

-continued

Val Val Thr Val Thr Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
215 220 225

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
230 235 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
245 250 255

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

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
275 280 285

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
290 295 300

Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305 310 315

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
320 325 330

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
335 340 345

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
350 355 360

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
365 370 375

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
380 385 390

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
395 400 405

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
410 415 420

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
425 430 435

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
440 445 450

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
455 460 465

Ser Pro Gly Lys
469

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 214 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Asp Val Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
1 5 10 15

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

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

Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser
50 55 60

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

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Ser	Asn	Leu	Asp	Gln	Glu	Asp	Ile	Ala	Thr	Tyr	Phe	Cys	Gln	Gln
				80						85				90
Gly	Asn	Thr	Leu	Pro	Pro	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu
				95					1	00				1 05
Ile	Lys	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro
				110						115				120
Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu
				125						130				135
Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val
				140						145				150
Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu
				155						160				165
Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr
				170						175				180
Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	Ala	Cys	Glu
				185						190				195
Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	Phe	Asn
				200						205				210
Arg	Gly	Glu	Cys											
				214										

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met	Gly	Trp	Ser	Cys	Ile	Ile	Leu	Phe	Leu	Val	Ala	Thr	Ala	Thr
1				5						10				15
Gly	Val	His	Ser	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu
				20						25				30
Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser
				35						40				45
Gln	Asp	Ile	Asn	Asn	Tyr	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
				50						55				60
Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Tyr	Thr	Ser	Thr	Leu	His	Ser
				65						70				75
Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Tyr
				80						85				90
Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr
				95						1 00				1 05
Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Pro	Thr	Phe	Gly	Gln	Gly
				110						115				120
Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe
				125						130				135
Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser
				140						145				150
Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val
				155						160				165
Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	Glu
				170						175				180
Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				185						190				195

-continued

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 200 205 210
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
 215 220 225
 Lys Ser Phe Asn Arg Gly Glu Cys
 230 233

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 122 amino acids
 - (B) TYPE: Amino Acid
 - (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 1 5 10 15
 Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ser Phe Thr
 20 25 30
 Gly Tyr Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 35 40 45
 Glu Trp Val Ala Leu Ile Asn Pro Tyr Lys Gly Val Thr Thr Tyr
 50 55 60
 Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Val Asp Lys Ser
 65 70 75
 Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 80 85 90
 Thr Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Asp Ser
 95 100 105
 Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
 110 115 120
 Ser Ser
 122

We claim:

1. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, utilizing the numbering system set forth in Kabat.
2. The humanized variable domain of claim 1 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.
3. The humanized variable domain of claim 1 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.
4. The humanized variable domain of claim 1 wherein the human antibody variable domain is a consensus human variable domain.
5. The humanized variable domain of claim 1 wherein the residue at site 4L has been substituted.
6. The humanized variable domain of claim 1 wherein the residue at site 38L has been substituted.
7. The humanized variable domain of claim 1 wherein the residue at site 43L has been substituted.

8. The humanized variable domain of claim 1 wherein the residue at site 44L has been substituted.
9. The humanized variable domain of claim 1 wherein the residue at site 58L has been substituted.
10. The humanized variable domain of claim 1 wherein the residue at site 62L has been substituted.
11. The humanized variable domain of claim 1 wherein the residue at site 65L has been substituted.
12. The humanized variable domain of claim 1 wherein the residue at site 66L has been substituted.
13. The humanized variable domain of claim 1 wherein the residue at site 67L has been substituted.
14. The humanized variable domain of claim 1 wherein the residue at site 68L has been substituted.
15. The humanized variable domain of claim 1 wherein the residue at site 69L has been substituted.
16. The humanized variable domain of claim 1 wherein the residue at site 73L has been substituted.
17. The humanized variable domain of claim 1 wherein the residue at site 85L has been substituted.
18. The humanized variable domain of claim 1 wherein the residue at site 98L has been substituted.
19. The humanized variable domain of claim 1 wherein the residue at site 2H has been substituted.
20. The humanized variable domain of claim 1 wherein the residue at site 4H has been substituted.

21. The humanized variable domain of claim 1 wherein the residue at site 36H has been substituted.
22. The humanized variable domain of claim 1 wherein the residue at site 39H has been substituted.
23. The humanized variable domain of claim 1 wherein the residue at site 43H has been substituted.
24. The humanized variable domain of claim 1 wherein the residue at site 45H has been substituted.
25. The humanized variable domain of claim 1 wherein the residue at site 69H has been substituted.
26. The humanized variable domain of claim 1 wherein the residue at site 70H has been substituted.
27. The humanized variable domain of claim 1 wherein the residue at site 74H has been substituted.
28. The humanized variable domain of claim 1 wherein the residue at site 92H has been substituted.
29. An antibody comprising the humanized variable domain of claim 1.
30. An antibody which binds p185^{HER2} and comprises a humanized antibody variable domain, wherein the humanized antibody variable domain comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind p185^{HER2} incorporated into a human antibody variable domain, and further comprises a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.
31. The antibody of claim 30 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.
32. The antibody of claim 30 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.
33. The antibody of claim 30 wherein the human antibody variable domain is a consensus human variable domain.
34. The antibody of claim 30 wherein the residue at site 4L has been substituted.
35. The antibody of claim 30 wherein the residue at site 38L has been substituted.
36. The antibody of claim 30 wherein the residue at site 43L has been substituted.
37. The antibody of claim 30 wherein the residue at site 44L has been substituted.
38. The antibody of claim 30 wherein the residue at site 46L has been substituted.
39. The antibody of claim 30 wherein the residue at site 58L has been substituted.
40. The antibody of claim 30 wherein the residue at site 62L has been substituted.
41. The antibody of claim 30 wherein the residue at site 65L has been substituted.
42. The antibody of claim 30 wherein the residue at site 66L has been substituted.
43. The antibody of claim 30 wherein the residue at site 67L has been substituted.
44. The antibody of claim 30 wherein the residue at site 68L has been substituted.
45. The antibody of claim 30 wherein the residue at site 69L has been substituted.
46. The antibody of claim 30 wherein the residue at site 73L has been substituted.
47. The antibody of claim 30 wherein the residue at site 85L has been substituted.
48. The antibody of claim 30 wherein the residue at site 98L has been substituted.

49. The antibody of claim 30 wherein the residue at site 2H has been substituted.
50. The antibody of claim 30 wherein the residue at site 4H has been substituted.
51. The antibody of claim 30 wherein the residue at site 36H has been substituted.
52. The antibody of claim 30 wherein the residue at site 39H has been substituted.
53. The antibody of claim 30 wherein the residue at site 43H has been substituted.
54. The antibody of claim 30 wherein the residue at site 45H has been substituted.
55. The antibody of claim 30 wherein the residue at site 69H has been substituted.
56. The antibody of claim 30 wherein the residue at site 70H has been substituted.
57. The antibody of claim 30 wherein the residue at site 74H has been substituted.
58. The antibody of claim 30 wherein the residue at site 75H has been substituted.
59. The antibody of claim 30 wherein the residue at site 76H has been substituted.
60. The antibody of claim 30 wherein the residue at site 78H has been substituted.
61. The antibody of claim 30 wherein the residue at site 92H has been substituted.
62. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a consensus human variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.
63. A humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient, wherein the humanized antibody comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.
64. A humanized variant of a non-human parent antibody which binds an antigen and comprises a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.
65. The humanized variant of claim 63 which binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen.
66. A humanized antibody heavy chain variable domain comprising non-human Complementarity Determining

Region (CDR) amino acid residues which bind antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 24H, 73H, 76H, 78H, and 93H, utilizing the numbering system set forth in Kabat.

67. The humanized variable domain of claim 66 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.

68. The humanized variable domain of claim 66 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

69. The humanized variable domain of claim 66 wherein the human antibody variable domain is a consensus human variable domain.

70. The humanized variable domain of claim 66 wherein the residue at site 24H has been substituted.

71. The humanized variable domain of claim 66 wherein the residue at site 73H has been substituted.

72. The humanized variable domain of claim 66 wherein the residue at site 76H has been substituted.

73. The humanized variable domain of claim 66 wherein the residue at site 78H has been substituted.

74. The humanized variable domain of claim 66 wherein the residue at site 93H has been substituted.

75. The humanized variable domain of claim 66 which further comprises an amino acid substitution at site 71H.

76. The humanized variable domain of claim 66 which further comprises amino acid substitutions at sites 71H and 73H.

77. The humanized variable domain of claim 66 which further comprises amino acid substitutions at sites 71H, 73H and 78H.

78. An antibody comprising the humanized variable domain of claim 66.

79. A humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat.

80. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution where the substituted FR residue:

(a) noncovalently binds antigen directly;

(b) interacts with a CDR; or

(c) participates in the V_L - V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another, and wherein the substituted FR residue is at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 24H, 36H, 39H, 43H, 45H, 69H, 70H, 73H, 74H, 76H, 78H, 92H and 93H, utilizing the numbering system set forth in Kabat.

81. The humanized variable domain of claim 80 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.

82. The humanized variable domain of claim 80 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

* * * * *

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