

SEQUENCE LISTING

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<110> F. Hoffmann-La Roche AG

<120> Bispecific anti-EGFR/anti-IGF-1R antibodies

<130> 25393

<150> EP 08016952.7

<151> 2008-09-26

<150> EP 09004908.1

<151> 2009-04-02

<160> 49

<170> PatentIn version 3.2

<210> 1

<211> 11

<212> PRT

<213> Artificial

<220>

<223> heavy chain CDR3, humanized <EGFR>ICR62

<400> 1

Leu	Ser	Pro	Gly	Gly	Tyr	Tyr	Val	Met	Asp	Ala
1			5						10	

<210> 2

<211> 17

<212> PRT

<213> Artificial

<220>

<223> heavy chain CDR2, humanized <EGFR>ICR62

<400> 2

Tyr	Phe	Asn	Pro	Asn	Ser	Gly	Tyr	Ser	Thr	Tyr	Ala	Gln	Lys	Phe	Gln
1				5					10					15	

Gly

<210> 3

<211> 5  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR1, humanized <EGFR>ICR62

<400> 3

Asp Tyr Lys Ile His  
1 5

<210> 4  
<211> 8  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR3, humanized <EGFR>ICR62

<400> 4

Leu Gln His Asn Ser Phe Pro Thr  
1 5

<210> 5  
<211> 7  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR2, humanized <EGFR>ICR62

<400> 5

Asn Thr Asn Asn Leu Gln Thr  
1 5

<210> 6  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR1, humanized <EGFR>ICR62

<400> 6

Arg Ala Ser Gln Gly Ile Asn Asn Tyr Leu Asn  
1 5 10

<210> 7  
<211> 120  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain variable domain, humanized <EGFR>ICR62-I-HHB  
<400> 7

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

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

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

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

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

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

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

Gly Thr Thr Val Thr Val Ser Ser  
115 120

<210> 8  
<211> 120  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain variable domain, humanized <EGFR>ICR62-I-HHD  
<400> 8

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

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

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

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

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

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

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

Gly Thr Thr Val Thr Val Ser Ser  
115 120

<210> 9  
<211> 109  
<212> PRT  
<213> Artificial

<220>  
<223> light chain variable domain, humanized <EGFR>ICR62 -I-KA

<400> 9

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

<210> 10

<211> 108

<212> PRT

<213> Artificial

<220>

<223> light chain variable domain, humanized <EGFR>ICR62 -I-KC

<400> 10

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

<210> 11

<211> 9

<212> PRT

<213> Artificial

<220>

<223> heavy chain CDR3, <IGF-1R> HUMAB-Clone 18

<400> 11

Glu Leu Gly Arg Arg Tyr Phe Asp Leu  
1 5

<210> 12

<211> 17

<212> PRT

<213> Artificial

<220>

<223> heavy chain CDR2, <IGF-1R> HUMAB-Clone 18

<400> 12

Ile Ile Trp Phe Asp Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Arg  
1 5 10 15

Gly

<210> 13

<211> 5

<212> PRT

<213> Artificial

<220>

<223> heavy chain CDR1, <IGF-1R> HUMAB-Clone 18

<400> 13

Ser Tyr Gly Met His  
1 5

<210> 14

<211> 10

<212> PRT

<213> Artificial

<220>

<223> light chain CDR3, <IGF-1R> HUMAB-Clone 18

<400> 14

Gln Gln Arg Ser Lys Trp Pro Pro Trp Thr  
1 5 10

<210> 15  
<211> 7  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR2, <IGF-1R> HUMAB-Clone 18  
  
<400> 15

Asp Ala Ser Lys Arg Ala Thr  
1 5

<210> 16  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR1, <IGF-1R> HUMAB-Clone 18  
  
<400> 16

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala  
1 5 10

<210> 17  
<211> 9  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR3, <IGF-1R> HUMAB-Clone 22  
  
<400> 17

Glu Leu Gly Arg Arg Tyr Phe Asp Leu  
1 5

<210> 18  
<211> 17  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR2, <IGF-1R> HUMAB-Clone 22  
  
<400> 18

Ile Ile Trp Phe Asp Gly Ser Ser Lys Tyr Tyr Gly Asp Ser Val Lys  
1 5 10 15

Gly

<210> 19  
<211> 5  
<212> PRT  
<213> Artificial

<220>  
<223> heavy chain CDR1, <IGF-1R> HUMAB-Clone 22  
  
<400> 19

Ser Tyr Gly Met His  
1 5

<210> 20  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR3, <IGF-1R> HUMAB-Clone 22  
  
<400> 20

Gln Gln Arg Ser Lys Trp Pro Pro Trp Thr  
1 5 10

<210> 21  
<211> 7  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR2, <IGF-1R> HUMAB-Clone 22  
  
<400> 21

Asp Ala Ser Asn Arg Ala Thr  
1 5

<210> 22  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> light chain CDR1, <IGF-1R> HUMAB-Clone 22



<400> 22

Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala  
1 5 10

<210> 23

<211> 118

<212> PRT

<213> Homo sapiens

<400> 23

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

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

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

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

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

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

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

Leu Val Ser Val Ser Ser  
115

<210> 24

<211> 117

<212> PRT

<213> Homo sapiens

<400> 24

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

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

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

Ile Ile Trp Phe Asp Gly Ser Ser Lys Tyr Tyr Gly Asp Ser Val Lys  
50 55 60

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

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

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

Val Thr Val Ser Ser  
115

<210> 25  
<211> 108  
<212> PRT  
<213> Homo sapiens

<400> 25

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ser Lys  
100 105

<210> 26  
<211> 108  
<212> PRT  
<213> Homo sapiens

<400> 26

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

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

<210> 27  
<211> 330  
<212> PRT  
<213> Homo sapiens

<400> 27

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 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 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> 28  
<211> 327  
<212> PRT  
<213> Homo sapiens

<400> 28

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg  
1 5 10 15

Ser Thr Ser Glu Ser 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 Lys Thr  
65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro  
100 105 110

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

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

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp  
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe  
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
180 185 190

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

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys  
225 230 235 240

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

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

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

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

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

Leu Ser Leu Ser Leu Gly Lys  
325

<210> 29  
<211> 107  
<212> PRT  
<213> Homo sapiens

<400> 29

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> 30  
<211> 450  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 1 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (VH/VL)

<400> 30

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

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

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

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

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

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

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

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Lys

450

<210> 31  
<211> 440  
<212> PRT  
<213> Artificial

<220>

<223> Heavy chain 2 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (VH/VL)

<400> 31

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

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

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

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro  
130 135 140

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val  
145 150 155 160

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

	165		170		175														
Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile				
			180					185					190						
Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val				
		195					200					205							
Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala				
	210					215					220								
Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro				
225					230					235					240				
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val				
			245						250					255					
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val				
		260						265					270						
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln				
		275					280					285							
Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln				
	290					295					300								
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala				
305					310					315					320				
Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro				
				325					330					335					
Arg	Glu	Pro	Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr				
		340						345					350						
Lys	Asn	Gln	Val	Ser	Leu	Ser	Cys	Ala	Val	Lys	Gly	Phe	Tyr	Pro	Ser				
		355					360					365							
Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr				
	370					375					380								

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val  
385 390 395 400

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

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys  
420 425 430

Ser Leu Ser Leu Ser Pro Gly Lys  
435 440

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

<220>  
<223> Light chain 1 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (VH/VL)

<400> 32

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Asn Arg Gly Glu Cys  
210

<210> 33  
<211> 225  
<212> PRT  
<213> Artificial

<220>  
<223> Light chain 2 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (VH/VL)

<400> 33

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

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

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

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

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

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

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

Leu Val Ser Val Ser Ser Ala Ser Val Ala Ala Pro Ser Val Phe Ile  
115 120 125

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val  
130 135 140

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys  
145 150 155 160

Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu  
165 170 175

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu  
180 185 190

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

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu  
210 215 220

Cys  
225

<210> 34  
<211> 450  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 1 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (CH/CL)

<400> 34

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

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

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

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

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

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

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

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



Gly Lys  
450

<210> 35  
<211> 452  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 2 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (CH/CL)

<400> 35

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

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

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

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

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

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

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

Leu Val Ser Val Ser Ser Ala Ser Val Ala Ala Pro Ser Val Phe Ile  
115 120 125

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val  
130 135 140

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys  
145 150 155 160

Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu  
165 170 175

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu  
180 185 190

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

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu  
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu  
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu  
245 250 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser  
260 265 270

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

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

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn  
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro  
325 330 335

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

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

Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val

370 375 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro  
385 390 395 400

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

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val  
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu  
435 440 445

Ser Pro Gly Lys  
450

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

<220>  
<223> Light chain 1 of bispecific, bivalent domain exchanged  
<EGFR-IGF1R> antibody molecule: Cross-Mab (CH/CL)

<400> 36

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Phe Pro Thr

85	90	95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro		
100	105	110
Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr		
115	120	125
Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys		
130	135	140
Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu		
145	150	155
Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser		
165	170	175
Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala		
180	185	190
Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe		
195	200	205
Asn Arg Gly Glu Cys		
210		
<210> 37		
<211> 213		
<212> PRT		
<213> Artificial		
<220>		
<223> Light chain 2 of bispecific, bivalent domain exchanged		
<EGFR-IGF1R> antibody molecule: Cross-Mab (CH/CL)		
<400> 37		
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly		
1	5	10
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr		
20	25	30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile		

35	40	45
Tyr Asp Ala Ser Lys Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly		
50	55	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro		
65	70	75 80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro		
	85	90 95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ser Lys Ser Ser Ala Ser		
	100	105 110
Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr		
	115	120 125
Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro		
	130	135 140
Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val		
	145	150 155 160
His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser		
	165	170 175
Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile		
	180	185 190
Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val		
	195	200 205
Glu Pro Lys Ser Cys		
210		

<210> 38  
 <211> 695  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Heavy chain 1 of bispecific, bivalent scFab-Fc fusion  
 <EGFR-IGF1R> antibody molecule: scFab-Fc

<400> 38

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
210 215 220

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly  
225 230 235 240

Gly Gly Ser Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val  
245 250 255

Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe  
260 265 270

Thr Phe Thr Asp Tyr Lys Ile His Trp Val Arg Gln Ala Pro Gly Gln  
275 280 285

Cys Leu Glu Trp Met Gly Tyr Phe Asn Pro Asn Ser Gly Tyr Ser Thr  
290 295 300

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser  
305 310 315 320

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr  
325 330 335

Ala Val Tyr Tyr Cys Ala Arg Leu Ser Pro Gly Gly Tyr Tyr Val Met  
340 345 350

Asp Ala Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr  
355 360 365

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser  
370 375 380

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu  
385 390 395 400

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His  
405 410 415

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser  
420 425 430

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys  
435 440 445

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu  
450 455 460

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro  
465 470 475 480

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
485 490 495

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
500 505 510

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp  
515 520 525

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr  
530 535 540

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
545 550 555 560

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu  
565 570 575

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
580 585 590

Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys  
595 600 605

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
610 615 620

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
625 630 635 640

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
645 650 655



Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser  
660 665 670

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser  
675 680 685

Leu Ser Leu Ser Pro Gly Lys  
690 695

<210> 39  
<211> 695  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 2 of bispecific, bivalent scFab-Fc fusion  
<EGFR-IGF1R> antibody molecule: scFab-Fc

<400> 39

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

Trp Thr Phe Gly Cys Gly Thr Lys Val Glu Ser Lys Arg Thr Val Ala  
100 105 110

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

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

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

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

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

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

Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly  
210 215 220

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
225 230 235 240

Gly Gly Gly Gly Ser Gly Gly Gln Val Glu Leu Val Glu Ser Gly Gly  
245 250 255

Gly Val Val Gln Pro Gly Arg Ser Gln Arg Leu Ser Cys Ala Ala Ser  
260 265 270

Gly Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro  
275 280 285

Gly Lys Cys Leu Glu Trp Val Ala Ile Ile Trp Phe Asp Gly Ser Ser  
290 295 300

Thr Tyr Tyr Ala Asp Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp  
305 310 315 320

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu  
325 330 335

Asp Thr Ala Val Tyr Phe Cys Ala Arg Glu Leu Gly Arg Arg Tyr Phe

340	345	350
Asp Leu Trp Gly Arg Gly Thr Leu Val Ser Val Ser Ser Ala Ser Thr		
355	360	365
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser		
370	375	380
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu		
385	390	395
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His		
405	410	415
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser		
420	425	430
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys		
435	440	445
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu		
450	455	460
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro		
465	470	475
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
485	490	495
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
500	505	510
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp		
515	520	525
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr		
530	535	540
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp		
545	550	555
		560

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu  
565 570 575

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
580 585 590

Glu Pro Gln Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys  
595 600 605

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp  
610 615 620

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
625 630 635 640

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser  
645 650 655

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser  
660 665 670

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser  
675 680 685

Leu Ser Leu Ser Pro Gly Lys  
690 695

<210> 40  
<211> 695  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 1 of bispecific, bivalent scFab-Fc fusion  
<EGFR-IGF1R> antibody molecule: N-scFabSS-Salt-bridge-s3

<400> 40

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
210 215 220

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly  
225 230 235 240

Gly Gly Ser Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val  
245 250 255

Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe  
260 265 270

Thr Phe Thr Asp Tyr Lys Ile His Trp Val Arg Gln Ala Pro Gly Gln  
275 280 285

Gly Leu Glu Trp Met Gly Tyr Phe Asn Pro Asn Ser Gly Tyr Ser Thr  
290 295 300

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser  
305 310 315 320

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr  
325 330 335

Ala Val Tyr Tyr Cys Ala Arg Leu Ser Pro Gly Gly Tyr Tyr Val Met  
340 345 350

Asp Ala Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr  
355 360 365

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser  
370 375 380

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu  
385 390 395 400

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His  
405 410 415

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser  
420 425 430

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys  
435 440 445

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu  
450 455 460

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro  
465 470 475 480

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
485 490 495

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
500 505 510

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp  
515 520 525

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr  
530 535 540

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
545 550 555 560

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu  
565 570 575

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
580 585 590

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys  
595 600 605

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
610 615 620

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
625 630 635 640

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
645 650 655

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser  
660 665 670

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Glu Ser  
675 680 685

Leu Ser Leu Ser Pro Gly Lys

690

695

<210> 41  
<211> 695  
<212> PRT  
<213> Artificial

<220>

<223> Heavy chain 2 of bispecific, bivalent scFab-Fc fusion  
<EGFR-IGF1R> antibody molecule: N-scFabSS-Salt-bridge-s3

<400> 41

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

Trp Thr Phe Gly Cys Gly Thr Lys Val Glu Ser Lys Arg Thr Val Ala  
100 105 110

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

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

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

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu



165							170							175						
Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val					
			180					185					190							
Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys					
		195					200					205								
Ser	Phe	Asn	Arg	Gly	Glu	Cys	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly					
	210					215					220									
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser					
225					230					235					240					
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gln	Val	Glu	Leu	Val	Glu	Ser	Gly	Gly					
				245					250					255						
Gly	Val	Val	Gln	Pro	Gly	Arg	Ser	Gln	Arg	Leu	Ser	Cys	Ala	Ala	Ser					
			260					265					270							
Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro					
		275					280					285								
Gly	Lys	Cys	Leu	Glu	Trp	Val	Ala	Ile	Ile	Trp	Phe	Asp	Gly	Ser	Ser					
	290					295					300									
Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Arg	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp					
305					310					315					320					
Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu					
				325					330					335						
Asp	Thr	Ala	Val	Tyr	Phe	Cys	Ala	Arg	Glu	Leu	Gly	Arg	Arg	Tyr	Phe					
			340					345					350							
Asp	Leu	Trp	Gly	Arg	Gly	Thr	Leu	Val	Ser	Val	Ser	Ser	Ala	Ser	Thr					
		355					360					365								
Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser					
	370					375					380									

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu  
385 390 395 400

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His  
405 410 415

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser  
420 425 430

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys  
435 440 445

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu  
450 455 460

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro  
465 470 475 480

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
485 490 495

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
500 505 510

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp  
515 520 525

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr  
530 535 540

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
545 550 555 560

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu  
565 570 575

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
580 585 590

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Leu Thr Lys  
595 600 605

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
610 615 620

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
625 630 635 640

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
645 650 655

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser  
660 665 670

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser  
675 680 685

Leu Ser Leu Ser Pro Gly Lys  
690 695

<210> 42  
<211> 695  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 1 of bispecific, bivalent scFab-Fc fusion  
<EGFR-IGF1R> antibody molecule: N-scFabSS-Salt bridge-w3C

<400> 42

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
210 215 220

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly  
225 230 235 240

Gly Gly Ser Gly Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val  
245 250 255

Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe  
260 265 270

Thr Phe Thr Asp Tyr Lys Ile His Trp Val Arg Gln Ala Pro Gly Gln  
275 280 285

Gly Leu Glu Trp Met Gly Tyr Phe Asn Pro Asn Ser Gly Tyr Ser Thr  
290 295 300

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser  
305 310 315 320

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr  
325 330 335

Ala Val Tyr Tyr Cys Ala Arg Leu Ser Pro Gly Gly Tyr Tyr Val Met  
340 345 350

Asp Ala Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr  
355 360 365

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser  
370 375 380

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu  
385 390 395 400

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His  
405 410 415

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser  
420 425 430

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys  
435 440 445

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu  
450 455 460

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro  
465 470 475 480

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
485 490 495

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
500 505 510

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

515					520					525						
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	
530					535					540						
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	
545					550					555					560	
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	
					565					570					575	
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	
					580					585					590	
Glu	Pro	Gln	Val	Cys	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	
595					600					605						
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Glu	Gly	Phe	Tyr	Pro	Ser	Asp	
610					615					620						
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	
625					630					635					640	
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	
					645					650					655	
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	
					660					665					670	
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Glu	Ser	
675					680					685						
Leu	Ser	Leu	Ser	Pro	Gly	Lys										
690					695											

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<210> 43
<211> 695
<212> PRT
<213> Artificial
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<220>
<223> Heavy chain 2 of bispecific, bivalent scFab-Fc fusion
<EGFR-IGF1R> antibody molecule: N-scFabSS-Salt bridge-w3C
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<400> 43

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

Trp Thr Phe Gly Cys Gly Thr Lys Val Glu Ser Lys Arg Thr Val Ala  
100 105 110

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

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

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

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

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

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

Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly  
210 215 220

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
225 230 235 240

Gly Gly Gly Gly Ser Gly Gly Gln Val Glu Leu Val Glu Ser Gly Gly  
245 250 255

Gly Val Val Gln Pro Gly Arg Ser Gln Arg Leu Ser Cys Ala Ala Ser  
260 265 270

Gly Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro  
275 280 285

Gly Lys Cys Leu Glu Trp Val Ala Ile Ile Trp Phe Asp Gly Ser Ser  
290 295 300

Thr Tyr Tyr Ala Asp Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp  
305 310 315 320

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu  
325 330 335

Asp Thr Ala Val Tyr Phe Cys Ala Arg Glu Leu Gly Arg Arg Tyr Phe  
340 345 350

Asp Leu Trp Gly Arg Gly Thr Leu Val Ser Val Ser Ser Ala Ser Thr  
355 360 365

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser  
370 375 380

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu  
385 390 395 400

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His  
405 410 415

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser  
420 425 430



Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys  
435 440 445

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu  
450 455 460

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro  
465 470 475 480

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
485 490 495

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
500 505 510

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp  
515 520 525

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr  
530 535 540

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp  
545 550 555 560

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu  
565 570 575

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg  
580 585 590

Glu Pro Gln Val Tyr Thr Leu Pro Pro Cys Arg Lys Lys Leu Thr Lys  
595 600 605

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
610 615 620

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
625 630 635 640

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
645 650 655

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser  
660 665 670

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser  
675 680 685

Leu Ser Leu Ser Pro Gly Lys  
690 695

<210> 44  
<211> 932  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 1 of bispecific, trivalent scFab-IgG fusion  
<EGFR-IGF1R> antibody molecule: KiH-C-scFab-1

<400> 44

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

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

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

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

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

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

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

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140

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

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

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

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

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

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

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

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

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

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

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

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

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

340	345	350
Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu		
355	360	365
Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
370	375	380
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val		
385	390	395
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
405	410	415
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
420	425	430
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
435	440	445
Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu		
450	455	460
Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr		
465	470	475
Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr		
485	490	495
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser		
500	505	510
Lys Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly		
515	520	525
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala		
530	535	540
Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro Trp Thr Phe Gly		
545	550	555
		560

Cys Gly Thr Lys Val Glu Ser Lys Arg Thr Val Ala Ala Pro Ser Val  
565 570 575

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser  
580 585 590

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln  
595 600 605

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val  
610 615 620

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu  
625 630 635 640

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu  
645 650 655

Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg  
660 665 670

Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
675 680 685

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
690 695 700

Ser Gly Gly Gln Val Glu Leu Val Glu Ser Gly Gly Gly Val Val Gln  
705 710 715 720

Pro Gly Arg Ser Gln Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe  
725 730 735

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Cys Leu  
740 745 750

Glu Trp Val Ala Ile Ile Trp Phe Asp Gly Ser Ser Thr Tyr Tyr Ala  
755 760 765

Asp Ser Val Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn  
770 775 780

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val  
785 790 795 800

Tyr Phe Cys Ala Arg Glu Leu Gly Arg Arg Tyr Phe Asp Leu Trp Gly  
805 810 815

Arg Gly Thr Leu Val Ser Val Ser Ser Ala Ser Thr Lys Gly Pro Ser  
820 825 830

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala  
835 840 845

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val  
850 855 860

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala  
865 870 875 880

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val  
885 890 895

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His  
900 905 910

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys  
915 920 925

Asp Lys Thr His  
930

<210> 45  
<211> 450  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 2 of bispecific, trivalent scFab-IgG fusion  
<EGFR-IGF1R> antibody molecule: KiH-C-scFab-1

<400> 45

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

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

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

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

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

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

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

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala  
130 135 140

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gly Lys



450

<210> 46  
<211> 213  
<212> PRT  
<213> Artificial

<220>  
<223> Light chain of bispecific, trivalent scFab-IgG fusion  
<EGFR-IGF1R> antibody molecule: KiH-C-scFab-1

<400> 46

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 Gly Ile Asn Asn Tyr  
20 25 30

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

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

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

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

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

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

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

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser

165 170 175

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

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

Asn Arg Gly Glu Cys  
210

<210> 47  
<211> 930  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 1 of bispecific, trivalent scFab-IgG fusion  
<EGFR-IGF1R> antibody molecule: KiH-C-scFab-2

<400> 47

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

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

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

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

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

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

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

Leu Val Ser 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 Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp 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

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln  
450 455 460

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr  
465 470 475 480

Cys Arg Ala Ser Gln Gly Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln  
485 490 495

Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile Tyr Asn Thr Asn Asn Leu  
500 505 510

Gln Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu  
515 520 525

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr  
530 535 540

Tyr Cys Leu Gln His Asn Ser Phe Pro Thr Phe Gly Cys Gly Thr Lys  
545 550 555 560

Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro  
565 570 575

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu  
580 585 590

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp  
595 600 605

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp  
610 615 620

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys  
625 630 635 640

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln  
645 650 655

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly  
660 665 670

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly  
675 680 685

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gln  
690 695 700

Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser  
705 710 715 720

Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr Lys  
725 730 735

Ile His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Met Gly  
740 745 750

Tyr Phe Asn Pro Asn Ser Gly Tyr Ser Thr Tyr Ala Gln Lys Phe Gln  
755 760 765

Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met  
770 775 780

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala  
785 790 795 800

Arg Leu Ser Pro Gly Gly Tyr Tyr Val Met Asp Ala Trp Gly Gln Gly  
805 810 815

Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe  
820 825 830

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu  
835 840 845

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp  
850 855 860

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu  
865 870 875 880

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser  
885 890 895

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro  
900 905 910

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys  
915 920 925

Thr His  
930

<210> 48  
<211> 448  
<212> PRT  
<213> Artificial

<220>  
<223> Heavy chain 2 of bispecific, trivalent scFab-IgG fusion  
<EGFR-IGF1R> antibody molecule: KiH-C-scFab-2

<400> 48

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

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

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

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

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

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

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

Leu Val Ser 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 Cys Thr Leu						
		340		345		350
Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys						
		355		360		365
Ala 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 Val 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> 49  
<211> 215  
<212> PRT  
<213> Artificial

<220>

<223> Light chain of bispecific, trivalent scFab-IgG fusion  
<EGFR-IGF1R> antibody molecule: KiH-C-scFab-2

<400> 49

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 Gln Ser Val Ser Ser Tyr  
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Lys Trp Pro Pro  
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ser Lys Arg Thr Val Ala  
100 105 110

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

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

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

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

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

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

Ser	Phe	Asn	Arg	Gly	Glu	Cys
	210					215

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