

SEQUENCE LISTING

<110> KOREA ADVANCED INSTITUTE OF SCIENCE AND TECHNOLOGY
 <120> CONJUGATE OF VEGF-GRAB PROTEIN AND DRUG, AND USE THEREOF
 <130> PF-B2296
 <140> PCT/KR2018/007465
 <141> 2018-07-02
 <150> KR 10-2017-0083747
 <151> 2017-06-30
 <160> 30
 <170> PatentIn version 3.5
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 <211> 19
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Leader sequence amino acid
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Val His Ser

<210> 2
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 <223> Leader sequence nucleotide

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57

<210> 3
 <211> 119
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 <213> Artificial Sequence

<220>

<223> Cetuximab_scFv_VH amino acid

<400> 3

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

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

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ala
115

<210> 4

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Cetuximab_scFv_VH nucleotide

<400> 4

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acctgcaccg tcagcggatt tagccttact aactatggcg tgcattgggt gaggcagagc 120

cctgggaaag gcctcgaatg gctaggcgtg atttgagcg gtggaaatac tgattacaat 180

acaccgttta caagcagact ctcaattaac aaagataaca gtaagtctca agtattcttt 240
 aaaatgaaca gtctgcaaag taatgatacc gccatttatt actgtgctcg agcattgact 300
 tactatgact atgaatttgc gtactgggga cagggtacac tcgttaccgt gagcgct 357

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

<220>
 <223> Cetuximab_scFv_VL amino acid

<400> 5

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

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
 20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
 35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
 65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
 100 105

<210> 6
 <211> 324
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Cetuximab_scFv_VL nucleotide

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ttcagttgcc gggcctcaca aagtatcggc acaaatatcc actggtacca acagcggacc 120
aacggtagcc caaggctgct gataaagtat gcaagcgaga gcattagcgg catcccctcc 180
cgcttctccg gctcaggctc tggcacggat tttacactga gcattaactc tgttgagtcc 240
gaagacatcg ccgactacta ttgtcagcag aacaataatt ggcccacgac cttcggcgcc 300
gggaccaagc tggagctgaa gcgc 324

<210> 7

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Cetuximab_scFv_VH-VL linker amino acid

<400> 7

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 8

<211> 45

<212> DNA

<213> Artificial Sequence

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<223> Cetuximab_scFv_VH-VL linker nucleotide

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<210> 9

<211> 242

<212> PRT

<213> Artificial Sequence

<220>

<223> Cetuximab_scFv amino acid

<400> 9

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1 5 10 15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

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

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Ser Gly Gly Gly Gly Ser Asp Ile Leu Leu Thr Gln Ser Pro Val Ile
130 135 140

Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser Cys Arg Ala Ser
145 150 155 160

Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln Arg Thr Asn Gly
165 170 175

Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser
195 200 205

Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln
 210 215 220

Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
 225 230 235 240

Lys Arg

<210> 10
 <211> 726
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Cetuximab_scFv nucleotide

<400> 10
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 cctgggaaag gcctcgaatg gctaggcgtg atttggagcg gtggaaatac tgattacaat 180
 acaccgttta caagcagact ctcaattaac aaagataaca gtaagtctca agtattcttt 240
 aaaatgaaca gtctgcaaag taatgatacc gccatttatt actgtgctcg agcattgact 300
 tactatgact atgaatttgc gtactgggga cagggtacac tcgttaccgt gagcgctgga 360
 ggcggcggat ctggcggcgg aggaagtggc ggaggcggaa gcgacatttt attgacacag 420
 agccctgtca tactgtcagt gagccccggc gagagagttt cgttcagttg ccgggcctca 480
 caaagtatcg gcacaaatat ccactggtac caacagcgga ccaacggtag cccaaggctg 540
 ctgataaagt atgcaagcga gagcattagc ggcatcccct cccgcttctc cggctcaggc 600
 tctggcacgg attttacact gagcattaac tctgttgagt ccgaagacat cgccgactac 660
 tattgtcagc agaacaataa ttggcccacg accttcggcg ccgggaccaa gctggagctg 720
 aagcgc 726

<210> 11
 <211> 672
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Cetuximab-VEGF-Grab amino acid

<400> 11

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

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr
20 25 30

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

Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr
50 55 60

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala
85 90 95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
100 105 110

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

Ser Gly Gly Gly Gly Ser Asp Ile Leu Leu Thr Gln Ser Pro Val Ile
130 135 140

Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe Ser Cys Arg Ala Ser
145 150 155 160

Gln Ser Ile Gly Thr Asn Ile His Trp Tyr Gln Gln Arg Thr Asn Gly
165 170 175

Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser
195 200 205

Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln
210 215 220

Asn Asn Asn Trp Pro Thr Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
225 230 235 240

Lys Arg Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile
245 250 255

Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr
260 265 270

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

Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile
290 295 300

Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala
305 310 315 320

Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln
325 330 335

Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Ser Pro Val Thr
340 345 350

Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr Pro
355 360 365

Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys Asn
370 375 380

Lys Asn Ala Ser Val Arg Arg Arg Ile Asp Gln Ser Asn Ser His Ala
385 390 395 400

Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys Asp
405 410 415

Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys Ser
420 425 430

Val Asn Thr Ser Val His Ile Tyr Asp Lys Ala Leu Glu Asp Lys Thr
435 440 445

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
450 455 460

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
465 470 475 480

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
485 490 495

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
500 505 510

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
515 520 525

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
530 535 540

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
545 550 555 560

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
565 570 575

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
580 585 590

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
595 600 605

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
610 615 620

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
625 630 635 640

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
645 650 655

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
660 665 670

<210> 12
<211> 2019
<212> DNA
<213> Artificial Sequence

<220>
<223> Cetuximab-VEGF-Grab nucleotide

<400> 12
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cctgggaaag gcctcgaatg gctaggcgtg atttggagcg gtggaaatac tgattacaat 180
acaccgttta caagcagact ctcaattaac aaagataaca gtaagtctca agtattcttt 240
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tattgtcagc agaacaataa ttggcccacg accttcggcg ccgggaccaa gctggagctg 720
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gaaggaaggg agctcgtcat tccctgccgg gttacgtcac ctaacatcac tgttacttta	840
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acagtcaatg ggcatttgta taagacaaac tatctcacac atcgacaaac caatacaatc	1020
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ctcaattgta ctgctaccac tcccttgaac acgagagttc aaatgacctg gagttaccct	1140
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aacatattct acagtgttct tactattgac aaaatgcaga acaaagacaa aggactttat	1260
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aattggtacg tggacggcgt ggaagtgcac aacgccaaga ccaagcccag agaggaacag	1560
tacaacagca cctaccgggt ggtgtccgtg ctgaccgtgc tgcaccagga ctggctgaac	1620
ggcaaagagt acaagtgcaa ggtctccaac aaggccctgc ctgcccccat cgagaaaacc	1680
atcagcaagg ccaagggcca gccccgcgag cctcaggtgt acacactgcc cccagccgg	1740
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gatatcgccg tggaatggga gagcaacggc cagcccgaga acaactacaa gaccaccct	1860
cccgtgctgg acagcgacgg ctcatcttct ctgtactcca agctgaccgt ggacaagagc	1920
cgggtggcagc agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac	1980
tacaccaga agtccctgag cctgagcccc ggcaaatga	2019

<210> 13

<211> 2076

<212> DNA

<213> Artificial Sequence

<220>

<223> Leader sequence + Cetuximab-VEGF-Grab nucleotide

<400> 13

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tgcaccgtca gcggatttag ccttactaac tatggcgtgc attgggtgag gcagagccct	180
gggaaaggcc tcgaatggct aggcgtgatt tggagcgggtg gaaatactga ttacaataca	240
ccgtttacaa gcagactctc aattaacaaa gataacagta agtctcaagt attctttaaa	300
atgaacagtc tgcaaagtaa tgataccgcc atttattact gtgctcgagc attgacttac	360
tatgactatg aatttgcgta ctggggacag ggtacactcg ttaccgtgag cgctggaggc	420
ggcggatctg gcggcggagg aagtggcgga ggcggaagcg acattttatt gacacagagc	480
cctgtcatac tgtcagttag ccccggcgag agagtttctg tcagttgccg ggcctcacia	540
agtatcggca caaatatcca ctggtaccaa cagcggacca acggtagccc aaggctgctg	600
ataaagtatg caagcgagag cattagcggc atccccctcc gcttctccgg ctcaggctct	660
ggcacggatt ttacactgag cattaactct gttgagtccg aagacatcg cgcactactat	720
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ggcttcatca tatcaaatgc aacgtacaaa gaaatagggc ttctgacctg tgaagcaaca	1020
gtcaatgggc atttgtataa gacaaactat ctacacatc gacaaaccaa tacaatcata	1080
gatgtccaaa taagcacacc aagcccagtc acattactta gaggccatac tcttgtcctc	1140
aattgtactg ctaccactcc cttgaacacg agagttcaaa tgacctggag ttaccctgat	1200
gaaaaaaata agaacgcttc cgtaaggcga cgaattgacc aaagcaattc ccatgccaac	1260
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tgtcgtgtaa ggagtggacc atcattcaaa tctgttaaca cctcagtgca tatatatgat	1380
aaagcactcg aggacaagac ccacacctgt ccccttgcc ctgcccctga gctgctggga	1440
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 aaagagtaca agtgcaaggt ctccaacaag gccctgcctg ccccatcga gaaaaccatc 1740
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 gagctgacca agaaccaggt gtccctgacc tgcctgggtca agggcttcta cccagcgat 1860
 atcgccgtgg aatgggagag caacggccag cccgagaaca actacaagac caccctccc 1920
 gtgctggaca gcgacggctc attcttctg tactccaagc tgaccgtgga caagagccgg 1980
 tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggcctgca caaccactac 2040
 acccagaagt ccctgagcct gagccccggc aaatga 2076

<210> 14
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Trastuzumab_scFv_VH amino acid

<400> 14

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

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

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

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
 50 55 60

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

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

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 15
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv_VH nucleotide

<400> 15
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agctgtgccg ccagcggctt caacatcaag gacacctaca tccactgggt ccgacaggcc 120
cctggcaagg gcctggaatg ggtggcccgg atctacccca ccaacggcta caccagatac 180
gccgacagcg tgaagggccg gttcaccatc agcgccgaca ccagcaagaa caccgcctac 240
ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcag cagatggggga 300
ggcgacggct tctacgcat ggactactgg ggccagggca ccctgggtcac cgtgtctagc 360

<210> 16
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv_VL amino acid

<400> 16

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

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

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

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

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

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

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

<210> 17
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv_VL nucleotide

<400> 17
gacatccaga tgacccagag cccagcagc ctgagcgcca gcgtgggcga cagagtgacc 60
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ggcaaggccc ccaagctgct gatctacagc gccagcttcc tgtacagcgg cgtgcccagc 180
cggttcagcg gcagcagaag cggcaccgac ttcaccctga ccatctccag cctgcagccc 240
gaggatttcg ccacctacta ttgccagcag cactacacca cccccccac cttcggacag 300
ggcaccaagg tggaaatcaa gcgc 324

<210> 18
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv_VH-VL linker amino acid

<400> 18

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 19
<211> 45
<212> DNA
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv_VH-VL linker nucleotide

<400> 19
ggaggcggcg gatctggcgg cggaggaagt ggcggaggcg gaagc

45

<210> 20
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv amino acid

<400> 20

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

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

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

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

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

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

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145 150 155 160

Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly
165 170 175

Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly
180 185 190

Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu
195 200 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
210 215 220

Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
225 230 235 240

Ile Lys Arg

<210> 21
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<223> Trastuzumab_scFv nucleotide

<400> 21
gaggtgcagc tggtggaaag cggcggaggc ctggtgcagc ctggcggaag cctgagactg 60
agctgtgccg ccagcggctt caacatcaag gacacctaca tccactgggt ccgacaggcc 120
cctggcaagg gcctggaatg ggtggcccgg atctacccca ccaacggcta caccagatac 180
gccgacagcg tgaagggccg gttcaccatc agcgccgaca ccagcaagaa caccgcctac 240

ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcag cagatgggga 300
 ggcgacggct tctacgcat ggactactgg ggccagggca ccctgggtcac cgtgtctagc 360
 ggaggcggcg gatctggcgg cggaggaagt ggcgaggcg gaagcgacat ccagatgacc 420
 cagagcccca gcagcctgag cgccagcgtg ggcgacagag tgaccatcac ctgtcgggcc 480
 agccaggacg tgaacacagc cgtggcctgg tatcagcaga agcccggcaa ggcccccaag 540
 ctgctgatct acagcgccag cttcctgtac agcggcgtgc ccagccggtt cagcggcagc 600
 agaagcggca ccgacttcac cctgaccatc tccagcctgc agcccaggga ttctgccacc 660
 tactattgcc agcagcacta caccacccc cccaccttcg gacagggcac caaggtggaa 720
 atcaagcgc 729

<210> 22
 <211> 430
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VEGF-Grab-hFc amino acid

<400> 22

Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His
 1 5 10 15

Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro
 20 25 30

Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro
 35 40 45

Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser
 50 55 60

Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val
 65 70 75 80

Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn
 85 90 95

Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Ser Pro Val Thr Leu Leu
100 105 110

Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr Pro Leu Asn
115 120 125

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

Ala Ser Val Arg Arg Arg Ile Asp Gln Ser Asn Ser His Ala Asn Ile
145 150 155 160

Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys Asp Lys Gly
165 170 175

Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys Ser Val Asn
180 185 190

Thr Ser Val His Ile Tyr Asp Lys Ala Leu Glu Asp Lys Thr His Thr
195 200 205

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
210 215 220

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
225 230 235 240

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
245 250 255

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
260 265 270

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
275 280 285

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
290 295 300

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
305 310 315 320

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
325 330 335

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
340 345 350

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
355 360 365

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
370 375 380

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
385 390 395 400

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
405 410 415

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
420 425 430

<210> 23
<211> 1293
<212> DNA
<213> Artificial Sequence

<220>
<223> VEGF-Grab-hFc nucleotide

<400> 23
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tttccacttg acactttgat ccctgatgga aaacgcataa tctgggacag tagaaagggc 180
ttcatcatat caaatgcaac gtacaaagaa atagggttc tgacctgtga agcaacagtc 240
aatgggcatt tgtataagac aaactatctc acacatcgac aaaccaatac aatcatagat 300

gtccaaataa gcacaccaag ccagtcaca ttacttagag gccatactct tgtcctcaat 360
 tgtactgcta ccactccctt gaacacgaga gttcaaata cctggagtta ccctgatgaa 420
 aaaaataaga acgcttccgt aaggcgacga attgaccaa gcaattccca tgccaacata 480
 ttctacagtg ttcttactat tgacaaaatg cagaacaaag acaaaggact ttatacttgt 540
 cgtgtaagga gtggaccatc attcaaactt gttaacacct cagtgcata atagataaa 600
 gcactcgagg acaagaccca cacctgtccc ccttgccctg cccctgagct gctgggaggc 660
 ccttccgtgt ttctgttccc cccaaagccc aaggataccc tgatgatcag ccggaccccc 720
 gaagtgcctt gcgtgggtgt ggacgtgtcc cacgaggacc ctgaagtga gttcaattgg 780
 tacgtggacg gcgtggaagt gcacaacgcc aagaccaagc ccagagagga acagtacaac 840
 agcacctacc ggggtggtgtc cgtgctgacc gtgctgcacc aggactggct gaacggcaaa 900
 gagtacaagt gcaaggtctc caacaaggcc ctgcctgccc ccatcgagaa aaccatcagc 960
 aaggccaagg gccagccccg cgagcctcag gtgtacacac tgccccccag ccgggacgag 1020
 ctgaccaaga accagggtgtc cctgacctgc ctggtcaagg gcttctaccc cagcgatata 1080
 gccgtggaat gggagagcaa cggccagccc gagaacaact acaagaccac cctcccgtg 1140
 ctggacagcg acggctcatt cttcctgtac tccaagctga ccgtggacaa gagccggtgg 1200
 cagcagggca acgtgttcag ctgcagcgtg atgcacgagg ccctgcacaa ccactacacc 1260
 cagaagtccc tgagcctgag ccccgcaaaa tga 1293

<210> 24
 <211> 673
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Trastuzumab-VEGF-Grab amino acid

<400> 24

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

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

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

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

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

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

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145 150 155 160

Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly
165 170 175

Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu Tyr Ser Gly
180 185 190

Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu
195 200 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
210 215 220

Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
225 230 235 240

Ile Lys Arg Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
245 250 255

Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
260 265 270

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

Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
290 295 300

Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
305 310 315 320

Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
325 330 335

Gln Thr Asn Thr Ile Ile Asp Val Gln Ile Ser Thr Pro Ser Pro Val
340 345 350

Thr Leu Leu Arg Gly His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr
355 360 365

Pro Leu Asn Thr Arg Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys
370 375 380

Asn Lys Asn Ala Ser Val Arg Arg Arg Ile Asp Gln Ser Asn Ser His
385 390 395 400

Ala Asn Ile Phe Tyr Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys
405 410 415

Asp Lys Gly Leu Tyr Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys
420 425 430

Ser Val Asn Thr Ser Val His Ile Tyr Asp Lys Ala Leu Glu Asp Lys
435 440 445

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
450 455 460

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
465 470 475 480

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
485 490 495

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
500 505 510

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
515 520 525

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
530 535 540

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
545 550 555 560

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
565 570 575

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
580 585 590

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
595 600 605

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
610 615 620

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
625 630 635 640

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
645 650 655

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665 670

Lys

<210> 25
<211> 2022
<212> DNA
<213> Artificial Sequence

<220>
<223> Trastuzumab-VEGF-Grab nucleotide

<400> 25
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cctggcaagg gcctggaatg ggtggcccgg atctacccca ccaacggcta caccagatac 180
gccgacagcg tgaagggccg gttcaccatc agcgcgcaca ccagcaagaa caccgcctac 240
ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgcag cagatgggga 300
ggcgacggct tctacgccat ggactactgg ggccagggca ccctgggtcac cgtgtctagc 360
ggaggcggcg gatctggcgg cggaggaagt ggcgaggcg gaagcgacat ccagatgacc 420
cagagcccca gcagcctgag cgccagcgtg ggcgacagag tgaccatcac ctgtcgggcc 480
agccaggacg tgaacacagc cgtggcctgg tatcagcaga agcccggcaa ggcccccaag 540
ctgctgatct acagcgccag cttcctgtac agcggcgtgc ccagccggtt cagcggcagc 600
agaagcggca ccgacttcac cctgaccatc tccagcctgc agcccaggga ttctgccacc 660
tactattgcc agcagcacta caccaccccc cccaccttcg gacagggcac caaggtggaa 720
atcaagcgcg gccgcccctt cgtagagatg tacagtgaaa tccccgaaat tatacacatg 780
actgaaggaa gggagctcgt cattccctgc cgggttacgt cacctaacad cactgttact 840
ttaaaaaagt ttccacttga cactttgatc cctgatggaa aacgcataat ctgggacagt 900
agaaagggct tcatcatatc aaatgcaacg taaaagaaa tagggcttct gacctgtgaa 960
gcaacagtca atgggcattt gtataagaca aactatctca cacatcgaca aaccaatata 1020

atcatagatg tccaaataag cacaccaagc ccagtcacat tacttagagg ccatactctt	1080
gtcctcaatt gtactgctac cactcccttg aacacgagag ttcaaattgac ctggagttac	1140
cctgatgaaa aaaataagaa cgcttccgta aggcgacgaa ttgaccaaag caattcccat	1200
gccaacatat tctacagtgt tcttactatt gacaaaatgc agaacaaga caaaggactt	1260
tatacttgtc gtgtaaggag tggaccatca ttcaaattctg ttaacacctc agtgcataata	1320
tatgataaag cactcgagga caagaccac acctgtcccc cttgccctgc ccctgagctg	1380
ctgggaggcc cttccgtgtt tctgttcccc ccaaagccca aggataccct gatgatcagc	1440
cggacccccg aagtgacctg cgtgggtggtg gacgtgtccc acgaggacct tgaagtgaag	1500
ttcaattggt acgtggacgg cgtggaagtg cacaacgcca agaccaagcc cagagaggaa	1560
cagtacaaca gcacctaccg ggtggtgtcc gtgctgaccg tgctgcacca ggactggctg	1620
aacggcaaag agtacaagt caaggtctcc aacaaggccc tgcctgcccc catcgagaaa	1680
accatcagca aggccaaggg ccagccccgc gagcctcagg tgtacacact gccccccagc	1740
cgggacgagc tgaccaagaa ccaggtgtcc ctgacctgcc tgggtcaaggg cttctacccc	1800
agcgatatcg ccgtggaatg ggagagcaac ggccagcccg agaacaacta caagaccacc	1860
cctcccgtgc tggacagcga cggctcattc ttctgtact ccaagctgac cgtggacaag	1920
agccggtggc agcagggcaa cgtgttcagc tgcagcgtga tgcacgaggc cctgcacaac	1980
cactacaccc agaagtcct gagcctgagc cccggcaaat ga	2022

<210> 26
 <211> 2079
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> leader sequence + Trastuzumab-VEGF-Grab nucleotide

<400> 26	
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gtgcagctgg tggaaagcgg cggaggcctg gtgcagcctg gcggaagcct gagactgagc	120
tgtgccgcca gcggcttcaa catcaaggac acctacatcc actgggtccg acaggcccct	180
ggcaagggcc tggaatgggt ggcccggatc taccacacca acggctacac cagatacgcc	240

gacagcgtga agggccggtt caccatcagc gccgacacca gcaagaacac cgcctacctg	300
cagatgaaca gcctgcgggc cgaggacacc gccgtgtact actgcagcag atggggaggc	360
gacggcttct acgccatgga ctactggggc cagggcacc tggtcaccgt gtctagcggg	420
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agccccagca gcctgagcgc cagcgtgggc gacagagtga ccatcacctg tcggggcagc	540
caggacgtga acacagccgt ggcttggtat cagcagaagc ccggcaaggc cccaagctg	600
ctgatctaca gcgccagctt cctgtacagc ggcgtgccc gccggttcag cggcagcaga	660
agcggcaccg acttcaccct gaccatctcc agcctgcagc ccgaggattt cgccacctac	720
tattgccagc agcactacac cccccccc accttcggac agggcaccaa ggtggaaatc	780
aagcgcggcc gcccttcgt agagatgtac agtgaaatcc ccgaaattat acacatgact	840
gaaggaaggg agctcgtcat tccctgccgg gttacgtcac ctaacatcac tgttacttta	900
aaaaagtttc cacttgacac tttgatccct gatggaaaac gcataatctg ggacagtaga	960
aagggttca tcatatcaaa tgcaacgtac aaagaaatag ggcttctgac ctgtgaagca	1020
acagtcaatg ggcatttgta taagacaaac tatctcacac atcgacaaac caatacaatc	1080
atagatgtcc aaataagcac accaagccca gtcacattac ttagaggcca tactcttgct	1140
ctcaattgta ctgctaccac tcccttgaac acgagagttc aaatgacctg gagttaccct	1200
gatgaaaaaa ataagaacgc ttccgtaagg cgacgaattg accaaagcaa ttcccatgcc	1260
aacatattct acagtgttct tactattgac aaaatgcaga acaaagacaa aggactttat	1320
acttgtcgtg taaggagtgg accatcattc aaatctgtta acacctcagt gcatatatat	1380
gataaagcac tcgaggacaa gaccacacc tgtccccctt gccctgcccc tgagctgctg	1440
ggaggccctt ccgtgtttct gttccccca aagcccaagg ataccctgat gatcagccgg	1500
acccccgaag tgacctgcgt ggtggtggac gtgtcccacg aggaccctga agtgaagttc	1560
aattggtacg tggacggcgt ggaagtgcac aacgccaaga ccaagcccag agaggaacag	1620
tacaacagca cctaccgggt ggtgtccgtg ctgaccgtgc tgcaccagga ctggctgaac	1680
ggcaaagagt acaagtgcaa ggtctccaac aaggccctgc ctgccccat cgagaaaacc	1740
atcagcaagg ccaagggcca gccccgcgag cctcaggtgt acacactgcc cccagccgg	1800

gacgagctga ccaagaacca ggtgtccctg acctgcctgg tcaagggctt ctaccccagc 1860
gatatcgccg tggaatggga gagcaacggc cagcccgaga acaactacaa gaccaccct 1920
cccgtgctgg acagcgacgg ctcatcttctc ctgtactcca agctgaccgt ggacaagagc 1980
cgggtggcagc agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac 2040
tacaccaga agtccctgag cctgagcccc ggcaaatga 2079

<210> 27
<211> 79
<212> PRT
<213> Artificial Sequence

<220>
<223> VEGFR1_D2 amino acid

<400> 27

Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
1 5 10 15

Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
20 25 30

Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
35 40 45

Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
50 55 60

Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile
65 70 75

<210> 28
<211> 237
<212> DNA
<213> Artificial Sequence

<220>
<223> VEGFR1_D2 nucleotide

<400> 28

ggaagggagc tcgtcattcc ctgccgggtt acgtcaccta acatcactgt tactttaaaa 60

aagtttccac ttgacacttt gatccctgat ggaaaacgca taatctggga cagtagaaag 120
 ggcttcatca tatcaaatgc aacgtacaaa gaaatagggc ttctgacctg tgaagcaaca 180
 gtcaatgggc atttgataaa gacaaactat ctcacacatc gacaaaccaa tacaatc 237

<210> 29
 <211> 98
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> VEGFR1_D3 amino acid

<400> 29

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

His Thr Leu Val Leu Asn Cys Thr Ala Thr Thr Pro Leu Asn Thr Arg
 20 25 30

Val Gln Met Thr Trp Ser Tyr Pro Asp Glu Lys Asn Lys Asn Ala Ser
 35 40 45

Val Arg Arg Arg Ile Asp Gln Ser Asn Ser His Ala Asn Ile Phe Tyr
 50 55 60

Ser Val Leu Thr Ile Asp Lys Met Gln Asn Lys Asp Lys Gly Leu Tyr
 65 70 75 80

Thr Cys Arg Val Arg Ser Gly Pro Ser Phe Lys Ser Val Asn Thr Ser
 85 90 95

Val His

<210> 30
 <211> 294
 <212> DNA
 <213> Artificial Sequence

<220>

<223> VEGFR1_D3 nucleotide

<400> 30

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gatgaaaaaa ataagaacgc ttccgtaagg cgacgaattg accaaagcaa ttcccatgcc	180
aacatattct acagtgttct tactattgac aaaatgcaga acaaagacaa aggactttat	240
acttgtcgtg taaggagtgg accatcattc aaatctgtta acacctcagt gcat	294