<110> BEIJING HANMI PHARMACEUTICAL CO., LTD.

<120> Anti-PD-1/anti-HER2 natural antibody structural heterodimeric bispecific antibody and method of preparing the same

<130> PX057895

<150> WO PCT/CN2017/111310
<151> 2017-11-16

<160> 18

<170> KoPatentIn 3.0

<210> 1
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the light chain variable region

<400> 1
gacattcaga tgactcagag cccttcttca ctgtcagctt ccgtgggcga cagagtcact 60

atcacctgcc gcgcaagtca ggatgtgaac accgcagtcg cctggtacca gcagaagcct 120

ggcaaagctc caaagctgct gatctacagc gcatctttcc tgtattctgg agtgcccagt 180

aggtttagtg ggtcacggtc cggtaccgac ttcacactga ctatctccag cctgcagcct 240

gaggattttg ccacatacta ttgccagcag cactatacca cacccctac tttcggccag 300

ggaaccaaag tggagatcaa g 321

<210> 2
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the light chain variable region

<400> 2
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
100 105

<210> 3
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the light chain constant region

<400> 3
cgaactgtgg ccgctccaag cgtcttcatt tttccaccct ctgacgaaca gctgaagtca 60

gggacagctt ccgtggtctg tctgctgaac aatttttacc ccagggaggc caaagtgcag 120

tggaaggtcg ataacgctct gcagagcgga aattctcagg agagtgtgac agaacaggac 180

tcaaaagatt ccacttatag cctgtctagt accctgacac tgtccaaggc agactacgaa 240

aagcataaag tgtatgcctg tgaggtcaca catcagggtc tgtcaagccc cgtcactaag 300

tccttcaatc gtggcgaatg c 321

<210> 4
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the light chain constant region

<400> 4
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

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

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 5
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the heavy chain variable region

<400> 5
gaggtgcagc tggtcgaaag tgggggtggg ctggtgcagc caggcggatc actgaggctg 60

tcctgcgccg ctagcggctt caacatcaaa gacacctata ttcactgggt ccgacaggca 120

ccagggaagg gtctggaatg ggtggctcgt atctacccta caaatggtta cactagatat 180

gccgactccg tgaaaggccg gtttactatt tctgctgata ccagtaagaa cacagcatac 240

ctgcagatga atagcctgag ggctgaggat accgcagtgt actattgctc tcggtggggg 300

ggtgacggct tctacgctat ggattattgg ggccagggaa ctctggtcac cgtgtccagc 360

360

<210> 6
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the heavy chain variable region

<400> 6
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> 7

<211> 990
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the heavy chain constant region

<400> 7
gcttcaacaa aaggaccttc cgtgtttcca ctggcaccct ctagtaagag tacttcagga 60

ggaaccgcag cactgggatg tctggtgaag gactacttcc cagagcccgt caccgtgtct 120

tggaacagtg gagcactgac ctccggggtc catacatttc ctgccgtgct gcagtcatcc 180

ggtctgtata gcctgagctc tgtggtcaca gtcccaagtt catccctggg cacccagaca 240

tacatctgca acgtgaatca caaaccttcc aatactaagg tcgacaagaa agtggaacca 300

aaaagctgtg ataagactca tacctgccca ccttgtcctg caccagagct gctgggaggt 360

ccaagcgtgt tcctgtttcc acccaagccc aaagacacac tgatgatttc tcgcacaccc 420

gaagtcactt gtgtggtcgt ggacgtgtcc cacgaggatc ctgaagtcaa gttcaactgg 480

tacgtggatg gcgtcgaggt gcataatgct aagaccaaac ccagagagga acagtacaac 540

agcacctatc gcgtcgtgtc tgtcctgaca gtgctgcacc aggattggct gaacggaaag 600

gagtacaagt gcaaagtgag caacaaggcc ctgcccgctc ctatcgagaa gaccatttct 660

aaggctaaag gccagcctag agaaccacag gtgtatacag agcctccaag tcgcgacgag 720

ctgacaaaaa accaggtctc cctgacttgt ctggtgaagg gattctaccc tagcgatatc 780

gcagtggagt gggaatctaa tgggcagcca gaaaacaatt ataagaccac acccccctgtg 840

ctggactcag atggttcctt ctttctgctg agtgtgctga ccgtggacaa gtccaggtgg 900

cagcagggga acgtcttttc ctgcagcgtg atgcatgagg ccctgcacaa tcattacaca 960

cagaaatctc tgagtctgtc accaggaaag 990

<210> 8
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the heavy chain constant region

<400> 8
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Glu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

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

Leu Leu Ser Val Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 9
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the light chain variable region

<400> 9
gagatcgtgc tgacccagag ccctgccaca ctgagcctga gccctggcga aagggccacc 60

ctgagctgca gggctagcaa gggcgtgagc accagcggct acagctacct gcactggtat 120

caacagaagc ccggccaggc tcctaggctg ctgatctacc tggccagcta tctggagagc 180

ggcgtgcccg ctagattcag cggaagcggc agcggcaccg acttcaccct gaccatcagc 240

agcctggagc ccgaggactt cgccgtgtac tactgccagc acagcaggga cctgcctctg 300

accttcggag gcggcaccaa ggtggagatc aag 333

<210> 10
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the light chain variable region

<400> 10

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

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

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

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

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

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
85 90 95

Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 11
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the heavy chain variable region

<400> 11

caggtgcagc tggtgcagag cggcgtggag gtgaagaagc ctggcgccag cgtgaaggtg 60

agctgcaagg ccagcggcta caccttcacc aactactaca tgtactgggt gaggcaggcc 120

cctggccaag gactggagtg gatgggcggc atcaacccca gcaacggcgg caccaacttc 180

aacgagaagt tcaagaacag ggtgaccctg accaccgaca gcagcaccac caccgcctac 240

atggagctga agagcctgca gttcgacgac accgccgtgt actactgcgc caggagggac 300

tacaggttcg acatgggctt cgactactgg ggccagggca ccacagtgac cgtgtccagc 360

360

<210> 12
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the heavy chain variable region

<400> 12
Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

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

Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe
50 55 60

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

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

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

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 13
<211> 990
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the heavy chain constant region

<400> 13
gcttcaacaa aaggaccttc cgtgtttcca ctggcaccct ctagtaagag tacttcagga 60

ggaaccgcag cactgggatg tctggtgaag gactacttcc cagagcccgt caccgtgtct 120

tggaacagtg gagcactgac ctccggggtc catacatttc ctgccgtgct gcagtcatcc 180

ggtctgtata gcctgagctc tgtggtcaca gtcccaagtt catccctggg cacccagaca 240

tacatctgca acgtgaatca caaaccttcc aatactaagg tcgacaagaa agtggaacca 300

aaaagctgtg ataagactca tacctgccca ccttgtcctg caccagagct gctgggaggt 360

ccaagcgtgt tcctgtttcc acccaagccc aaagacacac tgatgatttc tcgcacaccc 420

gaagtcactt gtgtggtcgt ggacgtgtcc cacgaggatc ctgaagtcaa gttcaactgg 480

tacgtggatg gcgtcgaggt gcataatgct aagaccaaac ccagagagga acagtacaac 540

agcacctatc gcgtcgtgtc tgtcctgaca gtgctgcacc aggattggct gaacggaaag 600

gagtacaagt gcaaagtgag caacaaggcc ctgcccgctc ctatcgagaa gaccatttct 660

aaggctaaag gccagcctag agaaccacag gtgtatacac tgcctccaag tcgcgacgag 720

ctgacaaaaa accaggtctc cctgctgtgt ctggtgaagg gattctaccc tagcgatatc 780

gcagtggagt gggaatctaa tgggcagcca gaaaacaatt ataagaccac acccccctgtg 840

ctgcggtcag atggttcctt ctttctgtac agtaaactga ccgtggacaa gtccaggtgg 900

cagcagggga acgtcttttc ctgcagcgtg atgcatgagg ccctgcacaa tcattacaca 960

cagaaatctc tgagtctgtc accaggaaag 990

<210> 14
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the heavy chain constant region

<400> 14
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu

225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Leu Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Arg Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

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

<220>
<223> a nucleotide sequence of the light chain variable region

<400> 15
gatatcgttc tcacccagtc tccagccacc ctgtctgtga ctccaggaga tagcgtcagt 60

ctttcctgca gggccaacca aagtattagc aacaacctac actggtatca acaaagatca 120

catgagtctc cgaggcttct catcagattt gcttcccagt ccatctctgg gatcccctcc 180

aggttcagtg gcagtggatc agggacagat ttcactctca gtatcaacag tgtggagact 240

gaagattttg gaatgtattt ctgtcaacag agtgacaact ggcctctcac gttcggtgct 300

gggaccaagc tggagatcaa g 321

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

<220>
<223> an amino acid sequence of the light chain variable region

<400> 16
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly
1 5 10 15

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

Leu His Trp Tyr Gln Gln Arg Ser His Glu Ser Pro Arg Leu Leu Ile
35 40 45

Arg Phe Ala Ser Gln 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 Thr
65 70 75 80

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

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

<210> 17
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> a nucleotide sequence of the heavy chain variable region

<400> 17
gaggttcagc tgcaggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt agctatggca tgtcttgggt tcgccagact 120

ccggagaaga ggctggagtg ggtcgcaagc attagtggtg gtggtcgtta tacctactat 180

ccagacagta tgaaggggcg attcaccatc tccagagaca atgccaagaa caacctgcac 240

ctgcaaatga gcagtctgag gtctgaggac acggccttgt attactgtgt ctatgaatat 300

ttttatacta tggactactg gggtcaagga acctcagtca ccgtctcctc a 351

<210> 18
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> an amino acid sequence of the heavy chain variable region

<400> 18
Glu Val Gln Leu Gln 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 Thr Phe Ser Ser Tyr
20 25 30

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

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

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

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

Val Tyr Glu Tyr Phe Tyr Thr Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115