

FIGURE 1

Anti-CD28 VH1 Sequences

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10      20      30      40      50      60      70      80      90     100
GAGGTGAAGCTGCAGCAGTCAGGACCTGGCCCTGGTGAAGCCCTCAGAGACCCCTGCTCCCTCAGTCTACTGCTCTCTGGGTTTTCATTAAAGCGACTATGGTG
E V K L Q Q S G P G L V K P S E T L S L T C T V S G F S L S D Y G
10      20      30
110     120     130     140     150     160     170     180     190     200
TTCATTGGGTTCCGCCAGGCTCCAGCAAGGAGCTGGAGTGGCTGGTGGAGTAAATATGGGCTGGTGGAGGCACGAATTATATTCGGCTCTCATGTCCAGAAA
V H W V R Q A P G K G L E W L G V I W A G G G T N Y N S A L M S R K
40      50      60
210     220     230     240     250     260     270     280     290     300
GACCATCAGCAAGACAACTCCAAGAGCCCAAGTTTCTTAAAAATCAACAGTCTGACAGCTGCTGACAGCCGTGTATTACTGTGCCAGAGATAAGGGA
T I S K D N S K S Q V F L K W N S L T A A D T A V Y Y C A R D K G
70      80     82     A B C
310     320     330     340     350     360
TACTCCTATTACTATTCTATGGACTACTGGGGCCAAAGGCACCCCTGGTCACCGTCTCTCA (SEQ ID NO. 1)
Y S Y Y Y S M O Y W G Q G T L V T V S S (SEQ ID NO. 2)
100 A B C D
110

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CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red

FIGURE 2

Anti-CD28 VH2 Sequences

10 20 30 40 50 60 70 80 90 100
GAGGTGAAGCTGCAGCAGTCCAGACCTGGTGAAGCCCTCAGAGACCTGCTGCTCTGCTGGGTTTCATTAAAGCGACTATGGTG
E V K L Q Q S G P G L V K P S E T L S L T C T V S G F S L S D Y G
10 20 30
110 120 130 140 150 160 170 180 190 200
TTCATTGGGTTCCGCCAGGCTCCAGGAAGGGACTGGAGTGGCTGGGAGTAATAATGGCTGGTGGAGGCACGAATTATATTGGCTCTCATGTCCAGAAA
V H W V R Q A P G K G L E W L G V I W A G G T N Y N S A L M S R K
40 50 60
210 220 230 240 250 260 270 280 290 300
GACCATCAGCAAGACAACCTCCAGAGGCAAGTTTCCTTAAATGAGCAGTGTGACAGCTGCTGACACAGCCGTGTATTACTGTGCCAGAGATAGGGA
T I S K D N S K S Q V S L K M S S V T A A D T A V Y Y C A R D K G
70 80 82 A B C 90
310 320 330 340 350 360
TATCCCTATTACTATTCTATGGACTACTGGGGCCAGGCCCTGGTCACCTCTCTCA (SEQ ID NO. 3)
Y S Y Y Y S M D Y W G Q G T L V T V S S (SEQ ID NO. 4)
100 A B C D 110

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red

FIGURE 3

Anti-CD28 VH3 Sequences

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10      20      30      40      50      60      70      80      90     100
GAGGTGAAGCTGCACCACTCAGGACCTGGCTGGTGAAGCCCTCAGAGACCCCTGTCCTCACTTGTACTGTCTCTCTGGGTTTTCATTAAAGCGACTATGGTG
E V K L Q Q S G P G L V K P S E T L S L T C T V S G F S L S D Y G

110     120     130     140     150     160     170     180     190     200
TTCATTGGGTTCCGCGAGGCTCCAGGAAGGCACTGGAGTGGCTGGGAGTAATATGGGCTGGTGGAGGCACGAATTATATTCGGCTCTCATGTCCAGAGT
V H W V R Q A P G K G L E W L G V I W A G G C T N Y N S A L M S R V

210     220     230     240     250     260     270     280     290     300
GACCATCAGCAAGACAACCTCCAAGAGCCCAAGTTCCTTAAACTGAGCAGTGTGACAGCTGCTGACACAGCCGCTGTATTACTGTGCCAGAGATAAGGSA
T I S K D N S K S Q V S L K L S S V T A A D T A V Y Y C A R D K G

310     320     330     340     350     360
TACTCCTATTACTATTCTATGACTACTGGGGCCCAAGGCACCCCTGGTCACCCGTCCTCA (SEQ ID NO. 5)
Y S Y Y Y S M D Y W G Q G T L V T V S S (SEQ ID NO. 6)
100 A B C D 110

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CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red.

FIGURE 4

Anti-CD28 VK1 Sequences

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10      20      30      40      50      60      70      80      90      10
GACATCGAGCTCAGTCTCCAGATTCCTTTGGCTGTCTCTAGGGGAGAGAGCCACCATCAACTGCAGAGCCAGTGCAGAGTGTGAATATTATGTC
D I E L T Q S P D S L A V S L G E R A T I N C R A S E S V E Y Y V
10      20      30      40      50      60      70      80      90      10
CAAGTTAATGAGTGGTACCAGCAGAGCCAGGACAGCCACCCCAACTCTCTCATCTTTGCTGCAATCCAACTGAGAACTCTGGGTCCTGACAGGTTTA
T S L M Q W Y Q Q K P G Q P P K L L I F A A S N V E S G V P D R F
30      40      50      60      70      80      90      100      110      120
TGGCAGTGGGTCTGGGACAAACTTCACCCCTCACCATCTCTTCTCTGAGGAGGAGGATGTTCGAATGTATTCTGTGAGCAAGTAGGAAGGTTCTTA
G S G S G T N F T L T I S S L Q E E D V A M Y F C Q Q S R K V P Y
70      80      90      100      110      120      130      140      150      160      170      180      190      200      210
ACGTTGGAGGGGGACCAAGGTGGAAATAAAA (SEQ ID NO. 7)
T F G G G T K V E I K (SEQ ID NO. 8)
110      120      130      140      150      160      170      180      190      200      210      220      230      240      250      260      270      280      290      300

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CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red

FIGURE 5

Anti-CD28 VK2 Sequences

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10      20      30      40      50      60      70      80      90     100
GACATCGAGCTCAGTCAGTCAGATTCCTTTGGCTGTGTCCTAGGGGAGAGAGCCACCATCAACTGCAGAGCCAGTGTGTAATATTATGTC
D I E L T O S P D S L A V S L G E R A T I N C R A S E S V E Y Y V
10      20      27 A B C D

110     120     130     140     150     160     170     180     190     200
CAAGTTTATCCAGTGGTACCAGCAGAGCCAGGACGACGCCAACCTCCTCATCTTTGCTGTCATCCCAACGTAGATCTGGGGTCCCTGACAGGTTTAG
T S L M Q W Y Q Q K P G Q P P K L L I F A A S N V E S G V P D R F S
30      40      50      60

210     220     230     240     250     260     270     280     290     300
TGCCAGTGGCTCTGGGACAACTTCACCCCTCAGCATCTCTTCTCTGAGGCCGAGATGTTGCAATGTATTTCTGTCAGCAAGTAGAAGGTTCCITAC
G S G S G T N F T L T I S S L Q A E D V A M Y F C Q Q S R K V P Y
70      80      90

310     320     330
ACGTTGCGAGGGGGACCAAGGTGGAAATAAAA (SEQ ID NO. 9)
T F G G G T K V E I K (SEQ ID NO. 10)
110

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CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red

FIGURE 6

Anti-CD28 VK3 Sequences

10 20 30 40 50 60 70 80 90 100
GACATCGAGCTCACTCAGTCTCCAGATTCTTTGGCTGTCTCTAGGGGAGAGAGCCACCATCACTGCCAGAGCCAGTGAAGTGTGATATTATGTCA
D I E L T Q S P D S L A V S L G E R A T I N C R A S E S V E Y Y V
10 20 27 A B C D
110 120 130 140 150 160 170 180 190 200
CAAGTTAATGCAGTGGTACCGAGCAGAGCCAGGACGCCACCAACTCCTCATCTTTGCTGCATCCAACTAGAACTCTGGGTCCTGCACAGGTTAG
T S L M Q W Y Q Q K P G Q P K L L I F A A S N V E S G V P D R F S
30 40 50 60
210 220 230 240 250 260 270 280 290 300
TGGCAGTGGGTCTGGGACAGACTTCACCCCTCACCCTCACCCTCTCTCTCTGCGAGCGAGGATGTTGCAATGTATTCTGTCTCAGCAAGTAGGAAGGTTCTTAC
G S G S G T D F T L T I S S L Q A E D V A M Y F C Q Q S R K V P Y
70 80 90
310 320 330
ACGTTGAGGAGGGGACCAAGGTGGAATATAA (SEQ ID NO. 11)
T P G G G T K V E I K (SEQ ID NO. 12)
110

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red

FIGURE 7 (continued)

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510      520      530      540      550      560      570      580      590      600
CAAGACAAAGCCGGGGAGGAGCAGTTTCACAGCAGCAGTACCGTGTGGTCAGCGTCTCTACCGCTGTCACAGGACTGGCTGAACGGCAAGGAGTACRAG
K T K P R E E Q F N S T Y R V V S V L T V L H Q D W L N G K E Y K
310      314 317      320      330

610      620      630      640      650      660      670      680      690      700
TGCAAGGTCTCCAAACAAGGCGCTCCGTCCTCCATCGAGAAACCATCTCCAAAGCCAGGCGAGCCGACAGGTGTACACCGCTGCCCGCAT
C R V S N K G L P S S I E K T I S K A K G Q P R E P Q V Y T L P P
340      350      355 357      360 361 363      370

710      720      730      740      750      760      770      780      790      800
CCGAGGAGGAGATGACCAAGACCAAGGTCAGGCTGACCTGCGTGGTCAAGGCTTCTACCCGACGACATCGCCGTGCGAGTGGGAGAGCAATGGGCAGCC
S Q E E M T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P
375 381      390      400      402 405      408 410 411 414

810      820      830      840      850      860      870      880      890      900
GGAGAACAACTACAGACCAAGCCCTCCCGTGGTGGACTCCGACGGCTCCTTCTCTACAGCAGGCTAACCGTGGACAAAGAGCAGGTGGCAGGAGGGG
E N N Y K T T P P V L D S D G S F F L Y S R L T V D K S R W Q E G
420      428 430 433      440      450

910      920      930      940      950      960      970      980
AATGTCTTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACAGAGAGCCCTGCTGCTCTCTGGGTAAATGA (SEQ ID NO. 13)
N V F S C S V M H E A L H N H Y T Q K S L C L S L G K * (SEQ ID NO. 14)
460      470

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Protein sequence numbering according to Kabat. Mutations are highlighted red.

FIGURE 8

Constant κ Light:

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10      20      30      40      50      60      70      80      90     100
CGAACTGTGGCTGCACCAATCTGTCTTCATCTTCCGGCCATCTGATGAGCAGTTGAAATCTGGAACTGCCCTCTGTTGTGTGCTGCTGAATAACTTCTATC
R T V A A P S V F I F P P S D E Q L K S G T A S V V C L L N N F Y
110      120      130      140      150      160      170      180      190     200
CCAGAGAGGCCCAAGTACAGTGGAAAGGTGGATACGCCCTCCATCGGTAACTCCAGGAGAGTGTACACAGAGCAGGACAGGACAGGACAGCAGCCTACAG
P R E A K V Q W K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S
110      120      130      140      150      160      170      180      190     200
CCTCAGCAGCACCCCTGACGCTGAGCAAGCAGACTACGAGAAACACAAAGTCTACGCCCTGGGAAGTCAACCCATCAGGGCCTCAGCTCGCCGTCACAAAG
L S S T L T L S K A D Y E K H K V Y A C E V T H Q G L S S P V T K
180      190      200
AGCTTCACACAGGGGAGAGTGTAG (SEQ ID NO. 15)
S F N R G E C . (SEQ ID NO. 16)
200

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Protein sequence numbering according to Kabat.

FIGURE 9

Potential Non-Antigen Binding Humanised Variant

10 20 30 40 50 60 70 80 90 100
GAGGTGAAGCTGCAGCAGTCACGACCTGGCCCTGCTGAAGCCCTCAGAGACCGCTGTCCTCACTTGTACTGTCTCTCGGTTTACATTACGCGCACTATGGTG
E V K L Q Q S G P G L V K P S E T L S L T C T V S G F T F S D Y G
10 20 30
110 120 130 140 150 160 170 180 190 200
TTCAATTGGAATTCGCCAGCCCTCCAGGAAGGGAAGGACTGGAGTGGAGTAAATATGGGCTGGTGGAGCCACGAATTATAATTCGGCTCTCATGTCCAGAGT
V H W I R Q P P G K Q L E W I G V I W A G G T N Y N S A L M S R V
40 50 60
210 220 230 240 250 260 270 280 290 300
GACCATCAGCGTGGACACCTCCAGAACCAATTTTCCTTAAACTGAGCAGTGTGACAGCTGCTGACACAGCCGCTGTATTACTGTGCCAGAGATAAGGGA
T I S V D T S K N Q F S L K L S S V T A A D T A V Y Y C A R D K G
70 80 90
310 320 330 340 350 360
TACTCGGCTGCCGGCTTCTATGCACTACTGGGGCAAGGCACCCCTGGTCACCGTCTCCTCA (SEQ ID NO. 17)
Y S A A A S M D Y W G Q G T L V T V S S (SEQ ID NO. 18)
100 A B C D 110

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and protein sequences are highlighted in red

FIGURE 10, continued

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
660 665 670

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
675 680 685

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln
690 695 700

Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
705 710 715 720

His Tyr Thr Gln Lys Ser Leu Cys Leu Ser Leu Gly Lys (SEQ ID NO. 19)
725 730

FIGURE 11

Asp Ile Glu Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr
 20 25 30
 Val Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
 35 40 45
 Lys Leu Leu Ile Phe Ala Ala Ser Asn Val Glu Ser Gly Val Pro Asp
 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 Gln Ala Glu Asp Val Ala Met Tyr Phe Cys Gln Gln Ser Arg
 85 90 95
 Lys Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
 100 105 110
 Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 115 120 125
 Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 130 135 140
 Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 145 150 155 160
 Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 165 170 175
 Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 180 185 190
 His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 195 200 205
 Val Thr Lys Ser Phe Asn Arg Gly Glu Cys (SEQ ID NO. 20)
 210 215

FIGURE 13, continued

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
 210 215 220

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

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

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

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

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

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

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

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

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

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

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

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

(SEQ ID NO. 21)

FIGURE 13, continued

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

420

425

430

His Asn His Tyr Thr Gln Lys Ser Leu Cys Leu Ser Leu Gly Lys

435

440

445

(SEQ ID NO. 22)