<110> GENENTECH, INC. et al.

<120> METHODS FOR IMPROVING SAFETY OF BLOOD-BRAIN BARRIER TRANSPORT

<130> P4908R1 WO

<141> 2013-05-20

<150> US 61/763,915
<151> 2013-02-12

<150> US 61/698,495
<151> 2012-09-07

<150> US 61/649,878
<151> 2012-05-21

<160> 15

<210> 1
<211> 108
<212> PRT
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<400> 1
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Ser Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 2
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 2
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

```
 Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
                  35                  40                  45

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

 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                  65                  70                  75

 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                  80                  85                  90

 Phe Pro Thr Tyr Leu Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
                  95                 100                 105

 Ile Lys Arg


<210> 3
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 3
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
   1               5                  10                  15

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

 Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
                  35                  40                  45

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

 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                  65                  70                  75

 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                  80                  85                  90

 Gly Tyr Asn Asp Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
                  95                 100                 105

 Ile Lys Arg


<210> 4
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 4
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
   1               5                  10                  15

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

 Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
```

35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Ser Ser Thr Asp Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 5
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 5
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

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

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Asp Ala Thr Ser Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 6
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 6
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Tyr Ala Thr Asp Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 7
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 7
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

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

Gly Tyr Ala Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
35 40 45

Glu Trp Val Gly Trp Ile Ser Pro Ala Gly Gly Ser Thr Asp Tyr
50 55 60

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

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Pro Phe Ser Pro Trp Val
95 100 105

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
110 115

<210> 8
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 8
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

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

Gly Tyr Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
35 40 45

Glu Trp Val Gly Trp Ile Ser Pro Ala Gly Gly Ser Thr Asp Tyr
50 55 60

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

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Pro Phe Ser Pro Trp Val
95 100 105

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
110 115

<210> 9
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 9
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

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

Leu Leu Ile Tyr Ser Ala Ser Ser Leu Tyr Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Tyr Ser Tyr Ser Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 10
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 10
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

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

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile

65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Tyr Ser Tyr Ser Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 11
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 11
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

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

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Tyr Ser Tyr Ser Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 12
<211> 108
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 12
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
1 5 10 15

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

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

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
80 85 90

Tyr Ser Tyr Ser Pro Phe Thr Phe Gly Gln Gly Thr Lys Val Glu
95 100 105

Ile Lys Arg

<210> 13
<211> 126
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 13
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe Tyr
20 25 30

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

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

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

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
80 85 90

Thr Ala Val Tyr Tyr Cys Ala Arg Gln Pro Thr His Tyr Tyr Tyr
95 100 105

Tyr Ala Lys Gly Tyr Lys Ala Met Asp Tyr Trp Gly Gln Gly Thr
110 115 120

Leu Val Thr Val Ser Ser
125

<210> 14
<211> 438
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 14
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
1 5 10 15

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

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

Glu Leu Val Ala Ser Ile Asn Ser Asn Gly Gly Ser Thr Tyr Tyr
50 55 60

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

```
Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Ser Gly Asp Tyr Trp Gly Gln Gly
 95                 100                 105

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
110                 115                 120

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
125                 130                 135

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
140                 145                 150

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
155                 160                 165

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
170                 175                 180

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
185                 190                 195

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
200                 205                 210

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
215                 220                 225

Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
230                 235                 240

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
245                 250                 255

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
260                 265                 270

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275                 280                 285

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
290                 295                 300

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys
320                 325                 330

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
335                 340                 345

Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
350                 355                 360

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
365                 370                 375

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
380                 385                 390

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
395                 400                 405

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
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410 415 420

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
425 430 435

Ser Leu Gly

<210> 15
<211> 219
<212> PRT
<213> Artificial sequence

<220>
<223> sequence is synthesized

<400> 15
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
1 5 10 15

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

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

Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe
50 55 60

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
65 70 75

Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val
80 85 90

Tyr Tyr Cys Ser Gln Ser Thr His Val Pro Trp Thr Phe Gly Gln
95 100 105

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala
125 130 135

Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
140 145 150

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
155 160 165

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
170 175 180

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
185 190 195

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
200 205 210

Thr Lys Ser Phe Asn Arg Gly Glu Cys
215