

SEQUENCE LISTING

<110> Laboratoires Serono SA
 <120> Single IFN-beta fused to a mutated IgG Fc fragment
 <130> 1162 WO/PCT
 <150> EP 07118980.7
 <151> 2007-10-22
 <150> US 61/007,142
 <151> 2007-12-11
 <160> 15
 <170> PatentIn version 3.3
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 <212> PRT
 <213> homo sapiens
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 <223> CH1 domain
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 <222> (99)..(110)
 <223> Hinge region
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 <222> (111)..(223)
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 <222> (224)..(330)
 <223> CH3 domain
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 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 2
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Fragment of the hinge region

<400> 2

Asp Lys Thr His Thr Cys Pro
1 5

<210> 3
<211> 227
<212> PRT
<213> Artificial sequence

<220>
<223> Fcmut arm

<400> 3

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly
1 5 10 15

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

115

120

125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 210 215 220

Pro Gly Lys
 225

<210> 4
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<220>
 <223> Fcmut arm

<400> 4
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 tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 180
 ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 240
 cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 300
 tgcaaggtct ccaacaaagc cctcccatcc tccatcgaga aaaccatctc caaagccaaa 360
 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 420
 aaccaggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 480
 tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 540
 gacggctcct tcttctctta cagcaagctc accgtggaca agagcaggtg gcagcagggg 600
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ctctccctgt ctccgggtaa a

681

<210> 5
<211> 247
<212> PRT
<213> Artificial sequence

<220>
<223> Fcmut arm with signal peptide of mouse Igk light chain

<220>
<221> SIGNAL
<222> (1)..(20)
<223> Signal peptide of mouse Igk light chain

<220>
<221> mat_peptide
<222> (21)..(247)
<223> Fcmut arm

<400> 5

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
-20 -15 -10 -5

Gly Ser Thr Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
-1 1 5 10

Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
15 20 25

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
30 35 40

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
45 50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65 70 75

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
80 85 90

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
95 100 105

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
110 115 120

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
125 130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
160 165 170

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
175 180 185

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
190 195 200

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
205 210 215 220

Leu Ser Leu Ser Pro Gly Lys
225

<210> 6
<211> 741
<212> DNA
<213> Artificial

<220>
<223> Fcmut arm with signal peptide of mouse Igk light chain

<220>
<221> sig_peptide
<222> (1)..(60)
<223> Signal peptide of mouse Igk light chain

<220>
<221> misc_feature
<222> (61)..(741)
<223> Fcmut arm

<400> 6
atggagacag acacactcct gctatgggta ctgctgctct gggttccagg ttccactggt 60
gacaaaactc acacatgccc accgtgccca gcacctgaag ccgagggggc accgtcagtc 120
ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 180
tgctgtggtg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 240
ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 300
cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 360
tgcaaggtct ccaacaaagc cctcccatcc tccatcgaga aaaccatctc caaagccaaa 420

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gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag    480
aaccaggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag    540
tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc    600
gacggctcct tcttctctta cagcaagctc accgtggaca agagcaggtg gcagcagggg    660
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc    720
ctctccctgt ctccgggtaa a                                              741

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<210> 7
<211> 166
<212> PRT
<213> homo sapiens

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<400> 7

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Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1          5          10          15

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Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
          20          25          30

```

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Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
          35          40          45

```

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Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
          50          55          60

```

```

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65          70          75          80

```

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Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
          85          90          95

```

```

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
          100          105          110

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```

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
          115          120          125

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```

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
          130          135          140

```

```

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145          150          155          160

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Thr Gly Tyr Leu Arg Asn
165

<210> 8
<211> 393
<212> PRT
<213> Artificial sequence

<220>
<223> IFNbeta-Fcmut arm

<220>
<221> mat_peptide
<222> (1)..(166)
<223> Mature human IFN-beta

<220>
<221> DOMAIN
<222> (167)..(393)
<223> Fcmut arm

<400> 8

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1 5 10 15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
20 25 30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro
165 170 175

Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
180 185 190

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
195 200 205

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
210 215 220

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
225 230 235 240

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
245 250 255

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
260 265 270

Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
275 280 285

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
290 295 300

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
305 310 315 320

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
325 330 335

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
340 345 350

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
355 360 365

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
370 375 380

Lys Ser Leu Ser Leu Ser Pro Gly Lys

385

390

<210> 9
 <211> 1179
 <212> DNA
 <213> Artificial sequence

<220>
 <223> IFNbeta-Fcmut arm

<220>
 <221> misc_feature
 <222> (1)..(498)
 <223> Mature human IFN-beta

<220>
 <221> misc_feature
 <222> (499)..(1179)
 <223> Fcmut arm

<400> 9
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 cctgaggaga ttaagcagct gcagcagttc cagaaggagg acgccgcatt gaccatctat 180
 gagatgctcc agaacatctt tgctattttc agacaagatt catctagcac tggctggaat 240
 gagactattg ttgagaacct cctggctaata gtctatcatc agataaacca tctgaagaca 300
 gtcttggaag aaaaactgga gaaagaagat ttcaccaggg gaaaactcat gagcagtcctg 360
 cacctgaaaa gatattatgg gaggattctg cattacctga aggccaagga gtacagtcac 420
 tgtgcctgga ccatagtcag agtggaatac ctaaggaact ttacttcat taacagactt 480
 acaggttacc tccgaaacga caaaactcac acatgcccac cgtgcccagc acctgaagcc 540
 gagggggcac cgtcagtcct cctcttcccc ccaaaaccca aggacacct catgatctcc 600
 cggacccttg aggtcacatg cgtgggtggtg gacgtgagcc acgaagacc tgaggtcaag 660
 ttcaactggt acgtggacgg cgtggagggtg cataatgcca agacaaagcc gcgggaggag 720
 cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 780
 aatggcaagg agtacaagtg caaggctctc aacaaagccc tcccatcctc catcgagaaa 840
 accatctcca aagccaaagg gcagccccga gaaccacagg tgtacacct gcccccatcc 900
 cgggaggaga tgaccaagaa ccaggtcagc ctgacctgcc tgggtcaaagg cttctatccc 960
 agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1020
 cctcccgtgc tggactccga cggctccttc ttctctaca gcaagctcac cgtggacaag 1080
 agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1140

cactacacgc agaagagcct ctcctgtct ccgggtaaa

1179

<210> 10
<211> 414
<212> PRT
<213> Artificial sequence

<220>
<223> IFNbeta-Fcmut arm with signal peptide of human IFN-beta

<220>
<221> SIGNAL
<222> (1)..(21)
<223> signal peptide of human IFN-beta

<220>
<221> mat_peptide
<222> (22)..(187)
<223> Mature human IFN-beta

<220>
<221> DOMAIN
<222> (188)..(414)
<223> Fcmut arm

<400> 10

Met Thr Asn Lys Cys Leu Leu Gln Ile Ala Leu Leu Leu Cys Phe Ser
-20 -15 -10

Thr Thr Ala Leu Ser Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg
-5 -1 1 5 10

Ser Ser Asn Phe Gln Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg
15 20 25

Leu Glu Tyr Cys Leu Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu
30 35 40

Ile Lys Gln Leu Gln Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile
45 50 55

Tyr Glu Met Leu Gln Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser
60 65 70 75

Ser Thr Gly Trp Asn Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val
80 85 90

Tyr His Gln Ile Asn His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu
95 100 105

Lys Glu Asp Phe Thr Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys
110 115 120

Arg Tyr Tyr Gly Arg Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser
125 130 135

His Cys Ala Trp Thr Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr
140 145 150 155

Phe Ile Asn Arg Leu Thr Gly Tyr Leu Arg Asn Asp Lys Thr His Thr
160 165 170

Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro Ser Val Phe
175 180 185

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
190 195 200

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
205 210 215

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
220 225 230 235

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
240 245 250

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
255 260 265

Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
270 275 280

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
285 290 295

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
300 305 310 315

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
320 325 330

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
335 340 345

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

350

355

360

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 365 370 375

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 380 385 390

<210> 11
 <211> 1242
 <212> DNA
 <213> Artificial sequence

<220>
 <223> IFNbeta-Fcmut arm with signal peptide of human IFN-beta

<220>
 <221> sig_peptide
 <222> (1)..(63)
 <223> Signal peptide of human IFN-beta

<220>
 <221> misc_feature
 <222> (64)..(561)
 <223> Mature human IFN-beta

<220>
 <221> misc_feature
 <222> (562)..(1242)
 <223> Fcmut arm

<400> 11
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 atccctgagg agattaagca gctgcagcag ttccagaagg aggacgccgc attgaccatc 240
 tatgagatgc tccagaacat ctttgctatt ttcagacaag attcatctag cactggctgg 300
 aatgagacta ttgttgagaa cctcctggct aatgtctatc atcagataaa ccatctgaag 360
 acagtcctgg aagaaaaact ggagaaagaa gatttcacca ggggaaaact catgagcagt 420
 ctgcacctga aaagatatta tgggaggatt ctgcattacc tgaaggccaa ggagtacagt 480
 cactgtgcct ggaccatagt cagagtggaa atcctaagga acttttactt cattaacaga 540
 cttacaggtt acctccgaaa cgacaaaact cacacatgcc caccgtgccc agcacctgaa 600
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 tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga gccacgaaga ccctgaggtc 720
 aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa gccgcgggag 780

gagcagtaca acagcacgta ccgtgtgggtc agcgtcctca ccgtcctgca ccaggactgg	840
ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccatc ctccatcgag	900
aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac cctgccccca	960
tcccgggagg agatgaccaa gaaccaggtc agcctgacct gcctgggtcaa aggtttctat	1020
cccagcgaca tcgccgtgga gtgggagagc aatgggcagc cggagaacaa ctacaagacc	1080
acgcctcccg tgctggactc cgacggctcc ttcttcctct acagcaagct caccgtggac	1140
aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg tgatgcatga ggctctgcac	1200
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<210> 12
 <211> 11014
 <212> DNA
 <213> Artificial sequence

<220>
 <223> C370 vector

<220>
 <221> misc_feature
 <222> (2499)..(3182)
 <223> Fcmut arm (reverse complementary strand)

<220>
 <221> sig_peptide
 <222> (3183)..(3242)
 <223> Signal peptide of mouse Igk light chain (reverse complementary strand)

<220>
 <221> sig_peptide
 <222> (6548)..(6610)
 <223> Signal peptide of human IFN-beta

<220>
 <221> misc_feature
 <222> (6611)..(7108)
 <223> Mature human IFN-beta

<220>
 <221> misc_feature
 <222> (7109)..(7789)
 <223> Fcmut arm

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gatagggttg agtggtgttc cagtttggaa caagagtcca ctattaaaga acgtggactc	180
caacgtcaaa gggcgaaaaa ccgtctatca gggcgatggc ccactacgtg aaccatcacc	240

ctaatacaagt	tttttggggg	cgaggtgccg	taaagcacta	aatcggaacc	ctaaagggag	300
cccccgattt	agagcttgac	ggggaaagcc	ggcgaacgtg	gcgagaaagg	aaggggaagaa	360
agcgaaagga	gcgggcgcta	gggcgctggc	aagtgtagcg	gtcacgctgc	gcgtaaccac	420
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caactgttgg	gaagggcgat	cgggtgcgggc	ctcttcgcta	ttacgccagc	tggcgaaagg	540
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ggatgcgggg	ggagcgccgg	accggagcag	agtctagttt	tttccccgta	tccccaggt	840
gtctgcaggc	tcaaagacag	cgagaagcgt	tcagaggaaa	gcgatcccgt	gccaccttcc	900
ccgtgcccgg	gctgtccccg	cacgctgccg	gctcggggat	gcggggggag	cgccggaccg	960
gagcagagtc	taggtaccgg	gccccccctc	gaggtcgacg	gtatcgattt	taccacattt	1020
gtagaggttt	tacttgcttt	aaaaaacctc	ccacacctcc	ccctgaacct	gaaacataaa	1080
atgaatgcaa	ttgttgttgt	taacttgttt	attgcagctt	ataatggtta	caaataaagc	1140
aatagcatca	caaatttcac	aaataaagca	tttttttcac	tgcattctag	ttgtggtttg	1200
tccaaactca	tcaatgtatc	ttatcatgtc	tggatcgaag	ctagctttgc	ggccgctcag	1260
gcaccgggct	tgcgggtcat	gcaccagggtg	cgcggtcctt	cgggcacctc	gacgtcggcg	1320
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aaggcgggca	ccccggcgcg	ctcggccgcc	tccactccgg	ggagcacgac	ggcgctgccc	1440
agacccttgc	cctggtggtc	gggagagacg	ccgacgggtg	ccaggaacca	cgcgggctcc	1500
ttgggccggg	gcggcgccag	gaggccttcc	atctgttgct	gcgcggccag	ccgggaaccg	1560
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35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
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His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
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Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
130 135 140

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

165

170

175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
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Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
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Pro Gly Lys
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Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
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Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
 35 40 45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
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Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
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Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
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His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
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Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
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Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
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Thr Gly Tyr Leu Arg Asn Glu Phe Ala Gly Ala Ala Ala Val Asp Lys
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Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
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Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
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Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
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Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
245 250 255

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
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Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
275 280 285

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
290 295 300

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr

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Lys