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<110> PIERRE FABRE MEDICAMENT

<120> NOVEL HUMANIZED ANTI CXCR4 ANTIBODIES FOR THE TREATMENT OF CANCER

<130> D28523

<150> EP 10290167.5
<151> 2010-03-30

<160> 96

<170> PatentIn version 3.3

<210> 1
<211> 352
<212> PRT
<213> homo sapiens

<400> 1

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Met Glu Gly Ile Ser Ile Tyr Thr Ser Asp Asn Tyr Thr Glu Glu Met
1               5                  10                  15

Gly Ser Gly Asp Tyr Asp Ser Met Lys Glu Pro Cys Phe Arg Glu Glu
            20                  25                  30

Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile Tyr Ser Ile Ile
        35                  40                  45

Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile Leu Val Met Gly
    50                  55                  60

Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr Arg Leu His Leu
65                  70                  75                  80

Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro Phe Trp Ala Val
                85                  90                  95

Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu Cys Lys Ala Val
            100                 105                 110

His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val Leu Ile Leu Ala
        115                 120                 125

Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His Ala Thr Asn Ser
    130                 135                 140

Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val Tyr Val Gly Val
145                 150                 155                 160

Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe Ile Phe Ala Asn
                165                 170                 175

Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg Phe Tyr Pro Asn
            180                 185                 190
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Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile Met Val Gly Leu
        195                 200                 205

Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys Ile Ile Ile Ser
    210                 215                 220

Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys Ala Leu Lys Thr
225                 230                 235                 240

Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp Leu Pro Tyr Tyr
                245                 250                 255

Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu Ile Ile Lys Gln
            260                 265                 270

Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile Ser Ile Thr Glu
        275                 280                 285

Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile Leu Tyr Ala Phe
    290                 295                 300

Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala Leu Thr Ser Val
305                 310                 315                 320

Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly Lys Arg Gly Gly
                325                 330                 335

His Ser Ser Val Ser Thr Glu Ser Glu Ser Ser Ser Phe His Ser Ser
            340                 345                 350
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<210> 2
<211> 356
<212> PRT
<213> homo sapiens

<400> 2

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Met Ser Ile Pro Leu Pro Leu Leu Gln Ile Tyr Thr Ser Asp Asn Tyr
1               5                   10                  15

Thr Glu Glu Met Gly Ser Gly Asp Tyr Asp Ser Met Lys Glu Pro Cys
            20                  25                  30

Phe Arg Glu Glu Asn Ala Asn Phe Asn Lys Ile Phe Leu Pro Thr Ile
        35                  40                  45

Tyr Ser Ile Ile Phe Leu Thr Gly Ile Val Gly Asn Gly Leu Val Ile
    50                  55                  60

Leu Val Met Gly Tyr Gln Lys Lys Leu Arg Ser Met Thr Asp Lys Tyr
65                  70                  75                  80
```

Arg Leu His Leu Ser Val Ala Asp Leu Leu Phe Val Ile Thr Leu Pro
85 90 95

Phe Trp Ala Val Asp Ala Val Ala Asn Trp Tyr Phe Gly Asn Phe Leu
100 105 110

Cys Lys Ala Val His Val Ile Tyr Thr Val Asn Leu Tyr Ser Ser Val
115 120 125

Leu Ile Leu Ala Phe Ile Ser Leu Asp Arg Tyr Leu Ala Ile Val His
130 135 140

Ala Thr Asn Ser Gln Arg Pro Arg Lys Leu Leu Ala Glu Lys Val Val
145 150 155 160

Tyr Val Gly Val Trp Ile Pro Ala Leu Leu Leu Thr Ile Pro Asp Phe
165 170 175

Ile Phe Ala Asn Val Ser Glu Ala Asp Asp Arg Tyr Ile Cys Asp Arg
180 185 190

Phe Tyr Pro Asn Asp Leu Trp Val Val Val Phe Gln Phe Gln His Ile
195 200 205

Met Val Gly Leu Ile Leu Pro Gly Ile Val Ile Leu Ser Cys Tyr Cys
210 215 220

Ile Ile Ile Ser Lys Leu Ser His Ser Lys Gly His Gln Lys Arg Lys
225 230 235 240

Ala Leu Lys Thr Thr Val Ile Leu Ile Leu Ala Phe Phe Ala Cys Trp
245 250 255

Leu Pro Tyr Tyr Ile Gly Ile Ser Ile Asp Ser Phe Ile Leu Leu Glu
260 265 270

Ile Ile Lys Gln Gly Cys Glu Phe Glu Asn Thr Val His Lys Trp Ile
275 280 285

Ser Ile Thr Glu Ala Leu Ala Phe Phe His Cys Cys Leu Asn Pro Ile
290 295 300

Leu Tyr Ala Phe Leu Gly Ala Lys Phe Lys Thr Ser Ala Gln His Ala
305 310 315 320

Leu Thr Ser Val Ser Arg Gly Ser Ser Leu Lys Ile Leu Ser Lys Gly
325 330 335

Lys Arg Gly Gly His Ser Ser Val Ser Thr Glu Ser Glu Ser Ser Ser
340 345 350

Phe His Ser Ser
355

<210> 3
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<212> PRT
<213> homo sapiens

<400> 3

Met Glu Asp Phe Asn Met Glu Ser Asp Ser Phe Glu Asp Phe Trp Lys
1 5 10 15

Gly Glu Asp Leu Ser Asn Tyr Ser Tyr Ser Ser Thr Leu Pro Pro Phe
20 25 30

Leu Leu Asp Ala Ala Pro Cys Glu Pro Glu Ser Leu Glu Ile Asn Lys
35 40 45

Tyr Phe Val Val Ile Ile Tyr Ala Leu Val Phe Leu Leu Ser Leu Leu
50 55 60

Gly Asn Ser Leu Val Met Leu Val Ile Leu Tyr Ser Arg Val Gly Arg
65 70 75 80

Ser Val Thr Asp Val Tyr Leu Leu Asn Leu Ala Leu Ala Asp Leu Leu
85 90 95

Phe Ala Leu Thr Leu Pro Ile Trp Ala Ala Ser Lys Val Asn Gly Trp
100 105 110

Ile Phe Gly Thr Phe Leu Cys Lys Val Val Ser Leu Leu Lys Glu Val
115 120 125

Asn Phe Tyr Ser Gly Ile Leu Leu Leu Ala Cys Ile Ser Val Asp Arg
130 135 140

Tyr Leu Ala Ile Val His Ala Thr Arg Thr Leu Thr Gln Lys Arg Tyr
145 150 155 160

Leu Val Lys Phe Ile Cys Leu Ser Ile Trp Gly Leu Ser Leu Leu Leu
165 170 175

Ala Leu Pro Val Leu Leu Phe Arg Arg Thr Val Tyr Ser Ser Asn Val
180 185 190

Ser Pro Ala Cys Tyr Glu Asp Met Gly Asn Asn Thr Ala Asn Trp Arg
195 200 205

Met Leu Leu Arg Ile Leu Pro Gln Ser Phe Gly Phe Ile Val Pro Leu
210 215 220

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Leu Ile Met Leu Phe Cys Tyr Gly Phe Thr Leu Arg Thr Leu Phe Lys
225 230 235 240

Ala His Met Gly Gln Lys His Arg Ala Met Arg Val Ile Phe Ala Val
245 250 255

Val Leu Ile Phe Leu Leu Cys Trp Leu Pro Tyr Asn Leu Val Leu Leu
260 265 270

Ala Asp Thr Leu Met Arg Thr Gln Val Ile Gln Glu Thr Cys Glu Arg
275 280 285

Arg Asn His Ile Asp Arg Ala Leu Asp Ala Thr Glu Ile Leu Gly Ile
290 295 300

Leu His Ser Cys Leu Asn Pro Leu Ile Tyr Ala Phe Ile Gly Gln Lys
305 310 315 320

Phe Arg His Gly Leu Leu Lys Ile Leu Ala Ile His Gly Leu Ile Ser
325 330 335

Lys Asp Ser Leu Pro Lys Asp Ser Arg Pro Ser Phe Val Gly Ser Ser
340 345 350

Ser Gly His Thr Ser Thr Thr Leu
355 360

<210> 4
<211> 8
<212> PRT
<213> mus musculus

<400> 4

Gly Phe Thr Phe Thr Asp Asn Tyr
1 5

<210> 5
<211> 10
<212> PRT
<213> mus musculus

<400> 5

Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr
1 5 10

<210> 6
<211> 11
<212> PRT
<213> mus musculus

<400> 6

Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr
1 5 10

<210> 7
<211> 12
<212> PRT
<213> mus musculus

<400> 7

Gln Ser Leu Phe Asn Ser Arg Thr Arg Lys Asn Tyr
1 5 10

<210> 8
<211> 3
<212> PRT
<213> mus musculus

<400> 8

Trp Ala Ser
1

<210> 9
<211> 8
<212> PRT
<213> mus musculus

<400> 9

Met Gln Ser Phe Asn Leu Arg Thr
1 5

<210> 10
<211> 120
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 10

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

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

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Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 11
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<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 11

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

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Ile
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 12
<211> 120
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 12

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

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Ile
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 13
<211> 120
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 13

Glu Val Asn Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Asp Tyr Ala Ala
50 55 60

Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Ile
65 70 75 80

Leu Tyr Leu Gln Met Asn Ala Leu Arg Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 14
<211> 112

<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 14

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 15
<211> 112
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 15

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95
```

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 16
<211> 112
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 16

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Ala Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65 70 75 80

Ile Ser Arg Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 17
<211> 112
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 17

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

```
Pro Asp Arg Phe Ser Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Arg Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 18
<211> 112
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 18

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Arg Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 19
<211> 112
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 19

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30
```

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 20
<211> 112
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 20

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 21
<211> 450
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 21

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ala Ala
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65                  70                  75                  80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270
```

```
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450
```

<210> 22
<211> 450
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 22

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
            20                  25                  30
```

```
Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ala Ala
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Ile
65                  70                  75                  80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300
```

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 23
<211> 450
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 23

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

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Ile
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 24
<211> 450
<212> PRT
<213> artificial

<220>
<223> VH humanized variant

<400> 24

Glu Val Asn Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Asp Tyr Ala Ala
50 55 60

Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Ser Ile
65 70 75 80

Leu Tyr Leu Gln Met Asn Ala Leu Arg Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

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Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380
```

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 25
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 25

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 26
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 26

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 27
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 27

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Ala Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65 70 75 80

Ile Ser Arg Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

```
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 28
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 28

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Arg Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175
```

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Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 29
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 29

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65 70 75 80

Ile Ser Arg Val Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

```
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 30
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 30

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

Glu Arg Ala Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Leu Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190
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Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 31
<211> 219
<212> PRT
<213> artificial

<220>
<223> VL humanized variant

<400> 31

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 32
<211> 24
<212> DNA
<213> artificial

<220>
<223> optimized humanized CDR

<400> 32
ggcttcacct tcaccgacaa ctac 24

<210> 33
<211> 30
<212> DNA
<213> artificial

<220>
<223> optimized humanized CDR

<400> 33
atccggaaca aggccaacgg ctacaccaca 30

<210> 34
<211> 33
<212> DNA
<213> artificial

<220>
<223> optimized humanized CDR

<400> 34
gccagggacg tgggcagcaa ctacttcgac tac 33

<210> 35
<211> 36
<212> DNA
<213> artificial

<220>
<223> optimized humanized CDR

<400> 35
cagagcctgt tcaacagccg gacccggaag aactac 36

<210> 36
<211> 9
<212> DNA
<213> artificial

<220>
<223> optimized humanized CDR

<400> 36
tgggccagc 9

<210> 37
<211> 24

<212> DNA
<213> artificial

<220>
<223> optimized humanized CDR

<400> 37
atgcagagct tcaacctgcg gacc 24

<210> 38
<211> 360
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 38
gaggtgcagc tggtggagtc tggcggagga ctggtgcagc ccggcagaag cctgagactg 60

agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg ggtgggcttc atccggaaca aggccaacgg ctacaccaca 180

gagtacgccg ccagcgtgaa gggccggttc accatcagcc gggacgacag caagagcatt 240

gcctacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

<210> 39
<211> 360
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 39
gaggtgcagc tggtggagtc tggcggagga ctggtgcagc ccggcagaag cctgagactg 60

agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg ggtgggcttc atccggaaca aggccaacgg ctacaccaca 180

gagtacgccg ccagcgtgaa gggccggttc accatcagcc gggacaacag caagagcatt 240

gcctacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

<210> 40
<211> 360
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 40
gaggtgcagc tggtggagtc tggcggagga ctggtgcagc ccggcagaag cctgagactg 60

agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg gctgggcttc atccggaaca aggccaacgg ctacaccaca 180

gagtacgccg ccagcgtgaa gggccggttc accatcagcc gggacaacag caagagcatt 240

gcctacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

<210> 41
<211> 360
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 41
gaggtgaacc tggtggagtc tggcggagga ctggtgcagc ccggcagaag cctgagactg 60

agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg gctgggcttc atccggaaca aggccaacgg ctacaccaca 180

gactacgccg ccagcgtgag aggccggttc accatcagcc gggacaacag caagagcatt 240

ctgtacctgc agatgaacgc cctgcggacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

<210> 42
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 42
gacatcgtga tgacccagag ccccgatagc ctggccgtgt ctctgggcga gcgggccacc 60

atcaactgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc cagcacaaga 180

gaaagcggcg tgcccgaccg cttttctggc agcggcagcg gcaccgactt caccctgacc 240

atcagctccc tgcaggccga ggacgtggcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaag 336

<210> 43
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 43
gacatcgtga tgacccagag ccccgatagc ctggccgtgt ctctgggcga gcgggccacc 60

atcaactgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc cagcgccaga 180

gacagcggcg tgcccgaccg cttttctggc agcggcagcg gcaccgactt caccctgacc 240

atcagctccc tgcaggccga ggacgtggcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaag 336

<210> 44
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 44
gacatcgtga tgacccagag ccccagcagc ctggccgtgt ctctgggcga gcgggccacc 60

atgagctgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagtccccc aagctgctga tctactgggc cagcgccaga 180

gatagcggcg tgcccgctcg ctttaccggc agcggcagcg agacctactt caccctgacc 240

atcagccggg tgcaggccga ggacctcgcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaag 336

<210> 45
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 45
gacatcgtga tgacccagtc ccccgactcc ctggccgtgt ctctgggcga gcgggccacc 60

atgtcctgca agtcctccca gtccctgttc aactcccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc ctctgctaga 180

gactctggcg tgcccgacag attctccggc tccggcagcg agacatactt caccctgacc 240

atctcccggg tgcaggccga ggatctggcc gtgtactact gcatgcagtc cttcaacctg 300

cggaccttcg gccagggcac caaggtggaa atcaag 336

<210> 46
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 46
gacatcgtga tgacccagtc ccccgactcc ctggccgtgt ctctgggcga gcgggccacc 60

atgtcctgca agtcctccca gtccctgttc aactcccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc ctctgctaga 180

gactctggcg tgcccgacag attcaccggc tccggcagcg agacatactt caccctgacc 240

atctcccggg tgcaggccga ggatgtggcc gtgtactact gcatgcagtc cttcaacctg 300

cggaccttcg gccagggcac caaggtggaa atcaag 336

<210> 47
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 47
gacatcgtga tgacccagtc ccccgactcc ctggccgtgt ctctgggcga gcgggccacc 60

atgtcctgca agtcctccca gtccctgttc aactcccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc ctctgctaga 180

gactctggcg tgcccgacag attcaccggc tccggcagcg agacatactt caccctgacc 240

atctccagcc tgcaggccga ggatctggcc gtgtactact gcatgcagtc cttcaacctg 300

cggaccttcg gccagggcac caaggtggaa atcaag 336

<210> 48
<211> 336
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 48
gacatcgtga tgacccagag ccccgatagc ctggccgtgt ctctgggcga gcgggccacc 60

atcaactgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc cagcgccaga 180

gatagcggcg tgcccgaccg ctttaccggc agcggcagcg agacctactt caccctgacc 240

atcagctccc tgcaggccga ggacgtggcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaag 336

<210> 49
<211> 1350
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 49
gaggtgcagc tggtggagtc tggcggagga ctggtgcagc ccggcagaag cctgagactg 60

agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg ggtgggcttc atccggaaca aggccaacgg ctacaccaca 180

gagtacgccg ccagcgtgaa gggccggttc accatcagcc gggacgacag caagagcatt 240

gcctacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

gccagcacaa agggcccaag cgtgttcccg ctagccccca gcagcaagag caccagcggc 420

ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgtcc 480

tggaacagcg gagccctgac ctccggcgtg cacaccttcc ccgccgtgct gcagagcagc 540

ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600

tacatctgta acgtgaacca caagcccagc aacaccaagg tggacaagag agtggagccc 660

aagagctgtg acaagaccca cacctgcccc ccctgcccag cccccgagct gctgggcgga 720

cccagcgtgt tcctgttccc ccccaagccc aaggacaccc tgatgatcag cagaaccccc 780

gaggtgacct gtgtggtggt ggacgtgtcc cacgaggacc cagaggtgaa gttcaactgg 840

tacgtggacg gcgtggaggt gcacaacgcc aagaccaagc ccagagagga gcagtacaac 900

agcacctaca gggtggtgtc cgtgctgacc gtgctgcacc aggactggct gaacggcaag 960

gagtacaagt gtaaggtgtc caacaaggcc ctgccagccc caatcgaaaa gaccatcagc 1020

aaggccaagg gccagccaag agagccccag gtgtacaccc tgccacccag cagggaggag 1080

atgaccaaga accaggtgtc cctgacctgt ctggtgaagg gcttctaccc aagcgacatc 1140

gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac cccccagtg 1200

ctggacagcg acggcagctt cttcctgtac agcaagctga ccgtggacaa gagcagatgg 1260

cagcagggca acgtgttcag ctgctccgtg atgcacgagg ccctgcacaa ccactacacc 1320

cagaagagcc tgagcctgtc cccaggcaag 1350

<210> 50
<211> 1350
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 50
gaggtgcagc tggtggagtc tggcggagga ctggtgcagc ccggcagaag cctgagactg 60

agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg ggtgggcttc atccggaaca aggccaacgg ctacaccaca 180

gagtacgccg ccagcgtgaa gggccggttc accatcagcc gggacaacag caagagcatt 240

gcctacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

gccagcacaa agggcccaag cgtgttcccg ctagccccca gcagcaagag caccagcggc 420

ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgtcc 480

tggaacagcg gagccctgac ctccggcgtg cacaccttcc ccgccgtgct gcagagcagc 540

ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600

tacatctgta acgtgaacca caagcccagc aacaccaagg tggacaagag agtggagccc 660

aagagctgtg acaagaccca cacctgcccc ccctgcccag cccccgagct gctgggcgga 720

cccagcgtgt tcctgttccc ccccaagccc aaggacaccc tgatgatcag cagaaccccc 780

gaggtgacct gtgtggtggt ggacgtgtcc cacgaggacc cagaggtgaa gttcaactgg 840

tacgtggacg gcgtggaggt gcacaacgcc aagaccaagc ccagagagga gcagtacaac 900

agcacctaca gggtggtgtc cgtgctgacc gtgctgcacc aggactggct gaacggcaag 960

gagtacaagt gtaaggtgtc caacaaggcc ctgccagccc caatcgaaaa gaccatcagc 1020

aaggccaagg gccagccaag agagccccag gtgtacaccc tgccacccag cagggaggag 1080

atgaccaaga accaggtgtc cctgacctgt ctggtgaagg gcttctaccc aagcgacatc 1140

gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac cccccagtg 1200

ctggacagcg acggcagctt cttcctgtac agcaagctga ccgtggacaa gagcagatgg 1260

cagcagggca acgtgttcag ctgctccgtg atgcacgagg ccctgcacaa ccactacacc 1320

cagaagagcc tgagcctgtc cccaggcaag 1350

<210> 51
<211> 1350
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 51
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agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg gctgggcttc atccggaaca aggccaacgg ctacaccaca 180

gagtacgccg ccagcgtgaa gggccggttc accatcagcc gggacaacag caagagcatt 240

gcctacctgc agatgaacag cctgaaaacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

gccagcacaa agggcccaag cgtgttcccg ctagccccca gcagcaagag caccagcggc 420

ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgtcc 480

tggaacagcg gagccctgac ctccggcgtg cacaccttcc ccgccgtgct gcagagcagc 540

ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600

tacatctgta acgtgaacca caagcccagc aacaccaagg tggacaagag agtggagccc 660

aagagctgtg acaagaccca cacctgcccc ccctgcccag cccccgagct gctgggcgga 720

cccagcgtgt tcctgttccc ccccaagccc aaggacaccc tgatgatcag cagaaccccc 780

gaggtgacct gtgtggtggt ggacgtgtcc cacgaggacc cagaggtgaa gttcaactgg 840

tacgtggacg gcgtggaggt gcacaacgcc aagaccaagc ccagagagga gcagtacaac 900

agcacctaca gggtggtgtc cgtgctgacc gtgctgcacc aggactggct gaacggcaag 960

gagtacaagt gtaaggtgtc caacaaggcc ctgccagccc caatcgaaaa gaccatcagc 1020

aaggccaagg gccagccaag agagccccag gtgtacaccc tgccacccag cagggaggag 1080

atgaccaaga accaggtgtc cctgacctgt ctggtgaagg gcttctaccc aagcgacatc 1140

gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac ccccccagtg 1200

ctggacagcg acggcagctt cttcctgtac agcaagctga ccgtggacaa gagcagatgg 1260

cagcagggca acgtgttcag ctgctccgtg atgcacgagg ccctgcacaa ccactacacc 1320

cagaagagcc tgagcctgtc cccaggcaag 1350

<210> 52
<211> 1350
<212> DNA
<213> artificial

<220>
<223> VH humanized variant

<400> 52
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agctgcaccg ccagcggctt caccttcacc gacaactaca tgtcctgggt gcgccaggcc 120

cctggaaagg gcctggaatg gctgggcttc atccggaaca aggccaacgg ctacaccaca 180

gactacgccg ccagcgtgag aggccggttc accatcagcc gggacaacag caagagcatt 240

ctgtacctgc agatgaacgc cctgcggacc gaggacaccg ccgtgtacta ctgcgccagg 300

gacgtgggca gcaactactt cgactactgg ggccagggca cactggtgac cgtgtctagc 360

gccagcacaa agggcccaag cgtgttcccg ctagccccca gcagcaagag caccagcggc 420

ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgtcc 480

tggaacagcg gagccctgac ctccggcgtg cacaccttcc ccgccgtgct gcagagcagc 540

ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600

tacatctgta acgtgaacca caagcccagc aacaccaagg tggacaagag agtggagccc 660

aagagctgtg acaagaccca cacctgcccc ccctgcccag cccccgagct gctgggcgga 720

cccagcgtgt tcctgttccc ccccaagccc aaggacaccc tgatgatcag cagaacccct 780

gaggtgacct gtgtggtggt ggacgtgtcc cacgaggacc cagaggtgaa gttcaactgg 840

tacgtggacg gcgtggaggt gcacaacgcc aagaccaagc ccagagagga gcagtacaac 900

agcacctaca gggtggtgtc cgtgctgacc gtgctgcacc aggactggct gaacggcaag 960

gagtacaagt gtaaggtgtc caacaaggcc ctgccagccc caatcgaaaa gaccatcagc 1020

aaggccaagg gccagccaag agagccccag gtgtacaccc tgccacccag cagggaggag 1080

atgaccaaga accaggtgtc cctgacctgt ctggtgaagg gcttctaccc aagcgacatc 1140

gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac ccccccagtg 1200

ctggacagcg acggcagctt cttcctgtac agcaagctga ccgtggacaa gagcagatgg 1260

cagcagggca acgtgttcag ctgctccgtg atgcacgagg ccctgcacaa ccactacacc 1320

cagaagagcc tgagcctgtc cccaggcaag 1350

<210> 53
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 53
gacatcgtga tgacccagag ccccgatagc ctggccgtgt ctctgggcga gcgggccacc 60

atcaactgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc cagcacaaga 180

gaaagcggcg tgcccgaccg cttttctggc agcggcagcg gcaccgactt caccctgacc 240

atcagctccc tgcaggccga ggacgtggcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 54
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 54
gacatcgtga tgacccagag ccccgatagc ctggccgtgt ctctgggcga gcgggccacc 60

atcaactgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc cagcgccaga 180

gacagcggcg tgcccgaccg cttttctggc agcggcagcg gcaccgactt caccctgacc 240

atcagctccc tgcaggccga ggacgtggcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 55
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 55
gacatcgtga tgacccagag ccccagcagc ctggccgtgt ctctgggcga gcgggccacc 60

atgagctgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagtccccc aagctgctga tctactgggc cagcgccaga 180

gatagcggcg tgcccgctcg ctttaccggc agcggcagcg agacctactt caccctgacc 240

atcagccggg tgcaggccga ggacctcgcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 56
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 56
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atgtcctgca agtcctccca gtccctgttc aactcccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc ctctgctaga 180

gactctggcg tgcccgacag attctccggc tccggcagcg agacatactt caccctgacc 240

atctcccggg tgcaggccga ggatctggcc gtgtactact gcatgcagtc cttcaacctg 300

cggaccttcg gccagggcac caaggtggaa atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 57
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 57
gacatcgtga tgacccagtc ccccgactcc ctggccgtgt ctctgggcga gcgggccacc 60

atgtcctgca agtcctccca gtccctgttc aactcccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc ctctgctaga 180

gactctggcg tgcccgacag attcaccggc tccggcagcg agacatactt caccctgacc 240

atctcccggg tgcaggccga ggatgtggcc gtgtactact gcatgcagtc cttcaacctg 300

cggaccttcg gccagggcac caaggtggaa atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

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gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 58
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 58
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atgtcctgca agtcctccca gtccctgttc aactcccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc ctctgctaga 180

gactctggcg tgcccgacag attcaccggc tccggcagcg agacatactt caccctgacc 240

atctccagcc tgcaggccga ggatctggcc gtgtactact gcatgcagtc cttcaacctg 300

cggaccttcg gccagggcac caaggtggaa atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 59
<211> 657
<212> DNA
<213> artificial

<220>
<223> VL humanized variant

<400> 59
gacatcgtga tgacccagag ccccgatagc ctggccgtgt ctctgggcga gcgggccacc 60

atcaactgca agagcagcca gagcctgttc aacagccgga cccggaagaa ctacctggcc 120

tggtatcagc agaagcccgg ccagcccccc aagctgctga tctactgggc cagcgccaga 180

gatagcggcg tgcccgaccg ctttaccggc agcggcagcg agacctactt caccctgacc 240

atcagctccc tgcaggccga ggacgtggcc gtgtactact gcatgcagag cttcaacctg 300

cggaccttcg gccagggcac caaggtggag atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc cagccccgtg accaagagct tcaacagggg cgagtgc 657

<210> 60
<211> 36
<212> DNA
<213> artificial

<220>
<223> optimized CDR

<400> 60
cagtccctgt tcaactcccg gacccggaag aactac 36

<210> 61
<211> 9
<212> DNA
<213> artificial

<220>
<223> optimized CDR

<400> 61
tgggcctct 9

<210> 62
<211> 24
<212> DNA
<213> artificial

<220>
<223> optimized CDR

<400> 62
atgcagtcct tcaacctgcg gacc 24

<210> 63
<211> 24
<212> DNA
<213> mus musculus

<400> 63
gaaactctgc attctcgctt cctg 24

<210> 64
<211> 22
<212> DNA

<213> mus musculus

<400> 64
aggactcgtt tgtacccgtt ga 22

<210> 65
<211> 26
<212> DNA
<213> mus musculus

<400> 65
tgcagattgg ctacccaact gttgca 26

<210> 66
<211> 22
<212> DNA
<213> mus musculus

<400> 66
ctccttcatc ctcctggaaa tc 22

<210> 67
<211> 22
<212> DNA
<213> mus musculus

<400> 67
ccaaggaaag catagaggat gg 22

<210> 68
<211> 22
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<213> mus musculus

<400> 68
gtggtcatta tctatgccct gg 22

<210> 69
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<213> mus musculus

<400> 69
cgaccctgct gtataagatg ac 22

<210> 70
<211> 25
<212> DNA
<213> mus musculus

<400> 70
tattcctgct gagcctgctg ggaaa 25

<210> 71
<211> 24
<212> DNA
<213> mus musculus

<400> 71
gggttcacct tcactgataa ctac 24

<210> 72
<211> 30
<212> DNA
<213> mus musculus

<400> 72
attagaaaca aagctaatgg ttacacaaca 30

<210> 73
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<212> DNA
<213> mus musculus

<400> 73
gcaagagatg tcggttccaa ctactttgac tac 33

<210> 74
<211> 36
<212> DNA
<213> mus musculus

<400> 74
cagagtctgt tcaacagtcg aacccgaaag aactac 36

<210> 75
<211> 9
<212> DNA
<213> mus musculus

<400> 75
tgggcatcc 9

<210> 76
<211> 24
<212> DNA
<213> mus musculus

<400> 76
atgcaatctt ttaatcttcg gacg 24

<210> 77
<211> 100
<212> PRT
<213> homo sapiens

<400> 77

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

Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Gly Asp Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Phe Ile Arg Ser Lys Ala Tyr Gly Gly Thr Thr Glu Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ile
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Arg
100

<210> 78
<211> 101
<212> PRT
<213> homo sapiens

<400> 78

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro
100

<210> 79
<211> 100
<212> PRT
<213> homo sapiens

<400> 79

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Ser
20 25 30

Ala Met His Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Arg Ser Lys Ala Asn Ser Tyr Ala Thr Ala Tyr Ala Ala

50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Arg
100

<210> 80
<211> 101
<212> PRT
<213> homo sapiens

<400> 80

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Asp Gly Asn Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
85 90 95

Arg Ile Glu Phe Pro
100

<210> 81
<211> 15
<212> PRT
<213> homo sapiens

<400> 81

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

<210> 82
<211> 12
<212> PRT
<213> homo sapiens

<400> 82

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

<210> 83
<211> 449
<212> PRT
<213> homo sapiens

<400> 83

Glu Val Asn Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Ser Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Leu
35 40 45

Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Asp Tyr Ser Ala
50 55 60

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

Leu Tyr Leu Gln Met Asn Ala Leu Arg Ala Glu Asp Ser Ala Thr Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 84
<211> 219
<212> PRT
<213> homo sapiens

<400> 84

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

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Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

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

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ala Arg Asp Ser Gly Val
    50                  55                  60

Pro Ala Arg Phe Thr Gly Ser Gly Ser Glu Thr Tyr Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Arg Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 85
<211> 120
<212> PRT
<213> homo sapiens

<220>
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<222> (35)..(35)
<223> Xaa is His or Ser

<220>
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<222> (48)..(48)

<223> Xaa is Val or Leu

<220>
<221> misc_feature
<222> (50)..(50)
<223> Xaa is Arg or Phe

<220>
<221> misc_feature
<222> (61)..(61)
<223> Xaa is Ala or Asp

<220>
<221> misc_feature
<222> (76)..(76)
<223> Xaa is Asp or Asn

<220>
<221> misc_feature
<222> (81)..(81)
<223> Xaa is Ala or Leu

<400> 85

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met Xaa Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Glu Trp Xaa
35 40 45

Gly Xaa Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Xaa Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Xaa Ser Lys Asn Thr
65 70 75 80

Xaa Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 86
<211> 112
<212> PRT
<213> homo sapiens

<220>
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<222> (9)..(9)
<223> Xaa is Leu or Ser

<220>

<221> misc_feature
<222> (21)..(21)
<223> Xaa is Ile or Met

<220>
<221> misc_feature
<222> (40)..(40)
<223> Xaa is Asp or Ala

<220>
<221> misc_feature
<222> (43)..(43)
<223> Xaa is Leu or Gln

<220>
<221> misc_feature
<222> (59)..(59)
<223> Xaa is Tyr or Ala

<220>
<221> misc_feature
<222> (61)..(61)
<223> Xaa is Ala or Asp

<220>
<221> misc_feature
<222> (66)..(66)
<223> Xaa is Asp or Ala

<220>
<221> misc_feature
<222> (69)..(69)
<223> Xaa is Ser or Thr

<220>
<221> misc_feature
<222> (74)..(74)
<223> Xaa is Gly or Glu

<220>
<221> misc_feature
<222> (76)..(76)
<223> Xaa is Asp or Tyr

<220>
<221> misc_feature
<222> (89)..(89)
<223> Xaa is Val or Leu

<400> 86

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

Glu Pro Ala Ser Xaa Ser Cys Arg Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

Arg Thr Arg Lys Asn Tyr Leu Xaa Trp Tyr Xaa Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Gln Leu Leu Ile Tyr Trp Ala Ser Xaa Arg Xaa Ser Gly Val
    50                  55                  60

Pro Xaa Arg Phe Xaa Gly Ser Gly Ser Xaa Thr Xaa Phe Thr Leu Lys
```

65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Xaa Gly Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 87
<211> 120
<212> PRT
<213> homo sapiens

<400> 87

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Asn
20 25 30

Tyr Met His Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Ala Tyr Ala Ala
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 88
<211> 112
<212> PRT
<213> homo sapiens

<400> 88

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Arg Thr Arg Lys Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

```
Ser Pro Gln Leu Leu Ile Tyr Trp Ala Ser Tyr Arg Ala Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65                  70                  75                  80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 89
<211> 449
<212> PRT
<213> homo sapiens

<220>
<221> misc_feature
<222> (35)..(35)
<223> Xaa is His or Ser

<220>
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<222> (48)..(48)
<223> Xaa is Val or Leu

<220>
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<222> (50)..(50)
<223> Xaa is Arg or Phe

<220>
<221> misc_feature
<222> (61)..(61)
<223> Xaa is Ala or Asp

<220>
<221> misc_feature
<222> (76)..(76)
<223> Xaa is Asp or Asn

<220>
<221> misc_feature
<222> (81)..(81)
<223> Xaa is Ala or Leu

<400> 89

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met Xaa Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Glu Trp Xaa
        35                  40                  45

Gly Xaa Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Xaa Tyr Ala Ala
```

```
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Xaa Ser Lys Asn Thr
65                  70                  75                  80

Xaa Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
```

325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 90
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa is Leu or Ser

<220>
<221> misc_feature
<222> (21)..(21)
<223> Xaa is Ile or Met

<220>
<221> misc_feature
<222> (40)..(40)
<223> Xaa is Asp or Ala

<220>
<221> misc_feature
<222> (43)..(43)
<223> Xaa is Leu or Gln

<220>
<221> misc_feature
<222> (59)..(59)
<223> Xaa is Tyr or Ala

<220>
<221> misc_feature

<222> (61)..(61)
<223> Xaa is Ala or Asp

<220>
<221> misc_feature
<222> (66)..(66)
<223> Xaa is Asp or Ala

<220>
<221> misc_feature
<222> (69)..(69)
<223> Xaa is Ser or Thr

<220>
<221> misc_feature
<222> (74)..(74)
<223> Xaa is Gly or Glu

<220>
<221> misc_feature
<222> (76)..(76)
<223> Xaa is Asp or Tyr

<220>
<221> misc_feature
<222> (89)..(89)
<223> Xaa is Val or Leu

<400> 90

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

Glu Pro Ala Ser Xaa Ser Cys Arg Ser Ser Gln Ser Leu Phe Asn Ser
            20                  25                  30

Arg Thr Arg Lys Asn Tyr Leu Xaa Trp Tyr Xaa Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Gln Leu Leu Ile Tyr Trp Ala Ser Xaa Arg Xaa Ser Gly Val
    50                  55                  60

Pro Xaa Arg Phe Xaa Gly Ser Gly Ser Xaa Thr Xaa Phe Thr Leu Lys
65                  70                  75                  80

Ile Ser Arg Val Glu Ala Glu Asp Xaa Gly Val Tyr Tyr Cys Met Gln
                85                  90                  95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160
```

```
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 91
<211> 449
<212> PRT
<213> homo sapiens

<400> 91

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Asn
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Arg Asn Lys Ala Asn Gly Tyr Thr Thr Ala Tyr Ala Ala
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Ala Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Ala Arg Asp Val Gly Ser Asn Tyr Phe Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
```

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385 390 395 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly

<210> 92
<211> 219
<212> PRT
<213> homo sapiens

<400> 92

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Phe Asn Ser
20 25 30

Arg Thr Arg Lys Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln
85 90 95

Ser Phe Asn Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 93
<211> 360
<212> DNA
<213> homo sapiens

<400> 93
gaggtacagt tggtggaatc tgggggtggc ctggttcagc caggtggttc attgaagctg 60

agctgtgccg cttctggatt cacattcact gataactata tgcactgggt gcgacaggcc 120

agcggcaaag gcctggaatg ggtgggacgc atacggaaca aggccaacgg ctataccaca 180

gcttatgcag catcagtcaa gggcagattt actatcagtc gtgacgattc taaaaatact 240

gcctatctcc aaatgaattc cctcaagacc gaggataccg cagtgtacta ctgcgctagg 300

gacgtaggat ccaattactt cgactactgg gggcagggaa ccacccttac agtgtccagt 360

<210> 94
<211> 336
<212> DNA
<213> homo sapiens

<400> 94
gacatcgtta tgacccagac ccctctctca ctcccagtca ctcctggaga gcccgcatcc 60

atatcctgta ggagttctca gagtctgttc aactccagga cacgtaaaaa ctacctggac 120

tggtacctgc agaaacccgg ccagagtcca caactgctga tctattgggc ctcttacaga 180

gcctcagggg tccccgatag attctctggg tccggcagcg gtaccgactt cactttgaag 240

attagccgcg tggaagctga agatgtgggt gtgtattatt gcatgcagag ctttaatctc 300

cggacatttg gccagggaac caaggtggag atcaag 336

<210> 95
<211> 1347
<212> DNA
<213> homo sapiens

<400> 95
gaggtacagt tggtggaatc tgggggtggc ctggttcagc caggtggttc attgaagctg 60

agctgtgccg cttctggatt cacattcact gataactata tgcactgggt gcgacaggcc 120

agcggcaaag gcctggaatg ggtgggacgc atacggaaca aggccaacgg ctataccaca 180

gcttatgcag catcagtcaa gggcagattt actatcagtc gtgacgattc taaaaatact 240

gcctatctcc aaatgaattc cctcaagacc gaggataccg cagtgtacta ctgcgctagg 300

gacgtaggat ccaattactt cgactactgg gggcagggaa ccacccttac agtgtccagt 360

gcaagcacaa aagggcctag cgttttcccg ctagccccca gcagcaagag caccagcggc 420

ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgtcc 480

tggaacagcg gagccctgac ctccggcgtg cacaccttcc ccgccgtgct gcagagcagc 540

ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600

tacatctgta acgtgaacca caagcccagc aacaccaagg tggacaagag agtggagccc 660

aagagctgtg acaagaccca cacctgcccc ccctgcccag cccccgagct gctgggcgga 720

cccagcgtgt tcctgttccc ccccaagccc aaggacaccc tgatgatcag cagaaccccc 780

gaggtgacct gtgtggtggt ggacgtgtcc cacgaggacc cagaggtgaa gttcaactgg 840

tacgtggacg gcgtggaggt gcacaacgcc aagaccaagc ccagagagga gcagtacaac 900

agcacctaca gggtggtgtc cgtgctgacc gtgctgcacc aggactggct gaacggcaag 960

gagtacaagt gtaaggtgtc caacaaggcc ctgccagccc caatcgaaaa gaccatcagc 1020

aaggccaagg gccagccaag agagccccag gtgtacaccc tgccacccag cagggaggag 1080

atgaccaaga accaggtgtc cctgacctgt ctggtgaagg gcttctaccc aagcgacatc 1140

gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac ccccccagtg 1200

ctggacagcg acggcagctt cttcctgtac agcaagctga ccgtggacaa gagcagatgg 1260

cagcagggca acgtgttcag ctgctccgtg atgcacgagg ccctgcacaa ccactacacc 1320

cagaagagcc tgagcctgtc cccaggc 1347

<210> 96
<211> 657
<212> DNA
<213> homo sapiens

<400> 96
gacatcgtta tgacccagac ccctctctca ctcccagtca ctcctggaga gcccgcatcc 60

atatcctgta ggagttctca gagtctgttc aactccagga cacgtaaaaa ctacctggac 120

tggtacctgc agaaacccgg ccagagtcca caactgctga tctattgggc ctcttacaga 180

gcctcagggg tccccgatag attctctggg tccggcagcg gtaccgactt cactttgaag 240

attagccgcg tggaagctga agatgtgggt gtgtattatt gcatgcagag ctttaatctc 300

cggacatttg gccagggaac caaggtggag atcaagcgta cggtggccgc tcccagcgtg 360

ttcatcttcc ccccaagcga cgagcagctg aagagcggca ccgccagcgt ggtgtgtctg 420

ctgaacaact tctaccccag ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480

agcggcaaca gccaggagag cgtcaccgag caggacagca aggactccac ctacagcctg 540

agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgtgag 600

gtgacccacc agggcctgtc agccccgtg accaagagct tcaacagggg cgagtgc 657