Dual receptor antagonistic antigen-binding proteins and uses thereof

Cross reference to related applications

[0001] This application claims the benefit of U.S. Provisional Application No. 61/658,237, filed June 11, 2012, the entire disclosure of which is hereby incorporated by reference in its entirety for all purposes.

Statement regarding federally sponsored research or development

[0002] Not applicable.

Reference to a sequence listing

[0003] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 20, 2013, is named 24078PCT_CRF_sequencelisting.txt and is 56,226 bytes in size.

Field of the invention

[0004] This disclosure relates to antagonistic dual receptor antigen-binding proteins, e.g. antibodies and methods of using the dual receptor antibodies. The dual receptor antibodies may comprise antibodies to ActRII receptors and may be used to stimulate muscle growth.

Background of the invention

[0005] The transforming growth factor β (TGF-β) family of proteins includes the transforming growth factors-β (TGF-β), activins, bone morphogenic proteins (BMP), nerve growth factors (NGFs), brain-derived neurotrophic factor (BDNF), and growth/ differentiation factors (GDFs). These family members are involved in the regulation of a wide range of biological processes including cell proliferation, differentiation, and other functions.

[0006] Growth/differentiation factor 8 (GDF-8), also referred to as myostatin, is a TGF-ß family member expressed for the most part in the cells of developing and adult skeletal muscle tissue. Myostatin appears to play an essential role in negatively controlling skeletal muscle growth (McPherron et al., Nature (London), 387:83-90, (1997); Zimmers et al., Science, 296:1486-1488, (2002)). Antagonizing myostatin has been shown to increase lean muscle mass in animals.

[0007] Another member of the TGF-β family of proteins is a related growth/ differentiation factor, growth/differentiation factor 11 (GDF-11). GDF-11 has approximately 90 % sequence identity to the amino acid sequence of myostatin. GDF-11 has a role in the axial patterning in developing animals (Oh et al., Genes Dev., 11:1812-26, (1997)), and also appears to play a role in skeletal muscle development and growth.

[0008] Activins A, B and AB are the homodimers and heterodimer respectively of two polypeptide chains, βA and βB (Vale et al., Nature, 321:776-779, (1986); Ling et al., Nature,

SEQUENCE LISTING

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<130> 29955-24078 PCT

<140> PCT/US2013/045245
<141> 2013-06-11

<150> 61/658,237
<151> 2012-06-11

<160> 33

<170> PatentIn version 3.5

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        35                  40                  45

Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
    50                  55                  60

Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65                  70                  75                  80

Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
                85                  90                  95

Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
            100                 105                 110

Phe Thr His Leu Pro Glu Ala Gly Gly Pro Glu Val Thr Tyr Glu Pro
        115                 120                 125

Pro Pro Thr Ala Pro Thr Val Asp Lys Thr His Thr Cys Pro Pro Cys
    130                 135                 140

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
145                 150                 155                 160
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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
165 170 175

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
180 185 190

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
195 200 205

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
210 215 220

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
225 230 235 240

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
260 265 270

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
275 280 285

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
290 295 300

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

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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<213> Homo sapiens

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35 40 45

Cys Glu Gly Glu Gln Asp Lys Arg Leu His Cys Tyr Ala Ser Trp Ala
50 55 60

Asn Ser Ser Gly Thr Ile Glu Leu Val Lys Lys Gly Cys Trp Leu Asp
65 70 75 80

Asp Phe Asn Cys Tyr Asp Arg Gln Glu Cys Val Ala Thr Glu Glu Asn
85 90 95

Pro Gln Val Tyr Phe Cys Cys Cys Glu Gly Asn Phe Cys Asn Glu Arg
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Pro Pro Thr Ala Pro Thr
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<223> Description of Artificial Sequence: Synthetic peptide

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Gly Arg

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Asn Tyr Ala Met Ser
1 5

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peptide

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Gly Arg

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            20                  25                  30

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

Ser Gly Ile Ser Val Thr Gly Gly Ser Thr Phe Tyr Thr Asp Ser Val
    50                  55                  60

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

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

Ala Lys Val Tyr Tyr Tyr Ser Phe Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130                 135                 140

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

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

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

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205

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

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240
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Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                245                 250                 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
            260                 265                 270

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

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

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305                 310                 315                 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
        355                 360                 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    370                 375                 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385                 390                 395                 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
                405                 410                 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
            420                 425                 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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<223> Description of Artificial Sequence: Synthetic
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1               5                   10                  15

Thr Val Thr Leu Thr Cys Gly Phe Asn Ser Gly Ser Val Ser Thr Ser
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Tyr Trp Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

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

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

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

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 17
<211> 342
<212> PRT
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<220>
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Asn Trp Glu Lys Asp Arg Thr Asn Gln Thr Gly Val Glu Pro Cys Tyr
20 25 30

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

Ser Gly Ser Ile Glu Ile Val Lys Gln Gly Cys Trp Leu Asp Asp Ile
    50                  55                  60

Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Lys Lys Asp Ser Pro Glu
65                  70                  75                  80

Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser
                85                  90                  95

Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr
            100                 105                 110

Pro Lys Pro Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        115                 120                 125

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    130                 135                 140

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
145                 150                 155                 160

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                165                 170                 175

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            180                 185                 190

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        195                 200                 205

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    210                 215                 220

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
225                 230                 235                 240

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
                245                 250                 255

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            260                 265                 270

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        275                 280                 285

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    290                 295                 300
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Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
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Leu Ser Leu Ser Pro Gly
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20 25 30

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

Ser Gly Ser Ile Glu Ile Val Lys Gln Gly Cys Trp Leu Asp Asp Ile
50 55 60

Asn Cys Tyr Asp Arg Thr Asp Cys Val Glu Lys Lys Asp Ser Pro Glu
65 70 75 80

Val Tyr Phe Cys Cys Cys Glu Gly Asn Met Cys Asn Glu Lys Phe Ser
85 90 95

Tyr Phe Pro Glu Met Glu Val Thr Gln Pro Thr Ser Asn Pro Val Thr
100 105 110

Pro Lys Pro Pro Tyr Tyr Asn Ile Leu Leu Tyr Ser Leu Val Pro Leu
115 120 125

Met Leu Ile Ala Gly Ile Val Ile Cys Ala Phe Trp Val Tyr Arg His
130 135 140

His Lys Met Ala Tyr Pro Pro Val Leu Val Pro Thr Gln Asp Pro Gly
145 150 155 160

Pro Pro Pro Pro Ser Pro Leu Leu Gly Leu Lys Pro Leu Gln Leu Leu
165 170 175

Glu Val Lys Ala Arg Gly Arg Phe Gly Cys Val Trp Lys Ala Gln Leu
180 185 190

Leu Asn Glu Tyr Val Ala Val Lys Ile Phe Pro Ile Gln Asp Lys Gln

195 200 205

Ser Trp Gln Asn Glu Tyr Glu Val Tyr Ser Leu Pro Gly Met Lys His
210 215 220

Glu Asn Ile Leu Gln Phe Ile Gly Ala Glu Lys Arg Gly Thr Ser Val
225 230 235 240

Asp Val Asp Leu Trp Leu Ile Thr Ala Phe His Glu Lys Gly Ser Leu
245 250 255

Ser Asp Phe Leu Lys Ala Asn Val Val Ser Trp Asn Glu Leu Cys His
260 265 270

Ile Ala Glu Thr Met Ala Arg Gly Leu Ala Tyr Leu His Glu Asp Ile
275 280 285

Pro Gly Leu Lys Asp Gly His Lys Pro Ala Ile Ser His Arg Asp Ile
290 295 300

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

Asp Phe Gly Leu Ala Leu Lys Phe Glu Ala Gly Lys Ser Ala Gly Asp
325 330 335

Thr His Gly Gln Val Gly Thr Arg Arg Tyr Met Ala Pro Glu Val Leu
340 345 350

Glu Gly Ala Ile Asn Phe Gln Arg Asp Ala Phe Leu Arg Ile Asp Met
355 360 365

Tyr Ala Met Gly Leu Val Leu Trp Glu Leu Ala Ser Arg Cys Thr Ala
370 375 380

Ala Asp Gly Pro Val Asp Glu Tyr Met Leu Pro Phe Glu Glu Glu Ile
385 390 395 400

Gly Gln His Pro Ser Leu Glu Asp Met Gln Glu Val Val Val His Lys
405 410 415

Lys Lys Arg Pro Val Leu Arg Asp Tyr Trp Gln Lys His Ala Gly Met
420 425 430

Ala Met Leu Cys Glu Thr Ile Glu Glu Cys Trp Asp His Asp Ala Glu
435 440 445

Ala Arg Leu Ser Ala Gly Cys Val Gly Glu Arg Ile Thr Gln Met Gln
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485 490

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<211> 1544
<212> DNA
<213> Homo sapiens

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ccagggaagg ggctggagtg ggtctcaggt attagtgtta ctggtggtag cacattttac 180

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tctccgggta aa 1332

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accccaggcc aggctccacg cacgctcatc tacaacacaa acactcgctc ttctggggtc 180

cctgatcgct tctctggctc catccttggg aacaaagctg ccctcaccat cacgggggcc 240

caggcagatg atgaatctga ttattactgt gtgctgtgga tgggtagtgg catttgggtg 300

ttcggcggag ggaccaagct gaccgtccta ggtcagccca aggccaaccc cactgtcact 360

ctgttcccgc cctcctctga ggagctccaa gccaacaagg ccacactagt gtgtctgatc 420

agtgacttct acccgggagc tgtgacagtg gcctggaagg cagatggcag ccccgtcaag 480

gcgggagtgg agaccaccaa accctccaaa cagagcaaca acaagtacgc ggccagcagc 540

tacctgagcc tgacgcccga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600

catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca 648

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caggccaact acacgtgtga gacagatggg gcctgcatgg tttccatttt caatctggat 180

gggatggagc accatgtgcg cacctgcatc cccaaagtgg agctggtccc tgccgggaag 240

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tgcaacagga tcgacttgag ggtgcccagt ggtcacctca aggagcctga gcacccgtcc 360

atgtggggcc cggtggagct ggtaggcatc atcgccggcc cggtgttcct cctgttcctc 420

atcatcatca ttgttttcct tgtcattaac tatcatcagc gtgtctatca caaccgccag 480

agactggaca tggaagatcc ctcatgtgag atgtgtctct ccaaagacaa gacgctccag 540

gatcttgtct acgatctctc cacctcaggg tctggctcag ggttacccct ctttgtccag 600

cgcacagtgg cccgaaccat cgttttacaa gagattattg gcaagggtcg gtttggggaa 660

gtatggcggg gccgctggag gggtggtgat gtggctgtga aaatattctc ttctcgtgaa 720

gaacggtctt ggttcaggga agcagagata taccagacgg tcatgctgcg ccatgaaaac 780

atccttggat ttattgctgc tgacaataaa gataatggca cctggacaca gctgtggctt 840

gtttctgact atcatgagca cgggtccctg tttgattatc tgaaccggta cacagtgaca 900

attgagggga tgattaagct ggccttgtct gctgctagtg ggctggcaca cctgcacatg 960

gagatcgtgg gcacccaagg gaagcctgga attgctcatc gagacttaaa gtcaaagaac 1020

attctggtga agaaaaatgg catgtgtgcc atagcagacc tgggcctggc tgtccgtcat 1080

gatgcagtca ctgacaccat tgacattgcc ccgaatcaga gggtggggac caaacgatac 1140

atggcccctg aagtacttga tgaaaccatt aatatgaaac actttgactc ctttaaatgt 1200

gctgatattt atgccctcgg gcttgtatat tgggagattg ctcgaagatg caattctgga 1260

ggagtccatg aagaatatca gctgccatat tacgacttag tgccctctga cccttccatt 1320

gaggaaatgc gaaaggttgt atgtgatcag aagctgcgtc ccaacatccc caactggtgg 1380

cagagttatg aggcactgcg ggtgatgggg aagatgatgc gagagtgttg gtatgccaac 1440

ggcgcagccc gcctgacggc cctgcgcatc aagaagaccc tctcccagct cagcgtgcag 1500

gaagacgtga agatctaa 1518

<210> 24
<211> 1086
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 24
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cgtggggagg ctgagacacg ggagtgcatc tactacaacg ccaactggga gctggagcgc 120

accaaccaga gcggcctgga gcgctgcgaa ggcgagcagg acaagcggct gcactgctac 180

gcctcctggg ccaacagctc tggcaccatc gagctcgtga agaagggctg ctggctagat 240

gacttcaact gctacgatag gcaggagtgt gtggccactg aggagaaccc ccaggtgtac 300

ttctgctgct gtgaaggcaa cttctgcaac gagcgcttca ctcatttgcc agaggctggg 360

ggcccggaag tcacgtacga gccacccccg acagccccca ccgtcgacaa aactcacaca 420

tgcccaccgt gcccagcacc tgaactcctg gggggaccgt cagtcttcct cttccccccа 480

aaacccaagg acaccctcat gatctcccgg acccctgagg tcacatgcgt ggtggtggac 540

gtgagccacg aagaccctga ggtcaagttc aactggtacg tggacggcgt ggaggtgcat 600

aatgccaaga caaagccgcg ggaggagcag tacaacagca cgtaccgtgt ggtcagcgtc 660

ctcaccgtcc tgcaccagga ctggctgaat ggcaaggagt acaagtgcaa ggtctccaac 720

aaagccctcc cagccccat cgagaaaacc atctccaaag ccaaagggca gccccgagaa 780

ccacaggtgt acaccctgcc cccatcccgg gatgagctga ccaagaacca ggtcagcctg 840

acctgcctgg tcaaaggctt ctatcccagc gacatcgccg tggagtggga gagcaatggg 900

cagccggaga acaactacaa gaccacgcct cccgtgctgg actccgacgg ctccttcttc 960

ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc 1020

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ggtaaa 1086

<210> 25
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 25
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

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

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

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

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

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

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr

165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 26
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 26
Glu Val Gln Leu Leu 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 Thr Phe Arg Asn Asp
20 25 30

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

Ser Gly Ile Ser Val Thr Gly Gly Ser Thr Phe Tyr Thr Asp Ser Val
50 55 60

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

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

Ala Lys Val Tyr Tyr Thr Ser Phe Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

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

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

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

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205

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

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225 230 235 240

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
260 265 270

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

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

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
325 330 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 27
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 27
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

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

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

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

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

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

Gly Ile His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 28

<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 28

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Glu Val Gln Leu Leu 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 Thr Phe Arg Asn Ser
            20                  25                  30

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

Ser Ala Ile Ser Val Thr Gly Gly Ser Thr Tyr Tyr Thr Asp Ser Val
    50                  55                  60

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

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

Ala Lys Val Tyr Tyr Tyr Ser Phe Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
    130                 135                 140

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

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

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

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
        195                 200                 205

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

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225                 230                 235                 240
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Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
245 250 255

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
260 265 270

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

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

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
325 330 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 29
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

Thr Val Thr Leu Thr Cys Gly Phe Asn Ser Gly Ser Val Ser Thr Ser

20 25 30

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

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

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

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

Gly Ile Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 30
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 30
Glu Val Gln Leu Leu 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 Thr Phe Arg Asn Tyr
20 25 30

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

Ser Gly Ile Ser Val Thr Gly Gly Ser Thr Phe Tyr Thr Asp Ser Val
50 55 60

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

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

Ala Lys Val Tyr Tyr Thr Ser Phe Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

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

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

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

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205

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

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225 230 235 240

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
260 265 270

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

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

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
325 330 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 31
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 31
Gln Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly
1 5 10 15

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

Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Ala Pro Arg Thr
35 40 45

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

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

Gln Ala Asp Asp Glu Ser Asp Tyr Tyr Cys Val Leu Tyr Met Gly Ser

85 90 95

Gly Ile His Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

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

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 32
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32
Glu Val Gln Leu Leu 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 Thr Phe Arg Asn Ser
20 25 30

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

Ser Ser Ile Ser Val Thr Gly Gly Ser Thr Tyr Tyr Thr Asp Ser Val
50 55 60

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

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

Ala Lys Val Tyr Tyr Tyr Ser Phe Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

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

Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly
130 135 140

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

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

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

Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser
195 200 205

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

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
225 230 235 240

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
260 265 270

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

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

Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
305 310 315 320

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
325 330 335

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

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
355 360 365

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
370 375 380

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
385 390 395 400

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
405 410 415

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
420 425 430

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 33
<211> 1539
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 33
atgacggcgc cctgggtggc cctcgccctc ctctggggat cgctgtgcgc cggctctggg 60

cgtggggagg ctgagacacg ggagtgcatc tactacaacg ccaactggga gctggagcgc 120

accaaccaga gcggcctgga gcgctgcgaa ggcgagcagg acaagcggct gcactgctac 180

gcctcctggc gcaacagctc tggcaccatc gagctcgtga agaagggctg ctggctagat 240

gacttcaact gctacgatag gcaggagtgt gtggccactg aggagaaccc ccaggtgtac 300

ttctgctgct gtgaaggcaa cttctgcaac gaacgcttca ctcatttgcc agaggctggg 360

ggcccggaag tcacgtacga gccacccccg acagccccca ccctgctcac ggtgctggcc 420

tactcactgc tgcccatcgg gggcctttcc ctcatcgtcc tgctggcctt ttggatgtac 480

cggcatcgca agcccccccta cggtcatgtg gacatccatg aggaccctgg gcctccacca 540

ccatcccctc tggtgggcct gaagccactg cagctgctgg agatcaaggc tcgggggcgc 600

tttggctgtg tctggaaggc ccagctcatg aatgactttg tagctgtcaa gatcttccca 660

ctccaggaca agcagtcgtg gcagagtgaa cgggagatct tcagcacacc tggcatgaag 720

cacgagaacc tgctacagtt cattgctgcc gagaagcgag gctccaacct cgaagtagag 780

ctgtggctca tcacggcctt ccatgacaag ggctccctca cggattacct caaggggaac 840

atcatcacat ggaacgaact gtgtcatgta gcagagacga tgtcacgagg cctctcatac 900

ctgcatgagg atgtgccctg gtgccgtggc gagggccaca agccgtctat tgcccacagg 960

gactttaaaa gtaagaatgt attgctgaag agcgacctca cagccgtgct ggctgacttt 1020

ggcttggctg ttcgatttga gccagggaaa cctccagggg acacccacgg acaggtaggc 1080

acgagacggt acatggctcc tgaggtgctc gagggagcca tcaacttcca gagagatgcc 1140

ttcctgcgca ttgacatgta tgccatgggg ttggtgctgt gggagcttgt gtctcgctgc 1200

aaggctgcag acggacccgt ggatgagtac atgctgccct ttgaggaaga gattggccag 1260

caccttcgt tggaggagct gcaggaggtg gtggtgcaca agaagatgag gcccaccatt 1320

aaagatcact ggttgaaaca cccgggcctg gcccagcttt gtgtgaccat cgaggagtgc 1380

tgggaccatg atgcagaggc tcgcttgtcc gcgggctgtg tggaggagcg ggtgtccctg 1440

attcggaggt cggtcaacgg cactacctcg gactgtctcg tttccctggt gacctctgtc 1500

accaatgtgg acctgccccc taaagagtca agcatctaa 1539

Claims

1. An isolated antigen-binding protein comprising a first polypeptide having at least 97% identity to SEQ ID NO: 15 and a second polypeptide having at least 97% sequence identity to SEQ ID NO: 16.

2. An isolated antigen-binding protein comprising SEQ ID NO: 15 and SEQ ID NO: 16.

3. The isolated antigen-binding protein of claim 1 or 2 that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18.

4. The antigen-binding protein of claim 1 or 2, that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18 and upon binding, stimulates muscle growth.

5. The antigen-binding protein of claim 1 or 2, wherein said antigen-binding protein is a monoclonal antibody or fragment thereof.

6. The antigen-binding protein of claim 1 or 2, wherein said antigen-binding protein is a mouse antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, or fragment of a mouse antibody, a humanized antibody, a chimeric antibody or a multispecific antibody.

7. An isolated antigen-binding protein that binds two activin receptors.

8. The isolated antigen-binding protein of claim 7 that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18.

9. The antigen-binding protein of claim 7, that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18 and, upon binding, stimulates muscle growth.

10. The antigen-binding protein of claim 7, wherein said antigen-binding protein is a monoclonal antibody or fragment thereof.

11. The antigen-binding protein of claim 7, wherein said antigen-binding protein is a mouse antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, or fragment of a mouse antibody, a humanized antibody, a chimeric antibody or a multispecific antibody.

12. An isolated antigen-binding protein comprising SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8.

13. The isolated antigen-binding protein of claim 12 that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18.

14. The antigen-binding protein of claim 12 , that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18 and upon binding, stimulates muscle growth.

15. The antigen-binding protein of claim 12 , wherein said antigen-binding protein is a monoclonal antibody or fragment thereof.

16. The antigen-binding protein of claim 12 , wherein said antigen-binding protein is a mouse antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, or fragment of a mouse antibody, a humanized antibody, a chimeric antibody or a multispecific antibody.

17. An isolated antigen-binding protein comprising SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5.

18. The isolated antigen-binding protein of claim 17 that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18.

19. The antigen-binding protein of claim 17, that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18 and upon binding, stimulates muscle growth.

20. The antigen-binding protein of claim 17 , wherein said antigen-binding protein is a monoclonal antibody or fragment thereof.

21. The antigen-binding protein of claim 17, wherein said antigen-binding protein is a mouse antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, or fragment of a mouse antibody, a humanized antibody, a chimeric antibody or a multispecific antibody.

22. An isolated antigen-binding protein comprising SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8.

23. The isolated antigen-binding protein of claim 22, that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18

24. The antigen-binding protein of claim 22, that specifically binds to SEQ ID NO: 2 and SEQ ID NO: 18 and upon binding, stimulates muscle growth.

25. The antigen-binding protein of claim 22, wherein said antigen-binding protein is a monoclonal antibody or fragment thereof.

26. The antigen-binding protein of claim 22, wherein said antigen-binding protein is a mouse antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific

~~26.~~27. antibody, or fragment of a mouse antibody, a humanized antibody, a chimeric antibody or a multispecific antibody.

~~27.~~28. An isolated nucleic acid encoding the antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52.

~~28.~~29. An expression vector comprising the nucleic acid of claim 27.

~~29.~~30. A host cell comprising the vector of claim 28.

~~30.~~31. The host cell of claim 29 wherein the cell is a eukaryotic or prokaryotic cell.

~~31.~~32. The host cell of claim 30 wherein the eukaryotic cell is a mammalian cell.

~~32.~~33. An isolated antigen-binding protein, comprising at least SEQ ID NOs: 3-5 or SEQ ID NOs: 4-6.

~~33.~~34. A method of producing an antigen-binding protein, comprising culturing the host cell of claim 29 under suitable conditions such that the nucleic acid is expressed to produce the antibody.

~~34.~~35. The method of claim 33, further comprising recovering the antibody from a culture of the host cell.

~~35.~~36. A composition comprising the antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52 and a pharmaceutically acceptable carrier, diluent or excipient.

~~36.~~37. A method of reducing or blocking myostatin, activin A or GDF-11 activity comprising administering a therapeutically effective amount of the antigen-binding protein or a pharmaceutical composition containing the antigen binding protein of any one of claims 1, 2, 7, 12, 17, 22 or 52 to a subject in need of such treatment.

~~37.~~38. A method of increasing lean muscle mass or increasing the ratio of lean muscle mass to fat mass in a subject in need of such treatment comprising administering an effective amount the antigen-binding protein or a pharmaceutical composition containing the antigen binding protein of any one of claims 1, 2, 7, 12, 17, 22 or 52 to a subject in need of such treatment.

~~38.~~39. A method of treating or preventing a muscle wasting disease in a subject suffering from such a disorder comprising administering an effective amount of a therapeutic composition containing the antigen-binding polypeptide of any one of claims 1, 2, 7, 12, 17, 22 or 52 to the subject.

~~39.~~40. The method of claim 38 wherein the muscle wasting disease comprises cancer cachexia, muscular dystrophy, amyotrophic lateral sclerosis, congestive obstructive pulmonary disease, chronic heart failure, chemical cachexia, cachexia from HIV/AIDS, renal failure, uremia, rheumatoid arthritis, age-related sarcopenia, age-related frailty, organ atrophy, carpal tunnel syndrome, androgen deprivation, or muscle-wasting due to inactivity from prolonged bed rest, spinal cord injury, stroke, bone fracture, burns, aging or insulin resistance.

~~40.~~41. An isolated antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52 wherein said antigen-binding protein has a K_D for ActRIIB of 10 pM or less in a BIAcore assay.

~~41.~~42. The antigen-binding protein of claim 40 wherein said antigen-binding protein has a K_D for ActRIIB of 1 pM or less.

~~42.~~43. An isolated antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52 wherein said antigen-binding protein has a K_D for ActRIIA of 4nM or less in a BIAcore assay.

~~43.~~44. The antigen-binding protein of claim 42 wherein said antigen-binding protein also has a K_D for ActRIIA of 1pM or less.

~~44.~~45. An antigen-binding protein, wherein said antigen-binding protein has a K_D for ActRIIB and ActRIIA of 1 pM or less in a BIAcore assay.

~~45.~~46. An isolated antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52 wherein said antigen-binding protein has an IC_{50} for ActRIIB of 8 nm or less in a cell-based assay.

~~46.~~47. The antigen-binding protein of claim 40 wherein said antigen-binding protein has an IC_{50} for ActRIIB of 2 nM or less.

~~47.~~48. An isolated antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52 wherein said antigen-binding protein has an IC_{50} for ActRIIA of 2nM or less in a cell-based assay.

~~48.~~49. The antigen-binding protein of claim 42 wherein said antigen-binding protein also has an IC_{50} for ActRIIA of 1 nM or less.

~~49.~~50. An antigen-binding protein, wherein said antigen-binding protein has a IC_{50} for ActRIIB of 2 nM or less and a IC_{50}ActRIIA of 1 nM or less in a cell-based assay.

~~50.~~51. The antigen-binding protein of any one of claims 1, 2, 7, 12, 17, 22, and 52 wherein the antigen-binding protein is an antagonistic dual-receptor antibody.

~~51.~~52. The antagonistic dual-receptor antibody of claim 50 wherein the dual-receptor antibody is a human antibody.

~~52.~~53. The isolated antigen-binding protein of claim 7 that specifically binds to SEQ ID NO: 1 and SEQ ID NO: 17.

~~53.~~54. The antigen-binding protein of claim 52, that specifically binds to SEQ ID NO: 1 and SEQ ID NO: 17 and upon binding, stimulates muscle growth.

~~54.~~55. The antigen-binding protein of claim 52, wherein said antigen-binding protein is a monoclonal antibody or fragment thereof.

~~55.~~56. The antigen-binding protein of claim 52, wherein said antigen-binding protein is a mouse antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, or fragment of a mouse antibody, a humanized antibody, a chimeric antibody or a multispecific antibody.