Figure 1:

Nucleic acid sequence encoding B4 antibody heavy chain variable region (B4 VH0)

CAGGTGCAACTGCAGCAGCCTGGGGCTGAAGTGGTGAAGCCTGGGGCTTCAGTGAGACTGTCCT
GCAAGACTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAAGCAGAGGCCTGGACA
AGGCCTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
AAGGGCAAGGCCAAGTTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCAGCC
TGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:1)

Figure 2:

Nucleic acid sequence encoding B4 antibody heavy chain variable region with codons for amino acid substitutions K23E, G42D, K69E, and S85D (B4 VHv1)

CAGGTGCAACTGCAGCAGCCTGGGGCTGAAGTGGTGAAGCCTGGGGCTTCAGTGAGACTGTCCT
GCGAGACTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAAGCAGAGGCCTGACCA
AGGACTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
AAGGGCAAGGCCGAATTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCGACC
TGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:2)

Figure 3:

Nucleic acid sequence encoding B4 antibody heavy chain variable region with codons for amino acid substitutions K69E, and S85D (B4 VHv2)

CAGGTGCAACTGCAGCAGCCTGGGGCTGAAGTGGTGAAGCCTGGGGCTTCAGTGAGACTGTCCT
GCAAGACTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAAGCAGAGACCTGGACA
AGGACTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
AAGGGCAAGGCCGAATTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCGACC
TGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:3)

Figure 4:

Nucleic acid sequence encoding B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, V12K, R19K, L20V, T24A, S85D, and S88A (B4 VHv3)

CAGGTGCAACTGGAGCAGCCTGGGGCTGAAGTGAAGAAGCCTGGGGCTTCAGTGAAGGTGTCCT
GCAAGGCTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAAGCAGAGGCCTGGACA
AGGACTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
AAGGGCAAGGCCAAGTTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCGACC
TGACAGCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:4)

Figure 5:

Nucleic acid sequence encoding B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, R19K, L20V, R40T, Q43K, K65D, S85D, S88A, and V93T (B4 VHv4)

CAGGTGCAACTGGAGCAGCCTGGGGCTGAAGTGGTGAAGCCTGGGGCTTCAGTGAAGGTGTCCT
GCAAGACTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAAGCAGACGCCTGGAAA
AGGACTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
GATGGCAAGGCCAAGTTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCGACC
TGACAGCTGAGGACTCTGCGACCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:5)

Figure 6:

Nucleic acid sequence encoding B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, V12K, R19K, L20V, T24A, K38R, R40A, Q43K, K65D, S85D, and V93T (B4 VHv5)

CAGGTGCAACTGGAGCAGCCTGGGGCTGAAGTGAAGAAGCCTGGGGCTTCAGTGAAGGTGTCCT
GCAAGGCTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAGACAGGCACCTGGAAA
AGGACTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
GATGGCAAGGCCAAGTTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCGACC
TGACATCTGAGGACTCTGCGACCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:6)

Figure 7:

Nucleic acid sequence encoding B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, R19K, L20V, K65D, S85D, and V93T (B4 VHv6)

CAGGTGCAACTGGAGCAGCCTGGGGCTGAAGTGGTGAAGCCTGGGGCTTCAGTGAAGGTGTCCT
GCAAGACTTCTGGCTACACCTTCACCAGCAACTGGATGCACTGGGTGAAGCAGAGGCCTGGACA
AGGACTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAAAAGTTC
GATGGCAAGGCCAAGTTGACTGTAGACAAATCCTCCAGCACAGCCTACATGGAAGTCAGCGACC
TGACATCTGAGGACTCTGCGACCTATTACTGTGCAAGAGGTAGCAACCCTTACTACTATGCTAT
GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA(SEQ ID NO:7)

Figure 8:

Nucleic acid sequence encoding B4 antibody light chain variable region (B4 VK0)

CAAATTGTTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCACCATGA
CCTGCAGTGCCAGCTCAGGTGTCAACTACATGCACTGGTACCAGCAGAAGCCAGGCACCTCCCC
CAAAAGATGGATTTATGACACATCCAAACTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGT
GGGTCTGGGACCTCTTATTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATT
ACTGCCATCAGCGAGGTAGTTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA(SEQ ID
NO:8)

Figure 9:

Nucleic acid sequence encoding B4 antibody light chain variable region with codons for amino acid substitutions V3A, S7E, and A54D (B4 VKv1)

CAAATTGCTCTCACCCAGGAGCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCACCATGA
CCTGCAGTGCCAGCTCAGGTGTCAACTACATGCACTGGTATCAGCAGAAGCCAGGCACCTCCCC
CAAAAGATGGATTTATGACACATCCAAACTGGATTCTGGAGTCCCTGCTCGCTTCAGTGGCAGT
GGGTCTGGGACCTCTTATTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATT
ACTGCCATCAGCGAGGTAGTTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA(SEQ ID NO:9)

Figure 10:

Nucleic acid sequence encoding B4 antibody light chain variable region with codons for amino acid substitutions Q1D, I10T, M11L, and A54D (B4 VKv2)

GACATTGTTCTCACCCAGTCTCCAGCAACTTTGTCTGCATCTCCAGGGGAGAAGGTCACCATGA
CCTGTAGTGCCAGCTCAGGTGTCAACTACATGCACTGGTATCAGCAGAAGCCAGGCACCTCCCC
CAAAAGATGGATTTATGACACATCCAAACTGGATTCTGGAGTCCCTGCTCGCTTCAGTGGCAGT
GGGTCTGGGACCTCTTATTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATT
ACTGCCATCAGCGAGGTAGTTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA(SEQ ID NO:10)

Figure 11:

Nucleic acid sequence encoding B4 antibody light chain variable region with codons for amino acid substitutions I10T, M11L, V19A, V29A, and S75E (B4 VKv3)

CAAATTGTTCTCACCCAGTCTCCAGCAACTTTGTCTGCATCTCCAGGGGAGAAGGCTACCATGA
CCTGCAGTGCCAGCTCAGGTGCTAACTACATGCACTGGTACCAGCAGAAGCCAGGCACCTCCCC
CAAAAGATGGATTTATGACACATCCAAACTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGT
GGGTCTGGGACCTCTTATTCTCTCACAATCGAGAGCATGGAGGCTGAAGATGCTGCCACTTATT
ACTGCCATCAGCGAGGTAGTTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA(SEQ ID NO:11)

Figure 12:

Nucleic acid sequence encoding B4 antibody light chain variable region with codons for amino acid substitutions I10T, M11L, V19A, S51D, and L53T (B4 VKv4)

CAAATTGTTCTCACCCAGTCTCCAGCAACTTTGTCTGCATCTCCAGGGGAGAAGGCTACCATGA
CCTGTAGTGCCAGCTCAGGTGTCAACTACATGCACTGGTACCAGCAGAAGCCAGGCACCTCCCC
CAAAAGATGGATTTATGACACAGACAAAACGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGT
GGGTCTGGGACCTCTTATTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATT
ACTGCCATCAGCGAGGTAGTTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA(SEQ ID NO:12)

Figure 13:

Amino acid sequence of B4 antibody heavy chain variable region (B4 VH0)

QVQLQQPGAEVVKPGASVRLSCKTSGYTFTSNWMHWVKQRPGQGLEWIGEIDPSDSYTNYNQKF
KGKAKLTVDKSSSTAYMEVSSLTSEDSAVYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID
NO:13)

Figure 14:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions K23E, G42D, K69E, and S85D (B4 VHv1)

QVQLQQPGAEVVKPGASVRLSCETSGYTFTSNWMHWVKQRPDQGLEWIGEIDPSDSYTNYNQKF
KGKAELTVDKSSSTAYMEVSDLTSEDSAVYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID
NO:14)

Figure 15:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions K69E, and S85D (B4 VHv2)

QVQLQQPGAEVVKPGASVRLSCKTSGYTFTSNWMHWVKQRPGQGLEWIGEIDPSDSYTNYNQKF
KGKAELTVDKSSSTAYMEVSDLTSEDSAVYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID
NO:15)

Figure 16:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, V12K, R19K, L20V, T24A, S85D, and S88A (B4 VHv3)

QVQLEQPGAEVKKPGASVKVSCKASGYTFTSNWMHWVKQRPGQGLEWIGEIDPSDSYTNYNQKF
KGKAKLTVDKSSSTAYMEVSDLTAEDSAVYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID
NO:16)

Figure 17:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, R19K, L20V, R40T, Q43K, K65D, S85D, S88A, and V93T (B4 VHv4)

QVQLEQPGAEVVKPGASVKVSCKTSGYTFTSNWMHWVKQTPGKGLEWIGEIDPSDSYTNYNQKF
DGKAKLTVDKSSSTAYMEVSDLTAEDSATYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID
NO:17)

Figure 18:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, V12K, R19K, L20V, T24A, K38R, R40A, Q43K, K65D, S85D, and V93T (B4 VHv5)

QVQLEQPGAEVKKPGASVKVSCKASGYTFTSNWMHWVRQAPGKGLEWIGEIDPSDSYTNYNQKF
DGKAKLTVDKSSSTAYMEVSDLTSEDSATYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID
NO: 18)

Figure 19:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, R19K, L20V, K65D, S85D, and V93T (B4 VHv6)

QVQLEQPGAEVVKPGASVKVSCKTSGYTFTSNWMHWVKQRPGQGLEWIGEIDPSDSYTNYNQKF DGKAKLTVDKSSSTAYMEVSDLTSEDSATYYCARGSNPYYYAMDYWGQGTSVTVSS (SEQ ID NO:19)

Figure 20:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions V12K, K23E, G42D, K65D, K69E, and S85D (B4 VHv11)

QVQLQQPGAEVKKPGASVRLSCETSGYTFTSNWMHWVKQRPDQGLEWIGEIDPSDSYTNYNQKF DGKAELTVDKSSSTAYMEVSDLTSEDSAVYYCARGSNPYYYAMDYWGQGTSVTVSS(SEQ ID NO:20)

Figure 21:

Amino acid sequence of B4 antibody heavy chain variable region with codons for amino acid substitutions Q5E, V12K, R19K, L20V, T24A, R40T, Q43K, K65D, S85D, S88A, and V93T (B4 VHv34)

QVQLEQPGAEVKKPGASVKVSCKASGYTFTSNWMHWVKQTPGKGLEWIGEIDPSDSYTNYNQKF DGKAKLTVDKSSSTAYMEVSDLTAEDSATYYCARGSNPYYYAMDYWGQGTSVTVSS(SEQ ID NO:21)

Figure 22:

Amino acid sequence of B4 antibody heavy chain framework region 1 with variable amino acid residues X5, X12, X19, X20, X23, and X24 (B4 VHfr1)

QVQLXQPGAEVXKPGASVXXSCXXSGYTFT(SEQ ID NO:22)

Figure 23:

Amino acid sequence of B4 antibody heavy chain framework region 2 with variable amino acid residues X3, X5, X7, and X8 (B4 VHfr2)

WVXQXPXXGLEWIG (SEQ ID NO:23)

Figure 24:

Amino acid sequence of B4 antibody heavy chain framework region 3 with variable amino acid residues X6, X10, X26, X29, and X34 (B4 VHfr3)

YNQKFXGKAXLTVDKSSSTAYMEVSXLTXEDSAXYYCAR(SEQ ID NO:24)

Figure 25:

Amino acid sequence of B4 antibody light chain variable region (B4 VK0)

QIVLTQSPAIMSASPGEKVTMTCSASSGVNYMHWYQQKPGTSPKRWIYDTSKLASGVPARFSGS GSGTSYSLTISSMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:25)

Figure 26:

Amino acid sequence of B4 antibody light chain variable region with codons for amino acid substitutions V3A, S7E, and A54D (B4 VKv1)

QIALTQEPAIMSASPGEKVTMTCSASSGVNYMHWYQQKPGTSPKRWIYDTSKLDSGVPARFSGS
GSGTSYSLTISSMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:26)

Figure 27:

Amino acid sequence of B4 antibody light chain variable region with codons for amino acid substitutions Q1D, I10T, M11L, and A54D (B4 VKv2)

DIVLTQSPATLSASPGEKVTMTCSASSGVNYMHWYQQKPGTSPKRWIYDTSKLDSGVPARFSGS
GSGTSYSLTISSMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:27)

Figure 28:

Amino acid sequence of B4 antibody light chain variable region with codons for amino acid substitutions I10T, M11L, V19A, V29A, and S75E (B4 VKv3)

QIVLTQSPATLSASPGEKATMTCSASSGANYMHWYQQKPGTSPKRWIYDTSKLASGVPARFSGS
GSGTSYSLTIESMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:28)

Figure 29:

Amino acid sequence of B4 antibody light chain variable region with codons for amino acid substitutions I10T, M11L, V19A, S51D, and L53T (B4 VKv4)

QIVLTQSPATLSASPGEKATMTCSASSGVNYMHWYQQKPGTSPKRWIYDTDKTASGVPARFSGS
GSGTSYSLTISSMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:29)

Figure 30:

Amino acid sequence of B4 antibody light chain variable region with codons for amino acid substitutions V3A, S7E, V19A, A54D, and S75E (B4 VKv11)

QIALTQEPAIMSASPGEKATMTCSASSGVNYMHWYQQKPGTSPKRWIYDTSKLDSGVPARFSGS
GSGTSYSLTIESMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:30)

Figure 31:

Amino acid sequence of B4 antibody light chain variable region with codons for amino acid substitutions I10T, M11L, V19A, V29A, S51D, L53T, and S75E (B4 VKv34)

QIVLTQSPATLSASPGEKATMTCSASSGANYMHWYQQKPGTSPKRWIYDTDKTASGVPARFSGS
GSGTSYSLTIESMEAEDAATYYCHQRGSYTFGGGTKLEIK(SEQ ID NO:31)

Figure 32:

Amino acid sequence of B4 antibody light chain framework region 1 with variable amino acid residues X1, X3, X7, X10, X11 and X19 (B4 VKfr1)

XIXLTQXPAXXSASPGEKXTMTC(SEQ ID NO:32)

Figure 33:

Amino acid sequence of B4 antibody light chain complementarity determining region 2 with variable amino acid residues X3, X5, and X6 (B4 VKcdr2)

DTXKXXS(SEQ ID NO:33)

Figure 34:

Amino acid sequence of B4 antibody heavy chain variable region with underlined CDRs and highlighted substitutable amino acids (B4 VH0) (SEQ ID NO:13)

```
  1 QVQLQQPGAEVVKPGASVRLSCKTSGYTFTSNWMHWVKQRPGQGLEWIGEIDPSD B4 VH0
 56 SYTNYNQKFKGKAKLTVDKSSSTAYMEVSSLTSEDSAVYYCARGSNPYYYAMDYW B4 VH0
111 GQGTSVTVSS                                               B4 VH0
```

Figure 35:

Amino acid sequence of B4 antibody light chain variable region with underlined CDRs and highlighted substitutable amino acids (B4 VK0) (SEQ ID NO:25)

```
  1 QIVLTQSPAIMSASPGEKVTMTCSASSGVNYMHWYQQKPGTSPKRWIYDTSKLAS B4 VK0
 56 GVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQRGSYTFGGGTKLEIK       B4 VK0
```

Figure 36:

Alignment of B4 antibody heavy chain variable region amino acid sequences

```
  1 QVQLQQPGAEVVKPGASVRLSCKTSGYTFTSNWMHWVKQRPGQGLEWIGEIDPSD B4 VH0
  1 .....................E.................D..............  B4 VHv1
  1 ........................................................  B4 VHv2
  1 ....E......K......KV...A.............................  B4 VHv3
  1 ....E............KV.....................T..K..........  B4 VHv4
  1 ....E......K......KV...A............R.A..K..........  B4 VHv5   1
  ..........K.........E.................D.............  B4 VHv11
  1 ....E......K......KV...A..............T..K..........  B4 VHv34

 56 SYTNYNQKFKGKAKLTVDKSSSTAYMEVSSLTSEDSAVYYCARGSNPYYYAMDYW B4 VH0
 56 ............E..............D.........................  B4 VHv1
 56 ............E..............D.........................  B4 VHv2
 56 ............................D..A.....................  B4 VHv3
 56 .........D..................D..A....T...............  B4 VHv4
 56 .........D..................D.......T...............  B4 VHv5
 56 .........D...E..............D.........................  B4 VHv11
 56 .........D..................D..A....T...............  B4 VHv34

                                                          SEQ ID NO:
111 GQGTSVTVSS                                            B4 VH0     13
111 ..........                                            B4 VHv1    14
111 ..........                                            B4 VHv2    15
111 ..........                                            B4 VHv3    16
111 ..........                                            B4 VHv4    17
111 ..........                                            B4 VHv5 111 18
..........                                             B4 VHv11      20
111 ..........                                            B4 VHv34   21
```

Figure 37:

Alignment of B4 antibody light chain variable region amino acid sequences

```
  1 QIVLTQSPAIMSASPGEKVTMTCSASSGVNYMHWYQQKPGTSPKRWIYDTSKLAS B4 VK0
  1 ..A...E.....................................................D. B4 VKv1
  1 D........TL.................................................D. B4 VKv2
  1 .........TL.......A.........A..................................... B4 VKv3
  1 .........TL.......A.....................................D.T.. B4 VKv4
  1 ..A...E..........A.....................................D. B4 VKv11
  1 .........TL.......A.........A.....................D.T.. B4 VKv34
                                                                SEQ ID NO:
 56 GVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQRGSYTFGGGTKLEIK        B4 VK0     25
 56 ..................................................        B4 VKv1    26
 56 ..................................................        B4 VKv2    27
 56 ..................E...............................        B4 VKv3    28
 56 ..................................................        B4 VKv4    29
 56 ..................E...............................        B4 VKv11   30
 56 ..................E...............................        B4 VKv34   31
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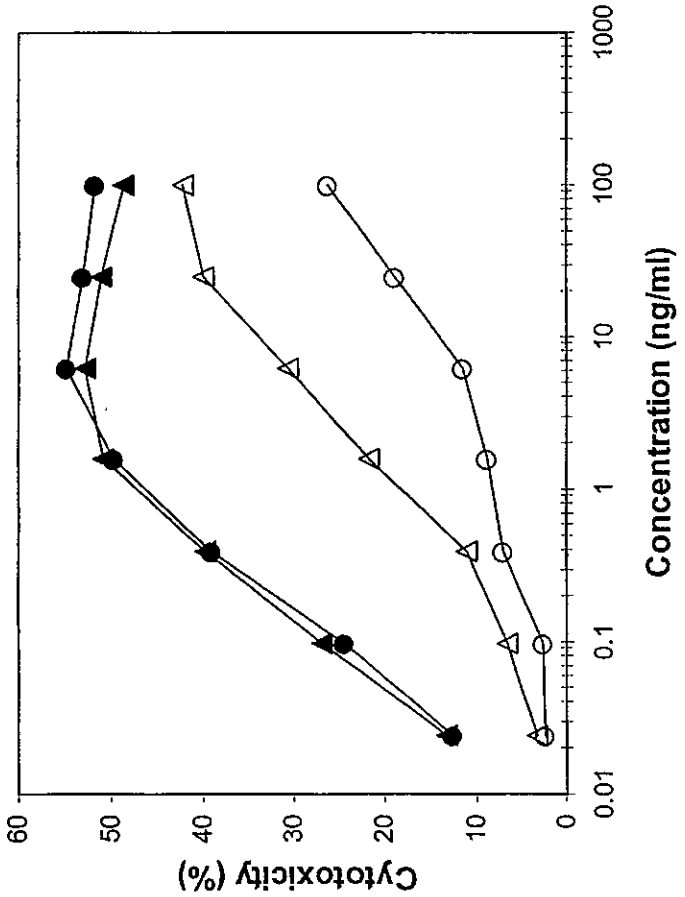

Cytotoxicity (%)
0
10
20
30
40
50
60
0.01
0.1
1
10
100
1000
Concentration (ng/ml)

Figure 38

Figure 39

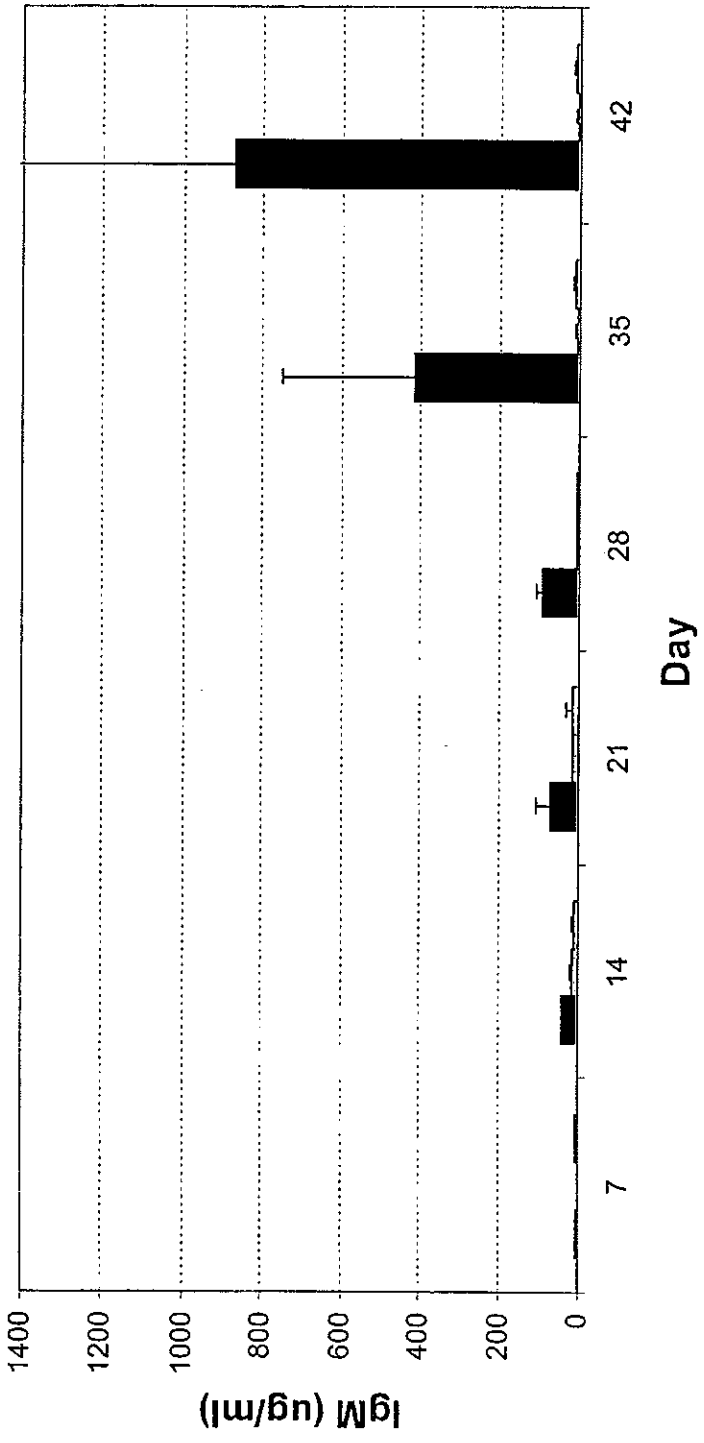


Figure 40

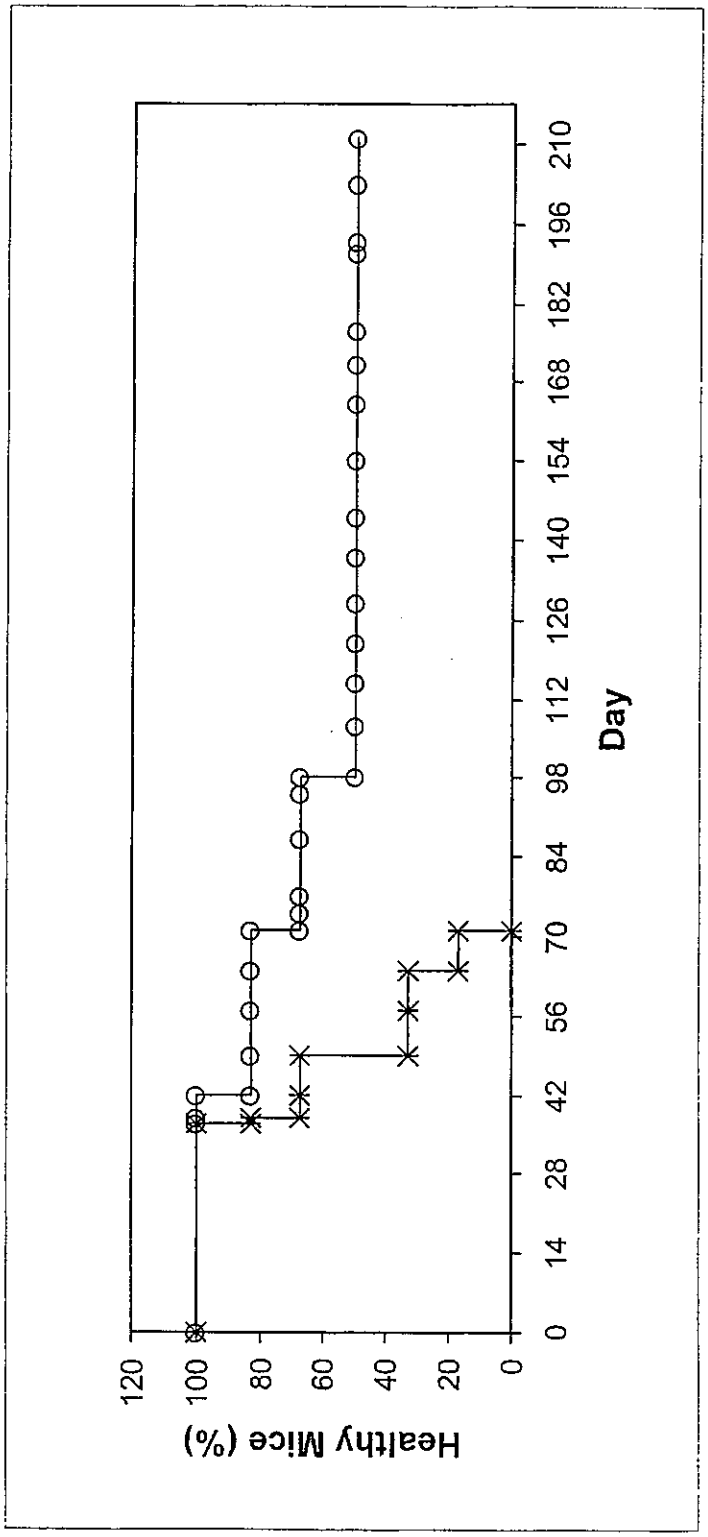

Healthy Mice (%)
120
100
80
60
40
20
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
196
210
Day

Figure 41

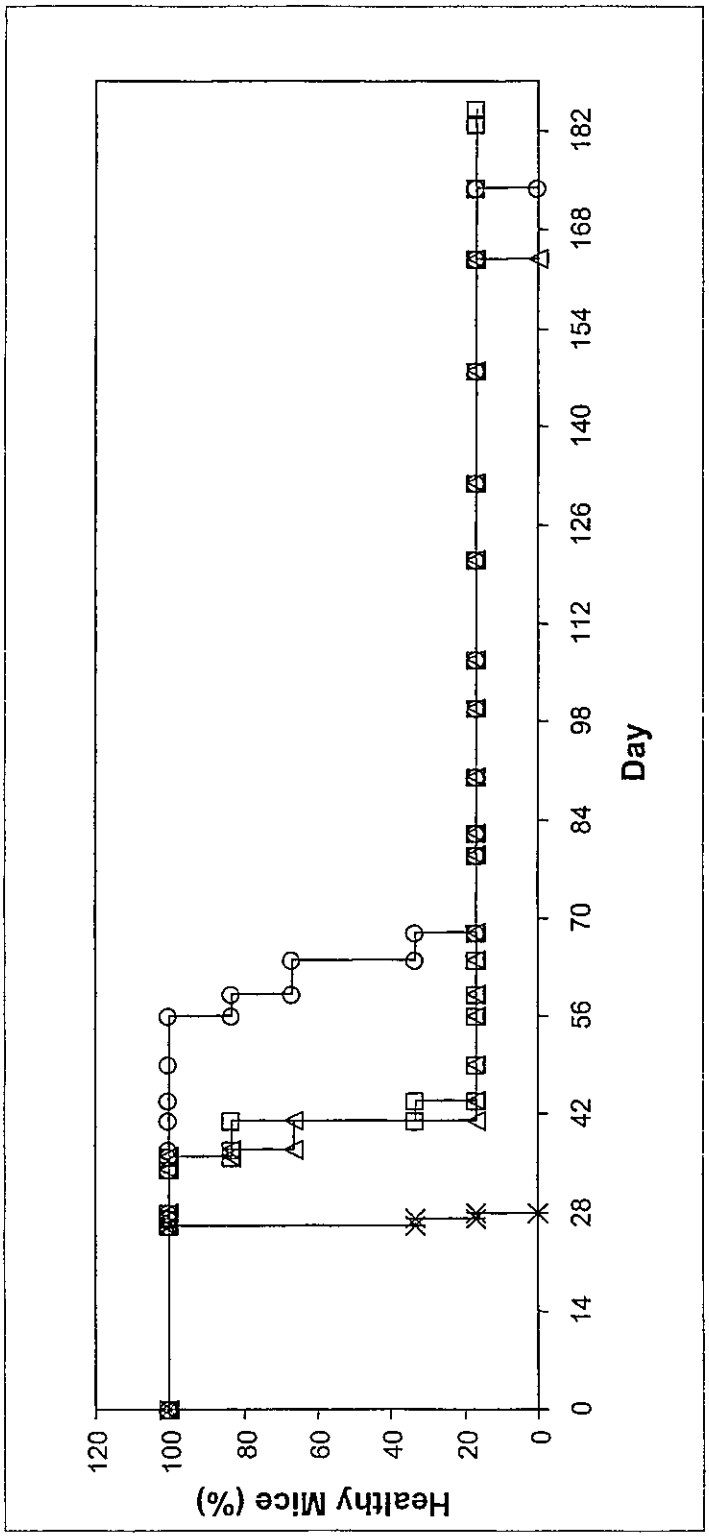
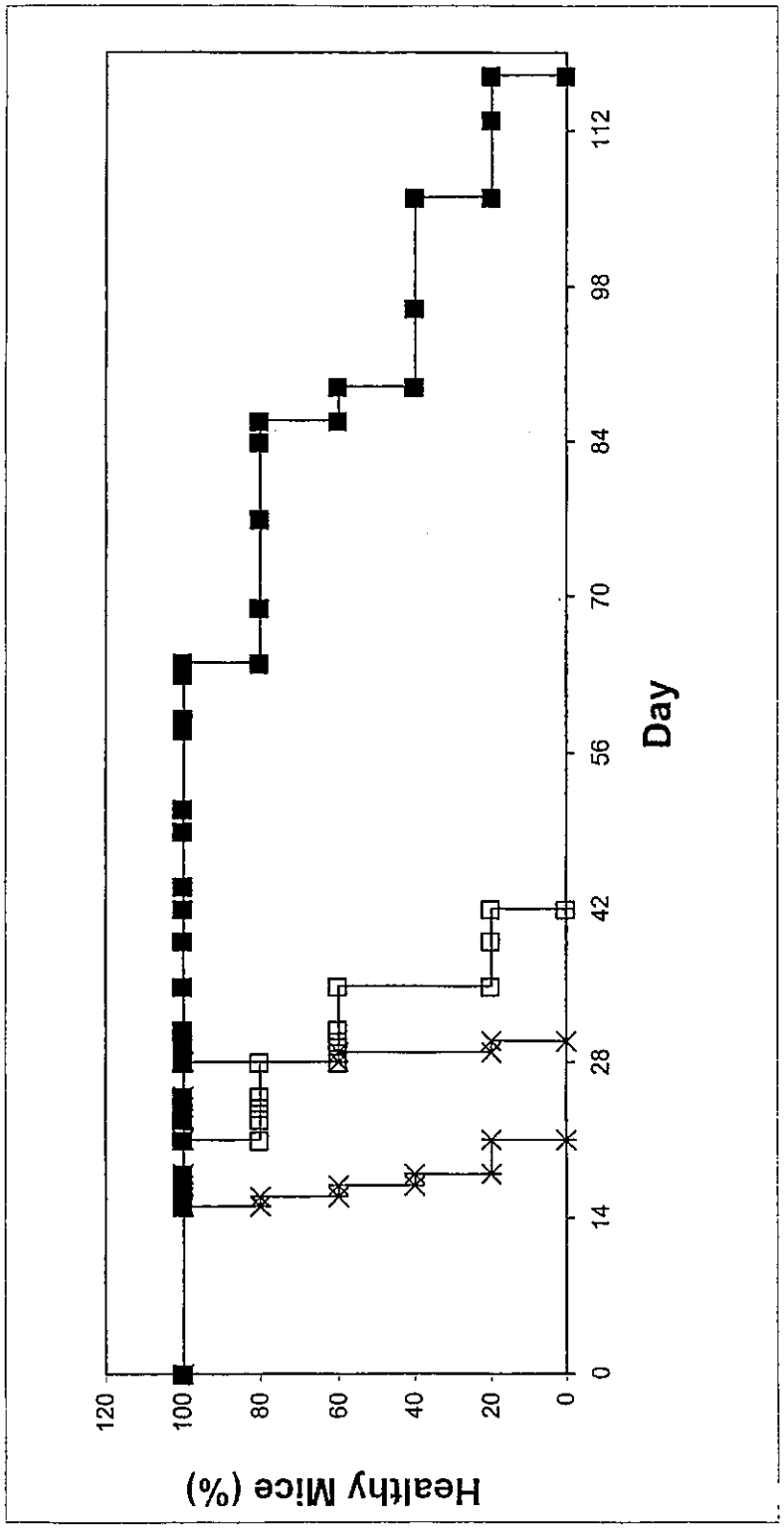

Healthy Mice (%)
120
100
80
60
40
20
0
0
14
28
42
56
70
84
98
112
126
140
154
168
182
Day

Figure 42(a)



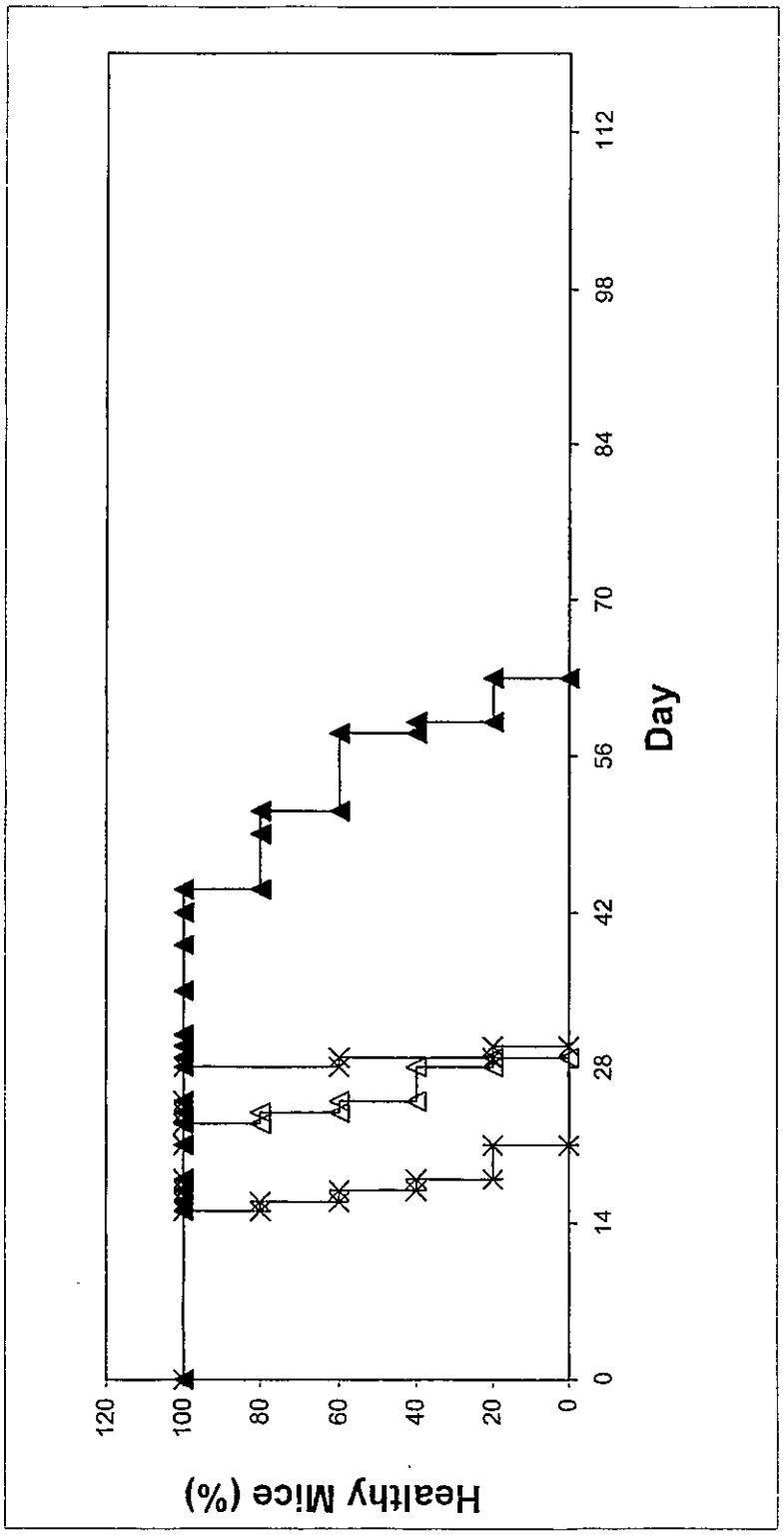


Figure 42(b)

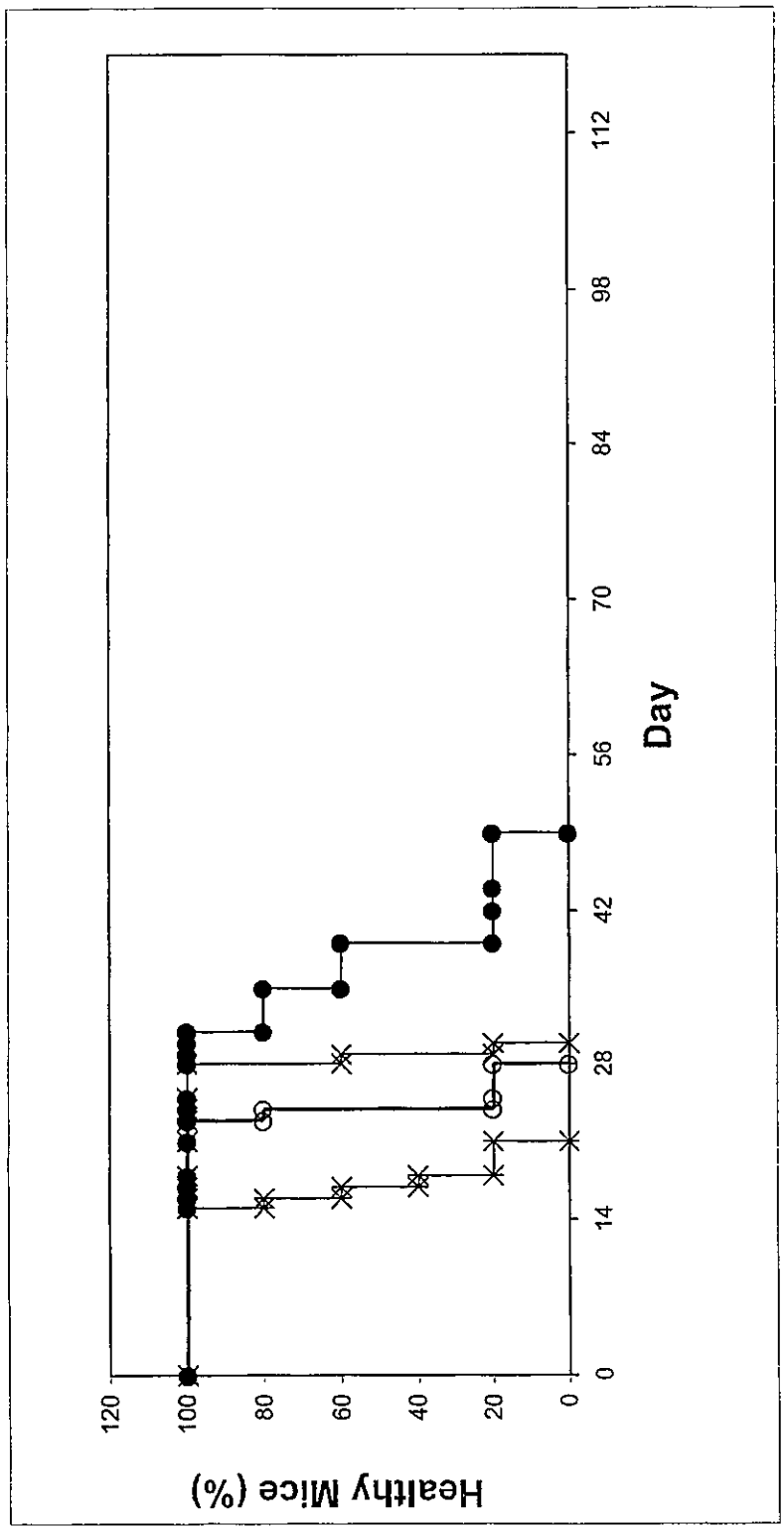


Figure 42(c)