

SEQUENCE LISTING

<110> AKESO BIOPHARMA, INC

<120> ANTI-PD-1/VEGFA BIFUNCTIONAL ANTIBODY, PHARMACEUTICAL COMPOSITION THEREOF AND USE THEREOF

<130> IEC190067PCT

<150> 201811002548.4

<151> 2018-08-30

<160> 26

<170> PatentIn version 3.2

<210> 1

<211> 171

<212> PRT

<213> Artificial

<220>

<223> The amino acid sequence of VEGFA-His

<400> 1

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Phe	Met	Asp	Val	Tyr	Gln	Arg	Ser	Tyr	Cys	His	Pro	Ile	Glu	Thr	Leu
			20					25					30		

Val	Asp	Ile	Phe	Gln	Glu	Tyr	Pro	Asp	Glu	Ile	Glu	Tyr	Ile	Phe	Lys
			35				40					45			

Pro	Ser	Cys	Val	Pro	Leu	Met	Arg	Cys	Gly	Gly	Cys	Cys	Asn	Asp	Glu
			50			55					60				

Gly	Leu	Glu	Cys	Val	Pro	Thr	Glu	Glu	Ser	Asn	Ile	Thr	Met	Gln	Ile
65					70					75				80	

Met	Arg	Ile	Lys	Pro	His	Gln	Gly	Gln	His	Ile	Gly	Glu	Met	Ser	Phe
				85					90					95	

Leu Gln His Asn Lys Cys Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg
100 105 110

Gln Glu Asn Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys His Leu Phe
115 120 125

Val Gln Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn Thr Asp Ser
130 135 140

Arg Cys Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr Cys Arg Cys
145 150 155 160

Asp Lys Pro Arg Arg His His His His His His
165 170

<210> 2
<211> 513
<212> DNA
<213> Artificial

<220>
<223> Nucleotide sequence of VEGFA-His

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taccagagaa gctactgccca ccccatcgag accctgggtgg acatcttcca ggagtacccc 120
gacgagatcg agtacatctt caagcccagc tgcgtgcccc tgatgagatg cggcggctgc 180
tgcaacgacg agggcctgga gtgcgtgccc accgaggaga gcaacatcac catgcagatc 240
atgagaatca agccccacca gggccagcac atcggcgaga tgagcttcct gcagcacaac 300
aagtgcgagt gcagacccaa gaaggacaga gccagacagg agaacccttg cggcccctgc 360
agcgagagaa gaaagcacct gttcgtgcag gacccccaga cctgcaagtg cagctgcaag 420
aacaccgaca gcagatgcaa ggccagacag ctggagctga acgagagaac ctgcagatgc 480
gacaagccca gaagacatca tcaccatcac cac 513

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<211> 998
<212> PRT
<213> Artificial

<220>

<223> The amino acid sequence of Fusion protein VEGFR2- hFc

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Thr Arg Ala Ala Ser Val Gly Leu Pro Ser Val Ser Leu Asp Leu Pro
20 25 30

Arg Leu Ser Ile Gln Lys Asp Ile Leu Thr Ile Lys Ala Asn Thr Thr
35 40 45

Leu Gln Ile Thr Cys Arg Gly Gln Arg Asp Leu Asp Trp Leu Trp Pro
50 55 60

Asn Asn Gln Ser Gly Ser Glu Gln Arg Val Glu Val Thr Glu Cys Ser
65 70 75 80

Asp Gly Leu Phe Cys Lys Thr Leu Thr Ile Pro Lys Val Ile Gly Asn
85 90 95

Asp Thr Gly Ala Tyr Lys Cys Phe Tyr Arg Glu Thr Asp Leu Ala Ser
100 105 110

Val Ile Tyr Val Tyr Val Gln Asp Tyr Arg Ser Pro Phe Ile Ala Ser
115 120 125

Val Ser Asp Gln His Gly Val Val Tyr Ile Thr Glu Asn Lys Asn Lys
130 135 140

Thr Val Val Ile Pro Cys Leu Gly Ser Ile Ser Asn Leu Asn Val Ser
145 150 155 160

Leu Cys Ala Arg Tyr Pro Glu Lys Arg Phe Val Pro Asp Gly Asn Arg
165 170 175

Ile Ser Trp Asp Ser Lys Lys Gly Phe Thr Ile Pro Ser Tyr Met Ile
180 185 190

Ser Tyr Ala Gly Met Val Phe Cys Glu Ala Lys Ile Asn Asp Glu Ser
195 200 205

Tyr Gln Ser Ile Met Tyr Ile Val Val Val Val Gly Tyr Arg Ile Tyr
210 215 220

Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
225 230 235 240

Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
245 250 255

Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
260 265 270

Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
275 280 285

Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
290 295 300

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

Phe Val Arg Val His Glu Lys Pro Phe Val Ala Phe Gly Ser Gly Met
325 330 335

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

Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile Lys Trp Tyr Lys Asn Gly

355

360

365

Ile Pro Leu Glu Ser Asn His Thr Ile Lys Ala Gly His Val Leu Thr
 370 375 380

Ile Met Glu Val Ser Glu Arg Asp Thr Gly Asn Tyr Thr Val Ile Leu
 385 390 395 400

Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser His Val Val Ser Leu Val
 405 410 415

Val Tyr Val Pro Pro Gln Ile Gly Glu Lys Ser Leu Ile Ser Pro Val
 420 425 430

Asp Ser Tyr Gln Tyr Gly Thr Thr Gln Thr Leu Thr Cys Thr Val Tyr
 435 440 445

Ala Ile Pro Pro Pro His His Ile His Trp Tyr Trp Gln Leu Glu Glu
 450 455 460

Glu Cys Ala Asn Glu Pro Ser Gln Ala Val Ser Val Thr Asn Pro Tyr
 465 470 475 480

Pro Cys Glu Glu Trp Arg Ser Val Glu Asp Phe Gln Gly Gly Asn Lys
 485 490 495

Ile Glu Val Asn Lys Asn Gln Phe Ala Leu Ile Glu Gly Lys Asn Lys
 500 505 510

Thr Val Ser Thr Leu Val Ile Gln Ala Ala Asn Val Ser Ala Leu Tyr
 515 520 525

Lys Cys Glu Ala Val Asn Lys Val Gly Arg Gly Glu Arg Val Ile Ser
 530 535 540

Phe His Val Thr Arg Gly Pro Glu Ile Thr Leu Gln Pro Asp Met Gln
 545 550 555 560

Pro Thr Glu Gln Glu Ser Val Ser Leu Trp Cys Thr Ala Asp Arg Ser
565 570 575

Thr Phe Glu Asn Leu Thr Trp Tyr Lys Leu Gly Pro Gln Pro Leu Pro
580 585 590

Ile His Val Gly Glu Leu Pro Thr Pro Val Cys Lys Asn Leu Asp Thr
595 600 605

Leu Trp Lys Leu Asn Ala Thr Met Phe Ser Asn Ser Thr Asn Asp Ile
610 615 620

Leu Ile Met Glu Leu Lys Asn Ala Ser Leu Gln Asp Gln Gly Asp Tyr
625 630 635 640

Val Cys Leu Ala Gln Asp Arg Lys Thr Lys Lys Arg His Cys Val Val
645 650 655

Arg Gln Leu Thr Val Leu Glu Arg Val Ala Pro Thr Ile Thr Gly Asn
660 665 670

Leu Glu Asn Gln Thr Thr Ser Ile Gly Glu Ser Ile Glu Val Ser Cys
675 680 685

Thr Ala Ser Gly Asn Pro Pro Pro Gln Ile Met Trp Phe Lys Asp Asn
690 695 700

Glu Thr Leu Val Glu Asp Ser Gly Ile Val Leu Lys Asp Gly Asn Arg
705 710 715 720

Asn Leu Thr Ile Arg Arg Val Arg Lys Glu Asp Glu Gly Leu Tyr Thr
725 730 735

Cys Gln Ala Cys Ser Val Leu Gly Cys Ala Lys Val Glu Ala Phe Phe
740 745 750

Ile Ile Glu Gly Ala Gln Glu Lys Thr Asn Leu Glu Ser Arg Glu Asn
755 760 765

Leu Tyr Phe Gln Gly Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
770 775 780

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
785 790 795 800

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
805 810 815

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
820 825 830

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
835 840 845

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
850 855 860

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
865 870 875 880

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
885 890 895

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
900 905 910

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
915 920 925

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
930 935 940

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 945 950 955 960

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
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Ser Leu Ser Pro Gly Lys
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 <211> 2997
 <212> DNA
 <213> Artificial

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 <223> Nucleotide sequence of Fusion protein VEGFR2- hFc

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 cttacaatta aggctaatac aactcttcaa attacttgca ggggacagag ggacttggac 180
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aacctcacta tccgcagagt gaggaaggag gacgaaggcc tctacacctg ccaggcatgc	2220

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<210> 5

<211> 123

<212> PRT

<213> Artificial

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

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

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

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Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Ala Asp Phe
50 55 60

Lys Arg Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser 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

Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 6
<211> 369
<212> DNA
<213> Artificial

<220>
<223> Nucleotide sequence of Bevacizumab heavy chain variable region

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ccaggaaagg gactggagtg ggtcggctgg atcaacactt acaccgggga acctacctat 180
gcagccgact ttaagcggcg gttcaccttc agcctggata caagcaaadc cactgcctac 240
ctgcagatga acagcctgcg agctgaggac accgcagtct actattgtgc taaatatccc 300
cactactatg ggagcagcca ttggtatttt gacgtgtggg ggcaggggac tctggtgaca 360
gtgagcagc 369

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

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<223> The amino acid sequence of Bevacizumab light chain variable region

<400> 7

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

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

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

Ser Gly 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 Tyr Ser Thr Val Pro Trp
85 90 95

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

<210> 8

<211> 321

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of Bevacizumab light chain variable region

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atcacatgca gtgcttcaca ggatatttcc aactacctga attggtatca gcagaagcca 120

ggaaaagcac ccaagggtgct gatctacttc actagctccc tgcactcagg agtgccaagc 180

cggttcagcg gatccggatc tggaaccgac ttactctga ccatttctag tctgcagcct 240
 gaggatttcg ctacatacta ttgccagcag tattctaccg tgccatggac atttggccag 300
 gggactaaag tcgagatcaa g 321

<210> 9
 <211> 118
 <212> PRT
 <213> Artificial

<220>
 <223> The amino acid sequence of humanized antibody 14C12H1L1 heavy chain variable region

<400> 9

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
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<210> 10
<211> 354
<212> DNA
<213> Artificial

<220>
<223> Nucleotide sequence of humanized antibody 14C12H1L1 heavy chain variable region

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cctgacagcg tcaagggccg gttcacaatc tctagagata acagtaagaa caatctgtat 240
ctgcagatga acagcctgag ggctgaggac accgcactgt actattgtgc caaccgctac 300
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<210> 11
<211> 107
<212> PRT
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<220>
<223> The amino acid sequence of humanized antibody 14C12H1L1 light chain variable region

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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> 12

<211> 321

<212> DNA

<213> Artificial

<220>

<223> Nucleotide sequence of humanized antibody 14C12H1L1 light chain variable region

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gggaaaagcc ccaagacact gatctaccgg gctaatagac tgggtgtctgg agtcccaagt 180

cggttcagtg gctcagggag cggacaggac tacactctga ccatcagctc cctgcagcct 240

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gggacaaaac tggagctgaa g 321

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<211> 20

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<213> Artificial

<220>

<223> The amino acid sequence of Linker 1

<400> 13

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1 5 10 15

Gly Gly Gly Ser
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<210> 14
<211> 5
<212> PRT
<213> Artificial

<220>
<223> linker fragment

<400> 14

Gly Gly Gly Gly Ser
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<210> 15
<211> 8
<212> PRT
<213> Artificial

<220>
<223> HCDR1 of Antibody Bevacizumab

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Gly Tyr Thr Phe Thr Asn Tyr Gly
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<210> 16
<211> 8
<212> PRT
<213> Artificial

<220>
<223> HCDR2 of Antibody Bevacizumab

<400> 16

Ile Asn Thr Tyr Thr Gly Glu Pro
1 5

<210> 17
<211> 16
<212> PRT
<213> Artificial

<220>
<223> HCDR3 of Antibody Bevacizumab

<400> 17

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

<220>
<223> LCDR1 of Antibody Bevacizumab

<400> 18

Gln	Asp	Ile	Ser	Asn	Tyr
1				5	

<210> 19
<211> 3
<212> PRT
<213> Artificial

<220>
<223> LCDR2 of Antibody Bevacizumab

<400> 19

Phe	Thr	Ser
1		

<210> 20
<211> 9
<212> PRT
<213> Artificial

<220>

<223> LCDR3 of Antibody Bevacizumab

<400> 20

Gln Gln Tyr Ser Thr Val Pro Trp Thr
1 5

<210> 21

<211> 8

<212> PRT

<213> Artificial

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<223> HCDR1 of Antibody 14C12H1L1

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<210> 22

<211> 8

<212> PRT

<213> Artificial

<220>

<223> HCDR2 of Antibody 14C12H1L1

<400> 22

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<210> 23

<211> 11

<212> PRT

<213> Artificial

<220>

<223> HCDR3 of Antibody 14C12H1L1

<400> 23

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

<220>
<223> LCDR1 of Antibody 14C12H1L1

<400> 24

Gln Asp Ile Asn Thr Tyr
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<210> 25
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<220>
<223> LCDR2 of Antibody 14C12H1L1

<400> 25

Arg Ala Asn
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<210> 26
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<212> PRT
<213> Artificial

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<223> LCDR3 of Antibody 14C12H1L1

<400> 26

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