

SEQUENCE LISTING

<110> AKESO PHARMACEUTICALS, INC.

<120> ANTI-CTLA4ANTI-PD-1 BISPECIFIC ANTIBODY AND USE THEREOF

<130> IEC200176PCT

<150> CN201910711122.4

<151> 2019-08-02

<150> CN201911224135.5

<151> 2019-12-02

<160> 44

<170> PatentIn version 3.5

<210> 1

<211> 372

<212> DNA

<213> Artificial

<220>

<223> Nucleic acid sequence of 4G10 heavy chain variable region

<400> 1

cagggtcaagc tgcaggagtc tggacctgag ctggtgaagc ctggagcttc aatgaagata 60

tcctgcaagg cttctgggta ctcatcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgaatg gattggactt attaatcctt acaataatat tactaactac 180

aaccagaagt tcatgggcaa ggccacattt actgtagaca agtcatccag cacagcctac 240

atggaactcc tcagactgac atctgaagac tctggagtct atttctgtgc aagactcgac 300

tataggtctt attggggcca agggactctg gtcactgtct ctgcagccaa aacgacaccc 360

ccatctgtct at 372

<210> 2

<211> 124

<212> PRT

<213> Artificial

<220>

<223> The amino acid sequence of 4G10 heavy chain variable region

<400> 2

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

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Tyr Asn Asn Ile Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Met Gly Lys Ala Thr Phe Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Leu Arg Leu Thr Ser Glu Asp Ser Gly Val Tyr Phe Cys
85 90 95

Ala Arg Leu Asp Tyr Arg Ser Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr
115 120

<210> 3

<211> 378

<212> DNA

<213> Artificial

<220>

<223> Nucleic acid sequence of 4G10 light chain variable region

<400> 3

caggctgttg tgactcagga atctgcactc accacatcac ctggtgaaac agtcacactc 60

acttgtcgct caagtactgg ggctgttaca actagtaact ttgccaaactg ggtccaagaa 120

aaaccagatc atttattcac tagtctaata ggtggtacca acaaccgagc tccaggtggt 180

cctgccagat tctcaggctc cctgattgga gacaaggctg ccctcaccat cacaggggca 240

cagactgagg atgaggcaat atatttctgt gctctatggt acagcaacca ttgggtgttc 300
 ggtggaggaa ccaaactgac tgtcctaggc cagcccaagt cttcgccatc agtcaccctg 360
 tttcaagggc aattctgc 378

<210> 4
 <211> 126
 <212> PRT
 <213> Artificial

<220>
 <223> The amino acid sequence of 4G10 light chain variable region

<400> 4

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

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

Asn Phe Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu Phe Thr Ser
 35 40 45

Leu Ile Gly Gly Thr Asn Asn Arg Ala Pro Gly Val Pro Ala Arg Phe
 50 55 60

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

Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
 100 105 110

Lys Ser Ser Pro Ser Val Thr Leu Phe Gln Gly Gln Phe Cys
 115 120 125

<210> 5
 <211> 345
 <212> DNA
 <213> Artificial

<220>
 <223> Nucleic acid sequence of 4G10H1V

<400> 5
 caggtgcagc tgggtggagtc tggggccgag ctggtgaagc ccggcgcctc catgaagatc 60
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 ccaggacagg gactggagtg gatcgggctg attaatcctt acaacaacat caccaactac 180
 aaccagaagt tcatgggaaa agcaaccttt acagtggaca agagcatttc cacagcctac 240
 atggaactga gccggctgac ttcagacgat agcgggggtct atttttgtgc aaggctggat 300
 tatcgctctt actggggggca gggaactctg gtcactgtct ccgct 345

<210> 6
 <211> 115
 <212> PRT
 <213> Artificial

<220>
 <223> Amino acid sequence of 4G10H1V

<400> 6

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

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
 20 25 30

Thr Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Leu Ile Asn Pro Tyr Asn Asn Ile Thr Asn Tyr Asn Gln Lys Phe
 50 55 60

Met Gly Lys Ala Thr Phe Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Arg Leu Thr Ser Asp Asp Ser Gly Val Tyr Phe Cys
85 90 95

Ala Arg Leu Asp Tyr Arg Ser Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> 7
<211> 327
<212> DNA
<213> Artificial

<220>
<223> Nucleic acid sequence of 4G10L1V

<400> 7
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acatgcggaa gctccaccgg agcagtgacc acatccaact tcgccaattg ggtccaggaa 120
aagccaggcc aggcatttcg atccctgac ggaggcaca acaatcgggc ttcttgggtg 180
cccgcaagat tctcaggaag cctgctgggg ggaaaagccg ctctgaccat tagtggcgct 240
cagcctgagg acgaagccga gtacttctgc gctctgtggt atagcaacca ctgggtgttt 300
ggcgggggaa caaagctgac tgtgctg 327

<210> 8
<211> 109
<212> PRT
<213> Artificial

<220>
<223> Amino acid sequence of 4G10L1V

<400> 8

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Phe Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Phe Arg Ser
35 40 45

Leu Ile Gly Gly Thr Asn Asn Arg Ala Ser Trp Val Pro Ala Arg Phe
50 55 60

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

Gln Pro Glu Asp Glu Ala Glu Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
85 90 95

His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 9
<211> 345
<212> DNA
<213> Artificial

<220>
<223> Nucleic acid sequence of 4G10H3V

<400> 9
caggtgcagc tggctcgagtc tggggccgaa gtgaagaaac ccggcgcctc agtgaaggtc 60
agctgcaagg ccagcgggta cagtttcact ggatatacca tgaactgggt ccgacaggcc 120
cctggccagg ggctggagtg gatcggcctg attaaccctt acaacaacat cactaactac 180
gcacagaagt tccaggggag agtgaccttt acagtggaca ccagcatttc cacagcctac 240
atggaactgt cccggctgag atctgacgat acaggcgtgt acttctgcgc taggctggat 300
taccgcagct attgggggaca gggcacactg gtgactgtca gcgca 345

<210> 10
<211> 115
<212> PRT
<213> Artificial

<220>

<223> Amino acid sequence of 4G10H3V

<400> 10

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Tyr Asn Asn Ile Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Gly Val Tyr Phe Cys
85 90 95

Ala Arg Leu Asp Tyr Arg Ser Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> 11

<211> 327

<212> DNA

<213> Artificial

<220>

<223> Nucleic acid sequence of 4G10L3V

<400> 11

caggctgtcg tcactcagga accttactg accgtgtctc ctggcgggac tgtcaccctg 60

acatgcggca gctccacagg ggccgtgacc acaagtaact tcccaaattg ggtccagcag 120

aagccaggac aggctccccg gagtctgatc ggaggcacca acaacaaggc cagctggaca 180
 cccgcacggg ttagcgggcag cctgctgggc ggcaaggccg ctctgacaat tagcggagcc 240
 cagcctgagg acgaagccga gtactattgc gctctgtggt actccaacca ctgggtgttc 300
 ggcgggcgga ccaagctgac tgtgctg 327

<210> 12
 <211> 109
 <212> PRT
 <213> Artificial

<220>
 <223> Amino acid sequence of 4G10L3V

<400> 12

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Thr Ser
 20 25 30

Asn Phe Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Ser
 35 40 45

Leu Ile Gly Gly Thr Asn Asn Lys Ala Ser Trp Thr Pro Ala Arg Phe
 50 55 60

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

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
 85 90 95

His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 13
 <211> 354

<212> DNA
<213> Artificial

<220>
<223> Nucleic acid sequence of 14C12 heavy chain variable region

<400> 13
gaggtcaaac tgggtggagag cggcggcggg ctggtgaagc ccggcgggtc actgaaactg 60
agctgcgccg cttccggctt cgcctttagc tcctacgaca tgtcatgggt gaggcagacc 120
cctgagaagc gcctggaatg ggctcgctact atcagcggag gcgggcgata cacctactat 180
cctgactctg tcaaagggag attcacaatt agtcgggata acgccagaaa tactctgtat 240
ctgcagatgt ctagtctgcg gtccgaggat acagctctgt actattgtgc aaaccggtac 300
ggcgaagcat ggtttgccta ttggggacag ggcaccctgg tgacagtctc tgcc 354

<210> 14
<211> 118
<212> PRT
<213> Artificial

<220>
<223> The amino acid sequence of 14C12 heavy chain variable region

<400> 14

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

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

Asp Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

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

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

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

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

Leu Val Thr Val Ser Ala
115

<210> 15
<211> 321
<212> DNA
<213> Artificial

<220>
<223> Nucleic acid sequence of 14C12 light chain variable region

<400> 15
gacattaaga tgacacagtc cccttcctca atgtacgcta gcctgggcga gcgagtgacc 60
ttcacatgca aagcatccca ggacatcaac acatacctgt cttggtttca gcagaagcca 120
ggcaaaagcc ccaagaccct gatctaccgg gccaatagac tggcggacgg ggtccccagc 180
agattctccg gatctggcag tgggcaggat tactccctga ccatcagctc cctggagtat 240
gaagacatgg gcatctacta ttgcctgcag tatgatgagt tccctctgac ctttggagca 300
ggcacaaaaac tggaactgaa g 321

<210> 16
<211> 107
<212> PRT
<213> Artificial

<220>
<223> The amino acid sequence of 14C12 light chain variable region

<400> 16

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

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

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

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

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95

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

<210> 17
<211> 354
<212> DNA
<213> Artificial

<220>
<223> Nucleic acid sequence of 14C12H1L1 heavy chain variable region

<400> 17
gaagtgcagc tggtcgagtc tgggggaggg ctggtgcagc ccggcgggtc actgcgactg 60
agctgcgcag cttccggatt cgccttttagc tcctacgaca tgtcctgggt gcgacaggca 120
ccaggaaagg gactggattg ggtcgctact atctcaggag gcgggagata cacctactat 180
cctgacagcg tcaagggccg gttcacaatc tctagagata acagtaagaa caatctgtat 240
ctgcagatga acagcctgag ggctgaggac accgcactgt actattgtgc caaccgctac 300
ggggaagcat ggtttgccta ttgggggcag ggaaccctgg tgacagtctc tagt 354

<210> 18
<211> 118
<212> PRT
<213> Artificial

<220>

<223> The amino acid sequence of 14C12H1L1 heavy chain variable region

<400> 18

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 Ala Phe Ser Ser Tyr
20 25 30

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

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

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

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

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

Leu Val Thr Val Ser Ser
115

<210> 19

<211> 321

<212> DNA

<213> Artificial

<220>

<223> Nucleic acid sequence of 14C12H1L1 light chain variable region

<400> 19

gacattcaga tgactcagag cccctcctcc atgtccgcct ctgtgggcga cagggtcacc 60

ttcacatgcc gcgctagtca ggatatcaac acctacctga gctggtttca gcagaagcca 120

gggaaaagcc ccaagacact gatctaccgg gctaatagac tgggtgtctgg agtcccaagt 180

cggttcagtg gctcagggag cggacaggac tacactctga ccatcagctc cctgcagcct 240
gaggacatgg caacctacta ttgcctgcag tatgatgagt tcccactgac ctttggcgcc 300
gggacaaaac tggagctgaa g 321

<210> 20
<211> 107
<212> PRT
<213> Artificial

<220>
<223> The amino acid sequence of 14C12H1L1 light chain variable region

<400> 20

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

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

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

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

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

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

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

<210> 21
<211> 1344
<212> DNA
<213> Artificial

<220>

<223> DNA sequence of 14C12H1

<400> 21

gaagtgcagc	tggtcgagtc	tgggggaggg	ctgggtgcagc	ccggcgggtc	actgcgactg	60
agctgcgcag	cttccggatt	cgcctttagc	tcctacgaca	tgtcctgggt	gcgacaggca	120
ccaggaaaagg	gactggattg	ggtcgctact	atctcaggag	gcgggagata	cacctactat	180
cctgacagcg	tcaagggccg	gttcacaatc	tctagagata	acagtaagaa	caatctgtat	240
ctgcagatga	acagcctgag	ggctgaggac	accgcactgt	actattgtgc	caaccgctac	300
ggggaagcat	ggtttgccta	ttgggggcag	ggaaccctgg	tgacagtctc	tagtgccagc	360
accaaaggac	ctagcgtgtt	tcctctcgcc	ccctcctcca	aaagcaccag	cggaggaacc	420
gctgctctcg	gatgtctggt	gaaggactac	ttccctgaac	ccgtcaccgt	gagctggaat	480
agcggcgctc	tgacaagcgg	agtccataca	ttccctgctg	tgctgcaaag	cagcggactc	540
tattccctgt	ccagcgtcgt	cacagtgccc	agcagcagcc	tgggcaccca	gacctacatc	600
tgtaacgtca	accacaagcc	ctccaacacc	aagggtggaca	agaaagtgga	gccccaaatcc	660
tgcgacaaga	cacacacctg	tccccctgt	cctgctcccg	aactcctcgg	aggccctagc	720
gtcttcctct	ttcctcccaa	acccaaggac	accctcatga	tcagcagaac	ccctgaagtc	780
acctgtgtcg	tcgtggatgt	cagccatgag	gaccccgagg	tgaaattcaa	ctggtatgtc	840
gatggcgtcg	aggtgcacaa	cgccaaaacc	aagcccaggg	aggaacagta	caactccacc	900
tacagggtgg	tgtccgtgct	gacagtcctc	caccaggact	ggctgaacgg	caaggagtac	960
aagtgcaagg	tgtccaacaa	ggctctccct	gccccattg	agaagaccat	cagcaaggcc	1020
aaaggccaac	ccaggagacc	ccaggcttat	acactgcctc	cctccaggga	cgaactcacc	1080
aagaaccagg	tgtccctgac	ctgcctggtc	aagggttttt	atcccagcga	catcgccgtc	1140
gagtgggagt	ccaacggaca	gcccgagaat	aactacaaga	ccacccctcc	tgtcctcgac	1200
tccgacggct	ccttcttcct	gtacagcaag	ctgaccgtgg	acaaaagcag	gtggcagcag	1260
ggaaacgtgt	tctcctgcag	cgtgatgcac	gaagccctcc	acaaccacta	caccagaaaa	1320
agcctgtccc	tgagccccgg	caaa				1344

<210> 22
<211> 448
<212> PRT
<213> Artificial

<220>
<223> Amino acid sequence of 14C12H1

<400> 22

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 Ala Phe Ser Ser Tyr
20 25 30

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

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

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

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

Ala Asn Arg Tyr Gly Glu Ala Trp Phe Ala 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 Ser Ser Lys Ser Thr Ser Gly Gly 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 23
 <211> 642
 <212> DNA
 <213> Artificial

<220>
 <223> DNA sequence of 14C12L1

<400> 23
 gacattcaga tgactcagag cccctcctcc atgtccgcct ctgtgggcga cagggtcacc 60
 ttcacatgcc gcgctagtca ggatatcaac acctacctga gctggtttca gcagaagcca 120
 gggaaaagcc ccaagacact gatctaccgg gctaatagac tgggtgtctgg agtcccaagt 180
 cggttcagtg gctcagggag cggacaggac tacactctga ccatcagctc cctgcagcct 240
 gaggacatgg caacctacta ttgcctgcag tatgatgagt tcccactgac ctttggcgcc 300
 gggacaaaac tggagctgaa gcgaactgtg gccgctccct ccgtcttcat ttttccccct 360
 tctgacgaac agctgaaatc aggcacagcc agcgtgggtct gtctgctgaa caatttctac 420
 cctagagagg caaaagtgca gtggaaggct gataacgccc tgcagtccgg caacagccag 480
 gagagtgtga ctgaacagga ctcaaaagat agcacctatt ccctgtctag tacactgact 540

ctgtccaagg ctgattacga gaagcacaaa gtgtatgcat gcgaagtgac acatcaggga 600

ctgtcaagcc ccgtgactaa gtcttttaac cggggcgaat gt 642

<210> 24

<211> 214

<212> PRT

<213> Artificial

<220>

<223> Amino acid sequence of 14C12L1

<400> 24

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

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

Leu Ser Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

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

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

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

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 25
<211> 15
<212> PRT
<213> Artificial

<220>
<223> Amino acid sequence of Linker1

<400> 25

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

<210> 26
<211> 20
<212> PRT
<213> Artificial

<220>
<223> Amino acid sequence of Linker2

<400> 26

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

Gly Gly Gly Ser
20

<210> 27
<211> 8
<212> PRT
<213> Artificial

<220>
<223> HCDR1

<400> 27

Gly Phe Ala Phe Ser Ser Tyr Asp
1 5

<210> 28
<211> 8
<212> PRT
<213> Artificial

<220>
<223> HCDR2

<400> 28

Ile Ser Gly Gly Gly Arg Tyr Thr
1 5

<210> 29
<211> 11
<212> PRT
<213> Artificial

<220>
<223> HCDR3

<400> 29

Ala Asn Arg Tyr Gly Glu Ala Trp Phe Ala Tyr
1 5 10

<210> 30
<211> 6
<212> PRT
<213> Artificial

<220>

<223> LCDR1

<400> 30

Gln Asp Ile Asn Thr Tyr
1 5

<210> 31

<211> 3

<212> PRT

<213> Artificial

<220>

<223> LCDR2

<400> 31

Arg Ala Asn
1

<210> 32

<211> 9

<212> PRT

<213> Artificial

<220>

<223> LCDR3

<400> 32

Leu Gln Tyr Asp Glu Phe Pro Leu Thr
1 5

<210> 33

<211> 8

<212> PRT

<213> Artificial

<220>

<223> HCDR1

<400> 33

Gly Tyr Ser Phe Thr Gly Tyr Thr
1 5

<210> 34
<211> 8
<212> PRT
<213> Artificial

<220>
<223> HCDR2

<400> 34

Ile Asn Pro Tyr Asn Asn Ile Thr
1 5

<210> 35
<211> 8
<212> PRT
<213> Artificial

<220>
<223> HCDR3

<400> 35

Ala Arg Leu Asp Tyr Arg Ser Tyr
1 5

<210> 36
<211> 9
<212> PRT
<213> Artificial

<220>
<223> LCDR1

<400> 36

Thr Gly Ala Val Thr Thr Ser Asn Phe
1 5

<210> 37
<211> 3
<212> PRT
<213> Artificial

<220>

<223> LCDR2

<400> 37

Gly Thr Asn
1

<210> 38

<211> 9

<212> PRT

<213> Artificial

<220>

<223> LCDR3

<400> 38

Ala Leu Trp Tyr Ser Asn His Trp Val
1 5

<210> 39

<211> 1344

<212> DNA

<213> Artificial

<220>

<223> Nucleic acid sequence of the heavy chain of the immunoglobulin portion of BiAb004(hG1TM)

<400> 39

gaagtgcagc tggtcgagtc tgggggaggg ctggtgcagc ccggcgggtc actgcgactg	60
agctgcgcag cttccggatt cgcctttagc tcctacgaca tgtcctgggt gcgacaggca	120
ccaggaaaagg gactggattg ggtcgctact atctcaggag gcgggagata cacctactat	180
cctgacagcg tcaagggccg gttcacaatc tctagagata acagtaagaa caatctgtat	240
ctgcagatga acagcctgag ggctgaggac accgcactgt actattgtgc caaccgctac	300
ggggaagcat ggtttgccta ttgggggcag ggaaccctgg tgacagtctc tagtgccagc	360
accaaagggc ccagcgtgtt tcctctcgcc ccctcctcca aaagcaccag cggaggaacc	420
gctgctctcg gatgtctggt gaaggactac ttccctgaac ccgtcaccgt gagctggaat	480
agcggcgctc tgacaagcgg agtccataca ttccctgctg tgctgcaaag cagcggactc	540

24

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

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

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

Ala Asn Arg Tyr Gly Glu Ala Trp Phe Ala 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 Ser Ser Lys Ser Thr Ser Gly Gly 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

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

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

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser
225 230 235 240

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

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

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

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

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

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

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

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

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

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

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

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

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

<210> 41
<211> 115
<212> PRT
<213> Artificial

<220>
<223> 4G10H1V(M)

<400> 41

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

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Lys Gln Ala Pro Gly Gln Cys Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Tyr Asn Asn Ile Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Met Gly Lys Ala Thr Phe Thr Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Thr Ser Asp Asp Ser Gly Val Tyr Phe Cys
85 90 95

Ala Arg Leu Asp Tyr Arg Ser Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> 42
<211> 110
<212> PRT
<213> Artificial

<220>

<223> 4G10L1V(M)

<400> 42

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Thr Ser
20 25 30

Asn Phe Ala Asn Trp Val Gln Glu Lys Pro Gly Gln Ala Phe Arg Ser
35 40 45

Leu Ile Gly Gly Thr Asn Asn Arg Ala Ser Trp Val Pro Ala Arg Phe
50 55 60

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

Gln Pro Glu Asp Glu Ala Glu Tyr Phe Cys Ala Leu Trp Tyr Ser Asn
85 90 95

His Trp Val Phe Gly Cys Gly Thr Lys Leu Thr Val Leu Arg
100 105 110

<210> 43

<211> 115

<212> PRT

<213> Artificial

<220>

<223> 4G10H3V(M)

<400> 43

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Ile
 35 40 45

Gly Leu Ile Asn Pro Tyr Asn Asn Ile Thr Asn Tyr Ala Gln Lys Phe
 50 55 60

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

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Gly Val Tyr Phe Cys
 85 90 95

Ala Arg Leu Asp Tyr Arg Ser Tyr Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110

Val Ser Ala
 115

<210> 44
 <211> 110
 <212> PRT
 <213> Artificial

<220>
 <223> 4G10L3V(M)

<400> 44

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Thr Ser
 20 25 30

Asn Phe Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Ser
 35 40 45

Leu Ile Gly Gly Thr Asn Asn Lys Ala Ser Trp Thr Pro Ala Arg Phe
 50 55 60

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

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

His Trp Val Phe Gly Cys Gly Thr Lys Leu Thr Val Leu Arg
100 105 110