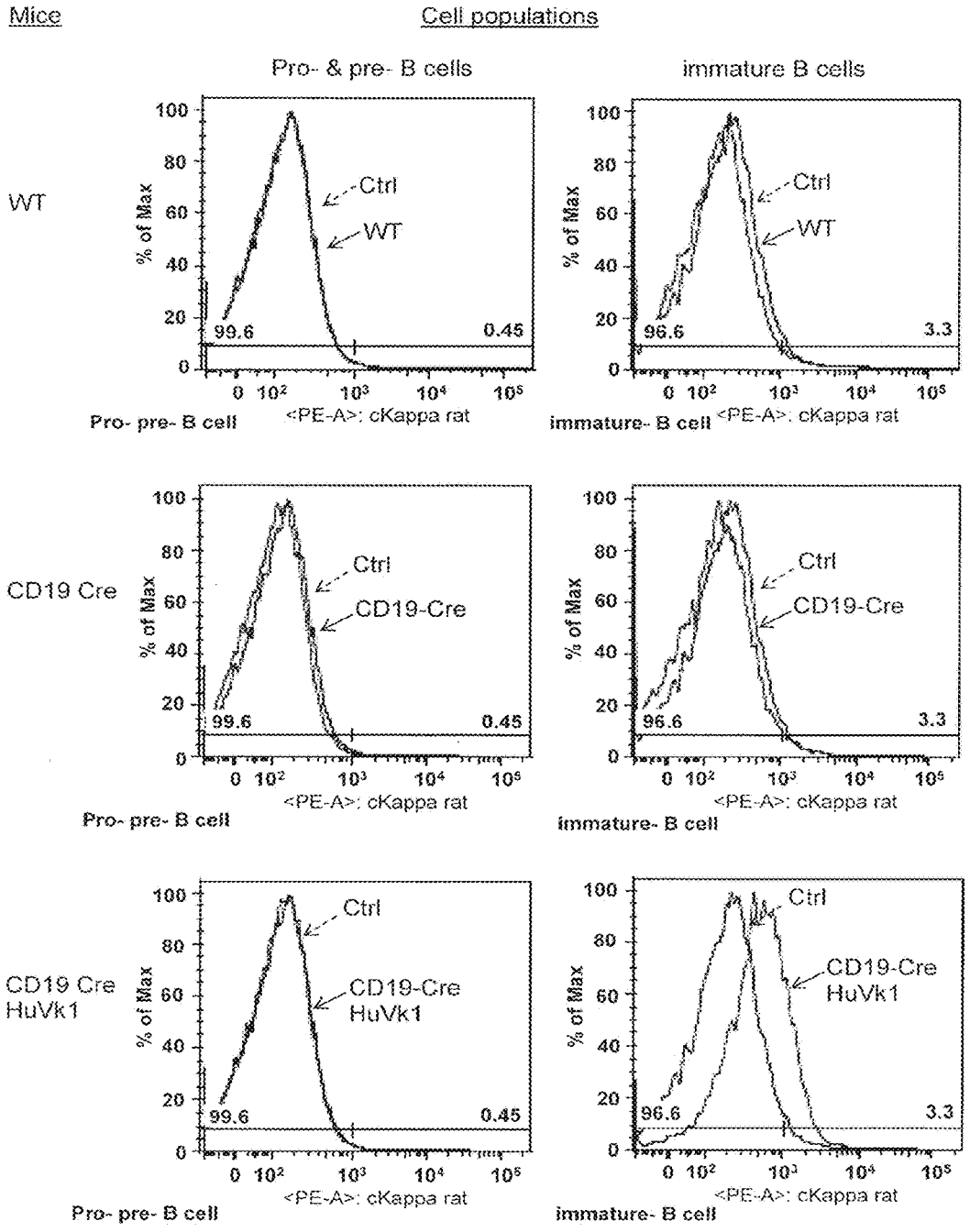

Mice
Cell populations
Pro- & pre- B cells
immature B cells
WT
CD19 Cre
CD19 Cre HuVk1
% of Max
Ctrl
WT
CD19-Cre
CD19-Cre HuVk1
99.6
0.45
96.6
3.3
<PE-A>: cKappa rat
Pro- pre- B cell
immature- B cell

Fig. 26B

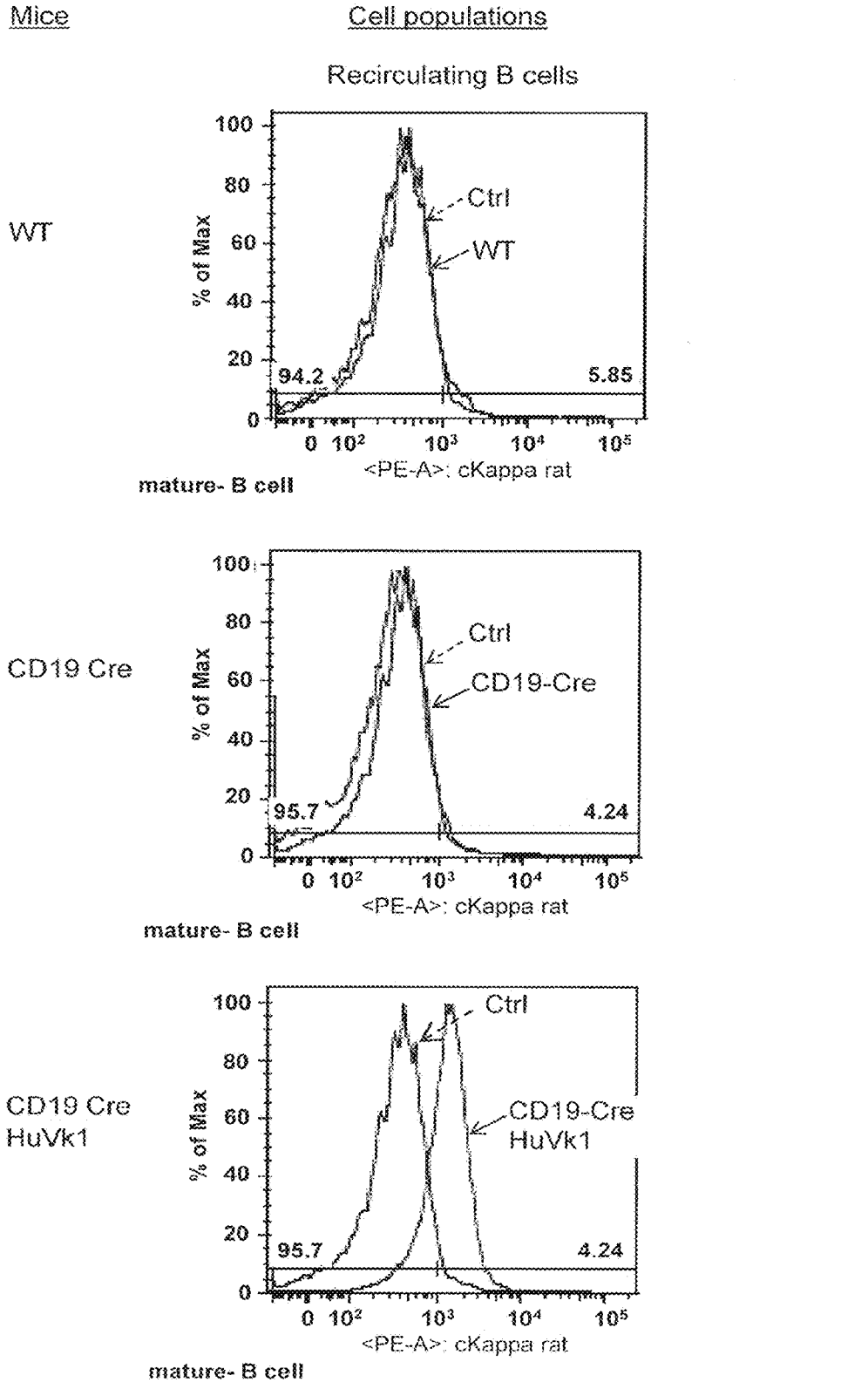


Fig. 26B, contd.

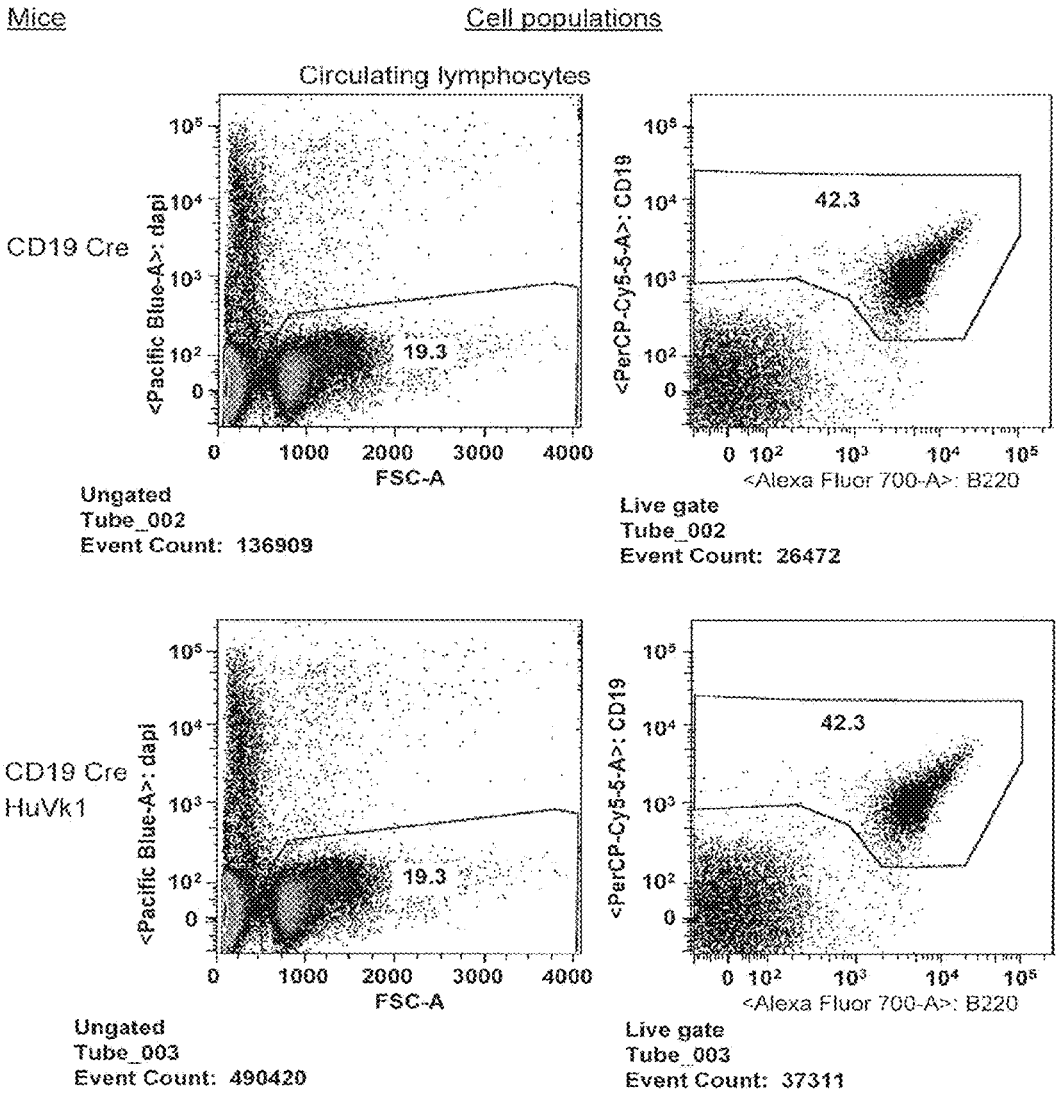

Mice
Cell populations
Circulating lymphocytes
CD19 Cre
<Pacific Blue-A>: dapi
FSC-A
19.3
Ungated
Tube_002
Event Count: 136909
<PerCP-Cy5-5-A>: CD19
<Alexa Fluor 700-A>: B220
42.3
Live gate
Tube_002
Event Count: 26472
CD19 Cre
HuVk1
Ungated
Tube_003
Event Count: 490420
Live gate
Tube_003
Event Count: 37311

Fig. 27

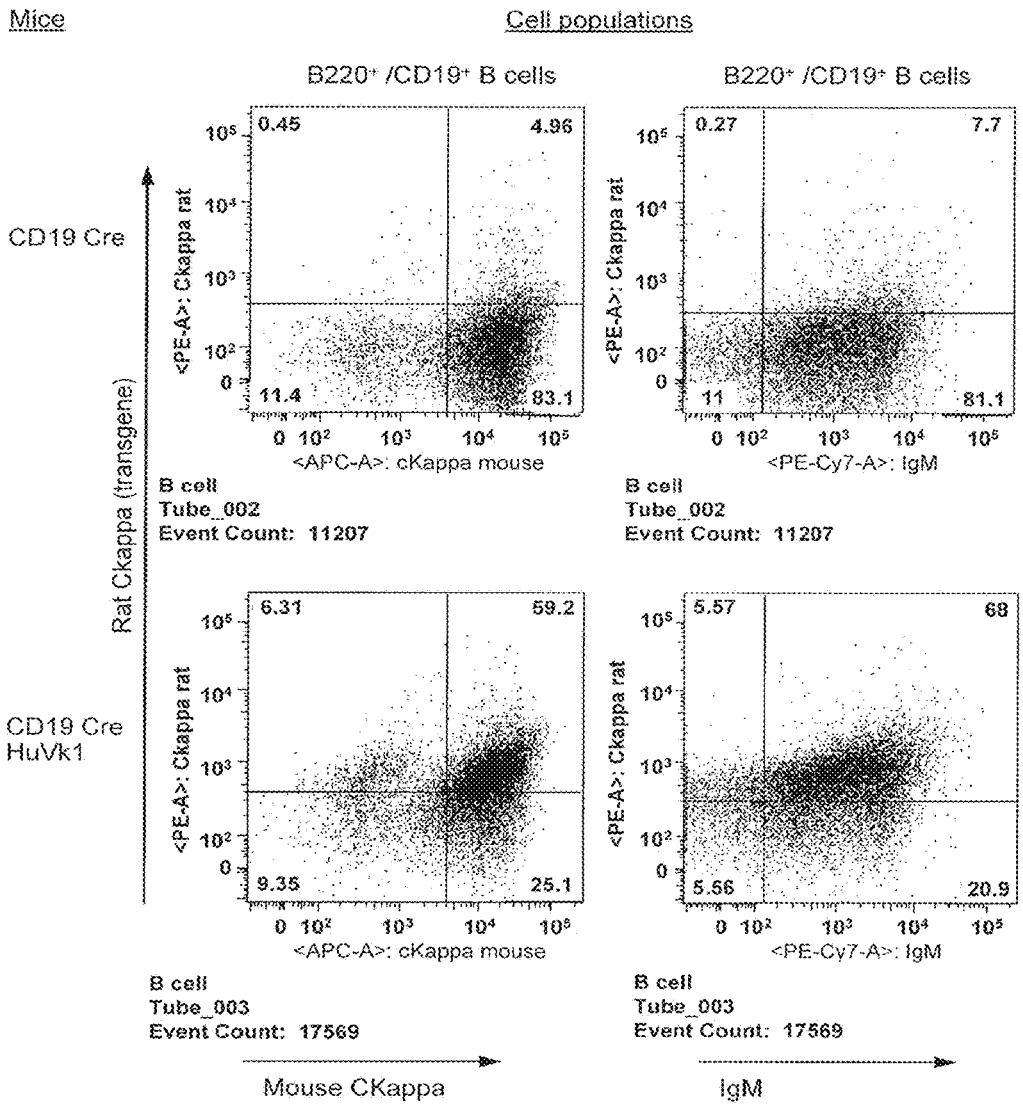

Mice
Cell populations
B220+ /CD19+ B cells
B220+ /CD19+ B cells
CD19 Cre
CD19 Cre HuVk1
Rat Ckappa (transgene)
<PE-A>: Ckappa rat
<APC-A>: cKappa mouse
<PE-Cy7-A>: IgM
0.45
4.96
11.4
83.1
0.27
7.7
11
81.1
6.31
59.2
9.35
25.1
5.57
68
5.56
20.9
B cell
Tube_002
Event Count: 11207
B cell
Tube_002
Event Count: 11207
B cell
Tube_003
Event Count: 17569
B cell
Tube_003
Event Count: 17569
Mouse CKappa
IgM

Fig. 27, contd.

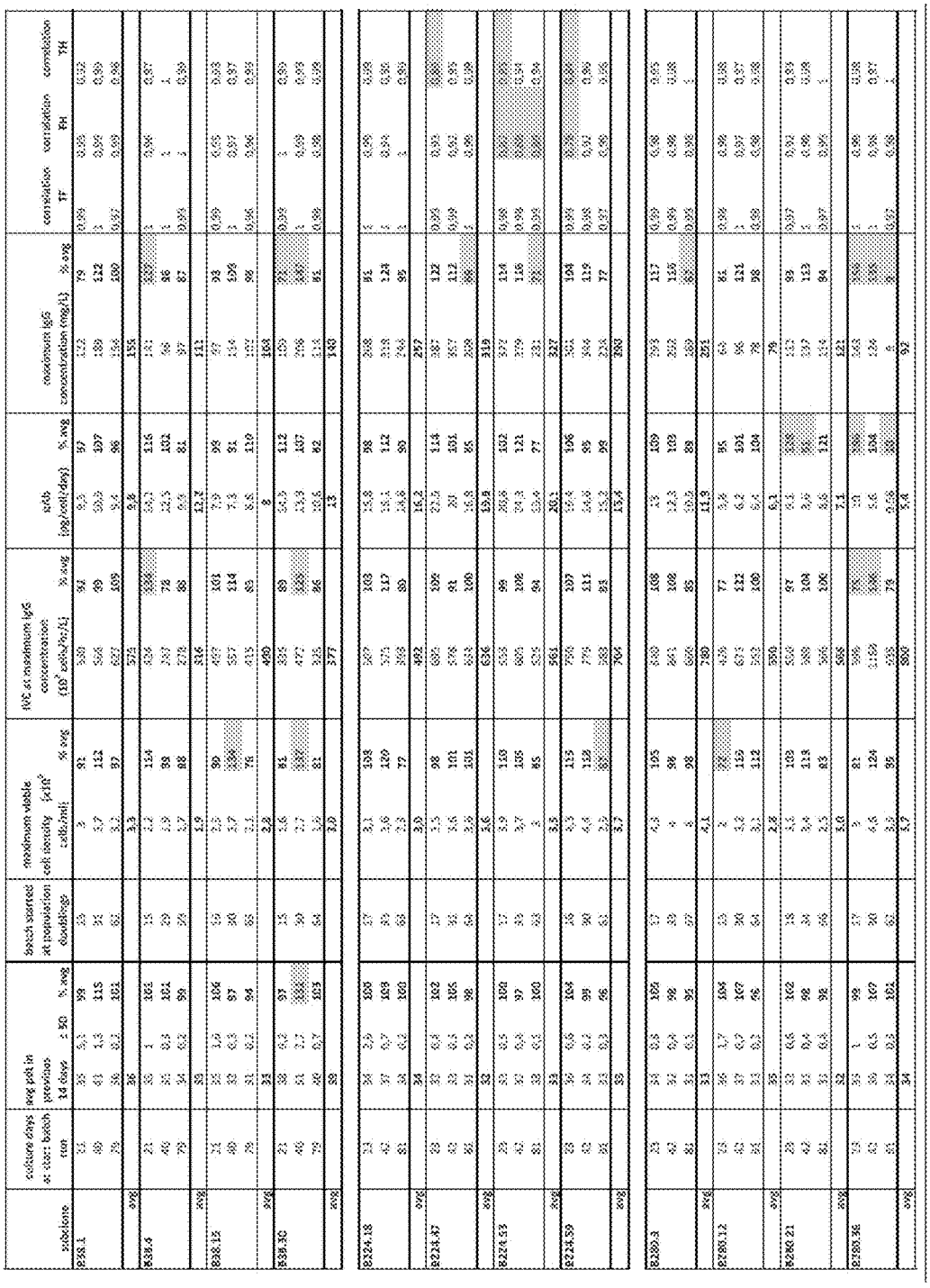


FIG. 28

	Stainings					Mixtures				
	#	Facs tubes #	Monoclonal	Work dilution		volume	1st step	2nd step	3rd step	Final diltion
A										
Spleen	1	1-8	CD21^{FITC}	640		320		0.50		
			Ckappa rat^{PE}	160			2.00			
			CD19$^{PerCP-Cy5.5}$	640				0.50		
			CD23^{PE-Cy7}	50	1:20			6.40		1000
			DAPI							
			Ckappa mouse$^{BIO-APC}$	100	1:50			3.20	APC	5000
			Clambda mouse$^{BIO-APC}$	100	1:30			3.20	APC	3000
			B220$^{Alex-700}$	160				2.00		
			FC block	400				0.80		
Spleen	2	9-16	IgD^{FITC}	640		640		1.00		
BM		17-24	Ckappa rat^{PE}	160			4.00			
			CD19$^{PerCP-Cy5.5}$	500				1.28		
			IgM^{PE-Cy7}	640				1.00		
			DAPI							
			Ckappa mouse$^{BIO-APC}$	100	1:50			6.40	APC	5000
			Clambda mouse$^{BIO-APC}$	100	1:30			6.40	APC	3000
			B220$^{Alex-700}$	160				4.00		
			FC block	400				1.60		
Spleen	3	25-32	Ckappa mouse^{FITC}	400		320		0.80		
			Ckappa rat^{PE}	160			2.00			
			CD19$^{PerCP-Cy5.5}$	500				0.64		
			IgM^{PE-Cy7}	640				0.50		
			DAPI							
			Clambda mouse$^{BIO-APC}$	100	1:30			3.20	APC	3000
			B220$^{Alex-700}$	160				2.00		
			FC block	400				0.80		
Spleen	4	33-40	Ckappa mouse^{FITC}	400		640		1.60		
		41-48	lambda^{FITC}	600				1.07		
PP			Ckappa rat^{PE}	160			4.00			
			CD19$^{PerCP-Cy5.5}$	500				1.28		

FIG. 29A

			IgM^{PE-Cy7}	640				1.00		
			DAPI							
			IgD^{A647}	1280				0.50		
			B220$^{Alex-700}$	160				4.00		
			PNA$^{BIO-SAV-APC-Cy7}$	300				2.13	APC-Cy7	
			FC block	400				1.60		
PC	5	49-56	IgM^{FITC}	160		320		2.00		
			Ckappa rat^{PE}	160			2.00			
			CD19$^{PerCP-Cy5.5}$	500				0.64		
			Ckappa mouse$^{BIO-PE-Cy7}$	100	1:50			3.20	PE-Cy7	5000
			Clambda mouse$^{BIO-PE-Cy7}$	100	1:30			3.20	PE-Cy7	3000
			DAPI							
			CD5^{APC}	320				1.00		
			B220$^{Alex-700}$	160				2.00		
			FC block	400				0.80		
BM	6	57-64	IgM^{FITC}	160		640		4.00		
			Ckappa rat^{PE}	160			4.00			
			CD19$^{PerCP-Cy5.5}$	500				1.28		
			Ckappa mouse$^{BIO-PE-Cy7}$	100	1:50			6.40	PE-Cy7	5000
			Clambda mouse$^{BIO-PE-Cy7}$	100	1:30			6.40	PE-Cy7	3000
			DAPI							
			CD25^{APC}	80				8.00		
			B220$^{Alex-700}$	160				4.00		
			FC block	400				1.60		
RAT spleen										
	7	144	Ckappa rat^{PE}	160		80	0.5			
			rat B220^{FITC}	160			0.5			
Spleen	8	97-104	cyt CD3^{FITC}	320		320		1		
			cyt Ckappa rat^{PE}	80			4.00			
			cyt CD11c$^{PE-TexasRED}$	75				4.27		
			cyt NK1.1$^{BIO-PE-Cy7}$	200				1.6	PE-Cy7	
			cyt CD19$^{PerCP-Cy5.5}$	320				1		
			cyt CD4^{APC}	500				0.64		
			cyt CD11b$^{Alex-700}$	50				6.40		

FIG. 29B

ANTIBODY PRODUCING NON-HUMAN ANIMALS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a divisional of U.S. patent application Ser. No. 12/589,181, filed Oct. 19, 2009, pending, which application is a continuation of U.S. patent application Ser. No. 12/459,285, filed Jun. 29, 2009, abandoned, which applications claim the benefit, under 35 U.S.C. § 119(e), to U.S. Provisional Patent Application Ser. No. 61/133,274, filed Jun. 27, 2008, for "Antibody Producing Non-Human Mammals," the entire contents of each of which are hereby incorporated herein by this reference.

STATEMENT ACCORDING TO 37 C.F.R. § 1.821(c) or (e)—SEQUENCE LISTING SUBMITTED AS ASCII TEXT FILE

[0002] Pursuant to 37 C.F.R. § 1.821(c) or (e), files containing a TXT version and a PDF version of the Sequence Listing have been submitted concomitant with this application, the contents of which are hereby incorporated by reference.

TECHNICAL FIELD

[0003] The invention relates to the production and use of non-human animals capable of producing antibodies or derivatives thereof, which are expressed from at least partially exogenous nucleic acids (transgenes). Transgenes to produce such transgenic animals and methods to produce such heterologous antibodies; methods and vectors for producing such transgenic animals are disclosed.

BACKGROUND

[0004] B cells mediate humoral immunity by producing specific antibodies. The basic structural subunit of an antibody (Ab) is an immunoglobulin (Ig) molecule. Ig molecules consist of a complex of two identical heavy (H) and two identical light (L) polypeptide chains. At the amino terminus of each H chain and L chain is a region that varies in amino acid sequence named the variable (V) region. The remaining portion of the H and L chains is relatively constant in amino acid sequence and is named the constant (C) region. In an Ig molecule, the H and L chain V regions (VH and VL) are juxtaposed to form the potential antigen-binding site. The genes that encode H and L chain V regions are assembled somatically from segments of germline DNA during precursor B (pre-B) cell differentiation: V, D and J gene segments for the H chain and V and J gene segments for the L chain. Within Ig V regions are three regions of greatest amino acid sequence variability that interact to form the antigen-recognition site and are thus referred to as complementarity determining regions (CDRs).

[0005] The V gene segment encodes the bulk of the V region domain, including CDR1 and CDR2. Diversity in CDR1 and CDR2 derives from sequence heterogeneity among multiple different germline-encoded V segments. CDR3 is encoded by sequences that are formed by the joining of H chain V, D, and J gene segments and L chain V and J segments and by mechanisms that create nucleotide sequence heterogeneity where these segments are combined. Additional diversity may be derived from pairing of different H and L chain V regions. Collectively these processes yield a primary repertoire of antibodies encoded by germline gene segments and expressed by newly formed B cells.

[0006] An additional source of antibody diversity is imposed on top of the diversity generated by recombination of Ig gene segments. B cells are able to introduce mutations into the antibody V regions that they express, a process called somatic hypermutation. Thus, when an animal first encounters an antigen, the antigen binds to a specific B cell which happens to carry antibodies which have a V domain which binds the antigen. This primary response may activate this B cell to go on to secrete the cognate antibody. These activated B cells can also now target a somatic mutation process to their rearranged antibody gene segments and thus allow the production of daughter cells which make variants of the antibodies of the primary response. A selection process amplifies those variant B cell descendants which make an antibody of improved affinity of the antigen. In B cells, somatic hypermutations are targeted to a restricted genomic region including both the rearranged VH and VL genes. Thus somatic mutation allows affinity maturation—the production and selection of high affinity antibodies. Therefore, somatic mutation is important for the generation of high affinity antibodies.

[0007] The exquisite specificity and high affinity of antibodies and the discovery of hybridoma technology allowing the generation of monoclonal antibodies (mAbs) has generated great expectations for their utilization as targeted therapeutics for human diseases. MAbs are identical because they are produced by a single B cell and its progeny. MAbs are made by fusing the spleen cells from a mouse that has been immunized with the desired antigen with myeloma cells to generate immortalized hybridomas. One of the major impediments facing the development of in vivo applications for mAbs in humans is the intrinsic immunogenicity of non-human Igs. Patients respond to therapeutic doses of mouse mAbs by making antibodies against the mouse Ig sequences (Human Anti Mouse Antibodies; HAMA), causing acute toxicity, alter their biodistribution and accelerate clearance, thus reducing the efficacy of subsequent administrations (Mirick et al. (2004), *Q. Nucl. Med. Mol. Imaging* 48:251-257).

[0008] To circumvent the generation of HAMA, antibody humanization methods have been developed in an attempt to produce mAbs with decreased immunogenicity when applied to humans. These endeavors have yielded various recombinant DNA-based approaches aimed at increasing the content of human amino acid sequences in mAbs while retaining the specificity and affinity of the parental non-human antibody. Humanization began with the construction of mouse-human chimeric mAbs (S. L. Morrison et al. (1984), *Proc. Natl. Acad. Sci. USA* 81:6851-5), in which the Ig C regions in murine mAbs were replaced by human C regions. Chimeric mAbs contain 60-70% of human amino acid sequences and are considerably less immunogenic than their murine counterparts when injected into humans, albeit that a human anti-chimeric antibody response was still observed (W. Y. Hwang et al. (2005), *Methods* 36:3-10).

[0009] In attempts to further humanize murine mAbs, CDR grafting was developed. In CDR grafting, murine antibodies are humanized by grafting their CDRs onto the VL and VH frameworks of human Ig molecules, while retaining those murine framework residues deemed essential for specificity and affinity (P. T. Jones et al. (1986), *Nature* 321:522). Overall, CDR-grafted antibodies consist of more

than 80% human amino acid sequences (C. Queen et al. (1989), *Proc. Natl. Acad. Sci. U.S.A.* 86:10029; P. Carter et al. (1992), *Proc. Natl. Acad. Sci. U.S.A.* 89:4285). Despite these efforts, CDR-grafted, humanized antibodies were shown to still evoke an antibody response against the grafted V region (W. Y. Hwang et al. (2005), *Methods* 36:3).

[0010] Subsequently to CDR grafting, humanization methods based on different paradigms such as resurfacing (E. A. Padlan et al. (1991), *Mol. Immunol.* 28:489), superhumanization (P. Tan D. A. et al. (2002), *J. Immunol.* 169:1119), human string content optimization (G. A. Lazar et al. (2007), *Mol. Immunol.* 44:1986) and humaneering have been developed in an attempt to further decrease the content of non-human sequences in therapeutic mAbs (J. C. Almagro et al. (2008), *Frontiers in Bioscience* 13:1619). As in CDR grafting approaches, these methods rely on analyses of the antibody structure and sequence comparison of the non-human and human mAbs in order to evaluate the impact of the humanization process into immunogenicity of the final product. When comparing the immunogenicity of chimeric and humanized antibodies, humanization of variable regions appears to decrease immunogenicity further (W. Y. Hwang et al. (2005), *Methods* 36:3-10).

[0011] De-immunization is another approach developed to reduce the immunogenicity of chimeric or mouse antibodies. It involves the identification of linear T-cell epitopes in the antibody of interest, using bioinformatics, and their subsequent replacement by site-directed mutagenesis to human or non-immunogenic sequences (WO 9852976 A1, the contents of which are incorporated by this reference). Although de-immunized antibodies exhibited reduced immunogenicity in primates, compared with their chimeric counterparts, some loss of binding affinity was observed (M. Jain et al. (2007), *Trends in Biotechnol.* 25:307).

[0012] The development of phage display technology complemented and extended humanization approaches in attempts to obtain less immunogenic mAbs for therapy in humans. In phage display, large collections ("libraries") of human antibody VH and VL regions are expressed on the surface of filamentous bacteriophage particles. From these libraries, rare phages are selected through binding interaction with antigen; soluble antibody fragments are expressed from infected bacteria and the affinity of binding of selected antibodies is improved by mutation (G. Winter et al. (1994), *Annu. Rev. Immunol.* 12:433). The process mimics immune selection, and antibodies with many different bindings specificities have been isolated using this approach (H. R. Hoogenboom et al. (2005), *Nat. Biotechnol.* 23:1105). Various sources of H and L chain V regions have been used to construct phage display libraries including those isolated from non-immune or immune donors. In addition, phage display libraries have been constructed of V regions that contain artificially randomized synthetic CDR regions in order to create additional diversity. Often, antibodies obtained from phage display libraries are subjected to in vitro affinity maturation to obtain high affinity antibodies (H. R. Hoogenboom et al. (2005), *Nat. Biotechnol.* 23:1105).

[0013] The creation of transgenic mouse strains producing human antibodies in the absence of mouse antibodies has provided another technology platform for the generation of specific and high affinity human mAbs for application in humans. In these transgenic animals, the endogenous mouse antibody machinery is inactivated and replaced by human Ig loci to substantially reproduce the human humoral immune system in mice (A. Jakobovits et al. (2007), *Nat. Biotechnol.* 25:1134; N. Lonberg (2005), *Nat. Biotechnol.* 23:1117). B cell development as well as Ig diversification by recombination of gene segments is faithfully reproduced in these mice, leading to a diverse repertoire of murine B cells expressing human Igs. By immunizing these mice with antigens, it was further demonstrated that these transgenic animals accumulated somatic mutations in the V regions of both heavy and light chains to produce a wide diversity of high-affinity human mAbs (N. Lonberg (2005), *Nat. Biotechnol.* 23:1117).

[0014] The question, whether "fully human" mAbs such as derived from phage display libraries or transgenic mice are less immunogenic than humanized mAbs cannot be answered yet, because full immunogenicity data are available for just two human mAbs. An anti-tumor necrosis factor mAb, developed from phage-displayed human libraries induced antibody responses in 12% of patients—at the higher end of the incidence of anti-antibody responses of the humanized antibodies (W. Y. Hwang et al. (2005), *Methods* 36:3-10).

[0015] Evaluation of the immunogenicity of the first registered human mAb generated by the transgenic approach demonstrated that mAb treatment resulted in the generation of antibodies in approximately 5.5% of treated cancer patients (A. Jakobovits et al. (2007), *Nat. Biotechnol.* 25:1134; J. A. Lofgren et al. (2007), *J. Immunol.* 178:7467).

DISCLOSURE OF THE INVENTION

[0016] Disclosed are a method and means for producing antibodies that are specific for their targets, but are less immunogenic. Described herein, the reduction of immunogenicity is at least partially achieved by providing a transgenic non-human mammal comprising, at least in its B cell lineage, a nucleic acid encoding at least an immunoglobulin light chain or heavy chain, wherein the heavy- or light chain encoding sequence is provided with a means that renders it resistant to DNA rearrangements and/or somatic hypermutations, preferably such a non-human animal is a rodent, more specifically a mouse. In certain embodiments, the nucleic acid encodes a human, human-like, or humanized immunoglobulin chain.

[0017] In the remainder of this specification, mice are typically used as examples of the non-human mammals. The transgenic, non-human, mammalian hosts are capable of mounting an immune response to an antigen, where the response produces antibodies having primate, particularly human, variable regions. Various transgenic hosts may be employed, particularly murine, lagomorpha, ovine, avine, porcine, equine, canine, feline, or the like. Mice have been used for the production of B-lymphocytes for immortalization for the production of antibodies. Since mice are easy to handle, can be bred in large numbers, and are known to have an extensive immune repertoire, mice will usually be the animal of choice. Therefore, in the following discussion, the discussion will refer to mice, but it should be understood that other animals, particularly non-primate mammals, may be readily substituted for the mice, following the same procedures.

[0018] The reason for preventing rearrangements and hypermutation is that in this manner a non-immunogenic polypeptide can be chosen beforehand knowing that this polypeptide chain will remain non-immunogenic. At least one of the chains of the resulting immunoglobulin is thus

less immunogenic. The resulting antibody needs to have (usually) both a light- and a heavy chain. The non-immunogenic chain must therefore be capable of pairing with the other chain. The other chain may be an endogenous chain, an exogenous chain or a hybrid of both. For human therapy, the non-immunogenic chain should be as close to human as possible.

[0019] A means for rendering a gene encoding an immunoglobulin chain (or chains) resistant to DNA rearrangement and/or mutation is of course removal of all genetic elements responsible for the rearrangement and/or mutation. The drawback thereof is that the variability of the two chains is eliminated, whereas the invention preferably retains the variability in one chain (preferably the heavy chain) and inhibits and/or prevents the rearrangement-mutation of the other chain (preferably the light chain).

[0020] The elements for rearrangement and/or hypermutation characterized so far are located within the loci for immunoglobulins. Therefore the means for rendering the immunoglobulin encoding sequence resistant to DNA rearrangement and/or mutation is inserting the gene in a locus outside the immunoglobulin loci.

[0021] Thus, described herein, a transgenic non-human mammal is provided wherein the light/heavy chain encoding sequence is integrated in the genome of the non-human mammal in a locus outside the immunoglobulin loci. Preferably the insertion is in a locus that is resistant to gene silencing. Described herein, the integration is in the Rosa-locus or a comparable locus.

[0022] In certain embodiments, provided is an expression cassette that can be inserted into a Rosa locus or comparable locus with a means that allows expression of the immunoglobulin chain(s) essentially limited to cells of B cell lineage, preferably with a means that allows expression of the light chain encoding nucleic acid during a certain stage of the development of B cells. The term "essentially limited expression" indicates that expression is predominantly in cells of the B-cell lineage, but that lower levels of expression in other cells, as compared to the level of expression in B-cells, is possible. In certain embodiments, the term "essentially limited expression" indicates that the expression is exclusively present in cells of the B-cell lineage. Such means typically and preferably include B cell (developmental stage) specific promoters such as CD19, CD20, μHC (all V-genes), VpreB1, VpreB2, VpreB3, λ5, Igα, Igβ, κLC (all genes), λLC (all genes), BSAP (Pax5). Although it is very well possible to direct the expression of the DNA rearrangement and/or mutation resistant chain by such promoters, they are relatively weak. A strong promoter will typically be required to ensure adequate surface expression of the B cell receptor (made up of the membrane attached Ig H and L chain) and to compete with the expression and pairing of endogenous chains (if present) through allelic exclusion. Such a promoter, however is usually not tissue specific. To confer tissue specificity, an indirect system employing Cre/lox or the like is preferred. The desired chain is put under control of a strong promoter inhibited by an element that can be removed by the action of a Cre-protein, leading to activation of the desired immunoglobulin encoding gene. This system is described in detail in F. T. Wunderlich (2004), "Generation of inducible Cre systems for conditional gene inactivation in mice," Inauguraldissertation zur Erlangung des Doktorgrades der Mathematisch-Naturwissenschaftlichen Fakultät der Universität zu Köln; on the internet at deposit. ddb.de/cgi-bin/dokserv?idn=97557230x&dok_var=d1&dok_ext=pdf&filename=975572 30x. pdf.

[0023] Preferably the immunoglobulin chain produced in a manner resistant to rearrangements and hypermutation is a light chain capable of pairing with different heavy chains encoded by the non-human mammal. The light chain will then be the same (and less immunogenic) in all antibodies, but variety in specificity is retained through rearrangements and hypermutations in the heavy chains. It may in that case be preferable to silence at least one of the endogenous loci encoding a light chain, although allelic exclusion may render this unnecessary.

[0024] According to this embodiment, preferably the endogenous kappa (κ) light chain locus is functionally silenced.

[0025] If the endogenous κ light chain locus is silenced, but also for other reasons, it is preferred that the resistant light chain is a κ light chain, preferably a light chain that has a germline-like sequence. Described herein such a light chain would lead to an antibody with reduced immunogenicity. The preferred germline sequence is based on the human IGKV1-39 (O12) as this light chain is very frequently observed in the human repertoire (de Wildt et al. 1999, *J Mol. Biol.* 285(3):895 and has superior thermodynamic stability, yield and solubility (Ewert et al. 2003, *J. Mol. Biol.* 325(3):531).

[0026] The following gives more specific embodiments of the expression cassette with which the non-human animal can be provided described herein. Although this is typically advantageous for immunoglobulins, other genes of interest are also contemplated.

[0027] Thus, provided in a specific embodiment is a transgenic non-human mammal wherein the light chain encoding nucleic acid comprises in 5'-3' direction: a B cell specific promoter, a leader, a rearranged human V gene, optionally a mouse κ-intron enhancer (MoEκi), a constant region (κ) and optionally a (truncated) mouse κ-3' enhancer (MoEκ3'). Neuberger identified and examined a novel B-cell specific enhancer located downstream of the kappa constant region (Neuberger, EP 00469025 B 1, the contents of which are incorporated herein by this reference). This enhancer has been shown to play a crucial role in the expression of kappa genes as removal of the 808 bp enhancer strongly reduced expression. Deletion of the 3' kappa enhancer also strongly reduced the level of somatic hypermutations (SHM). In transgenic and cell expression studies. it has been revealed that reduced, mutated or deleted 3' kappa enhancers not only lowered expression levels but also decreased the level of somatic hypermutations. Currently, it cannot be determined whether the 3' kappa enhancer is involved in SHM processes, expression regulation or both (review V. H. Odegard et al. (2006), *Nat. Rev. Immunol.* 6:573; M. Inlay et al. (2002), *Nat. Immunol.* 3:463).

[0028] Detailed expression studies using engineered variants of the 3' kappa enhancer indicated that a 50 nucleotide region is sufficient to drive expression. However for proper expression a reduced sequence of 145 nucleotides is preferred (EP04690251; K. B. Meyer et al. (1990), *Nucleic Acids Res.* 18(19):5609-15).

[0029] Thus, the invention in one aspect provides a nucleic acid for insertion into the genome of a non human animal that is an expression cassette for the expression of a desired proteinaceous molecule in cells developing into mature B cells during a certain stage of development, the

cassette comprising means for preventing silencing of expression of the desired proteinaceous molecule after introduction into a host cell, and means for timing expression of the desired proteinaceous molecule with the desired developmental stage of the host cell.

[0030] An expression cassette is defined as a nucleic acid that has been provided with means for introduction into the genome of a host cell, such as sequences which allow for homologous recombination with a certain site in the genome. Usually the nucleic acid will be DNA, typically double stranded. Typically the expression cassette will be provided to the cell in a vector from which it is transferred to the genome of the cell. The expression cassette further comprises all elements necessary for expression of the gene in a host cell, although in certain embodiments some of such elements may be present on a second nucleic acid to be introduced, whereby these elements act in trans. Elements necessary for expression in a host cell include promoters, enhancers and other regulatory elements. Only those elements are necessary that are not provided by the host cell.

[0031] The expression of the gene of interest should not be silenced in the genome of the host cell, especially not in the development stage where expression is required. This can be done by various means, such as insertion into the endogenous locus or by providing the cassette with nucleic acid elements that prevent silencing (Kwaks et al. (2006), *Trends Biotechnol.* 24(3):137-142, which is incorporated herein by reference). It is preferred that the expression cassette is inserted in a locus that is not silenced in the host cells (EP 01439234; which is incorporated herein by reference).

[0032] The means for prevention of silencing comprise STabilizing Anti-Repression-sequences (STAR®-sequences) and Matrix Attachment Regions (MARs). A STAR sequence is a nucleic acid sequence that comprises a capacity to influence transcription of genes in cis. Typically, although not necessarily, a STAR sequence does not code by itself for a functional protein element. In one embodiment one STAR element is used. Preferably, however, more than one STAR element is used. In a particularly preferred embodiment an expression cassette described herein is provided with two STAR sequences; one STAR sequence at the 5' side of the coding sequence of the immunoglobulin gene and one STAR sequence at the 3' side of the coding sequence of the immunoglobulin gene. MARs are DNA sequences that are involved in anchoring DNA/chromatin to the nuclear matrix and they have been described in both mammalian and plant species. MARs possess a number of features that facilitate the opening and maintenance of euchromatin. MARs can increase transgene expression and limit position-effects.

[0033] Expression from the cassette should only occur during a certain period in the development of a cell, in particular a developing B cell, more in particular a B cell in a transgenic non-human animal, in particular a mouse. In this particular case the developmental period is chosen such that the expression of the gene from the cassette (typically a light- or heavy chain-like polypeptide) does not significantly interfere with the normal differentiation and/or maturation of the cell and when applicable, allows for pairing of the polypeptide chain produced with its counterpart.

[0034] This may, in one embodiment, be achieved by providing a nucleic acid described herein, wherein the means for timing expression is a promoter of which the activity is essentially limited to the certain stage of development. In a developing B cell, which, e.g., after immunization is maturing and/or differentiating, the expression of the gene of interest, when it is one of the polypeptide chains of an immunoglobulin, must not interfere (significantly) with the maturation and/or differentiation and it needs to be timed such that the resulting polypeptide can pair with its counterparts. Therefore, provided is a nucleic acid described herein wherein the certain stage starts at a stage immediately preceding or coinciding with the onset of the expression of light chain molecules by the cells at a certain stage of development into a mature B cell. This may be achieved by selecting a promoter which is active only during the suitable period. Such a promoter may be a CD19 promoter, the Ig-α promoter, the Ig-β promoter, the μhc (all genes) promoter, the Vk promoter or analogues or homologues thereof.

[0035] In a specific embodiment, the promoter as disclosed above does not drive the expression of the gene of interest directly. Instead it drives the expression of a gene of which the product activates in trans the expression of the gene of interest. Such an activating gene may be a gene encoding a so-called Cre recombinase or Cre-like protein. The expression cassette for the gene of interest may, e.g., be provided with a sequence that inhibits expression of the gene of interest. The sequence can be removed by the action of the Cre recombinase, which is under control of the desired promoter (active during the proper stage of development). In this embodiment a set of expression cassettes is required.

[0036] Therefore, provided is a set of nucleic acids that are expression cassettes, wherein one nucleic acid comprises an expression cassette encoding a Cre-like protein under control of a promoter active during the desired stage of development of the host cell and the second nucleic acid comprises a sequence encoding a desired proteinaceous molecule under control of a constitutive promoter which can be activated by the action of a Cre-like protein. The activation is preferably achieved by removal of a stop sequence flanked by loxP sites. The Cre/lox system is described in detail in Rajewsky et al. (1996), *J. Clin. Invest.* 98:600-603, which is incorporated herein by reference. Such systems are reviewed in F. T. Wunderlich (2004), "Generation of inducible Cre systems for conditional gene inactivation in mice," Inauguraldissertation zur Erlangung des Doktorgrades der Mathematisch-Naturwissenschaftlichen Fakultat der Universitat zu Koln; on the World Wide Web at deposit.ddb.de/cgi-bin/dokserv?idn=97557230x&dok_var=d1&dok_ext=pdf&filename=97557230x.pd, which is incorporated herein by reference.

[0037] Further provided is a transgenic non-human animal that has been provided with an expression cassette hereof, wherein the desired proteinaceous molecule is a polypeptide chain of an immunoglobulin. A preferred polypeptide chain is a light chain. A more preferred polypeptide is a germline or germline-like light chain. A most preferred polypeptide is encoded by the immunoglobulin kappa variable 1-39 (IGKV1-39, also known as O12) gene segment, preferably the rearranged germline kappa light chain IGKV1-39*01/IGKJ1*01 (nomenclature according to the IMGT database, at [worldwideweb].imgt.org).

[0038] In certain embodiments, the polypeptide chain is rendered essentially incapable of rearrangement and/or of excluded of any sequence modification such as normally operating on Ig during the process of B cell affinity maturation. Therefore, provided is a transgenic non-human animal that has been provided with an expression cassette

described herein, wherein the rearrangement and/or sequence modifications are prevented by the absence of elements at least partially responsible for somatic hypermutation such as, for example, the MoEκi enhancer.

[0039] A preferred expression cassette described herein comprises means for prevention of silencing. In one embodiment, the means for prevention of silencing are means for insertion into a locus in the genome of the host cell that is resistant to silencing. The means for insertion are preferably means for homologous recombination into the site resistant to silencing. A preferred locus when the non-human animal is a mouse is the rosa-locus.

[0040] A further preferred expression cassette described herein comprises in 5'-3' direction: a Vκ promoter, a mouse leader, a human V gene, optionally a MoEκi enhancer, a rat constant region (Cκ) and optionally a (truncated) MoEκ3' enhancer.

[0041] Yet a further preferred expression cassette described herein comprises in 5'-3' direction: a Vκ promoter, a human leader, a human V gene, optionally a MoEκi enhancer, a rat constant region (Cκ) and optionally a (truncated) MoEκ3' enhancer.

[0042] Certain antibodies produced as described herein may be used in human therapeutics and diagnostics. Thus, provided is a method for producing a desired antibody comprising exposing a non-human mammal described herein to an antigen such that an antibody response is induced and isolating the antibodies specific for the antigen.

[0043] In certain embodiments, provided are methods for producing a desired antibody comprising exposing a non-human mammal described herein to an antigen such that an antibody response is induced and isolating cells producing such antibodies, culturing and optionally immortalizing the cells and harvesting the antibodies.

[0044] In certain embodiments, provided is a method for producing a desired antibody comprising exposing a non-human mammal described herein to an antigen such that an antibody response is induced and isolating a nucleic acid encoding at least part of such an antibody, inserting the nucleic acid or a copy or a derivative thereof in an expression cassette and expressing the antibody in a host cell.

[0045] The methods for producing antibodies from transgenic mice are known to a person skilled in the art. Particularly preferred are methods for production of mixtures of antibodies from one cell, whereby the nucleic acids encoding these antibodies have been derived from mice described herein.

[0046] These so-called oligoclonics are disclosed in WO04106375 and WO05068622, which are incorporated herein by reference.

[0047] Described herein are transgenic non-human mammals, preferably mice, capable of generating specific and high affinity hybrid mouse-human antibodies with preferably human immunoglobulin light chain variable (VL) regions in or near germline configuration and preferably murine immunoglobulin heavy chain variable (VH) regions that may have accumulated somatic mutations during the process of antigen-driven affinity maturation. It is envisaged that the murine VH regions of the hybrid antibodies may be subjected to humanization procedures to yield mAbs that have reduced immunogenicity when applied in humans based on germline or near-germline VL regions and murine VH regions that have been humanized.

[0048] In particular, we have shown that transgenic mice that harbor a DNA expression construct that encodes a rearranged human VL region under the control of cis-acting genetic elements that provide timely and regulated expression of the transgene on a significant proportion of B cells during B cell development, yet lack elements that direct the somatic hypermutation machinery to the transgene, are capable of generating specific and high affinity mouse-human hybrid antibodies with essentially unmutated L chains. It is shown that the rearranged human transgene is capable of pairing with a diversity of endogenous murine immunoglobulin H chains to form mouse-human hybrid immunoglobulins expressed on the surface of B cells and to sufficiently facilitate murine B cell development to obtain a sizeable and diverse peripheral B cell compartment.

[0049] In certain embodiments, the transgene expression construct harbors the coding sequences of a human rearranged L chain V region under the control of a human VL promoter to direct B-cell specific expression. In addition, the construct harbors the murine 3' Ck enhancer sequence for B cell specific and inducible and high level expression of the transgene. Furthermore, the construct is designed to lack regulatory elements that facilitate the recruitment of the somatic hypermutation machinery to the transgene, such as the intron enhancer and the 3' C-kappa enhancer.

[0050] In a related embodiment, the rearranged human VL gene is inserted in the murine Rosa26 locus by site-specific integration. The Rosa26 locus is useful in the context of the "targeted transgenesis" approach for efficient generation of transgenic organisms (such as mice) with a predictable transgene expression pattern.

[0051] In certain embodiments, the rearranged human VL region is selected for its capacity to pair with many different murine VH genes so as to ensure the generation of a population of B cells with a diverse VH gene repertoire. A method of obtaining such VL regions comprises amplifying a repertoire of rearranged VH genes from the B cells of mice and a repertoire of human rearranged germline VL regions from the B cells of humans and cloning them into phagemid display vectors to prepare diverse libraries of hybrid immunoglobulins in bacteria. By nucleotide sequence analysis of collections of unselected and antigen-selected VH/VL pairs, human germline VL genes that pair with many different murine VH genes are identified. A collection of human germline VL genes with this capacity is described.

[0052] In one embodiment, it is shown that upon immunization with antigen, the B cells are capable of mounting an immune response, leading to the generation of B cells that secrete hybrid antibodies with high specificity and affinity. The V regions encoding these antibodies are characterized by the human transgenic light chain that harbors no or very few mutations and a murine heavy chain that harbors a variable number of mutations introduced by the somatic hypermutation machinery.

[0053] In a related embodiment, strategies to obtain high affinity hybrid monoclonal antibodies from the transgenic mice by hybridoma and display technologies are contemplated as well as procedures to humanize the murine VH regions to obtain less immunogenic antibodies for application in humans.

[0054] In one embodiment, provided is an immunoglobulin L chain transgene construct comprising DNA sequences that encode a human immunoglobulin VL region in combination with a light chain constant region (CL) of an animal

immunoglobulin protein, which sequences are operably linked to transcription regulatory sequences that, when integrated in a non-human transgenic animal, produce an Ig VL-CL polypeptide with a human VL region that is not or marginally subject to somatic hypermutation. The Ig VL is capable of pairing with rearranged VH-CH polypeptides that are generated during B cell development in the non-human transgenic animal, with the VH-CH polypeptides retaining the capacity to undergo somatic hypermutation upon stimulation. The CL region may be of any animal species and is generally capable of pairing with the CH regions of the non-human transgenic animal.

[0055] Also included is the use of a transgene construct as above in producing a transgenic non-human animal capable of the production of hybrid antibodies consisting of VL-CL polypeptides and VH-CH polypeptides in which the VL region is of human origin and the CL, VH and CH may be of any animal species, including human. Upon immunization, these transgenic animals are capable of generating high affinity antibodies encoded by somatically hypermutated VH genes and essentially non-mutated VL genes encoded by the transgene.

[0056] In another aspect, provided is a process for the production of a transgenic non-human animal capable of the production of hybrid antibodies in response to antigenic challenge, comprising functionally disrupting the endogenous immunoglobulin light chain locus and inserting into the animal genome a transgene construct of the invention.

[0057] Included is the use of animals obtainable by this process in the production of B cells that produce immunoglobulin having human VL light chain. In another aspect of the invention there is provided a process for the production of B cells that produce immunoglobulin having human VL and binding to a selected antigen, comprising challenging an animal obtainable by a process as above with the antigen and screening for B cells from the animal that bind the antigen. Further included is B cells obtainable by this process and hybridomas obtainable by immortalizing such B cells, e.g., hybridomas obtained by fusing B cells as above with myeloma cells. Also included is a process for producing monoclonal antibody comprising cultivating such a hybridoma. In yet a further aspect, provided is the use of the above B cells in producing a hybridoma or corresponding monoclonal antibody.

[0058] Described herein is a process for the production of immunoglobulin having human VL chain and binding to a selected antigen, comprising challenging an animal obtainable as above with the antigen and obtaining immunoglobulin there from.

[0059] In one strategy, as an individual step, a rearranged VL region encoded by human germline V and J gene segments and a light chain constant region of any animal species but preferably a murine constant region is introduced into the mouse germ line. The transgene DNA may be introduced into the pronuclei of fertilized oocytes or embryonic stem cells. The integration may be random or homologous depending on the particular strategy to be employed. For example, the VL transgene may be introduced by random insertion, resulting in mice that bear one or multiple copies of the transgene in the genome. Alternatively, the human VL transgene may be targeted to a specific genomic locus using site-specific recombination as described in the art.

[0060] In certain embodiments, the VL transgene is targeted to the murine ROSA26 locus which is a suitable integration site allowing strong and predictable expression of inserted transgenes (European Patent Office document EP 1,439,234 A1, the contents of which are incorporated herein by this reference). The targeting vector allows insertion of a single copy of a gene expression cassette, thus avoiding modulation of transgene expression by the arrangement of multiple copies. By choosing the autosomal Rosa26 locus as insertion site, the expression pattern of the inserted transgene in the non-human animal is predictable. Furthermore, random X inactivation and/or modulation by chromosomal position effects are avoided. This also eliminates the need to generate and analyze multiple transgenic strains for any given transgene. Finally, the Rosa26 targeting vector for the site-specific integration can be used for multiple gene expression cassettes. Thus, it may be envisaged that two or more different rearranged germline human VL regions are inserted into the Rosa26 locus to further increase the diversity of the repertoire of hybrid or human antibodies.

[0061] In another embodiment, a rearranged human VL region may be targeted to the murine Ig kappa or lambda light chain locus so as to functionally inactivate the endogenous locus or mice containing the rearranged human VL region may be bred with mice that lack functional kappa or lambda Ig loci or both. Thus, by using transformation, using repetitive steps or in combination with breeding, transgenic animals may be obtained which are able to produce antibodies harboring the human VL transgene in the substantial absence of endogenous host immunoglobulin light chains.

[0062] In one embodiment, a human VL transgene is selected for its capacity to pair with a substantial portion of murine VH regions to form a diverse repertoire of functional mouse-human hybrid antibodies expressed on the surface of B cells. By a substantial portion of murine VH regions is meant that the human VL pairs with at least with 0.1% of the murine VH regions generated during B cell development, more preferably with at least 1% and most preferably with at least 10%. Methods to identify human VL genes with this characteristic include randomly pairing a repertoire of human VL regions with a repertoire of murine VH regions, co-expression of VH and VL regions in appropriate eukaryotic or prokaryotic expression vectors and screening for human VL regions that pair with a substantial portion of murine VH regions. In one embodiment, phagemid vectors may be used to direct expression of mouse-human antibody fragments in bacterial cells or to the surface of filamentous phage and analysis of binding capacity of antibody fragments by methods known in the art.

[0063] In another embodiment, a human VL transgene is selected for its capacity to pair with a substantial portion of human VH regions to form a diverse repertoire of human antibodies expressed on the surface of B cells. By a substantial portion of human VH regions is meant that the human VL pairs with at least with 0.1% of the human VH regions generated during B cell development, more preferably with at least 1% and most preferably with at least 10%.

[0064] In the latter embodiment, the human VL transgenic mice are crossed with mice that harbor functional rearranged or non-rearranged human H chain immunoglobulin loci and functionally inactivated endogenous H chain Ig loci as described in the art. The functional inactivation of the two copies of each of the three host Ig loci (heavy chain, kappa and lambda light chain), where the host contains the human

IgH and the rearranged human VL transgene would allow for the production of purely human antibody molecules without the production of host or host human chimeric antibodies. Such a host strain, by immunization with specific antigens, would respond by the production of mouse B-cells producing specific human antibodies, which B-cells are subsequently fused with mouse myeloma cells or are immortalized in any other manner for the continuous stable production of human monoclonal antibodies. Alternatively, the population of B cells is used as a source of VH regions that can be obtained by constructing cDNA libraries or by PCR amplification using primers for human VH regions as is known in the art.

[0065] A human rearranged VL gene is reconstructed in an appropriate eukaryotic or prokaryotic microorganism and the resulting DNA fragments can be introduced into pronuclei of fertilized mouse oocytes or embryonic stem cells. Various constructs that direct B cell specific expression of VL transgenes have been described in the art and have the following general format: a leader sequence and relevant upstream sequences to direct B cell specific expression of the transgene, a coding sequence of a human VL transgene, an enhancer sequence that directs B cell specific and high level expression of the transgene and a murine constant region gene. In a preferred format, the enhancer is the C-kappa 3' enhancer because it directs high level expression in B-lineage cells, but does not recruit somatic hypermutation when used in transgene constructs.

[0066] In one embodiment, animals, preferably mice, comprising one or multiple copies of the transgene in the genome are isolated and analyzed for stable expression. Animals are selected that show stable expression of the transgene over longer periods of time, preferably in B-cells. If required, different animal lines comprising independent insertions of one or multiple copies of the transgene, preferably on different chromosomes, are crossed to obtain animals with different insertions of one or multiple copies of the transgene to increase expression of the transgene in animals, preferably in B-cells.

[0067] Further provided is progeny of a transgenic non-human animal described herein, the progeny comprising, at least in its B-cell lineage, a heavy- or light chain encoding sequence together with a means that renders the sequence resistant to DNA rearrangements and/or somatic hypermutations.

[0068] Further provided is progeny of a transgenic non-human animal described herein, the progeny comprising an expression cassette for the expression of a desired proteinaceous molecule in cells during a certain stage of development in cells developing into mature B cells.

[0069] In addition, provided is a cell that is isolated from a transgenic non-human animal described herein, the cell comprising a heavy- or light chain encoding sequence together with a means that renders the sequence resistant to DNA rearrangements and/or somatic hypermutations. In addition, provided is a cell that is isolated from a transgenic non-human animal described herein, the cell comprising an expression cassette for the expression of a desired proteinaceous molecule in cells during a certain stage of development in cells developing into mature B cells. A cell described herein, preferably an antibody-producing B-cell or a cell that is capable of differentiating or maturating into an antibody-producing B-cell, can be used for in vitro production of antibodies, as is known to the skilled person, for example, from Gascan et al. 1991, *J. Exp. Med.* 173:747-750. Methods for immortalization of a cell described herein are known in the art and include the generation of hybridomas, for example, by fusion with a myeloma cell, transformation with Epstein Barr Virus; expression of the signal transducer of activation and transcription (STAT), activation via CD40 and IL4 receptor signaling, and/or expression of Bc16 (Shvarts et al. 2002, *Genes Dev.* 16: 681-686).

[0070] In a separate step, the mouse endogenous Kappa and Lambda light chain loci are rendered essentially non-functional such that at least the majority of B cells in the transgenic mice bear Ig receptors that contain the transgenic human VL region. Inactivation of the endogenous mouse immunoglobulin loci is achieved by targeted disruption of the appropriate loci by homologous recombination in mouse embryonic stem cells. The targeted disruption comprises alteration of the genomic sequence such that substantially no functional endogenous mouse immunoglobulin Kappa and/or Lambda light chain is produced. The term "substantially no functional endogenous mouse immunoglobulin" indicates that the endogenous Kappa and/or Lambda light chain loci are functionally silenced such that the level of functional protein expression of the endogenous Kappa and/or Lambda light chain loci, preferably the endogenous Kappa light chain locus, is reduced to about 20% of the level of expression in a reference mouse, more preferred to about 10%, more preferred to about 5%, more preferred to about 2% and more preferred to about 1%. In a most preferred embodiment, the level of functional protein expression of the endogenous Kappa and/or Lambda light chain loci is reduced to 0%. The level of functional protein expression can be determined by means known to the skilled person, including western blotting and pairing with a mouse heavy chain. The reference mouse is a mouse in which the endogenous Kappa and/or Lambda light chain loci is not disrupted. The alteration comprises mutation and/or deletion of gene sequences that are required for functional expression of the endogenous immunoglobulin genes. Alternatively, the alteration comprises insertion of a nucleic acid into the endogenous mouse immunoglobulin Kappa and/or Lambda light chain loci such that the functional expression of the endogenous immunoglobulin genes is reduced. In one embodiment, the nucleic acid comprises a silencing element resulting in transcriptional silencing of the endogenous immunoglobulin gene. In a further embodiment, or in addition, the nucleic acid comprises a sequence that disrupts splicing and/or translation of the endogenous immunoglobulin gene, for example, by introducing an exon that renders a frame shift in the coding sequence, or that comprises a premature stop codon. In each case chimeric animals are generated which are derived in part from the modified embryonic stem cells and are capable of transmitting the genetic modifications through the germ line. The mating of mouse strains with human immunoglobulin loci to strains with inactivated mouse loci yields animals which produce antibodies comprising essentially only human light chains.

[0071] A construct for homologous recombination is prepared by means known in the art and any undesirable sequences are removed, e.g., procaryotic sequences. Any convenient technique for introducing a construct for homologous recombination into a target cell may be employed. These techniques include spheroplast fusion, lipofection, electroporation, calcium phosphate-mediated DNA transfer or direct microinjection. After transformation

or transfection of the target cells, target cells are selected by means of positive and/or negative markers, for example, by neomycin resistance and/or acyclovir and/or gancyclovir resistance. Those cells which show the desired phenotype may then be further analyzed by restriction analysis, electrophoresis, Southern analysis, PCR, or the like. By identifying fragments which show the presence of the lesion(s) at the target locus, cells in which homologous recombination has occurred to inactivate a copy of the target locus are identified.

[0072] Furthermore, it is shown that upon immunization, the murine and human VH regions in the afore-mentioned transgenic mice but not the VL regions are capable of undergoing somatic hypermutations to generate high affinity antibodies. Advantageously, these antibodies encoded by germline VL regions are predicted to contribute to lower immunogenicity when applied in humans and result in more stable antibodies that are less prone to aggregation and thus safer for therapeutic use in humans.

[0073] MAbs derived from the afore-mentioned non-human transgenic animals or cells all share the same identical human VL regions. It has been described that mAbs that share the same identical VL region may be co-expressed in a single clonal cell for the production of mixtures of recombinant antibodies with functional binding sites (see the incorpoarated WO04106375 and WO05068622). Thus, provided is a platform for the generation of specific and high affinity mAbs that constitute the basis for mixtures of mAbs produced by clonal cells.

[0074] It is preferred that mAbs derived from the afore-mentioned non-human transgenic animals or cells are directed against cellular targets. Preferred targets are human surface-expressed or soluble proteins or carbohydrate molecules. Further preferred targets are surface-expressed proteins or carbohydrate molecules that are expressed on the surface of bacteria, viruses, and other pathogens, especially of humans.

[0075] More specifically, preferred targets include cytokines and chemokines, including but not limited to InterLeukin 1beta (IL1beta), IL2, IL4, IL5, IL7, IL8, IL12, IL13, IL15, IL18, IL21, IL23 and chemokines such as, for example, CXC chemokines, CC chemokines, C chemokines (or y chemokines) such as XCL1 (lymphotactin-a) and XCL2 (lymphotactin-B), and CX3C chemokines. Further included as preferred targets are receptor molecules of the cytokines and chemokines, including type I cytokine receptors such as, for example, the IL-2 receptor, type II cytokine receptors such as, for example, interferon receptors, immunoglobulin (Ig) superfamily receptors, tumor necrosis factor receptor family including receptors for CD40, CD27 and CD30, serine/threonine-protein kinase receptors such as TGF beta receptors, G-protein coupled receptors such as CXCR1-CXCR7, and tyrosine kinase receptors such as fibroblast growth factor receptor (FGFR) family members, EGF receptor family members including erbB1 (EGF-R; HER1), erbB2, (HER2), erbB3 (HER3), and erbB4 (HER4), insulin receptor family members including IGF-R1 and IGF-RII, PDGF receptor family members, Hepatocyte growth factor receptor family members including c-Met (HGF-R), Trk receptor family members, AXL receptor family members, LTK receptor family members, TIE receptor family members, ROR receptor family members, DDR receptor family members, KLG receptor family members, RYK receptor family members, MuSK receptor family members, and vascular endothelial growth factor receptor (VEGFR) family members.

[0076] Further preferred targets are targets that are over-expressed or selectively expressed in tumors such as, for example, VEGF, CD20, CD38, CD33, CEA, EpCAM, PSMA, CD54, Lewis Y, CD52, CD40, CD22, CD51/CD61, CD74, MUC-1, CD38, CD19, CD262 (TRAIL-R2), RANKL, CTLA4, and CD30; targets that are involved in chronic inflammation such as, for example, CD25, CD11a, TNF, CD4, CD80, CD23, CD3, CD14, IFNgamma, CD40L, CD50, CD122, TGFbeta and TGFalpha.

[0077] Preferred surface-expressed proteins or carbohydrate molecules that are expressed on the surface of bacteria, viruses, and other parasitic pathogens, especially of humans, include surface markers of influenza A and B viruses such as hemagglutinin (HA) and neuraminidase (NA), filoviruses such as Ebola virus, rabies, measles, rubella, mumps, flaviviruses such as Dengue virus types 1-4, tick-borne encephalitis virus, West Nile virus, Japanese encephalitis virus, and Yellow fever virus, Paramyxoviruses including Paramyxovirus such as Parainfluenza 1, 3, Rubulavirus such as Mumpsvirus and Parainfluenza 2, 4, Morbillivirus, and Pneumovirus such as Respiratory syncytial virus, Vaccinia, small pox, coronaviruses, including Severe Acute Respiratory Syndrome (SARS) virus, hepatitis virus A, B and C, Human Immunodeficiency Virus, Herpes viruses, including cytomegalovirus, Epstein Barr virus, Herpes simplex virus, and Varicella zoster virus, parvoviruses such as, for example, B19; *Legionella pneumophila; Listeria monocytogenes; Campylobacter jejuni; Staphylococcus aureus; E. coli* O157:H7; *Borrelia burgdorferi; Helicobacter pylori; Ehrlichia chaffeensis; Clostridium difficile; Vibrio cholera; Salmonella enterica* Serotype *Typhimurium; Bartonella henselae; Streptococcus pyogenes* (Group A Strep); *Streptococcus agalactiae* (Group B Strep); Multiple drug resistant *S. aureus* (e.g., MRSA); *Chlamydia pneumoniae; Clostridium botulinum; Vibrio vulnificus; Parachlamydia* pneumonia; *Corynebacterium amycolatum; Klebsiella pneumonia*; Linezolid-resistant enterococci (*E. faecalis* and *E. faecium*); and Multiple drug resistant *Acinetobacter baumannii.*

[0078] Most preferred targets are IL-6 and its receptor, IL-6Ralpha, glycoprotein-denominated gp130, RSV, especially the surface proteins F, G and SH and non-structural proteins such as N and M, and receptor tyrosine kinases, in particular erbB1 (EGF-R; HER1), erbB2, (HER2), erbB3 (HER3), erbB4 (HER4), IGF-R1 and IGF-RII, c-Met (HGF-R).

[0079] Therefore, provided is a platform for the generation of specific and high affinity mAbs against the above mentioned targets that constitute the basis for mixtures of mAbs produced by clonal cells. In certain embodiments, the specific and high affinity mAbs comprise mAbs that are directed against different epitopes on at least one of the targets. In a further preferred embodiment, the specific and high affinity mAbs comprise mAbs that are directed against different targets, such as, for example, one or more members of the EGF-receptor family, including erbB1 (EGF-R; HER1), erbB2, (HER2), erbB3 (HER3) and erbB4 (HER4).

[0080] Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required

by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (3rd edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001)), which is incorporated herein by reference. The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

DESCRIPTION OF THE DRAWINGS

[0081] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0082] FIG. **1**: A topology map of the annealing locations of mouse specific VH primers and the position of required restriction sites that are introduced by overhanging sequences at the 3' end of primers.

[0083] FIG. **2**: PCR amplification steps (Amplification, Intermediate and Site introduction). The location and names of the mouse VH amplification primers (and mixtures of primers) are indicated per step.

[0084] FIG. **3**: Topology of the MV1043 vector. This vector is used for the cloning of human or murine VH fragments. O12 (IGKV1-39) is indicated as the VL gene. Products of this vector in combination with helper phages in *E. coli* cells allow the generation of phages that display Fab fragments on the surface of the phage particles as a fusion product to the g3 protein and presence of the vector in the phage as the genetic content (F1 ORI).

[0085] FIG. **4**: The topology of the mouse Ckappa locus downstream of the J-segments. Both enhancers and Ckappa region are indicated. The lower arrow indicates the region that is removed in order to silence the locus.

[0086] FIG. **5**: The topology of the mouse C-lambda locus. All three active V-regions are indicated (Igl-V1, V2 and V3) as are the J-segments (Igl-J1, Igl-J2, Igl-J3, Igl-J4 and the pseudo segment Igl-J3p) and constant regions (Igl-C1, Igl-C2, Igl-C3 and Igl-C4). The regions that are deleted in order to silence the locus are indicated by deletion markers. These deletions include all active V genes (1, 2 and 3) and the intergenic segment between V2 and V3.

[0087] FIG. **6**: Construct topology of IGKV1-39/J-Ck with an intron located in the leader open reading frame (ORF).

[0088] FIG. **7**: Construct topology of IGLV2-14/J-Ck with an intron located in the leader open reading frame (ORF).

[0089] FIG. **8**: Construct topology of VkP-IGKV1-39/J-Ck (VkP-O12). The promoter originates from the IGKV1-39 gene and is placed directly in front of the required elements for efficient transcription and translation. Intergenic sequences (including the enhancers) are derived from mice and obtained from BAC clones. The C-kappa sequence codes for the kappa constant region of rat.

[0090] FIG. **9**: Construct topology of VkP-IGLV2-14/J-Ck (VkP-2a2). The promoter originates from the IGKV1-39 gene and is placed directly in front of the required elements for efficient transcription and translation. Intergenic sequences (including the enhancers) are derived from mice and obtained from BAC clones. The C-kappa sequence codes for the kappa constant region of rat.

[0091] FIG. **10**: Construct topology of VkP-IGKV1-39/J-Ck-A1 (VkP-O12-del1) is identical to VkP-IGKV1-39/J-Ck from FIG. **9** except that the intron enhancer region is removed.

[0092] FIG. **11**: Construct topology of VkP-IGKV1-39/J-Ck-A2 VkP-O12-de12) is identical to VkP-IGKV1-39/J-Ck-A1 from FIG. **10** except that a large piece of the intergenic region between the Ck gene and 3' enhancer is deleted. In addition, the 3' enhancer is reduced in size from 809 bp to 125 bp.

[0093] FIG. **12**: Overview of the sequences used or referred to in this application: Human germline IGKV1-39/J DNA (SEQ ID NO:84); human germline IGKV1-39/J Protein (SEQ ID NO:85); human germline IGLV2-14/J DNA (SEQ ID NO:86); human germline IGLV2-14/J Protein (SEQ ID NO:87); Rat IGCK allele a DNA (SEQ ID NO:88); Rat IGCK allele a protein (SEQ ID NO:89); IGKV1-39/J-Ck (SEQ ID NO:90); IGLV2-14/J-Ck (SEQ ID NO:91); VkP-IGKV1-39/J-Ck (SEQ ID NO:92); VkP-IGKV1-39/J-Ck-A1 (SEQ ID NO:93); VkP-IGKV1-39/J-Ck-A2 (SEQ ID NO:94); VkP-IGLV2-14/J-Ck (SEQ ID NO:95); pSELECT-IGKV1-39/J-Ck (SEQ ID NO:96); pSelect-IGLV2-14/J-Ck (SEQ ID NO:97); MV1043 (SEQ ID NO:98); and MV1057 (SEQ ID NO:99).

[0094] FIGS. **13**A-C: Generation of Rosa26-IgVk1-39 KI allele. FIG. **13**A Schematic drawing of the pCAGGS-IgVK1-39 targeting vector. FIG. **13**B Nucleotide sequence of the pCAGGS-IgVK1-39 targeting vector (SEQ ID NO:100). FIG. **13**C Targeting strategy.

[0095] FIGS. **14**A-C: FIG. **14**A Southern blot analysis of genomic DNA of ES clones comprising an insertion of the pCAGGS-IgVK1-39 targeting vector. Genomic DNA of four independent clones was digested with AseI and probed with 5e1 indicating the 5'-border of the targeting vector. All clones comprise a correct insertion of the targeting vector at the 5' end.

[0096] FIG. **14**B Southern blot analysis of genomic DNA of ES clones comprising an insertion of the pCAGGS-IgVK1-39 targeting vector. Genomic DNA of four independent clones was digested with MscI and probed with 3e1 indicating the 3'-border of the targeting vector. All clones comprise a correct insertion of the targeting vector at the 3' end. FIG. **14**C Southern blot analysis of genomic DNA of ES clones comprising an insertion of the pCAGGS-IgVK1-39 targeting vector. Genomic DNA of four independent clones

was digested with BamHI and probed with an internal Neo probe indicating the 5'-border of the targeting vector. All clones comprise a correct, single insertion of the targeting vector.

[0097] FIGS. **15**A-C: Generation of Rosa26-IgV12-14 KI allele. FIG. **15**A Schematic drawing of the pCAGGS-IgVL2-14 targeting vector. FIG. **15**B Nucleotide sequence of the pCAGGS-IgVL2-14 targeting vector containing the CAGGS expression insert (SEQ ID NO:101) based on the rearranged germline IGLV2-14/J V lambda region (IGLV2-14/J-Ck). FIG. **15**C Targeting strategy.

[0098] FIGS. **16**A-C: Epibase® profile of IGKV1-39 residues 1-107 (SEQ ID NO:85).

[0099] FIG. **16**A displays the binding strength for DRB1 allotypes, while FIG. **16**C displays the binding strength for DRB3/4/5, DQ and DP allotypes. The values in the figure represent dissociation constants (Kds) and are plotted on a logarithmic scale in the range 0.01 μM-0.1 μM (very strong binders may have run off the plot). For medium binding peptides, qualitative values are given only, and weak and non-binders are not shown. Values are plotted on the first residue of the peptide in the target sequence (the peptide itself extends by another nine residues). Importantly, only the strongest binding receptor for each peptide is shown: cross-reacting allotypes with lower affinity are not visible in this plot. The strongest binding receptor is indicated by its serotypic name. Finally, any germline-filtered peptides are plotted with a lighter color in the epitope map (in this case, no non-self epitopes were found). FIG. **16**B shows the HLA binding promiscuity for every decameric peptide (Y-axis: the number of HLA allotypes recognizing critical epitopes in each of the peptides starting at the indicated residue shown on the X-axis). The promiscuity is measured as the number of allotypes out of the total of 47 for which the peptide is a critical binder. White columns refer to self-peptides, and black columns (absent here) to non-self peptides.

[0100] FIG. **17**: Epitope map of IGKV1-39 showing the presence of peptide binders predicted in the sequence of IGKV1-39 by serotype in the 15-mer format. Each 15-mer is numbered as indicated in the top of the figure. The full sequence of the corresponding 15-mer is listed in Table 7. Black boxes indicate the presence of one or more critical self-epitopes in the 15-mer for the serotype listed on the left. Critical epitopes are operationally defined as strong or medium DRB1 binders and strong DRB3/4/5 or DP or DQ binders.

[0101] FIGS. **18**A-B: Constitutive knock-out (KO) of the Ig kappa locus. FIG. **18**A Targeting strategy. FIG. **18**B Schematic drawing of the pIgKappa targeting vector.

[0102] FIGS. **19**A-B: Constitutive KO of the Ig lambda locus. FIG. **19**A First step of the targeting strategy. FIG. **19**B Second step of the targeting strategy.

[0103] FIGS. **20**A-C: Schematic drawing of targeting vectors. FIG. **20**A pVkP-O12 (VkP-IGKV1-39/J-Ck); FIG. **20**B pVkP-O12-del1 (VkP-IGKV1-39/J-Ck-A1); FIG. **20**C pVkP-O12-de12 (VkP-IGKV1-39/J-Ck-A2).

[0104] FIGS. **21**A-C: Targeting strategies for insertion of transgene into the Rosa26 locus by targeted transgenesis using RMCE. FIG. **21**A VkP-O12 (VkP-IGKV1-39/J-Ck); FIG. **21**B VkP-O12-del1 (VkP-IGKV1-39/J-Ck-A1); FIG. **21**C VkP-O12-de12 (VkP-IGKV1-39/J-Ck-A2).

[0105] FIG. **22**: Topology of the MV1057 vector. Replacing the indicated stuffer fragment with a VH fragment yields an expression vector that can be transfected to eukaryotic cells for the production of IgG1 antibodies with light chains containing an O12 (IGKV1-39) VL gene.

[0106] FIG. **23**: Lack of transgenic human Vk1 light chain expression in non-B cell populations of the spleen.

[0107] FIG. **24**: Transgenic human Vk1 light chain is expressed in all B cell populations of the spleen.

[0108] FIG. **25**: Transgenic human Vk1 light chain is expressed in B1 cells of the peritoneal cavity.

[0109] FIGS. **26**A-B: Transgenic human Vk1 light chain is not expressed in pro- and pre-B cells but in the immature and recirculating populations B cells in the bone marrow. FIG. **26**A Gating of bone marrow cells. FIG. **26**B Histograms of transgene expression with overlay from one WT control.

[0110] FIG. **27**: Transgenic human Vk1 light chain is directly correlated with endogenous light chain and IgM expression in circulating B cells in the blood.

[0111] FIG. **28**: Parameters of stability for stable clones containing the germline IGKV1-39 gene.

[0112] FIG. **29**A-B: Antibody mixtures used for staining of lymphocyte populations. BM=bone marrow, PC=peritoneal cavity, PP=Peyer's patches.

DETAILED DESCRIPTION OF THE INVENTION

Examples

Example 1: Human Light Chain V-Gene Clones

[0113] This example describes the rationale behind the choice of two human light chain V-genes, one gene of the kappa type and one gene of the lambda type, that are used as a proof of concept for light chain expressing transgenic mice. De Wildt et al. 1999 (de Wildt et al. (1999), *J. Mol. Biol.* 285(3):895) analyzed the expression of human light chains in peripheral IgG-positive B-cells. Based on these data, IGKV1-39 (O12) and IGLV2-14 (2a2) were chosen as light chains as they were well represented in the B-cell repertoire. The J-segment sequence of the light chains has been chosen based upon sequences as presented in GenBank ABA26122 for IGKV1-39 (B. J. Rabquer, S. L. Smithson, A. K. Shriner and M. A. J. Westerink) and GenBank AAF20450 for IGLV2-14 (O. Ignatovich, I. M. Tomlinson, A. V. Popov, M. Bruggemann and G. J. Winter, *J. Mol. Biol.* 294 (2):457-465 (1999)).

[0114] All framework segments are converted into germline amino acid sequences to provide the lowest immunogenicity possible in potential clinical applications.

Example 2: Obtaining Mouse Heavy Chain V-Genes that Pair with Human IGKV1-39 Gene Segment to Form Functional Antibody Binding Sites

[0115] This example describes the identification of mouse heavy chain V-genes that are capable of pairing with a single, rearranged human germline IGKV1-39/J region. A spleen VH repertoire from mice that were immunized with tetanus toxoid was cloned in a phage display Fab vector with a single human IGKV1-39-C kappa light chain and subjected to panning against tetanus toxoid. Clones obtained after a single round of panning were analyzed for their binding specificity. The murine VH genes encoding tetanus toxoid-specific Fab fragments were subjected to sequence analysis to identify unique clones and assign VH, DH and JH utilization.

[0116] Many of the protocols described here are standard protocols for the construction of phage display libraries and the panning of phages for binding to an antigen of interest and described in Antibody Phage Display: Methods and Protocols (editor(s): Philippa M. O'Brien and Robert Aitken).

Immunizations

[0117] BALB/c mice received one immunization with tetanus toxoid and were boosted after six weeks with tetanus toxoid.

Splenocyte Isolation

[0118] Preparation of spleen cell suspension. After dissection, the spleen was washed with PBS and transferred to a 60 mm Petri dish with 20 ml PBS. A syringe capped with 20 ml PBS and a G20 needle was used to repeatedly flush the spleen. After washing the flushed cells with PBS, the cells were carefully brought into suspension using 20 ml PBS and left on a bench for five minutes to separate the splenocytes from the debris and cell clusters. The splenocytes suspension was transferred on top of a Ficoll-Paque™ PLUS-filled tube and processed according to the manufacturer's procedures for lymphocyte isolation (Amersham Biosciences).

RNA Isolation and cDNA Synthesis

[0119] After isolation and pelleting of lymphocytes, the cells were suspended in TRIzol LS Reagent (Invitrogen) for the isolation of total RNA according to the accompanying manufacturer's protocol and subjected to reverse transcription reaction using 1 microgram of RNA, Superscript III RT in combination with dT20 according to manufacturer's procedures (Invitrogen).

PCR Amplification of cDNA

[0120] The cDNA was amplified in a PCR reaction using primer combinations that allow the amplification of approximately 110 different murine V-genes belonging to 15 VH families (Table 1; RefSeq NG 005838; Thiebe et al. 1999, *European Journal of Immunology* 29:2072-2081). In the first round, primer combinations that bind to the 5' end of the V-genes and 3' end of the J regions were used. In the second round, PCR products that were generated with the MJH-Rev2 primer were amplified in order to introduce modifications in the 3' region to enable efficient cloning of the products. In the last round of amplification, all PCR products were amplified using primers that introduce a SfiI restriction site at the 5' end and a BstEII restriction site at the 3' end (see FIGS. **1** and **2**, and Table 1).

[0121] Reaction conditions for 1st round PCR: four different reactions combining all 25 forward primers (MVH1 to MVH25, Table 1 and FIG. **2**) and one reverse primer per reaction (MJH-Rev1, MJH-Rev2, MJH-Rev3 or MJH-Rev4; see Table 1 and FIG. **2**). Fifty microliters PCR volumes were composed of 2 microliters cDNA (from RT reactions), 10 microliters 5* Phusion polymerase HF buffer, 40 nM of each of the 25 forward primers (total concentration of 1 micromolar), 1 micromolar reverse primer, 1 microliter 10 mM dNTP stock, 1.25 unit Phusion polymerase and sterile MQ water. The thermocycler program consisted of a touch down program: one cycle 98° C. for 30 seconds, 30 cycles 98° C. for ten seconds, 58° C. decreasing 0.2° C. per cycle ten seconds, 72° C. 20 seconds and one cycle 72° C. for three minutes. The second round PCR program was set up only for the products of the first PCR that contain the MJH-Rev2 primer: two different reactions combining either the Ext-MVH-1 or ExtMVH-2 primers (Table 1 and FIG. **2**) in combination with the reverse primer ExtMJH-Rev2int (Table 1 and FIG. **2**). Fifty microliters PCR volumes were composed of 50 ng PCR product (from first PCR round), 10 microliters 5* Phusion polymerase HF buffer, 500 nM of each forward primer, 1 micromolar reverse primer, 1 microliter 10 mM dNTP stock, 1.25 unit Phusion polymerase and sterile MQ water. The thermocycler program consisted of a touch down program followed by a regular amplification step: one cycle 98° C. for 30 seconds, ten cycles 98° C. for ten seconds, 65° C. decreasing 1.5° C. per cycle ten seconds, 72° C. 20 seconds, ten cycles 98° C. for ten seconds, 55° C. ten seconds, 72° C. 20 seconds and one cycle 72° C. for three minutes. The third round PCR program was setup as described in FIG. **2**. Fifty microliters PCR volumes were composed of 50 ng PCR product (from earlier PCR rounds, FIG. **2**), 10 microliters 5* Phusion polymerase HF buffer, 1 micromolar forward primer (Table 1 and FIG. **2**), 1 micromolar reverse primer, 1 microliter 10 mM dNTP stock, 1.25 unit Phusion polymerase and sterile MQ water. The program consists of a touch down program followed by a regular amplification step: one cycle 98° C. for 30 seconds, ten cycles 98° C. for ten seconds, 65° C. decreasing 1.5° C. per cycle ten seconds, 72° C. 20 seconds, ten cycles 98° C. for ten seconds, 55° C. ten seconds, 72° C. 20 seconds and one cycle 72° C. for three minutes. After PCR amplifications, all PCR products were gel purified using Qiaex II according to the manufacturer's protocols.

Restriction Enzyme Digestions

[0122] Purified products were digested with BstEII and SfiI in two steps. First 1 microgram of DNA was digested in 100 microliters reactions consisting of 10 microliters of 10* NEB buffer 3 (New England Biolabs), 1 microliter 100* BSA, 12.5 unit BstEII and sterile water for six hours at 60° C. in a stove. The products were purified using Qiaquick PCR Purification kit from Qiagen according to the manual instructions and eluted in 40 microliters water. Next all products were further digested with SfiI in 100 microliters reactions consisting of 10 microliters of 10* NEB buffer 2 (New England Biolabs), 1 microliter 100* BSA, 12.5 unit SfiI and sterile water for 12 hours at 50° C. in a stove. The digested fragments were purified by Qiaquick Gel Extraction kit following gel separation on a 20 cm 1.5% agarose TBE plus ethidium bromide gel at 80 V. 100 micrograms of the acceptor vector (MV1043, FIGS. **3** and **12**) was digested with 50 units Eco91I in 600 microliters under standard conditions (Tango buffer) and next purified on a 0.9% agarose gel. After a second digestion step under prescribed conditions with 400 units SfiI in 500 microliters for 12 hours, 100 units BsrGI were added for three hours at 50° C.

Ligations

[0123] Each PCR product was ligated separately according to the following scheme: 70 ng digested PCR products, 300 ng digested acceptor vector, 100 units T4 Ligase (NEB), 1* ligase buffer in 30 microliters for 16 hours at 12° C. The ligation reactions were purified with phenol/chloroform/isoamyl alcohol extractions followed by glycogen precipitations (Sigma Aldrich #G1767) according to the manufacturer's protocol and finally dissolved in 25 microliters sterile water.

Transformations and Library Storage

[0124] The purified ligation products were transformed by electroporation using 1200 microliters TG1 electrocompetent bacteria (Stratagene #200123) per ligation batch and plated on LB carbenicillin plates containing 4% glucose. Libraries were harvested by scraping the bacteria in 50 ml LB carbenicillin. After centrifugation at 2000 g for 20 minutes at 4° C., the bacterial pellets were resuspended carefully in 2 ml ice cold 2*TY/30% glycerol on ice water and frozen on dry ice/ethanol before storage at −80° C.

Library Amplification

[0125] Libraries were grown and harvested according to procedures as described by Kramer et al. 2003 (Kramer et al. (2003), *Nucleic Acids Res.* 31(11):e59) using VCSM13 (Stratagene) as helper phage strain.

Selection of Phages on Coated Immunotubes

[0126] Tetanus toxoid was dissolved in PBS in a concentration of 2 μg/ml and coated to MAXISORP™ Nunc-Immuno Tube (Nunc 444474) overnight at 4° C. After discarding the coating solution, the tubes were blocked with 2% skim milk (ELK) in PBS (blocking buffer) for one hour at RT. In parallel, 0.5 ml of the phage library was mixed with 1 ml blocking buffer and incubated for 20 minutes at room temperature. After blocking the phages, the phage solution was added to the tetanus toxoid-coated tubes and incubated for two hours at RT on a slowly rotating platform to allow binding. Next, the tubes were washed ten times with PBS/0.05% TWEEN'-20 detergent followed by phage elution by an incubation with 1 ml 50 mM glycine-HCl pH 2.2 ten minutes at RT on rotating wheel and directly followed by neutralization of the harvested eluent with 0.5 ml 1 M Tris-HCl pH 7.5.

Harvesting Phage Clones

[0127] Five ml XL1-Blue MRF (Stratagene) culture at O.D. 0.4 was added to the harvested phage solution and incubated for 30 minutes at 37° C. without shaking to allow infection of the phages. Bacteria were plated on Carbenicillin/Tetracycline 4% glucose 2*TY plates and grown overnight at 37° C.

Phage Production

[0128] Phages were grown and processed as described by Kramer et al. 2003 (Kramer et al. 2003, *Nucleic Acids Res.* 31(11):e59) using VCSM13 as helper phage strain.

Phage ELISA

[0129] ELISA plates were coated with 100 microliters tetanus toxoid per well at a concentration of 2 micrograms/ml in PBS overnight at 4° C. Plates coated with 100 microliters thyroglobulin at a concentration of 2 micrograms/ml in PBS were used as a negative control. Wells were emptied, dried by tapping on a paper towel, filled completely with PBS-4% skimmed milk (ELK) and incubated for one hour at room temperature to block the wells. After discarding the block solution, phage minipreps premixed with 50 μl blocking solution were added and incubated for one hour at RT. Next five washing steps with PBS-0.05% Tween-20 removed unbound phages. Bound phages were detected by incubating the wells with 100 microliters anti-M13-HRP antibody conjugate (diluted 1/5000 in blocking buffer) for one hour at room temperature. Free antibody was removed by repeating the washing steps as described above, followed by TMB substrate incubation until color development was visible. The reaction was stopped by adding 100 microliters of 2 M H_2SO_4 per well and analyzed on an ELISA reader at 450 nm emission wavelength (Table 2). Higher numbers indicate stronger signals and thus higher incidence of specific binding of the phage-Fab complex.

Sequencing

[0130] Clones that gave signals at least three times above the background signal (Table 2) were propagated, used for DNA miniprep procedures (see procedures Qiagen miniPrep manual) and subjected to nucleotide sequence analysis. Sequencing was performed according to the Big Dye 1.1 kit accompanying manual (Applied Biosystems) using a reverse primer (CH1_Rev1, Table 1) recognizing a 5' sequence of the CH1 region of the human IgG1 heavy chain (present in the Fab display vector MV1043, FIGS. **3** and **12**). Mouse VH sequences of 28 tetanus toxoid binding clones are depicted in Table 3. The results show that the selected murine VH genes belong to different gene families, and different individual members from these gene families are able to pair with the rearranged human IGKV1-39/J VH region to form functional tetanus toxoid-specific antibody binding sites. From the sequence analyses, it was concluded that the murine VH regions utilize a diversity of DH and JH gene segments.

Example 3: Silencing of the Mouse Kappa Light Chain Locus

[0131] This example describes the silencing of the mouse endogenous kappa light chain locus. The endogenous kappa locus is modified by homologous recombination in ES cells, followed by the introduction of genetically modified ES cells in mouse embryos to obtain genetically adapted offspring.

[0132] A vector that contains an assembled nucleotide sequence consisting of a part comprising the J-region to 338 bp downstream of the J5 gene segment fused to a sequence ending 3' of the 3' CK enhancer is used for homologous recombination in ES cells. The assembled sequence is used to delete a genomic DNA fragment spanning from 3' of the JK region to just 3' of the 3' CK enhancer. As a consequence of this procedure, the CK constant gene, the 3' enhancer and some intergenic regions are removed (see FIGS. **4** and **18**A-B).

Construction of the Targeting Vector

[0133] A vector that received 4.5-8 kb flanking arms on the 3' and 5' end fused to the deletion segment was used for targeted homologous recombination in an ES cell line. Both arms were obtained by PCR means ensuring maximum homology. The targeting strategy allows generation of constitutive KO allele. The mouse genomic sequence encompassing the Igk intronic enhancer, Igk constant region and the Igk 3' enhancer was replaced with a PuroR cassette, which was flanked by F3 sites and inserted downstream of the Jk elements. Flp-mediated removal of the selection marker resulted in a constitutive KO allele. The replacement of the Igk MiEk-Igk C-Igk 3'E genomic region (approxi-

mately 10 kb) with a F3-Puro cassette (approx. 3 kb) was likely to decrease the efficiency of homologous recombination. Therefore, the arms of homology were extended accordingly and more ES cell colonies were analyzed after transfection in order to identify homologous recombinant clones.

Generation of ES Cells Bearing the Deleted Kappa Fragment

[0134] The generation of genetically modified ES cells was essentially performed as described (Seibler et al. (2003), *Nucleic Acids Res. February* 15; 31(4):e12). See also Example 14 for a detailed description.

Generation of ES Mice by Tetraploid Embryo Complementation

[0135] The production of mice by tetraploid embryo complementation using genetically modified ES cells was essentially performed as described (Eggan et al., *PNAS* 98:6209-6214; J. Seibler et al. (2003), *Nucleic Acids Res.* February 15; 31(4):e12; Hogan et al. (1994), Summary of mouse development, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y., pp. 253-289).

Example 4: Silencing of the Mouse Lambda Light Chain Locus

[0136] This example describes the silencing of the mouse endogenous lambda light chain locus. The endogenous lambda locus is modified by homologous recombination in ES cells followed by the introduction of genetically modified ES cells in mouse embryos to obtain genetically adapted offspring.

[0137] Two regions of the murine lambda locus that together contain all functional lambda V regions are subject to deletion.

[0138] The first region targeted for homologous recombination-based deletion is a region that is located 408 bp upstream of the start site of the IGLV2 gene segment and ends 215 bp downstream of IGLV3 gene segment, including the intergenic sequence stretch between these IGLV gene segments. The second region that is subject to a deletion involves the IGLV1 gene segment consisting of a fragment spanning from 392 bp upstream to 171 bp downstream of the IGLV1 gene segment. As a consequence of these two deletion steps, all functional V-lambda genes segments are deleted, rendering the locus functionally inactive (FIGS. **5** and **19**A-B).

Construction of the Targeting Vectors

[0139] Vectors that received 3-9.6 kb flanking arms on the 3' and 5' end fused to the deletion segment were used for targeted homologous recombination in an ES cell line. Both arms were obtained by PCR means ensuring maximum homology. In a first step, the mouse genomic sequence encompassing the Igl V2-V3 regions were replaced with a PuroR cassette flanked by F3 sites, which yields a constitutive KO allele after Flp-mediated removal of selection marker (see FIG. **19**A). In a second step, the mouse genomic sequence encompassing the Igl V1 region was replaced with a Neo cassette in ES cell clones which already carried a deletion of the Igl V2-V3 regions (see FIG. **19**B). The selection marker (NeoR) was flanked by FRT sites. A constitutive KO allele was obtained after Flp-mediated removal of selection markers.

Generation of ES Cells Bearing the Deleted Lambda Fragment

[0140] The generation of genetically modified ES cells was essentially performed as described (J. Seibler, B. Zevnik, B. KUter-Luks, S. Andreas, H. Kern, T. Hennek, A. Rode, C. Heimann, N. Faust, G. Kauselmann, M. Schoor, R. Jaenisch, K. Rajewsky, R. Kuhn, F. Schwenk (2003), *Nucleic Acids Res., February* 15; 31(4):e12). See also, Example 14 for a detailed description. To show that both targeting events occurred on the same chromosome several double targeted clones were selected for the in vitro deletion with pCMV C31deltaCpG. The clones were expanded under antibiotic pressure on a mitotically inactivated feeder layer comprised of mouse embryonic fibroblasts in DMEM High Glucose medium containing 20% FCS (PAN) and 1200μ/mL Leukemia Inhibitory Factor (Millipore ESG 1107). 1×10^7 cells from each clone were electroporated with 20 μg of circular pCMV C31deltaCpG at 240 V and 500 μF and plated on four 10 cm dishes each. Two to three days after electroporation, cells were harvested and analyzed by PCR. Primers used were:

(SEQ ID NO: 1)
20055: CCCTTTCCAATCTTTATGGG

(SEQ ID NO: 2)
20057: AGGTGGATTGGTGTCTTTTTCTC

(SEQ ID NO: 3)
20059: GTCATGTCGGCGACCCTACGCC

[0141] PCR reactions were performed in mixtures comprising 5 μl PCR Buffer 10x (Invitrogen), 2 μl $MgCl_2$ (50 mM), 1 μl dNTPs (10 mM), 1 μl first primer (5 μM), 1 μl second primer (5 μM), 0.4 μl Taq (5 U/ul, Invitrogen), 37.6 μl H_2O, and 2 μl DNA. The program used was 95° C. for five minutes; followed by 35 cycles of 95° C. for 30 seconds; 60° C. for 30 seconds; 72° C. for 1 minute; followed by 72° C. for ten minutes.

Generation of ES Mice by Tetraploid Embryo Complementation

[0142] The production of mice by tetraploid embryo complementation using genetically modified ES cells was essentially performed as described (Eggan et al., *PNAS* 98:6209-6214; J. Seibler, B. Zevnik, B. Kiiter-Luks, S. Andreas, H. Kern, T. Hennek, A. Rode, C. Heimann, N. Faust, G. Kauselmann, M. Schoor, R. Jaenisch, K. Rajewsky, R. Kuhn, and F. Schwenk (2003), *Nucleic Acids Res., February* 15; 31(4):e12; Hogan et al. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y.), pp. 253-289).

Example 5: Construction of the CAGGS Expression Insert Based on a Rearranged Human Germline IGKV1-39/J-Ck Gene (IGKV1-39/J-Ck)

[0143] This example describes the construction of a CAGGS expression cassette incorporating the rearranged human germline IGKV1-39/J region. This insert expression cassette encompasses cloning sites, a Kozak sequence, a leader sequence containing an intron, an open reading frame of the rearranged IGKV1-39 region, a rat CK constant

region from allele a and a translational stop sequence (IGKV1-39/J-Ck; FIG. **6**). The primary construct consists of naturally occurring sequences and has been analyzed and optimized by removing undesired cis acting elements like internal TATA-boxes, poly adenylation signals, chi-sites, ribosomal entry sites, AT-rich or GC-rich sequence stretches, ARE-, INS- and CRS sequence elements, repeat sequences, RNA secondary structures, (cryptic) splice donor and acceptor sites and splice branch points (GeneArt GmbH). In addition, the codon usage in the open reading frame regions is optimized for expression in mice. The intron sequence is unchanged and thus represents the sequence identical to the coding part of the human IGKV1-39 leader intron.

[0144] At the 5' end of the expression cassette, a NotI site was introduced and on the 3' site a NheI site. Both sites are used for cloning in the CAGGS expression module. After gene assembly according to methods used by GeneArt, the insert is digested with NotI-NheI and cloned into the expression module containing a CAGGS promoter, a stopper sequence flanked by LoxP sites ("foxed"), a polyadenylation signal sequence and, at the 5' and 3' end, sequences to facilitate homologous recombination into the Rosa26 locus of mouse ES cell lines. Promoter and/or cDNA fragments were amplified by PCR, confirmed by sequencing and/or cloned directly from delivered plasmids into an RMCE exchange vector harboring the indicated features. A schematic drawing and the confirmed sequence of the final targeting vector pCAGGS-IgVK1-39 are shown in FIGS. **13**A and **13**B. The targeting strategy is depicted in FIG. **13**C.

Example 6: CAGGS Expression Insert Based on the Rearranged Germline IGLV2-14/J V Lambda Region (IGLV2-14/J-Ck)

[0145] This example describes the sequence and insertion of an expression cassette incorporating the rearranged germline IGLV2-14/J V lambda region. This insert encompasses cloning sites, a Kozak sequence, a leader sequence containing an intron, an open reading frame of the rearranged IGLV2-14/J region, a rat CK constant region from allele a and a translational stop sequence (IGLV2-14/J-Ck; FIG. **7**). The primary construct consists of naturally-occurring sequences and has been analyzed and optimized by removing undesired cis acting elements like: internal TATA-boxes, poly adenylation signals, chi-sites, ribosomal entry sites, AT-rich or GC-rich sequence stretches, ARE-, INS- and CRS sequence elements, repeat sequences, RNA secondary structures, (cryptic) splice donor and acceptor sites and splice branch points (GeneArt GmbH). In addition, the codon usage in the open reading frame regions was optimized for expression in mice. The intron sequence is unchanged and thus represents the sequence identical to the human IGKV1-39 leader intron.

[0146] At the 5' end of the expression cassette, a NotI site was introduced and on the 3' site a NheI site. Both sites are used for cloning in the CAGGS expression module as described by TaconicArtemis. After gene assembly according to methods used by GeneArt, the insert was digested with NotI-NheI and cloned into the expression module containing a CAGGS promoter, a stopper sequence flanked by LoxP sites ("foxed"), a polyadenylation signal sequence and, at the 5' and 3' end, sequences to facilitate homologous recombination into the Rosa26 locus of mouse ES cell lines. To construct the final ROSA26 RMCE targeting vector, promoter and/or cDNA fragments were amplified by PCR. Amplified products were confirmed by sequencing and/or cloned directly from delivered plasmids into an RMCE exchange vector harboring the indicated features. A schematic drawing and the confirmed sequence of the final targeting vector pCAGGS-IgVL2-14 is shown in FIGS. **15**A and **15**B. The targeting strategy is depicted in FIG. **15**C.

Example 7: Expression of IGKV1-39/J-Ck in HEK293 Cell Lines (pSELECT-IGKV1-39/J-Ck)

[0147] This example describes a method to verify that the IGKV1-39/J-Ck constructs described in Example 5 enable expression and detection of the IGKV1-39/J-Ck L chain in HEK293 cells. The IGKV1-39/J insert (FIG. **6**) was modified at the 5' end by changing the NotI site into a SalI site. This change is required for cloning of the product into the expression cassette plasmid pSELECT-hygro (InvivoGen). The CAGGS expression insert IGKV1-39/J-Ck and pSELECT-hygro were digested with SalI and NheI, ligated and used to transform competent XL1-Blue cells using standard techniques. Colonies were picked and DNA purified using Qiagen Midi-prep columns according to the manufacturer's procedures. The resulting light chain (LC) expressing vector named 0817676pSELECT 0815426 was used to transfect HEK293 cells with Fugene6 (Roche) according to the manufacturer's protocols. Supernatants were screened for the presence of IGKV1-39/J-Ck light chains by ELISA and western blot using anti-rat-Ck antibodies (Beckton Dickinson #550336 and 553871) and protocols used in the art.

[0148] The VH of anti-tetanus toxoid (TT) IgG MG1494 was cloned into IgG expression vector MV1056 using restriction sites SfiI and BstEII. The resulting clone was sequence verified. HEK293T cells were transfected with five different vector combinations as shown in Table 4 (see Example 8 for details of vector 0817678_pSELECT_0815427). Supernatants were harvested and IgG concentrations determined (see Table 4). No IgG could be detected for supernatants A and B containing light chain only as expected (detection antibody recognized Fc part of IgG). IgG concentration in supernatants C and D was comparable to that of positive control supernatant E, indicating correct expression of the light chain constructs.

[0149] Binding to TT was analyzed by ELISA to check functionality of the produced antibodies, using hemoglobin as negative control antigen. No TT-specific binding could be detected for supernatants A and B containing light chain only, as expected. TT-specific binding for supernatants C and D was at least as good as for positive control supernatant E, confirming correct expression of the light chain constructs and functional assembly with heavy chain. Antibodies were detected not only using an anti-human IgG secondary antibody, but also an anti-rat Ckappa light chain secondary antibody. The results confirm that the anti-rat Ckappa antibody (BD Pharmingen #553871, clone MRK-1) recognizes the light chain expressed by the pSELECT vectors.

[0150] Supernatants were analyzed by non-reducing SDS-PAGE and Western blot (not shown). Detection using an anti-human IgG heavy chain antibody did not show bands for supernatants A and B containing light chain only, as expected. Results for supernatants C and D were comparable to positive control supernatant E, with a band close to the 170 kD marker as expected for intact IgG. Additional lower molecular weight bands were observed as well for supernatants C, D and E, which might represent degradation prod-

ucts, IgG fragments resulting from (partial) reduction and/or irrelevant protein bands due to non-specific binding of the detection antibody.

[0151] Detection using an anti-rat Ckappa light chain antibody showed a band close to the 26 kD marker for supernatants A and B, as expected for light chain only. This band was much more intense for A compared to B, indicating that the free IGKV1-39 light chain may be better expressed and/or more stable than the free IGLV2-14 light chain. No bands were detected for control supernatant E as expected, since the expressed IgG contains a human Ckappa light chain. For supernatants C and D, expected bands close to the 170 kD marker were observed; lower molecular weight bands were also observed, but to a lesser extent than above using the anti-human IgG antibody.

[0152] In conclusion, transfection of the light chain expression constructs combined with the heavy chain of anti-tetanus toxoid (TT) IgG MG1494 resulted in IgG production comparable to the positive control construct for both the pSELECT kappa and lambda light chain constructs. Both IgG productions yielded ELISA signals in a TT ELISA that were better than or comparable to the control IgG. SDS-PAGE and Western blot analysis confirmed the presence of intact IgG. The tested anti-rat Ckappa antibody worked efficiently in both ELISA and Western blot. Culture supernatant from cells transfected with light chain constructs only did not result in detectable IgG production nor in detectable TT-specific binding, while free light chain was detected on Western blot.

Example 8: Expression of IGLV2-14/J-Ck in HEK293 Cell Lines (pSELECT-IGLV2-14/J-Ck)

[0153] This example describes a method to verify that the IGLV2-14/J constructs described in Example 6 enable expression and detection of the IGLV2-14/J-Ck L chain in HEK293 cells. The IGLV2-14/J-Ck insert (FIG. **7**) was modified at the 5' end by changing the NotI site into a SalI site. This change is required for cloning of the product into the expression cassette plasmid pSELECT-hygro (InvivoGen). The CAGGS expression insert IGLV2-14/J-Ck and pSELECT-hygro were digested with SalI and NheI ligated and used to transform competent XL1-Blue cells using standard techniques. Colonies were picked and DNA purified using Qiagen Midi-prep columns according to the manufacturer's procedures. The resulting light chain (LC) expressing vector named 0817678pSELECT 0815427 was used to transfect HEK293 cells with Fugene6 (Roche) according to the manufacturer's protocols. Supernatants were screened for the presence of IGLV2-14/J-Ck light chains by ELISA and western blot using anti-rat-Ck antibodies (Becton Dickinson #550336 and 553871) and protocols used in the art. See Example 7 for details and results.

Example 9: Construction of a VK Promoter-Driven Expression Construct Containing an IGKV1-39/J Insert and Multiple Enhancer Elements Derived from the Murine CK Locus (VkP-IGKV1-39/J-Ck; VkP-O12)

[0154] This example describes the construction of an expression cassette that contains relevant elements to enable B-cell and developmental/differentiation stage-specific expression of the rearranged human IGKV1-39 VK region, based on the IGKV1-39 VK promoter region, leader containing an intron, germline V-gene, CDR3, IGKJ segment, mouse intergenic region located between Jk and CK, rat Ck allele a open reading frame, and a mouse intergenic fragment from the 3' end of the mouse CK gene ending just 3' of the 3' CK enhancer.

[0155] Optimized open reading frames of the leader, IGKV1-39 rearranged gene, and rat CK allele a gene, as described in Example 5, was used for the construction of the expression cassette. The VK promoter region was obtained by gene synthesis procedures (GeneArt, GmbH) and is almost identical to the sequence of the human IGKV1-39 region between −500 bp and the ATG (start site) of the gene. The only deviation from the natural sequence is the introduction of a GCCACCATGG Kozak sequence (SEQ ID NO:102) at the ATG (start) site in order to promote translation. A genomic fragment from a mouse BAC clone (TaconicArtemis) is used as the basis for the introduction of individual elements. This fragment is identical to the sequence of the mouse VK locus starting with the intron donor site located directly 3' of the JK5 region and ending just 3' of the 3' CK enhancer and covers approximately 12.5 kb.

[0156] The final construct contains from 5' to 3' end the following elements: human genomic IGKV1-39 promoter (500 bp), a Kozak sequence, a human IGKV1-39 leader part 1 (optimized), a human IGKV1-39 leader intron, a human IGKV1-39 leader part 2 (optimized), a human IGKV1-39 germline gene (optimized), a human J-region (optimized), a mouse intergenic region including the intron enhancer element, a rat (*Rattus norvegicus*) kappa constant region (optimized), and a mouse intergenic region including the 3' kappa enhancer. The elements of this expression cassette are shown in FIG. **8** and named VkP-IGKV1-39/J-Ck (VkP-O12). An outline of the pVkP-O12 vector and the targeting strategy is depicted in FIGS. **20**A and **21**A. The vector was introduced into ES cells following standard procedures (see Example 14).

Example 10: Construction of a VK Promoter-Driven Expression Construct Containing an IGLV2-14/J Clone and Multiple CK Locus-Derived Enhancer Elements (VkP-IGLVL2-14/J-Ck; VkP-2a2)

[0157] This example describes the same construct as described in Example 9, except that the IGKV1-39 gene and J-region are replaced by the optimized human IGLV2-14 germline gene including a unique V-J region (VkP-IGLV2-14/J-Ck; VkP-2a2; FIG. **9**).

Example 11: Construction of a VK Promoter-Driven Expression Construct Containing an IGKV1-39 Clone Lacking the CK Intron Enhancer Element (VkP-IGKV1-39/J-Ck-Δ1; VkP-O12-del1)

[0158] The construct described in Example 9 was modified by removing the CK intron enhancer element, located in the intergenic region between the human J region and the rat CK region by standard PCR modification and DNA cloning methodologies (GeneArt, GmBH). The resulting expression cassette is shown in FIG. **10** and named VkP-IGKV1-39/J-Ck-Δ1 (VkP-O12-del1).

[0159] An outline of the pVkP-O12-del1 vector and the targeting strategy is depicted in FIGS. **20**B and **21**B. The

vector was introduced into ES cells following standard procedures (see Example 14).

Example 12: Construction of a VK Promoter-Driven Expression Construct Containing an IGKV1-39 Clone Lacking the CK Intron Enhancer Element and a Truncated 3' CK Enhancer Element (VkP-IGKV1-39/J-Ck-Δ2; VkP-O12-De12)

[0160] The construct described in Example 11 was modified by truncating the 3' CK enhancer element and deleting part of the intergenic region 3' of the rat Ck gene, to remove potential inhibitory elements. This was achieved by removing the intergenic sequence between an EcoRV site (located 3' of the rat Ck gene) and the NcoI site present in the 3' enhancer (5993 bp) and further removing the sequence between the 3' enhancer BstXI site and the BstXI site 3' of the 3' enhancer (474 bp) using standard methods. The resulting expression cassette is shown in FIG. **11** and named VkP-IGKV1-39/J-Ck-Δ2 (VkP-O12-de12).

[0161] An outline of the pVkP-O12-de12 vector and the targeting strategy is depicted in FIGS. **20**C and **21**C. The vector was introduced into ES cells following standard procedures (see Example 14).

Example 13: Expression of Vk Constructs in Cell Lines

[0162] The constructs described in Examples 9-12 are tested for their ability to produce light chain proteins in the myeloma cell lines MPC11 (ATCC CCL167), B-cell lymphoma WEHI231 (ATCC CRL-1702), the T-cell lymphoma EL4 (ATCC TIB-39) and in HEK293 (ATCC CRL1573). The enhancer and promoter elements in the construct enable expression in the B-cell lines but not in cell lines derived from other tissues. After transfection of the cell lines using purified linearized DNA and Fugene6 (Roche) cells are cultured for transient expression. Cells and supernatant are harvested and subjected to SDS-PAGE analysis followed by western blotting using a specific anti-rat-C-kappa antibody. Supernatants are analyzed in ELISA for secreted L chains using the anti-rat CK antibody (Beckton Dickinson #550336).

Example 14: Generation of Transgenic ES Lines

[0163] All constructs as described in Examples 3, 4, 5, 6, 9, 10, 11 and 12 were used to generate individual stable transgenic ES lines by means of homologous recombination. The methods for generation of transgenic ES lines via homologous recombination are known in the field (e.g., Eggan et al., *PNAS* 98:6209-6214; J. Seibler, B. Zevnik, B. KUter-Luks, S. Andreas, H. Kern, T. Hennek, A. Rode, C. Heimann, N. Faust, G. Kauselmann, M. Schoor, R. Jaenisch, K. Rajewsky, R. Kuhn, F. Schwenk (2003), *Nucleic Acids Res., February* 15; 31(4):e12; Hogan et al. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y.), pp. 253-289).

[0164] For all constructs described in Examples 5 and 6, and Examples 9-12, the RMCE ES cell line (derived from mouse strain 129S6B6F1-Gt(ROSA)26Sortml0Arte) was grown on a mitotically inactivated feeder layer comprised of mouse embryonic fibroblasts (MEF) in DMEM High Glucose medium containing 15% FBS (PAN 1302-P220821). Leukemia Inhibitory Factor (Chemicon ESG 1107) was added to the medium at a concentration of 900 U/mL. For manipulation, 2×10^5 ES-cells were plated on 3.5 cm dishes in 2 ml medium. Directly before transfection, 2 ml fresh medium was added to the cells. Three μl Fugene6 Reagent (Roche; Catalog No. 1 814 443) was mixed with 100 μl serum free medium (OptiMEM I with Glutamax I; Invitrogen; Catalog No. 51985-035) and incubated for five minutes. One hundred μl of the Fugene/OptiMEM solution was added to 2 μg circular vector and 2 CAGGS-Flp and incubated for 20 minutes. This transfection complex was added dropwise to the cells and mixed. Fresh medium was added to the cells the following day. From day 2 onwards, the medium was replaced daily with medium containing 250 μg/mL G418 (Geneticin; Invitrogen; Catalog No. 10131-019). Seven days after transfection, single clones were isolated, expanded, and molecular analyzed by Southern blotting according to standard procedures.

[0165] For each construct, analysis of multiple clones by restriction enzyme digestion of genomic DNA of single clones followed by hybridization with 5' probes, 3' probes, and internal probes resulted in clones that comprised a correct, single insertion at the correct position in the Rosa26 locus. An example is provided in FIGS. **14**A-C.

Example 15: Generation of Transgenic Mouse Strains

[0166] All ES cell lines that were generated and verified for their modifications as described in Example 14 were used to generate stable transgenic mice by means of tetraploid recombination. The methods are known in the field. In general, after administration of hormones, superovulated Balb/c females were mated with Balb/c males. Blastocysts were isolated from the uterus at dpc 3.5. For microinjection, blastocysts were placed in a drop of DMEM with 15% FCS under mineral oil. A flat tip, piezo actuated microinjection-pipette with an internal diameter of 12-15 micrometers was used to inject 10-15 targeted C57BL/6 N.tac ES cells into each blastocyst. After recovery, injected blastocysts were transferred to each uterine horn of 2.5 days post coitum, pseudopregnant NMRI females. Chimerism was measured in chimeras (G0) by coat color contribution of ES cells to the Balb/c host (black/white). Highly chimeric mice were bred to strain C57BL/6 females. Depending on the project requirements, the C57BL/6 mating partners are non-mutant (W) or mutant for the presence of a recombinase gene (Flp-Deleter or Cre-deleter or CreER inducible deleter or combination of Flp-deleter/CreER). Germline transmission was identified by the presence of black, strain C57BL/6, offspring (G1).

[0167] For example, ESC clone IgVK1-39 2683 8 (see Examples 5 and 14) was injected in a total of 62 blastocysts in three independent experiments. Three litters were obtained with a total of six pups. All pups were chimeric. Three heterozygous offspring pups were obtained that were used for further crossing.

[0168] ESC Clone Kappa 2692 A-C10 (see Examples 3 and 14) was injected in a total of 54 blastocysts in three independent experiments. Three litters were obtained with a total of eleven pups, of which ten were chimeric. Eight heterozygous offspring pups were obtained that were used for further crossing.

[0169] ESC Clone Kappa 2692 B-C1 (see Examples 3 and 14) was injected in a total of 51 blastocysts in three independent experiments. Two litters were obtained with a

total of six pups, of which four were chimeric. Three heterozygous offspring pups were obtained that were used for further crossing.

Example 16: Breeding

[0170] This example describes the breeding for obtaining mice that contain transgenic expression cassettes as described Example 14 and knock-out mice in which the endogenous lambda and kappa loci have been silenced. The localization of V-lambda on chromosome 16 and CD19 on chromosome 7 allow standard breeding procedures. The breeding of the co-localized Vk locus and Rosa26 locus on chromosome 6 with a distance of about 24 cM requires special attention during the screening as only a percentage of the offspring shows crossover in a way that both modifications are brought together on one chromosome.

[0171] All four loci have to be combined in a single mouse strain that is homo- or heterozygous for CD19-cre (not described) and modified Rosa26 transgene and homozygous for the other loci. Breeding is performed by standard breeding and screening techniques as appropriate and offered by commercial breeding companies (e.g., TaconicArtemis).

Example 17: Immunizations of Mice

[0172] Primary and booster immunization of mice are performed using standard protocols.

[0173] To validate the transgenic expression of human rearranged Vκ O12 (IGKV1-39)—rat Cκ light chains (see Examples 5, 14-16) in B cells from CD19-HuVκ1 mice and to assess its impact on VH repertoire size, diversity of VH family usage and V(D)J recombination after immunization, the CD19-HuVκ1 transgenic mice are immunized with tetanus toxin vaccine (TT vaccine) and VH sequence diversity of randomly picked clones from CD19-HuVκ1 mice are compared with TT-immunized wt mice and CD19-Cre HuVk1 negative littermates. Data on the SHM frequency of the human Vκ O12 transgene in the immunized mice are obtained. A diverse collection of at least 40 TT-specific, clonally-unrelated mAbs containing the human Vκ O12 are recovered from CD19-HuVκ1 mice by phage display.

[0174] For this, three adult CD19-HuVκ1 mice are vaccinated with TT vaccine using standard immunization procedures. After immunization, serum titers are measured using TT specific ELISA (TT: Statens Serum Institute, Art. no. 2674) and spleen suspensions subjected to cell sorting by the FACS procedure after staining with a rat Cκ-specific monoclonal antibody to isolate transgenic B cells (clone RG7/9.1; BD Pharmingen#553901, Lot#06548). RNA from rat Cκ-positive B cells are extracted and the resulting cDNA material used for library building and SHM analysis.

[0175] The standard monoclonal mouse anti-rat Cκ antibody (clone RG7/9.1; BD Pharmingen#553901, Lot#06548) is used in FACS analysis of transgene expressing B cells (Meyer et al. (1996), *Int. Immunol.* 8:1561). The clone RG7/9.1 antibody reacts with a monotypic (common) kappa chain determinant. This anti-rat Cκ antibody (clone RG7/9.1 (BD Pharmingen#553901, Lot#06548) is labeled with R-phycoerythrin (PE) using the LYNX rapid conjugation kit according to the manufacturer's instructions for FACS analysis and sorting. The labeled antibody is firstly tested by flow cytometry for binding to rat Cκ-containing functional light chain proteins produced into transiently transfected HEK-293T cells; the un-conjugated antibody serves as a positive control. Two other antibodies shown to bind to rat Cκ by ELISA and Western-blot (see Example 7) are tested as well by flow cytometry.

[0176] Fab-phage display library building is carried out with a set of optimized degenerate PCR primers designed to amplify C57BL/6 VH genes; the minimal library size is 10^6 clones, and minimal insert frequency is 80%. The vector used, MV1043 (FIGS. **3** and **12**), contains the human Vκ O12 fused to a human Cκ region. The rat Cκ is therefore exchanged for the human counterpart in the library generation process.

[0177] Before selection, VH sequencing of 96 randomly picked clones is performed to validate VH repertoire diversity that is compared to diversity obtained from an unselected library previously generated using the same procedures from BALB/c mice immunized with TT. A library from C57Bl/6 wt mice that are immunized in the same way allows diversity comparison between two preselected libraries sharing the same vaccine and the same genetic background.

[0178] Several independent selections are performed on TT coated in immunotubes. Variables that may be included are selections using biotinylated antigens in solution or selections on captured TT. Based on the number and diversity of ELISA-positive clones obtained in the first selections, decisions on additional rounds of selection are made. Clones are considered positive when >3× positive over a negative control clone. Positive clones are analyzed by ELISA against a panel of negative control antigens to verify antigen specificity. The aim is to identify at least 40 unique VH regions, as based on unique CDR3 sequences and V_HDJ_H rearrangements.

[0179] Amplification of the cDNA material from rat CK-positive sorted B cells is performed with a PCR forward primer specific to the human leader sequence and a PCR reverse primer specific to the rat Cκ sequence, in a region not redundant with the mouse Cκ sequence, as reported in a recent study (Brady et al. (2006), *JIM* 315:61). Primer combinations and annealing temperatures are firstly tested on cDNA from HEK-293T cells transfected with 0817676_pSELECT_0815426=pSELECT vector with IGKV1-39 DNA cassette (see Example 7).

[0180] The amplification products is cloned in pJET-1 vector and after XL1-blue transformation, 96 colonies are sequenced for assessing VL SHM frequency by direct comparison to the Vκ O12 (IGKV1-39) germline sequence. The R/S ratio method, as described in our study on human TT-specific antibodies (de Kruif et al. (2009), *J. Mol. Biol.* 387:548) allows discrimination between random mutations and antigen-driven mutations that occurred on VL sequences.

Example 18: Immunofluorescent Analysis of B Cell Populations in Transgenic Mouse Lines

[0181] This example describes the use of antibodies and flow cytometry to analyze B cell populations in primary (bone marrow) and secondary (spleen, peritoneal) lymphoid organs and blood. Methods and reagents are described in Middendorp et al. (2002), *J. Immunol.* 168:2695; and Middendorp et al. (2004), *J. Immunol.* 172:1371. For analysis of early B cell development in bone marrow, cells were surface stained with combinations of antibodies (Becton Dickinson) specific for B220, CD19, CD25, IgM, IgD, mouse Ckappa, mouse Clambda and rat Ckappa to detect pro-B cells, pre-B

cells, large pre-B cells, early and late immature B cells and recirculating B cell populations expressing the transgene on their surface. DAPI staining (Invitrogen) was included to exclude dead cells from the analysis and FC block (Becton Dickinson) to inhibit antibody interaction with Fc receptors on myeloid cells. For analysis of surface transgene expression on B cell populations in peripheral lymphoid organs and blood, cells were stained with combinations of antibodies (Becton Dickinson) specific for B220, CD5, CD19, CD21, CD23, IgM, IgD, mouse Ckappa, mouse Clambda and rat Ckappa. DAPI staining was included to exclude dead cells from the analysis and FC block to inhibit antibody interaction with Fc receptors on myeloid cells. In addition, combinations of antibodies (Becton Dickinson) specific for CD3, CD4, CD11b, CD11c and NK1.1 were included to determine if transgene expression occurred in cell types outside of the B cell compartment.

[0182] Three mice heterozygous for the human IGKV1-39/rat Ckappa transgene and heterozygous for the CD19-Cre transgene on a C57BL6 background (HuVk1/CD19-Cre) were analyzed. As controls for the FACS analysis, three littermate mice wild-type for the human IGKV1-39/rat Ckappa transgene and heterozygous for the CD19-Cre transgene on a C57BL6 background (CD19-Cre) and two C57BL6/NTac mice (Wt) were included. All animals were allowed to acclimatize in the animal facility for one week before analysis and all mice were male and six weeks of age. Lymphocytes were isolated from the femurs, spleens, peritoneal cavity and blood of mice using conventional techniques as previously described (Middendorp et al. (2002), *J. Immunol.* 168:2695; and Middendorp et al. (2004), *J. Immunol.* 172:1371). Antibodies were pre-combined as shown in FIG. **29**A-B and staining was carried out in 96-well plates. Incubation with the PE-conjugated anti-rat C kappa (described above) was carried out before staining with the rat anti-murine antibodies to avoid non-specific binding. After completion of cell staining, labeled cells were analyzed on a Becton Dickinson LSR II FACS machine and the acquired data analyzed with FlowJo software (v6.4.7).

[0183] Transgenic mice were similar in weight, appearance and activity to wild-type mice. No gross anatomical alterations were observed during the harvesting of tissues. No difference was observed in the numbers of B cells in the bone marrow (BM) and spleen (Table 9) or in the numbers of B cells, T cells and myeloid cells in peripheral organs between transgenic and wild-type mice. In addition, the frequency or proportion of the cells in the different lymphocyte developmental pathways was not altered in transgenic mice when compared to wild-type mice. Thus in the double transgenic (HuVk1/CD19-Cre) and transgenic (CD19-Cre) mice lymphoid and most importantly B cell development was indistinguishable from wild-type mice.

[0184] In the peripheral lymphoid organs, staining with the transgene specific antibody (anti-ratCkappa-PE) was only observed in the B cell populations. T cell, myeloid cell and NK cell populations were all negative for surface expression of the transgene in the spleen (FIG. **23**). In contrast, in cells stained with the pan B cell markers B220 and CD19 all cells were shifted to the right in the FACS plot indicating cell surface expression of the transgene (FIG. **24**). A similar transgene-specific staining was measured in $CD5^+$ B1 cells of the peritoneum, a developmentally distinct population of B cells (FIG. **25**).

[0185] Differentiation of B cells from multilineage precursors to mature B cells occurs in the bone marrow. In the lymphocytes analyzed from the bone marrow, extracellular and transgene expression was not detectable in the earliest B cell progenitors the pro- and pre-B cell consistent with the pattern of normal light chain expression (FIGS. **26**A-B). Transgene expression first becomes detectable in immature B cells, the developmental stage at which the germline murine light chain undergoes rearrangement and is expressed at the cell surface in the context of the preselected heavy chain (FIGS. **26**A-B). Consistent with the staining in the spleen transgenic light chain expression is also detected on mature recirculating B cells (FIGS. **26**A-B). Thus the CD19-Cre driven expression of the transgene is consistent with the normal pattern of light chain expression. The staining with the endogenous light chain-specific antibody is more intense than that of the transgene-specific light chain antibody. This may indicate a higher expression level of the endogenous light chain, a more sensitive staining with the endogenous light chain-specific antibody or a combination of both. Importantly, the intensity of the surface expression of the transgenic light chain is correlated with both endogenous light chain and IgM surface expression as observed in staining of circulating B cells in the blood (FIG. **27**).

[0186] Thus, overall this analysis demonstrates that expression of the human IGKV1-39/Ckappa transgene is restricted to the B cell compartment and the temporal regulation of its expression is similar to the endogenous kappa and lambda light chains resulting in normal development of all B cell populations. The apparent lower level of expression of the transgene could be explained by the strength of the promoter in comparison to the promoter and enhancers present on endogenous light chain genes or by a delay in transgene expression that gives the endogenous light chains a competitive advantage in pairing with the rearranged heavy chain. This is consistent with the observation that as B cells mature the relative intensity of transgene staining increases compared to the endogenous light chains. In addition, the observation that B cells numbers are normal and that every surface Ig+B cell co-expresses an endogenous and transgenic light chain supports the conclusion that the IGKV1-39 variable region is capable of pairing with a normal repertoire of different murine heavy chain variable regions. We conclude from this analysis that insertion of the IGKV1-39/rat Ckappa transgene driven by the CD19-Cre activated CAGGS promoter in the Rosa locus facilitates timely and B cell-specific expression of the transgene and that the transgene is capable of pairing with a normal repertoire of murine heavy chains.

Example 19: Epibase® T-Cell Epitope Profile for IGKV1-39

[0187] The protein sequence of IGKV1-39 (FIG. **12**, human germline IGKV1-39/J Protein) was scanned for the presence of putative HLA class II restricted epitopes, also known as T_H-epitopes. For this, Algonomics' Epibase® platform was applied to IGKV1-39. In short, the platform analyzes the HLA binding specificities of all possible 10-mer peptides derived from a target sequence (Desmet et al. (1992), *Nature* 356:539-542; Desmet et al. (1997), *FASEB J.* 11:164-172; Desmet et al. (2002), *Proteins* 48:31-43; Desmet et al. (2005), *Proteins* 58:53-69). Profiling is done at the allotype level for 20 DRB1, 7 DRB3/4/5, 13 DQ and 7 DP, i.e., 47 HLA class II receptors in total (see Table

5). Epibase® calculates a quantitative estimate of the free energy of binding ΔG_{bind} of a peptide for each of the 47 HLA class II receptors. These data were then further processed as follows:

[0188] Free energies were converted into Kd-values through ΔG_{bind}=RT ln(Kd).

[0189] Peptides were classified as strong (S), medium (M), weak and non (N) binders. The following cutoffs were applied:

[0190] S: strong binder: Kd<0.1 μM.

[0191] M: medium binder: 0.1 μM≤Kd<0.8 μM.

[0192] N: weak and non-binder: 0.8 μM≤Kd.

[0193] Peptides corresponding to self-peptides were treated separately. The list of self-peptides was taken from 293 antibody germline sequences. They are referred to as "germline-filtered" peptides.

[0194] S- and M-peptides are mapped onto the target sequence in so-called epitope maps; S-affinities are plotted quantitatively; M-values are presented qualitatively. As a general overview of the results, Table 6 lists the number of strong and medium binders in the analyzed proteins, for the groups of HLA class II receptors corresponding to the DRB1, DQ, DP and DRB3/4/5 genes. Counting was done separately for strong and medium affinity binders. Peptides binding to multiple allotypes of the same group were counted as one. Values between brackets refer to germline-filtered peptides. In Table 7, the sequence is shown in a format suitable for experimental work. The sequence is broken down in consecutive 15-mers overlapping by 12 residues. For each 15-mer, the promiscuity is listed (the number of allotypes out of a total of 47 for which the 15-mer contains a critical binder), as well as the implied serotypes. The Epibase® profile and epitope maps are shown in FIGS. **16**A-C and **17**.

[0195] It was concluded that IGKV1-39 contains no strong non-self DRB1 binders. Typically, significantly more binders were found for DRB1 than for other HLA genes. This is in agreement with experimental evidence that allotypes belonging to the DRB1 group are more potent peptide binders. Medium strength epitopes for DRB1 allotypes are expected to contribute to the population response, and cannot be disregarded. Again, no non-self DRB1 binders were found in IGKV1-39.

[0196] In the humoral response raised against an antigen, the observed T_H cell activation/proliferation is generally interpreted in terms of the DRB1 specificity. However, one cannot ignore the possible contribution of the DRB3/4/5, DQ and DP genes. Given the lower expression levels of these genes as compared to DRB1, the focus was on the class of strong epitopes for DRB3/4/5, DQ and DP. "Critical epitopes" are those epitopes that are strong binders for any DRB1, DRB3/4/5, DQ or DP allotype or are medium binders for DRB1. IGKV1-39 contains no strong or medium non-self binders for DRB3/4/5, DQ, or DP.

[0197] A number of peptides are also present in germline sequences (values between brackets in Table 6). Such peptides may very well bind to HLA but they are assumed to be self and, hence, non-immunogenic. In total, six strong and 16 medium germline-filtered DRB1 binders were found in IGKV1-39. Framework region 1 up to framework region 3 is an exact match for germline V-segment VKI 2-1-(1) O12 (VBase), a.k.a. IGKV1-39*01 (IMGT). Framework region 4 is an exact match for germline J-segment JK1 (V-base) a.k.a. IGKJ1*01(IMGT). It is hardly surprising that these segments do not contain any non-self epitopes.

Example 20: Production Characteristics of IGKV1-39

[0198] There is a great demand for antibody discovery platforms that yield therapeutic antibodies that are thermodynamically stable and give good expression yields. These characteristics are important in ensuring the stability of the drug substance during production and after injection of the drug product into the patient. In addition good expression yields impact directly on the cost of drug manufacture and thus pricing, patient access and profitability. Virtually all therapeutic antibodies in clinical use today are composed of human IgG1 and kappa constant regions but use different heavy and light chain variable regions that confer specificity. Human variable heavy and light chain domains can be divided into families that have greater than 80% sequence divergence. When rearranged examples of these families in germline configuration are combined and compared for stability and yield it is clear that the gene families are not equal in terms of biophysical properties. In particular V_H3, V_H1 and V_H5 have favourable stability for the heavy chains and Vk1 and Vk3 have the best stability and yield of light chains. In addition when mutations are introduced as part of the somatic hypermutation process they can interfere with V_H/V_L pairing. To assess the effect that different light chain genes with different rates of mutation have on the production characteristics of a fixed V_H chain, a Fab phage display library was built of light chains (kappa and lambda) from six naïve healthy donors combined with a panel of 44 TT binding heavy chains from immunized donors. After one round of selection TT binding Fab clones were isolated. Several of these shared the same V_H gene as the TT clone PG1433 in combination with different light chains. The Fab light chain fragments were recloned into a kappa expression vector and transfected in combination with DNA encoding the heavy chain of PG1433 into 293 cells and specific IgG production measured by ELISA. As demonstrated in Table 8 the selected clones containing PG1433 V_H combined with different light chains had between five- and ten-fold lower protein expression PG1433 V_H combined with IGKV1-39. Note that all of the light chains contained amino acid mutations within their coding regions that might disrupt V_H paring and reduce production stability. Thus, in addition to reducing the chances of unwanted immunogenicity, it is expected that the use of the light chain IGKV1-39 without mutations contributes to improved production stability and yields of various specificity-contributing V_H genes. Indeed stable clones generated by the transfection of different V_H genes all paired with IGKV1-39 are able to be passaged extensively and still retain robust production characteristics as shown in Table 9 FIG. **28**.

Example 21: Generation of Mice Expressing Fully Human VH and VL Regions

[0199] Transgenic mice described herein are crossed with mice that already contain a human VH locus. Examples of appropriate mice comprising a human VH locus are disclosed in Taylor et al. (1992), *Nucleic Acids Res.* 20:6287-95; Lonberg et al. (1994), *Nature* 368:856-9; Green et al. (1994), *Nat. Genet.* 7:13-21; Dechiara et al. (2009), *Methods Mol. Biol.* 530:311-24.).

[0200] After crossing and selecting for mice that are at least heterozygous for the IGKV1-39 transgene and the human VH locus, selected mice are immunized with a target. VH genes are harvested as described hereinabove. This method has the advantage that the VH genes are already fully human and thus do not require humanization.

Example 22: Isolation, Characterization, Oligoclonics Formatting and Production of Antibodies Targeting Human IL6 for Treatment of Chronic Inflammatory Diseases Such as Rheumatoid Arthritis

[0201] A spleen VH repertoire from transgenic mice that are immunized with human recombinant IL6 is cloned in a phage display Fab vector with a single human IGKV1-39-C kappa light chain (identical to the mouse transgene) and subjected to panning against the immunogen human IL6. Clones that are obtained after two to four rounds of panning are analyzed for their binding specificity. VH genes encoding IL6-specific Fab fragments are subjected to sequence analysis to identify unique clones and assign VH, DH and JH utilization. The Fab fragments are reformatted as IgG1 molecules and transiently expressed. Unique clones are then grouped based on non-competition in binding assays and subjected to affinity and functional analysis. The most potent anti-IL6 IgG1 mAbs are subsequently expressed as combinations of two, three, four or five heavy chains comprising different VH-regions in the Oligoclonics format, together with one IGKV1-39-C-based kappa light chain and tested in vitro for complex formation with IL-6. The Oligoclonics are also tested in vivo for clearance of human IL-6 from mice. An Oligoclonic with the most potent clearance activity is chosen and the murine VH genes humanized according to conventional methods. The humanized IgG1 are transfected into a mammalian cell line to generate a stable clone. An optimal subclone is selected for the generation of a master cell bank and the generation of clinical trial material.

[0202] Many of the protocols described here are standard protocols for the construction of phage display libraries and the panning of phages for binding to an antigen of interest and are described, for example, in *Antibody Phage Display: Methods and Protocols* (2002), Editor(s) Philippa M. O'Brien, Robert Aitken, Humana Press, Totowa, N.J., USA.

Immunizations

[0203] Transgenic mice receive three immunizations with human IL6 every two weeks using the adjuvant Sigma titerMax according to manufacturer's instructions.

RNA Isolation and cDNA Synthesis

[0204] Three days after the last immunization, spleens and lymphnodes from the mice are removed and passed through a 70 micron filter into a tube containing PBS pH 7.4 to generate a single cell suspension. After washing and pelleting of lymphocytes, cells are suspended in TRIzol LS Reagent (Invitrogen) for the isolation of total RNA according to the manufacturer's protocol and subjected to reverse transcription reaction using 1 microgram of RNA, Superscript III RT in combination with dT20 according to manufacturer's procedures (Invitrogen).

[0205] The generation of Fab phage display libraries is carried out as described in Example 2.

Selection of Phages on Coated Immunotubes

[0206] Human recombinant IL6 is dissolved in PBS in a concentration of 5 μg/ml and coated to MAXISORP™ Nunc-Immuno Tube (Nunc 444474) overnight at 4° C. After discarding the coating solution, the tubes are blocked with 2% skim milk (ELK) in PBS (blocking buffer) for one hour at Room Temperature (RT). In parallel, 0.5 ml of the phage library is mixed with 1 ml blocking buffer and incubated for 20 minutes at room temperature. After blocking the phages, the phage solution is added to the IL6-coated tubes and incubated for two hours at RT on a slowly rotating platform to allow binding. Next, the tubes are washed ten times with PBS/0.05% TWEEN™-20 detergent followed by phage elution by incubating with 1 ml 50 mM glycine-HCl pH 2.2 ten minutes at RT on rotating wheel and directly followed by neutralization of the harvested eluent with 0.5 ml 1 M Tris-HCl pH 7.5.

Harvesting Phage Clones

[0207] A 5 ml XL1-Blue MRF (Stratagene) culture at O.D. 0.4 is added to the harvested phage solution and incubated for 30 minutes at 37° C. without shaking to allow infection of the phages. Bacteria are plated on Carbenicillin/Tetracycline 4% glucose 2*TY plates and grown overnight at 37° C.

Phage Production

[0208] Phages are grown and processed as described by Kramer et al. 2003 (Kramer et al. 2003, *Nucleic Acids Res.* 31(11):e59) using VCSM13 as helper phage strain.

Phage ELISA

[0209] ELISA plates are coated with 100 microliters human recombinant IL6 per well at a concentration of 2.5 micrograms/ml in PBS overnight at 4° C. Plates coated with 100 microliters thyroglobulin at a concentration of 2 micrograms/ml in PBS are used as a negative control. Wells are emptied, dried by tapping on a paper towel, filled completely with PBS-4% skimmed milk (ELK) and incubated for one hour at room temperature to block the wells. After discarding the block solution, phage minipreps pre-mixed with 50 μl blocking solution are added and incubated for one hour at RT. Unbound phages are subsequently removed by five washing steps with PBS-0.05% Tween-20. Bound phages are detected by incubating the wells with 100 microliters anti-M13-HRP antibody conjugate (diluted 1/5000 in blocking buffer) for one hour at room temperature. Free antibody is removed by repeating the washing steps as described above, followed by TMB substrate incubation until color development was visible. The reaction is stopped by adding 100 microliters of 2 M H2SO4 per well and analyzed on an ELISA reader at 450 nm emission wavelength.

Sequencing

[0210] Clones that give signals at least three times above the background signal are propagated, used for DNA miniprep procedures (see procedures Qiagen miniPrep manual) and subjected to nucleotide sequence analysis. Sequencing is performed according to the Big Dye 1.1 kit accompanying manual (Applied Biosystems) using a reverse primer (CH1_Rev1, Table 1) recognizing a 5' sequence of the CH1 region of the human IgG1 heavy chain (present in the Fab display

vector MV1043, FIGS. **3** and **12**). The sequences of the murine VH regions are analyzed for diversity of DH and JH gene segments.

Construction and Expression of Chimeric IgG1

[0211] Vector MV1057 (FIGS. **12** and **22**) was generated by cloning the transgene (IGKV1-39) L chain fragment into a derivative of vector pcDNA3000Neo (Crucell, Leiden, The Netherlands) that contains the human IgG1- and kappa constant regions. VH regions are cloned into MV1057 and nucleotide sequences for all constructs are verified according to standard techniques. The resulting constructs are transiently expressed in HEK293T cells and supernatants containing chimeric IgG1 are obtained and purified using standard procedures as described before (M. Throsby 2006, *J. Virol.* 80:6982-92).

IgG1 Binding and Competition Analysis

[0212] IgG1 antibodies are titrated in ELISA using IL6-coated plates as described above and an anti-human IgG peroxidase conjugate. Competition ELISAs to group antibodies based on epitope recognition are performed by incubating Fab phages together with IgG1 or with commercial antibodies against IL6 (e.g., Abcam cat. no. ab9324) in IL6-coated plates, followed by detection of bound Fab phage using an anti-M13 peroxidase conjugate.

IgG1 Affinity Measurements

[0213] The affinities of the antibodies to IL6 are determined with the Quantitative kinetic protocol on the Octet (ForteBio). Antibodies are captured onto an Anti-Human IgG Fc Capture biosensor and exposed to free IL6 and analyzed using proprietary software to calculate the Kd of each antibody.

Functional Activity of IL6 Antibodies

[0214] To test the ability of the selected antibodies to inhibit binding between IL6 and IL6 receptor (IL6R), an ELISA based assay is used. Various concentrations of antibody are mixed with a fixed concentration (10 ng/ml) of biotinylated IL6 as described by Naoko et al. 2007, *Can. Res.* 67:817-875. The IL6-antibody immune complex is added to immobilized IL6R. The binding of biotinylated IL6 to IL6R is detected with horseradish peroxidase-conjugated streptavidin. The reduction of ELISA signal is a measurement of inhibition. As positive control for inhibition of binding between IL6 and IL6R either anti-IL6R antibody (Abcam cat. no. ab34351; clone B-R6) or anti IL6 antibody (Abcam cat. no. ab9324) is used.

[0215] In vitro blocking activity of the selected anti-IL6 antibodies is measured in a proliferation assay using the IL6-dependent cell line 7TD1. Briefly, cells are incubated with different concentrations of human IL6 with or without the anti-IL6 antibody. The available amount of IL6 determines the degree of proliferation. Thus if an added antibody blocks IL6 binding the proliferation readout is reduced compared to a non binding antibody control. Proliferation is measured by the incorporation of 5-bromo-2'-deoxy-uridine (BrdU) into the DNA using the BrdU proliferation kit (Roche cat. no. 11444611001) according to the manufacturer's instructions.

Generation of Anti-IL6 Oligoclonics

[0216] The most potent anti-IL6 antibodies are selected from each epitope group. The expression constructs expressing these antibodies are transfected into HEK293T cells in non-competing groups of three in different ratios (1:1:1; 3:1:1; 1:3:1; 1:1:3; 3:3:1; 1:3:3; 3:1:3; 10:1:1; 1:10:1; 1:1:10; 10:10:1; 1:10:10; 10:1:10; 3:10:1; 10:3:1; 1:10:3; 3:1:10; 10:1:3; 1:3:10). Antibody containing supernatants are harvested and purified and characterized as above.

Complex Formation and In Vivo Clearance of Anti-IL6 Oligoclonics

[0217] To measure the ability of anti-IL6 Oligoclonics to form immune complexes and to analyze these complexes Size Exclusion Chromatography (SEC) is used according to the approach disclosed by Min-Soo Kim et al. (2007), *JMB* 374:1374-1388, to characterize the immune-complexes formed with different antibodies to TNFα. Different molar ratios of the anti-IL6 Oligoclonics are mixed with human IL6 and incubated for 20 hours at 4° C. or 25° C. The mixture is analyzed on an HPLC system fitted with a size exclusion column; different elution times are correlated to molecular weight using a molecular weight standards.

[0218] The ability of antibodies to form complexes with IL6 is correlated with their ability to rapidly clear the cytokine from the circulation in vivo. This is confirmed by measuring the clearance of radiolabelled IL6 from mice. Briefly, female, six- to eight-week-old Balb/c mice are obtained and 18 hours before the experiment, the animals are injected intravenously (IV) via the lateral tail vein with different doses of purified anti-IL6 Oligoclonics. On day 0, the mice are injected IV with 50 microliters of radiolabeled IL-6 (1×10E7 cpm/mL) under the same conditions. Blood samples (approximately 50 microliters) are collected at several time intervals and stored at 4° C. The samples are centrifuged for five minutes at 4000×g and the radioactivity of the serum determined. All pharmacokinetic experiments are performed simultaneously with three animals for each treatment.

Generation of Anti-IL6 Oligoclonics Stable Clones and Preclinical Development

[0219] A lead anti-IL6 Oligoclonic is selected based on the in vitro and in vivo potency as determined above. The murine VH genes are humanized according to standard methods and combined with the fully human IGKV1-39 light chain in an expression vector as described above. Examples of humanization methods include those based on paradigms such as resurfacing (E. A. Padlan et al. (1991), *Mol. Immunol.* 28:489), superhumanization (P. Tan, D. A., et al. (2002), *J. Immunol.* 169:1119) and human string content optimization (G. A. Lazar et al. (2007), *Mol. Immunol.* 44:1986). The three constructs are transfected into PER.C6 cells at the predetermined optimal ratio (described above) under the selective pressure of G418 according to standard methods. A stable high producing anti-IL6 Oligoclonic clone is selected and a working and qualified master cell bank generated.

TABLE 1

List of primers

DO-	Primer	Sequence
0012	CH1_Rev1	TGCCAGGGGGAAGACCGATG (SEQ ID NO: 4)
0656	MVH-1	GCCGGCCATGGCC**GAGGTRMAGCTTCAGGAGTCAGGAC** (SEQ ID NO: 5)
0657	MVH-2	GCCGGCCATGGCC**GAGGTSCAGCTKCAGCAGTCAGGAC** (SEQ ID NO: 6)
0658	MVH-3	GCCGGCCATGGCC**CAG**GTGCAGCTGAAGSASTCAGG (SEQ ID NO: 7)
0659	MVH-4	GCCGGCCATGGCC**GAG**GTGCAGCTTCAGGAGTCSGGAC (SEQ ID NO: 8)
0660	MVH-5	GCCGGCCATGGCC**GARGTCCAGCTGCAACAGTCYGGAC** (SEQ ID NO: 9)
0661	MVH-6	GCCGGCCATGGCC**CAGGTCCAGCTKCAGCAATCTGG** (SEQ ID NO: 10)
0662	MVH-7	GCCGGCCATGGCC**CAGSTBCAGCTGCAGCAGTCTGG** (SEQ ID NO: 11)
0663	MVH-8	GCCGGCCATGGCC**CAGGTYCAGCTGCAGCAGTCTGGRC** (SEQ ID NO: 12)
0664	MVH-9	GCCGGCCATGGCC**CAGGTYCAGCTYCAGCAGTCTGG** (SEQ ID NO: 13)
0665	MVH-10	GCCGGCCATGGCC**GAGGTCCARCTGCAACAATCTGGACC** (SEQ ID NO: 14)
0666	MVH-11	GCCGGCCATGGCC**CAGGTCCACGTGAAGCAGTCTGGG** (SEQ ID NO: 15)
0667	MVH-12	GCCGGCCATGGCC**GAGGTGAASSTGGTGGAATCTG** (SEQ ID NO: 16)
0668	MVH-13	GCCGGCCATGGCC**GAVGTGAAGYTGGTGGAGTCTG** (SEQ ID NO: 17)
0669	MVH-14	GCCGGCCATGGCC**GAGGTGCAGSKGGTGGAGTCTGGGG** (SEQ ID NO: 18)
0670	MVH-15	GCCGGCCATGGCC**GAKGTGCAMCTGGTGGAGTCTGGG** (SEQ ID NO: 19)
0671	MVH-16	GCCGGCCATGGCC**GAGGTGAAGCTGATGGARTCTGG** (SEQ ID NO: 20)
0672	MVH-17	GCCGGCCATGGCC**GAGGTGCARCTTGTTGAGTCTGGTG** (SEQ ID NO: 21)
0673	MVH-18	GCCGGCCATGGCC**GARGTRAAGCTTCTCGAGTCTGGA** (SEQ ID NO: 22)
0674	MVH-19	GCCGGCCATGGCC**GAAGTGAARSTTGAGGAGTCTGG** (SEQ ID NO: 23)
0675	MVH-20	GCCGGCCATGGCC**GAAGTGATGCTGGTGGAGTCTGGG** (SEQ ID NO: 24)
0676	MVH-21	GCCGGCCATGGCC**CAGGTTACTCTRAAAGWGTSTGGCC** (SEQ ID NO: 25)
0677	MVH-22	GCCGGCCATGGCC**CAGGTCCAACTVCAGCARCCTGG** (SEQ ID NO: 26)
0678	MVH-23	GCCGGCCATGGCC**CAGGTYCARCTGCAGCAGTCTG** (SEQ ID NO: 27)
0679	MVH-24	GCCGGCCATGGCC**GATGTGAACTTGGAAGTGTCTGG** (SEQ ID NO: 28)
0680	MVH-25	GCCGGCCATGGCC**GAGGTGAAGGTCATCGAGTCTGG** (SEQ ID NO: 29)
0681	ExtMVH-1	CAGTCACAGATCCTCGCGAATT*GGCCCA**GCCGGCC**ATGGCCSANG* (SEQ ID NO: 30)
0682	ExtMVH-2	CAGTCACAGATCCTCGCGAATT*GGCCCA**GCCGGCC**ATGGCCSANC* (SEQ ID NO: 31)
0683	MJH-Rev1	GGGGGTGTCGT**TTTGGCTGAGGAGAC***GGTGACC***GTGG** (SEQ ID NO: 32)
0684	MJH-Rev2	GGGGGTGTCGT**TTTGGCTGAGGAGAC***TGTGAGA***GTGG** (SEQ ID NO: 33)
0685	MJH-Rev3	GGGGGTGTCGT**TTTGGCTGCAGAGAC***AGTGACC***AGAG** (SEQ ID NO: 34)
0686	MJH-Rev4	GGGGGTGTCGT**TTTGGCTGAGGAGAC***GGTGACT***GAGG** (SEQ ID NO:3 5)
0687	ExtMJH-Rev1&	GGGGGTGTCGT**TTTGGCTGAGGAGAC***GGTGACC***GTGG** (SEQ ID NO: 36)
0688	ExtMJH-Rev2in	GGGGGTGTCGT**TTTGGCTGAGGAGAC***GGTGACA***GTGG** (SEQ ID NO: 37)

TABLE 1 -continued

List of primers

DO-	Primer	Sequence
0690	ExtMJH-Rev3	GGGGGTGTCGT**TTTGGCTGAGGAGAC*GGTGACC*AGAG** (SEQ ID NO: 38)
0691	ExtMJH-Rev4	GGGGGTGTCGT**TTTGGCTGAGGAGAC*GGTGACC*GAGG** (SEQ ID NO: 39)

TABLE 2

Phage ELISA signal levels as measured at 450 nm. TT-coated plates represent plates that were coated with tetanus toxoid. Thyroglobulin-coated plates are used as negative controls. 10/10 and 15/15 indicate the number of wash steps with PBS-Tween during panning procedures. The 10/10 tetanus toxoid and 10/10 thyroglobulin plates and the 15/15 tetanus toxoid and 15/15 thyroglobulin plates are duplicates from each other except for the coating agent. OD values higher than three times the background are assumed specific.

	1	2	3	4	5	6	7	8	9	10	11	12
TT-coated plate 10/10 washings												
A	0.139	0.093	0.089	0.121	0.117	0.598	0.146	0.115	0.18	0.155	0.543	0.601
B	0.136	0.404	0.159	0.187	0.489	0.134	0.216	0.092	0.222	0.108	0.181	0.484
C	0.197	0.526	0.09	0.213	0.395	0.155	0.108	0.12	0.183	0.136	0.092	0.866
D	0.143	0.258	0.101	0.422	0.088	0.243	0.485	0.251	0.304	0.198	0.478	0.091
E	0.445	0.169	0.526	0.481	0.206	0.285	0.111	0.119	0.128	0.2	0.118	0.098
F	0.237	0.291	0.594	0.139	0.206	0.565	0.543	0.091	0.136	0.227	0.228	0.099
G	0.459	0.102	0.152	0.659	0.203	0.452	0.152	0.133	0.094	0.102	0.375	0.098
H	0.341	0.623	0.745	0.415	0.682	0.527	0.655	0.114	0.258	0.284	0.685	0.113
TT-coated plate 15/15 washings												
A	0.247	0.582	0.421	0.428	0.133	0.082	0.262	0.079	0.343	0.414	0.095	0.292
B	0.065	0.364	0.073	0.042	0.049	0.071	0.046	0.103	0.078	0.057	0.048	0.155
C	0.081	0.044	0.066	0.082	0.225	0.444	0.203	0.362	0.122	0.047	0.052	0.309
D	0.092	0.11	0.59	0.22	0.33	0.544	0.058	0.159	0.047	0.174	0.086	0.05
E	0.469	0.577	0.206	0.304	0.13	0.749	0.431	0.062	0.167	0.049	0.056	0.049
F	0.846	0.07	0.561	0.656	0.882	0.094	0.383	0.13	0.152	0.098	0.134	0.048
G	0.537	0.052	0.49	0.105	0.337	0.193	0.514	0.294	0.068	0.35	0.525	0.05
H	0.061	0.306	0.157	0.853	0.054	0.534	0.102	0.235	0.441	0.412	0.565	0.061
Thyroglobulin-coated plate 10/10 washings												
A	0.047	0.051	0.045	0.043	0.051	0.044	0.046	0.042	0.047	0.048	0.049	0.05
B	0.042	0.042	0.042	0.042	0.043	0.041	0.041	0.042	0.043	0.045	0.042	0.046
C	0.044	0.043	0.043	0.044	0.043	0.044	0.043	0.042	0.043	0.041	0.044	0.046
D	0.045	0.044	0.044	0.044	0.045	0.046	0.045	0.056	0.045	0.049	0.048	0.73
E	0.046	0.045	0.046	0.044	0.045	0.044	0.044	0.044	0.047	0.046	0.047	0.926
F	0.048	0.045	0.044	0.046	0.044	0.043	0.044	0.046	0.046	0.046	0.046	0.792
G	0.051	0.048	0.045	0.045	0.044	0.043	0.048	0.045	0.048	0.051	0.045	0.053
H	0.064	0.05	0.049	0.047	0.05	0.051	0.047	0.046	0.047	0.047	0.047	0.056
Thyroglobulin-coated plate 15/15 washings												
A	0.036	0.049	0.045	0.044	0.046	0.047	0.046	0.042	0.042	0.043	0.042	0.041
B	0.045	0.042	0.041	0.043	0.043	0.043	0.045	0.045	0.047	0.048	0.044	0.045
C	0.049	0.047	0.047	0.046	0.046	0.046	0.045	0.047	0.046	0.045	0.045	0.052
D	0.047	0.049	0.048	0.048	0.048	0.048	0.047	0.052	0.048	0.046	0.048	0.456
E	0.049	0.047	0.047	0.047	0.047	0.049	0.047	0.048	0.047	0.046	0.048	0.412
F	0.05	0.047	0.046	0.046	0.046	0.046	0.046	0.046	0.046	0.047	0.048	0.528
G	0.05	0.048	0.045	0.045	0.046	0.049	0.048	0.046	0.053	0.049	0.05	0.057
H	0.057	0.05	0.046	0.045	0.047	0.049	0.047	0.047	0.046	0.047	0.053	0.048

TABLE 3

Protein sequence analysis of ELISA positive tetanus toxoid binders.

CDR3/SEQ ID NO:	CDR3 length	VH	DH	JH	V Gene family
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183

TABLE 3 -continued

Protein sequence analysis of ELISA positive tetanus toxoid binders.

CDR3/SEQ ID NO:	CDR3 length	VH	DH	JH	V Gene family
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAYYTYDEKAWFAY (SEQ ID NO: 40)	15	musIGHV192DSP2.11		JH3 mouse	VH7183
HGAFYTYDEKPWFAY (SEQ ID NO: 41)	15	musIGHV192IGHD2-14*01		JH3 mouse	VH7183
HISYYRYDEEVSFAY (SEQ ID NO: 42)	15	musIGHV192IGHD2-14*01		JH3 mouse	VH7183
HISYYRYDEEVSFAY (SEQ ID NO: 42)	15	musIGHV192IGHD2-14*01		JH3 mouse	VH7183
GWRAFAY (SEQ ID NO: 43)	7	musIGHV131DSP2.9		JH3 mouse	VH7183
GWRAFAY (SEQ ID NO: 43)	7	musIGHV131DSP2.9		JH3 mouse	VH7183
GWRAFAY (SEQ ID NO: 43)	7	musIGHV131DSP2.9		JH3 mouse	VH7183
DRGNYYGMDY (SEQ ID NO: 44)	10	musIGHV178DSP2.1		JH4 mouse	VH7183
LGDYYVDWFFAV (SEQ ID NO: 45)	12	musIGHV165DFL16.1		JH1 mouse	VH7183
NFPAWFAF (SEQ ID NO: 46)	8	musIGHV547DST4.3inv		JH3 mouse	VJH558
NFPAWFAY (SEQ ID NO: 46)	8	musIGHV547DSP2.1		JH3 mouse	VJH558
NFPAWFVY (SEQ ID NO: 46)	8	musIGHV547DSP2.1		JH3 mouse	VJH558
SFTPVPFYYGYDWYFDV (SEQ ID NO: 47)	17	musIGHV532DSP2.3		JH1 mouse	VJH558
SFTPVPFYYGYDWYFDV (SEQ ID NO: 47)	17	musIGHV532DSP2.3		JH1 mouse	VJH558
SDYDWYFDV (SEQ ID NO: 48)	9	musIGHV286DSP2.2		JH1 mouse	VJH558
SDYDWYFDV (SEQ ID NO: 48)	9	musIGHV286DSP2.2		JH1 mouse	VJH558
DSKWAYYFDY (SEQ ID NO: 49)	10	musIGHV532DST4.3		JH2 mouse	VJH558
GDYTGYGMDY (SEQ ID NO: 50)	10	musIGHV125DSP2.13		JH4 mouse	VHSM7
GDYTGYGMDY (SEQ ID NO: 50)	10	musIGHV125DSP2.13		JH4 mouse	VHSM7
GGYDGYWFPY (SEQ ID NO: 51)	10	musIGHV125DSP2.9		JH3 mouse	VHSM7

CDR3 sequence, CDR3 length, VH family members and specific name, JH origin and DH origin of the clones is indicated.

TABLE 4

Vector combinations that were transfected to HEK293T.

Code	HC vector	LC vector	Combined vector	Prep name	Conc. (μg/ml)
A	x	0817676_pSELECT_0815426 (IGKV1-39)	x	PIGKV1-39/ P1	—
B	x	0817678_pSELECT_0815427 (IGLV2-14)	x	PIGLV2-14/ P1	—

TABLE 4-continued

Vector combinations that were transfected to HEK293T.

Code	HC vector	LC vector	Combined vector	Prep name	Conc. (μg/ml)
C	MV1110	0817676_pSELECT_0815426 (IGKV1-39)	x	PMV1110/ IGKV1-39/P1	11.0
D	MV1110	0817678_pSELECT_0815427 (IGLV2-14)	x	PMV1110/ IGLV2-14/P1	15.4
E	x	x	MG1494	MG1494/P2	16.1

TABLE 5

HLA allotypes considered in T_H-epitope profiling. The corresponding serotypes are shown, as well as allotype frequencies in the Caucasian population (Klitz et al. (2003), *Tissue Antigens* 62: 296-307; Gjertson and Terasake (eds) in: *HLA* 1997; Gjertson and Terasake (eds) in: *HLA* 1998; Castelli et al. (2002), *J. Immunol.* 169: 6928-6934). Frequencies can add up to more than 100% since each individual has two alleles for each gene. If all allele frequencies of a single gene were known, they would add up to slightly less than 200% due to homozygous individuals.

HLA type	Serotype	Population %
DRB1*0101	DR1	17.4
DRB1*0102	DR1	4.9
DRB1*0301	DR17(3)	21.2
DRB1*0401	DR4	11.5
DRB1*0402	DR4	3.1
DRB1*0404	DR4	5.5
DRB1*0405	DR4	2.2
DRB1*0407	DR4	<2
DRB1*0701	DR7	23.4
DRB1*0801	DR8	3.3
DRB1*0802	DR8	<2
DRB1*0901	DR9	<2
DRB1*1101	DR11(5)	17
DRB1*1104	DR11(5)	5.7
DRB1*1201	DR12(5)	3.1
DRB1*1301	DR13(6)	15.4
DRB1*1302	DR13(6)	10.8
DRB1*1401	DR14(6)	4.2
DRB1*1501	DR15(2)	13.2
DRB1*1601	DR16(2)	5.5
DRB3*0101	DR52	24.6
DRB3*0202	DR52	43
DRB3*0301	DR52	10
DRB4*0101	DR53	25.5

TABLE 5-continued

HLA allotypes considered in T_H-epitope profiling. The corresponding serotypes are shown, as well as allotype frequencies in the Caucasian population (Klitz et al. (2003), *Tissue Antigens* 62: 296-307; Gjertson and Terasake (eds) in: *HLA* 1997; Gjertson and Terasake (eds) in: *HLA* 1998; Castelli et al. (2002), *J. Immunol.* 169: 6928-6934). Frequencies can add up to more than 100% since each individual has two alleles for each gene. If all allele frequencies of a single gene were known, they would add up to slightly less than 200% due to homozygous individuals.

HLA type	Serotype	Population %
DRB4*0103	DR53	21
DRB5*0101	DR51	15.8
DRB5*0202	DR51	5.7
DQA1*0101/DQB1*0501	DQ5(1)	20.5
DQA1*0102/DQB1*0502	DQ5(1)	2.6
DQA1*0102/DQB1*0602	DQ6(1)	26.5
DQA1*0102/DQB1*0604	DQ6(1)	6.7
DQA1*0103/DQB1*0603	DQ6(1)	11
DQA1*0104/DQB1*0503	DQ5(1)	4
DQA1*0201/DQB1*0202	DQ2	20.9
DQA1*0201/DQB1*0303	DQ9(3)	7.2
DQA1*0301/DQB1*0301	DQ7(3)	12.5
DQA1*0301/DQB1*0302	DQ8(3)	18.3
DQA1*0401/DQB1*0402	DQ4	4.5
DQA1*0501/DQB1*0201	DQ2	24.6
DQA1*0501/DQB1*0301	DQ7(3)	20.9
DPA1*0103/DPB1*0201	DPw2	19.9
DPA1*0103/DPB1*0401	DPw4	65.1
DPA1*0103/DPB1*0402	DPw4	24.3
DPA1*0201/DPB1*0101	DPw1	6.3
DPA1*0201/DPB1*0301	DPw3	<2
DPA1*0201/DPB1*0501	DPw5	<2
DPA1*0201/DPB1*0901	—	2.4

TABLE 6

T_H epitope counts for IGKV1-39. Peptides binding to multiple HLAs of the same group (DRB1, DRB3/4/5, DP, DQ) are counted as one. Values between brackets refer to germline-filtered peptides.

	DRB1		DRB3/4/5		DQ		DP	
	Strong	Medium	Strong	Medium	Strong	Medium	Strong	Medium
Merus IGKV1-39	0 (+6)	0 (+16)	0 (+0)	0 (+5)	0 (+3)	0 (+9)	0 (+0)	0 (+9)

TABLE 7

Mapping of Epibase ® predictions for Merus IGKV1-39 in the classical 15-mer peptide format.

15 mer	Start Position	15-mer sequence	Allotype count	Implicated serotypes
1	1	DIQMTQSPSSLSASV	6	DR1, DR4, DR7, DR9
2	4	MTQSPSSLSASVGDR	5	DR1, DR4, DR9
3	7	SPSSLSASVGDRVTI	0	
4	10	SLSASVGDRVTITCR	0	
5	13	ASVGDRVTITCRASQ	0	
6	16	GDRVTITCRASQSIS	2	DR11(5), DR7
7	19	VTITCRASQSISSYL	4	DQ2, DR11(5), DR4, DR7
8	22	TCRASQSISSYLNWY	2	DQ2, DR4
9	25	ASQSISSYLNWYQQK	5	DR13(6), DR15(2), DR4
10	28	SISSYLNWYQQKPGK	8	DR12(5), DR13(6), DR15(2), DR16(2), DR4, DR8
11	31	SYLNWYQQKPGKAPK	10	DR1, DR12(5), DR16(2), DR4, DR51, DR8
12	34	NWYQQKPGKAPKLLI	9	DR1, DR15(2), DR4, DR51, DR8
13	37	QQKPGKAPKLLIYAA	7	DQ4, DR1, DR11(5), DR15(2), DR51, DR8
14	40	PGKAPKLLIYAASSL	7	DQ4, DR1, DR11(5), DR4, DR8
15	43	APKLLIYAASSLQSG	15	DR1, DR11(5), DR12(5), DR13(6), DR14(6), DR15(2), DR4, DR51, DR8, DR9
16	46	LLIYAASSLQSGVPS	15	DR1, DR11(5), DR12(5), DR13(6), DR14(6), DR15(2), DR4, DR51, DR8, DR9
17	49	YAASSLQSGVPSRFS	1	DR15(2)
18	52	SSLQSGVPSRFSGSG	1	DR15(2)
19	55	QSGVPSRFSGSGSGT	0	
20	58	VPSRFSGSGSGTDFT	0	
21	61	RFSGSGSGTDFTLTI	0	
22	64	GSGSGTDFTLTISSL	1	DR52
23	67	SGTDFTLTISSLQPE	4	DR4, DR52, DR7, DR9
24	70	DFTLTISSLQPEDFA	4	DQ2, DR4, DR7, DR9
25	73	LTISSLQPEDFATYY	1	DQ2
26	76	SSLQPEDFATYYCQQ	0	
27	79	QPEDFATYYCQQSYS	1	DR4
28	82	DFATYYCQQSYSTPP	5	DR4, DR51, DR7
29	85	TYYCQQSYSTPPTFG	4	DR4, DR51, DR7
30	88	CQQSYSTPPTFGQGT	0	
31	91	SYSTPPTFGQGTKVE	0	
32	94	TPPTFGQGTKVEIK	0	

This table shows the allotype count of critical epitopes (SEQ ID NOs: 52-83) and implicated serotypes for each of the 15-mers spanning the Merus IGKV1-39 sequence.

TABLE 8

The V_H gene from PG1433 paired with various light chain genes with differing rates of amino acid mutation were compared for production levels with the original clone containing the IGKV1-39 gene.

IgG name	Light chain gene	Number of amino acid mutations	concentration (μg/ml)
PG1433	1-39	0	63, 45.5, 38.6 (avg = 49)
PG1631	1-12	4	10.5
PG1632	1-27	7	9.3
PG1634	1D-12	10	10.8
PG1635	1D-33	6	10.2
PG1642	1-5	8	7.1
PG1644	1-9	3	7.8
PG1650	1D-39	3	9.1
PG1652	2D-28	3	7.1
PG1653	3-15	14	7
PG1654	3-20	2	5.2
PG1674	1-40	7	8.2
PG1678	2-11	2	8.1
PG1680	2-14	15	10.8
PG1682	3-1	13	9.9
PG1683	6-57	6	13.9

TABLE 9

Numbers of lymphocytes harvested from the bone marrow and spleen of wild-type and transgenic mice

	*10e6/ml cells	total vol (ml)	total cells $*10^6$
Bone Marrow			
Wt	18.82	5.05	95.0
Wt	19.24	4.96	95.4
CD19-Cre	23.42	5.08	119.0
CD19-Cre	20.58	4.82	99.2
CD19-Cre	25.77	5.15	132.7
CD19-Cre/HuVk1	17.71	5.06	89.6
CD19-Cre/HuVk1	12.60	5.33	67.2
CD19-Cre/HuVk1	18.13	5.27	95.5
Spleen			
Wt	41.70	5.36	223.5
Wt	37.85	4.71	178.3
CD19-Cre	60.19	3.77	226.9
CD19-Cre	35.06	3.66	128.3
CD19-Cre	80.69	4.60	371.2
CD19-Cre/HuVk1	51.67	4.48	231.5
CD19-Cre/HuVk1	58.80	6.24	366.9
CD19-Cre/HuVk1	24.37	6.25	152.3

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<223> OTHER INFORMATION: CDR3

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<400> SEQUENCE: 47

Ser Phe Thr Pro Val Pro Phe Tyr Tyr Gly Tyr Asp Trp Tyr Phe Asp
1 5 10 15

Val

<210> SEQ ID NO 48
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR3

<400> SEQUENCE: 48

Ser Asp Tyr Asp Trp Tyr Phe Asp Val
1 5

<210> SEQ ID NO 49
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR3

<400> SEQUENCE: 49

Asp Ser Lys Trp Ala Tyr Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 50
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR3

<400> SEQUENCE: 50

Gly Asp Tyr Thr Gly Tyr Gly Met Asp Tyr
1 5 10

<210> SEQ ID NO 51
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: CDR3

<400> SEQUENCE: 51

Gly Gly Tyr Asp Gly Tyr Trp Phe Pro Tyr
1 5 10

<210> SEQ ID NO 52
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: epitope IGKV1-39

<400> SEQUENCE: 52

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

<210> SEQ ID NO 53
<211> LENGTH: 15

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: epitope IGKV1-39

<400> SEQUENCE: 53

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
1 5 10 15

<210> SEQ ID NO 54
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: epitope IGKV1-39

<400> SEQUENCE: 54

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
1 5 10 15

<210> SEQ ID NO 55
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: epitope IGKV1-39

<400> SEQUENCE: 55

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
1 5 10 15

<210> SEQ ID NO 56
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 56

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
1 5 10 15

<210> SEQ ID NO 57
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 57

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
1 5 10 15

<210> SEQ ID NO 58
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 58

Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu
1 5 10 15

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<210> SEQ ID NO 59
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 59

Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr
1 5 10 15

<210> SEQ ID NO 60
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 60

Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys
1 5 10 15

<210> SEQ ID NO 61
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 61

Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
1 5 10 15

<210> SEQ ID NO 62
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 62

Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
1 5 10 15

<210> SEQ ID NO 63
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 63

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
1 5 10 15

<210> SEQ ID NO 64
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 64

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala
1 5 10 15

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<210> SEQ ID NO 65
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 65

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu
1 5 10 15

<210> SEQ ID NO 66
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 66

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly
1 5 10 15

<210> SEQ ID NO 67
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 67

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
1 5 10 15

<210> SEQ ID NO 68
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 68

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
1 5 10 15

<210> SEQ ID NO 69
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 69

Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
1 5 10 15

<210> SEQ ID NO 70
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 70

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Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
1 5 10 15

<210> SEQ ID NO 71
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 71

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

<210> SEQ ID NO 72
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 72

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
1 5 10 15

<210> SEQ ID NO 73
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 73

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
1 5 10 15

<210> SEQ ID NO 74
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 74

Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
1 5 10 15

<210> SEQ ID NO 75
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 75

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
1 5 10 15

<210> SEQ ID NO 76
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

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<400> SEQUENCE: 76

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
1 5 10 15

<210> SEQ ID NO 77
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 77

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
1 5 10 15

<210> SEQ ID NO 78
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 78

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser
1 5 10 15

<210> SEQ ID NO 79
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 79

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
1 5 10 15

<210> SEQ ID NO 80
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 80

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro Thr Phe Gly
1 5 10 15

<210> SEQ ID NO 81
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 81

Cys Gln Gln Ser Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr
1 5 10 15

<210> SEQ ID NO 82
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 82

Ser Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
1 5 10 15

<210> SEQ ID NO 83
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Epitope IGKV1-39

<400> SEQUENCE: 83

Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> SEQ ID NO 84
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(321)

<400> SEQUENCE: 84

gac atc cag atg acc cag agc ccc agc agc ctg agc gcc agc gtg ggc 48
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

gac aga gtg acc atc acc tgc aga gcc agc cag agc atc agc agc tac 96
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

ctg aac tgg tat cag cag aag ccc ggc aag gcc ccc aag ctg ctg atc 144
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

tac gcc gcc agc tcc ctg cag agc ggc gtg ccc agc aga ttc agc ggc 192
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

agc ggc tcc ggc acc gac ttc acc ctg acc atc agc agc ctg cag ccc 240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

gag gac ttc gcc acc tac tac tgc cag cag agc tac agc acc ccc ccc 288
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

acc ttc ggc cag ggc acc aag gtg gag atc aag 321
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 85
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 86
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(330)

<400> SEQUENCE: 86

cag tct gcc ctg acc cag ccc gcc tct gtg tct ggc agc cct ggc cag       48
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

agc atc acc atc agc tgc acc ggc acc agc agc gac gtg ggc ggc tac       96
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30

aac tac gtg tcc tgg tat cag cag cac ccc ggc aag gcc ccc aag ctg      144
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

atg atc tac gag gtg tcc aac aga ccc agc ggc gtg agc aac aga ttc      192
Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

agc ggc agc aag agc ggc aac acc gcc agc ctg acc atc agc ggc ctc      240
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

cag gct gag gac gag gcc gac tac tac tgc agc agc tac acc agc agc      288
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95

tcc acc ctg gtg ttt ggc ggc gga aca aag ctg acc gtg ctg              330
Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> SEQ ID NO 87
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95
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Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> SEQ ID NO 88
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(321)

<400> SEQUENCE: 88

aga gcc gac gcc gct ccc acc gtg tcc atc ttc ccc ccc agc atg gaa       48
Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Met Glu
1               5                   10                  15

cag ctg acc tct ggc gga gcc acc gtg gtc tgc ttc gtg aac aac ttc       96
Gln Leu Thr Ser Gly Gly Ala Thr Val Val Cys Phe Val Asn Asn Phe
            20                  25                  30

tac ccc aga gac atc agc gtg aag tgg aag atc gac ggc agc gag cag      144
Tyr Pro Arg Asp Ile Ser Val Lys Trp Lys Ile Asp Gly Ser Glu Gln
        35                  40                  45

agg gac ggc gtg ctg gac agc gtg acc gac cag gac agc aag gac tcc      192
Arg Asp Gly Val Leu Asp Ser Val Thr Asp Gln Asp Ser Lys Asp Ser
    50                  55                  60

acc tac agc atg agc agc acc ctg agc ctg acc aag gtg gag tac gag      240
Thr Tyr Ser Met Ser Ser Thr Leu Ser Leu Thr Lys Val Glu Tyr Glu
65                  70                  75                  80

agg cac aac ctg tac acc tgc gag gtg gtg cac aag acc agc tcc agc      288
Arg His Asn Leu Tyr Thr Cys Glu Val Val His Lys Thr Ser Ser Ser
                85                  90                  95

ccc gtg gtc aag tcc ttc aac cgg aac gag tgt                          321
Pro Val Val Lys Ser Phe Asn Arg Asn Glu Cys
            100                 105


<210> SEQ ID NO 89
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 89

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Met Glu
1               5                   10                  15

Gln Leu Thr Ser Gly Gly Ala Thr Val Val Cys Phe Val Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Asp Ile Ser Val Lys Trp Lys Ile Asp Gly Ser Glu Gln
        35                  40                  45

Arg Asp Gly Val Leu Asp Ser Val Thr Asp Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Met Ser Ser Thr Leu Ser Leu Thr Lys Val Glu Tyr Glu
65                  70                  75                  80

Arg His Asn Leu Tyr Thr Cys Glu Val Val His Lys Thr Ser Ser Ser
                85                  90                  95

Pro Val Val Lys Ser Phe Asn Arg Asn Glu Cys
            100                 105


<210> SEQ ID NO 90
<211> LENGTH: 865
<212> TYPE: DNA
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IGKV1-39/J-Ck

<400> SEQUENCE: 90

ggtaccgcgg ccgccaccat ggacatgaga gtgcccgccc agctcctggg gctcctgcta 60

ctctggctcc gaggtaagga tggagaacac taggaattta ctcagccagt gtgctcagta 120

ctgactggaa cttcagggaa gttctctgat aacatgatta atagtaagaa tatttgtttt 180

tatgtttcca atctcaggtg ccagatgtga catccagatg acccagagcc ccagcagcct 240

gagcgccagc gtgggcgaca gagtgaccat cacctgcaga gccagccaga gcatcagcag 300

ctacctgaac tggtatcagc agaagcccgg caaggccccc aagctgctga tctacgccgc 360

cagctccctg cagagcggcg tgcccagcag attcagcggc agcggctccg gcaccgactt 420

caccctgacc atcagcagcc tgcagcccga ggacttcgcc acctactact gccagcagag 480

ctacagcacc ccccccacct tcggccaggg caccaaggtg gagatcaaga gagccgacgc 540

cgctcccacc gtgtccatct tcccccccag catggaacag ctgacctctg gcggagccac 600

cgtggtctgc ttcgtgaaca acttctaccc cagagacatc agcgtgaagt ggaagatcga 660

cggcagcgag cagagggacg gcgtgctgga cagcgtgacc gaccaggaca gcaaggactc 720

cacctacagc atgagcagca ccctgagcct gaccaaggtg gagtacgaga ggcacaacct 780

gtacacctgc gaggtggtgc acaagaccag ctccagcccc gtggtcaagt ccttcaaccg 840

gaacgagtgt tgagctagcg agctc 865

<210> SEQ ID NO 91
<211> LENGTH: 874
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IGLV2-14/J-Ck

<400> SEQUENCE: 91

ggtaccgcgg ccgccaccat ggacatgaga gtgcccgccc agctcctggg gctcctgcta 60

ctctggctcc gaggtaagga tggagaacac taggaattta ctcagccagt gtgctcagta 120

ctgactggaa cttcagggaa gttctctgat aacatgatta atagtaagaa tatttgtttt 180

tatgtttcca atctcaggtg ccagatgtca gtctgccctg acccagcccg cctctgtgtc 240

tggcagccct ggccagagca tcaccatcag ctgcaccggc accagcagcg acgtgggcgg 300

ctacaactac gtgtcctggt atcagcagca ccccggcaag gcccccaagc tgatgatcta 360

cgaggtgtcc aacagaccca gcggcgtgag caacagattc agcggcagca agagcggcaa 420

caccgccagc ctgaccatca gcggcctcca ggctgaggac gaggccgact actactgcag 480

cagctacacc agcagctcca ccctggtgtt tggcggcgga acaaagctga ccgtgctgag 540

agccgacgcc gctcccaccg tgtccatctt ccccccccagc atggaacagc tgacctctgg 600

cggagccacc gtggtctgct tcgtgaacaa cttctacccc agagacatca gcgtgaagtg 660

gaagatcgac ggcagcgagc agagggacgg cgtgctggac agcgtgaccg accaggacag 720

caaggactcc acctacagca tgagcagcac cctgagcctg accaaggtgg agtacgagag 780

gcacaacctg tacacctgcg aggtggtgca caagaccagc tccagccccg tggtcaagtc 840

cttcaaccgg aacgagtgtt gagctagcga gctc 874

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<210> SEQ ID NO 92
<211> LENGTH: 13373
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VkP-IGKV1-39/J-Ck

<400> SEQUENCE: 92

ggccggccca catgaaacaa tgggaaccat gtgacaatca cagaggtgtt gttactatag 60

caaaagggat tgttactctc cacatccctt taagtaactt gaaggcctga tagacccacc 120

ctctaagact tcattagaca ttccctacga atggttatac tctcctgtat actcccaata 180

caactctaaa atatattatt ccatatagtc cttaggtttg tattaaagtt tgacttttt 240

ccttcaaaat atctcttgtc acaacagcgg ctctagagag aaatacattc cctccaggca 300

aatctatgct gcgctggtct gacctgggac cctggggaca ttgcccctgt gctgagttac 360

taagatgagc cagccctgca gctgtgctca gcctgcccca tgccctgctg attgatttgc 420

atgttccaga gcacagcccc ctgccctgaa gacttttta tgggctggtc gcaccctgtg 480

caggagtcag tctcagtcag gagccaccat ggacatgaga gtgcccgccc agctcctggg 540

gctcctgcta ctctggctcc gaggtaagga tggagaacac taggaattta ctcagccagt 600

gtgctcagta ctgactggaa cttcagggaa gttctctgat aacatgatta atagtaagaa 660

tatttgtttt tatgtttcca atctcaggtg ccagatgtga catccagatg acccagagcc 720

ccagcagcct gagcgccagc gtgggcgaca gagtgaccat cacctgcaga gccagccaga 780

gcatcagcag ctacctgaac tggtatcagc agaagcccgg caaggccccc aagctgctga 840

tctacgccgc cagctccctg cagagcggcg tgcccagcag attcagcggc agcggctccg 900

gcaccgactt caccctgacc atcagcagcc tgcagcccga ggacttcgcc acctactact 960

gccagcagag ctacagcacc ccccccacct tcggccaggg caccaaggtg gagatcaaac 1020

gtaagtacac ttttctcatc tttttttatg tgtaagacac aggttttcat gttaggagtt 1080

aaagtcagtt cagaaaatct tgagaaaatg gagagggctc attatcagtt gacgtggcat 1140

acagtgtcag attttctgtt tatcaagcta gtgagattag gggcaaaaag aggctttagt 1200

tgagaggaaa gtaattaata ctatggtcac catccaagag attggatcgg agaataagca 1260

tgagtagtta ttgagatctg ggtctgactg caggtagcgt ggtcttctag acgtttaagt 1320

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1. A B cell that produces an antibody that binds to a desired antigen, which B cell is isolated from a transgenic non-human animal that has been immunized with the antigen, wherein the genome of said animal comprises a transgene encoding a rearranged human immunoglobulin variable region and wherein the transgene comprises an immunoglobulin constant region or said rearranged human immunoglobulin variable region is operatively linked to an endogenous immunoglobulin constant region, and wherein the transgenic animal has produced a repertoire of antibodies that bind said antigen having the rearranged human immunoglobulin variable region encoded by the rearranged human immunoglobulin variable region comprised in said transgene.

2. The B cell of claim 1, wherein the transgene encoding a rearranged human immunoglobulin variable region comprises a human germline light chain V gene segment joined to a human germline light chain J gene segment, wherein there is no mutation due to said joining and wherein said immunoglobulin constant region is a light chain constant region.

3. The B cell of claim 1, wherein the transgene encoding a rearranged human immunoglobulin variable region comprises a human germline heavy chain V gene segment joined to a human germline heavy chain D gene segment joined to a human heavy chain J gene segment, wherein there is no mutation due to said joining and wherein said immunoglobulin constant region is a heavy chain constant region.

4. The B cell of claim 1 wherein the transgenic animal is a mammal.

5. The B cell of claim 1 wherein the transgenic animal is a rodent.

6. The B cell of claim 5 wherein the transgenic animal is a mouse.

7. The B cell of claim 1 wherein, in said antibodies, the rearranged variable region is encoded by the transgene that has not undergone somatic hypermutation.

8. A method to obtain an antibody that binds to an antigen, the method comprising culturing the B cell of claim 1 to obtain a population of said B cells and recovering antibodies secreted by said B cells.

9. A method to obtain an antibody that binds to an antigen, the method comprising culturing the B cell of claim 2 to obtain a population of said B cells and recovering antibodies secreted by said B cells.

10. A method to obtain an antibody that binds to an antigen, the method comprising culturing the B cell of claim 3 to obtain a population of said B cells and recovering antibodies secreted by said B cells.

11. A method to obtain an antibody or fragment thereof that binds to an antigen, the method comprising

(a) isolating nucleic acid comprising nucleotide sequences encoding the antibody secreted by the B cell of claim 1;

(b) transfecting recombinant host cells with expression system(s) for production of the antibody or fragment encoded by the nucleotide sequences contained in the nucleic acid obtained in step (a);

(c) culturing said host cells, and

(d) recovering the antibodies or fragments secreted by the host cells.

12. Recombinant host cells that comprise nucleic acids that express nucleotide sequences encoding the antibody secreted by the B cell of claim 1 or an antigen-binding fragment thereof.

13. A method to obtain an antibody or fragment thereof that binds to an antigen which method comprises culturing the cells of claim 12 under conditions wherein said nucleotide sequences are expressed and recovering said antibody or fragment.

14. A method to obtain an antibody or fragment thereof that binds to an antigen, the method comprising

(a) isolating nucleic acid comprising nucleotide sequences encoding the antibody secreted by the B cell of claim 2;

(b) transfecting recombinant host cells with expression system(s) for production of the antibody or fragment encoded by the nucleotide sequences contained in the nucleic acid obtained in step (a);

(c) culturing said host cells, and

(d) recovering the antibodies or fragments secreted by the host cells.

15. Recombinant host cells that comprise nucleic acids that express nucleotide sequences encoding the antibody secreted by the B cell of claim 2 or an antigen-binding fragment thereof.

16. A method to obtain an antibody or fragment thereof that binds to an antigen which method comprises culturing the cells of claim 15 under conditions wherein said nucleotide sequences are expressed and recovering said antibody or fragment.

17. A method to obtain an antibody or fragment thereof that binds to an antigen, the method comprising

(a) isolating nucleic acid comprising nucleotide sequences encoding the antibody secreted by the B cell of claim 3;

(b) transfecting recombinant host cells with expression system(s) for production of the antibody or fragment encoded by the nucleotide sequences contained in the nucleic acid obtained in step (a);

(c) culturing said host cells, and

(d) recovering the antibodies or fragments secreted by the host cells.

18. Recombinant host cells that comprise nucleic acids that express nucleotide sequences encoding the antibody secreted by the B cell of claim 3 or an antigen-binding fragment thereof.

19. A method to obtain an antibody or fragment thereof that binds to an antigen which method comprises culturing the cells of claim 18 under conditions wherein said nucleotide sequences are expressed and recovering said antibody or fragment.

20. A recombinant expression system which system is a nucleic acid comprising a nucleotide sequence encoding at least a variable region of an antibody secreted by the B cell of claim 1, operatively linked to control sequences for expression.

21. A recombinant expression system which system is a nucleic acid comprising a nucleotide sequence encoding at least a variable region of an antibody secreted by the B cell of claim 2, operatively linked to control sequences for expression.

22. A recombinant expression system which system is a nucleic acid comprising a nucleotide sequence encoding at

least a variable region of an antibody secreted by the B cell of claim **3**, operatively linked to control sequences for expression.

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