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(54) **NUCLEIC ACIDS AND CORRESPONDING
PROTEINS ENTITLED 273P4B7 USEFUL IN
TREATMENT AND DETECTION OF
CANCER**

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(57) **ABSTRACT**

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Related U.S. Application Data

(62) Division of application No. 10/641,633, filed on Aug.
15, 2003, now Pat. No. 7,250,498.

A novel gene 273P4B7 and its encoded protein, and variants thereof, are described wherein 273P4B7 exhibits tissue specific expression in normal adult tissue, and is aberrantly expressed in the cancers listed in Table 1. Consequently, 273P4B7 provides a diagnostic, prognostic, prophylactic and/or therapeutic target for cancer. The 273P4B7 gene or fragment thereof, or its encoded protein, or variants thereof, or a fragment thereof, can be used to elicit a humoral or cellular immune response; antibodies or T cells reactive with 273P4B7 can be used in active or passive immunization.

Figure 1: 273P4B7 SSH sequence of 170 nucleotides (SEQ ID NO: 1).

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1 GATCCTGAAG TTATGCTCTT GACTTTAAGT TTGTATAAGC AACTTAATAA CAATTGAGAA
61 TGTAACCTGT TTAAGTATT TTAAAGTGAA ACTGAATATG AGGGAATTTT TGTTCCATA
121 ATTGGATTCT TTGGGAACAT GAAGCATTTA NGCTTAAGGC NAGAAAGATC
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Figure 2:

Figure 2A. The cDNA (SEQ ID. NO. : 2) and amino acid sequence (SEQ ID. NO. : 3) of 273P4B7 v.1. The Kozak initiation sequence is shown in bold, and the start methionine is underlined. The open reading frame extends from nucleic acid 95-3847 including the stop codon.

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1 aaattcaagctccaaactctaagctccaagctccaagctccaagctccaagctccaaact
1 M E A S R R F P E
61 cccgccggggtaactggaacccaatccgagggtcATGGAGGCATCCCGAAGGTTTCCGGA
10 A E A L S P E Q A A H Y L R Y V K E A K
121 AGCCGAGGCCTTGAGCCCAGAGCAGGCTGCTCATTACCTAAGATATGTGAAAGAGGCCAA
30 E A T K N G D L E E A F K L F N L A K D
181 AGAAGCAACTAAGAATGGAGACCTGGAAGAAGCATTAACTTTTCAATTTGGCAAAGGA
50 I F P N E K V L S R I Q K I Q E A L E E
241 CATTTTCCCAATGAAAAAGTGCTGAGCAGAATCCAAAAAATACAGGAAGCCTTGGAGGA
70 L A E Q G D D E F T D V C N S G L L L Y
301 GTTGGCAGAACAGGGAGATGATGAATTTACAGATGTGTGCAACTCTGGCTTGCTACTTTA
90 R E L H N Q L F E H Q K E G I A F L Y S
361 TCGAGAACTGCACAACCAACTCTTTGAGCACCAGAAGGAAGGCATAGCTTTCCTCTATAG
110 L Y R D G R K G G I L A D D M G L G K T
421 CCTGTATAGGGATGGAAGAAAAGGTGGTATATTGGCTGATGATATGGGATTAGGGAAGAC
130 V Q I I A F L S G M F D A S L V N H V L
481 TGTTCAAATCATTGCTTTCCTTTCCGGTATGTTTGATGCATCACTTGTGAATCATGTGCT
150 L I M P T N L I N T W V K E F I K W T P
541 GCTGATCATGCCAACCAATCTTATTAACACATGGGTAAAAGAATTCATCAAGTGGACTCC
170 G M R V K T F H G P S K D E R T R N L N
601 AGGAATGAGAGTCAAAACCTTTCATGGTCCTAGCAAGGATGAACGGACCAGAAACCTCAA
190 R I Q Q R N G V I I T T Y Q M L I N N W
661 TCGGATTACAGCAAAGGAATGGTGTATTATCACTACATAACCAATGTTAATCAATAACTG
210 Q Q L S S F R G Q E F V W D Y V I L D E
721 GCAGCAACTTTCAGCTTTAGGGGCCAAGAGTTTGTGTGGGACTATGTCATCCTCGATGA
230 A H K I K T S S T K S A I C A R A I P A
781 AGCACATAAAATAAAAAACCTCATCTACTAAGTCAGCAATATGTGCTCGTGCTATTTCCTGC
250 S N R L L L T G T P I Q N N L Q E L W S
841 AAGTAATCGCCTCCTCCTCACAGGAACCCCAATCCAGAATAATTTACAAGAACTATGGTC
270 L F D F A C Q G S L L G T L K T F K M E
901 CCTATTTGATTTTGCTTGTCAAGGGTCCCTGCTGGGAACATTAAAAACTTTTAAGATGGA
290 Y E N P I T R A R E K D A T P G E K A L
961 GTATGAAAATCCTATTACTAGAGCAAGAGAGAAGGATGCTACCCCAGGAGAAAAAGCCTT
310 G F K I S E N L M A I I K P Y F L R R T
1021 GGGATTTAAATATCTGAAAACCTAATGGCAATCATAAAACCCTATTTTCTCAGGAGGAC
330 K E D V Q K K K S S N P E A R L N E K N
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Figure 2A-2

1081 TAAAGAAGACGTACAGAAGAAAAAGTCAAGCAACCCAGAGGCCAGACTTAATGAAAAGAA
350 P D V D A I C E M P S L S R K N D L I I
1141 TCCAGATGTTGATGCCATTTGTGAAATGCCTTCCCTTTCCAGGAAAAATGATTTAATTAT
370 W I R L V P L Q E E I Y R K F V S L D H
1201 TTGGATACGACTTGTGCCTTTACAAGAAGAAATATACAGGAAATTTGTGTCTTTAGATCA
390 I K E L L M E T R S P L A E L G V L K K
1261 TATCAAGGAGTTGCTAATGGAGACGCGCTCACCTTTGGCTGAGCTAGGTGTCTTAAAGAA
410 L C D H P R L L S A R A C C L L N L G T
1321 GCTGTGTGATCATCCTAGGCTGCTGTCTGCACGGGCTTGTGTTTGCTAAATCTTGGGAC
430 F S A Q D G N E G E D S P D V D H I D Q
1381 ATTCTCTGCTCAAGATGGAAATGAGGGGGAAGATTCCCCAGATGTGGACCATATTGATCA
450 V T D D T L M E E S G K M I F L M D L L
1441 AGTAACTGATGACACATTGATGGAAGAATCTGGAAAAATGATATTCCTAATGGACCTACT
470 K R L R D E G H Q T L V F S Q S R Q I L
1501 TAAGAGGCTGCGAGATGAGGGACATCAAACCTCTGGTGTCTTCTCAATCGAGGCAAATTCT
490 N I I E R L L K N R H F K T L R I D G T
1561 AAACATCATTGAACGCCTCTTAAAGAATAGGCACTTTAAGACATTGCGAATCGATGGGAC
510 V T H L L E R E K R I N L F Q Q N K D Y
1621 AGTTACTCATCTTTTGAACGAGAAAAAAGAATTAACCTATTCCAGCAAAAATAAGATTA
530 S V F L L T T Q V G G V G L T L T A A T
1681 CTCTGTTTTTCTGCTTACCACTCAAGTAGGTGGTGTCTCGGTTTAACATTAACCTGCAGCAAC
550 R V V I F D P S W N P A T D A Q A V D R
1741 TAGAGTGGTCATTTTGGACCTAGCTGGAATCCTGCAACTGATGCTCAAGCTGTGGATAG
570 V Y R I G Q K E N V V V Y R L I T C G T
1801 AGTTTACCGAATTGGACAAAAGAGAATGTTGTGGTTTATAGGCTAATCACTTGTGGGAC
590 V E E K I Y R R Q V F K D S L I R Q T T
1861 TGTAGAGGAAAAAATATACAGAAGACAGGTTTTCAGGACTCATTAATAAGACAAACTAC
610 G E K K N P F R Y F S K Q E L R E L F T
1921 TGGTGAAAAAAGAACCCTTTCCGATATTTTAGTAACAAGAATTAAGAGAGCTCTTTAC
630 I E D L Q N S V T Q L Q L Q S L H A A Q
1981 AATCGAGGATCTTCAGAACTCTGTAACCCAGCTGCAGCTTCAGTCTTGCATGCTGCTCA
650 R K S D I K L D E H I A Y L Q S L G I A
2041 GAGGAAATCTGATATAAACTAGATGAACATATTGCCTACCTGCAGTCTTTGGGGATAGC
670 G I S D H D L M Y T C D L S V K E E L D
2101 TGGAACTCTCAGACCATGATTTGATGTACACATGTGATCTGTCTGTAAAGAAGAGCTTGA
690 V V E E S H Y I Q Q R V Q K A Q F L V E
2161 TGTGGTAGAAGAATCTCACTATATTCAACAAAGGGTTTCAGAAAGCTCAATTCCTCGTTGA
710 F E S Q N K E F L M E Q Q R T R N E G A
2221 ATTCGAGTCTCAAAATAAAGAGTTCCTGATGGAACAACAAAGAACTAGAAATGAGGGGGC

Figure 2A-3

730 W L R E P V F P S S T K K K C P K L N K
2281 CTGGCTAAGAGAACCTGTATTTCCTTCTTCAACAAAGAAGAAATGCCCTAAATTGAATAA
750 P Q P Q P S P L L S T H H T Q E E D I S
2341 ACCACAGCCTCAGCCTTCACCTCTTCTAAGTACTCATCATACTCAGGAAGAAGATATCAG
770 S K M A S V V I D D L P K E G E K Q D L
2401 TTCCAAAATGGCAAGTGTAGTCATTGATGATCTGCCCAAAGAGGGTGAGAAACAAGATCT
790 S S I K V N V T T L Q D G K G T G S A D
2461 CTCCAGTATAAAGGTGAATGTTACCACCTTGCAAGATGGTAAAGGTACAGGTAGTGCTGA
810 S I A T L P K G F G S V E E L C T N S S
2521 CTCTATAGCTACTTTACCAAAGGGGTTTGGAAAGTGTAGAAGAACTTTGTACTAACTCTTC
830 L G M E K S F A T K N E A V Q K E T L Q
2581 ATTGGGAATGGAAAAAGCTTTGCAACTAAAAATGAAGCTGTACAAAAAGAGACATTACA
850 E G P K Q E A L Q E D P L E S F N Y V L
2641 AGAGGGGCCTAAGCAAGAGGCACTGCAAGAGGATCCTCTGGAAAGTTTAAATTATGTACT
870 S K S T K A D I G P N L D Q L K D D E I
2701 TAGCAAATCAACCAAAGCTGATATTGGGCCAAATTTAGATCAACTAAAGGATGATGAGAT
890 L R H C N P W P I I S I T N E S Q N A E
2761 TTTACGTCATTGCAATCCTTGCCCCATTATTTCCATAACAAATGAAAGTCAAAATGCAGA
910 S N V S I I E I A D D L S A S H S A L Q
2821 ATCAAATGTATCCATTATTGAAATAGCTGATGACCTTTCAGCATCCCATAGTGCACTGCA
930 D A Q A S E A K L E E E P S A S S P Q Y
2881 GGATGCTCAAGCAAGTGAGGCCAAGTTGGAAGAGGAACCTTCAGCATCTTCACCACAGTA
950 A C D F N L F L E D S A D N R Q N F S S
2941 TGCATGTGATTTCAATCTTTTCTTGAAGACTCAGCAGACAACAGACAAAATTTTCCAG
970 Q S L E H V E K E N S L C G S A P N S R
3001 TCAGTCTTTAGAGCATGTTGAGAAAGAAAATAGCTTGTGTGGCTCTGCACCTAATTCCAG
990 A G F V H S K T C L S W E F S E K D D E
3061 AGCAGGGTTTGTGCATAGCAAAACATGTCTCAGTTGGGAGTTTTCTGAGAAAGACGATGA
1010 P E E V V V K A K I R S K A R R I V S D
3121 ACCAGAAGAAGTAGTAGTTAAAGCAAAAATCAGAAGTAAAGCTAGAAGGATTGTTTCAGA
1030 G E D E D D S F K D T S S I N P F N T S
3181 TGGCGAAGATGAAGATGATTCTTTTAAAGATACCTCAAGCATAAATCCATTCAACACATC
1050 L F Q F S S V K Q F D A S T P K N D I S
3241 TCTCTTTCAATTCTCATCTGTGAAACAATTTGATGCTTCAACTCCCCAAAATGACATCAG
1070 P P G R F F S S Q I P S S V N K S M N S
3301 TCCACCAGGAAGGTTCTTTTCATCTCAAATACCCAGTAGTGTAATAAGTCTATGAACCT
1090 R R S L A S R R S L I N M V L D H V E D
3361 TAGAAGATCTCTGGCTTCTAGGAGGTCTCTTATTAATATGGTTTTAGACCACGTGGAGGA
1110 M E E R L D D S S E A K G P E D Y P E E

Figure 2A-4

3421 CATGGAGGAAAGACTTGACGACAGCAGTGAAGCAAAGGGTCCTGAAGATTATCCAGAAGA
 1130 G V E E S S G E A S K Y T E E D P S G E
 3481 AGGGGTGGAGGAAAGCAGTGGCGAAGCCTCCAAGTATACAGAAGAGGATCCTTCCGGAGA
 1150 T L S S E N K S S W L M T S K P S A L A
 3541 AACACTGTCTTCAGAAAACAAGTCCAGCTGGTTAATGACGTCTAAGCCTAGTGCTCTAGC
 1170 Q E T S L G A P E P L S G E Q L V G S P
 3601 TCAAGAGACCTCTCTTGGTGGCCCTGAGCCTTTGTCTGGTGAACAGTTGGTTGGTTCTCC
 1190 Q D K A A E A T N D Y E T L V K R G K E
 3661 CCAGGATAAGGCGGCAGAGGCTACAAATGACTATGAGACTCTTGTAAGCGTGGAAGA
 1210 L K E C G K I Q E A L N C L V K A L D I
 3721 ACTAAAAGAGTGTGGAAAAATCCAGGAGGCCCTAACTGCTTAGTTAAAGCGCTTGACAT
 1230 K S A D P E V M L L T L S L Y K Q L N N
 3781 AAAAAGTGCAGATCCTGAAGTTATGCTCTTGACTTTAAGTTTGTATAAGCAACTTAATAA
 1250 N *
 3841 CAATTGAgaatgtaacctgtttattgtatttttaaagtgaactgaatatgaggggaatttt
 3901 tgttcccataaattggattccttgggaacatgaagcattcaggcctaaggcaagaagatc
 3961 tcaaaaagcaacttctgacctgcaacgccccccactccatagtctggtattctgagcact
 4021 agcttaatatcttcttcaacttgaatatcttatatttttaggcataattctataaatttaact
 4081 gtgttgtttcttggaaagtcttgtaaaattattctggtcattcttaattttactctgaaa
 4141 gtgatcatcttctgtatataacagttcagataagaaaattaaagttacttttctc

Figure 2B. The cDNA (SEQ ID. NO. : 4) and amino acid sequence (SEQ ID. NO. : 5) of 273P4B7 v.2. The Kozak initiation sequence is shown in bold, and the start methionine is underlined. The open reading frame extends from nucleic acid 604-3987 including the stop codon.

1 atgcgcggggcgaggatgagcgaaattcaagctccaaactctaagctccaagctccaagc
 61 tccaagctccaagctccaaactcccgccgggtaactggaacccaatccgagggatcatgg
 121 aggcataccgaaggtttccggaagccgaggccttgagcccagagcaggctgctcattacc
 181 taagggtcttctgtgtgcgccagactggaattcagtggcctgatcatagttcactgcag
 241 cctcgaactcctgggctcaagcagtcctcctgccccagcctccctagtagctgggactta
 301 agatatgtgaaagaggccaaagaagcaactaagaatggagacctggaagaagcattttaa
 361 cttttcaatttggaagacatttttcccaatgaaaaagtgtctgagcagaatccaaaaa
 421 atacaggaagccttgaggaggttggcagaacagggagatgatgaatttacagatgtgtgc
 481 aactctggcttgctactttatcgagaactgcacaaccaactctttgagcaccagaaggaa
 541 ggcatagctttcctctatagcctgtatagggatggaagaaaaggtggtatattggctgat
 1 M G L G K T V Q I I A F L S G M F D A
 601 **gat**ATGGGATTAGGGAAGACTGTTCAAATCATTGCTTTCCTTTCCGGTATGTTTGATGCA
 20 S L V N H V L L I M P T N L I N T W V K
 661 TCACTTGTGAATCATGTGCTGCTGATCATGCCAACCAATCTTATTAACACATGGGTAAAA
 40 E F I K W T P G M R V K T F H G P S K D

Figure 2B-2

721 GAATTCATCAAGTGGACTCCAGGAATGAGAGTCAAAACCTTTCATGGTCCTAGCAAGGAT
60 E R T R N L N R I Q Q R N G V I I T T Y
781 GAACGGACCAGAAACCTCAATCGGATTGAGCAAGGAATGGTGTATTATCACTACATAC
80 Q M L I N N W Q Q L S S F R G Q E F V W
841 CAAATGTTAATCAATAACTGGCAGCAACTTTCAGCTTTAGGGGCCAAGAGTTTGTGTGG
100 D Y V I L D E A H K I K T S S T K S A I
901 GACTATGTCATCCTCGATGAAGCACATAAAATAAAAACCTCATCTACTAAGTCAGCAATA
120 C A R A I P A S N R L L L T G T P I Q N
961 TGTGCTCGTGCTATTCCTGCAAGTAATCGCCTCCTCCTCACAGGAACCCCAATCCAGAAT
140 N L Q E L W S L F D F A C Q G S L L G T
1021 AATTTACAAGAACTATGGTCCCTATTTGATTTTGCTTGTCAAGGGTCCCTGCTGGGAACA
160 L K T F K M E Y E N P I T R A R E K D A
1081 TTAAAACTTTTAAGATGGAGTATGAAATCCTATTACTAGAGCAAGAGAGAAGGATGCT
180 T P G E K A L G F K I S E N L M A I I K
1141 ACCCCAGGAGAAAAAGCCTTGGGATTTAAATATCTGAAACTTAATGGCAATCATAAAA
200 P Y F L R R T K E D V Q K K K S S N P E
1201 CCCTATTTTCTCAGGAGGACTAAAGAAGACGTACAGAAGAAAAAGTCAAGCAACCCAGAG
220 A R L N E K N P D V D A I C E M P S L S
1261 GCCAGACTTAATGAAAAGAATCCAGATGTTGATGCCATTTGTGAAATGCCTTCCCTTTCC
240 R K N D L I I W I R L V P L Q E E I Y R
1321 AGGAAAAATGATTTAATTATTTGGATACGACTTGTGCCTTTACAAGAAGAAATATACAGG
260 K F V S L D H I K E L L M E T R S P L A
1381 AAATTTGTGTCTTTAGATCATATCAAGGAGTTGCTAATGGAGACGCGCTCACCTTTGGCT
280 E L G V L K K L C D H P R L L S A R A C
1441 GAGCTAGGTGTCTTAAAGAAGCTGTGTGATCATCCTAGGCTGCTGTCTGCACGGGCTTGT
300 C L L N L G T F S A Q D G N E G E D S P
1501 TGTTTGCTAAATCTTGGGACATTCTCTGCTCAAGATGGAAATGAGGGGGAAGATTCCCCA
320 D V D H I D Q V T D D T L M E E S G K M
1561 GATGTGGACCATATTGATCAAGTAAGTATGATGACACATTGATGGAAGAATCTGAAAAATG
340 I F L M D L L K R L R D E G H Q T L V F
1621 ATATTCCTAATGGACCTACTTAAGAGGCTGCGAGATGAGGGACATCAAACCTCTGGTGTTT
360 S Q S R Q I L N I I E R L L K N R H F K
1681 TCTCAATCGAGGCAAATTCTAAACATCATTGAACGCCTCTTAAAGAATAGGCACTTTAAG
380 T L R I D G T V T H L L E R E K R I N L
1741 ACATTGCGAATCGATGGGACAGTTACTCATCTTTTGAACGAGAAAAAAGAATTAACCTA
400 F Q Q N K D Y S V F L L T T Q V G G V G
1801 TTCCAGCAAAATAAAGATTACTCTGTTTTTCTGCTTACCACTCAAGTAGGTGGTGTGCGGT
420 L T L T A A T R V V I F D P S W N P A T
1861 TTAACATTAAGTGCAGCAACTAGAGTGGTCATTTTTGACCCTAGCTGGAATCCTGCAACT

Figure 2B-3

440 D A Q A V D R V Y R I G Q K E N V V V Y
1921 GATGCTCAAGCTGTGGATAGAGTTTACCGAATTGGACAAAAGAGAATGTTGTGGTTTAT
460 R L I T C G T V E E K I Y R R Q V F K D
1981 AGGCTAATCACTTGTGGGACTGTAGAGGAAAAAATATACAGAAGACAGTTTTTCAAGGAC
480 S L I R Q T T G E K K N P F R Y F S K Q
2041 TCATTAATAAGACAAACTACTGGTGAAAAAAGAACCCTTTCCGATATTTTAGTAAACAA
500 E L R E L F T I E D L Q N S V T Q L Q L
2101 GAATTAAGAGAGCTCTTTACAATCGAGGATCTTCAGAACTCTGTAACCCAGCTGCAGCTT
520 Q S L H A A Q R K S D I K L D E H I A Y
2161 CAGTCTTTGCATGCTGCTCAGAGGAAATCTGATATAAACTAGATGAACATATTGCCTAC
540 L Q S L G I A G I S D H D L M Y T C D L
2221 CTGCAGTCTTTGGGGATAGCTGGAATCTCAGACCATGATTTGATGTACACATGTGATCTG
560 S V K E E L D V V E E S H Y I Q Q R V Q
2281 TCTGTAAAGAAGAGCTTGATGTGGTAGAAGAATCTCACTATATTCAACAAAGGGTTCAG
580 K A Q F L V E F E S Q N K E F L M E Q Q
2341 AAAGCTCAATTCCTCGTTGAATTCGAGTCTCAAATAAAGAGTTCCTGATGGAACAACAA
600 R T R N E G A W L R E P V F P S S T K K
2401 AGAACTAGAAATGAGGGGGCCTGGCTAAGAGAACCTGTATTTCTTCTTCAACAAAGAAG
620 K C P K L N K P Q P Q P S P L L S T H H
2461 AAATGCCCTAAATTGAATAAACCACAGCCTCAGCCTTCACCTCTTCTAAGTACTCATCAT
640 T Q E E D I S S K M A S V V I D D L P K
2521 ACTCAGGAAGAAGATATCAGTTCCAAAATGGCAAGTGTAGTCATTGATGATCTGCCCAAA
660 E G E K Q D L S S I K V N V T T L Q D G
2581 GAGGGTGAGAAACAAGATCTCTCCAGTATAAAGGTGAATGTTACCACCTTGCAAGATGGT
680 K G T G S A D S I A T L P K G F G S V E
2641 AAAGGTACAGGTAGTGCTGACTCTATAGCTACTTTACCAAAGGGGTTTGGAACTGTAGAA
700 E L C T N S S L G M E K S F A T K N E A
2701 GAACTTTGTACTAACTCTTCATTGGGAATGGAAAAAGCTTTGCAACTAAAAATGAAGCT
720 V Q K E T L Q E G P K Q E A L Q E D P L
2761 GTACAAAAGAGACATTACAAGAGGGGCCTAAGCAAGAGGCACTGCAAGAGGATCCTCTG
740 E S F N Y V L S K S T K A D I G P N L D
2821 GAAAGTTTAAATTATGTACTTAGCAAATCAACCAAGCTGATATTGGGCCAAATTTAGAT
760 Q L K D D E I L R H C N P W P I I S I T
2881 CAACTAAAGGATGATGAGATTTTACGTCATTGCAATCCTTGGCCCATTATTTCCATAACA
780 N E S Q N A E S N V S I I E I A D D L S
2941 AATGAAAGTCAAAATGCAGAATCAAATGTATCCATTATTGAAATAGCTGATGACCTTTTCA
800 A S H S A L Q D A Q A S E A K L E E E P
3001 GCATCCCATAGTGCAGTGCAGGATGCTCAAGCAAGTGAGGCCAAGTTGGAAGAGGAACCT
820 S A S S P Q Y A C D F N L F L E D S A D

Figure 2B-4

3061 TCAGCATCTTCACCACAGTATGCATGTGATTTCAATCTTTTCTTGGAAGACTCAGCAGAC
840 N R Q N F S S Q S L E H V E K E N S L C
3121 AACAGACAAAATTTTCCAGTCAGTCTTTAGAGCATGTTGAGAAAGAAAATAGCTTGTGT
860 G S A P N S R A G F V H S K T C L S W E
3181 GGCTCTGCACCTAATTCAGAGCAGGGTTTGTGCATAGCAAAACATGTCTCAGTTGGGAG
880 F S E K D D E P E E V V V K A K I R S K
3241 TTTTCTGAGAAAGACGATGAACCAGAAGAAGTAGTAGTTAAAGCAAAAATCAGAAGTAA
900 A R R I V S D G E D E D D S F K D T S S
3301 GCTAGAAGGATTGTTTCAGATGGCGAAGATGAAGATGATTCTTTTAAAGATACCTCAAGC
920 I N P F N T S L F Q F S S V K Q F D A S
3361 ATAAATCCATTCAACACATCTCTCTTTCAATTCTCATCTGTGAAACAATTTGATGCTTCA
940 T P K N D I S P P G R F F S S Q I P S S
3421 ACTCCCCAAAATGACATCAGTCCACCAGGAAGGTTCTTTTCATCTCAAATACCCAGTAGT
960 V N K S M N S R R S L A S R R S L I N M
3481 GTAAATAAGTCTATGAACTCTAGAAGATCTCTGGCTTCTAGGAGGTCTCTTATTAATATG
980 V L D H V E D M E E R L D D S S E A K G
3541 GTTTTAGACCACGTGGAGGACATGGAGGAAAGACTTGACGACAGCAGTGAAGCAAAGGGT
1000 P E D Y P E E G V E E S S G E A S K Y T
3601 CCTGAAGATTATCCAGAAGAAGGGGTGGAGGAAAGCAGTGGCGAAGCCTCCAAGTATACA
1020 E E D P S G E T L S S E N K S S W L M T
3661 GAAGAGGATCCTTCCGGAGAAACACTGTCTTCAGAAAACAAGTCCAGCTGGTTAATGACG
1040 S K P S A L A Q E T S L G A P E P L S G
3721 TCTAAGCCTAGTGCTCTAGCTCAAGAGACCTCTCTTGGTGCCCCTGAGCCTTTGTCTGGT
1060 E Q L V G S P Q D K A A E A T N D Y E T
3781 GAACAGTTGGTTGGTTCTCCCCAGGATAAGGCGGCAGAGGCTACAAATGACTATGAGACT
1080 L V K R G K E L K E C G K I Q E A L N C
3841 CTTGTAAAGCGTGGAAAAGAACTAAAAGAGTGTGGAAAATCCAGGAGGCCCTAAACTGC
1100 L V K A L D I K S A D P E V M L L T L S
3901 TTAGTTAAAGCGCTTGACATAAAAAGTGCAGATCCTGAAGTTATGCTCTTGACTTTAAGT
1120 L Y K Q L N N N *
3961 TTGTATAAGCAACTTAATAACAATTGAgaatgtaacctgtttattgtatttttaagtga
4021 actgaatatgagggaatttttgttcccataattggattctttgggaacatgaagcattca
4081 ggcttaaggcaagaaagatctcaaaaagcaacttctgacctgcaacgccccccactccat
4141 agtctggtattctgagcactagcttaatatcttctcacttgaatattcttatatttttagg
4201 catattctataaatttaactgtgttgtttcttggaaagttttgtaaaattattctggtca
4261 ttcttaattttactctgaaagtgatcatctttgtatataacagttcagataagaaaatta
4321 aagttactttttctc

Figure 2C. 273P4B7 v.3 through v.8, SNP variants of 273P4B7 v.1. The 273P4B7 v.3 through v.8 are variants with single nucleotide difference from 273P4B7 v.1. 273P4B7 v.3, v.7, and v.8 code for the same protein as v.1. 273P4B7 v.4, v.5, and v.6 proteins differ from 273P4B7 v.1 by one amino acid. Though these SNP variants are shown separately, they can also occur in any combinations and in any of the transcript variants listed above in Figures 2A and 2B.

Variant	Nucleic acid position	Nucleic Acid Variation	Amino/Acid Position	Amino/Acid Variation
273P4B7 v.3	571	A/T	Silent variant	
273P4B7 v.4	608	A/G	172	R=>G
273P4B7 v.5	1185	A/G	364	K=>R
273P4B7 v.6	2759	A/G	889	I=>V
273P4B7 v.7	3658	T/C	Silent variant	
273P4B7 v.8	3850	A/G	Silent variant	

Figure 2D. The cDNA (SEQ ID. NO. : 6) and amino acid sequence (SEQ ID. NO. : 7) of 273P4B7 v.9. The start methionine is underlined. The open reading frame extends from nucleic acid 4-3324 including the stop codon.

```

1   M N H V L L I M P T N L I N T W V K E
1   aaaATGAATCATGTGCTGCTGATCATGCCAACCAATCTTATTAACACTTGGGTAAAAGAA
20  F I K W T P G M G V K T F H G P S K D E
61  TTCATCAAGTGGACTCCAGGAATGGGAGTCAAAACCTTTCATGGTCCTAGCAAGGATGAA
40  R T R N L N R I Q Q R N G V I I T T Y Q
121 CGGACCAGAAAACCTCAATCGGATTACGCAAAGGAATGGTGTATTATCACTACATACCAA
60  M L I N N W Q Q L S S F R G Q E F V W D
181 ATGTTAATCAATAACTGGCAGCAACTTTCAGCTTTAGGGGCCAAGAGTTTGTGTGGGAC
80  Y V I L D E A H K I K T S S T K S A I C
241 TATGTCATCCTCGATGAAGCACATAAAATAAAAACCTCATCTACTAAGTCAGCAATATGT
100 A R A I P A S N R L L L T G T P I Q N N
301 GCTCGTGCTATTTCCTGCAAGTAATCGCCTCCTCCTCACAGGAACCCCAATCCAGAATAAT
120 L Q E L W S L F D F A C Q G S L L G T L
361 TTACAAGAAGTATGGTCCCTATTTGATTTTGCTTGTCAAGGGTCCCTGCTGGGAACATTA
140 K T F K M E Y E N P I T R A R E K D A T
421 AAAACTTTTAAAGATGGAGTATGAAAATCCTATTACTAGAGCAAGAGAGAAGGATGCTACC
160 P G E K A L G F K I S E N L M A I I K P
481 CCAGGAGAAAAAGCCTTGGGATTTAAATATCTGAAAACCTTAATGGCAATCATAAAACCC
180 Y F L R R T K E D V Q K K K S S N P E A

```

Figure 2D-2

541 TATTTTCTCAGGAGGACTAAAGAAGACGTACAGAAGAAAAAGTCAAGCAACCCAGAGGCC
200 R L N E K N P D V D A I C E M P S L S R
601 AGACTTAATGAAAAGAATCCAGATGTTGATGCCATTTGTGAAATGCCTTCCCTTTCCAGG
220 K N D L I I W I R L V P L Q E E I Y R K
661 AAAAATGATTTAATTATTTGGATACGACTTGTGCCTTTACAAGAAGAAATATACAGGAAA
240 F V S L D H I K E L L M E T R S P L A E
721 TTTGTGTCTTTAGATCATATCAAGGAGTTGCTAATGGAGACGCGCTCACCTTTGGCTGAG
260 L G V L K K L C D H P R L L S A R A C C
781 CTAGGTGTCTTAAAGAAGCTGTGTGATCATCCTAGGCTGCTGTCTGCACGGGCTTGTGT
280 L L N L G T F S A Q D G N E G E D S P D
841 TTGCTAAATCTTGGGACATTCTCTGCTCAAGATGGAAATGAGGGGGAAGATTCCCCAGAT
300 V D H I D Q V T D D T L M E E S G K M I
901 GTGGACCATATTGATCAAGTAAGTATGATGACACATTGATGGAAGAATCTGGAAAAATGATA
320 F L M D L L K R L R D E G H Q T L V F S
961 TTCCTAATGGACCTACTTAAGAGGCTGCGAGATGAGGGACATCAAATCTGGTGTCTTCT
340 Q S R Q I L N I I E R L L K N R H F K T
1021 CAATCGAGGCAAATTCTAAACATCATTGAACGCCTCTTAAAGAATAGGCACTTTAAGACA
360 L R I D G T V T H L L E R E K R I N L F
1081 TTGCGAATCGATGGGACAGTTACTCATCTTTTGAACGAGAAAAAGAATTAAGTTATTC
380 Q Q N K D Y S V F L L T T Q V G G V G L
1141 CAGCAAAATAAAGATTACTCTGTCTTTCTGCTTACCACTCAAGTAGGTGGTGTCTGGTTTA
400 T L T A A T R V V I F D P S W N P A T D
1201 ACATTAACTGCAGCAACTAGAGTGGTCATTTTGGACCCTAGCTGGAATCCTGCAACTGAT
420 A Q A V D R V Y R I G Q K E N V V V Y R
1261 GCTCAAGCTGTGGATAGAGTTTACCGAATTGGACAAAAAGAGAATGTTGTGGTTTATAGG
440 L I T C G T V E E K I Y R R Q V F K D S
1321 CTAATCACTTGTGGGACTGTAGAGGAAAAATATACAGAAGACAGGTTTTCAAGGACTCA
460 L I R Q T T G E K K N P F R Y F S K Q E
1381 TTAATAAGACAACTACTGGTGAAAAAAGAACCCTTTCCGATATTTTAGTAAACAAGAA
480 L R E L F T I E D L Q N S V T Q L Q L Q
1441 TTAAGAGAGCTCTTTACAATCGAGGATCTTCAGAACTCTGTAACCCAGCTGCAGCTTCAG
500 S L H A A Q R K S D I K L D E H I A Y L
1501 TCTTTGCATGCTGCTCAGAGGAAATCTGATATAAACTAGATGAACATATTGCCTACCTG
520 Q S L G I A G I S D H D L M Y T C D L S
1561 CAGTCTTTGGGGATAGCTGGAATCTCAGACCATGATTTGATGTACACATGTGATCTGTCT
540 V K E E L D V V E E S H Y I Q Q R V Q K
1621 GTTAAAGAAGAGCTTGATGTGGTAGAAGAATCTCACTATATTCAACAAAGGGTTAGAAA
560 A Q F L V E F E S Q N K E F L M E Q Q R
1681 GCTCAATTCTCGTTGAATTCGAGTCTCAAATAAAGAGTTCCTGATGGAACAACAAAGA

Figure 2D-3

580 T R N E G A W L R E P V F P S S T K K K
1741 ACTAGAAATGAGGGGCGCTGGCTAAGAGAACCTGTATTTCTTCTTCAACAAAGAAGAAA
600 C P K L N K P Q P Q P S P L L S T H H T
1801 TGCCCTAAATTGAATAAACCACAGCCTCAGCCTTCACCTCTTCTAAGTACTCATCATACT
620 Q E E D I S S K M A S V V I D D L P K E
1861 CAGGAAGAAGATATCAGTTCCAAAATGGCAAGTGTAGTCATTGATGATCTGCCCAAAGAG
640 G E K Q D L S S I K V N V T T L Q D G K
1921 GGTGAGAAACAAGATCTCTCCAGTATAAAGGTGAATGTTACCACCTTGCAAGATGGTAAA
660 G T G S A D S I A T L P K G F G S V E E
1981 GGTACAGGTAGTGCTGACTCTATAGCTACTTTACCAAAGGGGTTTGGAAGTGTAGAAGAA
680 L C T N S S L G M E K S F A T K N E A V
2041 CTTTGTACTAACTCTTCATTGGGAATGGAAAAAGCTTTGCAACTAAAAATGAAGCTGTA
700 Q K E T L Q E G P K Q E A L Q E D P L E
2101 CAAAAAGAGACATTACAAGAGGGGCGCTAAGCAAGAGGCACTGCAAGAGGATCCTCTGGAA
720 S F N Y V L S K S T K A D I G P N L D Q
2161 AGTTTTAATTATGTACTTAGCAAATCAACCAAAGCTGATATTGGGCCAAATTTAGATCAA
740 L K D D E V L R H C N P W P I I S I T N
2221 CTAAAGGATGATGAGGTTTTACGTCATTGCAATCCTTGGCCCATTATTTCCATAACAAAT
760 E S Q N A E S N V S I I E I A D D L S A
2281 GAAAGTCAAAATGCAGAATCAAATGTATCCATTATTGAAATAGCTGATGACCTTTCAGCA
780 S H S A L Q D A Q A S E A K L E E E P S
2341 TCCCATAGTGCACTGCAGGATGCTCAAGCAAGTGAGGCCAAGTTGGAAGAGGAACCTTCA
800 A S S P Q Y A C D F N L F L E D S A D N
2401 GCATCTTCAACACAGTATGCATGTGATTTCAATCTTTTCTTGAAGACTCAGCAGACAAC
820 R Q N F S S Q S L E H V E K E N S L C G
2461 AGACAAAATTTTTCCAGTCAGTCTTTAGAGCATGTTGAGAAAAGAAAATAGCTTGTGTGGC
840 S A P N S R A G F V H S K T C L S W E F
2521 TCTGCACCTAATTCCAGAGCAGGTTTTGTGCATAGCAAAACATGTCTCAGTTGGGAGTTT
860 S E K D D E P E E V V V K A K I R S K A
2581 TCTGAGAAAGACGATGAACCAGAAGAAGTAGTAGTTAAAGCAAAAATCAGAAGTAAAGCT
880 R R I V S D G E D E D D S F K D T S S I
2641 AGAAGGATTGTTTCAGATGGCGAAGATGAAGATGATTCTTTTAAAGATACCTCAAGCATA
900 N P F N T S L F Q F S S V K Q F D A S T
2701 AATCCATTCAACACATCTCTCTTTCAATTCTCATCTGTGAAACAATTTGATGCTTCAACT
920 P K N D I S P P G R F F S S Q I P S S V
2761 CCCAAAAATGACATCAGTCCACCAGGAAGGTTCTTTTCATCTCAAATACCCAGTAGTGTA
940 N K S M N S R R S L A S R R S L I N M V
2821 AATAAGTCTATGAACCTCTAGAAGATCTCTGGCTTCTAGGAGGTCTCTTATTAATATGGTT
960 L D H V E D M E E R L D D S S E A K G P

Figure 2D-4

2881 TTAGACCACGTGGAGGACATGGAGGAAAGACTTGACGACAGCAGTGAAGCAAAGGGTCCT
 980 E D Y P E E G V E E S S G E A S K Y T E
 2941 GAAGATTATCCAGAAGAAGGGGTGGAGGAAAGCAGTGGCGAAGCCTCCAAGTATACAGAA
 1000 E D P S G E T L S S E N K S S W L M T S
 3001 GAGGATCCTTCCGGAGAAACACTGTCTTCAGAAAACAAGTCCAGCTGGTTAATGACGCTCT
 1020 K P S A L A Q E T S L G A P E P L S G E
 3061 AAGCCTAGTGCTCTAGCTCAAGAGACCTCTCTTGGTGCCCCTGAGCCTTTGTCTGGTGAA
 1040 Q L V G S P Q D K A A E A T N D Y E T L
 3121 CAGTTGGTTGGTTCCCCCAGGATAAGGCGGCAGAGGCTACAAATGACTATGAGACTCTT
 1060 V K R G K E L K E C G K I Q E A L N C L
 3181 GTAAAGCGTGGAAAAGAACTAAAAGAGTGTGGAAAAATCCAGGAGGCCCTAAACTGCTTA
 1080 V K A L D I K S A D P E V M L L T L S L
 3241 GTTAAAGCGCTTGACATAAAAAGTGCAGATCCTGAAGTTATGCTCTTGACTTTAAGTTTG
 1100 Y K Q L N N N *
 3301 TATAAGCAACTTAATAACAATTGAgaatgtaacctgtttattgtatttttaaagtgaact
 3361 gaatatgaggggaatttttgttcccataattggattctttgggaacatgaagcattcaggc
 3421 ttaaggcaagaaagatctcaaaaagcaacttctgccttgcaacgccccccactccatagt
 3481 ctggtattctgagcactagcttaatatcttcttacttgaatattcttatatttttaggcatt
 3541 attctataaaatttaactgtgtgtttcttggaaagttttgtaaaattattctggtcattc
 3601 ttaattttactctgaaagtgatcatctttgtatataacagttcagataagaaaattaaag
 3661 ttactttttctc

Figure 2E. The cDNA (SEQ ID. NO. : 8) and amino acid sequence (SEQ ID. NO. : 9) of 273P4B7 v.10. The start methionine is underlined. The open reading frame extends from nucleic acid 688-1947 including the stop codon.

1 tcattaataagacaaactactggtgaaaaaaagaaccctttccgatatttttagtaaacaa
 61 gaattaagagagctctttacaatcgaggatcttcagaactctgtaaccagctgcagctt
 121 cagtctttgcatgctgctcagaggaaatctgatataaaactagatgaacatattgcctac
 181 ctgcagtcctttggggatagctggaatctcagaccatgatttgatgtacacatgtgatctg
 241 tctgttaaagaagagcttgatgtggtagaagaatctcactatattcaacaaagggttcag
 301 aaagctcaattcctcgttgaattcgagctctcaaaataaagagttcctgatggaacaacaa
 361 agaactagaaatgagggggcctggctaagagaacctgtatttccttcttcaacaaagaag
 421 aaatgccctaaattgaataaaccacagcctcagccttcacctcttctaagtactcatcat
 481 actcaggaagaagatatcagttccaaaatggcaagtgtagtcattgatgatctgccccaa
 541 gagggtgagaaacaagatctctccagtataaagggtgaatgttaccaccttgcaagatggg
 601 taagggtacaggtagtgctgactctataactactttaccaaaggggtttggaagtgtagaa
 1 M E K S F A T K N E A
 661 gaactttgtactaactcttcattgggaATGGAAAAAAGCTTTGCAACTAAAAATGAAGCT
 12 V Q K E T L Q E G P K Q E A L Q E D P L

Figure 2E-2

721 GTACAAAAAGAGACATTACAAGAGGGGCCTAAGCAGGAGGCACTGCAAGAGGATCCTCTG
32 E S F N Y V L S K S T K A D I G P N L D
781 GAAAGTTTAAATTATGTACTTAGCAAATCAACCAAAGCTGATATTGGGCCAAATTTAGAT
52 Q L K D D E I L R H C N P W P I I S I T
841 CAACTAAAGGATGATGAGATTTTACGTCATTGCAATCCTTGGCCCATTATTTCCATAACA
72 N E S Q N A E S N V S I I E I A D D L S
901 AATGAAAGTCAAAATGCAGAATCAAATGTATCCATTATTGAAATAGCTGATGACCTTTCA
92 A S H S A L Q D A Q A S E A K L E E E P
961 GCATCCCATAGTGCCTGCGAGGATGCTCAAGCAAGTGAGGCCAAGTTGGAAGAGGAACCT
112 S A S S P Q Y A C D F N L F L E D S A D
1021 TCAGCATCTTCACACAGTATGCATGTGATTTCATCTTTTCTTGAAGACTCAGCAGAC
132 N R Q N F S S Q S L E H V E K E N S L C
1081 AACAGACAAAATTTTCCAGTCAGTCTTTAGAGCATGTTGAGAAAGAAAATAGCTTGTGT
152 G S A P N S K A G F V H S K T C L S W E
1141 GGCTCTGCACCTAATTCCAAAGCAGGGTTTGTGCATAGCAAAACATGTCTCAGTTGGGAG
172 F S E K D D E P E E V V V K A K I R S K
1201 TTTTCTGAGAAAGACGATGAACCAGAAGAAGTAGTAGTTAAAGCAAAAATCAGAAGTAAA
192 A R R I V S D G E D E D D S F K D T S S
1261 GCTAGAAGGATTGTTTCAGATGGCGAAGATGAAGATGATTCTTTTAAAGATACCTCAAGC
212 I N P F N T S L F Q F S S V K Q F D A S
1321 ATAAATCCATTCAACACATCTCTCTTTCAATTCTCATCTGTGAAACAATTTGATGCTTCA
232 T P K N D I S P P G R F F S S Q I P S S
1381 ACTCCCAAAAATGACATCAGTCCACCAGGAAGGTTCTTTTCATCTCAAATACCCAGTAGT
252 V N K S M N S R R S L A S R R S L I N M
1441 GTAAATAAGTCTATGAACTCTAGAAGATCTCTGGCTTCTAGGAGGTCTCTTATTAATATG
272 V L D H V E D M E E R L D D S S E A K G
1501 GTTTTAGACCACGTGGAGGACATGGAGGAAAGACTTGACGACAGCAGTGAAGCAAAGGGT
292 P E D Y P E E G V E E S S G E A S K Y T
1561 CCTGAAGATTATCCAGAAGAAGGGTGGAGGAAAGCAGTGGCGAAGCCTCCAAGTATACA
312 E E D P S G E T L S S E N K S S W L M T
1621 GAAGAGGATCCTTCCGGAGAAACACTGTCTTCAGAAAACAAGTCCAGCTGGTTAATGACG
332 S K P S A L A Q E T S L G A P E P L S G
1681 TCTAAGCCTAGTGCTCTAGCTCAAGAGACCTCTCTTGGTGGCCCTGAGCCTTTGTCTGGT
352 E Q L V G S P Q D K A A E A T N D Y E T
1741 GAACAGTTGGTTGGTTCTCCCCAGGATAAGGCGGCAGAGGCTACAAATGACTATGAGACT
372 L V K R G K E L K E C G K I Q E A L N C
1801 CTTGTAAAGCGTGGAAAAGAACTAAAAGAGTGTGGAAAAATCCAGGAGGCCCTAACTGC
392 L V K A L D I K S A D P E V M L L T L S
1861 TTAGTTAAAGCGCTTGACATAAAAAGTGCAGATCCTGAAGTTATGCTCTTGACTTTAAGT

Figure 2E-3

412 L Y K Q L N N N *
1921 TTGTATAAGCAACTTAATAACAATTGAgaatgtaacctgtttattgtattttaaagttaa
1981 actgaatatgaggaatttttgttcccataattggattctttgggaacatgaagcattca
2041 ggcttaaggcaagaaagatctcaaaaagcaacttctgccctgcaacgccccccactccat
2101 agtctggtattctgagcactagcttaatatcttctcacttgaatattcttatatttttagg
2161 catattctataaaatttaactgtgttgtttcttggaaagttttgtaaaattattctggtca
2221 ttcttaattttactctgaaagtgatcatctttgtatataacagttcagataagaaaatta
2281 aagttacttttctcaaaaaaaaaaaaaaaaaa

Figure 2F. The cDNA (SEQ ID. NO. : 10) and amino acid sequence (SEQ ID. NO. : 11) of 273P4B7 v.11. The start methionine is underlined. The open reading frame extends from nucleic acid 114-1373 including the stop codon.

1 ggcacgaggccaccttgcaagatggtaaaggtacaggtagtgtgactctatagctactt
1 M E K
61 taccaaaggggtttggaagtgtagaagaactttgtactaactcttcattgggaATGGAAA
4 S F A T K N E A V Q K E T L Q E G P K Q
121 AAAGCTTTGCAACTAAAAATGAAGCTGTACAAAAAGAGACATTACAAGAGGGGCCCTAAGC
24 E A L Q E D P L E S F N Y V L S K S T K
181 AAGAGGCACTGCAAGAGGATCCTCTGGAAAGTTTTAATTATGTACTTAGCAAATCAACCA
44 A D I G P N L D Q L K D D E I L R H C N
241 AAGCTGATATTGGGCCAAATTTAGATCAACTAAAGGATGATGAGATTTTACGTCATTGCA
64 P W P I I S I T N E S Q N A E S N V S I
301 ATCCTTGGCCCATTATTTCCATAACAAATGAAAGTCAAAATGCAGAATCAAATGTATCCA
84 I E I A D D L S A S H S A L Q D A Q A S
361 TTATTGAAATAGCTGATGACCTTTCAGCATCCCATAGTGCCTGCAGGATGCTCAAGCAA
104 E A K L E E E P S A S S P Q Y A C D F N
421 GTGAGGCCAAGTTGGAAGAGGAACCTTCAGCATCTTCACCACAGTATGCATGTGATTTCA
124 L F L E D S A D N R Q N F S S Q S L E H
481 ATCTTTTCTTGGAAGACTCAGCAGACAACAGACAAAATTTTCCAGTCAGTCTTTAGAGC
144 V E K E N S L C G S A P N S R A G F V H
541 ATGTTGAGAAAGAAAATAGCTTGTGTGGCTCTGCACCTAATTCAGAGCAGGGTTTGTGC
164 S K T C L S W E F S E K D D E P E E V V
601 ATAGCAAAACATGTCTCAGTTGGGAGTTTTCTGAGAAAGACGATGAACCAGAAGAAGTAG
184 V K A K I R S K A R R I V S D G E D E D
661 TAGTTAAAGCAAAATCAGAAGTAAAGCTAGAAGGATTGTTTCAGATGGCGAAGATGAAG
204 D S F K D T S S I N P F N T S L F Q F S
721 ATGATTCTTTTAAAGATACCTCAAGCATAAATCCATTCAACACATCTCTCTTCAATTCT
224 S V K Q F D A S T P K N D I S P P G R F
781 CATCTGTGAAACAATTTGATGCTTCAACTCCCAAAATGACATCAGTCCACCAGGAAGGT

Figure 2F-2

244 F S S Q I P S S V N K S M N S R R S L A
841 TCTTTTCATCTCAAATACCCAGTAGTGTAATAAGTCTATGAACTCTAGAAGATCTCTGG
264 S R R S L I N M V L D H V E D M E E R L
901 CTTCTAGGAGGTCTCTTATTAATATGGTTTTAGACCACGTGGAGGACATGGAGGAAAGAC
284 D D S S E A K G P E D Y P E E G V E E S
961 TTGACGACAGCAGTGAAGCAAAGGGTCCTGAAGATTATCCAGAAGAAGGGGTGGAGGAAA
304 S G E A S K Y T E E D P S G E T L S S E
1021 GCAGTGGCGAAGCCTCCAAGTATACAGAAGAGGATCCTTCCGGAGAAACACTGTCTTCAG
324 N K S S W L M T S K P S A L A Q E T S L
1081 AAAACAAGTCCAGCTGGTTAATGACGTCTAAGCCTAGTGCTCTAGCTCAAGAGACCTCTC
344 G A P E P L S G E Q L V G S P Q D K A A
1141 TTGGTGCCCCTGAGCCTTTGTCTGGTGAACAGTTGGTTGGTTCTCCCCAGGATAAGGCGG
364 E A T N D Y E T L V K R G K E L K E C G
1201 CAGAGGCTACAAATGACTATGAGACTCTTGTAAGCGTGGAAGAAGAACTAAAAGAGTGTG
384 K I Q E A L N C L V K A L D I K S A D P
1261 GAAAAATCCAGGAGGCCCTAAACTGCTTAGTTAAAGCGCTTGACATAAAAAGTGCAGATC
404 E V M L L T L S L Y K Q L N N N *
1321 CTGAAGTTATGCTCTTGACTTTAAGTTTGTATAAGCAACTTAATAACAATTGAgaatgta
1381 acctgtttattgtattttaagtgaactgaatatgagggaatttttgttcccataattg
1441 gattcttttggaacatgaagcattcaggcttaaggcaagaaagatctcaaaaagcaactt
1501 ctgccctgcaacgccccccactccatagtctggtattctgagcactagcttaatatatttct
1561 tcacttgaatatattcttatatttttaggcataattctataaatttaactgtgttggtttcttg
1621 aaagttttgtaaaattattctggtcattcttaattttactctgaaagtgatcatctttgt
1681 atataacagttcagataagaaaattaaagttactttttctc

Figure 3:

Figure 3A. Amino acid sequence of 273P4B7 v.1 (SEQ ID. NO. : 12). The 273P4B7 v.1 protein has 1250 amino acids.

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1 MEASRRFPEA EALSPEQAAH YLRYVKEAKE ATKNGDLEEA FKLFLNLAKEI FPNEKVLRSI
61 QKIQEAELEEL AEQGDDEFTD VCNSGLLLYR ELHNQLFEHQ KEGIAFLYSL YRDGRKGGIL
121 ADDMGLGKTV QIIAFLSGMF DASLVNHVLL IMPTNLINTW VKEFIKWTPG MRVKTFHGPS
181 KDERTRNLNR IQQRNGVIIT TYQMLINNWQ QLSSFRGQEF VWDYVILDEA HKIKTSSTKS
241 AICARAIPAS NRLLLTGTPI QNNLQELWSL FDFACQGSLL GTLKTFKMEY ENPITRAREK
301 DATPGEKALG FKISENLMAI IKPYFLRRTK EDVQKKKSSN PEARLNEKNP DVDAICEMPS
361 LSRKNDLIW IRLVPLQEEI YRKFSVLDHI KELLMETRSP LAELGVLLKKL CDHPRLLSAR
421 ACCLNLGTF SAQDGNEDG SPDVDHIDQV TDDTLMEESG KMIFLMDLLK RLRDEGHQTL
481 VFSQSRQILN IIERLLKNRH FKTLRIDGTV THLLEREKRI NLFQQNKDYS VELLTTQVGG
541 VGLTLTAATR VVIFDPSWNP ATDAQAVDRV YRIGQKENVV VYRLITCGTV EEKIYRRQVF
601 KDSLIRQTTG EKKNPFYFYS KQELRELFTI EDLQNSVTQL QLQSLHAAQR KSDIKLDEHI
661 AYLQSLGIAG ISDHDLMYTC DLSVKEELDV VEESHYIQQR VQKAQFLVEF ESQNKEFLME
721 QQRTRNEGAW LREPVEPSST KKKCPKLNKP QPQPSPLLST HHTQEEDISS KMASVVIDDL
781 PKEGEKQDLS SIKVNVTTLQ DGKGTGSADS IATLPKGFGS VEELCTNSSL GMEKSFATKN
841 EAVQKETLQE GPKQEALQED PLESFNYVLS KSTKADIGPN LDQLKDDEIL RHCNPWPIIS
901 ITNESQNAES NVSIIIEIADD LSASHSALQD AQASEAKLEE EPSASSPQYA CDFNLFLEDS
961 ADNRQNFSSQ SLEHVEKENS LCGSAPNSRA GFVHSKTCLS WEFSEKDDEP EEVVVKAKIR
1021 SKARRIVSDG EDEDDSFKDT SSINPFNTSL FQFSSVKQFD ASTPKNDISP PGRFFSSQIP
1081 SSVNKSMSNR RSLASRRSLI NMVLHDHVEDM EERLDDSSSEA KGPEDYPEEG VEESSGEASK
1141 YTEEDPSGET LSSENKSSWL MTSKPSALAQ ETSLGAPPEPL SGEQLVGSPQ DKAAEATNDY
1201 ETLVKRGKEL KECGKIQEAL NCLVKALDIK SADPEVMLLT LSLYKQLNNN

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Figure 3B. Amino acid sequence of 273P4B7 v.2 (SEQ ID. NO. : 13). The 273P4B7 v.2 protein has 1127 amino acids.

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1 MGLGKTVQII AFLSGMFDAS LVNHVLLIMP TNLINTWVKE FIKWTPGMRV KTFHGPSKDE
61 RTRNLNRIQQ RNGVIITTYQ MLINNWQQLS SFRGQEFVWD YVILDEAHKI KTSSTKSAIC
121 ARAIPASNRL LLTGTPIQNN LQELWSLFD FDFACQGSLLGT LKTFKMEYENP ITRAREKDAT
181 PGEKALGFKI SENLMAI IKPYFLRRTKEDV QKKKSSNPEA RLNEKNPDVD AICEMPSLSR
241 KNDLIWIRL VPLQEEIYRK FVSLDHIEL LMETRSP LAE LGVLKKLCDH PRLLSARACC
301 LLNLGTFSAQ DGNEDGSPD VDHIDQVTD TDDTLMEESGKM IFLMDLLKRLR DEGHQTLVFS
361 QSRQILNIE RLLKNRHFKT LRIDGTVTHL LEREKRLNLF QQNKDYSVFL LTTQVGGVGL
421 TLTAATRVVI FDPSPNPATD AQAVDRVYRI GQKENVVVYR LITCGTVEEK IYRRQVFKDS
481 LIRQTTGEKK NPFYFYSKQE LRELFTIEDL QNSVTQLQLQ SLHAAQRKSD IKLDEHIAYL
541 QSLGIAGISD HDLMYTCDSL VKEELDVVEE SHYIQQRVQK AQFLVEFESQ NKEFLMEQQR
601 TRNEGAWLRE PVFSPSTKKK CPKLNKPQPQ PSPLLSTHHT QEEDISSKMA SVVIDDLPEK
661 GEKQDLSSIK VNVTTLDQDG GTGSADSIAT LPKGFGSVVEE LCTNSSLGME KSFATKNEAV
721 QKETLQEGPK QEALQEDPLE SFNYVLSKST KADIGPNLDQ LKDDEILRHC NPWPIISITN

```

Figure 3B-2

```

781 ESQNAESNVS IIEIADDLSA SHSALQDAQA SEAKLEEEPS ASSPQYACDF NLFLEDSADN
841 RQNFSSQSLE HVEKENS LCG SAPNSRAGFV HSKTCLSWEF SEKDEPEEV VVKAKIRSKA
901 RRIVSDGEDE DDSFKDTSSI NPFNTSLFQF SSVKQFDAST PKNDISPPGR FFSSQIPSSV
961 NKSMNSRRSL ASRRSLINMV LDHVEDMEER LDDSSEAKGP EDYPEEGVEE SSGEASKYTE
1021 EDPSGETLSS ENKSSWLMTS KPSALAQETS LGAPEPLSGE QLVGSPQDKA AEATNDYETL
1081 VKRGKELKEC GKIQEALNCL VKALDIKSAD PEVMLLTLSL YKQLNNN

```

Figure 3C. Amino acid sequence of 273P4B7 v.4 (SEQ ID. NO. : 14). The 273P4B7 v.4 protein has 1250 amino acids.

```

1 MEASRRFPEA EALSPEQAAH YLRYVKEAKE ATKNGDLEEA FKLFLNLAKEI FPNEKVLRSRI
61 QKIQEAL EEL AEQGDDEFTD VCNSG LLLYR ELHNQLFEHQ KEGIAFLYSL YRDGRKGGIL
121 ADDMGLGKTV QIIAFLSGMF DASLVNHVLL IMPTNLINTW VKEFIKWTPG MGVKTFHGPS
181 KDERTRNLNR IQQRNGVIIT TYQMLINN WQ QLSSFRGQEF VWDYVILDEA HKIKTSSTKS
241 AICARAIPAS NRLLLTGTPI QNNLQELWSL FDFACQGSLL GTLKTFKMEY ENPITRAREK
301 DATPGEKALG FKISENLMAI IKPYFLRRTK EDVQKKKSSN PEARLNEKNP DVDAICEMPS
361 LSRKNDLIW IRLVPLQEEI YRKFSVLDHI KELLMETRSP LAELGV LKKL CDHPRLLSAR
421 ACCLNLGTF SAQDGN EGED SPDVDHIDQV TDDTLMEESG KMIFLMDLLK RLRDEGHQTL
481 VFSQSRQILN IIERLLKNRH FKTLRIDGT V THLLEREKRI NLFQQNKDYS VELLTTQVGG
541 VGLTLTAATR VVIFDPSWNP ATDAQAVDRV YRIGQKENVV VYRLITCGTV EEKIYRRQVF
601 KDSLIRQT TG EKKNPFRYFS KQELRELFTI EDLQNSVTQL QLQSLHAAQR KSDIKLDEHI
661 AYLQSLGIAG ISDHDLMYTC DLSVKEELDV VEESHYIQQR VQKAQFLVEF ESQNKEFLME
721 QQRTNEGAW LREPVPFSST KKKCPKLNKP QPQPSPLLST HHTQEEDISS KMASVVIDDL
781 PKEGEKQDLS SIKVNVTTLQ DGKGTGSADS IATLPKGFGS VEELCTNSSL GMEKSFATKN
841 EAVQKETLQE GPKQEALQED PLESFNYVLS KSTKADIGPN LDQLKDDEIL RHCNPWPIIS
901 ITNESQNAES NVSII EIAADD LSASHSALQD AQASEAKLEE EPSASSPQYA CDFNLFLEDS
961 ADN RQNFSSQ SLEHVEKENS LCGSAPNSRA GFVHSKTCLS WEFSEKDEP EEVVVKAKIR
1021 SKARRIVSDG EDEDDSFKDT SSINPFNTSL FQFSSVKQFD ASTPKNDISP PGRFFSSQIP
1081 SSVNKSMNSR RSLASRRSLI NMVLDHVEDM EERLDDSSEA KGPEDYPEEG VEESSGEASK
1141 YTEEDPSGET LSSENKSSWL MTSKPSALAQ ETS LGAPEPL SGEQLVGSPQ DKAAEATNDY
1201 ETLVKRGKEL KECGKIQEAL NCLVKALDIK SADPEVMLLT LSLYKQLNNN

```

Figure 3D. Amino acid sequence of 273P4B7 v.5 (SEQ ID. NO. : 15). The 273P4B7 v.5 protein has 1250 amino acids.

```

1 MEASRRFPEA EALSPEQAAH YLRYVKEAKE ATKNGDLEEA FKLFLNLAKEI FPNEKVLRSRI
61 QKIQEAL EEL AEQGDDEFTD VCNSG LLLYR ELHNQLFEHQ KEGIAFLYSL YRDGRKGGIL
121 ADDMGLGKTV QIIAFLSGMF DASLVNHVLL IMPTNLINTW VKEFIKWTPG MRVKTFHGPS
181 KDERTRNLNR IQQRNGVIIT TYQMLINN WQ QLSSFRGQEF VWDYVILDEA HKIKTSSTKS
241 AICARAIPAS NRLLLTGTPI QNNLQELWSL FDFACQGSLL GTLKTFKMEY ENPITRAREK
301 DATPGEKALG FKISENLMAI IKPYFLRRTK EDVQKKKSSN PEARLNEKNP DVDAICEMPS

```

Figure 3D-2

```

361 LSRRLNDLIIW IRLVPLQEEI YRKFSVSLDHI KELLMETRSP LAELGVLKKL CDHPRLLSAR
421 ACCLLNLTGF SAQDGNEDG SPDVDHIDQV TDDTLMEESG KMIFLMDLLK RLRDEGHQTL
481 VFSQSRQILN IIERLLKNRH FKTLRIDGTV THLLEREKRI NLFQQNKDYS VFLLTQVGG
541 VGLTLTAATR VVIFDPSWNP ATDAQAVDRV YRIGQKENVV VYRLITCGTV EEKIYRRQVF
601 KDSLIRQTTG EKKNPFRYFS KQELRELFTI EDLQNSVTQL QLQSLHAAQR KSDIKLDEHI
661 AYLQSLGIAG ISDHDLMYTC DLSVKEELDV VEESHYIQQR VQKAQFLVEF ESQNKEFLME
721 QQRTTRNEGAW LREPVFPSST KKKCPKLNKP QPQPSPLLST HHTQEEDISS KMASVVIDDL
781 PKEGEKQDLS SIKVNVTTLQ DGKGTGSADS IATLPKGFGS VEELCTNSSL GMEKSFATKN
841 EAVQKETLQE GPKQEALQED PLESFNYVLS KSTKADIGPN LDQLKDDEIL RHCNPWPIIS
901 ITNESQNAES NVSIIEIADD LSASHSALQD AQASEAKLEE EPSASSPQYA CDFNLFLEDS
961 ADNRRQNFSSQ SLEHVEKENS LCGSAPNSRA GFVHSTCLTS WEFSEKDEP EEVVVKAKIR
1021 SKARRIVSDG EDEDDSFKDT SSINPFNTSL FQFSSVKQFD ASTPKNDISP PGRFFSSQIP
1081 SSVNKSMSNR RSLASRRSLI NMVLHDVEDM EERLDDSSSEA KGPEDYPEEG VEESGEASK
1141 YTEEDPSGET LSENKSSWL MTSKPSALAQ ETSLGAPEPL SGEQLVGSPQ DKAEEATNDY
1201 ETLVKRGKEL KECGKIQEAL NCLVKALDIK SADPEVMLLT LSLYKQLNNN

```

Figure 3E. Amino acid sequence of 273P4B7 v.6 (SEQ ID. NO. : 16). The 273P4B7 v.6 protein has 1250 amino acids.

```

1 MEASRRFPEA EALSPEQAAH YLRYVKEAKE ATKNGDLEEA FKLFNLAKDI FPNEKVLRSI
61 QKIQEAELEL AEQGDDEFTD VCNSGLLLYR ELHNQLFEHQ KEGIAFLYSL YRDGRKGGL
121 ADDMGLGKTQ QIIAFLSGMF DASLVNHVLL IMPTNLINTW VKEFIKWTPG MRVKTFFHGPS
181 KDERTRNLNR IQQRNGVIIT TYQMLINWQ QLSSFRGQEF VWDYVILDEA HKIKTSSTKS
241 AICARAIPAS NRLLLTGTP I QNNLQELWSL FDFACQGSLL GTLKTFKMEY ENPITRAREK
301 DATPGEKALG FKISENLMAI IKPYFLRRTK EDVQKKKSSN PEARLNEKNP DVDAICEMPS
361 LSRKNDLIIW IRLVPLQEEI YRKFSVSLDHI KELLMETRSP LAELGVLKKL CDHPRLLSAR
421 ACCLLNLTGF SAQDGNEDG SPDVDHIDQV TDDTLMEESG KMIFLMDLLK RLRDEGHQTL
481 VFSQSRQILN IIERLLKNRH FKTLRIDGTV THLLEREKRI NLFQQNKDYS VFLLTQVGG
541 VGLTLTAATR VVIFDPSWNP ATDAQAVDRV YRIGQKENVV VYRLITCGTV EEKIYRRQVF
601 KDSLIRQTTG EKKNPFRYFS KQELRELFTI EDLQNSVTQL QLQSLHAAQR KSDIKLDEHI
661 AYLQSLGIAG ISDHDLMYTC DLSVKEELDV VEESHYIQQR VQKAQFLVEF ESQNKEFLME
721 QQRTTRNEGAW LREPVFPSST KKKCPKLNKP QPQPSPLLST HHTQEEDISS KMASVVIDDL
781 PKEGEKQDLS SIKVNVTTLQ DGKGTGSADS IATLPKGFGS VEELCTNSSL GMEKSFATKN
841 EAVQKETLQE GPKQEALQED PLESFNYVLS KSTKADIGPN LDQLKDDEVL RHCNPWPIIS
901 ITNESQNAES NVSIIEIADD LSASHSALQD AQASEAKLEE EPSASSPQYA CDFNLFLEDS
961 ADNRRQNFSSQ SLEHVEKENS LCGSAPNSRA GFVHSTCLTS WEFSEKDEP EEVVVKAKIR
1021 SKARRIVSDG EDEDDSFKDT SSINPFNTSL FQFSSVKQFD ASTPKNDISP PGRFFSSQIP
1081 SSVNKSMSNR RSLASRRSLI NMVLHDVEDM EERLDDSSSEA KGPEDYPEEG VEESGEASK
1141 YTEEDPSGET LSENKSSWL MTSKPSALAQ ETSLGAPEPL SGEQLVGSPQ DKAEEATNDY
1201 ETLVKRGKEL KECGKIQEAL NCLVKALDIK SADPEVMLLT LSLYKQLNNN

```

Figure 3F. Amino acid sequence of 273P4B7 v.9 (SEQ ID. NO. : 17). The 273P4B7 v.9 protein has 1106 amino acids.

```

1 MNHVLLIMPT NLINTWVKEF IKWTPGMGVK TFHGPSKDER TRNLNRIQQR NGVIITTYQM
61 LINNWQQLSS FRGQEFVWDY VILDEAHKIK TSSTKSAICA RAIPASNRLT LTGTPIQNNL
121 QELWSLFDFA CQGSLLGTLK TFKMEYENPI TRAREKDATP GEKALGFKIS ENLMAIIKPY
181 FLRRTKEDVQ KKKSSNPEAR LNEKNPDVDA ICEMPSLSRK NDLIWIRLV PLQEEIYRKF
241 VSLDHIKELL METRSPLAEL GVLKKLCDHP RLLSARACCL LNLGTFSAQD GNEGEDSPDV
301 DHIDQVTDDT LMEESGKMIF LMDLLKRLRD EGHQTLVFSQ SRQILNIER LLKNRHFKTL
361 RIDGTVTHLL EREKRINLFQ QNKDYSVFLT TTQVGGVGLT LTAATRNVIF DPSWNPATDA
421 QAVDRVYRIG QKENVVVYRL ITCGTVEEKI YRRQVFKDSL IRQTTGEKKK PFRYFSKQEL
481 RELFTIEDLQ NSVTQLQLQS LHAAQRKSDI KLDEHIAYLQ SLGIAGISDH DLMYTCDSLVS
541 KEELDVEES HYIQQRVQKA QFLVEFESQN KEFLMEQQRT RNEGAWLREP VFPSSTKKKC
601 PKLNKPQPP SPLSTHTQ EEDISSKMAS VVIDDLPEKG EKQDLSSIKV NVTTLQDGKG
661 TGSADSIATL PKGFGSVEEL CTNSSLGMEK SFATKNEAVQ KETLQEGPKQ EALQEDPLES
721 FNYVLSKSTK ADIGPNLDQL KDDEVLRCN PWPIISITNE SQNAESNVS I EIADDLSAS
781 HSALQDAQAS EAKLEEPSA SSPQYACDFN LFLEDSADNR QNFSSQSLEH VEKENS LCGS
841 APNSRAGFVH SKTCLSWEF EKDDEPEEV VKAKIRSKAR RIVSDGEDED DSFKDTSSIN
901 PFNTSLFQFS SVKQFDASTP KNDISPPGRF FSSQIPSSVN KSMNSRRSLA SRRSLINMVL
961 DHVEDMEERL DDSSEAKGPE DYPEGVEES SGEASKYTEE DPSGETLSSE NKSSWLMTSK
1021 PSALAQETSL GAPEPLSGEQ LVGSPQDKAA EATNDYETLV KRGKELKECG KIQEALNCLV
1081 KALDIKSADP EVMLLTSLY KQLNNN

```

Figure 3G. Amino acid sequence of 273P4B7 v.10 (SEQ ID. NO. : 18). The 273P4B7 v.10 protein has 419 amino acids.

```

1 MEKSFATKNE AVQKETLQEG PKQEALQEDP LESFNYVLSK STKADIGPNL DQLKDDEILR
61 HCNPWPIISI TNESQNAESN VSIIEIADDL SASHALQDA QASEAKLEEE PSASSPQYAC
121 DFNLFLEDSA DNRQNFSSQS LEHVEKENSL CGSAPNSKAG FVHSKTCLSW EFSEKDDEPE
181 EVVVKAKIRS KARRIVSDGE DEDDSFKDTS SINPFNTSLF QFSSVKQFDA STPKNDISPP
241 GRFFSSQIPS SVNKSMNSRR SLASRRSLIN MVLHDHVEDME ERLDSSSEAK GPEDYPEEGV
301 EESSGEASKY TEEDPSGETL SSENKSSWLM TSKPSALAE TSLGAPEPLS GEQLVGSPQD
361 KAAEATNDYE TLVKRGKELK ECGKIQEALN CLVKALDIKS ADPEVMLLT SLYKQLNNN

```

Figure 3H. Amino acid sequence of 273P4B7 v.11 (SEQ ID. NO. : 19). The 273P4B7 v.11 protein has 419 amino acids.

```

1 MEKSFATKNE AVQKETLQEG PKQEALQEDP LESFNYVLSK STKADIGPNL DQLKDDEILR
61 HCNPWPIISI TNESQNAESN VSIIEIADDL SASHALQDA QASEAKLEEE PSASSPQYAC
121 DFNLFLEDSA DNRQNFSSQS LEHVEKENSL CGSAPNSRAG FVHSKTCLSW EFSEKDDEPE
181 EVVVKAKIRS KARRIVSDGE DEDDSFKDTS SINPFNTSLF QFSSVKQFDA STPKNDISPP
241 GRFFSSQIPS SVNKSMNSRR SLASRRSLIN MVLHDHVEDME ERLDSSSEAK GPEDYPEEGV
301 EESSGEASKY TEEDPSGETL SSENKSSWLM TSKPSALAE TSLGAPEPLS GEQLVGSPQD
361 KAAEATNDYE TLVKRGKELK ECGKIQEALN CLVKALDIKS ADPEVMLLT SLYKQLNNN

```

Figure 4: Alignment of 273P4B7 with known homologs

Figure 4A: Alignment of 273P4B7 (SEQ ID NO: 20) with human un-named protein (gi|22760345) (SEQ ID NO: 21)
Identities = 1103/1106 (99%), Positives = 1105/1106 (99%)

```

Query: 145  VNHVLLIMPTNLINTWVKEFIKWTPGMRVKT FHGPSKDERTNRLNRIQQRNGVIITTYQM 204
           +NHVLLIMPTNLINTWVKEFIKWTPGM  VKTFHGPSKDERTNRLNRIQQRNGVIITTYQM
Sbjct: 1     MNHVLLIMPTNLINTWVKEFIKWTPGMRVKT FHGPSKDERTNRLNRIQQRNGVIITTYQM 60

Query: 205  LINNWQQLSSFRGQEFVWDYVILDEAHKIKTSSTKSAICARAIPASNRLLLTGTPIQNNL 264
           LINNWQQLSSFRGQEFVWDYVILDEAHKIKTSSTKSAICARAIPASNRLLLTGTPIQNNL
Sbjct: 61    LINNWQQLSSFRGQEFVWDYVILDEAHKIKTSSTKSAICARAIPASNRLLLTGTPIQNNL 120

Query: 265  QELWSLDFDFACQGSLLGLTKTFKMEYENPITRAREKDATPGEKALGFKISENLMIAIKPY 324
           QELWSLDFDFACQGSLLGLTKTFKMEYENPITRAREKDATPGEKALGFKISENLMIAIKPY
Sbjct: 121   QELWSLDFDFACQGSLLGLTKTFKMEYENPITRAREKDATPGEKALGFKISENLMIAIKPY 180

Query: 325  FLRRTKEDVQKKKSSNPEARLNEKNPDVDAICEMPSSLRKNDLIIWIRLVPLQE EIYRKF 384
           FLRRTKEDVQKKKSSNPEARLNEKNPDVDAICEMPSSLRKNDLIIWIRLVPLQE EIYRKF
Sbjct: 181   FLRRTKEDVQKKKSSNPEARLNEKNPDVDAICEMPSSLRKNDLIIWIRLVPLQE EIYRKF 240

Query: 385  VSLDHKELLMETRSPLAELGVLLKCLDHPRLLSARACCLLNLTGTFSAQDGNEGEDSPDV 444
           VSLDHKELLMETRSPLAELGVLLKCLDHPRLLSARACCLLNLTGTFSAQDGNEGEDSPDV
Sbjct: 241   VSLDHKELLMETRSPLAELGVLLKCLDHPRLLSARACCLLNLTGTFSAQDGNEGEDSPDV 300

Query: 445  DHIDQVTD DTLMEESGKMI FLMDLLKRLRDEGHQTLVFSQSRQILNIIERLLKNRHFCTL 504
           DHIDQVTD DTLMEESGKMI FLMDLLKRLRDEGHQTLVFSQSRQILNIIERLLKNRHFCTL
Sbjct: 301   DHIDQVTD DTLMEESGKMI FLMDLLKRLRDEGHQTLVFSQSRQILNIIERLLKNRHFCTL 360

Query: 505  RIDGTVTHLLEREKRINLFQQNKDYSVFLLTQVGGVGLTLTAATRVVIFDPSWNPATDA 564
           RIDGTVTHLLEREKRINLFQQNKDYSVFLLTQVGGVGLTLTAATRVVIFDPSWNPATDA
Sbjct: 361   RIDGTVTHLLEREKRINLFQQNKDYSVFLLTQVGGVGLTLTAATRVVIFDPSWNPATDA 420

Query: 565  QAVDRVYRIGQKENVVVYRLITCGTVEEKIYRRQVFKDSLIRQTTGEKKNPFYFYSKQEL 624
           QAVDRVYRIGQKENVVVYRLITCGTVEEKIYRRQVFKDSLIRQTTGEKKNPFYFYSKQEL
Sbjct: 421   QAVDRVYRIGQKENVVVYRLITCGTVEEKIYRRQVFKDSLIRQTTGEKKNPFYFYSKQEL 480

Query: 625  RELFTIEDLQNSVTQLQLQSLHAAQRKSDIKLDEHIAYLQSLGIAGISDHDLMYTCDLSV 684
           RELFTIEDLQNSVTQLQLQSLHAAQRKSDIKLDEHIAYLQSLGIAGISDHDLMYTCDLSV
Sbjct: 481   RELFTIEDLQNSVTQLQLQSLHAAQRKSDIKLDEHIAYLQSLGIAGISDHDLMYTCDLSV 540

Query: 685  KEELDVVEESHYIQQRVQKAQFLVEFESQNKEFLMEQQRTRNEGAWLREPVPFSPSTK KKC 744
           KEELDVVEESHYIQQRVQKAQFLVEFESQNKEFLMEQQRTRNEGAWLREPVPFSPSTK KKC
Sbjct: 541   KEELDVVEESHYIQQRVQKAQFLVEFESQNKEFLMEQQRTRNEGAWLREPVPFSPSTK KKC 600

Query: 745  PKLNKPQPQPSPLLSTHHTQEEDISSKMASVVIDDLPEKEGEKQDLSSIKVNVTTLQDGKG 804
           PKLNKPQPQPSPLLSTHHTQEEDISSKMASVVIDDLPEKEGEKQDLSSIKVNVTTLQDGKG
Sbjct: 601   PKLNKPQPQPSPLLSTHHTQEEDISSKMASVVIDDLPEKEGEKQDLSSIKVNVTTLQDGKG 660

Query: 805  TGSADSIATLPKGFGSVEELCTNSSLGMEKSFATKNEAVQKETLQEGPKQEALQEDPLES 864
           TGSADSIATLPKGFGSVEELCTNSSLGMEKSFATKNEAVQKETLQEGPKQEALQEDPLES
Sbjct: 661   TGSADSIATLPKGFGSVEELCTNSSLGMEKSFATKNEAVQKETLQEGPKQEALQEDPLES 720

Query: 865  FNYVLSKSTKADIGPNLDQLKDDEILRHCPWPPIISITNESQNAESNVSIIEIADDL SAS 924
           FNYVLSKSTKADIGPNLDQLKDDE+LRHCPWPPIISITNESQNAESNVSIIEIADDL SAS
Sbjct: 721   FNYVLSKSTKADIGPNLDQLKDDEVLRHCPWPPIISITNESQNAESNVSIIEIADDL SAS 780

Query: 925  HSAHQDAQASEAKLEEEPSASSPQYACDFNLFLFEDSADNRQNFSSQSLEHVEKENSLCGS 984
           HSAHQDAQASEAKLEEEPSASSPQYACDFNLFLFEDSADNRQNFSSQSLEHVEKENSLCGS
Sbjct: 781   HSAHQDAQASEAKLEEEPSASSPQYACDFNLFLFEDSADNRQNFSSQSLEHVEKENSLCGS 840

Query: 985  APNSRAGFVHSKTCLSWEFSEKDDEPEEVVVKAKIRSKARRIVSDGEDEDDSFKDTSSIN 1044
           APNSRAGFVHSKTCLSWEFSEKDDEPEEVVVKAKIRSKARRIVSDGEDEDDSFKDTSSIN
Sbjct: 841   APNSRAGFVHSKTCLSWEFSEKDDEPEEVVVKAKIRSKARRIVSDGEDEDDSFKDTSSIN 900

Query: 1045 PFNTSLFQFSSVKQFDASTPKNDISPPGRFFSSQIPSSVNKSMNSRRSLASRRSLINMVL 1104
           PFNTSLFQFSSVKQFDASTPKNDISPPGRFFSSQIPSSVNKSMNSRRSLASRRSLINMVL
Sbjct: 901   PFNTSLFQFSSVKQFDASTPKNDISPPGRFFSSQIPSSVNKSMNSRRSLASRRSLINMVL 960

```

Figure 4A-2

Query: 1105 DHVEDMEERLDDSSSEAKGPEDYPEEGVEESSGEASKYTEEDPSGETLSSSENKSSWLMTSK 1164
 DHVEDMEERLDDSSSEAKGPEDYPEEGVEESSGEASKYTEEDPSGETLSSSENKSSWLMTSK
 Sbjct: 961 DHVEDMEERLDDSSSEAKGPEDYPEEGVEESSGEASKYTEEDPSGETLSSSENKSSWLMTSK 1020

Query: 1165 PSALAQETSLGAPEPLSGEQLVGSPQDKAAEATNDYETLVKRGKELKECGKIQEALNCLV 1224
 PSALAQETSLGAPEPLSGEQLVGSPQDKAAEATNDYETLVKRGKELKECGKIQEALNCLV
 Sbjct: 1021 PSALAQETSLGAPEPLSGEQLVGSPQDKAAEATNDYETLVKRGKELKECGKIQEALNCLV 1080

Query: 1225 KALDIKSADPEVMLLTLSLYKQLNNN 1250
 KALDIKSADPEVMLLTLSLYKQLNNN
 Sbjct: 1081 KALDIKSADPEVMLLTLSLYKQLNNN 1106

Figure 4B: Alignment of 273P4B7 (SEQ ID NO: 22) with human BJ-HCC-15 tumor antigen (gi|22002580) (SEQ ID NO: 23) Identities = 418/419 (99%), Positives = 419/419 (100%)

Query: 832 MEKSFATKNEAVQKETLQEGPKQEALQEDPLESFNYVLSKSTKADIGPNLDQLKDEILR 891
 MEKSFATKNEAVQKETLQEGPKQEALQEDPLESFNYVLSKSTKADIGPNLDQLKDEILR
 Sbjct: 1 MEKSFATKNEAVQKETLQEGPKQEALQEDPLESFNYVLSKSTKADIGPNLDQLKDEILR 60

Query: 892 HCNPWPIISITNESQNAESNVSIIEIADDLASHSALQDAQASEAKLEEEPSASSPQYAC 951
 HCNPWPIISITNESQNAESNVSIIEIADDLASHSALQDAQASEAKLEEEPSASSPQYAC
 Sbjct: 61 HCNPWPIISITNESQNAESNVSIIEIADDLASHSALQDAQASEAKLEEEPSASSPQYAC 120

Query: 952 DFNLFLEDSADNRQNFSSQSLEHVEKENS LCGSAPNSRAGFVHSKTCLSWEFSEKDDEPE 1011
 DFNLFLEDSADNRQNFSSQSLEHVEKENS LCGSAPNS+AGFVHSKTCLSWEFSEKDDEPE
 Sbjct: 121 DFNLFLEDSADNRQNFSSQSLEHVEKENS LCGSAPNSKAGFVHSKTCLSWEFSEKDDEPE 180

Query: 1012 EVVVKAKIRSKARRIVSDGEDEDDSFKDTSSINPFNTSLFQFSSVKQFDASTPKNDISPP 1071
 EVVVKAKIRSKARRIVSDGEDEDDSFKDTSSINPFNTSLFQFSSVKQFDASTPKNDISPP
 Sbjct: 181 EVVVKAKIRSKARRIVSDGEDEDDSFKDTSSINPFNTSLFQFSSVKQFDASTPKNDISPP 240

Query: 1072 GRFFSSQIPSSVNKSMNSRRSLASRRSLINMVLVDHVEDMEERLDDSSSEAKGPEDYPEEGV 1131
 GRFFSSQIPSSVNKSMNSRRSLASRRSLINMVLVDHVEDMEERLDDSSSEAKGPEDYPEEGV
 Sbjct: 241 GRFFSSQIPSSVNKSMNSRRSLASRRSLINMVLVDHVEDMEERLDDSSSEAKGPEDYPEEGV 300

Query: 1132 EESSGEASKYTEEDPSGETLSSSENKSSWLMTSKPSALAQETSLGAPEPLSGEQLVGSPQD 1191
 EESSGEASKYTEEDPSGETLSSSENKSSWLMTSKPSALAQETSLGAPEPLSGEQLVGSPQD
 Sbjct: 301 EESSGEASKYTEEDPSGETLSSSENKSSWLMTSKPSALAQETSLGAPEPLSGEQLVGSPQD 360

Query: 1192 KAAEATNDYETLVKRGKELKECGKIQEALNCLVKALDIKSADPEVMLLTLSLYKQLNNN 1250
 KAAEATNDYETLVKRGKELKECGKIQEALNCLVKALDIKSADPEVMLLTLSLYKQLNNN
 Sbjct: 361 KAAEATNDYETLVKRGKELKECGKIQEALNCLVKALDIKSADPEVMLLTLSLYKQLNNN 419

Figure 4C: Alignment of 273P4B7 (SEQ ID NO: 24) with Mouse Protein (gi|27706852) (SEQ ID NO: 25) Identities = 912/1256 (72%), Positives = 1026/1256 (81%), Gaps = 35/1256 (2%)

Query: 1 MEASRRFPEAEALSPEQAAHYLVYVKEAKEATKNGDLEEAFLKFNLAKDIFPNEKVLSRI 60
 MEAS+ E LSP+ A YLRY +EAKA KNGDLEEA KLFNLAKDIFP +KV+SRI
 Sbjct: 1 MEASQGLAEVGTLSPLAESYLRYSQEAKAAKNGDLEEAFLKFNLAKDIFPTKKVISRI 60

Query: 61 QKIQEALAELEAQGDDEFTDVCNSGLLLYRELHNQLFEHQKEGIAFLYSLYRDGRKGGIL 120
 QK+QEALE+LAE+ DDEFTDVCNSGLLLYREL+ +LFEHQKEGIAFLYSLY++GRKGGIL
 Sbjct: 61 QKLQEALEQLAEEDDEFTDVCNSGLLLYRELYEKLFEHQKEGIAFLYSLYKNGRKGIL 120

Query: 121 ADDMGLGKTVQIIAFLSGMFDASLVNHVLLIMPTNLINTWVKEFIKWTPGMRVKTFHGPS 180
 ADDMGLGKTVQIIAFLSGMFDASLVNHVLLIMPTNLINTWVKEF KWTPGMRVKTFHG S
 Sbjct: 121 ADDMGLGKTVQIIAFLSGMFDASLVNHVLLIMPTNLINTWVKEFAKWTPGMRVKTFHGSS 180

Query: 181 KDERTRNLNRIQQRNGVIITTYQMLNNWQQLSSFRGQEFVWDYVILDEAHKIKTSSTKS 240
 K+ER RNL RIQQRNGV+ITTYQML+NNWQQL+SF GQ FVWDYVILDEAHKIK++STKS
 Sbjct: 181 KNERIRNLTRIQRNGVVITTYQMLNNWQQLASFNQAFVWDYVILDEAHKIKSASTKS 240

Query: 241 AICARAIPASNRLLLTGTFPIQNNLQELWSLFDACQGSLLGLTKTFKMEYENPITRAREK 300

Figure 4C-2

Sbjct: 241 A+CARA+PASNRLLLTGTPIQNNLQELWSLDFACQGSLLGTLKTFKMEYENPI RAREK
AVCARAVPASNRLLLTGTPIQNNLQELWSLDFACQGSLLGTLKTFKMEYENPIIRAREK 300

Query: 301 DATPGEKALGFKISENLMIAIKPYFLRRTKEDVQKKSSNPEARLNEKNPDVDAICEMPS 360
DATPGEKALGFK+SENLM IIKPYFLRRTKE+V KK+ PE R EKN V+ ICEM S

Sbjct: 301 DATPGEKALGFKMSENLMIEIKPYFLRRTKEEVHMKKADKPEVRPGEKNSGVEDICEMLS 360

Query: 361 LSRKNDLIWIRLVPLQEEIYRKFSVSLDHKEKLLMETRSPLAELGVLKKLCDHPRLLSAR 420
L+RKNDLI+WIRLVPLQEEIYRKFSVSLDHKEKLLMETRSPLAELGVLKKLCDHPRLLSAR

Sbjct: 361 LTRKNDLIVWIRLVPLQEEIYRKFSVSLDHKEKLLMETRSPLAELGVLKKLCDHPRLLSAR 420

Query: 421 ACCLNLG--TFSAQDGNEDGSDPDVDHIDQVTDLMEESGKMIFLMDLLKRLRDEGHQ 478
AC LLNLG TFSA+D NE ED+ ++ ID ++D+ LM+ESGKMIFLM LL+RL+DEGHQ

Sbjct: 421 ACHLLNLGTVTFSAEDENEQEDASNMGSIDHLSDNALMQESGKMIFLMALLERLQDEGHQ 480

Query: 479 TLVFSQSRQILNIIERLLKNRHFKTLRIDGTVTHLLEREKRINLFQQNKDYSVFLTTQV 538
TLVFSQSRQILNIIERLLKN+HFKTLRIDGTVTHL EREKRI LFQQNK+YSVFLTTQV

Sbjct: 481 TLVFSQSRQILNIIERLLKNKHFKTLRIDGTVTHLWEREKRIQLFQQNKEYSVFLTTQV 540

Query: 539 GGVGLTLTAATRVVIFDPSWNPATDAQAVDRVYRIGQKENVVYRLITCGTVEEKIYRRQ 598
GGVGLTLTAA+RVVIFDPSWNPATDAQAVDRVYRIGQKENVVYRLITCGTVEEKIYRRQ

Sbjct: 541 GGVGLTLTAASRVVIFDPSWNPATDAQAVDRVYRIGQKENVVYRLITCGTVEEKIYRRQ 600

Query: 599 VFKDSLIRQTTGEKKNPFYFSKQELRELFTIEDLQNSVTQLQLQSLHAAQRKSDIKLDE 658
VFKDSLIRQTTG+KKNPFYF+KQEL+ELFT+ DL NS TQ+QLQ LHAQRKSD KLDE

Sbjct: 601 VFKDSLIRQTTGDKKNPFYFTKQELKELFTVGDLLNSATQMLQCLHAAQRKSDIKLDE 660

Query: 659 HIAYLQSLGIAGISDHDLMTCDLSVKEELDVEESHYIQRVQKAQFLVEFESQNKEFL 718
HIAYL SLGIAGISDHDLMTCDLSVKEELD++E++ YIQ RVQKAQFLVE ESQN

Sbjct: 661 HIAYLHSLGIAGISDHDLMTCDLSVKEELDMLEDAQYIQRVQKAQFLVESESQNT--- 717

Query: 719 MEQQRTNREGAWLREPVPFSSSTKKKCPKLNKPQPSPLLSTHHTQEEDISSKMASVVID 778
++R E WL+ FPS +KK NKQPQPS LL+ + TQ E ISS+MAS+ I

Sbjct: 718 --KERPSEEN-WLKAQEFPSQQRKKG---NKPQPQPSRLLA-NPTQVEAISSQMASISY 770

Query: 779 DLPKEGEKQDLSSIKVNVTTLDQDGK----GTGSADSIATLPKGFGSVEELCTNSSLGMEK 834
D E E Q+LS +VT+LQ + T A +IA+LP+G S+ + T+S L K

Sbjct: 771 DQSTSEFPQELSEAH-DVTSLQGDQHHFESTSDAGTIASLPQGAESIGGVWTDLSLSPAK 829

Query: 835 SFATKNEAVQKETLQEGPKQEQALQEDPLESFNYVLSKSTKADIGPNLDQLKODEILRHCN 894
FA NEAVQK LQ P QEAL E+ L SF+Y+ +S+KAD+ PNLD ++D +L H +

Sbjct: 830 GFAADNEAVQKNELQASPGQEALSEN-LGSFHYLPRQSSKADLEPNLD-VQDSVVLYHQS 887

Query: 895 WPPIISITNESQNAESNVSIIEIADDLASASHALQDAQASEAKLE--EEPSASSPQYACD 952
P NE+QN ESN +IEI+DDLAS SALQ AQA EA+LE ++P S PQY CD

Sbjct: 888 P-----TANENQNLESNEPMIEISDDLASPSALQGAQAMEAQLELKKDPLESPQYECD 942

Query: 953 FNLFLSDSADNRQNFSSQSLHVEKENS LCGSAPNSRAGFVHSKTCLSWEFSEKDDEPEE 1012
FNLFLSDSAD RQN SS+ LEHVEKENSL A NS H+ LS + S K DE E

Sbjct: 943 FNLFLSDSADTRQNLSSKFLHVEKENS LQRPAGNSGEESAHN---LSLSDSSNKIDESE 999

Query: 1013 VVVKAKIRSKARRIVSDGEDEDDSFKDTSSINPFNTSLFQFSSVKQFDASTPKNDISPPG 1072
V+ K ++KARRI+SD EDE+D+FKDTS+ N F+ S FSSVK FDASTP+ND +P

Sbjct: 1000 VIT-VKTKNKARRILSDDEDEEDAFKDTST-NSFSVSLTFSSVKHFDASTPQNDNSNPSR 1057

Query: 1073 RFFSSQIPSSVKNKSMNSRRSLASRRSLINMVLHDHVEDMEERLDDSSSEAKGPEDYPEEGVE 1132
RFFS +IP VN S++ RRLASRRSLIN+VLD +EDMEERLD SSE + + E+ E

Sbjct: 1058 RFFSPKIPDDVNTSLHPRRSLASRRSLINVLDDMEDMEERLDTSSSEEESEPELSEDSNE 1117

Query: 1133 ESSGEASKYTEEDPSGETLSSSENKSSWLMTSKPSALAQETSLGAPEPLSGEQLVGSPODK 1192
EA TEE SG TL+S NK S L S+P++ A ++S APEP S + L+ PQD

Sbjct: 1118 ----EAVACTEQRSGATLASGNKHSSLTESEPTSPAPQSSPCAPEPSSSDPLDPPQDP 1173

Query: 1193 AAEATNDYETLVKRGKELKECGKIQEALNCLVKALDIKSADPEVMLLTLSLYKQLN 1248
A EA NDYE+LV RGKELKECGK QEALNCLVKALDIKSADPEVM +TSLYKQLN

Sbjct: 1174 AVEAANDYESLVARGKELKECGKTQEALNCLVKALDIKSADPEVMRMTLSLYKQLN 1229

Figure 5: 273P4B7 variant 1
Hydrophilicity profile
(Hopp T.P., Woods K.R., 1981.
Proc. Natl. Acad. Sci. U.S.A. 78:3824-3828)

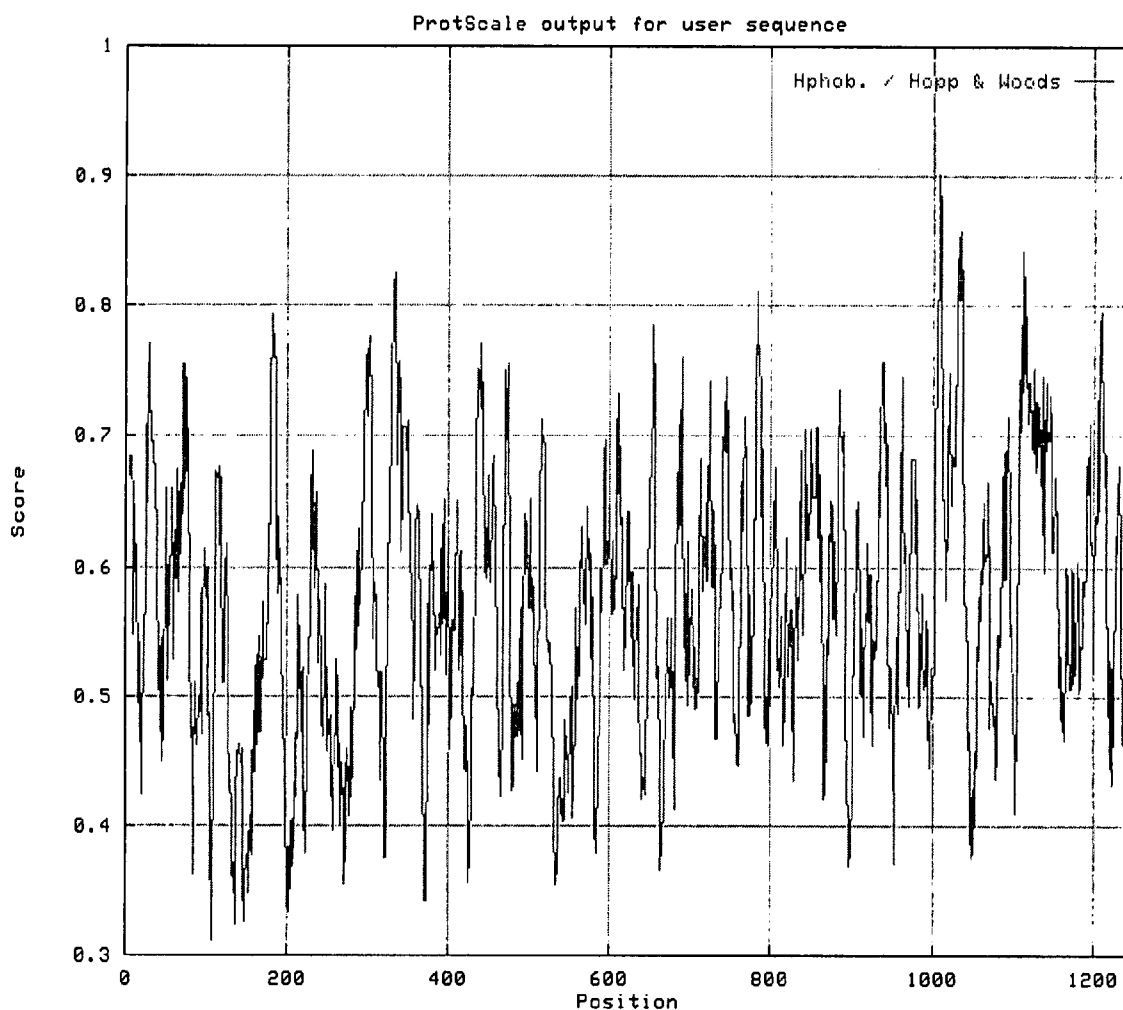


Figure 6: 273P4B7 variant 1
Hydropathicity Profile
(Kyte J., Doolittle R.F., 1982. J. Mol. Biol. 157:105-132)

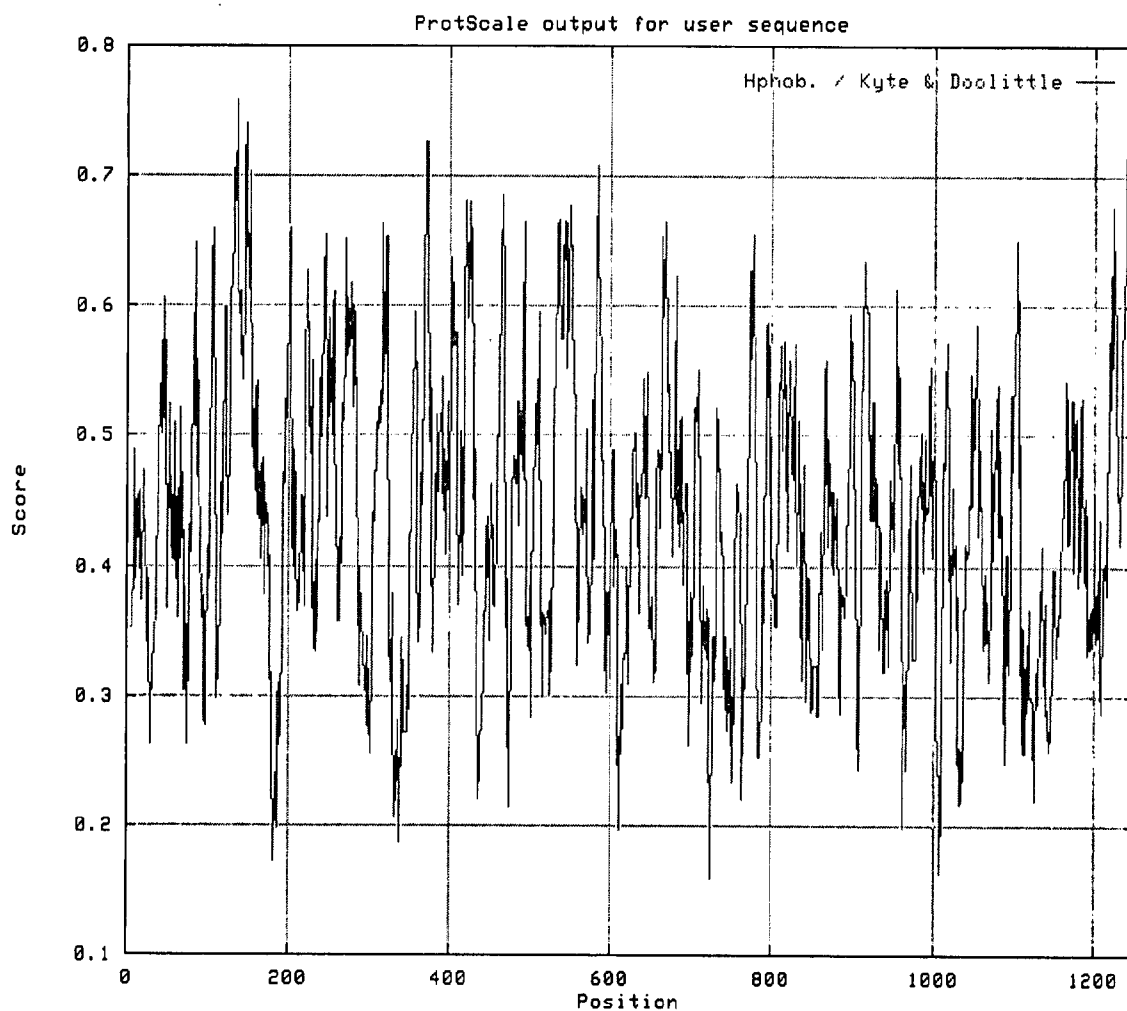


Figure 7: 273P4B7 variant 1 %
Accessible Residues Profile
(Janin J., 1979. Nature 277:491-492)

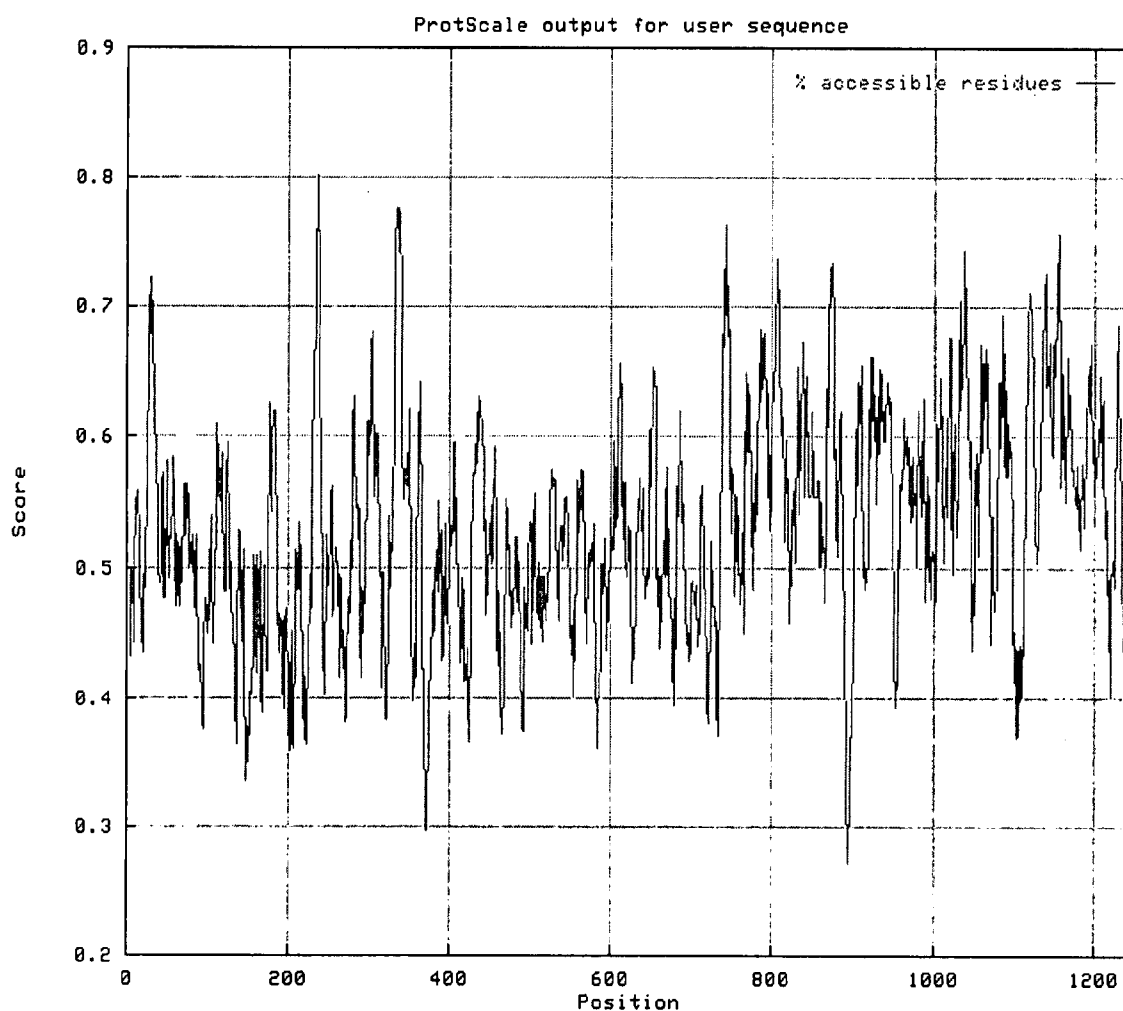


Figure 8: 273P4B7 variant 1
Average Flexibility Profile
(Bhaskaran R., Ponnuswamy P.K., 1988.
Int. J. Pept. Protein Res. 32:242-255)

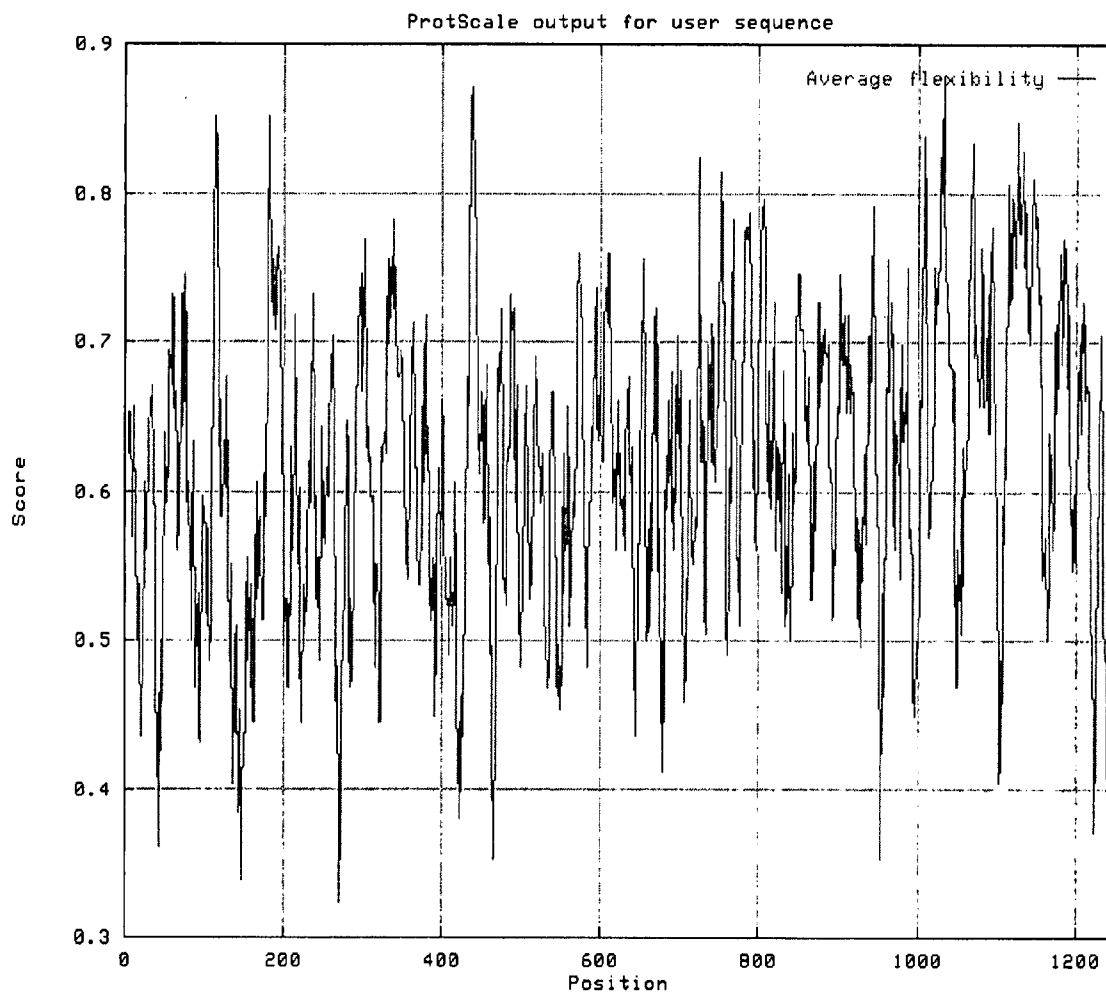


Figure 9: 273P4B7 variant 1

Beta-turn Profile

(Deleage, G., Roux B. 1987.
Protein Engineering 1:289-294)

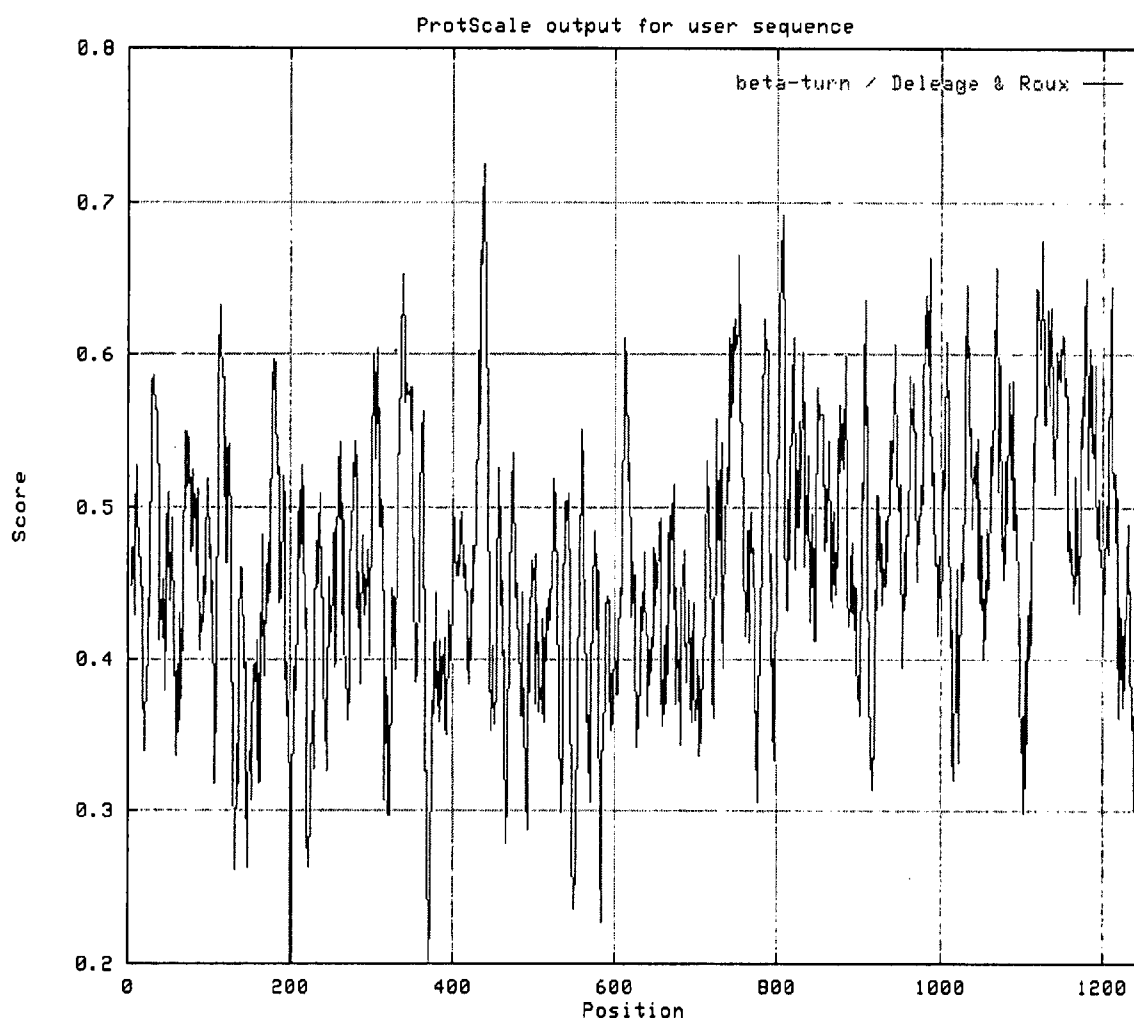


Figure 10

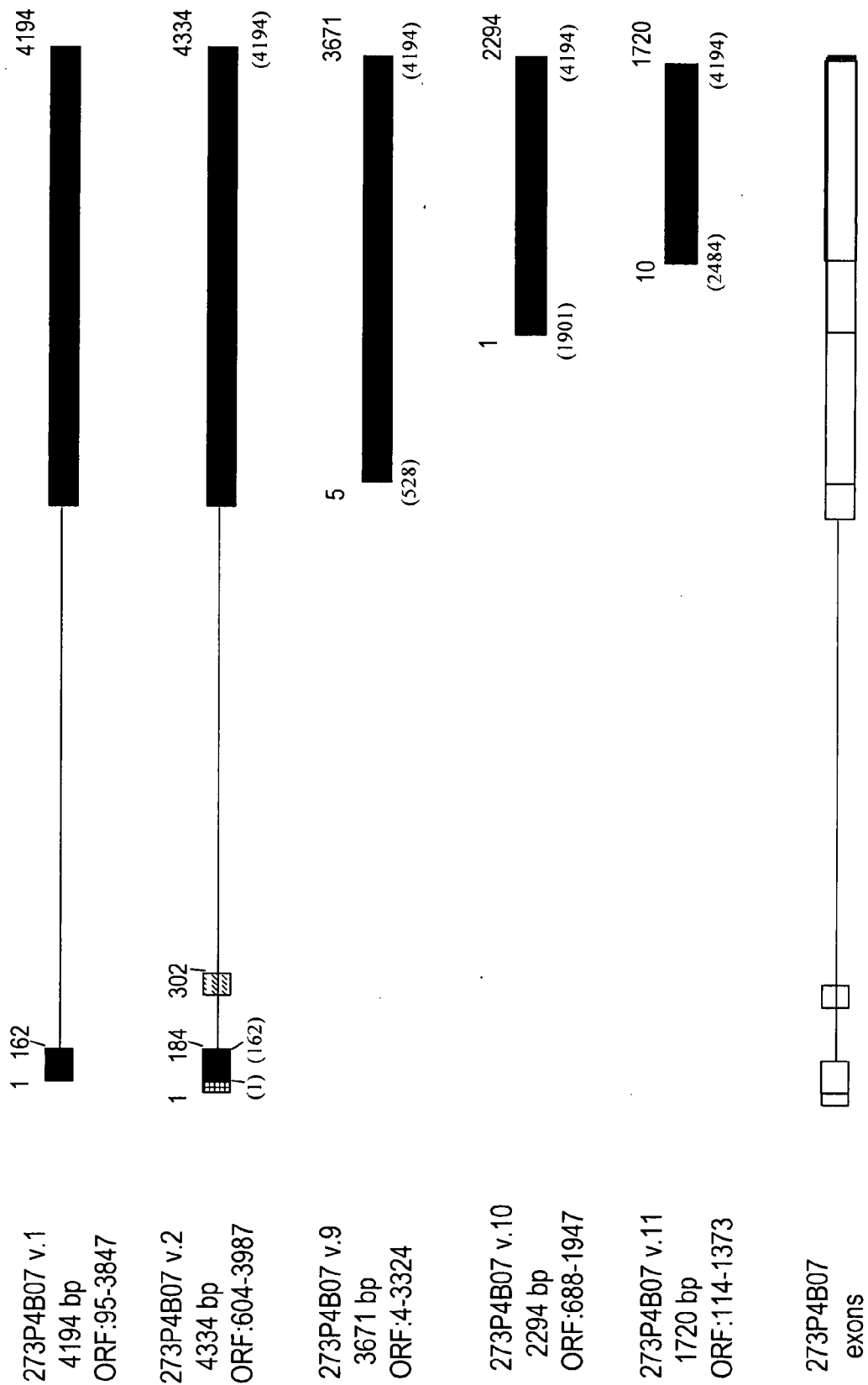


Figure 11

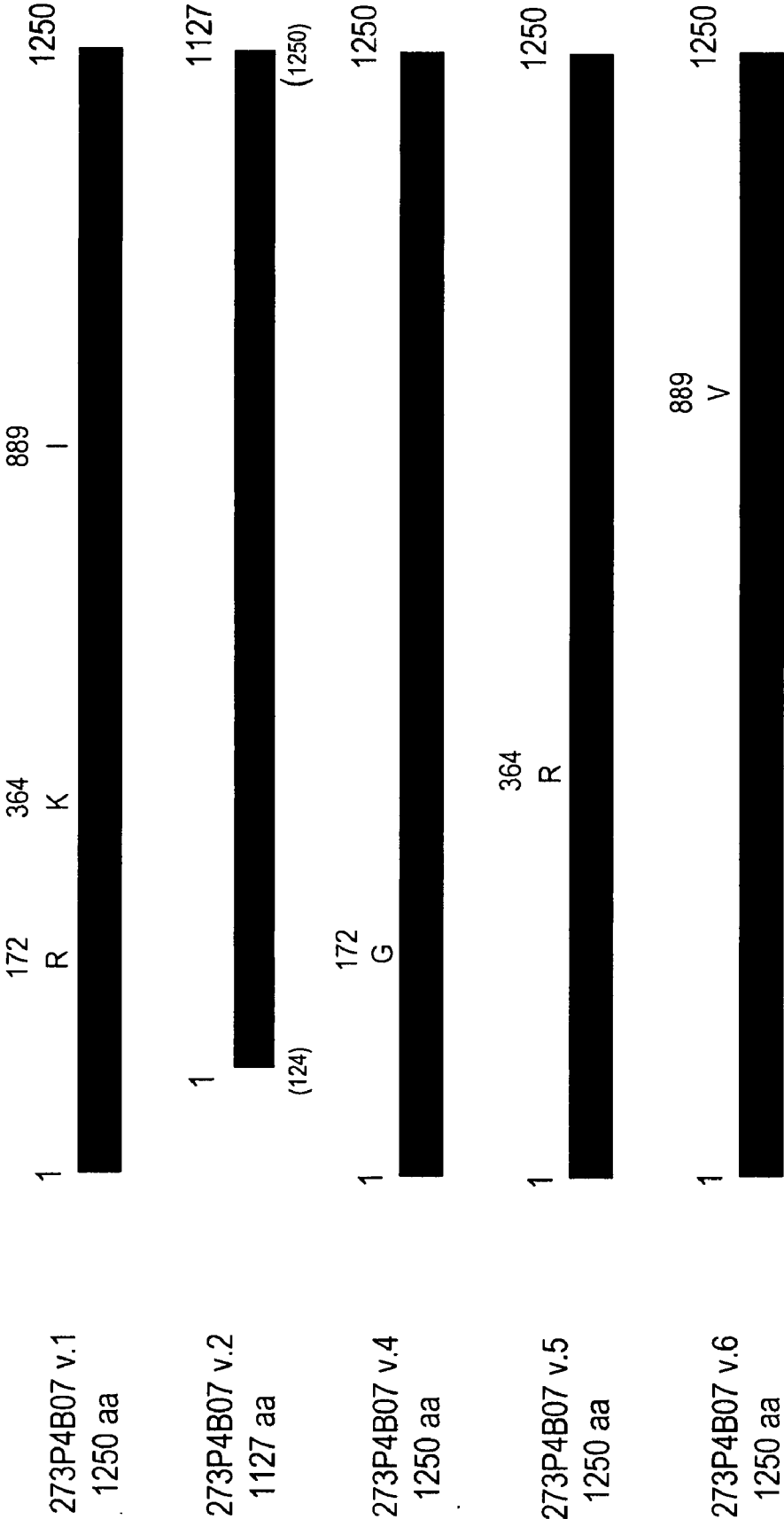


Figure 11-2

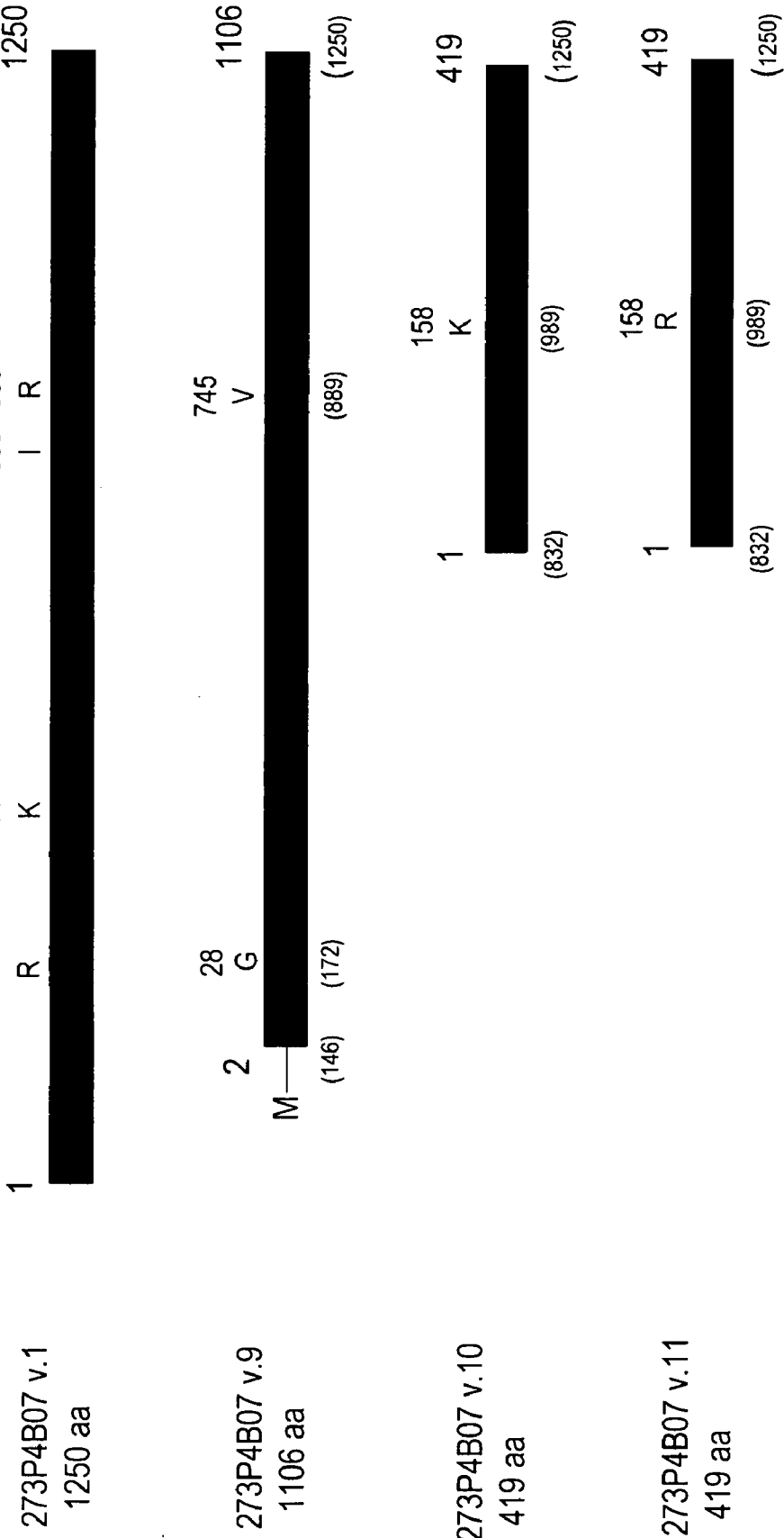


Figure 12

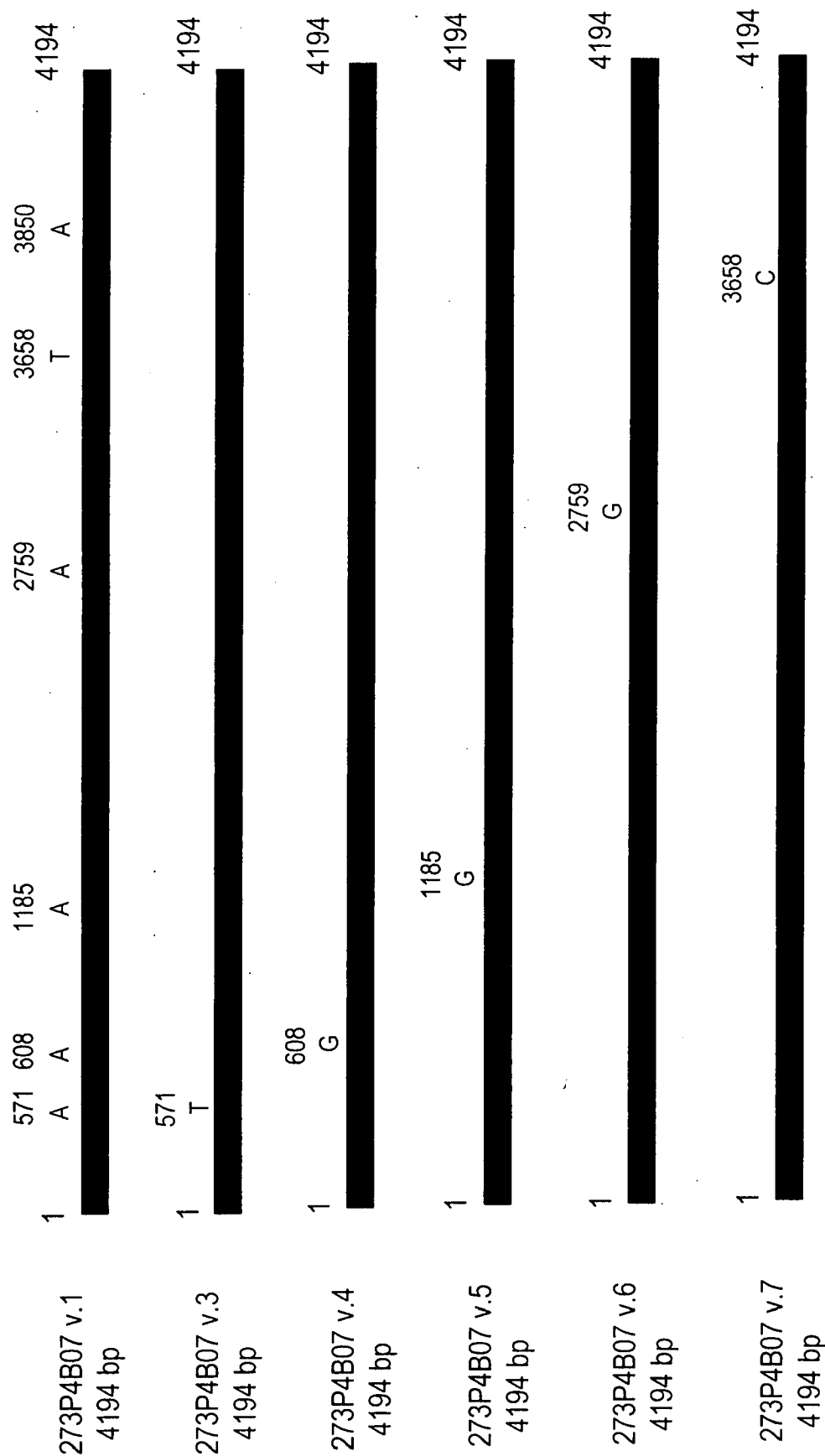


Figure 12-2

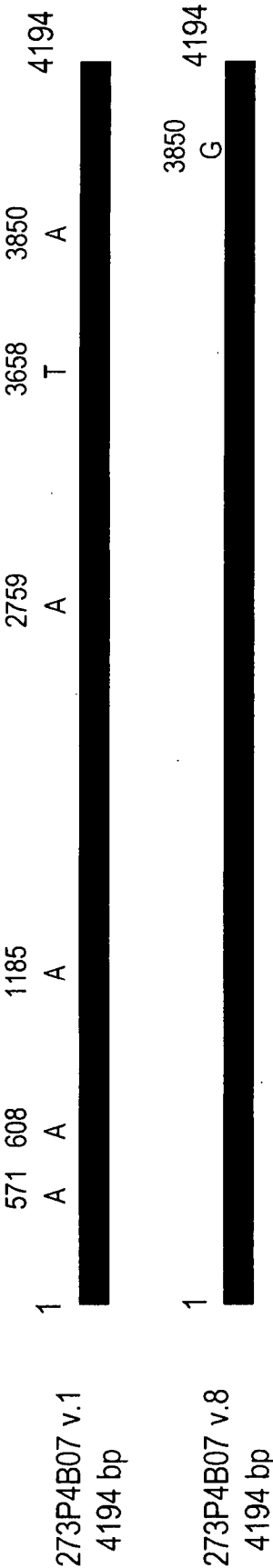


Figure 13A

Secondary structure prediction of 273P4B7 variant 1

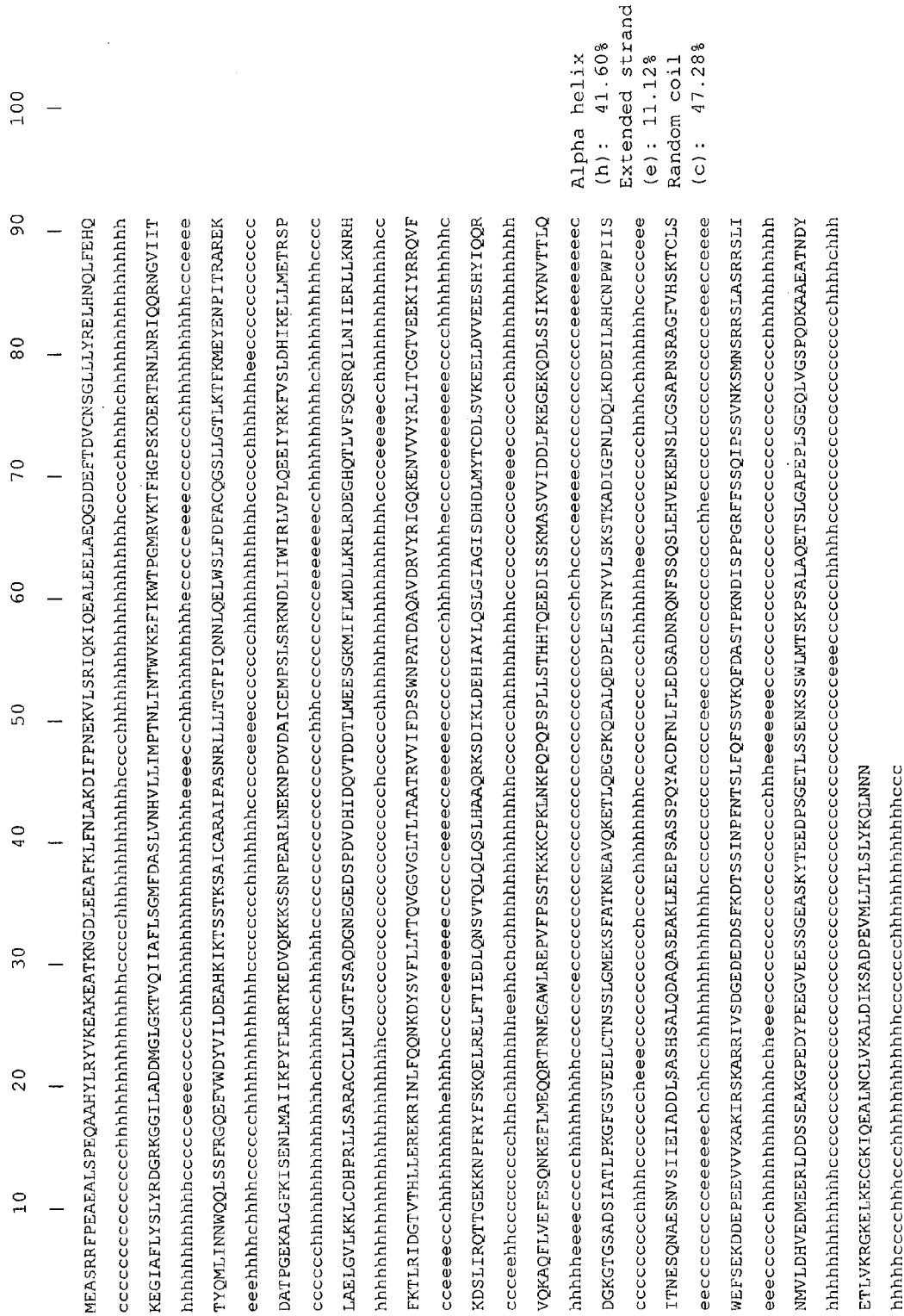


Figure 13B

Transmembrane prediction for 273P4B6 variant 1

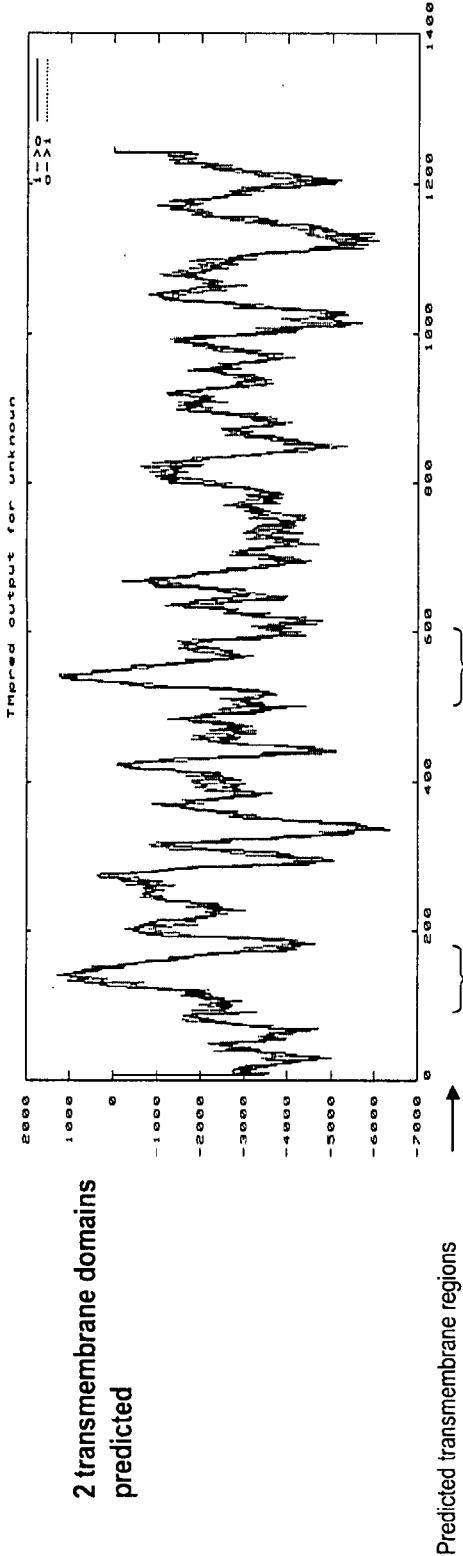


Figure 13C

No transmembrane domain predicted

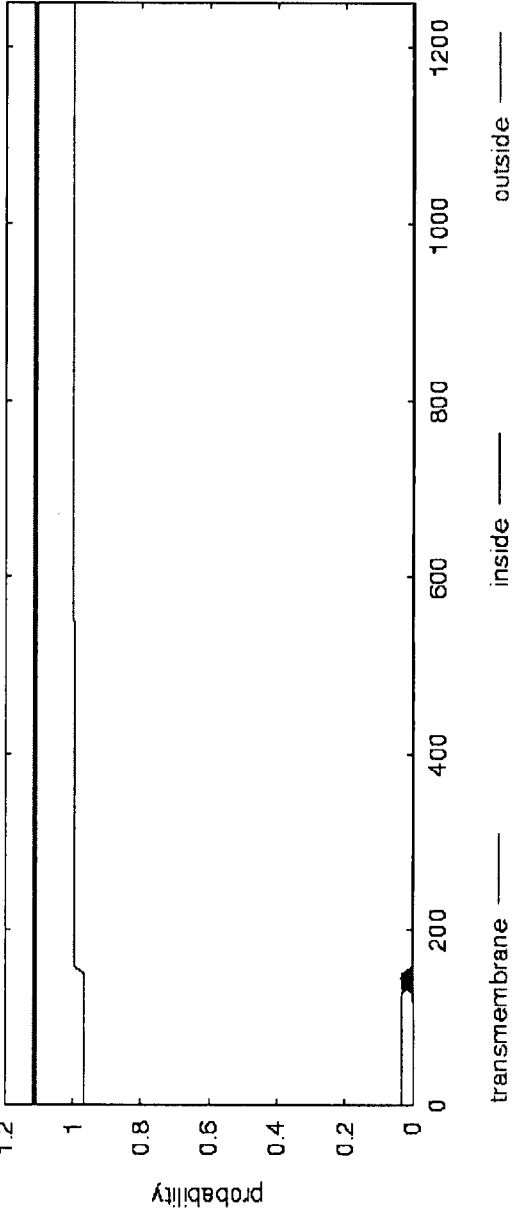


Figure 14A 273P4B7 Expression by RT-PCR

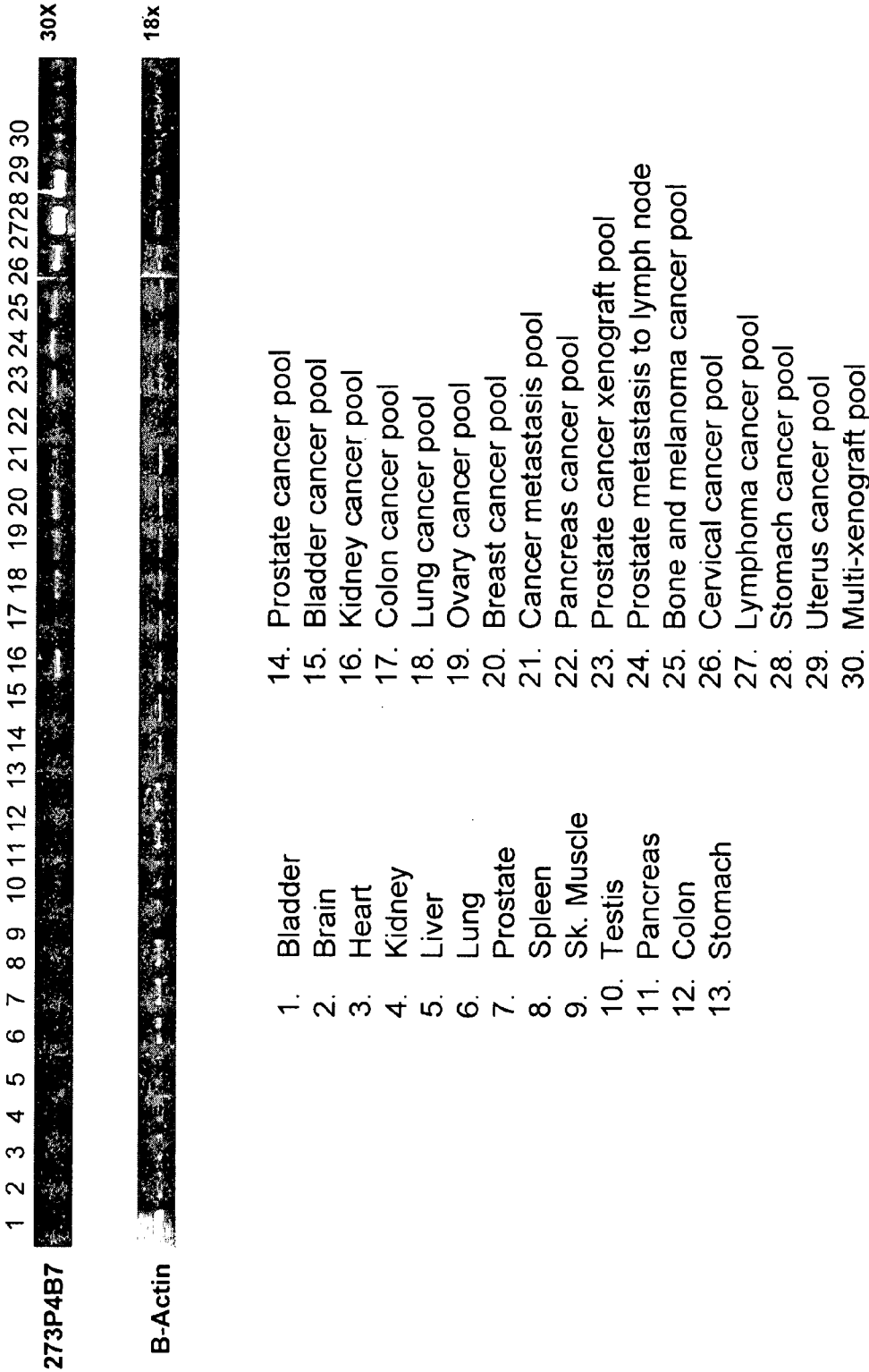


Figure 14B 273P4B7 Expression by RT-PCR

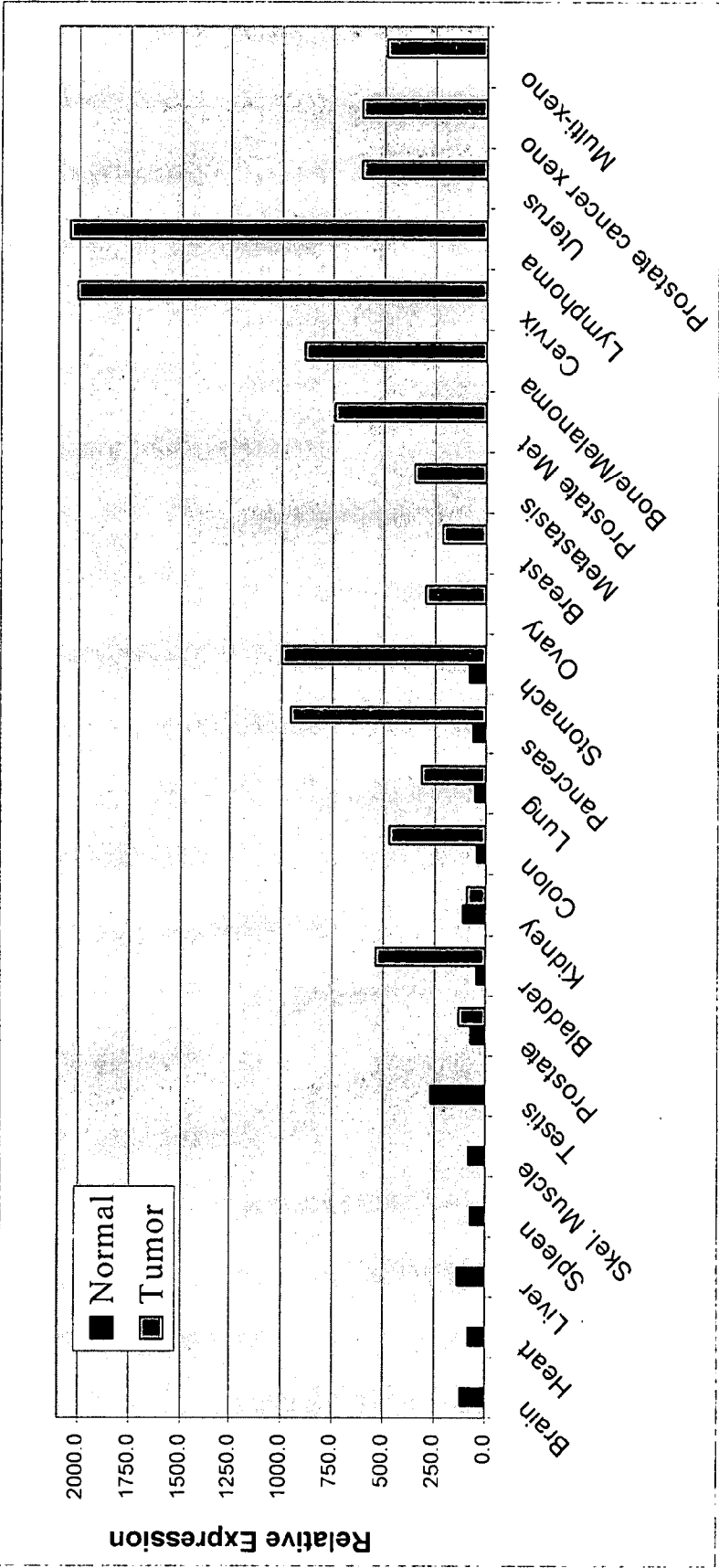


Figure 15 273P4B7 Expression in Normal Tissues

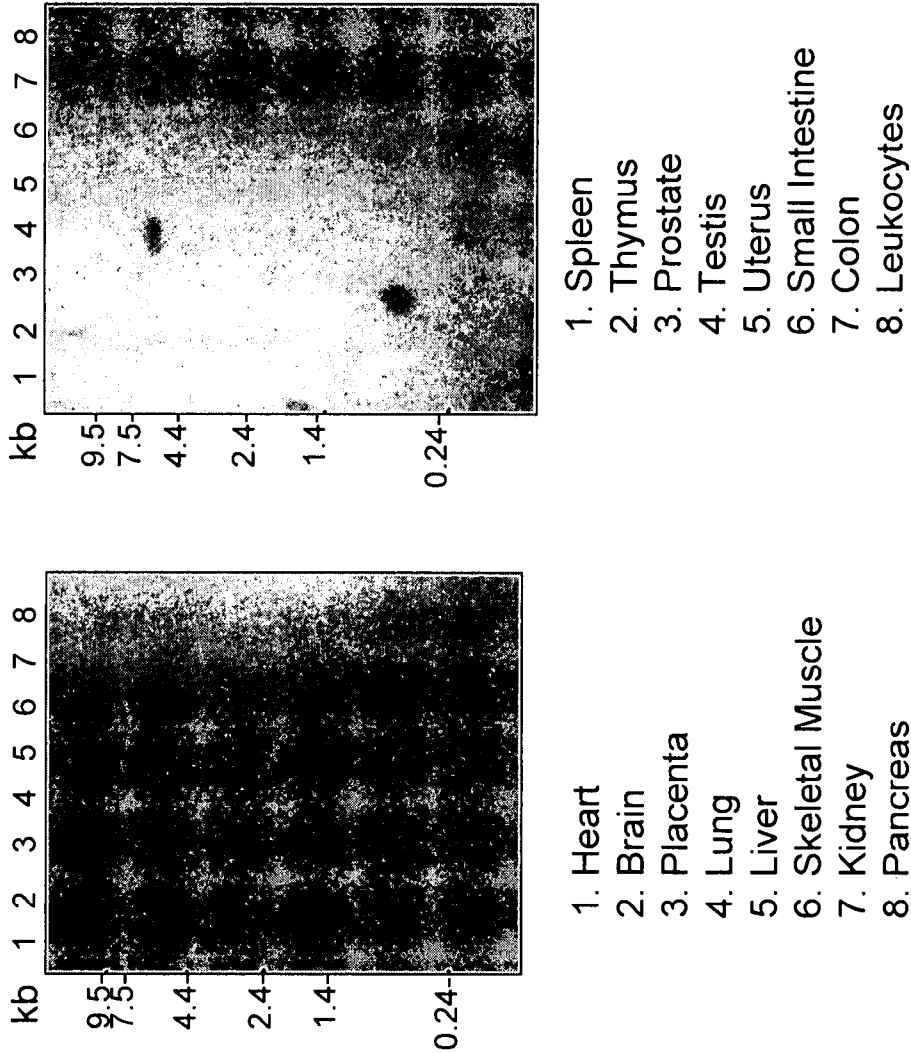


Figure 16 Expression of 273P4B7 in Pancreas, Ovary and Testis
Cancer Patient Specimens

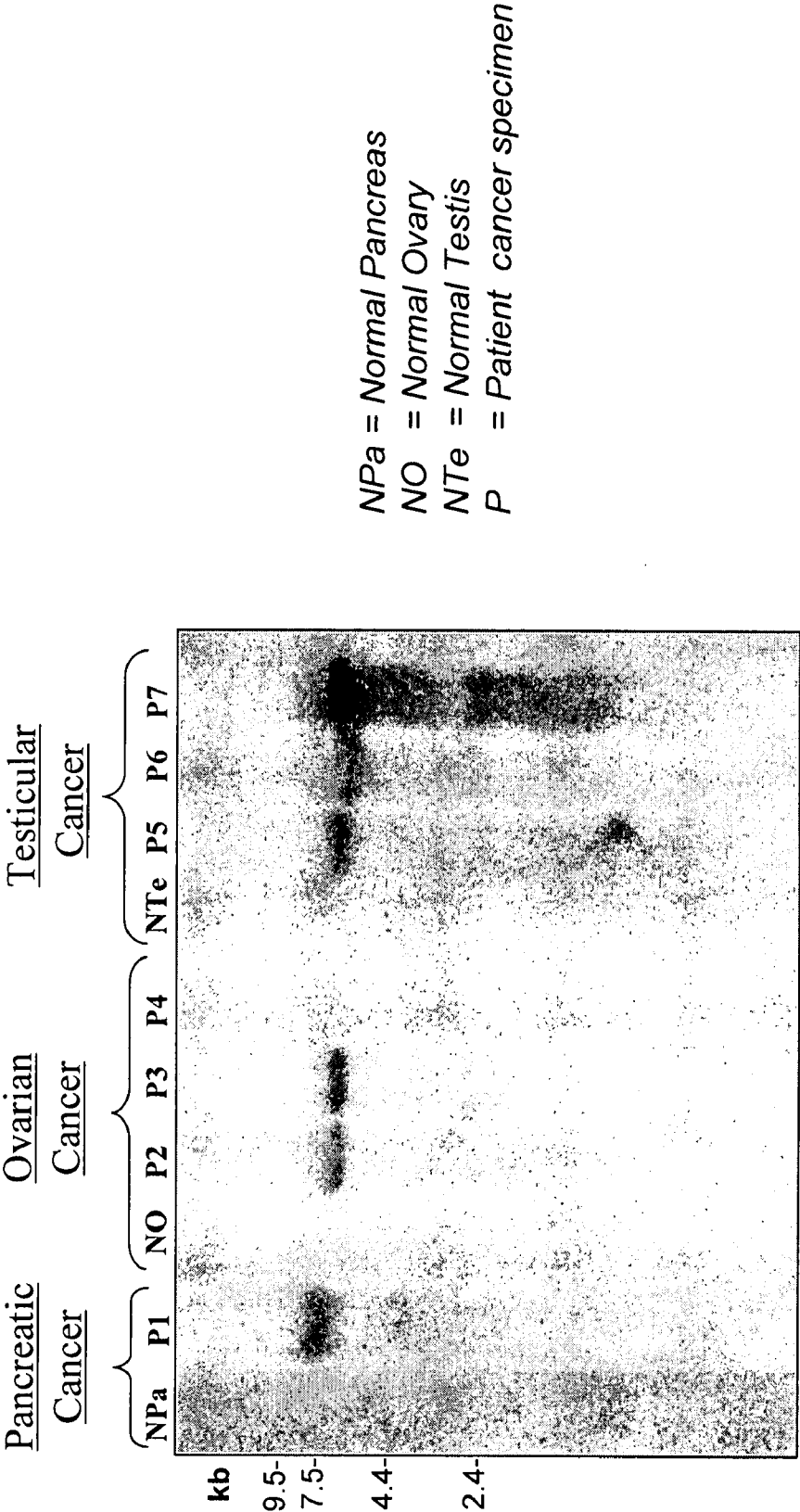


Figure 17 Expression of 273P4B7 in Cervical Cancer Patient Specimens

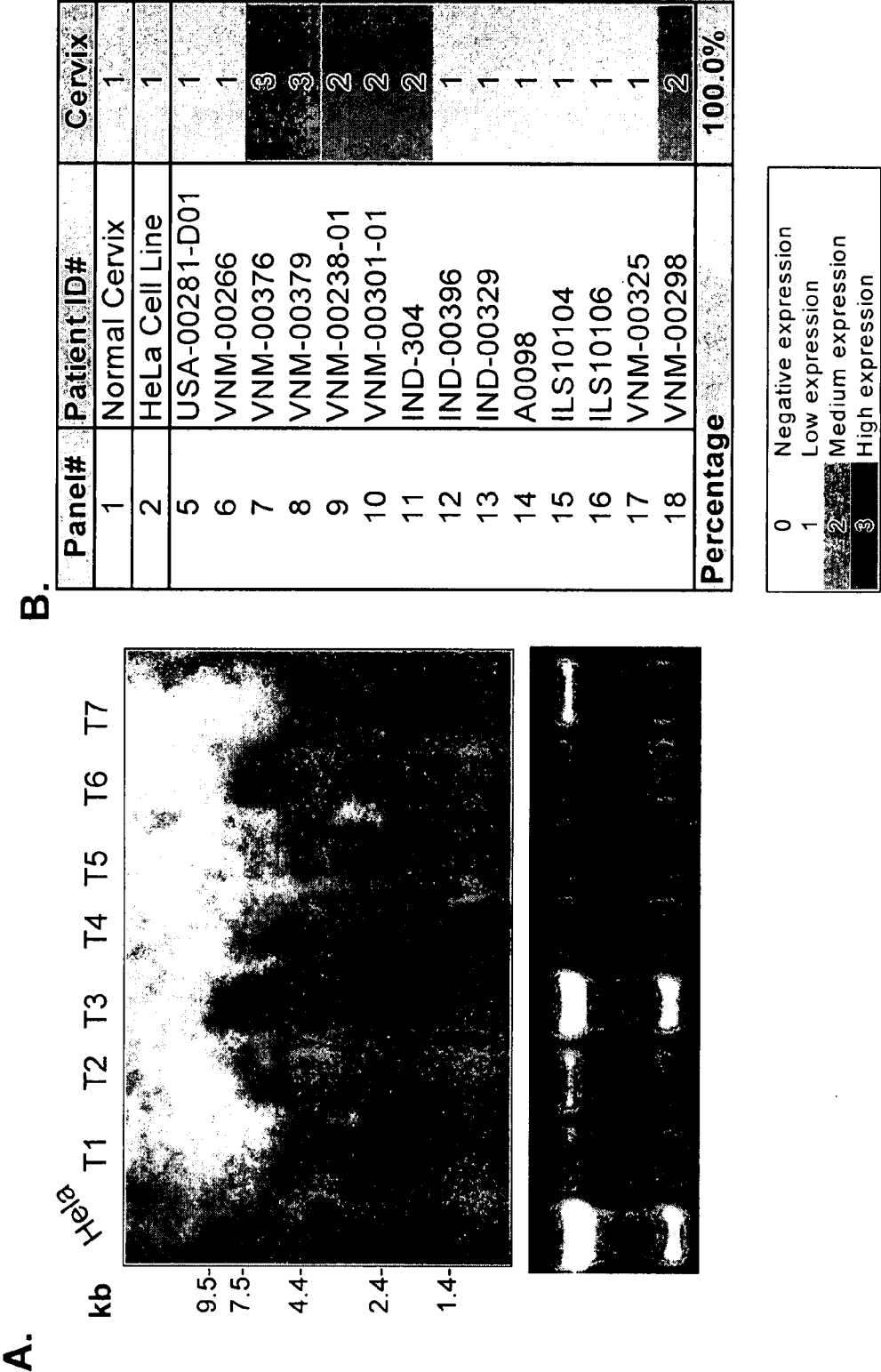
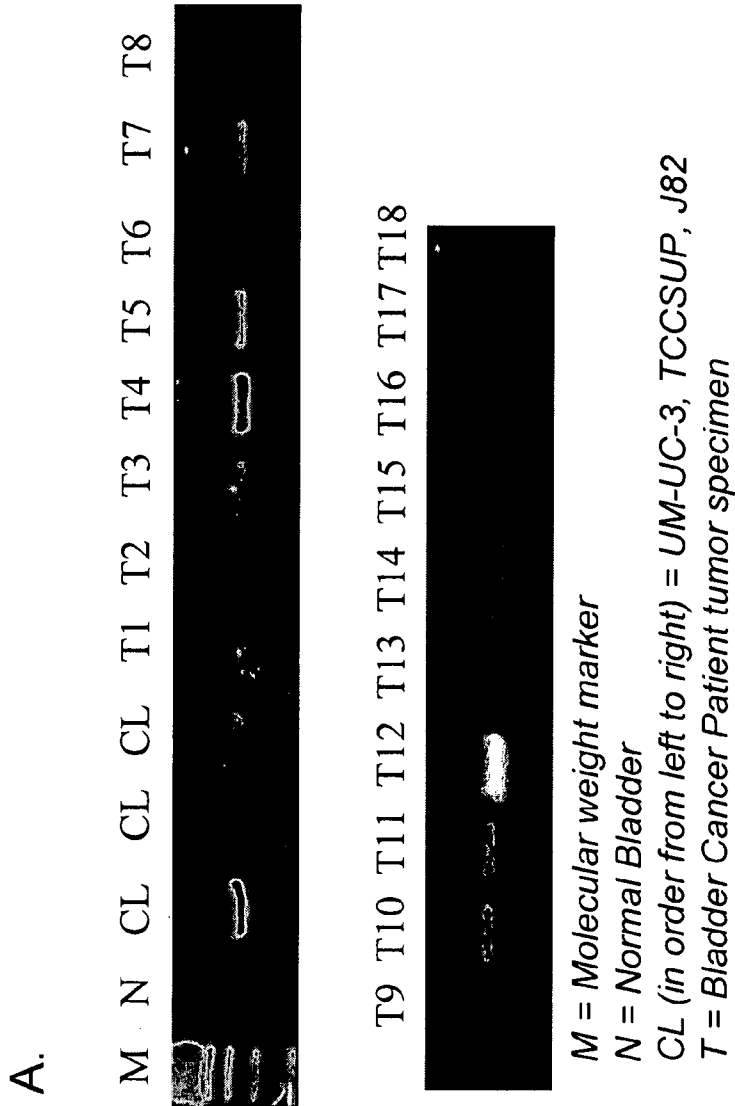


Figure 18 273P4B7 Expression in Bladder Cancer Patient Specimens



B.

Panel#	Pathology	Grade	Expression
1	Normal		0
1b	Normal		0
2	Cell line	UM-UC-3	3
3	Cell line	TCCSUP	1
4	Cell line	J82	2
5	Papillary	1	2
6	Papillary	3	2
7	Papillary	3	1
8	Squamous		2
9	Squamous		1
10	Transitional	2	0
11	Transitional	2	1
12	Transitional	2	1
13	Transitional	3	1
14	Transitional	3	1
15	Transitional	3	1
16	Transitional	3	1
17	Transitional	3	2
18	Transitional	3	1
22	Transitional	3	1
23	Transitional		1
24	ND		2

0

Negative expression

1

Low expression

2

Medium expression

3

High expression

Figure 19 273P4B7 Expression in Colon Cancer Patient Specimens

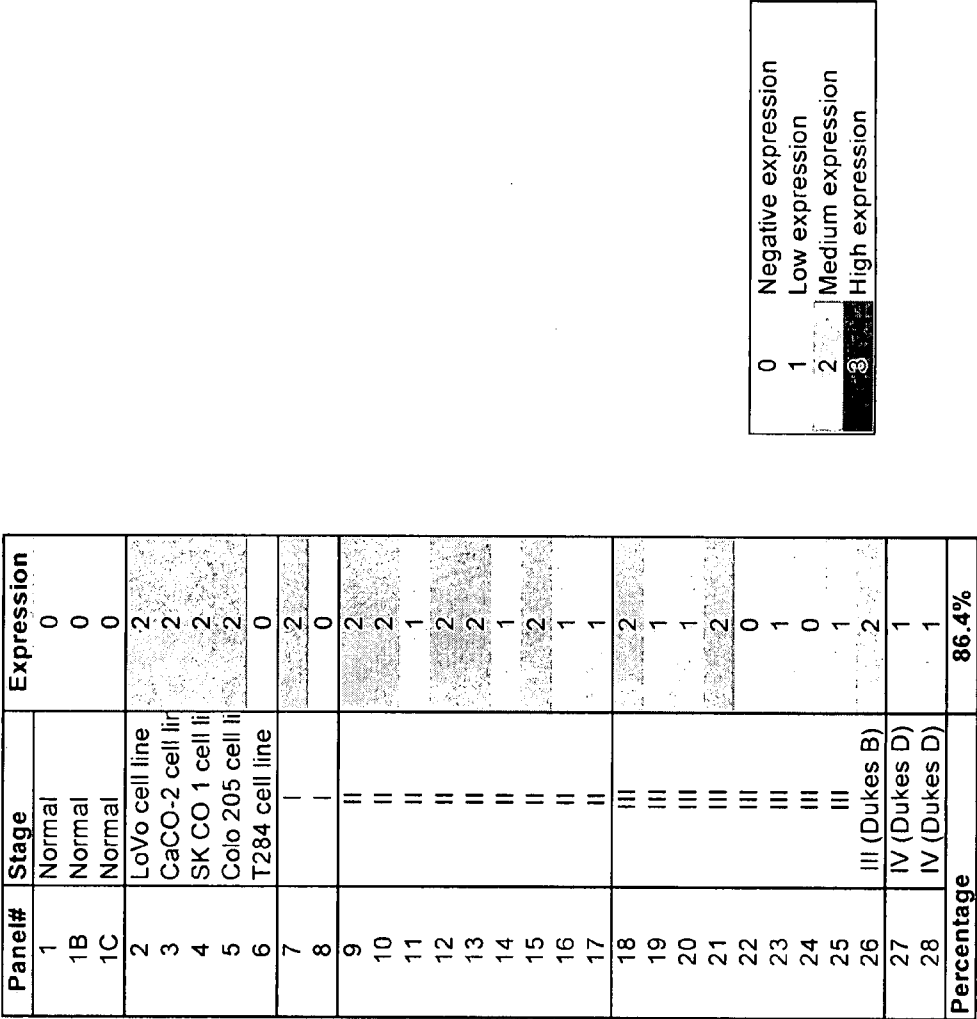
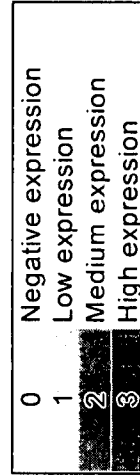


Figure 20 273P4B7 Expression in Ovary Cancer Patient Specimens

Panel#	Diagnosis	Stage	Ovary CA
1	Normal		0
2	OV-1063	Cell line	1
3	PA-1	Cell line	2
4	SW 626	Cell line	1
5	Serous CA	3	1
6	Mucinous CystadenoCA		1
7	Mucinous CystadenoCA		0
8	Mucinous CystadenoCA	2	1
9	Granulosa	Figo Ia1	0
10	Papillary serous CA	3	3
11	Endometrioid AdenoCA	2	3
12	Papillary serous CA	3	3
13	Squamous	3	1
14	Adeno CA Met to Omentum		0
15	Papillary serous CA	Figo III	1
16	Endometrioid AdenoCA		2
17	Met to omentum		1
18	Met to Intestine		1
19	Met to Intestine	Undiff.	0



**NUCLEIC ACIDS AND CORRESPONDING
PROTEINS ENTITLED 273P4B7 USEFUL IN
TREATMENT AND DETECTION OF CANCER**

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a divisional of U.S. patent application Ser. No. 10/641,633, filed Aug. 15, 2003, and now U.S. Pat. No. _____, which claims the benefit of priority of U.S. Provisional Application No. 60/404,306, filed Aug. 16, 2002 (expired), and U.S. Provisional Application No. 60/423,290 Nov. 1, 2002 (expired), all of which are hereby incorporated by reference in their entirety.

**REFERENCE TO LIST OF TABLES
(APPENDIX) SUBMITTED ON COMPACT DISC**

[0002] The Compact Disc Appendix, which is a part of the present disclosure, is provided in duplicate on compact discs (CD-Rs). Each contains the following file: 511582008710 Tables, having a date of creation of Feb. 14, 2007 and a file size of 253,952 bytes. All the material on the compact discs is hereby expressly incorporated by reference into the present application.

TECHNICAL FIELD

[0003] The invention described herein relates to genes and their encoded proteins, termed 273P4B7 and variants thereof, expressed in certain cancers, and to diagnostic and therapeutic methods and compositions useful in the management of cancers that express 273P4B7.

BACKGROUND ART

[0004] Cancer is the second leading cause of human death next to coronary disease. Worldwide, millions of people die from cancer every year. In the United States alone, as reported by the American Cancer Society, cancer causes the death of well over a half-million people annually, with over 1.2 million new cases diagnosed per year. While deaths from heart disease have been declining significantly, those resulting from cancer generally are on the rise. In the early part of the next century, cancer is predicted to become the leading cause of death.

[0005] Worldwide, several cancers stand out as the leading killers. In particular, carcinomas of the lung, prostate, breast, colon, pancreas, and ovary represent the primary causes of cancer death. These and virtually all other carcinomas share a common lethal feature. With very few exceptions, metastatic disease from a carcinoma is fatal. Moreover, even for those cancer patients who initially survive their primary cancers, common experience has shown that their lives are dramatically altered. Many cancer patients experience strong anxieties driven by the awareness of the potential for recurrence or treatment failure. Many cancer patients experience physical debilitations following treatment. Furthermore, many cancer patients experience a recurrence.

[0006] Worldwide, prostate cancer is the fourth most prevalent cancer in men. In North America and Northern Europe, it is by far the most common cancer in males and is the second leading cause of cancer death in men. In the United States alone, well over 30,000 men die annually of this disease—second only to lung cancer. Despite the magnitude of these figures, there is still no effective treatment for

metastatic prostate cancer. Surgical prostatectomy, radiation therapy, hormone ablation therapy, surgical castration and chemotherapy continue to be the main treatment modalities. Unfortunately, these treatments are ineffective for many and are often associated with undesirable consequences.

[0007] On the diagnostic front, the lack of a prostate tumor marker that can accurately detect early-stage, localized tumors remains a significant limitation in the diagnosis and management of this disease. Although the serum prostate specific antigen (PSA) assay has been a very useful tool, however its specificity and general utility is widely regarded as lacking in several important respects.

[0008] Progress in identifying additional specific markers for prostate cancer has been improved by the generation of prostate cancer xenografts that can recapitulate different stages of the disease in mice. The LAPC (Los Angeles Prostate Cancer) xenografts are prostate cancer xenografts that have survived passage in severe combined immune deficient (SCID) mice and have exhibited the capacity to mimic the transition from androgen dependence to androgen independence (Klein et al., 1997, Nat. Med. 3:402). More recently identified prostate cancer markers include PCTA-1 (Su et al., 1996, Proc. Natl. Acad. Sci. USA 93: 7252), prostate-specific membrane (PSM) antigen (Pinto et al., Clin Cancer Res 1996 Sep. 2 (9): 1445-51), STEAP (Hubert, et al., Proc Natl Acad Sci USA. 1999 Dec. 7; 96(25): 14523-8) and prostate stem cell antigen (PSCA) (Reiter et al., 1998, Proc. Natl. Acad. Sci. USA 95: 1735).

[0009] While previously identified markers such as PSA, PSM, PCTA and PSCA have facilitated efforts to diagnose and treat prostate cancer, there is need for the identification of additional markers and therapeutic targets for prostate and related cancers in order to further improve diagnosis and therapy. Renal cell carcinoma (RCC) accounts for approximately 3 percent of adult malignancies. Once adenomas reach a diameter of 2 to 3 cm, malignant potential exists. In the adult, the two principal malignant renal tumors are renal cell adenocarcinoma and transitional cell carcinoma of the renal pelvis or ureter. The incidence of renal cell adenocarcinoma is estimated at more than 29,000 cases in the United States, and more than 11,600 patients died of this disease in 1998. Transitional cell carcinoma is less frequent, with an incidence of approximately 500 cases per year in the United States.

[0010] Surgery has been the primary therapy for renal cell adenocarcinoma for many decades. Until recently, metastatic disease has been refractory to any systemic therapy. With recent developments in systemic therapies, particularly immunotherapies, metastatic renal cell carcinoma may be approached aggressively in appropriate patients with a possibility of durable responses. Nevertheless, there is a remaining need for effective therapies for these patients.

[0011] Of all new cases of cancer in the United States, bladder cancer represents approximately 5 percent in men (fifth most common neoplasm) and 3 percent in women (eighth most common neoplasm). The incidence is increasing slowly, concurrent with an increasing older population. In 1998, there was an estimated 54,500 cases, including 39,500 in men and 15,000 in women. The age-adjusted incidence in the United States is 32 per 100,000 for men and eight per 100,000 in women. The historic male to female ratio of 3:1 may be decreasing related to smoking patterns in

women. There were an estimated 11,000 deaths from bladder cancer in 1998 (7,800 in men and 3,900 in women). Bladder cancer incidence and mortality strongly increase with age and will be an increasing problem as the population becomes more elderly.

[0012] Most bladder cancers recur in the bladder. Bladder cancer is managed with a combination of transurethral resection of the bladder (TUR) and intravesical chemotherapy or immunotherapy. The multifocal and recurrent nature of bladder cancer points out the limitations of TUR. Most muscle-invasive cancers are not cured by TUR alone. Radical cystectomy and urinary diversion is the most effective means to eliminate the cancer but carry an undeniable impact on urinary and sexual function. There continues to be a significant need for treatment modalities that are beneficial for bladder cancer patients.

[0013] An estimated 130,200 cases of colorectal cancer occurred in 2000 in the United States, including 93,800 cases of colon cancer and 36,400 of rectal cancer. Colorectal cancers are the third most common cancers in men and women. Incidence rates declined significantly during 1992-1996 (-2.1% per year). Research suggests that these declines have been due to increased screening and polyp removal, preventing progression of polyps to invasive cancers. There were an estimated 56,300 deaths (47,700 from colon cancer, 8,600 from rectal cancer) in 2000, accounting for about 11% of all U.S. cancer deaths.

[0014] At present, surgery is the most common form of therapy for colorectal cancer, and for cancers that have not spread, it is frequently curative. Chemotherapy, or chemotherapy plus radiation, is given before or after surgery to most patients whose cancer has deeply perforated the bowel wall or has spread to the lymph nodes. A permanent colostomy (creation of an abdominal opening for elimination of body wastes) is occasionally needed for colon cancer and is infrequently required for rectal cancer. There continues to be a need for effective diagnostic and treatment modalities for colorectal cancer.

[0015] There were an estimated 164,100 new cases of lung and bronchial cancer in 2000, accounting for 14% of all U.S. cancer diagnoses. The incidence rate of lung and bronchial cancer is declining significantly in men, from a high of 86.5 per 100,000 in 1984 to 70.0 in 1996. In the 1990s, the rate of increase among women began to slow. In 1996, the incidence rate in women was 42.3 per 100,000.

[0016] Lung and bronchial cancer caused an estimated 156,900 deaths in 2000, accounting for 28% of all cancer deaths. During 1992-1996, mortality from lung cancer declined significantly among men (-1.7% per year) while rates for women were still significantly increasing (0.9% per year). Since 1987, more women have died each year of lung cancer than breast cancer, which, for over 40 years, was the major cause of cancer death in women. Decreasing lung cancer incidence and mortality rates most likely resulted from decreased smoking rates over the previous 30 years; however, decreasing smoking patterns among women lag behind those of men. Of concern, although the declines in adult tobacco use have slowed, tobacco use in youth is increasing again.

[0017] Treatment options for lung and bronchial cancer are determined by the type and stage of the cancer and

include surgery, radiation therapy, and chemotherapy. For many localized cancers, surgery is usually the treatment of choice. Because the disease has usually spread by the time it is discovered, radiation therapy and chemotherapy are often needed in combination with surgery. Chemotherapy alone or combined with radiation is the treatment of choice for small cell lung cancer; on this regimen, a large percentage of patients experience remission, which in some cases is long lasting. There is however, an ongoing need for effective treatment and diagnostic approaches for lung and bronchial cancers.

[0018] An estimated 182,800 new invasive cases of breast cancer were expected to occur among women in the United States during 2000. Additionally, about 1,400 new cases of breast cancer were expected to be diagnosed in men in 2000. After increasing about 4% per year in the 1980s, breast cancer incidence rates in women have leveled off in the 1990s to about 110.6 cases per 100,000.

[0019] In the U.S. alone, there were an estimated 41,200 deaths (40,800 women, 400 men) in 2000 due to breast cancer. Breast cancer ranks second among cancer deaths in women. According to the most recent data, mortality rates declined significantly during 1992-1996 with the largest decreases in younger women, both white and black. These decreases were probably the result of earlier detection and improved treatment.

[0020] Taking into account the medical circumstances and the patients preferences, treatment of breast cancer may involve lumpectomy (local removal of the tumor) and removal of the lymph nodes under the arm; mastectomy (surgical removal of the breast) and removal of the lymph nodes under the arm; radiation therapy; chemotherapy; or hormone therapy. Often, two or more methods are used in combination. Numerous studies have shown that, for early stage disease, long-term survival rates after lumpectomy plus radiotherapy are similar to survival rates after modified radical mastectomy. Significant advances in reconstruction techniques provide several options for breast reconstruction after mastectomy. Recently, such reconstruction has been done at the same time as the mastectomy.

[0021] Local excision of ductal carcinoma in situ (DCIS) with adequate amounts of surrounding normal breast tissue may prevent the local recurrence of the DCIS. Radiation to the breast and/or tamoxifen may reduce the chance of DCIS occurring in the remaining breast tissue. This is important because DCIS, if left untreated, may develop into invasive breast cancer. Nevertheless, there are serious side effects or sequelae to these treatments. There is, therefore, a need for efficacious breast cancer treatments.

[0022] There were an estimated 23,100 new cases of ovarian cancer in the United States in 2000. It accounts for 4% of all cancers among women and ranks second among gynecologic cancers. During 1992-1996, ovarian cancer incidence rates were significantly declining. Consequent to ovarian cancer, there were an estimated 14,000 deaths in 2000. Ovarian cancer causes more deaths than any other cancer of the female reproductive system.

[0023] Surgery, radiation therapy, and chemotherapy are treatment options for ovarian cancer. Surgery usually includes the removal of one or both ovaries, the fallopian tubes (salpingo-oophorectomy), and the uterus (hysterectomy).

tomy). In some very early tumors, only the involved ovary will be removed, especially in young women who wish to have children. In advanced disease, an attempt is made to remove all intra-abdominal disease to enhance the effect of chemotherapy. There continues to be an important need for effective treatment options for ovarian cancer.

[0024] There were an estimated 28,300 new cases of pancreatic cancer in the United States in 2000. Over the past 20 years, rates of pancreatic cancer have declined in men. Rates among women have remained approximately constant but may be beginning to decline. Pancreatic cancer caused an estimated 28,200 deaths in 2000 in the United States. Over the past 20 years, there has been a slight but significant decrease in mortality rates among men (about -0.9% per year) while rates have increased slightly among women.

[0025] Surgery, radiation therapy, and chemotherapy are treatment options for pancreatic cancer. These treatment options can extend survival and/or relieve symptoms in many patients but are not likely to produce a cure for most. There is a significant need for additional therapeutic and diagnostic options for pancreatic cancer.

SUMMARY OF THE INVENTION

[0026] The present invention relates to a gene, designated 273P4B7, that has now been found to be over-expressed in the cancer(s) listed in Table I. Northern blot expression analysis of 273P4B7 gene expression in normal tissues shows a restricted expression pattern in adult tissues. The nucleotide (FIG. 2) and amino acid (FIG. 2, and FIG. 3) sequences of 273P4B7 are provided. The tissue-related profile of 273P4B7 in normal adult tissues, combined with the over-expression observed in the tissues listed in Table I, shows that 273P4B7 is aberrantly over-expressed in at least some cancers, and thus serves as a useful diagnostic, prophylactic, prognostic, and/or therapeutic target for cancers of the tissue(s) such as those listed in Table I.

[0027] The invention provides polynucleotides corresponding or complementary to all or part of the 273P4B7 genes, mRNAs, and/or coding sequences, preferably in isolated form, including polynucleotides encoding 273P4B7-related proteins and fragments of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more than 25 contiguous amino acids; at least 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 85, 90, 95, 100 or more than 100 contiguous amino acids of a 273P4B7-related protein, as well as the peptides/proteins themselves; DNA, RNA, DNA/RNA hybrids, and related molecules, polynucleotides or oligonucleotides complementary or having at least a 90% homology to the 273P4B7 genes or mRNA sequences or parts thereof, and polynucleotides or oligonucleotides that hybridize to the 273P4B7 genes, mRNAs, or to 273P4B7-encoding polynucleotides. Also provided are means for isolating cDNAs and the genes encoding 273P4B7. Recombinant DNA molecules containing 273P4B7 polynucleotides, cells transformed or transduced with such molecules, and host-vector systems for the expression of 273P4B7 gene products are also provided. The invention further provides antibodies that bind to 273P4B7 proteins and polypeptide fragments thereof, including polyclonal and monoclonal antibodies, murine and other mammalian antibodies, chimeric antibodies, humanized and fully human antibodies, and antibodies labeled with a detectable marker or thera-

peutic agent. In certain embodiments, there is a proviso that the entire nucleic acid sequence of FIG. 2 is not encoded and/or the entire amino acid sequence of FIG. 2 is not prepared. In certain embodiments, the entire nucleic acid sequence of FIG. 2 is encoded and/or the entire amino acid sequence of FIG. 2 is prepared, either of which are in respective human unit dose forms.

[0028] The invention further provides methods for detecting the presence and status of 273P4B7 polynucleotides and proteins in various biological samples, as well as methods for identifying cells that express 273P4B7. A typical embodiment of this invention provides methods for monitoring 273P4B7 gene products in a tissue or hematology sample having or suspected of having some form of growth dysregulation such as cancer.

[0029] The invention further provides various immunogenic or therapeutic compositions and strategies for treating cancers that express 273P4B7 such as cancers of tissues listed in Table I, including therapies aimed at inhibiting the transcription, translation, processing or function of 273P4B7 as well as cancer vaccines. In one aspect, the invention provides compositions, and methods comprising them, for treating a cancer that expresses 273P4B7 in a human subject wherein the composition comprises a carrier suitable for human use and a human unit dose of one or more than one agent that inhibits the production or function of 273P4B7. Preferably, the carrier is a uniquely human carrier. In another aspect of the invention, the agent is a moiety that is immunoreactive with 273P4B7 protein. Non-limiting examples of such moieties include, but are not limited to, antibodies (such as single chain, monoclonal, polyclonal, humanized, chimeric, or human antibodies), functional equivalents thereof (whether naturally occurring or synthetic), and combinations thereof. The antibodies can be conjugated to a diagnostic or therapeutic moiety. In another aspect, the agent is a small molecule as defined herein.

[0030] In another aspect, the agent comprises one or more than one peptide which comprises a cytotoxic T lymphocyte (CTL) epitope that binds an HLA class I molecule in a human to elicit a CTL response to 273P4B7 and/or one or more than one peptide which comprises a helper T lymphocyte (HTL) epitope which binds an HLA class II molecule in a human to elicit an HTL response. The peptides of the invention may be on the same or on one or more separate polypeptide molecules. In a further aspect of the invention, the agent comprises one or more than one nucleic acid molecule that expresses one or more than one of the CTL or HTL response stimulating peptides as described above. In yet another aspect of the invention, the one or more than one nucleic acid molecule may express a moiety that is immunologically reactive with 273P4B7 as described above. The one or more than one nucleic acid molecule may also be, or encode, a molecule that inhibits production of 273P4B7. Non-limiting examples of such molecules include, but are not limited to, those complementary to a nucleotide sequence essential for production of 273P4B7 (e.g. antisense sequences or molecules that form a triple helix with a nucleotide double helix essential for 273P4B7 production) or a ribozyme effective to lyse 273P4B7 mRNA.

[0031] Note that to determine the starting position of any peptide set forth in Tables VIII-XXI and XXII to XLIX (collectively HLA Peptide Tables) respective to its parental

protein, e.g., variant 1, variant 2, etc., reference is made to three factors: the particular variant, the length of the peptide in an HLA Peptide Table, and the Search Peptides in Table VII. Generally, a unique Search Peptide is used to obtain HLA peptides of a particular for a particular variant. The position of each Search Peptide relative to its respective parent molecule is listed in Table VII. Accordingly, if a Search Peptide begins at position "X", one must add the value "X-1" to each position in Tables VIII-XXI and XXII to XLIX to obtain the actual position of the HLA peptides in their parental molecule. For example, if a particular Search Peptide begins at position 150 of its parental molecule, one must add 150-1, i.e., 149 to each HLA peptide amino acid position to calculate the position of that amino acid in the parent molecule.

[0032] One embodiment of the invention comprises an HLA peptide, that occurs at least twice in Tables VIII-XXI and XXII to XLIX collectively, or an oligonucleotide that encodes the HLA peptide. Another embodiment of the invention comprises an HLA peptide that occurs at least once in Tables VIII-XXI and at least once in tables XXII to XLIX, or an oligonucleotide that encodes the HLA peptide.

[0033] Another embodiment of the invention is antibody epitopes, which comprise a peptide regions, or an oligonucleotide encoding the peptide region, that has one two, three, four, or five of the following characteristics:

[0034] i) a peptide region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Hydrophilicity profile of FIG. 5;

[0035] ii) a peptide region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or less than 0.5, 0.4, 0.3, 0.2, 0.1, or having a value equal to 0.0, in the Hydrophaticity profile of FIG. 6;

[0036] iii) a peptide region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Percent Accessible Residues profile of FIG. 7;

[0037] iv) a peptide region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Average Flexibility profile of FIG. 8; or

[0038] v) a peptide region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Beta-turn profile of FIG. 9.

[0039] Moreover, the invention comprises 273P4B7 nucleic acid and amino acid sequences. Further, the invention comprises variants of 273P4B7, and fragments thereof. In an embodiment of the invention a protein fragment is: a

subsequence of at least 158, or 262, or 420 contiguous amino acids of a protein of 273P4B7 v. 1; is an amino acid subsequence of a protein of 273P4B7 v. 1 with a proviso that 273P4B7 v. 1 protein is such that it does not include an valine (V) or methionine (M) at position 145; arginine (R) or glycine (G) at position 172; isoleucine (I) or valine (V) at position 889; or, lysine (K) or arginine (R) at position 989. An embodiment of an amino acid sequence of the invention is a fragment of a protein of 273P4B7 v. 1 with a proviso that it is not a protein of 273P4B7 v. 9, v. 10 or v.11. In an embodiment, an amino acid fragment of the invention is 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 175, 180, 185, 190, 195, 200, 225, 250, 260, 261, 262, 263, 264, 265, 270, 275, 300, 325, 350, 375, 400, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 422, 434, 435, 450, 475, 500, 525, 550, 575, 600, 650, 675, 700, 705, 710, 715, 716, 717, 718, 719, 720, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1125, 1127, 1150, 1175, 1200, 1025, or 1250 contiguous amino acids of a protein of FIG. 2; in certain embodiments the fragment subsequence comprises a functional or structural motif, e.g., as set forth herein, or comprises an immune system (antibody or T cell) epitope. Embodiments of a nucleic acid sequence of the invention comprise a sequence that encodes an amino acid sequence as set forth herein.

DESCRIPTION OF THE FIGURES

[0040] FIG. 1. The 273P4B7 SSH sequence of 170 nucleotides.

[0041] FIG. 2. A) The cDNA and amino acid sequence of 273P4B7 variant 1 (also called "273P4B7 v.1" or "273P4B7 variant 1") is shown in FIG. 2A. The start methionine is underlined. The open reading frame extends from nucleic acid 95-3847 including the stop codon. B) The cDNA and amino acid sequence of 273P4B7 variant 2 (also called "273P4B7 v.2") is shown in FIG. 2B. The codon for the start methionine is underlined. The open reading frame extends from nucleic acid 604-3987 including the stop codon. C) 273P4B7 v.3 through v.8, SNP variants of 273P4B7 v.1. The 273P4B7 v.3 through v.8 are variants with single nucleotide difference from 273P4B7 v.1. 273P4B7 v.3, v.7, and v.8 code for the same protein as v.1. 273P4B7 v.4, v.5, and v.6 proteins differ from 273P4B7 v.1 by one amino acid. Though these SNP variants are shown separately, they can also occur in any combinations and in any of the transcript variants listed above in FIGS. 2A and 2B. D) The cDNA and amino acid sequence of 273P4B7 variant 9 (also called "273P4B7 v.9") is shown in FIG. 2D. The codon for the start methionine is underlined. The open reading frame extends from nucleic acid 4-3324 including the stop codon. E) The cDNA and amino acid sequence of 273P4B7 variant 10 (also called "273P4B7 v.10") is shown in FIG. 2E. The codon for the start methionine is underlined. The open reading frame extends from nucleic acid 688-1947 including the stop codon. F) The cDNA and amino acid sequence of 273P4B7 variant 11 (also called "273P4B7 v.11") is shown in FIG. 2F. The codon for the start methionine is underlined. The open reading frame extends from nucleic acid 114-1373 including the stop codon.

[0042] FIG. 3. A) The amino acid sequence of 273P4B7 v.1 is shown in FIG. 3A; it has 150 amino acids. B) The amino acid sequence of 273P4B7 v.2 is shown in FIG. 3B; it has 1127 amino acids. C) The amino acid sequence of 273P4B7 v.4 is shown in FIG. 3C; it has 1250 amino acids. D) The amino acid sequence of 273P4B7 v.5 is shown in FIG. 3D; it has 1250 amino acids. E) The amino acid sequence of 273P4B7 v.6 is shown in FIG. 3E; it has 1250 amino acids. F) The amino acid sequence of 273P4B7 v.9 is shown in FIG. 3F; it has 1106 amino acids. G) The amino acid sequence of 273P4B7 v.10 is shown in FIG. 3G; it has 419 amino acids. H) The amino acid sequence of 273P4B7 v.11 is shown in FIG. 3H; it has 419 amino acids. As used herein, a reference to 273P4B7 includes all variants thereof, including those shown in FIGS. 2, 3, 10, and 11, unless the context clearly indicates otherwise.

[0043] FIG. 4. Alignment of 273P4B7 with known homologs. FIG. 4(A) Alignment of 273P4B7 with human un-named protein (gi.vertline.22760345). FIG. 4(B) Alignment of 273P4B7 with human BJ-HCC-15 tumor antigen (gi.vertline.22002580). FIG. 4(C) Alignment of 273P4B7 with Mouse Protein (gi.vertline.27706852).

[0044] FIG. 5. Hydrophilicity amino acid profile of 273P4B7 v.1 determined by computer algorithm sequence analysis using the method of Hopp and Woods (Hopp T. P., Woods K. R., 1981. Proc. Natl. Acad. Sci. U.S.A. 78:3824-3828) accessed on the ProtScale website located on the World Wide Web through the ExPasy molecular biology server.

[0045] FIG. 6. Hydrophobicity amino acid profile of 273P4B7 v.1 determined by computer algorithm sequence analysis using the method of Kyte and Doolittle (Kyte J., Doolittle R. F., 1982. J. Mol. Biol. 157:105-132) accessed on the ProtScale website located on the World Wide Web through the ExPasy molecular biology server.

[0046] FIG. 7. Percent accessible residues amino acid profile of 273P4B7 v.1 determined by computer algorithm sequence analysis using the method of Janin (Janin J., 1979 Nature 277:491-492) accessed on the ProtScale website located on the World Wide Web through the ExPasy molecular biology server.

[0047] FIG. 8. Average flexibility amino acid profile of 273P4B7 v.1 determined by computer algorithm sequence analysis using the method of Bhaskaran and Ponnuswamy (Bhaskaran R., and Ponnuswamy P. K., 1988. Int. J. Pept. Protein Res. 32:242-255) accessed on the ProtScale website located on the World Wide Web through the ExPasy molecular biology server.

[0048] FIG. 9. Beta-turn amino acid profile of 273P4B7 v.1 determined by computer algorithm sequence analysis using the method of Deleage and Roux (Deleage, G., Roux B. 1987 Protein Engineering 1:289-294) accessed on the ProtScale website located on the World Wide Web through the ExPasy molecular biology server.

[0049] FIG. 10. Structures of transcript variants of 273P4B07. Variant 273P4B07 v.2 was identified as a transcript variant of 273P4B07 v.1. Variant 273P4B07 v.2 extended exon 1 by 22 bp as compared to v.1 and added an exon in between exons 1 and 2 of variant v.1. Variants v.9, v.10 and v.11 were part of the last exon of v.1 or v.2. Poly A tails and SNP are not shown here. Numbers in "()"

underneath the boxes correspond to those of 273P4B07 v.1. Lengths of introns and exons are not proportional.

[0050] FIG. 11. Schematic alignment of protein variants of 273P4B07. Protein variants correspond to nucleotide variants. Nucleotide variants 273P4B07 v.3, v.7, and v.8 coded for the same protein as v.1. Variant v.2 coded a protein that was 123 amino acids shorter than v.1. Nucleotide variant 273P4B07 v.2 was a transcript variant of v.1, as shown in FIG. 10. Variants v.9 and v.10 were shorter and had some different amino acid as compared with v.1 in the corresponding positions shown in the figure. Variant v.11 was the same as the C-terminal part of v.1 and different from v.10 by one amino acid at position 158. SNP in v.1 could also appear in v.2. Single amino acid differences were indicated above the boxes. Black boxes represent the same sequence as 273P4B07 v.1. Numbers underneath the box correspond to 273P4B07 v.1.

[0051] FIG. 12. Schematic alignment of SNP variants of 273P4B07. Variants 273P4B07 v.3 through v.8 were variants with single nucleotide differences as compared to variant v.1 (ORF:29-1858). Though these SNP variants were shown separately, they could also occur in any combinations and in any transcript variants that contained the base pairs, such as v.2 shown in FIG. 10. Numbers correspond to those of 273P4B07 v.1. Black box shows the same sequence as 273P4B07 v.1. SNPs are indicated above the box.

[0052] FIG. 13. Secondary structure and transmembrane domains prediction for 273P4B7 protein variant 1. FIG. 13A: The secondary structure of 273P4B7 protein variant 1 (FIG. 13A) (SEQ ID NO: 134) was predicted using the HNN—Hierarchical Neural Network method (NPS@: Network Protein Sequence Analysis TIBS 2000 March Vol. 25, No 3 [291]:147-150, accessed from the ExPasy molecular biology server located on the World Wide Web. This method predicts the presence and location of alpha helices, extended strands, and random coils from the primary protein sequence. The percent of the protein in a given secondary structure is also listed. FIG. 13B: Schematic representation of the probability of existence of transmembrane regions of 273P4B7 variant 1 based on the TMpred algorithm of Hofmann and Stoffel which utilizes TMBASE (K. Hofmann, W. Stoffel. TMBASE—A database of membrane spanning protein segments Biol. Chem. Hoppe-Seyler 374:166, 1993).

[0053] FIG. 13C: Schematic representation of the probability of the existence of transmembrane regions of 273P4B7 variant 1, based on the TMHMM algorithm of Sonnhammer, von Heijne, and Krogh (Erik L. L. Sonnhammer, Gunnar von Heijne, and Anders Krogh: A hidden Markov model for predicting transmembrane helices in protein sequences. In Proc. of Sixth Int. Conf. on Intelligent Systems for Molecular Biology, p 175-182 Ed J. Glasgow, T. Littlejohn, F. Major, R. Lathrop, D. Sankoff, and C. Sensen Menlo Park, Calif.: AAAI Press, 1998). The TMpred and TMHMM algorithms are accessed from the ExPasy molecular biology server located on the World Wide Web.

[0054] FIG. 14. 273P4B7 expression by RT-PCR. First strand cDNA was prepared from normal tissues (bladder, brain, heart, kidney, liver, lung, prostate, spleen, skeletal muscle, testis, pancreas, colon and stomach), and from pools of patient cancer specimens (prostate cancer pool, bladder cancer pool, kidney cancer pool, colon cancer pool, lung

cancer pool, ovary cancer pool, breast cancer pool, cancer metastasis pool, pancreas cancer pool, prostate cancer xenograft pool, prostate metastasis to lymph node, bone and melanoma cancer pool, cervical cancer pool, lymphoma cancer pool, stomach cancer pool, uterus cancer pool, and multi-xenograft pool). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 22, 26 and 30 cycles of amplification. In (FIG. 14A) picture of the RT-PCR agarose gel is shown. In (FIG. 14B) PCR products were quantitated using the AlphaMager software. Results show strong of expression of 273P4B7 in prostate cancer pool, bladder cancer pool, kidney cancer pool, colon cancer pool, lung cancer pool, ovary cancer pool, breast cancer pool, cancer metastasis pool, pancreas cancer pool, prostate cancer xenograft pool, prostate metastasis to lymph node, bone and melanoma cancer pool, cervical cancer pool, lymphoma cancer pool, stomach cancer pool, uterus cancer pool and multi-xenograft pool (prostate cancer, kidney cancer and bladder cancer xenograft pool). In normal tissues, 273P4B7 is predominantly expressed in testis and not in any other normal tissue tested.

[0055] FIG. 15. 273P4B7 expression in normal tissues. Two multiple tissue northern blots (Clontech) both with 2 ug of mRNA/lane were probed with the 273P4B7 sequence. Size standards in kilobases (kb) are indicated on the side. Results show expression of an approximately 7 kb 273P4B7 transcript in normal testis but not in the other normal tissues tested.

[0056] FIG. 16. Expression of 273P4B7 in pancreas, ovary, and testis cancer patient specimens. RNA was extracted from normal pancreas (NP_a), normal ovary (NO), normal testis (NT_e), pancreas cancer patient specimen (P1), ovary cancer patient specimen (P2, P3, P4), and testis cancer patient specimen (P5, P6, P7). Northern blot with 10 ug of total RNA/lane was probed with 273P4B7 SSH sequence. Size standards in kilobases (kb) are indicated on the side. 273P4B7 transcript was detected in the patient specimens, but not in the normal tissues.

[0057] FIG. 17. Expression of 273P4B7 in cervical cancer patient specimens. FIG. 17(A): Total RNA was extracted from cervical cancer patient specimens (T1-T7), and HeLa cell line. Northern blot with 10 ug of total RNA/lane was probed with 273P4B7 SSH sequence. Size standards in kilobases (kb) are indicated on the side. 273P4B7 transcript was detected in all patient specimens tested as well as in the HeLa cell line. FIG. 17(B): First strand cDNA was prepared from a panel of cervical cancer patient specimens, normal cervix and HeLa cervical cell line. Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the AlphaMager software. Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in most of the cervical cancer tissues tested.

[0058] FIG. 18. Expression of 273P4B7 in bladder cancer patient specimens. First strand cDNA was prepared from a panel of bladder cancer patient specimens, normal bladder (N) and bladder cancer cell lines (UM-UC-3, TCCSUP, J82). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7,

was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel (FIG. 18(A)), and PCR products were quantitated using the AlphaMager software (FIG. 18(B)). Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in most of the bladder cancer tissues tested, but not in the normal bladder tissues.

[0059] FIG. 19. Expression of 273P4B7 in colon cancer patient specimens. First strand cDNA was prepared from a panel of colon cancer patient specimens, normal colon, and colon cancer cell lines (LoVo, CaCo-2, SK-CO1, Colo205, and T284). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the AlphaMager software. Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in the majority of the colon cancer tissues tested, but not in the normal colon tissues. Expression was also detected in the cell lines LoVo, CaCo-2, SK-CO1, Colo205, but not in the T284 cell line.

[0060] FIG. 20. Expression of 273P4B7 in ovary cancer patient specimens. First strand cDNA was prepared from a panel of ovarian cancer patient specimens, normal ovary and ovarian cancer cell lines (OV-1063, PA-1, SW626). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the AlphaMager software. Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in the majority of ovary cancer tissues tested as well as in the cell lines, but not in normal ovary.

DETAILED DESCRIPTION OF THE INVENTION

- [0061] Outline of Sections:
- [0062] I.) Definitions
- [0063] II.) 273P4B7 Polynucleotides
- [0064] II.A.) Uses of 273P4B7 Polynucleotides
- [0065] II.A.1.) Monitoring of Genetic Abnormalities
- [0066] II.A.2.) Antisense Embodiments
- [0067] II.A.3.) Primers and Primer Pairs
- [0068] II.A.4.) Isolation of 273P4B7-Encoding Nucleic Acid Molecules
- [0069] II.A.5.) Recombinant Nucleic Acid Molecules and Host-Vector Systems
- [0070] III.) 273P4B7-Related Proteins
- [0071] III.A.) Motif-bearing Protein Embodiments
- [0072] III.B.) Expression of 273P4B7-Related Proteins
- [0073] III.C.) Modifications of 273P4B7-Related Proteins
- [0074] III.D.) Uses of 273P4B7-Related Proteins
- [0075] IV.) 273P4B7 Antibodies
- [0076] V.) 273P4B7 Cellular Immune Responses

- [0077] VI.) 273P4B7 Transgenic Animals
- [0078] VII.) Methods for the Detection of 273P4B7
- [0079] VIII.) Methods for Monitoring the Status of 273P4B7-related Genes and Their Products
- [0080] IX.) Identification of Molecules That Interact With 273P4B7
- [0081] X.) Therapeutic Methods and Compositions
- [0082] X.A.) Anti-Cancer Vaccines
- [0083] X.B.) 273P4B7 as a Target for Antibody-Based Therapy
- [0084] X.C.) 273P4B7 as a Target for Cellular Immune Responses
- [0085] X.C.1. Minigene Vaccines
- [0086] X.C.2. Combinations of CTL Peptides with Helper Peptides
- [0087] X.C.3. Combinations of CTL Peptides with T Cell Priming Agents
- [0088] X.C.4. Vaccine Compositions Comprising DC Pulsed with CTL and/or HTL Peptides
- [0089] X.D.) Adoptive Immunotherapy
- [0090] X.E.) Administration of Vaccines for Therapeutic or Prophylactic Purposes
- [0091] XI.) Diagnostic and Prognostic Embodiments of 273P4B7.
- [0092] XII.) Inhibition of 273P4B7 Protein Function
- [0093] XII.A.) Inhibition of 273P4B7 With Intracellular Antibodies
- [0094] XII.B.) Inhibition of 273P4B7 with Recombinant Proteins
- [0095] XII.C.) Inhibition of 273P4B7 Transcription or Translation
- [0096] XII.D.) General Considerations for Therapeutic Strategies
- [0097] XIII.) Identification, Characterization and Use of Modulators of 273P4B7
- [0098] XIV.) KITS/Articles of Manufacture
- [0099] I. Definitions:

[0100] Unless otherwise defined, all terms of art, notations and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. Many of the techniques and procedures described or referenced herein are well understood and commonly employed using conventional methodology by those skilled in the art, such as, for example, the widely utilized molecular cloning methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 2nd. edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. As appropriate, procedures

involving the use of commercially available kits and reagents are generally carried out in accordance with manufacturer defined protocols and/or parameters unless otherwise noted.

[0101] The terms “advanced prostate cancer”, “locally advanced prostate cancer”, “advanced disease” and “locally advanced disease” mean prostate cancers that have extended through the prostate capsule, and are meant to include stage C disease under the American Urological Association (AUA) system, stage C₁-C₂ disease under the Whitmore-Jewett system, and stage T3-T4 and N+ disease under the TNM (tumor, node, metastasis) system. In general, surgery is not recommended for patients with locally advanced disease, and these patients have substantially less favorable outcomes compared to patients having clinically localized (organ-confined) prostate cancer. Locally advanced disease is clinically identified by palpable evidence of induration beyond the lateral border of the prostate, or asymmetry or induration above the prostate base. Locally advanced prostate cancer is presently diagnosed pathologically following radical prostatectomy if the tumor invades or penetrates the prostatic capsule, extends into the surgical margin, or invades the seminal vesicles.

[0102] “Altering the native glycosylation pattern” is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence 273P4B7 (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence 273P4B7. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

[0103] The term “analog” refers to a molecule which is structurally similar or shares similar or corresponding attributes with another molecule (e.g. a 273P4B7-related protein). For example, an analog of a 273P4B7 protein can be specifically bound by an antibody or T cell that specifically binds to 273P4B7.

[0104] The term “antibody” is used in the broadest sense. Therefore, an “antibody” can be naturally occurring or man-made such as monoclonal antibodies produced by conventional hybridoma technology. Anti-273P4B7 antibodies comprise monoclonal and polyclonal antibodies as well as fragments containing the antigen-binding domain and/or one or more complementarity determining regions of these antibodies.

[0105] An “antibody fragment” is defined as at least a portion of the variable region of the immunoglobulin molecule that binds to its target, i.e., the antigen-binding region. In one embodiment it specifically covers single anti-273P4B7 antibodies and clones thereof (including agonist, antagonist and neutralizing antibodies) and anti-273P4B7 antibody compositions with polyepitopic specificity.

[0106] The term “codon optimized sequences” refers to nucleotide sequences that have been optimized for a particular host species by replacing any codons having a usage frequency of less than about 20%. Nucleotide sequences that have been optimized for expression in a given host species by elimination of spurious polyadenylation sequences, elimination of exon/intron splicing signals, elimination of

transposon-like repeats and/or optimization of GC content in addition to codon optimization are referred to herein as an "expression enhanced sequences."

[0107] A "combinatorial library" is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical "building blocks" such as reagents. For example, a linear combinatorial chemical library, such as a polypeptide (e.g., mutein) library, is formed by combining a set of chemical building blocks called amino acids in every possible way for a given compound length (i.e., the number of amino acids in a polypeptide compound). Numerous chemical compounds are synthesized through such combinatorial mixing of chemical building blocks (Gallop et al., *J. Med. Chem.* 37(9): 1233-1251 (1994)).

[0108] Preparation and screening of combinatorial libraries is well known to those of skill in the art. Such combinatorial chemical libraries include, but are not limited to, peptide libraries (see, e.g., U.S. Pat. No. 5,010,175, Furka, *Pept. Prot. Res.* 37:487-493 (1991), Houghton et al., *Nature*, 354:84-88 (1991)), peptoids (PCT Publication No WO 91/19735), encoded peptides (PCT Publication WO 93/20242), random bio-oligomers (PCT Publication WO 92/00091), benzodiazepines (U.S. Pat. No. 5,288,514), diversomers such as hydantoins, benzodiazepines and dipeptides (Hobbs et al., *Proc. Nat. Acad. Sci. USA* 90:6909-6913 (1993)), vinylogous polypeptides (Hagihara et al., *J. Amer. Chem. Soc.* 114:6568 (1992)), nonpeptidic peptidomimetics with a Beta-D-Glucose scaffolding (Hirschmann et al., *J. Amer. Chem. Soc.* 114:9217-9218 (1992)), analogous organic syntheses of small compound libraries (Chen et al., *J. Amer. Chem. Soc.* 116:2661 (1994)), oligocarbamates (Cho, et al., *Science* 261:1303 (1993)), and/or peptidyl phosphonates (Campbell et al., *J. Org. Chem.* 59:658 (1994)). See, generally, Gordon et al., *J. Med. Chem.* 37:1385 (1994), nucleic acid libraries (see, e.g., Stratagene, Corp.), peptide nucleic acid libraries (see, e.g., U.S. Pat. No. 5,539,083), antibody libraries (see, e.g., Vaughn et al., *Nature Biotechnology* 14(3): 309-314 (1996), and PCT/US96/10287), carbohydrate libraries (see, e.g., Liang et al., *Science* 274:1520-1522 (1996), and U.S. Pat. No. 5,593,853), and small organic molecule libraries (see, e.g., benzodiazepines, Baum, *C&EN*, Jan. 18, page 33 (1993); isoprenoids, U.S. Pat. No. 5,569,588; thiazolidinones and metathiazanones, U.S. Pat. No. 5,549,974; pyrrolidines, U.S. Pat. Nos. 5,525,735 and 5,519,134; morpholino compounds, U.S. Pat. No. 5,506,337; benzodiazepines, U.S. Pat. No. 5,288,514; and the like).

[0109] Devices for the preparation of combinatorial libraries are commercially available (see, e.g., 357 NIPS, 390 NIPS, Advanced Chem Tech, Louisville Ky.; Symphony, Rainin, Woburn, Mass.; 433A, Applied Biosystems, Foster City, Calif.; 9050, Plus, Millipore, Bedford, NIA). A number of well-known robotic systems have also been developed for solution phase chemistries. These systems include automated workstations such as the automated synthesis apparatus developed by Takeda Chemical Industries, LTD. (Osaka, Japan) and many robotic systems utilizing robotic arms (Zymate H, Zymark Corporation, Hopkinton, Mass.; Orca, Hewlett-Packard, Palo Alto, Calif.), which mimic the manual synthetic operations performed by a chemist. Any of the above devices are suitable for use with the present invention. The nature and implementation of modifications

to these devices (if any) so that they can operate as discussed herein will be apparent to persons skilled in the relevant art. In addition, numerous combinatorial libraries are themselves commercially available (see, e.g., ComGenex, Princeton, N.J.; Asinex, Moscow, RU; Tripos, Inc., St. Louis, Mo.; ChemStar, Ltd, Moscow, RU; 3D Pharmaceuticals, Exton, Pa.; Martek Biosciences, Columbia, Md.; etc.).

[0110] The term "cytotoxic agent" refers to a substance that inhibits or prevents the expression activity of cells, function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes chemotherapeutic agents, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Examples of cytotoxic agents include, but are not limited to auristatins, auromycins, maytansinoids, yttrium, bismuth, ricin, ricin A-chain, combrestatin, duocarmycins, dolostatins, doxorubicin, daunorubicin, taxol, cisplatin, cc1065, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, abrin A chain, modeccin A chain, alpha-sarcin, gelonin, mitogellin, retstrictocin, phenomycin, enomycin, curicin, crotin, calicheamicin, *Sapona officinalis* inhibitor, and glucocorticoid and other chemotherapeutic agents, as well as radioisotopes such as At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹² or 213, P³² and radioactive isotopes of Lu including Lu¹⁷⁷. Antibodies may also be conjugated to an anti-cancer pro-drug activating enzyme capable of converting the pro-drug to its active form.

[0111] The "gene product" is sometimes referred to herein as a protein or mRNA. For example, a "gene product of the invention" is sometimes referred to herein as a "cancer amino acid sequence", "cancer protein", "protein of a cancer listed in Table I", a "cancer mRNA", "mRNA of a cancer listed in Table I", etc. In one embodiment, the cancer protein is encoded by a nucleic acid of FIG. 2. The cancer protein can be a fragment, or alternatively, be the full-length protein to the fragment encoded by the nucleic acids of FIG. 2. In one embodiment, a cancer amino acid sequence is used to determine sequence identity or similarity. In another embodiment, the sequences are naturally occurring allelic variants of a protein encoded by a nucleic acid of FIG. 2. In another embodiment, the sequences are sequence variants as further described herein. "High throughput screening" assays for the presence, absence, quantification, or other properties of particular nucleic acids or protein products are well known to those of skill in the art. Similarly, binding assays and reporter gene assays are similarly well known. Thus, e.g., U.S. Pat. No. 5,559,410 discloses high throughput screening methods for proteins; U.S. Pat. No. 5,585,639 discloses high throughput screening methods for nucleic acid binding (i.e., in arrays); while U.S. Pat. Nos. 5,576,220 and 5,541,061 disclose high throughput methods of screening for ligand/antibody binding.

[0112] In addition, high throughput screening systems are commercially available (see, e.g., Amersham Biosciences, Piscataway, N.J.; Zymark Corp., Hopkinton, Mass.; Air Technical Industries, Mentor, Ohio; Beckman Instruments, Inc. Fullerton, Calif.; Precision Systems, Inc., Natick, Mass.; etc.). These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate

in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, e.g., Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

[0113] The term “homolog” refers to a molecule which exhibits homology to another molecule, by for example, having sequences of chemical residues that are the same or similar at corresponding positions.

[0114] “Human Leukocyte Antigen” or “HLA” is a human class I or class II Major Histocompatibility Complex (MHC) protein (see, e.g., Stites, et al., IMMUNOLOGY, 8TH ED., Lange Publishing, Los Altos, Calif. (1994).

[0115] The terms “hybridize”, “hybridizing”, “hybridizes” and the like, used in the context of polynucleotides, are meant to refer to conventional hybridization conditions, preferably such as hybridization in 50% formamide/6×SSC/0.1% SDS/100 µg/ml ssDNA, in which temperatures for hybridization are above 37 degrees C. and temperatures for washing in 0.1×SSC/0.1% SDS are above 55 degrees C.

[0116] The phrases “isolated” or “biologically pure” refer to material which is substantially or essentially free from components which normally accompany the material as it is found in its native state. Thus, isolated peptides in accordance with the invention preferably do not contain materials normally associated with the peptides in their in situ environment. For example, a polynucleotide is said to be “isolated” when it is substantially separated from contaminant polynucleotides that correspond or are complementary to genes other than the 273P4B7 genes or that encode polypeptides other than 273P4B7 gene product or fragments thereof. A skilled artisan can readily employ nucleic acid isolation procedures to obtain an isolated 273P4B7 polynucleotide. A protein is said to be “isolated,” for example, when physical, mechanical or chemical methods are employed to remove the 273P4B7 proteins from cellular constituents that are normally associated with the protein. A skilled artisan can readily employ standard purification methods to obtain an isolated 273P4B7 protein. Alternatively, an isolated protein can be prepared by chemical means.

[0117] The term “mammal” refers to any organism classified as a mammal, including mice, rats, rabbits, dogs, cats, cows, horses and humans. In one embodiment of the invention, the mammal is a mouse. In another embodiment of the invention, the mammal is a human.

[0118] The terms “metastatic prostate cancer” and “metastatic disease” mean prostate cancers that have spread to regional lymph nodes or to distant sites, and are meant to include stage D disease under the AUA system and stage T×N×M+ under the TNM system. As is the case with locally advanced prostate cancer, surgery is generally not indicated for patients with metastatic disease, and hormonal (androgen ablation) therapy is a preferred treatment modality. Patients with metastatic prostate cancer eventually develop an androgen-refractory state within 12 to 18 months of treatment initiation. Approximately half of these androgen-refractory patients die within 6 months after developing that status. The most common site for prostate cancer metastasis is bone.

Prostate cancer bone metastases are often osteoblastic rather than osteolytic (i.e., resulting in net bone formation). Bone metastases are found most frequently in the spine, followed by the femur, pelvis, rib cage, skull and humerus. Other common sites for metastasis include lymph nodes, lung, liver and brain. Metastatic prostate cancer is typically diagnosed by open or laparoscopic pelvic lymphadenectomy, whole body radionuclide scans, skeletal radiography, and/or bone lesion biopsy.

[0119] The term “modulator” or “test compound” or “drug candidate” or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for the capacity to directly or indirectly alter the cancer phenotype or the expression of a cancer sequence, e.g., a nucleic acid or protein sequences, or effects of cancer sequences (e.g., signaling, gene expression, protein interaction, etc.) In one aspect, a modulator will neutralize the effect of a cancer protein of the invention. By “neutralize” is meant that an activity of a protein is inhibited or blocked, along with the consequent effect on the cell. In another aspect, a modulator will neutralize the effect of a gene, and its corresponding protein, of the invention by normalizing levels of said protein. In preferred embodiments, modulators alter expression profiles, or expression profile nucleic acids or proteins provided herein, or downstream effector pathways. In one embodiment, the modulator suppresses a cancer phenotype, e.g. to a normal tissue fingerprint. In another embodiment, a modulator induced a cancer phenotype. Generally, a plurality of assay mixtures is run in parallel with different agent concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration or below the level of detection.

[0120] Modulators, drug candidates or test compounds encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 100 and less than about 2,500 Daltons. Preferred small molecules are less than 2000, or less than 1500 or less than 1000 or less than 500 D. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Modulators also comprise biomolecules such as peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Particularly preferred are peptides. One class of modulators are peptides, for example of from about five to about 35 amino acids, with from about five to about 20 amino acids being preferred, and from about 7 to about 15 being particularly preferred. Preferably, the cancer modulatory protein is soluble, includes a non-transmembrane region, and/or, has an N-terminal Cys to aid in solubility. In one embodiment, the C-terminus of the fragment is kept as a free acid and the N-terminus is a free amine to aid in coupling, i.e., to cysteine. In one embodiment, a cancer protein of the invention is conjugated to an immunogenic agent as discussed herein. In one embodiment, the cancer protein is conjugated to BSA. The peptides of the

invention, e.g., of preferred lengths, can be linked to each other or to other amino acids to create a longer peptide/protein. The modulatory peptides can be digests of naturally occurring proteins as is outlined above, random peptides, or “biased” random peptides. In a preferred embodiment, peptide/protein-based modulators are antibodies, and fragments thereof, as defined herein.

[0121] Modulators of cancer can also be nucleic acids. Nucleic acid modulating agents can be naturally occurring nucleic acids, random nucleic acids, or “biased” random nucleic acids. For example, digests of prokaryotic or eukaryotic genomes can be used in an approach analogous to that outlined above for proteins.

[0122] The term “monoclonal antibody” refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the antibodies comprising the population are identical except for possible naturally occurring mutations that are present in minor amounts.

[0123] A “motif”, as in biological motif of a 273P4B7-related protein, refers to any pattern of amino acids forming part of the primary sequence of a protein, that is associated with a particular function (e.g. protein-protein interaction, protein-DNA interaction, etc) or modification (e.g. that is phosphorylated, glycosylated or amidated), or localization (e.g. secretory sequence, nuclear localization sequence, etc.) or a sequence that is correlated with being immunogenic, either humorally or cellularly. A motif can be either contiguous or capable of being aligned to certain positions that are generally correlated with a certain function or property. In the context of HLA motifs, “motif” refers to the pattern of residues in a peptide of defined length, usually a peptide of from about 8 to about 13 amino acids for a class I HLA motif and from about 6 to about 25 amino acids for a class II HLA motif, which is recognized by a particular HLA molecule. Peptide motifs for HLA binding are typically different for each protein encoded by each human HLA allele and differ in the pattern of the primary and secondary anchor residues.

[0124] A “pharmaceutical excipient” comprises a material such as an adjuvant, a carrier, pH-adjusting and buffering agents, tonicity adjusting agents, wetting agents, preservative, and the like.

[0125] “Pharmaceutically acceptable” refers to a non-toxic, inert, and/or composition that is physiologically compatible with humans or other mammals.

[0126] The term “polynucleotide” means a polymeric form of nucleotides of at least 10 bases or base pairs in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide, and is meant to include single and double stranded forms of DNA and/or RNA. In the art, this term is often used interchangeably with “oligonucleotide”. A polynucleotide can comprise a nucleotide sequence disclosed herein wherein thymidine (T), as shown for example in FIG. 2, can also be uracil (U); this definition pertains to the differences between the chemical structures of DNA and RNA, in particular the observation that one of the four major bases in RNA is uracil (U) instead of thymidine (T).

[0127] The term “polypeptide” means a polymer of at least about 4, 5, 6, 7, or 8 amino acids. Throughout the specification, standard three letter or single letter designations for

amino acids are used. In the art, this term is often used interchangeably with “peptide” or “protein”.

[0128] An HLA “primary anchor residue” is an amino acid at a specific position along a peptide sequence which is understood to provide a contact point between the immunogenic peptide and the HLA molecule. One to three, usually two, primary anchor residues within a peptide of defined length generally defines a “motif” for an immunogenic peptide. These residues are understood to fit in close contact with peptide binding groove of an HLA molecule, with their side chains buried in specific pockets of the binding groove. In one embodiment, for example, the primary anchor residues for an HLA class I molecule are located at position 2 (from the amino terminal position) and at the carboxyl terminal position of a 8, 9, 10, 11, or 12 residue peptide epitope in accordance with the invention. Alternatively, in another embodiment, the primary anchor residues of a peptide binds an HLA class II molecule are spaced relative to each other, rather than to the termini of a peptide, where the peptide is generally of at least 9 amino acids in length. The primary anchor positions for each motif and supermotif are set forth in Table IV. For example, analog peptides can be created by altering the presence or absence of particular residues in the primary and/or secondary anchor positions shown in Table IV. Such analogs are used to modulate the binding affinity and/or population coverage of a peptide comprising a particular HLA motif or supermotif.

[0129] “Radioisotopes” include, but are not limited to the following (non-limiting exemplary uses are also set forth):

[0130] 1 Examples of Medical Isotopes: Isotope Description of use Actinium-225 See Thorium-229 (Th-229) (AC-225) Actinium-227 Parent of Radium-223 (Ra-223) which is an (AC-227) alpha emitter used to treat metastases in the skeleton resulting from cancer (i.e., breast and prostate cancers), and cancer radioimmunotherapy Bismuth-212 See Thorium-228 (Th-228) (Bi-212) Bismuth-213 See Thorium-229 (Th-229) (Bi-213) Cadmium-109 Cancer detection (Cd-109) Cobalt-60 Radiation source for radiotherapy of cancer, (Co-60) for food irradiators, and for sterilization of medical supplies Copper-64 A positron emitter used for cancer therapy (Cu-64) and SPECT imaging Copper-67 Beta/gamma emitter used in cancer (Cu-67) radioimmunotherapy and diagnostic studies (i.e., breast and colon cancers, and lymphoma) Dysprosium-166 Cancer radioimmunotherapy (Dy-166) Erbium-169 Rheumatoid arthritis treatment, particularly (Er-169) for the small joints associated with fingers and toes Europium-152 Radiation source for food irradiation and for (Eu-152) sterilization of medical supplies Europium-154 Radiation source for food irradiation and for (Eu-154) sterilization of medical supplies Gadolinium-153 Osteoporosis detection and nuclear medical (Gd-153) quality assurance devices Gold-198 Implant and intracavity therapy of ovarian, (Au-198) prostate, and brain cancers Holmium-166 Multiple myeloma treatment in targeted (Ho-166) skeletal therapy, cancer radioimmunotherapy, bone marrow ablation, and rheumatoid arthritis treatment Iodine-125 Osteoporosis detection, diagnostic imaging, (I-125) tracer drugs, brain cancer treatment, radiolabeling, tumor imaging, mapping of receptors in the brain, interstitial radiation therapy, brachytherapy for treatment of prostate cancer, determination of glomerular filtration rate (GFR), determination of plasma volume, detection of deep vein

thrombosis of the legs Iodine-131 Thyroid function evaluation, thyroid disease (I-131) detection, treatment of thyroid cancer as well as other non-malignant thyroid diseases (i.e., Graves disease, goiters, and hyperthyroidism), treatment of leukemia, lymphoma, and other forms of cancer (e.g., breast cancer) using radioimmunotherapy Iridium-192 Brachytherapy, brain and spinal cord tumor (Ir-192) treatment, treatment of blocked arteries (i.e., arteriosclerosis and restenosis), and implants for breast and prostate tumors Lutetium-177 Cancer radioimmunotherapy and treatment of (Lu-177) blocked arteries (i.e., arteriosclerosis and restenosis) Molybdenum-99 Parent of Technetium-99m (Tc-99m) which is (Mo-99) used for imaging the brain, liver, lungs, heart, and other organs. Currently, Tc-99m is the most widely used radioisotope used for diagnostic imaging of various cancers and diseases involving the brain, heart, liver, lungs; also used in detection of deep vein thrombosis of the legs Osmium-194 Cancer radioimmunotherapy (Os-194) Palladium-103 Prostate cancer treatment (Pd-103) Platinum-195m Studies on biodistribution and metabolism of (Pt-195m) cisplatin, a chemotherapeutic drug Phosphorus-32 Polycythemia rubra vera (blood cell disease) (P-32) and leukemia treatment, bone cancer diagnosis/treatment; colon, pancreatic, and liver cancer treatment; radiolabeling nucleic acids for in vitro research, diagnosis of superficial tumors, treatment of blocked arteries (i.e., arteriosclerosis and restenosis), and intracavity therapy Phosphorus-33 Leukemia treatment, bone disease (P-33) diagnosis/treatment, radiolabeling, and treatment of blocked arteries (i.e., arteriosclerosis and restenosis) Radium-223 See Actinium-227 (Ac-227) (Ra-223) Rhenium-186 Bone cancer pain relief, rheumatoid arthritis (Re-186) treatment, and diagnosis and treatment of lymphoma and bone, breast, colon, and liver cancers using radioimmunotherapy Rhenium-188 Cancer diagnosis and treatment using (Re-188) radioimmunotherapy, bone cancer pain relief, treatment of rheumatoid arthritis, and treatment of prostate cancer Rhodium-105 Cancer radioimmunotherapy (Rh-105) Samarium-145 Ocular cancer treatment (Sm-145) Samarium-153 Cancer radioimmunotherapy and bone cancer (Sm-153) pain relief Scandium-47 Cancer radioimmunotherapy and bone cancer (Sc-47) pain relief Selenium-75 Radiotracer used in brain studies, imaging of (Se-75) adrenal cortex by gamma-scintigraphy, lateral locations of steroid secreting tumors, pancreatic scanning, detection of hyperactive parathyroid glands, measure rate of bile acid loss from the endogenous pool Strontium-85 Bone cancer detection and brain scans (Sr-85) Strontium-89 Bone cancer pain relief, multiple myeloma (Sr-89) treatment, and osteoblastic therapy Technetium-99m See Molybdenum-99 (Mo-99) (Tc-99m) Thorium-228 Parent of Bismuth-212 (Bi-212) which is an (Th-228) alpha emitter used in cancer radioimmunotherapy Thorium-229 Parent of Actinium-225 (Ac-225) and (Th-229) grandparent of Bismuth-213 (Bi-213) which are alpha emitters used in cancer radioimmunotherapy Thulium-170 Gamma source for blood irradiators, energy (Tm-170) source for implanted medical devices Tin-117m Cancer immunotherapy and bone cancer (Sn-117m) pain relief Tungsten-188 Parent for Rhenium-188 (Re-188) which is used (W-188) for cancer diagnostics/treatment, bone cancer pain relief, rheumatoid arthritis treatment, and treatment of blocked arteries (i.e., arteriosclerosis and restenosis) Xenon-127 Neuroimaging of brain disorders, high (Xe-127) resolution SPECT studies, pulmonary function tests, and cerebral blood flow studies Ytterbium-175

Cancer radioimmunotherapy (Yb-175) Yttrium-90 Microseeds obtained from irradiating (Y-90) Yttrium-89 (Y-89) for liver cancer treatment Yttrium-91 A gamma-emitting label for Yttrium-90 (Y-90) (Y-91) which is used for cancer radioimmunotherapy (i.e., lymphoma, breast, colon, kidney, lung, ovarian, prostate, pancreatic, and inoperable liver cancers)

[0131] By “randomized” or grammatical equivalents as herein applied to nucleic acids and proteins is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. These random peptides (or nucleic acids, discussed herein) can incorporate any nucleotide or amino acid at any position. The synthetic process can be designed to generate randomized proteins or nucleic acids, to allow the formation of all or most of the possible combinations over the length of the sequence, thus forming a library of randomized candidate bioactive proteinaceous agents.

[0132] In one embodiment, a library is “fully randomized,” with no sequence preferences or constants at any position. In another embodiment, the library is a “biased random” library. That is, some positions within the sequence either are held constant, or are selected from a limited number of possibilities. For example, the nucleotides or amino acid residues are randomized within a defined class, e.g., of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of nucleic acid binding domains, the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, etc., or to purines, etc.

[0133] A “recombinant” DNA or RNA molecule is a DNA or RNA molecule that has been subjected to molecular manipulation in vitro.

[0134] Non-limiting examples of small molecules include compounds that bind or interact with 273P4B7, ligands including hormones, neuropeptides, chemokines, odorants, phospholipids, and functional equivalents thereof that bind and preferably inhibit 273P4B7 protein function. Such non-limiting small molecules preferably have a molecular weight of less than about 10 kDa, more preferably below about 9, about 8, about 7, about 6, about 5 or about 4 kDa. In certain embodiments, small molecules physically associate with, or bind, 273P4B7 protein; are not found in naturally occurring metabolic pathways; and/or are more soluble in aqueous than non-aqueous solutions

[0135] “Stringency” of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured nucleic acid sequences to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature that can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation

of stringency of hybridization reactions, see Ausubel et al., *Current Protocols in Molecular Biology*, Wiley Interscience Publishers, (1995).

[0136] “Stringent conditions” or “high stringency conditions”, as defined herein, are identified by, but not limited to, those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50° C.; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42° C.; or (3) employ 50% formamide, 5×SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5×Denhardt’s solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42° C., with washes at 42° C. in 0.2×SSC (sodium chloride/sodium citrate) and 50% formamide at 55° C., followed by a high-stringency wash consisting of 0.1×SSC containing EDTA at 55° C. “Moderately stringent conditions” are described by, but not limited to, those in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and % SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37° C. in a solution comprising: 20% formamide, 5×SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5×Denhardt’s solution, 10% dextran sulfate, and 20 mg/mL denatured sheared salmon sperm DNA, followed by washing the filters in 1×SSC at about 37-50° C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

[0137] An HLA “supermotif” is a peptide binding specificity shared by HLA molecules encoded by two or more HLA alleles. Overall phenotypic frequencies of HLA-supertypes in different ethnic populations are set forth in Table IV (F). The non-limiting constituents of various supertypes are as follows:

A2: A*0201, A*0202, A*0203, A*0204, A*0205, A*0206, A*6802, A*6901, A*0207

A3: A3, A11, A31, A*3301, A*6801, A*0301, A*1101, A*3101

B7: B7, B*3501-03, B*51, B*5301, B*5401, B*5501, B*5502, B*5601, B*6701, B*7801, B*0702, B*5101, B*5602

B44: B*3701, B*4402, B*4403, B*60 (B*4001), B61 (B*4006)

A1: A*0102, A*2604, A*3601, A*4301, A*8001

A24: A*24, A*30, A*2403, A*2404, A*3002, A*3003

B27: B*1401-02, B*1503, B*1509, B*1510, B*1518, B*3801-02, B*3901, B*3902, B*3903-04, B*4801-02, B*7301, B*2701-08

B58: B*1516, B*1517, B*5701, B*5702, B58

B62: B*4601, B52, B*1501 (B62), B*1502 (B75), B*1513 (B77)

[0138] Calculated population coverage afforded by different HLA-supertype combinations are set forth in Table IV (G).

[0139] As used herein “to treat” or “therapeutic” and grammatically related terms, refer to any improvement of any consequence of disease, such as prolonged survival, less morbidity, and/or a lessening of side effects which are the byproducts of an alternative therapeutic modality; full eradication of disease is not required.

[0140] A “transgenic animal” (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A “transgene” is a DNA that is integrated into the genome of a cell from which a transgenic animal develops.

[0141] As used herein, an HLA or cellular immune response “vaccine” is a composition that contains or encodes one or more peptides of the invention. There are numerous embodiments of such vaccines, such as a cocktail of one or more individual peptides; one or more peptides of the invention comprised by a polypeptidic peptide; or nucleic acids that encode such individual peptides or polypeptides, e.g., a minigene that encodes a polypeptidic peptide. The “one or more peptides” can include any whole unit integer from 1-150 or more, e.g., at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, or 150 or more peptides of the invention. The peptides or polypeptides can optionally be modified, such as by lipidation, addition of targeting or other sequences. HLA class I peptides of the invention can be admixed with, or linked to, HLA class II peptides, to facilitate activation of both cytotoxic T lymphocytes and helper T lymphocytes. HLA vaccines can also comprise peptide-pulsed antigen presenting cells, e.g., dendritic cells.

[0142] The term “variant” refers to a molecule that exhibits a variable from a described type or norm, such as a protein that has one or more different amino acid residues in the corresponding position(s) of a specifically described protein (e.g. the 273P4B7 protein shown in FIG. 2 or FIG. 3. An analog is an example of a variant protein. Splice isoforms and single nucleotides polymorphisms (SNPs) are further examples of variants.

[0143] The “273P4B7-related proteins” of the invention include those specifically identified herein, as well as allelic variants, conservative substitution variants, analogs and homologs that can be isolated/generated and characterized without undue experimentation following the methods outlined herein or readily available in the art. Fusion proteins that combine parts of different 273P4B7 proteins or fragments thereof, as well as fusion proteins of a 273P4B7 protein and a heterologous polypeptide are also included. Such 273P4B7 proteins are collectively referred to as the 273P4B7-related proteins, the proteins of the invention, or 273P4B7. The term “273P4B7-related protein” refers to a polypeptide fragment or a 273P4B7 protein sequence of 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more than 25 amino acids; or, at least 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170,

175, 180, 185, 190, 195, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, or 576 or more amino acids.

[0144] II.) 273P4B7 Polynucleotides

[0145] One aspect of the invention provides polynucleotides corresponding or complementary to all or part of a 273P4B7 gene, mRNA, and/or coding sequence, preferably in isolated form, including polynucleotides encoding a 273P4B7-related protein and fragments thereof, DNA, RNA, DNA/RNA hybrid, and related molecules, polynucleotides or oligonucleotides complementary to a 273P4B7 gene or mRNA sequence or a part thereof, and polynucleotides or oligonucleotides that hybridize to a 273P4B7 gene, mRNA, or to a 273P4B7 encoding polynucleotide (collectively, "273P4B7 polynucleotides"). In all instances when referred to in this section, T can also be U in FIG. 2.

[0146] Embodiments of a 273P4B7 polynucleotide include: a 273P4B7 polynucleotide having the sequence shown in FIG. 2, the nucleotide sequence of 273P4B7 as shown in FIG. 2 wherein T is U; at least 10 contiguous nucleotides of a polynucleotide having the sequence as shown in FIG. 2; or, at least 10 contiguous nucleotides of a polynucleotide having the sequence as shown in FIG. 2 where T is U. For example, embodiments of 273P4B7 nucleotides comprise, without limitation:

(I) a polynucleotide comprising, consisting essentially of, or consisting of a sequence as shown in FIG. 2, wherein T can also be U;

(II) a polynucleotide comprising, consisting essentially of, or consisting of the sequence as shown in FIG. 2A, from nucleotide residue number 95 through nucleotide residue number 3847, including the stop codon, wherein T can also be U;

(III) a polynucleotide comprising, consisting essentially of, or consisting of the sequence as shown in FIG. 2B, from nucleotide residue number 604 through nucleotide residue number 3987, including the stop codon, wherein T can also be U;

(IV) a polynucleotide that encodes a 273P4B7-related protein that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homologous to an entire amino acid sequence shown in FIG. 2A-F;

(V) a polynucleotide that encodes a 273P4B7-related protein that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identical to an entire amino acid sequence shown in FIG. 2A-F;

(VI) a polynucleotide that encodes at least one peptide set forth in Tables VIII-XXI and XXII-XLIX;

[0147] (VII) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIGS. 3A and 3C-3E in any whole number increment up to 1250 that includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Hydrophilicity profile of FIG. 5;

[0148] (VIII) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,

18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIGS. 3A and 3C-3E in any whole number increment up to 1250 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value less than 0.5 in the Hydrophobicity profile of FIG. 6;

[0149] (IX) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIGS. 3A and 3C-3E in any whole number increment up to 1250 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Percent Accessible Residues profile of FIG. 7;

[0150] (X) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIGS. 3A and 3C-3E in any whole number increment up to 1250 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Average Flexibility profile of FIG. 8;

[0151] (XI) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIGS. 3A and 3C-3E in any whole number increment up to 1250 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Beta-turn profile of FIG. 9;

[0152] (XII) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIG. 3B in any whole number increment up to 1127 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acid position(s) having a value greater than 0.5 in the Hydrophobicity profile of FIG. 5;

[0153] (XIII) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIG. 3B in any whole number increment up to 1127 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acid position(s) having a value less than 0.5 in the Hydrophobicity profile of FIG. 6;

[0154] (XIV) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIG. 3B in any whole number increment up to 1127 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acid position(s) having a value greater than 0.5 in the Percent Accessible Residues profile of FIG. 7;

[0155] (XV) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIG. 3B in any whole number increment up to 1127 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acid position(s) having a value greater than 0.5 in the Average Flexibility profile of FIG. 8;

[0156] (XVI) a polynucleotide that encodes a peptide region of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a peptide of FIG. 3B in any whole number increment up to 1127 that includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acid position(s) having a value greater than 0.5 in the Beta-turn profile of FIG. 9;

(XVII) a polynucleotide that is fully complementary to a polynucleotide of any one of (I)-(XVI);

(XVIII) a polynucleotide that is fully complementary to a polynucleotide of any one of (I)-(XVII);

(XIX) a peptide that is encoded by any of (I) to (XVIII); and;

(XX) a composition comprising a polynucleotide of any of (I)-(XVIII) or peptide of (XIX) together with a pharmaceutical excipient and/or in a human unit dose form;

(XXI) a method of using a polynucleotide of any (I)-(XVIII) or peptide of (XIX) or a composition of (XX) in a method to modulate a cell expressing 273P4B7;

(XXII) a method of using a polynucleotide of any (I)-(XVIII) or peptide of (XIX) or a composition of (XX) in a method to diagnose, prophylax, prognose, or treat an individual who bears a cell expressing 273P4B7;

[0157] (XXIII) a method of using a polynucleotide of any (I)-(XVIII) or peptide of (XIX) or a composition of (XX) in a method to diagnose, prophylax, prognose, or treat an individual who bears a cell expressing 273P4B7, said cell from a cancer of a tissue listed in Table I;

(XXIV) a method of using a polynucleotide of any (I)-(XXVIII) or peptide of (XIX) or a composition of (XX) in a method to diagnose, prophylax, prognose, or treat a cancer;

(XXV) a method of using a polynucleotide of any (I)-(XXVIII) or peptide of (XIX) or a composition of (XX) in a method to diagnose, prophylax, prognose, or treat a cancer of a tissue listed in Table I; and;

(XXVI) a method of using a polynucleotide of any (I)-(XXVIII) or peptide of (XIX) or a composition of (XX) in a method to identify or characterize a modulator of a cell expressing 273P4B7.

[0158] As used herein, a range is understood to disclose specifically all whole unit positions thereof.

[0159] Typical embodiments of the invention disclosed herein include 273P4B7 polynucleotides that encode specific portions of 273P4B7 mRNA sequences (and those which are complementary to such sequences) such as those that encode the proteins and/or fragments thereof, for example:

[0160] (a) 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1125, 1150, 1175, 1200, 1225, 1235, 1240, 1245, 1250 or more contiguous amino acids of 273P4B7 variant 1; the maximal lengths relevant for other variants are: variant 2, 1127 amino acids; variant 4, 1250 amino acids, variant 5, 1250 amino acids, variant 6, 1250 amino acids, variant 9, 1106 amino acids; variant 10, 419 amino acids; and variant 11, 419 amino acids.

[0161] For example, representative embodiments of the invention disclosed herein include: polynucleotides and their encoded peptides themselves encoding about amino acid 1 to about amino acid 10 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 10 to about amino acid 20 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 20 to about amino acid 30 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 30 to about amino acid 40 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 40 to about amino acid 50 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 50 to about amino acid 60 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 60 to about amino acid 70 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 70 to about amino acid 80 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 80 to about amino acid 90 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, polynucleotides encoding about amino acid 90 to about amino acid 100 of the 273P4B7 protein shown in FIG. 2 or FIG. 3, in increments of about 10 amino acids, ending at the carboxyl terminal amino acid set forth in FIG. 2 or FIG. 3. Accordingly, polynucleotides encoding portions of the amino acid sequence (of about 10 amino acids), of amino acids, 100 through the carboxyl terminal amino acid of the 273P4B7 protein are embodiments of the invention. Wherein it is understood that each particular amino acid position discloses that position plus or minus five amino acid residues.

[0162] Polynucleotides encoding relatively long portions of a 273P4B7 protein are also within the scope of the invention. For example, polynucleotides encoding from about amino acid 1 (or 20 or 30 or 40 etc.) to about amino acid 20, (or 30, or 40 or 50 etc.) of the 273P4B7 protein "or variant" shown in FIG. 2 or FIG. 3 can be generated by a variety of techniques well known in the art. These polynucleotide fragments can include any portion of the 273P4B7 sequence as shown in FIG. 2.

[0163] Additional illustrative embodiments of the invention disclosed herein include 273P4B7 polynucleotide fragments encoding one or more of the biological motifs contained within a 273P4B7 protein "or variant" sequence, including one or more of the motif-bearing subsequences of a 273P4B7 protein "or variant" set forth in Tables VIII-XXI and XXII-XLIX. In another embodiment, typical polynucleotide fragments of the invention encode one or more of the regions of 273P4B7 protein or variant that exhibit homology

to a known molecule. In another embodiment of the invention, typical polynucleotide fragments can encode one or more of the 273P4B7 protein or variant N-glycosylation sites, cAMP and cGMP-dependent protein kinase phosphorylation sites, casein kinase 11 phosphorylation sites or N-myristoylation site and amidation sites.

[0164] Note that to determine the starting position of any peptide set forth in Tables VIII-XXI and Tables XXII to XLIX (collectively HLA Peptide Tables) respective to its parental protein, e.g., variant 1, variant 2, etc., reference is made to three factors: the particular variant, the length of the peptide in an HLA Peptide Table, and the Search Peptides listed in Table VII. Generally, a unique Search Peptide is used to obtain HLA peptides for a particular variant. The position of each Search Peptide relative to its respective parent molecule is listed in Table VII. Accordingly, if a Search Peptide begins at position "X", one must add the value "X minus 1" to each position in Tables VIII-XXI and Tables XXII-IL to obtain the actual position of the HLA peptides in their parental molecule. For example if a particular Search Peptide begins at position 150 of its parental molecule, one must add 150-1, i.e., 149 to each HLA peptide amino acid position to calculate the position of that amino acid in the parent molecule.

[0165] II.A.) Uses of 273P4B7 Polynucleotides

[0166] II.A.1.) Monitoring of Genetic Abnormalities

[0167] The polynucleotides of the preceding paragraphs have a number of different specific uses. The human 273P4B7 gene maps to the chromosomal location set forth in the Example entitled "Chromosomal Mapping of 273P4B7." For example, because the 273P4B7 gene maps to this chromosome, polynucleotides that encode different regions of the 273P4B7 proteins are used to characterize cytogenetic abnormalities of this chromosomal locale, such as abnormalities that are identified as being associated with various cancers. In certain genes, a variety of chromosomal abnormalities including rearrangements have been identified as frequent cytogenetic abnormalities in a number of different cancers (see e.g. Krajcinovic et al., *Mutat. Res.* 382(3-4): 81-83 (1998); Johansson et al., *Blood* 86(10): 3905-3914 (1995) and Finger et al., *P.N.A.S.* 85(23): 9158-9162 (1988)). Thus, polynucleotides encoding specific regions of the 273P4B7 proteins provide new tools that can be used to delineate, with greater precision than previously possible, cytogenetic abnormalities in the chromosomal region that encodes 273P4B7 that may contribute to the malignant phenotype. In this context, these polynucleotides satisfy a need in the art for expanding the sensitivity of chromosomal screening in order to identify more subtle and less common chromosomal abnormalities (see e.g. Evans et al., *Am. J. Obstet. Gynecol* 171(4): 1055-1057(1994)).

[0168] Furthermore, as 273P4B7 was shown to be highly expressed in prostate and other cancers, 273P4B7 polynucleotides are used in methods assessing the status of 273P4B7 gene products in normal versus cancerous tissues. Typically, polynucleotides that encode specific regions of the 273P4B7 proteins are used to assess the presence of perturbations (such as deletions, insertions, point mutations, or alterations resulting in a loss of an antigen etc.) in specific regions of the 273P4B7 gene, such as regions containing one or more motifs. Exemplary assays include both RT-PCR assays as well as single-strand conformation polymorphism

(SSCP) analysis (see, e.g., Marrogi et al., *J. Cutan. Pathol.* 26(8): 369-378 (1999), both of which utilize polynucleotides encoding specific regions of a protein to examine these regions within the protein.

[0169] II.A.2.) Antisense Embodiments

[0170] Other specifically contemplated nucleic acid related embodiments of the invention disclosed herein are genomic DNA, cDNAs, ribozymes, and antisense molecules, as well as nucleic acid molecules based on an alternative backbone, or including alternative bases, whether derived from natural sources or synthesized, and include molecules capable of inhibiting the RNA or protein expression of 273P4B7. For example, antisense molecules can be RNAs or other molecules, including peptide nucleic acids (PNAs) or non-nucleic acid molecules such as phosphorothioate derivatives that specifically bind DNA or RNA in a base pair-dependent manner. A skilled artisan can readily obtain these classes of nucleic acid molecules using the 273P4B7 polynucleotides and polynucleotide sequences disclosed herein.

[0171] Antisense technology entails the administration of exogenous oligonucleotides that bind to a target polynucleotide located within the cells. The term "antisense" refers to the fact that such oligonucleotides are complementary to their intracellular targets, e.g., 273P4B7. See for example, Jack Cohen, *Oligodeoxynucleotides, Antisense Inhibitors of Gene Expression*, CRC Press, 1989; and *Synthesis 1:1-5* (1988). The 273P4B7 antisense oligonucleotides of the present invention include derivatives such as S-oligonucleotides (phosphorothioate derivatives or S-oligos, see, Jack Cohen, *supra*), which exhibit enhanced cancer cell growth inhibitory action. S-oligos (nucleoside phosphorothioates) are isoelectronic analogs of an oligonucleotide (O-oligo) in which a nonbridging oxygen atom of the phosphate group is replaced by a sulfur atom. The S-oligos of the present invention can be prepared by treatment of the corresponding O-oligos with 3H-1,2-benzodithiol-3-one-1,1-dioxide, which is a sulfur transfer reagent. See, e.g., Iyer, R. P. et al., *J. Org. Chem.* 55:4693-4698 (1990); and Iyer, R. P. et al., *J. Am. Chem. Soc.* 112:1253-1254 (1990). Additional 273P4B7 antisense oligonucleotides of the present invention include morpholino antisense oligonucleotides known in the art (see, e.g., Partridge et al., 1996, *Antisense & Nucleic Acid Drug Development* 6: 169-175).

[0172] The 273P4B7 antisense oligonucleotides of the present invention typically can be RNA or DNA that is complementary to and stably hybridizes with the first 100 5' codons or last 100 3' codons of a 273P4B7 genomic sequence or the corresponding mRNA. Absolute complementarity is not required, although high degrees of complementarity are preferred. Use of an oligonucleotide complementary to this region allows for the selective hybridization to 273P4B7 mRNA and not to mRNA specifying other regulatory subunits of protein kinase. In one embodiment, 273P4B7 antisense oligonucleotides of the present invention are 15 to 30-mer fragments of the antisense DNA molecule that have a sequence that hybridizes to 273P4B7 mRNA. Optionally, 273P4B7 antisense oligonucleotide is a 30-mer oligonucleotide that is complementary to a region in the first 10 5' codons or last 10 3' codons of 273P4B7. Alternatively, the antisense molecules are modified to employ ribozymes

in the inhibition of 273P4B7 expression, see, e.g., L. A. Couture & D. T. Stinchcomb; Trends Genet. 12: 510-515 (1996).

[0173] II.A.3.) Primers and Primer Pairs

[0174] Further specific embodiments of these nucleotides of the invention include primers and primer pairs, which allow the specific amplification of polynucleotides of the invention or of any specific parts thereof, and probes that selectively or specifically hybridize to nucleic acid molecules of the invention or to any part thereof. Probes can be labeled with a detectable marker, such as, for example, a radioisotope, fluorescent compound, bioluminescent compound, a chemiluminescent compound, metal chelator or enzyme. Such probes and primers are used to detect the presence of a 273P4B7 polynucleotide in a sample and as a means for detecting a cell expressing a 273P4B7 protein.

[0175] Examples of such probes include polypeptides comprising all or part of the human 273P4B7 cDNA sequence shown in FIG. 2. Examples of primer pairs capable of specifically amplifying 273P4B7 mRNAs are also described in the Examples. As will be understood by the skilled artisan, a great many different primers and probes can be prepared based on the sequences provided herein and used effectively to amplify and/or detect a 273P4B7 mRNA.

[0176] The 273P4B7 polynucleotides of the invention are useful for a variety of purposes, including but not limited to their use as probes and primers for the amplification and/or detection of the 273P4B7 gene(s), mRNA(s), or fragments thereof; as reagents for the diagnosis and/or prognosis of prostate cancer and other cancers; as coding sequences capable of directing the expression of 273P4B7 polypeptides; as tools for modulating or inhibiting the expression of the 273P4B7 gene(s) and/or translation of the 273P4B7 transcript(s); and as therapeutic agents.

[0177] The present invention includes the use of any probe as described herein to identify and isolate a 273P4B7 or 273P4B7 related nucleic acid sequence from a naturally occurring source, such as humans or other mammals, as well as the isolated nucleic acid sequence per se, which would comprise all or most of the sequences found in the probe used.

[0178] II.A.4.) Isolation of 273P4B7-Encoding Nucleic Acid Molecules

[0179] The 273P4B7 cDNA sequences described herein enable the isolation of other polynucleotides encoding 273P4B7 gene product(s), as well as the isolation of polynucleotides encoding 273P4B7 gene product homologs, alternatively spliced isoforms, allelic variants, and mutant forms of a 273P4B7 gene product as well as polynucleotides that encode analogs of 273P4B7-related proteins. Various molecular cloning methods that can be employed to isolate full length cDNAs encoding a 273P4B7 gene are well known (see, for example, Sambrook, J. et al., Molecular Cloning: A Laboratory Manual, 2d edition, Cold Spring Harbor Press, New York, 1989; Current Protocols in Molecular Biology, Ausubel et al., Eds., Wiley and Sons, 1995). For example, lambda phage cloning methodologies can be conveniently employed, using commercially available cloning systems (e.g., Lambda ZAP Express, Stratagene). Phage clones containing 273P4B7 gene cDNAs can be identified by probing with a labeled 273P4B7 cDNA or

a fragment thereof. For example, in one embodiment, a 273P4B7 cDNA (e.g., FIG. 2) or a portion thereof can be synthesized and used as a probe to retrieve overlapping and full-length cDNAs corresponding to a 273P4B7 gene. A 273P4B7 gene itself can be isolated by screening genomic DNA libraries, bacterial artificial chromosome libraries (BACs), yeast artificial chromosome libraries (YACs), and the like, with 273P4B7 DNA probes or primers.

[0180] II.A.5.) Recombinant Nucleic Acid Molecules and Host-Vector Systems

[0181] The invention also provides recombinant DNA or RNA molecules containing a 273P4B7 polynucleotide, a fragment, analog or homologue thereof, including but not limited to phages, plasmids, phagemids, cosmids, YACs, BACs, as well as various viral and non-viral vectors well known in the art, and cells transformed or transfected with such recombinant DNA or RNA molecules. Methods for generating such molecules are well known (see, for example, Sambrook et al., 1989, supra).

[0182] The invention further provides a host-vector system comprising a recombinant DNA molecule containing a 273P4B7 polynucleotide, fragment, analog or homologue thereof within a suitable prokaryotic or eukaryotic host cell. Examples of suitable eukaryotic host cells include a yeast cell, a plant cell, or an animal cell, such as a mammalian cell or an insect cell (e.g., a baculovirus-infectible cell such as an Sf9 or HighFive cell). Examples of suitable mammalian cells include various prostate cancer cell lines such as DU145 and TsuPr1, other transfectable or transducible prostate cancer cell lines, primary cells (PrEC), as well as a number of mammalian cells routinely used for the expression of recombinant proteins (e.g., COS, CHO, 293, 293T cells). More particularly, a polynucleotide comprising the coding sequence of 273P4B7 or a fragment, analog or homologue thereof can be used to generate 273P4B7 proteins or fragments thereof using any number of host-vector systems routinely used and widely known in the art.

[0183] A wide range of host-vector systems suitable for the expression of 273P4B7 proteins or fragments thereof are available, see for example, Sambrook et al., 1989, supra; Current Protocols in Molecular Biology, 1995, supra). Preferred vectors for mammalian expression include but are not limited to pcDNA 3.1 myc-His-tag (Invitrogen) and the retroviral vector pSR.alpha.tkneo (Muller et al., 1991, MCB 111:1785). Using these expression vectors, 273P4B7 can be expressed in several prostate cancer and non-prostate cell lines, including for example 293, 293T, rat-1, NIH 3T3 and TsuPr1. The host-vector systems of the invention are useful for the production of a 273P4B7 protein or fragment thereof. Such host-vector systems can be employed to study the functional properties of 273P4B7 and 273P4B7 mutations or analogs.

[0184] Recombinant human 273P4B7 protein or an analog or homolog or fragment thereof can be produced by mammalian cells transfected with a construct encoding a 273P4B7-related nucleotide. For example, 293T cells can be transfected with an expression plasmid encoding 273P4B7 or fragment, analog or homolog thereof, a 273P4B7-related protein is expressed in the 293T cells, and the recombinant 273P4B7 protein is isolated using standard purification methods (e.g., affinity purification using anti-273P4B7 antibodies). In another embodiment, a 273P4B7 coding

sequence is subcloned into the retroviral vector pSR.alpha.-MSVtkneo and used to infect various mammalian cell lines, such as NIH 3T3, TsuPr1, 293 and rat-1 in order to establish 273P4B7 expressing cell lines. Various other expression systems well known in the art can also be employed. Expression constructs encoding a leader peptide joined in frame to a 273P4B7 coding sequence can be used for the generation of a secreted form of recombinant 273P4B7 protein.

[0185] As discussed herein, redundancy in the genetic code permits variation in 273P4B7 gene sequences. In particular, it is known in the art that specific host species often have specific codon preferences, and thus one can adapt the disclosed sequence as preferred for a desired host. For example, preferred analog codon sequences typically have rare codons (i.e., codons having a usage frequency of less than about 20% in known sequences of the desired host) replaced with higher frequency codons. Codon preferences for a specific species are calculated, for example, by utilizing codon usage tables available on the INTERNET such as at URL dna.affrc.go.jp/about.nakamura/codon.html.

[0186] Additional sequence modifications are known to enhance protein expression in a cellular host. These include elimination of sequences encoding spurious polyadenylation signals, exon/intron splice site signals, transposon-like repeats, and/or other such well-characterized sequences that are deleterious to gene expression. The GC content of the sequence is adjusted to levels average for a given cellular host, as calculated by reference to known genes expressed in the host cell. Where possible, the sequence is modified to avoid predicted hairpin secondary mRNA structures. Other useful modifications include the addition of a translational initiation consensus sequence at the start of the open reading frame, as described in Kozak, *Mol. Cell. Biol.*, 9:5073-5080 (1989). Skilled artisans understand that the general rule that eukaryotic ribosomes initiate translation exclusively at the 5' proximal AUG codon is abrogated only under rare conditions (see, e.g., Kozak *PNAS* 92(7): 2662-2666, (1995) and Kozak *NAR* 15(20): 8125-8148 (1987)).

[0187] III.) 273P4B7-Related Proteins

[0188] Another aspect of the present invention provides 273P4B7-related proteins. Specific embodiments of 273P4B7 proteins comprise a polypeptide having all or part of the amino acid sequence of human 273P4B7 as shown in FIG. 2 or FIG. 3. Alternatively, embodiments of 273P4B7 proteins comprise variant, homolog or analog polypeptides that have alterations in the amino acid sequence of 273P4B7 shown in FIG. 2 or FIG. 3.

[0189] Embodiments of a 273P4B7 polypeptide include: a 273P4B7 polypeptide having a sequence shown in FIG. 2, a peptide sequence of a 273P4B7 as shown in FIG. 2 wherein T is U; at least 10 contiguous nucleotides of a polypeptide having the sequence as shown in FIG. 2; or, at least 10 contiguous peptides of a polypeptide having the sequence as shown in FIG. 2 where T is U. For example, embodiments of 273P4B7 peptides comprise, without limitation:

(I) a protein comprising, consisting essentially of, or consisting of an amino acid sequence as shown in FIG. 2A-F or FIG. 3A-H;

(II) a 273P4B7-related protein that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% homologous to an entire amino acid sequence shown in FIG. 2A-F or 3A-H;

(III) a 273P4B7-related protein that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% identical to an entire amino acid sequence shown in FIG. 2A-F or 3A-H;

(IV) a protein that comprises at least one peptide set forth in Tables VIII to XLIX, optionally with a proviso that it is not an entire protein of FIG. 2;

(V) a protein that comprises at least one peptide set forth in Tables VIII-XXI, collectively, which peptide is also set forth in Tables XXII to XLIX, collectively, optionally with a proviso that it is not an entire protein of FIG. 2;

(VI) a protein that comprises at least two peptides selected from the peptides set forth in Tables VIII-XLIX, optionally with a proviso that it is not an entire protein of FIG. 2;

(VII) a protein that comprises at least two peptides selected from the peptides set forth in Tables VIII to XLIX collectively, with a proviso that the protein is not a contiguous sequence from an amino acid sequence of FIG. 2;

[0190] (VIII) a protein that comprises at least one peptide selected from the peptides set forth in Tables VIII-XXI; and at least one peptide selected from the peptides set forth in Tables XXII to XLIX, with a proviso that the protein is not a contiguous sequence from an amino acid sequence of FIG. 2;

[0191] (IX) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIGS. 3A, 3C-3E in any whole number increment up to 1250 respectively that includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acid position(s) having a value greater than 0.5 in the Hydrophilicity profile of FIG. 5;

[0192] (X) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIGS. 3A, 3C-3E, in any whole number increment up to 1250 respectively that includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value less than 0.5 in the Hydropathicity profile of FIG. 6;

[0193] (XI) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIGS. 3A, 3C-3E, in any whole number increment up to 1250 respectively that includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Percent Accessible Residues profile of FIG. 7;

[0194] (XII) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIGS. 3A, 3C-3E, in any whole number increment up to 1250 respectively that includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Average Flexibility profile of FIG. 8;

[0195] (XIII) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acids of a protein of FIGS. 3A, 3C-3E in any whole number increment up to 1250 respectively that includes at least at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Beta-turn profile of FIG. 9;

[0196] (XIV) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIG. 3B, in any whole number increment up to 1127 respectively that includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Hydrophilicity profile of FIG. 5;

[0197] (XV) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIG. 3B, in any whole number increment up to 1127 respectively that includes at least at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value less than 0.5 in the Hydropathicity profile of FIG. 6;

[0198] (XVI) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIG. 3B, in any whole number increment up to 1127 respectively that includes at least at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Percent Accessible Residues profile of FIG. 7;

[0199] (XVII) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acids of a protein of FIG. 3B, in any whole number increment up to 1127 respectively that includes at least at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Average Flexibility profile of FIG. 8;

[0200] (XVIII) a polypeptide comprising at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, amino acids of a protein of FIG. 3B in any whole number increment up to 1127 respectively that includes at least at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 amino acid position(s) having a value greater than 0.5 in the Beta-turn profile of FIG. 9;

(XIX) a peptide that occurs at least twice in Tables VIII-XXI and XXII to XLIX, collectively;

(XX) a peptide that occurs at least three times in Tables VIII-XXI and XXII to XLIX, collectively;

(XXI) a peptide that occurs at least four times in Tables VIII-XXI and XXII to XLIX, collectively;

(XXII) a peptide that occurs at least five times in Tables VIII-XXI and XXII to XLIX, collectively;

(XXIII) a peptide that occurs at least once in Tables VIII-XXI, and at least once in tables XXII to XLIX;

(XXIV) a peptide that occurs at least once in Tables VIII-XXI, and at least twice in tables XXII to XLIX;

(XXV) a peptide that occurs at least twice in Tables VIII-XXI, and at least once in tables XXII to XLIX;

(XXVI) a peptide that occurs at least twice in Tables VIII-XXI, and at least twice in tables XXII to XLIX;

(XXVII) a peptide which comprises one two, three, four, or five of the following characteristics, or an oligonucleotide encoding such peptide:

[0201] i) a region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Hydrophilicity profile of FIG. 5;

[0202] ii) a region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or less than 0.5, 0.4, 0.3, 0.2, 0.1, or having a value equal to 0.0, in the Hydropathicity profile of FIG. 6;

[0203] iii) a region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Percent Accessible Residues profile of FIG. 7;

[0204] iv) a region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Average Flexibility profile of FIG. 8; or,

[0205] v) a region of at least 5 amino acids of a particular peptide of FIG. 3, in any whole number increment up to the full length of that protein in FIG. 3, that includes an amino acid position having a value equal to or greater than 0.5, 0.6, 0.7, 0.8, 0.9, or having a value equal to 1.0, in the Beta-turn profile of FIG. 9;

(XXVIII) a composition comprising a peptide of (I)-(XXVII) or an antibody or binding region thereof together with a pharmaceutical excipient and/or in a human unit dose form.

(XXIX) a method of using a peptide of (I)-(XXVII), or an antibody or binding region thereof or a composition of (XXVIII) in a method to modulate a cell expressing 273P4B7;

(XXX) a method of using a peptide of (I)-(XXVII) or an antibody or binding region thereof or a composition of (XXVIII) in a method to diagnose, prophylax, prognose, or treat an individual who bears a cell expressing 273P4B7;

[0206] (XXXI) a method of using a peptide of (I)-(XXVII) or an antibody or binding region thereof or a composition

(XXVIII) in a method to diagnose, prophylax, prognose, or treat an individual who bears a cell expressing 273P4B7, said cell from a cancer of a tissue listed in Table I;

(XXXII) a method of using a peptide of (I)-(XXVII) or an antibody or binding region thereof or a composition of (XXVIII) in a method to diagnose, prophylax, prognose, or treat a cancer;

(XXXIII) a method of using a peptide of (I)-(XXVII) or an antibody or binding region thereof or a composition of (XXVIII) in a method to diagnose, prophylax, prognose, or treat a cancer of a tissue listed in Table I; and;

(XXXIV) a method of using a peptide of (I)-(XXVII) or an antibody or binding region thereof or a composition (XXVIII) in a method to identify or characterize a modulator of a cell expressing 273P4B7.

[0207] As used herein, a range is understood to specifically disclose all whole unit positions thereof.

[0208] Typical embodiments of the invention disclosed herein include 273P4B7 polynucleotides that encode specific portions of 273P4B7 mRNA sequences (and those which are complementary to such sequences) such as those that encode the proteins and/or fragments thereof, for example:

[0209] (a)4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1125, 1150, 1175, 1200, 1225, 1235, 1240, 1245, and 1250, or more contiguous amino acids of 273P4B7 variant 1; the maximal lengths relevant for other variants are: variant 2, 1127 amino acids; variant 4, 1250 amino acids; variant 5, 1250 amino acids; variant 6, 1250 amino acids; variant 9, 1106 amino acids; variant 10, 419 amino acids; and variant 11, 419 amino acids.

[0210] In general, naturally occurring allelic variants of human 273P4B7 share a high degree of structural identity and homology (e.g., 90% or more homology). Typically, allelic variants of a 273P4B7 protein contain conservative amino acid substitutions within the 273P4B7 sequences described herein or contain a substitution of an amino acid from a corresponding position in a homologue of 273P4B7. One class of 273P4B7 allelic variants are proteins that share a high degree of homology with at least a small region of a particular 273P4B7 amino acid sequence, but further contain a radical departure from the sequence, such as a nonconservative substitution, truncation, insertion or frame shift. In comparisons of protein sequences, the terms, similarity, identity, and homology each have a distinct meaning as appreciated in the field of genetics. Moreover, orthology and paralogy can be important concepts describing the relationship of members of a given protein family in one organism to the members of the same family in other organisms.

[0211] Amino acid abbreviations are provided in Table II. Conservative amino acid substitutions can frequently be made in a protein without altering either the conformation or the function of the protein. Proteins of the invention can comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15

conservative substitutions. Such changes include substituting any of isoleucine (I), valine (V), and leucine (L) for any other of these hydrophobic amino acids; aspartic acid (D) for glutamic acid (E) and vice versa; glutamine (Q) for asparagine (N) and vice versa; and serine (S) for threonine (T) and vice versa. Other substitutions can also be considered conservative, depending on the environment of the particular amino acid and its role in the three-dimensional structure of the protein. For example, glycine (G) and alanine (A) can frequently be interchangeable, as can alanine (A) and valine (V). Methionine (M), which is relatively hydrophobic, can frequently be interchanged with leucine and isoleucine, and sometimes with valine. Lysine (K) and arginine (R) are frequently interchangeable in locations in which the significant feature of the amino acid residue is its charge and the differing pK's of these two amino acid residues are not significant. Still other changes can be considered "conservative" in particular environments (see, e.g. Table III herein; pages 13-15 "Biochemistry" 2nd ED. Lubert Stryer ed (Stanford University); Henikoff et al., PNAS 1992 Vol 89 10915-10919; Lei et al., J Biol Chem 1995 May 19; 270(20):11882-6).

[0212] Embodiments of the invention disclosed herein include a wide variety of art-accepted variants or analogs of 273P4B7 proteins such as polypeptides having amino acid insertions, deletions and substitutions. 273P4B7 variants can be made using methods known in the art such as site-directed mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis (Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)), cassette mutagenesis (Wells et al., Gene, 34:315 (1985)), restriction selection mutagenesis (Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)) or other known techniques can be performed on the cloned DNA to produce the 273P4B7 variant DNA.

[0213] Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence that is involved in a specific biological activity such as a protein-protein interaction. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions (Creighton, The Proteins, (W.H. Freeman & Co., New York); Chothia, J. Mol. Biol., 150:1 (1976)). If alanine substitution does not yield adequate amounts of variant, an isosteric amino acid can be used.

[0214] As defined herein, 273P4B7 variants, analogs or homologs, have the distinguishing attribute of having at least one epitope that is "cross reactive" with a 273P4B7 protein having an amino acid sequence of FIG. 3. As used in this sentence, "cross reactive" means that an antibody or T cell that specifically binds to a 273P4B7 variant also specifically binds to a 273P4B7 protein having an amino acid sequence set forth in FIG. 3. A polypeptide ceases to be a variant of a protein shown in FIG. 3, when it no longer contains any epitope capable of being recognized by an antibody or T cell that specifically binds to the starting 273P4B7 protein. Those skilled in the art understand that

antibodies that recognize proteins bind to epitopes of varying size, and a grouping of the order of about four or five amino acids, contiguous or not, is regarded as a typical number of amino acids in a minimal epitope. See, e.g., Nair et al., *J. Immunol.* 2000 165(12): 6949-6955; Hebbes et al., *Mol Immunol* (1989) 26(9):865-73; Schwartz et al., *J Immunol* (1985) 135(4):2598-608.

[0215] Other classes of 273P4B7-related protein variants share 70%, 75%, 80%, 85% or 90% or more similarity with an amino acid sequence of FIG. 3, or a fragment thereof. Another specific class of 273P4B7 protein variants or analogs comprises one or more of the 273P4B7 biological motifs described herein or presently known in the art. Thus, encompassed by the present invention are analogs of 273P4B7 fragments (nucleic or amino acid) that have altered functional (e.g. immunogenic) properties relative to the starting fragment. It is to be appreciated that motifs now or which become part of the art are to be applied to the nucleic or amino acid sequences of FIG. 2 or FIG. 3.

[0216] As discussed herein, embodiments of the claimed invention include polypeptides containing less than the full amino acid sequence of a 273P4B7 protein shown in FIG. 2 or FIG. 3. For example, representative embodiments of the invention comprise peptides/proteins having any 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more contiguous amino acids of a 273P4B7 protein shown in FIG. 2 or FIG. 3.

[0217] Moreover, representative embodiments of the invention disclosed herein include polypeptides consisting of about amino acid 1 to about amino acid 10 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 10 to about amino acid 20 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 20 to about amino acid 30 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 30 to about amino acid 40 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 40 to about amino acid 50 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 50 to about amino acid 60 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 60 to about amino acid 70 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 70 to about amino acid 80 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 80 to about amino acid 90 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, polypeptides consisting of about amino acid 90 to about amino acid 100 of a 273P4B7 protein shown in FIG. 2 or FIG. 3, etc. throughout the entirety of a 273P4B7 amino acid sequence. Moreover, polypeptides consisting of about amino acid 1 (or 20 or 30 or 40 etc.) to about amino acid 20, (or 130, or 140 or 150 etc.) of a 273P4B7 protein shown in FIG. 2 or FIG. 3 are embodiments of the invention. It is to be appreciated that the starting and stopping positions in this paragraph refer to the specified position as well as that position plus or minus 5 residues.

[0218] 273P4B7-related proteins are generated using standard peptide synthesis technology or using chemical cleavage methods well known in the art. Alternatively, recombinant methods can be used to generate nucleic acid molecules that encode a 273P4B7-related protein. In one embodiment,

nucleic acid molecules provide a means to generate defined fragments of a 273P4B7 protein (or variants, homologs or analogs thereof).

[0219] Moreover the invention comprises 273P4B7 nucleic acid and amino acid sequences. Further, the invention comprises variants of 273P4B7, and fragments thereof. In an embodiment of the invention a protein fragment is: a subsequence of at least 158, or 262, or 420 contiguous amino acids of a protein of 273P4B7 v. 1; is an amino acid subsequence of a protein of 273P4B7 v. 1 with a proviso that 273P4B7 v. 1 protein is such that it does not include an valine (V) or methionine (M) at position 145; arginine (R) or glycine (G) at position 172; isoleucine (I) or valine (V) at position 889; or, lysine (K) or arginine (R) at position 989. An embodiment of an amino acid sequence of the invention is a fragment of a protein of 273P4B7 v. 1 with a proviso that it is not a protein of 273P4B7 v. 9, v. 10 or v.11. In an embodiment, an amino acid fragment of the invention is 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 170, 175, 180, 185, 190, 195, 200, 225, 250, 260, 261, 262, 263, 264, 265, 270, 275, 300, 325, 350, 375, 400, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 422, 434, 435, 450, 475, 500, 525, 550, 575, 600, 650, 675, 700, 705, 710, 715, 716, 717, 718, 719, 720, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1025, 1050, 1075, 1100, 1125, 1127, 1150, 1175, 1200, 1025, or 1250 contiguous amino acids of a protein of FIG. 2; in certain embodiments the fragment/subsequence comprises a functional or structural motif, e.g., as set forth herein, or comprises an immune system (antibody or T cell) epitope. Embodiments of a nucleic acid sequence of the invention comprise a sequence that encodes an amino acid sequence as set forth herein.

[0220] III.A.) Motif-Bearing Protein Embodiments

[0221] Additional illustrative embodiments of the invention disclosed herein include 273P4B7 polypeptides comprising the amino acid residues of one or more of the biological motifs contained within a 273P4B7 polypeptide sequence set forth in FIG. 2 or FIG. 3. Various motifs are known in the art, and a protein can be evaluated for the presence of such motifs by a number of publicly available Internet sites (see, e.g., URL addresses: pfam.wustl.edu/; searchlauncher.bcm.tmc.edu/seqsearch/struc-pr-edict.html; psort.ims.u-tokyo.ac.jp/; cbs.dtu.dk/; ebi.ac.uk/interpro/scan-.html; expasy.ch/tools/scnpsit1.html; Epimatrix™ and Epimer™, Brown University, brown.edu/Research/TB-HIV-Lab/epimatrix/epimatrix.html; and BIMAS, bimas.dcert.nih.gov/).

[0222] Motif bearing subsequences of all 273P4B7 variant proteins are set forth and identified in Tables VIII-XXI and XXII-XLIX.

[0223] Table V sets forth several frequently occurring motifs based on pfam searches (see URL address pfam.wustl.edu/). The columns of Table V list (1) motif name abbreviation, (2) percent identity found amongst the different member of the motif family, (3) motif name or description and (4) most common function; location information is included if the motif is relevant for location.

[0224] Polypeptides comprising one or more of the 273P4B7 motifs discussed above are useful in elucidating

the specific characteristics of a malignant phenotype in view of the observation that the 273P4B7 motifs discussed above are associated with growth dysregulation and because 273P4B7 is overexpressed in certain cancers (See, e.g., Table I). Casein kinase II, cAMP and camp-dependent protein kinase, and Protein Kinase C, for example, are enzymes known to be associated with the development of the malignant phenotype (see e.g. Chen et al., *Lab Invest.*, 78(2): 165-174 (1998); Gaiddon et al., *Endocrinology* 136(10): 4331-4338 (1995); Hall et al., *Nucleic Acids Research* 24(6): 1119-1126 (1996); Peterziel et al., *Oncogene* 18(46): 6322-6329 (1999) and O'Brian, *Oncol. Rep.* 5(2): 305-309 (1998)). Moreover, both glycosylation and myristoylation are protein modifications also associated with cancer and cancer progression (see e.g. Dennis et al., *Biochem. Biophys. Acta* 1473(1):21-34 (1999); Raju et al., *Exp. Cell Res.* 235(1): 145-154 (1997)). Amidation is another protein modification also associated with cancer and cancer progression (see e.g. Trestone et al., *J. Natl Cancer Inst. Monogr.* (13): 169-175 (1992)).

[0225] In another embodiment, proteins of the invention comprise one or more of the immunoreactive epitopes identified in accordance with art-accepted methods, such as the peptides set forth in Tables VIII-XXI and XXII-XLIX. CTL epitopes can be determined using specific algorithms to identify peptides within a 273P4B7 protein that are capable of optimally binding to specified HLA alleles (e.g., Table IV; Epimatrix™ and Epimer™, Brown University, URL brown.edu/Research/TB-HIV_Lab/epima-trix/epimatrix.html; and BIMAS, URL bimas.dcrt.nih.gov/.) Moreover, processes for identifying peptides that have sufficient binding affinity for HLA molecules and which are correlated with being immunogenic epitopes, are well known in the art, and are carried out without undue experimentation. In addition, processes for identifying peptides that are immunogenic epitopes, are well known in the art, and are carried out without undue experimentation either in vitro or in vivo.

[0226] Also known in the art are principles for creating analogs of such epitopes in order to modulate immunogenicity. For example, one begins with an epitope that bears a CTL or HTL motif (see, e.g., the HLA Class I and HLA Class II motifs/supermotifs of Table IV). The epitope is analogized by substituting out an amino acid at one of the specified positions, and replacing it with another amino acid specified for that position. For example, on the basis of residues defined in Table IV, one can substitute out a deleterious residue in favor of any other residue, such as a preferred residue; substitute a less-preferred residue with a preferred residue; or substitute an originally-occurring preferred residue with another preferred residue. Substitutions can occur at primary anchor positions or at other positions in a peptide; see, e.g., Table IV.

[0227] A variety of references reflect the art regarding the identification and generation of epitopes in a protein of interest as well as analogs thereof. See, for example, WO 97/33602 to Chesnut et al.; Sette, *Immunogenetics* 1999 50(3-4): 201-212; Sette et al., *J. Immunol.* 2001 166(2): 1389-1397; Sidney et al., *Hum. Immunol.* 1997 58(1): 12-20; Kondo et al., *Immunogenetics* 1997 45(4): 249-258; Sidney et al., *J. Immunol.* 1996 157(8): 3480-90; and Falk et al., *Nature* 351: 290-6 (1991); Hunt et al., *Science* 255:1261-3 (1992); Parker et al., *J. Immunol.* 149:3580-7 (1992); Parker et al., *J. Immunol.* 152:163-75 (1994)); Kast

et al., 1994 152(8): 3904-12; Borrás-Cuesta et al., *Hum. Immunol.* 2000 61(3): 266-278; Alexander et al., *J. Immunol.* 2000 164(3): 164(3): 1625-1633; Alexander et al., PMID: 7895164, UI: 95202582; O'Sullivan et al., *J. Immunol.* 1991 147(8): 2663-2669; Alexander et al., *Immunity* 1994 1(9): 751-761 and Alexander et al., *Immunol. Res.* 1998 18(2): 79-92.

[0228] Related embodiments of the invention include polypeptides comprising combinations of the different motifs set forth in Table VI, and/or, one or more of the predicted CTL epitopes of Tables VIII-XXI and XXII-XLIX, and/or, one or more of the predicted HTL epitopes of Tables XLVI-XLIX, and/or, one or more of the T cell binding motifs known in the art. Preferred embodiments contain no insertions, deletions or substitutions either within the motifs or within the intervening sequences of the polypeptides. In addition, embodiments which include a number of either N-terminal and/or C-terminal amino acid residues on either side of these motifs may be desirable (to, for example, include a greater portion of the polypeptide architecture in which the motif is located). Typically, the number of N-terminal and/or C-terminal amino acid residues on either side of a motif is between about 1 to about 100 amino acid residues, preferably 5 to about 50 amino acid residues.

[0229] 273P4B7-related proteins are embodied in many forms, preferably in isolated form. A purified 273P4B7 protein molecule will be substantially free of other proteins or molecules that impair the binding of 273P4B7 to antibody, T cell or other ligand. The nature and degree of isolation and purification will depend on the intended use. Embodiments of a 273P4B7-related proteins include purified 273P4B7-related proteins and functional, soluble 273P4B7-related proteins. In one embodiment, a functional, soluble 273P4B7 protein or fragment thereof retains the ability to be bound by antibody, T cell or other ligand.

[0230] The invention also provides 273P4B7 proteins comprising biologically active fragments of a 273P4B7 amino acid sequence shown in FIG. 2 or FIG. 3. Such proteins exhibit properties of the starting 273P4B7 protein, such as the ability to elicit the generation of antibodies that specifically bind an epitope associated with the starting 273P4B7 protein; to be bound by such antibodies; to elicit the activation of HTL or CTL; and/or, to be recognized by HTL or CTL that also specifically bind to the starting protein.

[0231] 273P4B7-related polypeptides that contain particularly interesting structures can be predicted and/or identified using various analytical techniques well known in the art, including, for example, the methods of Chou-Fasman, Garnier-Robson, Kyte-Doolittle, Eisenberg, Karplus-Schultz or Jameson-Wolf analysis, or based on immunogenicity. Fragments that contain such structures are particularly useful in generating subunit-specific anti-273P4B7 antibodies or T cells or in identifying cellular factors that bind to 273P4B7. For example, hydrophilicity profiles can be generated, and immunogenic peptide fragments identified, using the method of Hopp, T. P. and Woods, K. R., 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:3824-3828. Hydrophobicity profiles can be generated, and immunogenic peptide fragments identified, using the method of Kyte, J. and Doolittle, R. F., 1982, *J. Mol. Biol.* 157:105-132. Percent (%) Accessible Residues

profiles can be generated, and immunogenic peptide fragments identified, using the method of Janin J., 1979, *Nature* 277:491-492. Average Flexibility profiles can be generated, and immunogenic peptide fragments identified, using the method of Bhaskaran R., Ponnuswamy P. K., 1988, *Int. J. Pept. Protein Res.* 32:242-255. Beta-turn profiles can be generated, and immunogenic peptide fragments identified, using the method of Deleage, G., Roux B., 1987, *Protein Engineering* 1:289-294.

[0232] CTL epitopes can be determined using specific algorithms to identify peptides within a 273P4B7 protein that are capable of optimally binding to specified HLA alleles (e.g., by using the SYFPEITHI site at World Wide Web URL syfpeithi.bmi-heidelberg.com/; the listings in Table IV(A)-(E); Epimatrix™ and Epimer™, Brown University, URL (brown.edu/Research/TB-HIV_Lab/epimatrix/epimatrix.html); and BIMAS, URL bimas.dcrf.nih.gov/). Illustrating this, peptide epitopes from 273P4B7 that are presented in the context of human MHC Class I molecules, e.g., HLA-A1, A2, A3, A11, A24, B7 and B35 were predicted (see, e.g., Tables VIII-XXI, XXII-XLIX). Specifically, the complete amino acid sequence of the 273P4B7 protein and relevant portions of other variants, i.e., for HLA Class I predictions 9 flanking residues on either side of a point mutation or exon junction, and for HLA Class II predictions 14 flanking residues on either side of a point mutation or exon junction corresponding to that variant, were entered into the HLA Peptide Motif Search algorithm found in the Bioinformatics and Molecular Analysis Section (BIMAS) web site listed above; in addition to the site SYFPEITHI, at URL syfpeithi.bmi-heidelberg.com/.

[0233] The HLA peptide motif search algorithm was developed by Dr. Ken Parker based on binding of specific peptide sequences in the groove of HLA Class I molecules, in particular HLA-A2 (see, e.g., Falk et al., *Nature* 351: 290-6 (1991); Hunt et al., *Science* 255:1261-3 (1992); Parker et al., *J. Immunol.* 149:3580-7 (1992); Parker et al., *J. Immunol.* 152:163-75 (1994)). This algorithm allows location and ranking of 8-mer, 9-mer, and 10-mer peptides from a complete protein sequence for predicted binding to HLA-A2 as well as numerous other HLA Class I molecules. Many HLA class I binding peptides are 8-, 9-, 10 or 11-mers. For example, for Class I HLA-A2, the epitopes preferably contain a leucine (L) or methionine (M) at position 2 and a valine (V) or leucine (L) at the C-terminus (see, e.g., Parker et al., *J. Immunol.* 149:3580-7 (1992)). Selected results of 273P4B7 predicted binding peptides are shown in Tables VIII-XXI and XXII-XLIX herein. In Tables VIII-XXI and XXII-XLVII, selected candidates, 9-mers and 10-mers, for each family member are shown along with their location, the amino acid sequence of each specific peptide, and an estimated binding score. In Tables XLVI-XLIX, selected candidates, 15-mers, for each family member are shown along with their location, the amino acid sequence of each specific peptide, and an estimated binding score. The binding score corresponds to the estimated half time of dissociation of complexes containing the peptide at 37° C. at pH 6.5. Peptides with the highest binding score are predicted to be the most tightly bound to HLA Class I on the cell surface for the greatest period of time and thus represent the best immunogenic targets for T-cell recognition.

[0234] Actual binding of peptides to an HLA allele can be evaluated by stabilization of HLA expression on the antigen-

processing defective cell line T2 (see, e.g., Xue et al., *Prostate* 30:73-8 (1997) and Peshwa et al., *Prostate* 36:129-38 (1998)). Immunogenicity of specific peptides can be evaluated in vitro by stimulation of CD8+ cytotoxic T lymphocytes (CTL) in the presence of antigen presenting cells such as dendritic cells.

[0235] It is to be appreciated that every epitope predicted by the BIMAS site, Epimer™ and Epimatrix™ sites, or specified by the HLA class I or class II motifs available in the art or which become part of the art such as set forth in Table IV (or determined using World Wide Web site URL syfpeithi.bmi-heidelberg.com/, or BIMAS, bimas.dcrf.nih.gov/) are to be “applied” to a 273P4B7 protein in accordance with the invention. As used in this context “applied” means that a 273P4B7 protein is evaluated, e.g., visually or by computer-based pattern finding methods, as appreciated by those of skill in the relevant art. Every subsequence of a 273P4B7 protein of 8, 9, 10, or 11 amino acid residues that bears an HLA Class I motif, or a subsequence of 9 or more amino acid residues that bear an HLA Class II motif are within the scope of the invention.

[0236] III.B.) Expression of 273P4B7-Related Proteins

[0237] In an embodiment described in the examples that follow, 73P4B7 can be conveniently expressed in cells (such as 293T cells) transfected with a commercially available expression vector such as a CMV-driven expression vector encoding 273P4B7 with a C-terminal 6xHis and MYC tag (pcDNA3.1/mycHis, Invitrogen or Tag5, GenHunter Corporation, Nashville Tenn.). The Tag5 vector provides an IgGK secretion signal that can be used to facilitate the production of a secreted 273P4B7 protein in transfected cells. The secreted HIS-tagged 273P4B7 in the culture media can be purified, e.g., using a nickel column using standard techniques.

[0238] III.C.) Modifications of 273P4B7-Related Proteins

[0239] Modifications of 273P4B7-related proteins such as covalent modifications are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a 273P4B7 polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of a 273P4B7 protein. Another type of covalent modification of a 273P4B7 polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of a protein of the invention. Another type of covalent modification of 273P4B7 comprises linking a 273P4B7 polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Pat. No. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

[0240] The 273P4B7-related proteins of the present invention can also be modified to form a chimeric molecule comprising 273P4B7 fused to another, heterologous polypeptide or amino acid sequence. Such a chimeric molecule can be synthesized chemically or recombinantly. A chimeric molecule can have a protein of the invention fused to another tumor-associated antigen or fragment thereof. Alternatively, a protein in accordance with the invention can comprise a fusion of fragments of a 273P4B7 sequence (amino or nucleic acid) such that a molecule is created that

is not, through its length, directly homologous to the amino or nucleic acid sequences shown in FIG. 2 or FIG. 3. Such a chimeric molecule can comprise multiples of the same subsequence of 273P4B7. A chimeric molecule can comprise a fusion of a 273P4B7-related protein with a polyhistidine epitope tag, which provides an epitope to which immobilized nickel can selectively bind, with cytokines or with growth factors. The epitope tag is generally placed at the amino- or carboxyl-terminus of a 273P4B7 protein. In an alternative embodiment, the chimeric molecule can comprise a fusion of a 273P4B7-related protein with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a 273P4B7 polypeptide in place of at least one variable region within an Ig molecule. In a preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see, e.g., U.S. Pat. No. 5,428,130 issued Jun. 27, 1995.

[0241] III.D.) Uses of 273P4B7-Related Proteins

[0242] The proteins of the invention have a number of different specific uses. As 273P4B7 is highly expressed in prostate and other cancers, 273P4B7-related proteins are used in methods that assess the status of 273P4B7 gene products in normal versus cancerous tissues, thereby elucidating the malignant phenotype. Typically, polypeptides from specific regions of a 273P4B7 protein are used to assess the presence of perturbations (such as deletions, insertions, point mutations etc.) in those regions (such as regions containing one or more motifs). Exemplary assays utilize antibodies or T cells targeting 273P4B7-related proteins comprising the amino acid residues of one or more of the biological motifs contained within a 273P4B7 polypeptide sequence in order to evaluate the characteristics of this region in normal versus cancerous tissues or to elicit an immune response to the epitope. Alternatively, 273P4B7-related proteins that contain the amino acid residues of one or more of the biological motifs in a 273P4B7 protein are used to screen for factors that interact with that region of 273P4B7.

[0243] 273P4B7 protein fragments/subsequences are particularly useful in generating and characterizing domain-specific antibodies (e.g., antibodies recognizing an extracellular or intracellular epitope of a 273P4B7 protein), for identifying agents or cellular factors that bind to 273P4B7 or a particular structural domain thereof, and in various therapeutic and diagnostic contexts, including but not limited to diagnostic assays, cancer vaccines and methods of preparing such vaccines.

[0244] Proteins encoded by the 273P4B7 genes, or by analogs, homologs or fragments thereof, have a variety of uses, including but not limited to generating antibodies and in methods for identifying ligands and other agents and cellular constituents that bind to a 273P4B7 gene product. Antibodies raised against a 273P4B7 protein or fragment thereof are useful in diagnostic and prognostic assays, and imaging methodologies in the management of human cancers characterized by expression of 273P4B7 protein, such

as those listed in Table I. Such antibodies can be expressed intracellularly and used in methods of treating patients with such cancers. 273P4B7-related nucleic acids or proteins are also used in generating HTL or CTL responses.

[0245] Various immunological assays useful for the detection of 273P4B7 proteins are used, including but not limited to various types of radioimmunoassays, enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunofluorescent assays (ELIFA), immunocytochemical methods, and the like. Antibodies can be labeled and used as immunological imaging reagents capable of detecting 273P4B7-expressing cells (e.g., in radioscintigraphic imaging methods). 273P4B7 proteins are also particularly useful in generating cancer vaccines, as further described herein.

[0246] IV.) 273P4B7 Antibodies

[0247] Another aspect of the invention provides antibodies that bind to 273P4B7-related proteins. Preferred antibodies specifically bind to a 273P4B7-related protein and do not bind (or bind weakly) to peptides or proteins that are not 273P4B7-related proteins under physiological conditions. In this context, examples of physiological conditions include: 1) phosphate buffered saline; 2) Tris-buffered saline containing 25 mM Tris and 150 mM NaCl; or normal saline (0.9% NaCl); 4) animal serum such as human serum; or, 5) a combination of any of 1) through 4); these reactions preferably taking place at pH 7.5, alternatively in a range of pH 7.0 to 8.0, or alternatively in a range of pH 6.5 to 8.5; also, these reactions taking place at a temperature between 4° C. to 37° C. For example, antibodies that bind 273P4B7 can bind 273P4B7-related proteins such as the homologs or analogs thereof.

[0248] 273P4B7 antibodies of the invention are particularly useful in cancer (see, e.g., Table I) diagnostic and prognostic assays, and imaging methodologies. Similarly, such antibodies are useful in the treatment, diagnosis, and/or prognosis of other cancers, to the extent 273P4B7 is also expressed or overexpressed in these other cancers. Moreover, intracellularly expressed antibodies (e.g., single chain antibodies) are therapeutically useful in treating cancers in which the expression of 273P4B7 is involved, such as advanced or metastatic prostate cancers.

[0249] The invention also provides various immunological assays useful for the detection and quantification of 273P4B7 and mutant 273P4B7-related proteins. Such assays can comprise one or more 273P4B7 antibodies capable of recognizing and binding a 273P4B7-related protein, as appropriate. These assays are performed within various immunological assay formats well known in the art, including but not limited to various types of radioimmunoassays, enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunofluorescent assays (ELIFA), and the like.

[0250] Immunological non-antibody assays of the invention also comprise T cell immunogenicity assays (inhibitory or stimulatory) as well as major histocompatibility complex (MHC) binding assays.

[0251] In addition, immunological imaging methods capable of detecting prostate cancer and other cancers expressing 273P4B7 are also provided by the invention, including but not limited to radioscintigraphic imaging methods using labeled 273P4B7 antibodies. Such assays are

clinically useful in the detection, monitoring, and prognosis of 273P4B7 expressing cancers such as prostate cancer.

[0252] 273P4B7 antibodies are also used in methods for purifying a 273P4B7-related protein and for isolating 273P4B7 homologues and related molecules. For example, a method of purifying a 273P4B7-related protein comprises incubating a 273P4B7 antibody, which has been coupled to a solid matrix, with a lysate or other solution containing a 273P4B7-related protein under conditions that permit the 273P4B7 antibody to bind to the 273P4B7-related protein; washing the solid matrix to eliminate impurities; and eluting the 273P4B7-related protein from the coupled antibody. Other uses of 273P4B7 antibodies in accordance with the invention include generating anti-idiotypic antibodies that mimic a 273P4B7 protein.

[0253] Various methods for the preparation of antibodies are well known in the art. For example, antibodies can be prepared by immunizing a suitable mammalian host using a 273P4B7-related protein, peptide, or fragment, in isolated or immunoconjugated form (Antibodies: A Laboratory Manual, CSH Press, Eds., Harlow, and Lane (1988); Harlow, Antibodies, Cold Spring Harbor Press, NY (1989)). In addition, fusion proteins of 273P4B7 can also be used, such as a 273P4B7 GST-fusion protein. In a particular embodiment, a GST fusion protein comprising all or most of the amino acid sequence of FIG. 2 or FIG. 3 is produced, then used as an immunogen to generate appropriate antibodies. In another embodiment, a 273P4B7-related protein is synthesized and used as an immunogen.

[0254] In addition, naked DNA immunization techniques known in the art are used (with or without purified 273P4B7-related protein or 273P4B7 expressing cells) to generate an immune response to the encoded immunogen (for review, see Donnelly et al., 1997, *Ann. Rev. Immunol.* 15: 617-648).

[0255] The amino acid sequence of a 273P4B7 protein as shown in FIG. 2 or FIG. 3 can be analyzed to select specific regions of the 273P4B7 protein for generating antibodies. For example, hydrophobicity and hydrophilicity analyses of a 273P4B7 amino acid sequence are used to identify hydrophilic regions in the 273P4B7 structure. Regions of a 273P4B7 protein that show immunogenic structure, as well as other regions and domains, can readily be identified using various other methods known in the art, such as Chou-Fasman, Garnier-Robson, Kyte-Doolittle, Eisenberg, Karplus-Schultz or Jameson-Wolf analysis. Hydrophilicity profiles can be generated using the method of Hopp, T. P. and Woods, K. R., 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:3824-3828. Hydrophobicity profiles can be generated using the method of Kyte, J. and Doolittle, R. F., 1982, *J. Mol. Biol.* 157:105-132. Percent (%) Accessible Residues profiles can be generated using the method of Janin J., 1979, *Nature* 277:491-492. Average Flexibility profiles can be generated using the method of Bhaskaran R., Ponnuswamy P. K., 1988, *Int. J. Pept. Protein Res.* 32:242-255. Beta-turn profiles can be generated using the method of Deleage, G., Roux B., 1987, *Protein Engineering* 1:289-294. Thus, each region identified by any of these programs or methods is within the scope of the present invention. Methods for the generation of 273P4B7 antibodies are further illustrated by way of the examples provided herein. Methods for preparing a protein or polypeptide for use as an immunogen are well known in the art. Also well known in the art are methods for preparing

immunogenic conjugates of a protein with a carrier, such as BSA, KLH or other carrier protein. In some circumstances, direct conjugation using, for example, carbodiimide reagents are used; in other instances linking reagents such as those supplied by Pierce Chemical Co., Rockford, Ill., are effective. Administration of a 273P4B7 immunogen is often conducted by injection over a suitable time period and with use of a suitable adjuvant, as is understood in the art. During the immunization schedule, titers of antibodies can be taken to determine adequacy of antibody formation.

[0256] 273P4B7 monoclonal antibodies can be produced by various means well known in the art. For example, immortalized cell lines that secrete a desired monoclonal antibody are prepared using the standard hybridoma technology of Kohler and Milstein or modifications that immortalize antibody-producing B cells, as is generally known. Immortalized cell lines that secrete the desired antibodies are screened by immunoassay in which the antigen is a 273P4B7-related protein. When the appropriate immortalized cell culture is identified, the cells can be expanded and antibodies produced either from in vitro cultures or from ascites fluid.

[0257] The antibodies or fragments of the invention can also be produced, by recombinant means. Regions that bind specifically to the desired regions of a 273P4B7 protein can also be produced in the context of chimeric or complementarity-determining region (CDR) grafted antibodies of multiple species origin. Humanized or human 273P4B7 antibodies can also be produced, and are preferred for use in therapeutic contexts. Methods for humanizing murine and other non-human antibodies, by substituting one or more of the non-human antibody CDRs for corresponding human antibody sequences, are well known (see for example, Jones et al., 1986, *Nature* 321: 522-525; Riechmann et al., 1988, *Nature* 332: 323-327; Verhoeyen et al., 1988, *Science* 239: 1534-1536). See also, Carter et al., 1993, *Proc. Natl. Acad. Sci. USA* 89: 4285 and Sims et al., 1993, *J. Immunol.* 151: 2296.

[0258] Methods for producing fully human monoclonal antibodies include phage display and transgenic methods (for review, see Vaughan et al., 1998, *Nature Biotechnology* 16: 535-539). Fully human 273P4B7 monoclonal antibodies can be generated using cloning technologies employing large human Ig gene combinatorial libraries (i.e., phage display) (Griffiths and Hoogenboom, Building an in vitro immune system: human antibodies from phage display libraries. In: *Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man*, Clark, M. (Ed.), Nottingham Academic, pp 45-64 (1993); Burton and Barbas, Human Antibodies from combinatorial libraries. Id., pp 65-82). Fully human 273P4B7 monoclonal antibodies can also be produced using transgenic mice engineered to contain human immunoglobulin gene loci as described in PCT Patent Application WO98/24893, Kucherlapati and Jakobovits et al., published Dec. 3, 1997 (see also, Jakobovits, 1998, *Exp. Opin. Invest. Drugs* 7(4): 607-614; U.S. Pat. No. 6,162,963 issued 19 Dec. 2000; U.S. Pat. No. 6,150,584 issued 12 Nov. 2000; and, U.S. Pat. No. 6,114,598 issued 5 Sep. 2000). This method avoids the in vitro manipulation required with phage display technology and efficiently produces high affinity authentic human antibodies.

[0259] Reactivity of 273P4B7 antibodies with a 273P4B7-related protein can be established by a number of well

known means, including Western blot, immunoprecipitation, ELISA, and FACS analyses using, as appropriate, 273P4B7-related proteins, 273P4B7-expressing cells or extracts thereof. A 273P4B7 antibody or fragment thereof can be labeled with a detectable marker or conjugated to a second molecule. Suitable detectable markers include, but are not limited to, a radioisotope, a fluorescent compound, a bioluminescent compound, chemiluminescent compound, a metal chelator or an enzyme. Further, bi-specific antibodies specific for two or more 273P4B7 epitopes are generated using methods generally known in the art. Homodimeric antibodies can also be generated by cross-linking techniques known in the art (e.g., Wolff et al., *Cancer Res.* 53: 2560-2565).

[0260] V.) 273P4B7 Cellular Immune Responses

[0261] The mechanism by which T cells recognize antigens has been delineated. Efficacious peptide epitope vaccine compositions of the invention induce a therapeutic or prophylactic immune responses in very broad segments of the world-wide population. For an understanding of the value and efficacy of compositions of the invention that induce cellular immune responses, a brief review of immunology-related technology is provided.

[0262] A complex of an HLA molecule and a peptidic antigen acts as the ligand recognized by HLA-restricted T cells (Buus, S. et al., *Cell* 47:1071, 1986; Babbitt, B. P. et al., *Nature* 317:359, 1985; Townsend, A. and Bodmer, H., *Annu. Rev. Immunol.* 7:601, 1989; Germain, R. N., *Annu. Rev. Immunol.* 11:403, 1993). Through the study of single amino acid substituted antigen analogs and the sequencing of endogenously bound, naturally processed peptides, critical residues that correspond to motifs required for specific binding to HLA antigen molecules have been identified and are set forth in Table IV (see also, e.g., Southwood, et al., *J. Immunol.* 160:3363, 1998; Rammensee, et al., *Immunogenetics* 41:178, 1995; Rammensee et al., SYFPEITHI, access via World Wide Web); Sette, A. and Sidney, J. *Curr. Opin. Immunol.* 10:478, 1998; Engelhard, V. H., *Curr. Opin. Immunol.* 6:13, 1994; Sette, A. and Grey, H. M., *Curr. Opin. Immunol.* 4:79, 1992; Sinigaglia, F. and Hammer, J. *Curr. Biol.* 6:52, 1994; Ruppert et al., *Cell* 74:929-937, 1993; Kondo et al., *J. Immunol.* 155:4307-4312, 1995; Sidney et al., *J. Immunol.* 157:3480-3490, 1996; Sidney et al., *Human Immunol.* 45:79-93, 1996; Sette, A. and Sidney, J. *Immunogenetics* 1999 November; 50(3-4):201-1Z Review).

[0263] Furthermore, x-ray crystallographic analyses of HLA-peptide complexes have revealed pockets within the peptide binding cleft/groove of HLA molecules which accommodate, in an allele-specific mode, residues borne by peptide ligands; these residues in turn determine the HLA binding capacity of the peptides in which they are present. (See, e.g., Madden, D. R. *Annu. Rev. Immunol.* 13:587, 1995; Smith, et al., *Immunity* 4:203, 1996; Fremont et al., *Immunity* 8:305, 1998; Stern et al., *Structure* 2:245, 1994; Jones, E. Y. *Curr. Opin. Immunol.* 9:75, 1997; Brown, J. H. et al., *Nature* 364:33, 1993; Guo, H. C. et al., *Proc. Natl. Acad. Sci. USA* 90:8053, 1993; Guo, H. C. et al., *Nature* 360:364, 1992; Silver, M. L. et al., *Nature* 360:367, 1992; Matsumura, M. et al., *Science* 257:927, 1992; Madden et al., *Cell* 70:1035, 1992; Fremont, D. H. et al., *Science* 257:919, 1992; Saper, M. A., Bjorkman, P. J. and Wiley, D. C., *J. Mol. Biol.* 219:277, 1991.)

[0264] Accordingly, the definition of class I and class II allele-specific HLA binding motifs, or class I or class II

supermotifs allows identification of regions within a protein that are correlated with binding to particular HLA antigen(s).

[0265] Thus, by a process of HLA motif identification, candidates for epitope-based vaccines have been identified; such candidates can be further evaluated by HLA-peptide binding assays to determine binding affinity and/or the time period of association of the epitope and its corresponding HLA molecule. Additional confirmatory work can be performed to select, amongst these vaccine candidates, epitopes with preferred characteristics in terms of population coverage, and/or immunogenicity.

[0266] Various strategies can be utilized to evaluate cellular immunogenicity, including: 1) Evaluation of primary T cell cultures from normal individuals (see, e.g., Wentworth, P. A. et al., *Mol. Immunol.* 32:603, 1995; Celis, E. et al., *Proc. Natl. Acad. Sci. USA* 91:2105, 1994; Tsai, V. et al., *J. Immunol.* 158:1796, 1997; Kawashima, I. et al., *Human Immunol.* 59:1, 1998). This procedure involves the stimulation of peripheral blood lymphocytes (PBL) from normal subjects with a test peptide in the presence of antigen presenting cells in vitro over a period of several weeks. T cells specific for the peptide become activated during this time and are detected using, e.g., a lymphokine- or ⁵¹Cr-release assay involving peptide sensitized target cells.

[0267] 2) Immunization of HLA transgenic mice (see, e.g., Wentworth, P. A. et al., *J. Immunol.* 26:97, 1996; Wentworth, P. A. et al., *Int. Immunol.* 8:651, 1996; Alexander, J. et al., *J. Immunol.* 159:4753, 1997). For example, in such methods peptides in incomplete Freund's adjuvant are administered subcutaneously to HLA transgenic mice. Several weeks following immunization, splenocytes are removed and cultured in vitro in the presence of test peptide for approximately one week. Peptide-specific T cells are detected using, e.g., a ⁵¹Cr-release assay involving peptide sensitized target cells and target cells expressing endogenously generated antigen.

[0268] 3) Demonstration of recall T cell responses from immune individuals who have been either effectively vaccinated and/or from chronically ill patients (see, e.g., Rehermann, B. et al., *J. Exp. Med.* 181:1047, 1995; Doolan, D. L. et al., *Immunity* 7:97, 1997; Bertoni, R. et al., *J. Clin. Invest.* 100:503, 1997; Threlkeld, S. C. et al., *J. Immunol.* 159:1648, 1997; Diepolder, H. M. et al., *J. Virol.* 71:6011, 1997). Accordingly, recall responses are detected by culturing PBL from subjects that have been exposed to the antigen due to disease and thus have generated an immune response "naturally", or from patients who were vaccinated against the antigen. PBL from subjects are cultured in vitro for 1-2 weeks in the presence of test peptide plus antigen presenting cells (APC) to allow activation of "memory" T cells, as compared to "naive" T cells. At the end of the culture period, T cell activity is detected using assays including ⁵¹Cr release involving peptide-sensitized targets, T cell proliferation, or lymphokine release.

[0269] VI.) 273P4B7 Transgenic Animals

[0270] Nucleic acids that encode a 273P4B7-related protein can also be used to generate either transgenic animals or "knock out" animals that, in turn, are useful in the development and screening of therapeutically useful reagents. In accordance with established techniques, cDNA encoding 273P4B7 can be used to clone genomic DNA that encodes

273P4B7. The cloned genomic sequences can then be used to generate transgenic animals containing cells that express DNA that encode 273P4B7. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Pat. No. 4,736,866 issued 12 Apr. 1988, and U.S. Pat. No. 4,870,009 issued 26 Sep. 1989. Typically, particular cells would be targeted for 273P4B7 transgene incorporation with tissue-specific enhancers.

[0271] Transgenic animals that include a copy of a transgene encoding 273P4B7 can be used to examine the effect of increased expression of DNA that encodes 273P4B7. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this aspect of the invention, an animal is treated with a reagent and a reduced incidence of a pathological condition, compared to untreated animals that bear the transgene, would indicate a potential therapeutic intervention for the pathological condition.

[0272] Alternatively, non-human homologues of 273P4B7 can be used to construct a 273P4B7 “knock out” animal that has a defective or altered gene encoding 273P4B7 as a result of homologous recombination between the endogenous gene encoding 273P4B7 and altered genomic DNA encoding 273P4B7 introduced into an embryonic cell of the animal. For example, cDNA that encodes 273P4B7 can be used to clone genomic DNA encoding 273P4B7 in accordance with established techniques. A portion of the genomic DNA encoding 273P4B7 can be deleted or replaced with another gene, such as a gene encoding a selectable marker that can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector (see, e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected (see, e.g., Li et al., *Cell*, 69:915 (1992)). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras (see, e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal, and the embryo brought to term to create a “knock out” animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knock out animals can be characterized, for example, for their ability to defend against certain pathological conditions or for their development of pathological conditions due to absence of a 273P4B7 polypeptide.

[0273] VII.) Methods for the Detection of 273P4B7

[0274] Another aspect of the present invention relates to methods for detecting 273P4B7 polynucleotides and 273P4B7-related proteins, as well as methods for identifying a cell that expresses 273P4B7. The expression profile of 273P4B7 makes it a diagnostic marker for metastasized disease. Accordingly, the status of 273P4B7 gene products

provides information useful for predicting a variety of factors including susceptibility to advanced stage disease, rate of progression, and/or tumor aggressiveness. As discussed in detail herein, the status of 273P4B7 gene products in patient samples can be analyzed by a variety of protocols that are well known in the art including immunohistochemical analysis, the variety of Northern blotting techniques including in situ hybridization, RT-PCR analysis (for example on laser capture micro-dissected samples), Western blot analysis and tissue array analysis.

[0275] More particularly, the invention provides assays for the detection of 273P4B7 polynucleotides in a biological sample, such as serum, bone, prostate, and other tissues, urine, semen, cell preparations, and the like. Detectable 273P4B7 polynucleotides include, for example, a 273P4B7 gene or fragment thereof, 273P4B7 mRNA, alternative splice variant 273P4B7 mRNAs, and recombinant DNA or RNA molecules that contain a 273P4B7 polynucleotide. A number of methods for amplifying and/or detecting the presence of 273P4B7 polynucleotides are well known in the art and can be employed in the practice of this aspect of the invention.

[0276] In one embodiment, a method for detecting a 273P4B7 mRNA in a biological sample comprises producing cDNA from the sample by reverse transcription using at least one primer; amplifying the cDNA so produced using a 273P4B7 polynucleotides as sense and antisense primers to amplify 273P4B7 cDNAs therein; and detecting the presence of the amplified 273P4B7 cDNA. Optionally, the sequence of the amplified 273P4B7 cDNA can be determined.

[0277] In another embodiment, a method of detecting a 273P4B7 gene in a biological sample comprises first isolating genomic DNA from the sample; amplifying the isolated genomic DNA using 273P4B7 polynucleotides as sense and antisense primers; and detecting the presence of the amplified 273P4B7 gene. Any number of appropriate sense and antisense probe combinations can be designed from a 273P4B7 nucleotide sequence (see, e.g., FIG. 2) and used for this purpose.

[0278] The invention also provides assays for detecting the presence of a 273P4B7 protein in a tissue or other biological sample such as serum, semen, bone, prostate, urine, cell preparations, and the like. Methods for detecting a 273P4B7-related protein are also well known and include, for example, immunoprecipitation, immunohistochemical analysis, Western blot analysis, molecular binding assays, ELISA, ELIFA and the like. For example, a method of detecting the presence of a 273P4B7-related protein in a biological sample comprises first contacting the sample with a 273P4B7 antibody, a 273P4B7-reactive fragment thereof, or a recombinant protein containing an antigen-binding region of a 273P4B7 antibody; and then detecting the binding of 273P4B7-related protein in the sample.

[0279] Methods for identifying a cell that expresses 273P4B7 are also within the scope of the invention. In one embodiment, an assay for identifying a cell that expresses a 273P4B7 gene comprises detecting the presence of 273P4B7 mRNA in the cell. Methods for the detection of particular mRNAs in cells are well known and include, for example, hybridization assays using complementary DNA probes (such as in situ hybridization using labeled 273P4B7 ribo-

probes, Northern blot and related techniques) and various nucleic acid amplification assays (such as RT-PCR using complementary primers specific for 273P4B7, and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like). Alternatively, an assay for identifying a cell that expresses a 273P4B7 gene comprises detecting the presence of 273P4B7-related protein in the cell or secreted by the cell. Various methods for the detection of proteins are well known in the art and are employed for the detection of 273P4B7-related proteins and cells that express 273P4B7-related proteins.

[0280] 273P4B7 expression analysis is also useful as a tool for identifying and evaluating agents that modulate 273P4B7 gene expression. For example, 273P4B7 expression is significantly upregulated in prostate cancer, and is expressed in cancers of the tissues listed in Table I. Identification of a molecule or biological agent that inhibits 273P4B7 expression or over-expression in cancer cells is of therapeutic value. For example, such an agent can be identified by using a screen that quantifies 273P4B7 expression by RT-PCR, nucleic acid hybridization or antibody binding.

[0281] VIII.) Methods for Monitoring the Status of 273P4B7-Related Genes and their Products

[0282] Oncogenesis is known to be a multistep process where cellular growth becomes progressively dysregulated and cells progress from a normal physiological state to precancerous and then cancerous states (see, e.g., Alers et al., *Lab Invest.* 77(5): 437-438 (1997) and Isaacs et al., *Cancer Surv.* 23: 19-32 (1995)). In this context, examining a biological sample for evidence of dysregulated cell growth (such as aberrant 273P4B7 expression in cancers) allows for early detection of such aberrant physiology, before a pathologic state such as cancer has progressed to a stage that therapeutic options are more limited and/or the prognosis is worse. In such examinations, the status of 273P4B7 in a biological sample of interest can be compared, for example, to the status of 273P4B7 in a corresponding normal sample (e.g. a sample from that individual or alternatively another individual that is not affected by a pathology). An alteration in the status of 273P4B7 in the biological sample (as compared to the normal sample) provides evidence of dysregulated cellular growth. In addition to using a biological sample that is not affected by a pathology as a normal sample, one can also use a predetermined normative value such as a predetermined normal level of mRNA expression (see, e.g., Grever et al., *J. Comp. Neurol.* 1996 Dec. 9; 376(2): 306-14 and U.S. Pat. No. 5,837,501) to compare 273P4B7 status in a sample.

[0283] The term "status" in this context is used according to its art accepted meaning and refers to the condition or state of a gene and its products. Typically, skilled artisans use a number of parameters to evaluate the condition or state of a gene and its products. These include, but are not limited to the location of expressed gene products (including the location of 273P4B7 expressing cells) as well as the level, and biological activity of expressed gene products (such as 273P4B7 mRNA, polynucleotides and polypeptides). Typically, an alteration in the status of 273P4B7 comprises a change in the location of 273P4B7 and/or 273P4B7 expressing cells and/or an increase in 273P4B7 mRNA and/or protein expression.

[0284] 273P4B7 status in a sample can be analyzed by a number of means well known in the art, including without

limitation, immunohistochemical analysis, in situ hybridization, RT-PCR analysis on laser capture micro-dissected samples, Western blot analysis, and tissue array analysis. Typical protocols for evaluating the status of a 273P4B7 gene and gene products are found, for example in Ausubel et al. eds., 1995, *Current Protocols In Molecular Biology*, Units 2 (Northern Blotting), 4 (Southern Blotting), 15 (Immunoblotting) and 18 (PCR Analysis). Thus, the status of 273P4B7 in a biological sample is evaluated by various methods utilized by skilled artisans including, but not limited to genomic Southern analysis (to examine, for example perturbations in a 273P4B7 gene), Northern analysis and/or PCR analysis of 273P4B7 mRNA (to examine, for example alterations in the polynucleotide sequences or expression levels of 273P4B7 mRNAs), and, Western and/or immunohistochemical analysis (to examine, for example alterations in polypeptide sequences, alterations in polypeptide localization within a sample, alterations in expression levels of 273P4B7 proteins and/or associations of 273P4B7 proteins with polypeptide binding partners). Detectable 273P4B7 polynucleotides include, for example, a 273P4B7 gene or fragment thereof, 273P4B7 mRNA, alternative splice variants, 273P4B7 mRNAs, and recombinant DNA or RNA molecules containing a 273P4B7 polynucleotide.

[0285] The expression profile of 273P4B7 makes it a diagnostic marker for local and/or metastasized disease, and provides information on the growth or oncogenic potential of a biological sample. In particular, the status of 273P4B7 provides information useful for predicting susceptibility to particular disease stages, progression, and/or tumor aggressiveness. The invention provides methods and assays for determining 273P4B7 status and diagnosing cancers that express 273P4B7, such as cancers of the tissues listed in Table I. For example, because 273P4B7 mRNA is so highly expressed in prostate and other cancers relative to normal prostate tissue, assays that evaluate the levels of 273P4B7 mRNA transcripts or proteins in a biological sample can be used to diagnose a disease associated with 273P4B7 dysregulation, and can provide prognostic information useful in defining appropriate therapeutic options.

[0286] The expression status of 273P4B7 provides information including the presence, stage and location of dysplastic, precancerous and cancerous cells, predicting susceptibility to various stages of disease, and/or for gauging tumor aggressiveness. Moreover, the expression profile makes it useful as an imaging reagent for metastasized disease. Consequently, an aspect of the invention is directed to the various molecular prognostic and diagnostic methods for examining the status of 273P4B7 in biological samples such as those from individuals suffering from, or suspected of suffering from a pathology characterized by dysregulated cellular growth, such as cancer.

[0287] As described above, the status of 273P4B7 in a biological sample can be examined by a number of well-known procedures in the art. For example, the status of 273P4B7 in a biological sample taken from a specific location in the body can be examined by evaluating the sample for the presence or absence of 273P4B7 expressing cells (e.g. those that express 273P4B7 mRNAs or proteins). This examination can provide evidence of dysregulated cellular growth, for example, when 273P4B7-expressing cells are found in a biological sample that does not normally contain such cells (such as a lymph node), because such

alterations in the status of 273P4B7 in a biological sample are often associated with dysregulated cellular growth. Specifically, one indicator of dysregulated cellular growth is the metastases of cancer cells from an organ of origin (such as the prostate) to a different area of the body (such as a lymph node). In this context, evidence of dysregulated cellular growth is important for example because occult lymph node metastases can be detected in a substantial proportion of patients with prostate cancer, and such metastases are associated with known predictors of disease progression (see, e.g., Murphy et al., *Prostate* 42(4): 315-317 (2000); Su et al., *Semin. Surg. Oncol.* 18(1): 17-28 (2000) and Freeman et al., *J Urol* 1995 August 154(2 Pt 1):474-8).

[0288] In one aspect, the invention provides methods for monitoring 273P4B7 gene products by determining the status of 273P4B7 gene products expressed by cells from an individual suspected of having a disease associated with dysregulated cell growth (such as hyperplasia or cancer) and then comparing the status so determined to the status of 273P4B7 gene products in a corresponding normal sample. The presence of aberrant 273P4B7 gene products in the test sample relative to the normal sample provides an indication of the presence of dysregulated cell growth within the cells of the individual.

[0289] In another aspect, the invention provides assays useful in determining the presence of cancer in an individual, comprising detecting a significant increase in 273P4B7 mRNA or protein expression in a test cell or tissue sample relative to expression levels in the corresponding normal cell or tissue. The presence of 273P4B7 mRNA can, for example, be evaluated in tissues including but not limited to those listed in Table I. The presence of significant 273P4B7 expression in any of these tissues is useful to indicate the emergence, presence and/or severity of a cancer, since the corresponding normal tissues do not express 273P4B7 mRNA or express it at lower levels.

[0290] In a related embodiment, 273P4B7 status is determined at the protein level rather than at the nucleic acid level. For example, such a method comprises determining the level of 273P4B7 protein expressed by cells in a test tissue sample and comparing the level so determined to the level of 273P4B7 expressed in a corresponding normal sample. In one embodiment, the presence of 273P4B7 protein is evaluated, for example, using immunohistochemical methods. 273P4B7 antibodies or binding partners capable of detecting 273P4B7 protein expression are used in a variety of assay formats well known in the art for this purpose.

[0291] In a further embodiment, one can evaluate the status of 273P4B7 nucleotide and amino acid sequences in a biological sample in order to identify perturbations in the structure of these molecules. These perturbations can include insertions, deletions, substitutions and the like. Such evaluations are useful because perturbations in the nucleotide and amino acid sequences are observed in a large number of proteins associated with a growth dysregulated phenotype (see, e.g., Marrogi et al., 1999, *J. Cutan. Pathol.* 26(8):369-378). For example, a mutation in the sequence of 273P4B7 may be indicative of the presence or promotion of a tumor. Such assays therefore have diagnostic and predictive value where a mutation in 273P4B7 indicates a potential loss of function or increase in tumor growth.

[0292] A wide variety of assays for observing perturbations in nucleotide and amino acid sequences are well known in the art. For example, the size and structure of nucleic acid or amino acid sequences of 273P4B7 gene products are observed by the Northern, Southern, Western, PCR and DNA sequencing protocols discussed herein. In addition, other methods for observing perturbations in nucleotide and amino acid sequences such as single strand conformation polymorphism analysis are well known in the art (see, e.g., U.S. Pat. No. 5,382,510 issued 7 Sep. 1999, and U.S. Pat. No. 5,952,170 issued 17 Jan. 1995).

[0293] Additionally, one can examine the methylation status of a 273P4B7 gene in a biological sample. Aberrant demethylation and/or hypermethylation of CpG islands in gene 5' regulatory regions frequently occurs in immortalized and transformed cells, and can result in altered expression of various genes. For example, promoter hypermethylation of the pi-class glutathione S-transferase (a protein expressed in normal prostate but not expressed in >90% of prostate carcinomas) appears to permanently silence transcription of this gene and is the most frequently detected genomic alteration in prostate carcinomas (De Marzo et al., *Am. J. Pathol.* 155(6): 1985-1992 (1999)). In addition, this alteration is present in at least 70% of cases of high-grade prostatic intraepithelial neoplasia (PIN) (Brooks et al., *Cancer Epidemiol. Biomarkers Prev.*, 1998, 7:531-536). In another example, expression of the LAGE-1 tumor specific gene (which is not expressed in normal prostate but is expressed in 25-50% of prostate cancers) is induced by deoxy-azacytidine in lymphoblastoid cells, suggesting that tumoral expression is due to demethylation (Lethe et al., *Int. J. Cancer* 76(6): 903-908 (1998)). A variety of assays for examining methylation status of a gene are well known in the art. For example, one can utilize, in Southern hybridization approaches, methylation-sensitive restriction enzymes that cannot cleave sequences that contain methylated CpG sites to assess the methylation status of CpG islands. In addition, MSP (methylation specific PCR) can rapidly profile the methylation status of all the CpG sites present in a CpG island of a given gene. This procedure involves initial modification of DNA by sodium bisulfite (which will convert all unmethylated cytosines to uracil) followed by amplification using primers specific for methylated versus unmethylated DNA. Protocols involving methylation interference can also be found for example in *Current Protocols In Molecular Biology*, Unit 12, Frederick M. Ausubel et al. eds., 1995.

[0294] Gene amplification is an additional method for assessing the status of 273P4B7. Gene amplification is measured in a sample directly, for example, by conventional Southern blotting or Northern blotting to quantitate the transcription of mRNA (Thomas, 1980, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205), dot blotting (DNA analysis), or in situ hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies are employed that recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn are labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

[0295] Biopsied tissue or peripheral blood can be conveniently assayed for the presence of cancer cells using for example, Northern, dot blot or RT-PCR analysis to detect 273P4B7 expression. The presence of RT-PCR amplifiable 273P4B7 mRNA provides an indication of the presence of cancer. RT-PCR assays are well known in the art. RT-PCR detection assays for tumor cells in peripheral blood are currently being evaluated for use in the diagnosis and management of a number of human solid tumors. In the prostate cancer field, these include RT-PCR assays for the detection of cells expressing PSA and PSM (Verkaik et al., 1997, *Urol. Res.* 25:373-384; Ghossein et al., 1995, *J. Clin. Oncol.* 13:1195-2000; Heston et al., 1995, *Clin. Chem.* 41:1687-1688).

[0296] A further aspect of the invention is an assessment of the susceptibility that an individual has for developing cancer. In one embodiment, a method for predicting susceptibility to cancer comprises detecting 273P4B7 mRNA or 273P4B7 protein in a tissue sample, its presence indicating susceptibility to cancer, wherein the degree of 273P4B7 mRNA expression correlates to the degree of susceptibility. In a specific embodiment, the presence of 273P4B7 in prostate or other tissue is examined, with the presence of 273P4B7 in the sample providing an indication of prostate cancer susceptibility (or the emergence or existence of a prostate tumor). Similarly, one can evaluate the integrity 273P4B7 nucleotide and amino acid sequences in a biological sample, in order to identify perturbations in the structure of these molecules such as insertions, deletions, substitutions and the like. The presence of one or more perturbations in 273P4B7 gene products in the sample is an indication of cancer susceptibility (or the emergence or existence of a tumor).

[0297] The invention also comprises methods for gauging tumor aggressiveness. In one embodiment, a method for gauging aggressiveness of a tumor comprises determining the level of 273P4B7 mRNA or 273P4B7 protein expressed by tumor cells, comparing the level so determined to the level of 273P4B7 mRNA or 273P4B7 protein expressed in a corresponding normal tissue taken from the same individual or a normal tissue reference sample, wherein the degree of 273P4B7 mRNA or 273P4B7 protein expression in the tumor sample relative to the normal sample indicates the degree of aggressiveness. In a specific embodiment, aggressiveness of a tumor is evaluated by determining the extent to which 273P4B7 is expressed in the tumor cells, with higher expression levels indicating more aggressive tumors. Another embodiment is the evaluation of the integrity of 273P4B7 nucleotide and amino acid sequences in a biological sample, in order to identify perturbations in the structure of these molecules such as insertions, deletions, substitutions and the like. The presence of one or more perturbations indicates more aggressive tumors.

[0298] Another embodiment of the invention is directed to methods for observing the progression of a malignancy in an individual over time. In one embodiment, methods for observing the progression of a malignancy in an individual over time comprise determining the level of 273P4B7 mRNA or 273P4B7 protein expressed by cells in a sample of the tumor, comparing the level so determined to the level of 273P4B7 mRNA or 273P4B7 protein expressed in an equivalent tissue sample taken from the same individual at a different time, wherein the degree of 273P4B7 mRNA or

273P4B7 protein expression in the tumor sample over time provides information on the progression of the cancer. In a specific embodiment, the progression of a cancer is evaluated by determining 273P4B7 expression in the tumor cells over time, where increased expression over time indicates a progression of the cancer. Also, one can evaluate the integrity 273P4B7 nucleotide and amino acid sequences in a biological sample in order to identify perturbations in the structure of these molecules such as insertions, deletions, substitutions and the like, where the presence of one or more perturbations indicates a progression of the cancer.

[0299] The above diagnostic approaches can be combined with any one of a wide variety of prognostic and diagnostic protocols known in the art. For example, another embodiment of the invention is directed to methods for observing a coincidence between the expression of 273P4B7 gene and 273P4B7 gene products (or perturbations in 273P4B7 gene and 273P4B7 gene products) and a factor that is associated with malignancy, as a means for diagnosing and prognosticating the status of a tissue sample. A wide variety of factors associated with malignancy can be utilized, such as the expression of genes associated with malignancy (e.g. PSA, PSCA and PSM expression for prostate cancer etc.) as well as gross cytological observations (see, e.g., Bocking et al., 1984, *Anal. Quant. Cytol.* 6(2):74-88; Epstein, 1995, *Hum. Pathol.* 26(2):223-9; Thorson et al., 1998, *Mod. Pathol.* 11(6):543-51; Baisden et al., 1999, *Am. J. Surg. Pathol.* 23(8):918-24). Methods for observing a coincidence between the expression of 273P4B7 gene and 273P4B7 gene products (or perturbations in 273P4B7 gene and 273P4B7 gene products) and another factor that is associated with malignancy are useful, for example, because the presence of a set of specific factors that coincide with disease provides information crucial for diagnosing and prognosticating the status of a tissue sample.

[0300] In one embodiment, methods for observing a coincidence between the expression of 273P4B7 gene and 273P4B7 gene products (or perturbations in 273P4B7 gene and 273P4B7 gene products) and another factor associated with malignancy entails detecting the overexpression of 273P4B7 mRNA or protein in a tissue sample, detecting the overexpression of PSA mRNA or protein in a tissue sample (or PSCA or PSM expression), and observing a coincidence of 273P4B7 mRNA or protein and PSA mRNA or protein overexpression (or PSCA or PSM expression). In a specific embodiment, the expression of 273P4B7 and PSA mRNA in prostate tissue is examined, where the coincidence of 273P4B7 and PSA mRNA overexpression in the sample indicates the existence of prostate cancer, prostate cancer susceptibility or the emergence or status of a prostate tumor.

[0301] Methods for detecting and quantifying the expression of 273P4B7 mRNA or protein are described herein, and standard nucleic acid and protein detection and quantification technologies are well known in the art. Standard methods for the detection and quantification of 273P4B7 mRNA include in situ hybridization using labeled 273P4B7 riboprobes, Northern blot and related techniques using 273P4B7 polynucleotide probes, RT-PCR analysis using primers specific for 273P4B7, and other amplification type detection methods, such as, for example, branched DNA, SISBA, TMA and the like. In a specific embodiment, semi-quantitative RT-PCR is used to detect and quantify 273P4B7 mRNA expression. Any number of primers capable of

amplifying 273P4B7 can be used for this purpose, including but not limited to the various primer sets specifically described herein. In a specific embodiment, polyclonal or monoclonal antibodies specifically reactive with the wild-type 273P4B7 protein can be used in an immunohistochemical assay of biopsied tissue.

[0302] IX.) Identification of Molecules that Interact with 273P4B7

[0303] The 273P4B7 protein and nucleic acid sequences disclosed herein allow a skilled artisan to identify proteins, small molecules and other agents that interact with 273P4B7, as well as pathways activated by 273P4B7 via any one of a variety of art accepted protocols. For example, one can utilize one of the so-called interaction trap systems (also referred to as the "two-hybrid assay"). In such systems, molecules interact and reconstitute a transcription factor which directs expression of a reporter gene, whereupon the expression of the reporter gene is assayed. Other systems identify protein-protein interactions *in vivo* through reconstitution of a eukaryotic transcriptional activator, see, e.g., U.S. Pat. No. 5,955,280 issued 21 Sep. 1999, U.S. Pat. No. 5,925,523 issued 20 Jul. 1999, U.S. Pat. No. 5,846,722 issued 8 Dec. 1998 and U.S. Pat. No. 6,004,746 issued 21 Dec. 1999. Algorithms are also available in the art for genome-based predictions of protein function (see, e.g., Marcotte, et al., *Nature* 402: 4 November 1999, 83-86).

[0304] Alternatively one can screen peptide libraries to identify molecules that interact with 273P4B7 protein sequences. In such methods, peptides that bind to 273P4B7 are identified by screening libraries that encode a random or controlled collection of amino acids. Peptides encoded by the libraries are expressed as fusion proteins of bacteriophage coat proteins, the bacteriophage particles are then screened against the 273P4B7 protein(s).

[0305] Accordingly, peptides having a wide variety of uses, such as therapeutic, prognostic or diagnostic reagents, are thus identified without any prior information on the structure of the expected ligand or receptor molecule. Typical peptide libraries and screening methods that can be used to identify molecules that interact with 273P4B7 protein sequences are disclosed for example in U.S. Pat. No. 5,723,286 issued 3 Mar. 1998 and U.S. Pat. No. 5,733,731 issued 31 Mar. 1998.

[0306] Alternatively, cell lines that express 273P4B7 are used to identify protein-protein interactions mediated by 273P4B7. Such interactions can be examined using immunoprecipitation techniques (see, e.g., Hamilton B. J., et al. *Biochem. Biophys. Res. Commun.* 1999, 261:646-51). 273P4B7 protein can be immunoprecipitated from 273P4B7-expressing cell lines using anti-273P4B7 antibodies. Alternatively, antibodies against His-tag can be used in a cell line engineered to express fusions of 273P4B7 and a His-tag (vectors mentioned above). The immunoprecipitated complex can be examined for protein association by procedures such as Western blotting, ³⁵S-methionine labeling of proteins, protein microsequencing, silver staining and two-dimensional gel electrophoresis.

[0307] Small molecules and ligands that interact with 273P4B7 can be identified through related embodiments of such screening assays. For example, small molecules can be identified that interfere with protein function, including

molecules that interfere with 273P4B7's ability to mediate phosphorylation and de-phosphorylation, interaction with DNA or RNA molecules as an indication of regulation of cell cycles, second messenger signaling or tumorigenesis. Similarly, small molecules that modulate 273P4B7-related ion channel, protein pump, or cell communication functions are identified and used to treat patients that have a cancer that expresses 273P4B7 (see, e.g., Hille, B., *Ionic Channels of Excitable Membranes* 2nd Ed., Sinauer Assoc., Sunderland, Mass., 1992). Moreover, ligands that regulate 273P4B7 function can be identified based on their ability to bind 273P4B7 and activate a reporter construct. Typical methods are discussed for example in U.S. Pat. No. 5,928,868 issued 27 Jul. 1999, and include methods for forming hybrid ligands in which at least one ligand is a small molecule. In an illustrative embodiment, cells engineered to express a fusion protein of 273P4B7 and a DNA-binding protein are used to co-express a fusion protein of a hybrid ligand/small molecule and a cDNA library transcriptional activator protein. The cells further contain a reporter gene, the expression of which is conditioned on the proximity of the first and second fusion proteins to each other, an event that occurs only if the hybrid ligand binds to target sites on both hybrid proteins. Those cells that express the reporter gene are selected and the unknown small molecule or the unknown ligand is identified. This method provides a means of identifying modulators, which activate or inhibit 273P4B7.

[0308] An embodiment of this invention comprises a method of screening for a molecule that interacts with a 273P4B7 amino acid sequence shown in FIG. 2 or FIG. 3, comprising the steps of contacting a population of molecules with a 273P4B7 amino acid sequence, allowing the population of molecules and the 273P4B7 amino acid sequence to interact under conditions that facilitate an interaction, determining the presence of a molecule that interacts with the 273P4B7 amino acid sequence, and then separating molecules that do not interact with the 273P4B7 amino acid sequence from molecules that do. In a specific embodiment, the method further comprises purifying, characterizing and identifying a molecule that interacts with the 273P4B7 amino acid sequence. The identified molecule can be used to modulate a function performed by 273P4B7. In a preferred embodiment, the 273P4B7 amino acid sequence is contacted with a library of peptides.

[0309] X.) Therapeutic Methods and Compositions

[0310] The identification of 273P4B7 as a protein that is normally expressed in a restricted set of tissues, but which is also expressed in cancers such as those listed in Table I, opens a number of therapeutic approaches to the treatment of such cancers.

[0311] Of note, targeted antitumor therapies have been useful even when the targeted protein is expressed on normal tissues, even vital normal organ tissues. A vital organ is one that is necessary to sustain life, such as the heart or colon. A non-vital organ is one that can be removed whereupon the individual is still able to survive. Examples of non-vital organs are ovary, breast, and prostate.

[0312] For example, Herceptin® is an FDA approved pharmaceutical that has as its active ingredient an antibody which is immunoreactive with the protein variously known as HER2, HER2/neu, and erb-b-2. It is marketed by Genentech and has been a commercially successful antitumor

agent. Herceptin sales reached almost \$400 million in 2002. Herceptin is a treatment for HER2 positive metastatic breast cancer. However, the expression of HER2 is not limited to such tumors. The same protein is expressed in a number of normal tissues. In particular, it is known that HER2/neu is present in normal kidney and heart, thus these tissues are present in all human recipients of Herceptin. The presence of HER2/neu in normal kidney is also confirmed by Latif, Z., et al., B.J.U. International (2002) 89:5-9. As shown in this article (which evaluated whether renal cell carcinoma should be a preferred indication for anti-HER2 antibodies such as Herceptin) both protein and mRNA are produced in benign renal tissues. Notably, HER2/neu protein was strongly over-expressed in benign renal tissue. Despite the fact that HER2/neu is expressed in such vital tissues as heart and kidney, Herceptin is a very useful, FDA approved, and commercially successful drug. The effect of Herceptin on cardiac tissue, i.e., "cardiotoxicity," has merely been a side effect to treatment. When patients were treated with Herceptin alone, significant cardiotoxicity occurred in a very low percentage of patients.

[0313] Of particular note, although kidney tissue is indicated to exhibit normal expression, possibly even higher expression than cardiac tissue, kidney has no appreciable Herceptin side effect whatsoever. Moreover, of the diverse array of normal tissues in which HER2 is expressed, there is very little occurrence of any side effect. Only cardiac tissue has manifested any appreciable side effect at all. A tissue such as kidney, where HER2/neu expression is especially notable, has not been the basis for any side effect.

[0314] Furthermore, favorable therapeutic effects have been found for antitumor therapies that target epidermal growth factor receptor (EGFR). EGFR is also expressed in numerous normal tissues. There have been very limited side effects in normal tissues following use of anti-EGFR therapeutics.

[0315] Thus, expression of a target protein in normal tissue, even vital normal tissue, does not defeat the utility of a targeting agent for the protein as a therapeutic for certain tumors in which the protein is also overexpressed.

[0316] Accordingly, therapeutic approaches that inhibit the activity of a 273P4B7 protein are useful for patients suffering from a cancer that expresses 273P4B7. These therapeutic approaches generally fall into two classes. One class comprises various methods for inhibiting the binding or association of a 273P4B7 protein with its binding partner or with other proteins. Another class comprises a variety of methods for inhibiting the transcription of a 273P4B7 gene or translation of 273P4B7 mRNA.

[0317] X.A.) Anti-Cancer Vaccines

[0318] The invention provides cancer vaccines comprising a 273P4B7-related protein or 273P4B7-related nucleic acid. In view of the expression of 273P4B7, cancer vaccines prevent and/or treat 273P4B7-expressing cancers with minimal or no effects on non-target tissues. The use of a tumor antigen in a vaccine that generates humoral and/or cell-mediated immune responses as anti-cancer therapy is well known in the art and has been employed in prostate cancer using human PSMA and rodent PAP immunogens (Hodge et al., 1995, Int. J. Cancer 63:231-237; Fong et al., 1997, J. Immunol. 159:3113-3117).

[0319] Such methods can be readily practiced by employing a 273P4B7-related protein, or a 273P4B7-encoding nucleic acid molecule and recombinant vectors capable of expressing and presenting the 273P4B7 immunogen (which typically comprises a number of antibody or T cell epitopes). Skilled artisans understand that a wide variety of vaccine systems for delivery of immunoreactive epitopes are known in the art (see, e.g., Heryln et al., Ann Med 1999 February 31(1):66-78; Maruyama et al., Cancer Immunol Immunother 2000 June 49(3):123-32). Briefly, such methods of generating an immune response (e.g. humoral and/or cell-mediated) in a mammal, comprise the steps of: exposing the mammal's immune system to an immunoreactive epitope (e.g. an epitope present in a 273P4B7 protein shown in FIG. 3 or analog or homolog thereof) so that the mammal generates an immune response that is specific for that epitope (e.g. generates antibodies that specifically recognize that epitope). In a preferred method, a 273P4B7 immunogen contains a biological motif, see e.g., Tables VIII-XXI and XXII-XLIX, or a peptide of a size range from 273P4B7 indicated in FIG. 5, FIG. 6, FIG. 7, FIG. 8, and FIG. 9.

[0320] The entire 273P4B7 protein, immunogenic regions or epitopes thereof can be combined and delivered by various means. Such vaccine compositions can include, for example, lipopeptides (e.g., Vitiello, A. et al., J. Clin. Invest. 95:341, 1995), peptide compositions encapsulated in poly(DL-lactide-co-glycolide) ("PLG") microspheres (see, e.g., Eldridge, et al., Molec. Immunol. 28:287-294, 1991; Alonso et al., Vaccine 12:299-306, 1994; Jones et al., Vaccine 13:675-681, 1995), peptide compositions contained in immune stimulating complexes (ISCOMS) (see, e.g., Takahashi et al., Nature 344:873-875, 1990; Hu et al., Clin Exp Immunol. 113:235-243, 1998), multiple antigen peptide systems (MAPs) (see e.g., Tam, J. P., Proc. Natl. Acad. Sci. U.S.A. 85:5409-5413, 1988; Tam, J. P., J. Immunol. Methods 196:17-32, 1996), peptides formulated as multivalent peptides; peptides for use in ballistic delivery systems, typically crystallized peptides, viral delivery vectors (Perkus, M. E. et al., In: Concepts in vaccine development, Kaufmann, S. H. E., ed., p. 379, 1996; Chakrabarti, S. et al., Nature 320:535, 1986; Hu, S. L. et al., Nature 320:537, 1986; Kieny, M.-P. et al., AIDS Bio/Technology 4:790, 1986; Top, F. H. et al., J. Infect. Dis. 124:148, 1971; Chanda, P. K. et al., Virology 175:535, 1990), particles of viral or synthetic origin (e.g., Kofler, N. et al., J. Immunol. Methods. 192:25, 1996; Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993; Falo, L. D., Jr. et al., Nature Med. 7:649, 1995), adjuvants (Warren, H. S., Vogel, F. R., and Chedid, L. A. Annu. Rev. Immunol. 4:369, 1986; Gupta, R. K. et al., Vaccine 11:293, 1993), liposomes (Reddy, R. et al., J. Immunol. 148:1585, 1992; Rock, K. L., Immunol. Today 17:131, 1996), or, naked or particle absorbed cDNA (Ulmer, J. B. et al., Science 259:1745, 1993; Robinson, H. L., Hunt, L. A., and Webster, R. G., Vaccine 11:957, 1993; Shiver, J. W. et al., In: Concepts in vaccine development, Kaufmann, S. H. E., ed., p. 423, 1996; Cease, K. B., and Berzofsky, J. A., Annu. Rev. Immunol. 12:923, 1994 and Eldridge, J. H. et al., Sem. Hematol. 30:16, 1993). Toxin-targeted delivery technologies, also known as receptor mediated targeting, such as those of Avant Immunotherapeutics, Inc. (Needham, Mass.) may also be used.

[0321] In patients with 273P4B7-associated cancer, the vaccine compositions of the invention can also be used in conjunction with other treatments used for cancer, e.g.,

surgery, chemotherapy, drug therapies, radiation therapies, etc. including use in combination with immune adjuvants such as IL-2, IL-12, GM-CSF, and the like.

[0322] Cellular Vaccines:

[0323] CTL epitopes can be determined using specific algorithms to identify peptides within 273P4B7 protein that bind corresponding HLA alleles (see e.g., Table IV; Epimer™ and Epimatrix™, Brown University (URL brown.edu/Research/TB-HIV_Lab/epimatrix/epimatrix.html); and, BIMAS, (URL bimas.dcrn.nih.gov/; SYFPEITHI at URL syfpeithi.bmi-heidelberg.com/). In a preferred embodiment, a 273P4B7 immunogen contains one or more amino acid sequences identified using techniques well known in the art, such as the sequences shown in Tables VIII-XXI and XXII-XLIX or a peptide of 8, 9, 10 or 11 amino acids specified by an HLA Class I motif/supermotif (e.g., Table IV (A), Table IV (D), or Table IV (E)) and/or a peptide of at least 9 amino acids that comprises an HLA Class II motif/supermotif (e.g., Table IV (B) or Table IV (C)). As is appreciated in the art, the HLA Class I binding groove is essentially closed ended so that peptides of only a particular size range can fit into the groove and be bound, generally HLA Class I epitopes are 8, 9, 10, or 11 amino acids long. In contrast, the HLA Class II binding groove is essentially open ended; therefore a peptide of about 9 or more amino acids can be bound by an HLA Class II molecule. Due to the binding groove differences between HLA Class I and II, HLA Class I motifs are length specific, i.e., position two of a Class I motif is the second amino acid in an amino to carboxyl direction of the peptide. The amino acid positions in a Class II motif are relative only to each other, not the overall peptide, i.e., additional amino acids can be attached to the amino and/or carboxyl termini of a motif-bearing sequence. HLA Class II epitopes are often 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acids long, or longer than 25 amino acids.

[0324] Antibody-Based Vaccines

[0325] A wide variety of methods for generating an immune response in a mammal are known in the art (for example as the first step in the generation of hybridomas). Methods of generating an immune response in a mammal comprise exposing the mammal's immune system to an immunogenic epitope on a protein (e.g. a 273P4B7 protein) so that an immune response is generated. A typical embodiment consists of a method for generating an immune response to 273P4B7 in a host, by contacting the host with a sufficient amount of at least one 273P4B7 B cell or cytotoxic T-cell epitope or analog thereof; and at least one periodic interval thereafter re-contacting the host with the 273P4B7 B cell or cytotoxic T-cell epitope or analog thereof. A specific embodiment consists of a method of generating an immune response against a 273P4B7-related protein or a man-made multi-epitopic peptide comprising: administering 273P4B7 immunogen (e.g. a 273P4B7 protein or a peptide fragment thereof, a 273P4B7 fusion protein or analog etc.) in a vaccine preparation to a human or another mammal. Typically, such vaccine preparations further contain a suitable adjuvant (see, e.g., U.S. Pat. No. 6,146,635) or a universal helper epitope such as a PADRE peptide (Epimmune Inc., San Diego, Calif.; see, e.g., Alexander et al., J. Immunol. 2000 164(3): 1625-1633; Alexander et al., Immunity 1994 1(9): 751-761 and Alexander et al., Immu-

nol. Res. 1998 18(2): 79-92). An alternative method comprises generating an immune response in an individual against a 273P4B7 immunogen by: administering in vivo to muscle or skin of the individual's body a DNA molecule that comprises a DNA sequence that encodes a 273P4B7 immunogen, the DNA sequence operatively linked to regulatory sequences which control the expression of the DNA sequence; wherein the DNA molecule is taken up by cells, the DNA sequence is expressed in the cells and an immune response is generated against the immunogen (see, e.g., U.S. Pat. No. 5,962,428). Optionally a genetic vaccine facilitator such as anionic lipids; saponins; lectins; estrogenic compounds; hydroxylated lower alkyls; dimethyl sulfoxide; and urea is also administered. In addition, an anti-idiotypic antibody can be administered that mimics 273P4B7, in order to generate a response to the target antigen.

[0326] Nucleic Acid Vaccines:

[0327] Vaccine compositions of the invention include nucleic acid-mediated modalities. DNA or RNA that encode protein(s) of the invention can be administered to a patient. Genetic immunization methods can be employed to generate prophylactic or therapeutic humoral and cellular immune responses directed against cancer cells expressing 273P4B7. Constructs comprising DNA encoding a 273P4B7-related protein/immunogen and appropriate regulatory sequences can be injected directly into muscle or skin of an individual, such that the cells of the muscle or skin take-up the construct and express the encoded 273P4B7 protein/immunogen. Alternatively, a vaccine comprises a 273P4B7-related protein. Expression of the 273P4B7-related protein immunogen results in the generation of prophylactic or therapeutic humoral and cellular immunity against cells that bear a 273P4B7 protein. Various prophylactic and therapeutic genetic immunization techniques known in the art can be used (for review, see information and references published at Internet address genweb.com). Nucleic acid-based delivery is described, for instance, in Wolff et al., Science 247:1465 (1990) as well as U.S. Pat. Nos. 5,580,859; 5,589,466; 5,804,566; 5,739,118; 5,736,524; 5,679,647; WO 98/04720. Examples of DNA-based delivery technologies include "naked DNA", facilitated (bupivacaine, polymers, peptide-mediated) delivery, cationic lipid complexes, and particle-mediated ("gene gun") or pressure-mediated delivery (see, e.g., U.S. Pat. No. 5,922,687).

[0328] For therapeutic or prophylactic immunization purposes, proteins of the invention can be expressed via viral or bacterial vectors. Various viral gene delivery systems that can be used in the practice of the invention include, but are not limited to, vaccinia, fowlpox, canarypox, adenovirus, influenza, poliovirus, adeno-associated virus, lentivirus, and sindbis virus (see, e.g., Restifo, 1996, Curr. Opin. Immunol. 8:658-663; Tsang et al. J. Natl. Cancer Inst. 87:982-990 (1995)). Non-viral delivery systems can also be employed by introducing naked DNA encoding a 273P4B7-related protein into the patient (e.g., intramuscularly or intradermally) to induce an anti-tumor response.

[0329] Vaccinia virus is used, for example, as a vector to express nucleotide sequences that encode the peptides of the invention. Upon introduction into a host, the recombinant vaccinia virus expresses the protein immunogenic peptide, and thereby elicits a host immune response. Vaccinia vectors and methods useful in immunization protocols are described

in, e.g., U.S. Pat. No. 4,722,848. Another vector is BCG (Bacille Calmette Guerin). BCG vectors are described in Stover et al., *Nature* 351:456-460 (1991). A wide variety of other vectors useful for therapeutic administration or immunization of the peptides of the invention, e.g. adeno and adeno-associated virus vectors, retroviral vectors, *Salmonella typhi* vectors, detoxified anthrax toxin vectors, and the like, will be apparent to those skilled in the art from the description herein.

[0330] Thus, gene delivery systems are used to deliver a 273P4B7-related nucleic acid molecule. In one embodiment, the full-length human 273P4B7 cDNA is employed. In another embodiment, 273P4B7 nucleic acid molecules encoding specific cytotoxic T lymphocyte (CTL) and/or antibody epitopes are employed.

[0331] Ex Vivo Vaccines

[0332] Various ex vivo strategies can also be employed to generate an immune response. One approach involves the use of antigen presenting cells (APCs) such as dendritic cells (DC) to present 273P4B7 antigen to a patient's immune system. Dendritic cells express MHC class I and II molecules, B7 co-stimulator, and IL-12, and are thus highly specialized antigen presenting cells. In prostate cancer, autologous dendritic cells pulsed with peptides of the prostate-specific membrane antigen (PSMA) are being used in a Phase I clinical trial to stimulate prostate cancer patients' immune systems (Tjoa et al., 1996, *Prostate* 28:65-69; Murphy et al., 1996, *Prostate* 29:371-380). Thus, dendritic cells can be used to present 273P4B7 peptides to T cells in the context of MHC class I or II molecules. In one embodiment, autologous dendritic cells are pulsed with 273P4B7 peptides capable of binding to MHC class I and/or class II molecules. In another embodiment, dendritic cells are pulsed with the complete 273P4B7 protein. Yet another embodiment involves engineering the overexpression of a 273P4B7 gene in dendritic cells using various implementing vectors known in the art, such as adenovirus (Arthur et al., 1997, *Cancer Gene Ther.* 4:17-25), retrovirus (Henderson et al., 1996, *Cancer Res.* 56:3763-3770), lentivirus, adeno-associated virus, DNA transfection (Ribas et al., 1997, *Cancer Res.* 57:2865-2869), or tumor-derived RNA transfection (Ashley et al., 1997, *J. Exp. Med.* 186:1177-1182). Cells that express 273P4B7 can also be engineered to express immune modulators, such as GM-CSF, and used as immunizing agents.

[0333] X.B.) 273P4B7 as a Target for Antibody-Based Therapy

[0334] 273P4B7 is an attractive target for antibody-based therapeutic strategies. A number of antibody strategies are known in the art for targeting both extracellular and intracellular molecules (see, e.g., complement and ADCC mediated killing as well as the use of intrabodies). Because 273P4B7 is expressed by cancer cells of various lineages relative to corresponding normal cells, systemic administration of 273P4B7-immunoreactive compositions are prepared that exhibit excellent sensitivity without toxic, non-specific and/or non-target effects caused by binding of the immunoreactive composition to non-target organs and tissues. Antibodies specifically reactive with domains of 273P4B7 are useful to treat 273P4B7-expressing cancers systemically, either as conjugates with a toxin or therapeutic agent, or as naked antibodies capable of inhibiting cell proliferation or function.

[0335] 273P4B7 antibodies can be introduced into a patient such that the antibody binds to 273P4B7 and modulates a function, such as an interaction with a binding partner, and consequently mediates destruction of the tumor cells and/or inhibits the growth of the tumor cells. Mechanisms by which such antibodies exert a therapeutic effect can include complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, modulation of the physiological function of 273P4B7, inhibition of ligand binding or signal transduction pathways, modulation of tumor cell differentiation, alteration of tumor angiogenesis factor profiles, and/or apoptosis.

[0336] Those skilled in the art understand that antibodies can be used to specifically target and bind immunogenic molecules such as an immunogenic region of a 273P4B7 sequence shown in FIG. 2 or FIG. 3. In addition, skilled artisans understand that it is routine to conjugate antibodies to cytotoxic agents (see, e.g., Slevers et al. *Blood* 93:113678-3684 (Jun. 1, 1999)). When cytotoxic and/or therapeutic agents are delivered directly to cells, such as by conjugating them to antibodies specific for a molecule expressed by that cell (e.g. 273P4B7), the cytotoxic agent will exert its known biological effect (i.e. cytotoxicity) on those cells.

[0337] A wide variety of compositions and methods for using antibody-cytotoxic agent conjugates to kill cells are known in the art. In the context of cancers, typical methods entail administering to an animal having a tumor a biologically effective amount of a conjugate comprising a selected cytotoxic and/or therapeutic agent linked to a targeting agent (e.g. an anti-273P4B7 antibody) that binds to a marker (e.g. 273P4B7) expressed, accessible to binding or localized on the cell surfaces. A typical embodiment is a method of delivering a cytotoxic and/or therapeutic agent to a cell expressing 273P4B7, comprising conjugating the cytotoxic agent to an antibody that immunospecifically binds to a 273P4B7 epitope, and, exposing the cell to the antibody-agent conjugate. Another illustrative embodiment is a method of treating an individual suspected of suffering from metastasized cancer, comprising a step of administering parenterally to said individual a pharmaceutical composition comprising a therapeutically effective amount of an antibody conjugated to a cytotoxic and/or therapeutic agent.

[0338] Cancer immunotherapy using anti-273P4B7 antibodies can be done in accordance with various approaches that have been successfully employed in the treatment of other types of cancer, including but not limited to colon cancer (Arlen et al., 1998, *Crit. Rev. Immunol.* 18:133-138), multiple myeloma (Ozaki et al., 1997, *Blood* 90:3179-3186, Tsunenari et al., 1997, *Blood* 90:2437-2444), gastric cancer (Kasprzyk et al., 1992, *Cancer Res.* 52:2771-2776), B-cell lymphoma (Funakoshi et al., 1996, *J. Immunother. Emphasis Tumor Immunol.* 19:93-101), leukemia (Zhong et al., 1996, *Leuk. Res.* 20:581-589), colorectal cancer (Moun et al., 1994, *Cancer Res.* 54:6160-6166; Velders et al., 1995, *Cancer Res.* 55:4398-4403), and breast cancer (Shepard et al., 1991, *J. Clin. Immunol.* 11:117-127). Some therapeutic approaches involve conjugation of naked antibody to a toxin or radioisotope, such as the conjugation of Y^{90} or I^{131} to anti-CD20 antibodies (e.g., Zevalin™, IDEC Pharmaceuticals Corp. or Bexxar™, Coulter Pharmaceuticals), while others involve co-administration of antibodies and other therapeutic agents, such as Herceptin™ (trastuzumab) with

paclitaxel (Genentech, Inc.). The antibodies can be conjugated to a therapeutic agent. To treat prostate cancer, for example, 273P4B7 antibodies can be administered in conjunction with radiation, chemotherapy or hormone ablation. Also, antibodies can be conjugated to a toxin such as calicheamicin (e.g., Mylotarg™, Wyeth-Ayerst, Madison, N.J., a recombinant humanized IgG.sub.4 kappa antibody conjugated to antitumor antibiotic calicheamicin) or a maytansinoid (e.g., taxane-based Tumor-Activated Prodrug, TAP, platform, ImmunoGen, Cambridge, Mass., also see e.g., U.S. Pat. No. 5,416,064).

[0339] Although 273P4B7 antibody therapy is useful for all stages of cancer, antibody therapy can be particularly appropriate in advanced or metastatic cancers. Treatment with the antibody therapy of the invention is indicated for patients who have received one or more rounds of chemotherapy. Alternatively, antibody therapy of the invention is combined with a chemotherapeutic or radiation regimen for patients who have not received chemotherapeutic treatment. Additionally, antibody therapy can enable the use of reduced dosages of concomitant chemotherapy, particularly for patients who do not tolerate the toxicity of the chemotherapeutic agent very well. Fan et al. (Cancer Res. 53:4637-4642, 1993), Prewett et al. (International J. of Onco. 9:217-224, 1996), and Hancock et al. (Cancer Res. 51:4575-4580, 1991) describe the use of various antibodies together with chemotherapeutic agents.

[0340] Although 273P4B7 antibody therapy is useful for all stages of cancer, antibody therapy can be particularly appropriate in advanced or metastatic cancers. Treatment with the antibody therapy of the invention is indicated for patients who have received one or more rounds of chemotherapy. Alternatively, antibody therapy of the invention is combined with a chemotherapeutic or radiation regimen for patients who have not received chemotherapeutic treatment. Additionally, antibody therapy can enable the use of reduced dosages of concomitant chemotherapy, particularly for patients who do not tolerate the toxicity of the chemotherapeutic agent very well.

[0341] Cancer patients can be evaluated for the presence and level of 273P4B7 expression, preferably using immunohistochemical assessments of tumor tissue, quantitative 273P4B7 imaging, or other techniques that reliably indicate the presence and degree of 273P4B7 expression. Immunohistochemical analysis of tumor biopsies or surgical specimens is preferred for this purpose. Methods for immunohistochemical analysis of tumor tissues are well known in the art.

[0342] Anti-273P4B7 monoclonal antibodies that treat prostate and other cancers include those that initiate a potent immune response against the tumor or those that are directly cytotoxic. In this regard, anti-273P4B7 monoclonal antibodies (mAbs) can elicit tumor cell lysis by either complement-mediated or antibody-dependent cell cytotoxicity (ADCC) mechanisms, both of which require an intact Fc portion of the immunoglobulin molecule for interaction with effector cell Fc receptor sites on complement proteins. In addition, anti-273P4B7 mAbs that exert a direct biological effect on tumor growth are useful to treat cancers that express 273P4B7. Mechanisms by which directly cytotoxic mAbs act include: inhibition of cell growth, modulation of cellular differentiation, modulation of tumor angiogenesis factor

profiles, and the induction of apoptosis. The mechanism(s) by which a particular anti-273P4B7 mAb exerts an anti-tumor effect is evaluated using any number of in vitro assays that evaluate cell death such as ADCC, ADMMC, complement-mediated cell lysis, and so forth, as is generally known in the art.

[0343] In some patients, the use of murine or other non-human monoclonal antibodies, or human/mouse chimeric mAbs can induce moderate to strong immune responses against the non-human antibody. This can result in clearance of the antibody from circulation and reduced efficacy. In the most severe cases, such an immune response can lead to the extensive formation of immune complexes which, potentially, can cause renal failure. Accordingly, preferred monoclonal antibodies used in the therapeutic methods of the invention are those that are either fully human or humanized and that bind specifically to the target 273P4B7 antigen with high affinity but exhibit low or no antigenicity in the patient.

[0344] Therapeutic methods of the invention contemplate the administration of single anti-273P4B7 mAbs as well as combinations, or cocktails, of different mAbs. Such mAb cocktails can have certain advantages inasmuch as they contain mAbs that target different epitopes, exploit different effector mechanisms or combine directly cytotoxic mAbs with mAbs that rely on immune effector functionality. Such mAbs in combination can exhibit synergistic therapeutic effects. In addition, anti-273P4B7 mAbs can be administered concomitantly with other therapeutic modalities, including but not limited to various chemotherapeutic agents, androgen-blockers, immune modulators (e.g., IL-2, GM-CSF), surgery or radiation. The anti-273P4B7 mAbs are administered in their "naked" or unconjugated form, or can have a therapeutic agent(s) conjugated to them.

[0345] Anti-273P4B7 antibody formulations are administered via any route capable of delivering the antibodies to a tumor cell. Routes of administration include, but are not limited to, intravenous, intraperitoneal, intramuscular, intratumor, intradermal, and the like. Treatment generally involves repeated administration of the anti-273P4B7 antibody preparation, via an acceptable route of administration such as intravenous injection (IV), typically at a dose in the range of about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 25 mg/kg body weight. In general, doses in the range of 10-1000 mg mAb per week are effective and well tolerated.

[0346] Based on clinical experience with the Herceptin™ mAb in the treatment of metastatic breast cancer, an initial loading dose of approximately 4 mg/kg patient body weight IV, followed by weekly doses of about 2 mg/kg IV of the anti-273P4B7 mAb preparation represents an acceptable dosing regimen. Preferably, the initial loading dose is administered as a 90-minute or longer infusion. The periodic maintenance dose is administered as a 30 minute or longer infusion, provided the initial dose was well tolerated. As appreciated by those of skill in the art, various factors can influence the ideal dose regimen in a particular case. Such factors include, for example, the binding affinity and half life of the Ab or mAbs used, the degree of 273P4B7 expression in the patient, the extent of circulating shed 273P4B7 antigen, the desired steady-state antibody concentration level, frequency of treatment, and the influence of chemo-

therapeutic or other agents used in combination with the treatment method of the invention, as well as the health status of a particular patient.

[0347] Optionally, patients should be evaluated for the levels of 273P4B7 in a given sample (e.g. the levels of circulating 273P4B7 antigen and/or 273P4B7 expressing cells) in order to assist in the determination of the most effective dosing regimen, etc. Such evaluations are also used for monitoring purposes throughout therapy, and are useful to gauge therapeutic success in combination with the evaluation of other parameters (for example, urine cytology and/or ImmunoCyt levels in bladder cancer therapy, or by analogy, serum PSA levels in prostate cancer therapy).

[0348] Anti-idiotypic anti-273P4B7 antibodies can also be used in anti-cancer therapy as a vaccine for inducing an immune response to cells expressing a 273P4B7-related protein. In particular, the generation of anti-idiotypic antibodies is well known in the art; this methodology can readily be adapted to generate anti-idiotypic anti-273P4B7 antibodies that mimic an epitope on a 273P4B7-related protein (see, for example, Wagner et al., 1997, *Hybridoma* 16: 33-40; Foon et al., 1995, *J. Clin. Invest.* 96:334-342; Herlyn et al., 1996, *Cancer Immunol. Immunother.* 43:65-76). Such an anti-idiotypic antibody can be used in cancer vaccine strategies.

[0349] X.C.) 273P4B7 as a Target for Cellular Immune Responses

[0350] Vaccines and methods of preparing vaccines that contain an immunogenically effective amount of one or more HLA-binding peptides as described herein are further embodiments of the invention. Furthermore, vaccines in accordance with the invention encompass compositions of one or more of the claimed peptides. A peptide can be present in a vaccine individually. Alternatively, the peptide can exist as a homopolymer comprising multiple copies of the same peptide, or as a heteropolymer of various peptides. Polymers have the advantage of increased immunological reaction and, where different peptide epitopes are used to make up the polymer, the additional ability to induce antibodies and/or CTLs that react with different antigenic determinants of the pathogenic organism or tumor-related peptide targeted for an immune response. The composition can be a naturally occurring region of an antigen or can be prepared, e.g., recombinantly or by chemical synthesis.

[0351] Carriers that can be used with vaccines of the invention are well known in the art, and include, e.g., thyroglobulin, albumins such as human serum albumin, tetanus toxoid, polyamino acids such as poly L-lysine, poly L-glutamic acid, influenza, hepatitis B virus core protein, and the like. The vaccines can contain a physiologically tolerable (i.e., acceptable) diluent such as water, or saline, preferably phosphate buffered saline. The vaccines also typically include an adjuvant. Adjuvants such as incomplete Freund's adjuvant, aluminum phosphate, aluminum hydroxide, or alum are examples of materials well known in the art. Additionally, as disclosed herein, CTL responses can be primed by conjugating peptides of the invention to lipids, such as tripalmitoyl-S-glycerylcysteinylserine (P3CSS). Moreover, an adjuvant such as a synthetic cytosine-phosphorothiolated-guanine-containing (CpG) oligonucleotides has been found to increase CTL responses 10- to 100-fold. (see, e.g. Davila and Celis, *J. Immunol.* 165:539-547 (2000))

[0352] Upon immunization with a peptide composition in accordance with the invention, via injection, aerosol, oral, transdermal, transmucosal, intrapleural, intrathecal, or other suitable routes, the immune system of the host responds to the vaccine by producing large amounts of CTLs and/or HTLs specific for the desired antigen. Consequently, the host becomes at least partially immune to later development of cells that express or overexpress 273P4B7 antigen, or derives at least some therapeutic benefit when the antigen was tumor-associated.

[0353] In some embodiments, it may be desirable to combine the class I peptide components with components that induce or facilitate neutralizing antibody and/or helper T cell responses directed to the target antigen. A preferred embodiment of such a composition comprises class I and class II epitopes in accordance with the invention. An alternative embodiment of such a composition comprises a class I and/or class II epitope in accordance with the invention, along with a cross reactive HTL epitope such as PADRE™ (Epimmune, San Diego, Calif.) molecule (described e.g., in U.S. Pat. No. 5,736,142).

[0354] A vaccine of the invention can also include antigen-presenting cells (APC), such as dendritic cells (DC), as a vehicle to present peptides of the invention. Vaccine compositions can be created in vitro, following dendritic cell mobilization and harvesting, whereby loading of dendritic cells occurs in vitro. For example, dendritic cells are transfected, e.g., with a minigene in accordance with the invention, or are pulsed with peptides. The dendritic cell can then be administered to a patient to elicit immune responses in vivo. Vaccine compositions, either DNA- or peptide-based, can also be administered in vivo in combination with dendritic cell mobilization whereby loading of dendritic cells occurs in vivo.

[0355] Preferably, the following principles are utilized when selecting an array of epitopes for inclusion in a polypeptidic composition for use in a vaccine, or for selecting discrete epitopes to be included in a vaccine and/or to be encoded by nucleic acids such as a minigene. It is preferred that each of the following principles be balanced in order to make the selection. The multiple epitopes to be incorporated in a given vaccine composition may be, but need not be, contiguous in sequence in the native antigen from which the epitopes are derived.

[0356] 1.) Epitopes are selected which, upon administration, mimic immune responses that have been observed to be correlated with tumor clearance. For HLA Class I this includes 3-4 epitopes that come from at least one tumor associated antigen (TAA). For HLA Class II a similar rationale is employed; again 3-4 epitopes are selected from at least one TAA (see, e.g., Rosenberg et al., *Science* 278:1447-1450). Epitopes from one TAA may be used in combination with epitopes from one or more additional TAAs to produce a vaccine that targets tumors with varying expression patterns of frequently-expressed TAAs.

[0357] 2.) Epitopes are selected that have the requisite binding affinity established to be correlated with immunogenicity: for HLA Class I an IC₅₀ of 500 nM or less, often 200 nM or less; and for Class II an IC₅₀ of 1000 nM or less.

[0358] 3.) Sufficient supermotif bearing-peptides, or a sufficient array of allele-specific motif-bearing peptides, are

selected to give broad population coverage. For example, it is preferable to have at least 80% population coverage. A Monte Carlo analysis, a statistical evaluation known in the art, can be employed to assess the breadth, or redundancy of, population coverage.

[0359] 4.) When selecting epitopes from cancer-related antigens it is often useful to select analogs because the patient may have developed tolerance to the native epitope.

[0360] 5.) Of particular relevance are epitopes referred to as "nested epitopes." Nested epitopes occur where at least two epitopes overlap in a given peptide sequence. A nested peptide sequence can comprise B cell, HLA class I and/or HLA class II epitopes. When providing nested epitopes, a general objective is to provide the greatest number of epitopes per sequence. Thus, an aspect is to avoid providing a peptide that is any longer than the amino terminus of the amino terminal epitope and the carboxyl terminus of the carboxyl terminal epitope in the peptide. When providing a multi-epitopic sequence, such as a sequence comprising nested epitopes, it is generally important to screen the sequence in order to insure that it does not have pathological or other deleterious biological properties.

[0361] 6.) If a polyepitopic protein is created, or when creating a minigene, an objective is to generate the smallest peptide that encompasses the epitopes of interest. This principle is similar, if not the same as that employed when selecting a peptide comprising nested epitopes. However, with an artificial polyepitopic peptide, the size minimization objective is balanced against the need to integrate any spacer sequences between epitopes in the polyepitopic protein. Spacer amino acid residues can, for example, be introduced to avoid junctional epitopes (an epitope recognized by the immune system, not present in the target antigen, and only created by the man-made juxtaposition of epitopes), or to facilitate cleavage between epitopes and thereby enhance epitope presentation. Junctional epitopes are generally to be avoided because the recipient may generate an immune response to that non-native epitope. Of particular concern is a junctional epitope that is a "dominant epitope." A dominant epitope may lead to such a zealous response that immune responses to other epitopes are diminished or suppressed.

[0362] 7.) Where the sequences of multiple variants of the same target protein are present, potential peptide epitopes can also be selected on the basis of their conservancy. For example, a criterion for conservancy may define that the entire sequence of an HLA class I binding peptide or the entire 9-mer core of a class II binding peptide be conserved in a designated percentage of the sequences evaluated for a specific protein antigen.

[0363] X.C.1. Minigene Vaccines

[0364] A number of different approaches are available which allow simultaneous delivery of multiple epitopes. Nucleic acids encoding the peptides of the invention are a particularly useful embodiment of the invention. Epitopes for inclusion in a minigene are preferably selected according to the guidelines set forth in the previous section. A preferred means of administering nucleic acids encoding the peptides of the invention uses minigene constructs encoding a peptide comprising one or multiple epitopes of the invention.

[0365] The use of multi-epitope minigenes is described below and in, Ishioka et al., J. Immunol. 162:3915-3925,

1999; An, L. and Whitton, J. L., J. Virol. 71:2292, 1997; Thomson, S. A. et al., J. Immunol. 157:822, 1996; Whitton, J. L. et al., J. Virol. 67:348, 1993; Hanke, R. et al., Vaccine 16:426, 1998. For example, a multi-epitope DNA plasmid encoding supermotif- and/or motif-bearing epitopes derived 273P4B7, the PADRE® universal helper T cell epitope or multiple HTL epitopes from 273P4B7 (see e.g., Tables VIII-XXI and XXII to XLIX), and an endoplasmic reticulum-translocating signal sequence can be engineered. A vaccine may also comprise epitopes that are derived from other TAAs.

[0366] The immunogenicity of a multi-epitopic minigene can be confirmed in transgenic mice to evaluate the magnitude of CTL induction responses against the epitopes tested. Further, the immunogenicity of DNA-encoded epitopes in vivo can be correlated with the in vitro responses of specific CTL lines against target cells transfected with the DNA plasmid. Thus, these experiments can show that the minigene serves to both: 1.) generate a CTL response and 2.) that the induced CTLs recognized cells expressing the encoded epitopes.

[0367] For example, to create a DNA sequence encoding the selected epitopes (minigene) for expression in human cells, the amino acid sequences of the epitopes may be reverse translated. A human codon usage table can be used to guide the codon choice for each amino acid. These epitope-encoding DNA sequences may be directly adjoined, so that when translated, a continuous polypeptide sequence is created. To optimize expression and/or immunogenicity, additional elements can be incorporated into the minigene design. Examples of amino acid sequences that can be reverse translated and included in the minigene sequence include: HLA class I epitopes, HLA class II epitopes, antibody epitopes, a ubiquitination signal sequence, and/or an endoplasmic reticulum targeting signal. In addition, HLA presentation of CTL and HTL epitopes may be improved by including synthetic (e.g. poly-alanine) or naturally-occurring flanking sequences adjacent to the CTL or HTL epitopes; these larger peptides comprising the epitope(s) are within the scope of the invention.

[0368] The minigene sequence may be converted to DNA by assembling oligonucleotides that encode the plus and minus strands of the minigene. Overlapping oligonucleotides (30-100 bases long) may be synthesized, phosphorylated, purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. This synthetic minigene, encoding the epitope polypeptide, can then be cloned into a desired expression vector.

[0369] Standard regulatory sequences well known to those of skill in the art are preferably included in the vector to ensure expression in the target cells. Several vector elements are desirable: a promoter with a down-stream cloning site for minigene insertion; a polyadenylation signal for efficient transcription termination; an *E. coli* origin of replication; and an *E. coli* selectable marker (e.g. ampicillin or kanamycin resistance). Numerous promoters can be used for this purpose, e.g., the human cytomegalovirus (hCMV) promoter. See, e.g., U.S. Pat. Nos. 5,580,859 and 5,589,466 for other suitable promoter sequences.

[0370] Additional vector modifications may be desired to optimize minigene expression and immunogenicity. In some

cases, introns are required for efficient gene expression, and one or more synthetic or naturally-occurring introns could be incorporated into the transcribed region of the minigene. The inclusion of mRNA stabilization sequences and sequences for replication in mammalian cells may also be considered for increasing minigene expression.

[0371] Once an expression vector is selected, the minigene is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate *E. coli* strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the minigene, as well as all other elements included in the vector, are confirmed using restriction mapping and DNA sequence analysis. Bacterial cells harboring the correct plasmid can be stored as a master cell bank and a working cell bank.

[0372] In addition, immunostimulatory sequences (ISSs or CpGs) appear to play a role in the immunogenicity of DNA vaccines. These sequences may be included in the vector, outside the minigene coding sequence, if desired to enhance immunogenicity.

[0373] In some embodiments, a bi-cistronic expression vector which allows production of both the minigene-encoded epitopes and a second protein (included to enhance or decrease immunogenicity) can be used. Examples of proteins or polypeptides that could beneficially enhance the immune response if co-expressed include cytokines (e.g., IL-2, IL-12, GM-CSF), cytokine-inducing molecules (e.g., LeIF), costimulatory molecules, or for HTL responses, pan-DR binding proteins (PADRE™, Epimmune, San Diego, Calif.). Helper (HTL) epitopes can be joined to intracellular targeting signals and expressed separately from expressed CTL epitopes; this allows direction of the HTL epitopes to a cell compartment different than that of the CTL epitopes. If required, this could facilitate more efficient entry of HTL epitopes into the HLA class II pathway, thereby improving HTL induction. In contrast to HTL or CTL induction, specifically decreasing the immune response by co-expression of immunosuppressive molecules (e.g. TGF-P) may be beneficial in certain diseases.

[0374] Therapeutic quantities of plasmid DNA can be produced for example, by fermentation in *E. coli*, followed by purification. Aliquots from the working cell bank are used to inoculate growth medium, and grown to saturation in shaker flasks or a bioreactor according to well-known techniques. Plasmid DNA can be purified using standard bio-separation technologies such as solid phase anion-exchange resins supplied by QIAGEN, Inc. (Valencia, Calif.). If required, supercoiled DNA can be isolated from the open circular and linear forms using gel electrophoresis or other methods.

[0375] Purified plasmid DNA can be prepared for injection using a variety of formulations. The simplest of these is reconstitution of lyophilized DNA in sterile phosphate-buffer saline (PBS). This approach, known as "naked DNA," is currently being used for intramuscular (IM) administration in clinical trials. To maximize the immunotherapeutic effects of minigene DNA vaccines, an alternative method for formulating purified plasmid DNA may be desirable. A variety of methods have been described, and new techniques may become available. Cationic lipids, glycolipids, and fusogenic liposomes can also be used in the formulation (see, e.g., as described by WO 93/24640; Mannino &

Gould-Fogerite, Bio Techniques 6(7):682 (1988); U.S. Pat. No. 5,279,833; WO 91/06309; and Feigner, et al., Proc. Nat'l Acad. Sci. USA 84:7413 (1987). In addition, peptides and compounds referred to collectively as protective, interactive, non-condensing compounds (PINC) could also be complexed to purified plasmid DNA to influence variables such as stability, intramuscular dispersion, or trafficking to specific organs or cell types.

[0376] Target cell sensitization can be used as a functional assay for expression and HLA class I presentation of minigene-encoded CTL epitopes. For example, the plasmid DNA is introduced into a mammalian cell line that is suitable as a target for standard CTL chromium release assays. The transfection method used will be dependent on the final formulation. Electroporation can be used for "naked" DNA, whereas cationic lipids allow direct in vitro transfection. A plasmid expressing green fluorescent protein (GFP) can be co-transfected to allow enrichment of transfected cells using fluorescence activated cell sorting (FACS). These cells are then chromium-51 (⁵¹Cr) labeled and used as target cells for epitope-specific CTL lines; cytotoxicity, detected by ⁵¹Cr release, indicates both production of, and HLA presentation of, minigene-encoded CTL epitopes. Expression of HTL epitopes may be evaluated in an analogous manner using assays to assess HTL activity.

[0377] In vivo immunogenicity is a second approach for functional testing of minigene DNA formulations. Transgenic mice expressing appropriate human HLA proteins are immunized with the DNA product. The dose and route of administration are formulation dependent (e.g., IM for DNA in PBS, intraperitoneal (i.p.) for lipid-complexed DNA). Twenty-one days after immunization, splenocytes are harvested and restimulated for one week in the presence of peptides encoding each epitope being tested. Thereafter, for CTL effector cells, assays are conducted for cytotoxicity of peptide-loaded, ⁵¹Cr-labeled target cells using standard techniques. Lysis of target cells that were sensitized by HLA loaded with peptide epitopes, corresponding to minigene-encoded epitopes, demonstrates DNA vaccine function for in vivo induction of CTLs. Immunogenicity of HTL epitopes is confirmed in transgenic mice in an analogous manner.

[0378] Alternatively, the nucleic acids can be administered using ballistic delivery as described, for instance, in U.S. Pat. No. 5,204,253. Using this technique, particles comprised solely of DNA are administered. In a further alternative embodiment, DNA can be adhered to particles, such as gold particles.

[0379] Minigenes can also be delivered using other bacterial or viral delivery systems well known in the art, e.g., an expression construct encoding epitopes of the invention can be incorporated into a viral vector such as vaccinia.

[0380] X.C.2. Combinations of CTL Peptides with Helper Peptides

[0381] Vaccine compositions comprising CTL peptides of the invention can be modified, e.g., analogized, to provide desired attributes, such as improved serum half life, broadened population coverage or enhanced immunogenicity.

[0382] For instance, the ability of a peptide to induce CTL activity can be enhanced by linking the peptide to a sequence which contains at least one epitope that is capable of inducing a T helper cell response. Although a CTL peptide

can be directly linked to a T helper peptide, often CTL epitope/HTL epitope conjugates are linked by a spacer molecule. The spacer is typically comprised of relatively small, neutral molecules, such as amino acids or amino acid mimetics, which are substantially uncharged under physiological conditions. The spacers are typically selected from, e.g., Ala, Gly, or other neutral spacers of nonpolar amino acids or neutral polar amino acids. It will be understood that the optionally present spacer need not be comprised of the same residues and thus may be a hetero- or homo-oligomer. When present, the spacer will usually be at least one or two residues, more usually three to six residues and sometimes 10 or more residues. The CTL peptide epitope can be linked to the T helper peptide epitope either directly or via a spacer either at the amino or carboxy terminus of the CTL peptide. The amino terminus of either the immunogenic peptide or the T helper peptide may be acylated.

[0383] In certain embodiments, the T helper peptide is one that is recognized by T helper cells present in a majority of a genetically diverse population. This can be accomplished by selecting peptides that bind to many, most, or all of the HLA class II molecules. Examples of such amino acid bind many HLA Class II molecules include sequences from antigens such as tetanus toxoid at positions 830-843 (QYI-KANSKFIGITE; SEQ ID NO: 26), *Plasmodium falciparum* circumsporozoite (CS) protein at positions 378-398 (DIEK-KIAKMEKASSVFNVNS; SEQ ID NO: 27), and *Streptococcus* 18 kD protein at positions 116-131 (GAVDSILG-GVATYGAA; SEQ ID NO: 28). Other examples include peptides bearing a DR 1-4-7 supermotif, or either of the DR3 motifs.

[0384] Alternatively, it is possible to prepare synthetic peptides capable of stimulating T helper lymphocytes, in a loosely HLA-restricted fashion, using amino acid sequences not found in nature (see, e.g., PCT publication WO 95/07707). These synthetic compounds called Pan-DR-binding epitopes (e.g., PADRE™, Epimmune, Inc., San Diego, Calif.) are designed, most preferably, to bind most HLA-DR (human HLA class II) molecules. For instance, a pan-DR-binding epitope peptide having the formula: aKXVAAW-TLKAa (SEQ ID NO: 29), where "X" is either cyclohexylalanine, phenylalanine, or tyrosine, and a is either D-alanine or L-alanine, has been found to bind to most HLA-DR alleles, and to stimulate the response of T helper lymphocytes from most individuals, regardless of their HLA type. An alternative of a pan-DR binding epitope comprises all "L" natural amino acids and can be provided in the form of nucleic acids that encode the epitope.

[0385] HTL peptide epitopes can also be modified to alter their biological properties. For example, they can be modified to include D-amino acids to increase their resistance to proteases and thus extend their serum half life, or they can be conjugated to other molecules such as lipids, proteins, carbohydrates, and the like to increase their biological activity. For example, a T helper peptide can be conjugated to one or more palmitic acid chains at either the amino or carboxyl termini.

[0386] X.C.3. Combinations of CTL Peptides with T Cell Priming Agents

[0387] In some embodiments it may be desirable to include in the pharmaceutical compositions of the invention at least one component which primes B lymphocytes or T

lymphocytes. Lipids have been identified as agents capable of priming CTL in vivo. For example, palmitic acid residues can be attached to the E- and α-amino groups of a lysine residue and then linked, e.g., via one or more linking residues such as Gly, Gly-Gly-, Ser, Ser-Ser, or the like, to an immunogenic peptide. The lipidated peptide can then be administered either directly in a micelle or particle, incorporated into a liposome, or emulsified in an adjuvant, e.g., incomplete Freund's adjuvant. In a preferred embodiment, a particularly effective immunogenic composition comprises palmitic acid attached to E- and α-amino groups of Lys, which is attached via linkage, e.g., Ser-Ser, to the amino terminus of the immunogenic peptide.

[0388] As another example of lipid priming of CTL responses, *E. coli* lipoproteins, such as tripalmitoyl-S-glycerylcysteinylserine (P.sub.3CSS) can be used to prime virus specific CTL when covalently attached to an appropriate peptide (see, e.g., Deres, et al., Nature 342:561, 1989). Peptides of the invention can be coupled to P.sub.3CSS, for example, and the lipopeptide administered to an individual to prime specifically an immune response to the target antigen. Moreover, because the induction of neutralizing antibodies can also be primed with P3CSS-conjugated epitopes, two such compositions can be combined to more effectively elicit both humoral and cell-mediated responses.

[0389] X.C.4. Vaccine Compositions Comprising DC Pulsed with CTL and/or HTL Peptides

[0390] An embodiment of a vaccine composition in accordance with the invention comprises ex vivo administration of a cocktail of epitope-bearing peptides to PBMC, or isolated DC therefrom, from the patient's blood. A pharmaceutical to facilitate harvesting of DC can be used, such as Progenipoiectin™ (Pharmacia-Monsanto, St. Louis, Mo.) or GM-CSF/IL-4. After pulsing the DC with peptides and prior to reinfusion into patients, the DC are washed to remove unbound peptides. In this embodiment, a vaccine comprises peptide-pulsed DCs which present the pulsed peptide epitopes complexed with HLA molecules on their surfaces.

[0391] The DC can be pulsed ex vivo with a cocktail of peptides, some of which stimulate CTL responses to 273P4B7. Optionally, a helper T cell (HTL) peptide, such as a natural or artificial loosely restricted HLA Class II peptide, can be included to facilitate the CTL response. Thus, a vaccine in accordance with the invention is used to treat a cancer which expresses or overexpresses 273P4B7.

[0392] X.D. Adoptive Immunotherapy

[0393] Antigenic 273P4B7-related peptides are used to elicit a CTL and/or HTL response ex vivo, as well. The resulting CTL or HTL cells, can be used to treat tumors in patients that do not respond to other conventional forms of therapy, or will not respond to a therapeutic vaccine peptide or nucleic acid in accordance with the invention. Ex vivo CTL or HTL responses to a particular antigen are induced by incubating in tissue culture the patient's, or genetically compatible, CTL or HTL precursor cells together with a source of antigen-presenting cells (APC), such as dendritic cells, and the appropriate immunogenic peptide. After an appropriate incubation time (typically about 7-28 days), in which the precursor cells are activated and expanded into effector cells, the cells are infused back into the patient, where they will destroy (CTL) or facilitate destruction

(HTL) of their specific target cell (e.g., a tumor cell). Transfected dendritic cells may also be used as antigen presenting cells.

[0394] X.E. Administration of Vaccines for Therapeutic or Prophylactic Purposes

[0395] Pharmaceutical and vaccine compositions of the invention are typically used to treat and/or prevent a cancer that expresses or overexpresses 273P4B7. In therapeutic applications, peptide and/or nucleic acid compositions are administered to a patient in an amount sufficient to elicit an effective B cell, CTL and/or HTL response to the antigen and to cure or at least partially arrest or slow symptoms and/or complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on, e.g., the particular composition administered, the manner of administration, the stage and severity of the disease being treated, the weight and general state of health of the patient, and the judgment of the prescribing physician.

[0396] For pharmaceutical compositions, the immunogenic peptides of the invention, or DNA encoding them, are generally administered to an individual already bearing a tumor that expresses 273P4B7. The peptides or DNA encoding them can be administered individually or as fusions of one or more peptide sequences. Patients can be treated with the immunogenic peptides separately or in conjunction with other treatments, such as surgery, as appropriate.

[0397] For therapeutic use, administration should generally begin at the first diagnosis of 273P4B7-associated cancer. This is followed by boosting doses until at least symptoms are substantially abated and for a period thereafter. The embodiment of the vaccine composition (i.e., including, but not limited to embodiments such as peptide cocktails, polypeptidic polypeptides, minigenes, or TAA-specific CTLs or pulsed dendritic cells) delivered to the patient may vary according to the stage of the disease or the patient's health status. For example, in a patient with a tumor that expresses 273P4B7, a vaccine comprising 273P4B7-specific CTL may be more efficacious in killing tumor cells in patient with advanced disease than alternative embodiments.

[0398] It is generally important to provide an amount of the peptide epitope delivered by a mode of administration sufficient to stimulate effectively a cytotoxic T cell response; compositions which stimulate helper T cell responses can also be given in accordance with this embodiment of the invention.

[0399] The dosage for an initial therapeutic immunization generally occurs in a unit dosage range where the lower value is about 1, 5, 50, 500, or 1,000 μg and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg . Dosage values for a human typically range from about 500 μg to about 50,000 μg per 70 kilogram patient. Boosting dosages of between about 1.0 μg to about 50,000 μg of peptide pursuant to a boosting regimen over weeks to months may be administered depending upon the patient's response and condition as determined by measuring the specific activity of CTL and HTL obtained from the patient's blood. Administration should continue until at least clinical symptoms or laboratory tests indicate that the neoplasia, has been eliminated or reduced and for a period thereafter. The dosages,

routes of administration, and dose schedules are adjusted in accordance with methodologies known in the art.

[0400] In certain embodiments, the peptides and compositions of the present invention are employed in serious disease states, that is, life-threatening or potentially life threatening situations. In such cases, as a result of the minimal amounts of extraneous substances and the relative nontoxic nature of the peptides in preferred compositions of the invention, it is possible and may be felt desirable by the treating physician to administer substantial excesses of these peptide compositions relative to these stated dosage amounts.

[0401] The vaccine compositions of the invention can also be used purely as prophylactic agents. Generally the dosage for an initial prophylactic immunization generally occurs in a unit dosage range where the lower value is about 1, 5, 50, 500, or 1000 μg and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg . Dosage values for a human typically range from about 500 μg to about 50,000 μg per 70 kilogram patient. This is followed by boosting dosages of between about 1.0 μg to about 50,000 μg of peptide administered at defined intervals from about four weeks to six months after the initial administration of vaccine. The immunogenicity of the vaccine can be assessed by measuring the specific activity of CTL and HTL obtained from a sample of the patient's blood.

[0402] The pharmaceutical compositions for therapeutic treatment are intended for parenteral, topical, oral, nasal, intrathecal, or local (e.g. as a cream or topical ointment) administration. Preferably, the pharmaceutical compositions are administered parentally, e.g., intravenously, subcutaneously, intradermally, or intramuscularly. Thus, the invention provides compositions for parenteral administration which comprise a solution of the immunogenic peptides dissolved or suspended in an acceptable carrier, preferably an aqueous carrier.

[0403] A variety of aqueous carriers may be used, e.g., water, buffered water, 0.8% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well-known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration.

[0404] The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH-adjusting and buffering agents, tonicity adjusting agents, wetting agents, preservatives, and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

[0405] The concentration of peptides of the invention in the pharmaceutical formulations can vary widely, i.e., from less than about 0.1%, usually at or at least about 2% to as much as 20% to 50% or more by weight, and will be selected primarily by fluid volumes, viscosities, etc., in accordance with the particular mode of administration selected.

[0406] A human unit dose form of a composition is typically included in a pharmaceutical composition that comprises a human unit dose of an acceptable carrier, in one embodiment an aqueous carrier, and is administered in a

volume/quantity that is known by those of skill in the art to be used for administration of such compositions to humans (see, e.g., Remington's Pharmaceutical Sciences, 17th Edition, A. Gennaro, Editor, Mack Publishing Co., Easton, Pa., 1985). For example a peptide dose for initial immunization can be from about 1 to about 50,000 μg , generally 100-5,000 μg , for a 70 kg patient. For example, for nucleic acids an initial immunization may be performed using an expression vector in the form of naked nucleic acid administered IM (or SC or ID) in the amounts of 0.5-5 mg at multiple sites. The nucleic acid (0.1 to 1000 μg) can also be administered using a gene gun. Following an incubation period of 3-4 weeks, a booster dose is then administered. The booster can be recombinant fowlpox virus administered at a dose of $5\text{-}10^7$ to 5×10^9 pfu.

[0407] For antibodies, a treatment generally involves repeated administration of the anti-273P4B7 antibody preparation, via an acceptable route of administration such as intravenous injection (IV), typically at a dose in the range of about 0.1 to about 10 mg/kg body weight. In general, doses in the range of 10-500 mg mAb per week are effective and well tolerated. Moreover, an initial loading dose of approximately 4 mg/kg patient body weight IV, followed by weekly doses of about 2 mg/kg IV of the anti-273P4B7 mAb preparation represents an acceptable dosing regimen. As appreciated by those of skill in the art, various factors can influence the ideal dose in a particular case. Such factors include, for example, half life of a composition, the binding affinity of an Ab, the immunogenicity of a substance, the degree of 273P4B7 expression in the patient, the extent of circulating shed 273P4B7 antigen, the desired steady-state concentration level, frequency of treatment, and the influence of chemotherapeutic or other agents used in combination with the treatment method of the invention, as well as the health status of a particular patient. Non-limiting preferred human unit doses are, for example, 500 μg -1 mg, 1 mg-50 mg, 50 mg-100 mg, 100 mg-200 mg, 200 mg-300 mg, 300 mg-400 mg, 400 mg-500 mg, 500 mg-600 mg, 600 mg-700 mg, 700 mg-800 mg, 800 mg-900 mg, 900 mg-1 g, or 1 mg-700 mg. In certain embodiments, the dose is in a range of 2-5 mg/kg body weight, e.g., with follow on weekly doses of 1-3 mg/kg; 0.5 mg, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mg/kg body weight followed, e.g., in two, three or four weeks by weekly doses; 0.5-10 mg/kg body weight, e.g., followed in two, three or four weeks by weekly doses; 225, 250, 275, 300, 325, 350, 375, 400 mg m^2 of body area weekly; 1-600 mg m^2 of body area weekly; 225-400 mg m^2 of body area weekly; these doses can be followed by weekly doses for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more weeks.

[0408] In one embodiment, human unit dose forms of polynucleotides comprise a suitable dosage range or effective amount that provides any therapeutic effect. As appreciated by one of ordinary skill in the art a therapeutic effect depends on a number of factors, including the sequence of the polynucleotide, molecular weight of the polynucleotide and route of administration. Dosages are generally selected by the physician or other health care professional in accordance with a variety of parameters known in the art, such as severity of symptoms, history of the patient and the like. Generally, for a polynucleotide of about 20 bases, a dosage range may be selected from, for example, an independently selected lower limit such as about 0.1, 0.25, 0.5, 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 mg/kg up to an independently selected upper limit, greater

than the lower limit, of about 60, 80, 100, 200, 300, 400, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000 or 10,000 mg/kg. For example, a dose may be about any of the following: 0.1 to 100 mg/kg, 0.1 to 50 mg/kg, 0.1 to 25 mg/kg, 0.1 to 10 mg/kg, 1 to 500 mg/kg, 100 to 400 mg/kg, 200 to 300 mg/kg, 1 to 100 mg/kg, 100 to 200 mg/kg, 300 to 400 mg/kg, 400 to 500 mg/kg, 500 to 1000 mg/kg, 500 to 5000 mg/kg, or 500 to 10,000 mg/kg. Generally, parenteral routes of administration may require higher doses of polynucleotide compared to more direct application to the nucleotide to diseased tissue, as do polynucleotides of increasing length.

[0409] In one embodiment, human unit dose forms of T-cells comprise a suitable dosage range or effective amount that provides any therapeutic effect. As appreciated by one of ordinary skill in the art, a therapeutic effect depends on a number of factors. Dosages are generally selected by the physician or other health care professional in accordance with a variety of parameters known in the art, such as severity of symptoms, history of the patient and the like. A dose may be about $10\text{.sup.}4$ cells to about $10\text{.sup.}6$ cells, about $10\text{.sup.}6$ cells to about $10\text{.sup.}8$ cells, about $10\text{.sup.}8$ to about $10\text{.sup.}11$ cells, or about $10\text{.sup.}8$ to about $5\times 10\text{.sup.}10$ cells. A dose may also be about $10\text{.sup.}6$ cells/m $\text{sup.}2$ to about $10\text{.sup.}10$ cells/m $\text{sup.}2$, or about $10\text{.sup.}6$ cells/m $\text{sup.}2$ to about $10\text{.sup.}8$ cells/m $\text{sup.}2$.

[0410] Proteins(s) of the invention, and/or nucleic acids encoding the protein(s), can also be administered via liposomes, which may also serve to: 1) target the proteins(s) to a particular tissue, such as lymphoid tissue; 2) to target selectively to diseased cells; or, 3) to increase the half-life of the peptide composition. Liposomes include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. In these preparations, the peptide to be delivered is incorporated as part of a liposome, alone or in conjunction with a molecule which binds to a receptor prevalent among lymphoid cells, such as monoclonal antibodies which bind to the CD45 antigen, or with other therapeutic or immunogenic compositions. Thus, liposomes either filled or decorated with a desired peptide of the invention can be directed to the site of lymphoid cells, where the liposomes then deliver the peptide compositions. Liposomes for use in accordance with the invention are formed from standard vesicle-forming lipids, which generally include neutral and negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of, e.g., liposome size, acid lability and stability of the liposomes in the blood stream. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., Ann. Rev. Biophys. Bioeng. 9:467 (1980), and U.S. Pat. Nos. 4,235,871, 4,501,728, 4,837,028, and 5,019,369.

[0411] For targeting cells of the immune system, a ligand to be incorporated into the liposome can include, e.g., antibodies or fragments thereof specific for cell surface determinants of the desired immune system cells. A liposome suspension containing a peptide may be administered intravenously, locally, topically, etc. in a dose which varies according to, inter alia, the manner of administration, the peptide being delivered, and the stage of the disease being treated.

[0412] For solid compositions, conventional nontoxic solid carriers may be used which include, for example,

pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10-95% of active ingredient, that is, one or more peptides of the invention, and more preferably at a concentration of 25%-75%.

[0413] For aerosol administration, immunogenic peptides are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of peptides are about 0.01%-20% by weight, preferably about 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from about 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute about 0.1%-20% by weight of the composition, preferably about 0.25-5%. The balance of the composition is ordinarily propellant. A carrier can also be included, as desired, as with, e.g., lecithin for intranasal delivery.

[0414] XI.) Diagnostic and Prognostic Embodiments of 273P4B7.

[0415] As disclosed herein, 273P4B7 polynucleotides, polypeptides, reactive cytotoxic T cells (CTL), reactive helper T cells (HTL) and anti-polypeptide antibodies are used in well known diagnostic, prognostic and therapeutic assays that examine conditions associated with dysregulated cell growth such as cancer, in particular the cancers listed in Table I (see, e.g., both its specific pattern of tissue expression as well as its overexpression in certain cancers as described for example in the Example entitled "Expression analysis of 273P4B7 in normal tissues, and patient specimens").

[0416] 273P4B7 can be analogized to a prostate associated antigen PSA, the archetypal marker that has been used by medical practitioners for years to identify and monitor the presence of prostate cancer (see, e.g., Merrill et al., *J. Urol.* 163(2): 503-5120 (2000); Polascik et al., *J. Urol.* August; 162(2):293-306 (1999) and Fortier et al., *J. Nat. Cancer Inst.* 91(19): 1635-1640(1999)). A variety of other diagnostic markers are also used in similar contexts including p53 and K-ras (see, e.g., Tulchinsky et al., *Int J Mol Med* 1999 July 4(1):99-102 and Minimoto et al., *Cancer Detect Prev* 2000; 24(1):1-12). Therefore, this disclosure of 273P4B7 polynucleotides and polypeptides (as well as 273P4B7 polynucleotide probes and anti-273P4B7 antibodies used to identify the presence of these molecules) and their properties allows skilled artisans to utilize these molecules in methods that are analogous to those used, for example, in a variety of diagnostic assays directed to examining conditions associated with cancer.

[0417] Typical embodiments of diagnostic methods which utilize the 273P4B7 polynucleotides, polypeptides, reactive T cells and antibodies are analogous to those methods from well-established diagnostic assays, which employ, e.g., PSA polynucleotides, polypeptides, reactive T cells and antibodies. For example, just as PSA polynucleotides are used as

probes (for example in Northern analysis, see, e.g., Sharief et al., *Biochem. Mol. Biol. Int.* 33(3):567-74(1994)) and primers (for example in PCR analysis, see, e.g., Okegawa et al., *J. Urol.* 163(4): 1189-1190 (2000)) to observe the presence and/or the level of PSA mRNAs in methods of monitoring PSA overexpression or the metastasis of prostate cancers, the 273P4B7 polynucleotides described herein can be utilized in the same way to detect 273P4B7 overexpression or the metastasis of prostate and other cancers expressing this gene. Alternatively, just as PSA polypeptides are used to generate antibodies specific for PSA which can then be used to observe the presence and/or the level of PSA proteins in methods to monitor PSA protein overexpression (see, e.g., Stephan et al., *Urology* 55(4):560-3 (2000)) or the metastasis of prostate cells (see, e.g., Alanen et al., *Pathol. Res. Pract.* 192(3):233-7 (1996)), the 273P4B7 polypeptides described herein can be utilized to generate antibodies for use in detecting 273P4B7 overexpression or the metastasis of prostate cells and cells of other cancers expressing this gene.

[0418] Specifically, because metastases involves the movement of cancer cells from an organ of origin (such as the lung or prostate gland etc.) to a different area of the body (such as a lymph node), assays which examine a biological sample for the presence of cells expressing 273P4B7 polynucleotides and/or polypeptides can be used to provide evidence of metastasis. For example, when a biological sample from tissue that does not normally contain 273P4B7-expressing cells (lymph node) is found to contain 273P4B7-expressing cells such as the 273P4B7 expression seen in LAPC4 and LAPC9, xenografts isolated from lymph node and bone metastasis, respectively, this finding is indicative of metastasis.

[0419] Alternatively 273P4B7 polynucleotides and/or polypeptides can be used to provide evidence of cancer, for example, when cells in a biological sample that do not normally express 273P4B7 or express 273P4B7 at a different level are found to express 273P4B7 or have an increased expression of 273P4B7 (see, e.g., the 273P4B7 expression in the cancers listed in Table I and in patient samples etc. shown in the accompanying Figures). In such assays, artisans may further wish to generate supplementary evidence of metastasis by testing the biological sample for the presence of a second tissue restricted marker (in addition to 273P4B7) such as PSA, PSCA etc. (see, e.g., Alanen et al., *Pathol. Res. Pract.* 192(3): 233-237 (1996)).

[0420] The use of immunohistochemistry to identify the presence of a 273P4B7 polypeptide within a tissue section can indicate an altered state of certain cells within that tissue. It is well understood in the art that the ability of an antibody to localize to a polypeptide that is expressed in cancer cells is a way of diagnosing presence of disease, disease stage, progression and/or tumor aggressiveness. Such an antibody can also detect an altered distribution of the polypeptide within the cancer cells, as compared to corresponding non-malignant tissue.

[0421] The 273P4B7 polypeptide and immunogenic compositions are also useful in view of the phenomena of altered subcellular protein localization in disease states. Alteration of cells from normal to diseased state causes changes in cellular morphology and is often associated with changes in subcellular protein localization/distribution. For example,

cell membrane proteins that are expressed in a polarized manner in normal cells can be altered in disease, resulting in distribution of the protein in a non-polar manner over the whole cell surface.

[0422] The phenomenon of altered subcellular protein localization in a disease state has been demonstrated with MUC1 and Her2 protein expression by use of immunohistochemical means. Normal epithelial cells have a typical apical distribution of MUC1, in addition to some supranuclear localization of the glycoprotein, whereas malignant lesions often demonstrate an apolar staining pattern (Diaz et al., *The Breast Journal*, 7: 40-45 (2001); Zhang et al., *Clinical Cancer Research*, 4: 2669-2676 (1998); Cao, et al., *The Journal of Histochemistry and Cytochemistry*, 45: 1547-1557 (1997)). In addition, normal breast epithelium is either negative for Her2 protein or exhibits only a basolateral distribution whereas malignant cells can express the protein over the whole cell surface (De Potter, et al., *International Journal of Cancer*, 44: 969-974 (1989); McCormick, et al., 117: 935-943 (2002)). Alternatively, distribution of the protein may be altered from a surface only localization to include diffuse cytoplasmic expression in the diseased state. Such an example can be seen with MUC1 (Diaz, et al., *The Breast Journal*, 7: 40-45 (2001)).

[0423] Alteration in the localization/distribution of a protein in the cell, as detected by immunohistochemical methods, can also provide valuable information concerning the favorability of certain treatment modalities. This last point is illustrated by a situation where a protein may be intracellular in normal tissue, but cell surface in malignant cells; the cell surface location makes the cells favorably amenable to antibody-based diagnostic and treatment regimens. When such an alteration of protein localization occurs for 273P4B7, the 273P4B7 protein and immune responses related thereto are very useful. Accordingly, the ability to determine whether alteration of subcellular protein localization occurred for 24P4C12 make the 273P4B7 protein and immune responses related thereto very useful. Use of the 273P4B7 compositions allows those skilled in the art to make important diagnostic and therapeutic decisions. Immunohistochemical reagents specific to 273P4B7 are also useful to detect metastases of tumors expressing 273P4B7 when the polypeptide appears in tissues where 273P4B7 is not normally produced.

[0424] Thus, 273P4B7 polypeptides and antibodies resulting from immune responses thereto are useful in a variety of important contexts such as diagnostic, prognostic, preventative and/or therapeutic purposes known to those skilled in the art.

[0425] Just as PSA polynucleotide fragments and polynucleotide variants are employed by skilled artisans for use in methods of monitoring PSA, 273P4B7 polynucleotide fragments and polynucleotide variants are used in an analogous manner. In particular, typical PSA polynucleotides used in methods of monitoring PSA are probes or primers which consist of fragments of the PSA cDNA sequence. Illustrating this, primers used to PCR amplify a PSA polynucleotide must include less than the whole PSA sequence to function in the polymerase chain reaction. In the context of such PCR reactions, skilled artisans generally create a variety of different polynucleotide fragments that can be used as primers in order to amplify different portions of a

polynucleotide of interest or to optimize amplification reactions (see, e.g., Caetano-Anolles, G. *Biotechniques* 25(3): 472-476, 478-480 (1998); Robertson et al., *Methods Mol. Biol.* 98:121-154 (1998)). An additional illustration of the use of such fragments is provided in the Example entitled "Expression analysis of 273P4B7 in normal tissues, and patient specimens, where a 273P4B7 polynucleotide fragment is used as a probe to show the expression of 273P4B7 RNAs in cancer cells. In addition, variant polynucleotide sequences are typically used as primers and probes for the corresponding mRNAs in PCR and Northern analyses (see, e.g., Sawai et al., *Fetal Diagn. Ther.* 1996 November-December 11(6):407-13 and *Current Protocols In Molecular Biology*, Volume 2, Unit 2, Frederick M. Ausubel et al eds., 1995)). Polynucleotide fragments and variants are useful in this context where they are capable of binding to a target polynucleotide sequence (e.g., a 273P4B7 polynucleotide shown in FIG. 2 or variant thereof) under conditions of high stringency.

[0426] Furthermore, PSA polypeptides which contain an epitope that can be recognized by an antibody or T cell that specifically binds to that epitope are used in methods of monitoring PSA. 273P4B7 polypeptide fragments and polypeptide analogs or variants can also be used in an analogous manner. This practice of using polypeptide fragments or polypeptide variants to generate antibodies (such as anti-PSA antibodies or T cells) is typical in the art with a wide variety of systems such as fusion proteins being used by practitioners (see, e.g., *Current Protocols In Molecular Biology*, Volume 2, Unit 16, Frederick M. Ausubel et al. eds., 1995). In this context, each epitope(s) functions to provide the architecture with which an antibody or T cell is reactive. Typically, skilled artisans create a variety of different polypeptide fragments that can be used in order to generate immune responses specific for different portions of a polypeptide of interest (see, e.g., U.S. Pat. No. 5,840,501 and U.S. Pat. No. 5,939,533). For example it may be preferable to utilize a polypeptide comprising one of the 273P4B7 biological motifs discussed herein or a motif-bearing subsequence which is readily identified by one of skill in the art based on motifs available in the art. Polypeptide fragments, variants or analogs are typically useful in this context as long as they comprise an epitope capable of generating an antibody or T cell specific for a target polypeptide sequence (e.g. a 273P4B7 polypeptide shown in FIG. 3).

[0427] As shown herein, the 273P4B7 polynucleotides and polypeptides (as well as the 273P4B7 polynucleotide probes and anti-273P4B7 antibodies or T cells used to identify the presence of these molecules) exhibit specific properties that make them useful in diagnosing cancers such as those listed in Table I. Diagnostic assays that measure the presence of 273P4B7 gene products, in order to evaluate the presence or onset of a disease condition described herein, such as prostate cancer, are used to identify patients for preventive measures or further monitoring, as has been done so successfully with PSA. Moreover, these materials satisfy a need in the art for molecules having similar or complementary characteristics to PSA in situations where, for example, a definite diagnosis of metastasis of prostatic origin cannot be made on the basis of a test for PSA alone (see, e.g., Alanen et al., *Pathol. Res. Pract.* 192(3): 233-237 (1996)), and consequently, materials such as 273P4B7 polynucleotides and polypeptides (as well as the 273P4B7 polynucleotide probes and anti-273P4B7 antibodies used to

identify the presence of these molecules) need to be employed to confirm a metastases of prostatic origin.

[0428] Finally, in addition to their use in diagnostic assays, the 273P4B7 polynucleotides disclosed herein have a number of other utilities such as their use in the identification of oncogenetic associated chromosomal abnormalities in the chromosomal region to which the 273P4B7 gene maps (see the Example entitled "Chromosomal Mapping of 273P4B7" below). Moreover, in addition to their use in diagnostic assays, the 273P4B7-related proteins and polynucleotides disclosed herein have other utilities such as their use in the forensic analysis of tissues of unknown origin (see, e.g., Takahama K *Forensic Sci Int* 1996 Jun. 28; 80(1-2): 63-9).

[0429] Additionally, 273P4B7-related proteins or polynucleotides of the invention can be used to treat a pathologic condition characterized by the over-expression of 273P4B7. For example, the amino acid or nucleic acid sequence of FIG. 2 or FIG. 3, or fragments of either, can be used to generate an immune response to a 273P4B7 antigen. Antibodies or other molecules that react with 273P4B7 can be used to modulate the function of this molecule, and thereby provide a therapeutic benefit.

[0430] XII.) Inhibition of 273P4B7 Protein Function

[0431] The invention includes various methods and compositions for inhibiting the binding of 273P4B7 to its binding partner or its association with other protein(s) as well as methods for inhibiting 273P4B7 function.

[0432] XII.A.) Inhibition of 273P4B7 with Intracellular Antibodies

[0433] In one approach, a recombinant vector that encodes single chain antibodies that specifically bind to 273P4B7 are introduced into 273P4B7 expressing cells via gene transfer technologies. Accordingly, the encoded single chain anti-273P4B7 antibody is expressed intracellularly, binds to 273P4B7 protein, and thereby inhibits its function. Methods for engineering such intracellular single chain antibodies are well known. Such intracellular antibodies, also known as "intrabodies", are specifically targeted to a particular compartment within the cell, providing control over where the inhibitory activity of the treatment is focused. This technology has been successfully applied in the art (for review, see Richardson and Marasco, 1995, *TIBTECH* vol. 13). Intrabodies have been shown to virtually eliminate the expression of otherwise abundant cell surface receptors (see, e.g., Richardson et al., 1995, *Proc. Natl. Acad. Sci. USA* 92: 3137-3141; Beerli et al., 1994, *J. Biol. Chem.* 269: 23931-23936; Deshane et al., 1994, *Gene Ther.* 1: 332-337).

[0434] Single chain antibodies comprise the variable domains of the heavy and light chain joined by a flexible linker polypeptide, and are expressed as a single polypeptide. Optionally, single chain antibodies are expressed as a single chain variable region fragment joined to the light chain constant region. Well-known intracellular trafficking signals are engineered into recombinant polynucleotide vectors encoding such single chain antibodies in order to target precisely the intrabody to the desired intracellular compartment. For example, intrabodies targeted to the endoplasmic reticulum (ER) are engineered to incorporate a leader peptide and, optionally, a C-terminal ER retention signal, such as the KDEL amino acid motif. Intrabodies intended to exert activity in the nucleus are engineered to include a nuclear

localization signal. Lipid moieties are joined to intrabodies in order to tether the intrabody to the cytosolic side of the plasma membrane. Intrabodies can also be targeted to exert function in the cytosol. For example, cytosolic intrabodies are used to sequester factors within the cytosol, thereby preventing them from being transported to their natural cellular destination.

[0435] In one embodiment, intrabodies are used to capture 273P4B7 in the nucleus, thereby preventing its activity within the nucleus. Nuclear targeting signals are engineered into such 273P4B7 intrabodies in order to achieve the desired targeting. Such 273P4B7 intrabodies are designed to bind specifically to a particular 273P4B7 domain. In another embodiment, cytosolic intrabodies that specifically bind to a 273P4B7 protein are used to prevent 273P4B7 from gaining access to the nucleus, thereby preventing it from exerting any biological activity within the nucleus (e.g., preventing 273P4B7 from forming transcription complexes with other factors).

[0436] In order to specifically direct the expression of such intrabodies to particular cells, the transcription of the intrabody is placed under the regulatory control of an appropriate tumor-specific promoter and/or enhancer. In order to target intrabody expression specifically to prostate, for example, the PSA promoter and/or promoter/enhancer can be utilized (See, for example, U.S. Pat. No. 5,919,652 issued 6 Jul. 1999).

[0437] XII.B.) Inhibition of 273P4B7 with Recombinant Proteins

[0438] In another approach, recombinant molecules bind to 273P4B7 and thereby inhibit 273P4B7 function. For example, these recombinant molecules prevent or inhibit 273P4B7 from accessing/binding to its binding partner(s) or associating with other protein(s). Such recombinant molecules can, for example, contain the reactive part(s) of a 273P4B7 specific antibody molecule. In a particular embodiment, the 273P4B7 binding domain of a 273P4B7 binding partner is engineered into a dimeric fusion protein, whereby the fusion protein comprises two 273P4B7 ligand binding domains linked to the Fc portion of a human IgG, such as human IgG1. Such IgG portion can contain, for example, the C_{H2} and C_{H3} domains and the hinge region, but not the C_{H1} domain. Such dimeric fusion proteins are administered in soluble form to patients suffering from a cancer associated with the expression of 273P4B7, whereby the dimeric fusion protein specifically binds to 273P4B7 and blocks 273P4B7 interaction with a binding partner. Such dimeric fusion proteins are further combined into multimeric proteins using known antibody linking technologies.

[0439] XII.C.) Inhibition of 273P4B7 Transcription or Translation

[0440] The present invention also comprises various methods and compositions for inhibiting the transcription of the 273P4B7 gene. Similarly, the invention also provides methods and compositions for inhibiting the translation of 273P4B7 mRNA into protein.

[0441] In one approach, a method of inhibiting the transcription of the 273P4B7 gene comprises contacting the 273P4B7 gene with a 273P4B7 antisense polynucleotide. In another approach, a method of inhibiting 273P4B7 mRNA translation comprises contacting a 273P4B7 mRNA with an

antisense polynucleotide. In another approach, a 273P4B7 specific ribozyme is used to cleave a 273P4B7 message, thereby inhibiting translation. Such antisense and ribozyme based methods can also be directed to the regulatory regions of the 273P4B7 gene, such as 273P4B7 promoter and/or enhancer elements. Similarly, proteins capable of inhibiting a 273P4B7 gene transcription factor are used to inhibit 273P4B7 mRNA transcription. The various polynucleotides and compositions useful in the aforementioned methods have been described above. The use of antisense and ribozyme molecules to inhibit transcription and translation is well known in the art.

[0442] Other factors that inhibit the transcription of 273P4B7 by interfering with 273P4B7 transcriptional activation are also useful to treat cancers expressing 273P4B7. Similarly, factors that interfere with 273P4B7 processing are useful to treat cancers that express 273P4B7. Cancer treatment methods utilizing such factors are also within the scope of the invention.

[0443] XII.D.) General Considerations for Therapeutic Strategies

[0444] Gene transfer and gene therapy technologies can be used to deliver therapeutic polynucleotide molecules to tumor cells synthesizing 273P4B7 (i.e., antisense, ribozyme, polynucleotides encoding intrabodies and other 273P4B7 inhibitory molecules). A number of gene therapy approaches are known in the art. Recombinant vectors encoding 273P4B7 antisense polynucleotides, ribozymes, factors capable of interfering with 273P4B7 transcription, and so forth, can be delivered to target tumor cells using such gene therapy approaches.

[0445] The above therapeutic approaches can be combined with any one of a wide variety of surgical, chemotherapy or radiation therapy regimens. The therapeutic approaches of the invention can enable the use of reduced dosages of chemotherapy (or other therapies) and/or less frequent administration, an advantage for all patients and particularly for those that do not tolerate the toxicity of the chemotherapeutic agent well.

[0446] The anti-tumor activity of a particular composition (e.g., antisense, ribozyme, intrabody), or a combination of such compositions, can be evaluated using various in vitro and in vivo assay systems. In vitro assays that evaluate therapeutic activity include cell growth assays, soft agar assays and other assays indicative of tumor promoting activity, binding assays capable of determining the extent to which a therapeutic composition will inhibit the binding of 273P4B7 to a binding partner, etc.

[0447] In vivo, the effect of a 273P4B7 therapeutic composition can be evaluated in a suitable animal model. For example, xenogenic prostate cancer models can be used, wherein human prostate cancer explants or passaged xenograft tissues are introduced into immune compromised animals, such as nude or SCID mice (Klein et al., 1997, *Nature Medicine* 3: 402-408). For example, PCT Patent Application WO98/16628 and U.S. Pat. No. 6,107,540 describe various xenograft models of human prostate cancer capable of recapitulating the development of primary tumors, micrometastasis, and the formation of osteoblastic metastases characteristic of late stage disease. Efficacy can be predicted using assays that measure inhibition of tumor formation, tumor regression or metastasis, and the like.

[0448] In vivo assays that evaluate the promotion of apoptosis are useful in evaluating therapeutic compositions. In one embodiment, xenografts from tumor bearing mice treated with the therapeutic composition can be examined for the presence of apoptotic foci and compared to untreated control xenograft-bearing mice. The extent to which apoptotic foci are found in the tumors of the treated mice provides an indication of the therapeutic efficacy of the composition.

[0449] The therapeutic compositions used in the practice of the foregoing methods can be formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Suitable carriers include any material that when combined with the therapeutic composition retains the anti-tumor function of the therapeutic composition and is generally non-reactive with the patient's immune system. Examples include, but are not limited to, any of a number of standard pharmaceutical carriers such as sterile phosphate buffered saline solutions, bacteriostatic water, and the like (see, generally, *Remington's Pharmaceutical Sciences* 16^{sup}.th Edition, A. Osal., Ed., 1980).

[0450] Therapeutic formulations can be solubilized and administered via any route capable of delivering the therapeutic composition to the tumor site. Potentially effective routes of administration include, but are not limited to, intravenous, parenteral, intraperitoneal, intramuscular, intratumor, intradermal, intraorgan, orthotopic, and the like. A preferred formulation for intravenous injection comprises the therapeutic composition in a solution of preserved bacteriostatic water, sterile unpreserved water, and/or diluted in polyvinylchloride or polyethylene bags containing 0.9% sterile Sodium Chloride for Injection, USP. Therapeutic protein preparations can be lyophilized and stored as sterile powders, preferably under vacuum, and then reconstituted in bacteriostatic water (containing for example, benzyl alcohol preservative) or in sterile water prior to injection.

[0451] Dosages and administration protocols for the treatment of cancers using the foregoing methods will vary with the method and the target cancer, and will generally depend on a number of other factors appreciated in the art.

[0452] XIII.) Identification, Characterization and Use of Modulators of 273P4B7

[0453] Methods to Identify and Use Modulators

[0454] In one embodiment, screening is performed to identify modulators that induce or suppress a particular expression profile, suppress or induce specific pathways, preferably generating the associated phenotype thereby. In another embodiment, having identified differentially expressed genes important in a particular state; screens are performed to identify modulators that alter expression of individual genes, either increase or decrease. In another embodiment, screening is performed to identify modulators that alter a biological function of the expression product of a differentially expressed gene. Again, having identified the importance of a gene in a particular state, screens are performed to identify agents that bind and/or modulate the biological activity of the gene product.

[0455] In addition, screens are done for genes that are induced in response to a candidate agent. After identifying a modulator (one that suppresses a cancer expression pattern leading to a normal expression pattern, or a modulator of a

cancer gene that leads to expression of the gene as in normal tissue) a screen is performed to identify genes that are specifically modulated in response to the agent. Comparing expression profiles between normal tissue and agent-treated cancer tissue reveals genes that are not expressed in normal tissue or cancer tissue, but are expressed in agent treated tissue, and vice versa. These agent-specific sequences are identified and used by methods described herein for cancer genes or proteins. In particular these sequences and the proteins they encode are used in marking or identifying agent-treated cells. In addition, antibodies are raised against the agent-induced proteins and used to target novel therapeutics to the treated cancer tissue sample.

[0456] Modulator-Related Identification and Screening Assays:

[0457] Gene Expression-Related Assays

[0458] Proteins, nucleic acids, and antibodies of the invention are used in screening assays. The cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing these sequences are used in screening assays, such as evaluating the effect of drug candidates on a "gene expression profile," expression profile of polypeptides or alteration of biological function. In one embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes after treatment with a candidate agent (e.g., Davis, G F, et al., *J Biol Screen* 7:69 (2002); Zlokam, et al., *Science* 279:84-8 (1998); Heid, *Genome Res* 6:986-94, 1996).

[0459] The cancer proteins, antibodies, nucleic acids, modified proteins and cells containing the native or modified cancer proteins or genes are used in screening assays. That is, the present invention comprises methods for screening for compositions which modulate the cancer phenotype or a physiological function of a cancer protein of the invention. This is done on a gene itself or by evaluating the effect of drug candidates on a "gene expression profile" or biological function. In one embodiment, expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring after treatment with a candidate agent, see Zlokam, supra.

[0460] A variety of assays are executed directed to the genes and proteins of the invention. Assays are run on an individual nucleic acid or protein level. That is, having identified a particular gene as up regulated in cancer, test compounds are screened for the ability to modulate gene expression or for binding to the cancer protein of the invention. "Modulation" in this context includes an increase or a decrease in gene expression. The preferred amount of modulation will depend on the original change of the gene expression in normal versus tissue undergoing cancer, with changes of at least 10%, preferably 50%, more preferably 100-300%, and in some embodiments 300-1000% or greater. Thus, if a gene exhibits a 4-fold increase in cancer tissue compared to normal tissue, a decrease of about four-fold is often desired; similarly, a 10-fold decrease in cancer tissue compared to normal tissue a target value of a 10-fold increase in expression by the test compound is often desired. Modulators that exacerbate the type of gene expression seen in cancer are also useful, e.g., as an upregulated target in further analyses.

[0461] The amount of gene expression is monitored using nucleic acid probes and the quantification of gene expression

levels, or, alternatively, a gene product itself is monitored, e.g., through the use of antibodies to the cancer protein and standard immunoassays. Proteomics and separation techniques also allow for quantification of expression.

[0462] Expression Monitoring to Identify Compounds that Modify Gene Expression

[0463] In one embodiment, gene expression monitoring, i.e., an expression profile, is monitored simultaneously for a number of entities. Such profiles will typically involve one or more of the genes of FIG. 2. In this embodiment, e.g., cancer nucleic acid probes are attached to biochips to detect and quantify cancer sequences in a particular cell. Alternatively, PCR can be used. Thus, a series, e.g., wells of a microtiter plate, can be used with dispensed primers in desired wells. A PCR reaction can then be performed and analyzed for each well.

[0464] Expression monitoring is performed to identify compounds that modify the expression of one or more cancer-associated sequences, e.g., a polynucleotide sequence set out in FIG. 2. Generally, a test modulator is added to the cells prior to analysis. Moreover, screens are also provided to identify agents that modulate cancer, modulate cancer proteins of the invention, bind to a cancer protein of the invention, or interfere with the binding of a cancer protein of the invention and an antibody or other binding partner.

[0465] In one embodiment, high throughput screening methods involve providing a library containing a large number of potential therapeutic compounds (candidate compounds). Such "combinatorial chemical libraries" are then screened in one or more assays to identify those library members (particular chemical species or subclasses) that display a desired characteristic activity. The compounds thus identified can serve as conventional "lead compounds," as compounds for screening, or as therapeutics.

[0466] In certain embodiments, combinatorial libraries of potential modulators are screened for an ability to bind to a cancer polypeptide or to modulate activity. Conventionally, new chemical entities with useful properties are generated by identifying a chemical compound (called a "lead compound") with some desirable property or activity, e.g., inhibiting activity, creating variants of the lead compound, and evaluating the property and activity of those variant compounds. Often, high throughput screening (HTS) methods are employed for such an analysis.

[0467] As noted above, gene expression monitoring is conveniently used to test candidate modulators (e.g., protein, nucleic acid or small molecule). After the candidate agent has been added and the cells allowed to incubate for a period, the sample containing a target sequence to be analyzed is, e.g., added to a biochip.

[0468] If required, the target sequence is prepared using known techniques. For example, a sample is treated to lyse the cells, using known lysis buffers, electroporation, etc., with purification and/or amplification such as PCR performed as appropriate. For example, an in vitro transcription with labels covalently attached to the nucleotides is performed. Generally, the nucleic acids are labeled with biotin-FITC or PE, or with cy3 or cy5.

[0469] The target sequence can be labeled with, e.g., a fluorescent, a chemiluminescent, a chemical, or a radioac-

tive signal, to provide a means of detecting the target sequence's specific binding to a probe. The label also can be an enzyme, such as alkaline phosphatase or horseradish peroxidase, which when provided with an appropriate substrate produces a product that is detected. Alternatively, the label is a labeled compound or small molecule, such as an enzyme inhibitor, that binds but is not catalyzed or altered by the enzyme. The label also can be a moiety or compound, such as, an epitope tag or biotin which specifically binds to streptavidin. For the example of biotin, the streptavidin is labeled as described above, thereby, providing a detectable signal for the bound target sequence. Unbound labeled streptavidin is typically removed prior to analysis.

[0470] As will be appreciated by those in the art, these assays can be direct hybridization assays or can comprise "sandwich assays", which include the use of multiple probes, as is generally outlined in U.S. Pat. Nos. 5,681,702; 5,597,909; 5,545,730; 5,594,117; 5,591,584; 5,571,670; 5,580,731; 5,571,670; 5,591,584; 5,624,802; 5,635,352; 5,594,118; 5,359,100; 5,124,246; and 5,681,697. In this embodiment, in general, the target nucleic acid is prepared as outlined above, and then added to the biochip comprising a plurality of nucleic acid probes, under conditions that allow the formation of a hybridization complex.

[0471] A variety of hybridization conditions are used in the present invention, including high, moderate and low stringency conditions as outlined above. The assays are generally run under stringency conditions which allow formation of the label probe hybridization complex only in the presence of target. Stringency can be controlled by altering a step parameter that is a thermodynamic variable, including, but not limited to, temperature, formamide concentration, salt concentration, chaotropic salt concentration pH, organic solvent concentration, etc. These parameters may also be used to control non-specific binding, as is generally outlined in U.S. Pat. No. 5,681,697. Thus, it can be desirable to perform certain steps at higher stringency conditions to reduce non-specific binding.

[0472] The reactions outlined herein can be accomplished in a variety of ways. Components of the reaction can be added simultaneously, or sequentially, in different orders, with preferred embodiments outlined below. In addition, the reaction may include a variety of other reagents. These include salts, buffers, neutral proteins, e.g. albumin, detergents, etc. which can be used to facilitate optimal hybridization and detection, and/or reduce nonspecific or background interactions. Reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may also be used as appropriate, depending on the sample preparation methods and purity of the target. The assay data are analyzed to determine the expression levels of individual genes, and changes in expression levels as between states, forming a gene expression profile.

[0473] Biological Activity-Related Assays

[0474] The invention provides methods identify or screen for a compound that modulates the activity of a cancer-related gene or protein of the invention. The methods comprise adding a test compound, as defined above, to a cell comprising a cancer protein of the invention. The cells contain a recombinant nucleic acid that encodes a cancer protein of the invention. In another embodiment, a library of candidate agents is tested on a plurality of cells.

[0475] In one aspect, the assays are evaluated in the presence or absence or previous or subsequent exposure of physiological signals, e.g. hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, pharmacological agents including chemotherapeutics, radiation, carcinogenics, or other cells (i.e., cell-cell contacts). In another example, the determinations are made at different stages of the cell cycle process. In this way, compounds that modulate genes or proteins of the invention are identified. Compounds with pharmacological activity are able to enhance or interfere with the activity of the cancer protein of the invention. Once identified, similar structures are evaluated to identify critical structural features of the compound.

[0476] In one embodiment, a method of modulating (e.g., inhibiting) cancer cell division is provided; the method comprises administration of a cancer modulator. In another embodiment, a method of modulating (e.g., inhibiting) cancer is provided; the method comprises administration of a cancer modulator. In a further embodiment, methods of treating cells or individuals with cancer are provided; the method comprises administration of a cancer modulator.

[0477] In one embodiment, a method for modulating the status of a cell that expresses a gene of the invention is provided. As used herein status comprises such art-accepted parameters such as growth, proliferation, survival, function, apoptosis, senescence, location, enzymatic activity, signal transduction, etc. of a cell. In one embodiment, a cancer inhibitor is an antibody as discussed above. In another embodiment, the cancer inhibitor is an antisense molecule. A variety of cell growth, proliferation, and metastasis assays are known to those of skill in the art, as described herein.

[0478] High Throughput Screening to Identify Modulators

[0479] The assays to identify suitable modulators are amenable to high throughput screening. Preferred assays thus detect enhancement or inhibition of cancer gene transcription, inhibition or enhancement of polypeptide expression, and inhibition or enhancement of polypeptide activity.

[0480] In one embodiment, modulators evaluated in high throughput screening methods are proteins, often naturally occurring proteins or fragments of naturally occurring proteins. Thus, e.g., cellular extracts containing proteins, or random or directed digests of proteinaceous cellular extracts, are used. In this way, libraries of proteins are made for screening in the methods of the invention. Particularly preferred in this embodiment are libraries of bacterial, fungal, viral, and mammalian proteins, with the latter being preferred, and human proteins being especially preferred. Particularly useful test compound will be directed to the class of proteins to which the target belongs, e.g., substrates for enzymes, or ligands and receptors.

[0481] Use of Soft Agar Growth and Colony Formation to Identify and Characterize Modulators

[0482] Normal cells require a solid substrate to attach and grow. When cells are transformed, they lose this phenotype and grow detached from the substrate. For example, transformed cells can grow in stirred suspension culture or suspended in semi-solid media, such as semi-solid or soft agar. The transformed cells, when transfected with tumor suppressor genes, can regenerate normal phenotype and once again require a solid substrate to attach to and grow. Soft agar growth or colony formation in assays are used to

identify modulators of cancer sequences, which when expressed in host cells, inhibit abnormal cellular proliferation and transformation. A modulator reduces or eliminates the host cells' ability to grow suspended in solid or semisolid media, such as agar.

[0483] Techniques for soft agar growth or colony formation in suspension assays are described in Freshney, *Culture of Animal Cells a Manual of Basic Technique* (3rd ed., 1994). See also, the methods section of Garkavtsev et al. (1996), *supra*.

[0484] Evaluation of Contact Inhibition and Growth Density Limitation to Identify and Characterize Modulators

[0485] Normal cells typically grow in a flat and organized pattern in cell culture until they touch other cells. When the cells touch one another, they are contact inhibited and stop growing. Transformed cells, however, are not contact inhibited and continue to grow to high densities in disorganized foci. Thus, transformed cells grow to a higher saturation density than corresponding normal cells. This is detected morphologically by the formation of a disoriented monolayer of cells or cells in foci. Alternatively, labeling index with (sup.3H)-thymidine at saturation density is used to measure density limitation of growth, similarly an MTT or Alamar blue assay will reveal proliferation capacity of cells and the ability of modulators to affect same. See Freshney (1994), *supra*. Transformed cells, when transfected with tumor suppressor genes, can regenerate a normal phenotype and become contact inhibited and would grow to a lower density.

[0486] In this assay, labeling index with ³H-thymidine at saturation density is a preferred method of measuring density limitation of growth. Transformed host cells are transfected with a cancer-associated sequence and are grown for 24 hours at saturation density in non-limiting medium conditions. The percentage of cells labeling with (3H)-thymidine is determined by incorporated cpm.

[0487] Contact independent growth is used to identify modulators of cancer sequences, which had led to abnormal cellular proliferation and transformation. A modulator reduces or eliminates contact independent growth, and returns the cells to a normal phenotype.

[0488] Evaluation of Growth Factor or Serum Dependence to Identify and Characterize Modulators

[0489] Transformed cells have lower serum dependence than their normal counterparts (see, e.g., Temin, J. Natl. Cancer Inst. 37:167-175 (1966); Eagle et al., J. Exp. Med. 131:836-879 (1970)); Freshney, *supra*. This is in part due to release of various growth factors by the transformed cells. The degree of growth factor or serum dependence of transformed host cells can be compared with that of control. For example, growth factor or serum dependence of a cell is monitored in methods to identify and characterize compounds that modulate cancer-associated sequences of the invention.

[0490] Use of Tumor-Specific Marker Levels to Identify and Characterize Modulators

[0491] Tumor cells release an increased amount of certain factors (hereinafter "tumor specific markers") than their normal counterparts. For example, plasminogen activator (PA) is released from human glioma at a higher level than

from normal brain cells (see, e.g., Gullino, *Angiogenesis, Tumor Vascularization, and Potential Interference with Tumor Growth*, in *Biological Responses in Cancer*, pp. 178-184 (Mihich (ed.) 1985)). Similarly, Tumor Angiogenesis Factor (TAF) is released at a higher level in tumor cells than their normal counterparts. See, e.g., Folkman, *Angiogenesis and Cancer*, *Sem Cancer Biol.* (1992)), while bFGF is released from endothelial tumors (Ensoli, B et al).

[0492] Various techniques which measure the release of these factors are described in Freshney (1994), *supra*. Also, see, Unkless et al., J. Biol. Chem. 249:4295-4305 (1974); Strickland & Beers, J. Biol. Chem. 251:5694-5702 (1976); Whur et al., Br. J. Cancer 42:305 312 (1980); Gullino, *Angiogenesis, Tumor Vascularization, and Potential Interference with Tumor Growth*, in *Biological Responses in Cancer*, pp. 178-184 (Mihich (ed.) 1985); Freshney, *Anticancer Res.* 5:111-130 (1985). For example, tumor specific marker levels are monitored in methods to identify and characterize compounds that modulate cancer-associated sequences of the invention.

[0493] Invasiveness into Matrigel to Identify and Characterize Modulators

[0494] The degree of invasiveness into Matrigel or an extracellular matrix constituent can be used as an assay to identify and characterize compounds that modulate cancer associated sequences. Tumor cells exhibit a positive correlation between malignancy and invasiveness of cells into Matrigel or some other extracellular matrix constituent. In this assay, tumorigenic cells are typically used as host cells. Expression of a tumor suppressor gene in these host cells would decrease invasiveness of the host cells. Techniques described in *Cancer Res.* 1999; 59:6010; Freshney (1994), *supra*, can be used. Briefly, the level of invasion of host cells is measured by using filters coated with Matrigel or some other extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and distance moved, or by prelabeling the cells with sup. 1251 and counting the radioactivity on the distal side of the filter or bottom of the dish. See, e.g., Freshney (1984), *supra*.

[0495] Evaluation of Tumor Growth In Vivo to Identify and Characterize Modulators

[0496] Effects of cancer-associated sequences on cell growth are tested in transgenic or immune-suppressed organisms. Transgenic organisms are prepared in a variety of art-accepted ways. For example, knock-out transgenic organisms, e.g., mammals such as mice, are made, in which a cancer gene is disrupted or in which a cancer gene is inserted. Knock-out transgenic mice are made by insertion of a marker gene or other heterologous gene into the endogenous cancer gene site in the mouse genome via homologous recombination. Such mice can also be made by substituting the endogenous cancer gene with a mutated version of the cancer gene, or by mutating the endogenous cancer gene, e.g., by exposure to carcinogens.

[0497] To prepare transgenic chimeric animals, e.g., mice, a DNA construct is introduced into the nuclei of embryonic stem cells. Cells containing the newly engineered genetic lesion are injected into a host mouse embryo, which is re-implanted into a recipient female. Some of these embryos develop into chimeric mice that possess germ cells some of

which are derived from the mutant cell line. Therefore, by breeding the chimeric mice it is possible to obtain a new line of mice containing the introduced genetic lesion (see, e.g., Capecchi et al., *Science* 244:1288 (1989)). Chimeric mice can be derived according to U.S. Pat. No. 6,365,797, issued 2 Apr. 2002; U.S. Pat. No. 6,107,540 issued 22 Aug. 2000; Hogan et al., *Manipulating the Mouse Embryo: A laboratory Manual*, Cold Spring Harbor Laboratory (1988) and *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed., IRL Press, Washington, D.C., (1987).

[0498] Alternatively, various immune-suppressed or immune-deficient host animals can be used. For example, a genetically athymic “nude” mouse (see, e.g., Giovanella et al., *J. Natl Cancer Inst.* 52:921 (1974)), a SCID mouse, a thymectomized mouse, or an irradiated mouse (see, e.g., Bradley et al., *Br. J. Cancer* 38:263 (1978); Selby et al., *Br. J. Cancer* 41:52 (1980)) can be used as a host. Transplantable tumor cells (typically about 10⁵ cells) injected into isogenic hosts produce invasive tumors in a high proportion of cases, while normal cells of similar origin will not. In hosts which developed invasive tumors, cells expressing cancer-associated sequences are injected subcutaneously or orthotopically. Mice are then separated into groups, including control groups and treated experimental groups (e.g. treated with a modulator). After a suitable length of time, preferably 4-8 weeks, tumor growth is measured (e.g., by volume or by its two largest dimensions, or weight) and compared to the control. Tumors that have statistically significant reduction (using, e.g., Student’s *t* test) are said to have inhibited growth.

[0499] In Vitro Assays to Identify and Characterize Modulators

[0500] Assays to identify compounds with modulating activity can be performed in vitro. For example, a cancer polypeptide is first contacted with a potential modulator and incubated for a suitable amount of time, e.g., from 0.5 to 48 hours. In one embodiment, the cancer polypeptide levels are determined in vitro by measuring the level of protein or mRNA. The level of protein is measured using immunoassays such as Western blotting, ELISA and the like with an antibody that selectively binds to the cancer polypeptide or a fragment thereof. For measurement of mRNA, amplification, e.g., using PCR, LCR, or hybridization assays, e.g., Northern hybridization, RNase protection, dot blotting, are preferred. The level of protein or mRNA is detected using directly or indirectly labeled detection agents, e.g., fluorescently or radioactively labeled nucleic acids, radioactively or enzymatically labeled antibodies, and the like, as described herein.

[0501] Alternatively, a reporter gene system can be devised using a cancer protein promoter operably linked to a reporter gene such as luciferase, green fluorescent protein, CAT, or P-gal. The reporter construct is typically transfected into a cell. After treatment with a potential modulator, the amount of reporter gene transcription, translation, or activity is measured according to standard techniques known to those of skill in the art (Davis G F, supra; Gonzalez, J. & Negulescu, P. *Curr. Opin. Biotechnol.* 1998: 9:624).

[0502] As outlined above, in vitro screens are done on individual genes and gene products. That is, having identified a particular differentially expressed gene as important in

a particular state, screening of modulators of the expression of the gene or the gene product itself is performed.

[0503] In one embodiment, screening for modulators of expression of specific gene(s) is performed. Typically, the expression of only one or a few genes is evaluated. In another embodiment, screens are designed to first find compounds that bind to differentially expressed proteins. These compounds are then evaluated for the ability to modulate differentially expressed activity. Moreover, once initial candidate compounds are identified, variants can be further screened to better evaluate structure activity relationships.

[0504] Binding Assays to Identify and Characterize Modulators

[0505] In binding assays in accordance with the invention, a purified or isolated gene the invention is generally used. For example, antibodies are generated to a protein of the invention, and immunoassays are run to determine the amount and/or location of protein. Alternatively, cells comprising the cancer proteins are used in the assays.

[0506] Thus, the methods comprise combining a cancer protein of the invention and a candidate compound such as a ligand, and determining the binding of the compound to the cancer protein of the invention. Preferred embodiments utilize the human cancer protein; animal models of human disease of can also be developed and used. Also, other analogous mammalian proteins also can be used as appreciated by those of skill in the art. Moreover, in some embodiments variant or derivative cancer proteins are used.

[0507] Generally, the cancer protein of the invention, or the ligand, is non-diffusibly bound to an insoluble support. The support can, e.g., be one having isolated sample receiving areas (a microtiter plate, an array, etc.). The insoluble supports can be made of any composition to which the compositions can be bound, is readily separated from soluble material, and is otherwise compatible with the overall method of screening. The surface of such supports can be solid or porous and of any convenient shape.

[0508] Examples of suitable insoluble supports include microtiter plates, arrays, membranes and beads. These are typically made of glass, plastic (e.g., polystyrene), polysaccharide, nylon, nitrocellulose, or TEFLON, etc. Microtiter plates and arrays are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples. The particular manner of binding of the composition to the support is not crucial so long as it is compatible with the reagents and overall methods of the invention, maintains the activity of the composition and is nondiffusible. Preferred methods of binding include the use of antibodies which do not sterically block either the ligand binding site or activation sequence when attaching the protein to the support, direct binding to “sticky” or ionic supports, chemical crosslinking, the synthesis of the protein or agent on the surface, etc. Following binding of the protein or ligand/binding agent to the support, excess unbound material is removed by washing. The sample receiving areas may then be blocked through incubation with bovine serum albumin (BSA), casein or other innocuous protein or other moiety.

[0509] Once a cancer protein of the invention is bound to the support, and a test compound is added to the assay.

Alternatively, the candidate binding agent is bound to the support and the cancer protein of the invention is then added. Binding agents include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc.

[0510] Of particular interest are assays to identify agents that have a low toxicity for human cells. A wide variety of assays can be used for this purpose, including proliferation assays, cAMP assays, labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0511] A determination of binding of the test compound (ligand, binding agent, modulator, etc.) to a cancer protein of the invention can be done in a number of ways. The test compound can be labeled, and binding determined directly, e.g., by attaching all or a portion of the cancer protein of the invention to a solid support, adding a labeled candidate compound (e.g., a fluorescent label), washing off excess reagent, and determining whether the label is present on the solid support. Various blocking and washing steps can be utilized as appropriate.

[0512] In certain embodiments, only one of the components is labeled, e.g., a protein of the invention or ligands labeled. Alternatively, more than one component is labeled with different labels, e.g., 1.sup.125, for the proteins and a fluorophor for the compound. Proximity reagents, e.g., quenching or energy transfer reagents are also useful.

[0513] Competitive Binding to Identify and Characterize Modulators

[0514] In one embodiment, the binding of the "test compound" is determined by competitive binding assay with a "competitor." The competitor is a binding moiety that binds to the target molecule (e.g., a cancer protein of the invention). Competitors include compounds such as antibodies, peptides, binding partners, ligands, etc. Under certain circumstances, the competitive binding between the test compound and the competitor displaces the test compound. In one embodiment, the test compound is labeled. Either the test compound, the competitor, or both, is added to the protein for a time sufficient to allow binding. Incubations are performed at a temperature that facilitates optimal activity, typically between four and 40° C. Incubation periods are typically optimized, e.g., to facilitate rapid high throughput screening; typically between zero and one hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0515] In one embodiment, the competitor is added first, followed by the test compound. Displacement of the competitor is an indication that the test compound is binding to the cancer protein and thus is capable of binding to, and potentially modulating, the activity of the cancer protein. In this embodiment, either component can be labeled. Thus, e.g., if the competitor is labeled, the presence of label in the post-test compound wash solution indicates displacement by the test compound. Alternatively, if the test compound is labeled, the presence of the label on the support indicates displacement.

[0516] In an alternative embodiment, the test compound is added first, with incubation and washing, followed by the

competitor. The absence of binding by the competitor indicates that the test compound binds to the cancer protein with higher affinity than the competitor. Thus, if the test compound is labeled, the presence of the label on the support, coupled with a lack of competitor binding, indicates that the test compound binds to and thus potentially modulates the cancer protein of the invention.

[0517] Accordingly, the competitive binding methods comprise differential screening to identify agents that are capable of modulating the activity of the cancer proteins of the invention. In this embodiment, the methods comprise combining a cancer protein and a competitor in a first sample. A second sample comprises a test compound, the cancer protein, and a competitor. The binding of the competitor is determined for both samples, and a change, or difference in binding between the two samples indicates the presence of an agent capable of binding to the cancer protein and potentially modulating its activity. That is, if the binding of the competitor is different in the second sample relative to the first sample, the agent is capable of binding to the cancer protein.

[0518] Alternatively, differential screening is used to identify drug candidates that bind to the native cancer protein, but cannot bind to modified cancer proteins. For example the structure of the cancer protein is modeled and used in rational drug design to synthesize agents that interact with that site, agents which generally do not bind to site-modified proteins. Moreover, such drug candidates that affect the activity of a native cancer protein are also identified by screening drugs for the ability to either enhance or reduce the activity of such proteins.

[0519] Positive controls and negative controls can be used in the assays. Preferably control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of all samples occurs for a time sufficient to allow for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples can be counted in a scintillation counter to determine the amount of bound compound.

[0520] A variety of other reagents can be included in the screening assays. These include reagents like salts, neutral proteins, e.g. albumin, detergents, etc. which are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., can be used. The mixture of components is added in an order that provides for the requisite binding.

[0521] Use of Polynucleotides to Down-Regulate or Inhibit a Protein of the Invention.

[0522] Polynucleotide modulators of cancer can be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand-binding molecule, as described in WO 91/04753. Suitable ligand-binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corre-

sponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell. Alternatively, a polynucleotide modulator of cancer can be introduced into a cell containing the target nucleic acid sequence, e.g., by formation of a polynucleotide-lipid complex, as described in WO 90/10448. It is understood that the use of antisense molecules or knock out and knock in models may also be used in screening assays as discussed above, in addition to methods of treatment.

[0523] Inhibitory and Antisense Nucleotides

[0524] In certain embodiments, the activity of a cancer-associated protein is down-regulated, or entirely inhibited, by the use of antisense polynucleotide or inhibitory small nuclear RNA (snRNA), i.e., a nucleic acid complementary to, and which can preferably hybridize specifically to, a coding mRNA nucleic acid sequence, e.g., a cancer protein of the invention, mRNA, or a subsequence thereof. Binding of the antisense polynucleotide to the mRNA reduces the translation and/or stability of the mRNA.

[0525] In the context of this invention, antisense polynucleotides can comprise naturally occurring nucleotides, or synthetic species formed from naturally occurring subunits or their close homologs. Antisense polynucleotides may also have altered sugar moieties or inter-sugar linkages. Exemplary among these are the phosphorothioate and other sulfur containing species which are known for use in the art. Analogs are comprised by this invention so long as they function effectively to hybridize with nucleotides of the invention. See, e.g., Isis Pharmaceuticals, Carlsbad, Calif.; Sequitor, Inc., Natick, Mass.

[0526] Such antisense polynucleotides can readily be synthesized using recombinant means, or can be synthesized in vitro. Equipment for such synthesis is sold by several vendors, including Applied Biosystems. The preparation of other oligonucleotides such as phosphorothioates and alkylated derivatives is also well known to those of skill in the art.

[0527] Antisense molecules as used herein include antisense or sense oligonucleotides. Sense oligonucleotides can, e.g., be employed to block transcription by binding to the anti-sense strand. The antisense and sense oligonucleotide comprise a single stranded nucleic acid sequence (either RNA or DNA) capable of binding to target mRNA (sense) or DNA (antisense) sequences for cancer molecules. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment generally at least about 12 nucleotides, preferably from about 12 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, e.g., Stein & Cohen (Cancer Res. 48:2659 (1988 and van der Krol et al. (Bio Techniques 6:958 (1988)).

[0528] Ribozymes

[0529] In addition to antisense polynucleotides, ribozymes can be used to target and inhibit transcription of cancer-associated nucleotide sequences. A ribozyme is an RNA molecule that catalytically cleaves other RNA molecules. Different kinds of ribozymes have been described, including group I ribozymes, hammerhead ribozymes, hairpin ribozymes, RNase P, and axhead ribozymes (see, e.g., Castanotto et al., Adv. in Pharmacology 25: 289-317 (1994) for a general review of the properties of different ribozymes).

[0530] The general features of hairpin ribozymes are described, e.g., in Hampel et al., Nucl. Acids Res. 18:299-304 (1990); European Patent Publication No. 0360257; U.S. Pat. No. 5,254,678. Methods of preparing are well known to those of skill in the art (see, e.g., WO 94/26877; Ojwang et al., Proc. Natl. Acad. Sci. USA 90:6340-6344 (1993); Yamada et al., Human Gene Therapy 1:39-45 (1994); Leavitt et al., Proc. Natl. Acad. Sci. USA 92:699-703 (1995); Leavitt et al., Human Gene Therapy 5: 1151-120 (1994); and Yamada et al., Virology 205: 121-126 (1994)).

[0531] Use of Modulators in Phenotypic Screening

[0532] In one embodiment, a test compound is administered to a population of cancer cells, which have an associated cancer expression profile. By "administration" or "contacting" herein is meant that the modulator is added to the cells in such a manner as to allow the modulator to act upon the cell, whether by uptake and intracellular action, or by action at the cell surface. In some embodiments, a nucleic acid encoding a proteinaceous agent (i.e., a peptide) is put into a viral construct such as an adenoviral or retroviral construct, and added to the cell, such that expression of the peptide agent is accomplished, e.g., PCT US97/01019. Regulatable gene therapy systems can also be used. Once the modulator has been administered to the cells, the cells are washed if desired and are allowed to incubate under preferably physiological conditions for some period. The cells are then harvested and a new gene expression profile is generated. Thus, e.g., cancer tissue is screened for agents that modulate, e.g., induce or suppress, the cancer phenotype. A change in at least one gene, preferably many, of the expression profile indicates that the agent has an effect on cancer activity. Similarly, altering a biological function or a signaling pathway is indicative of modulator activity. By defining such a signature for the cancer phenotype, screens for new drugs that alter the phenotype are devised. With this approach, the drug target need not be known and need not be represented in the original gene/protein expression screening platform, nor does the level of transcript for the target protein need to change. The modulator inhibiting function will serve as a surrogate marker

[0533] As outlined above, screens are done to assess genes or gene products. That is, having identified a particular differentially expressed gene as important in a particular state, screening of modulators of either the expression of the gene or the gene product itself is performed.

[0534] Use of Modulators to Affect Peptides of the Invention

[0535] Measurements of cancer polypeptide activity, or of the cancer phenotype are performed using a variety of assays. For example, the effects of modulators upon the function of a cancer polypeptide(s) are measured by examining parameters described above. A physiological change that affects activity is used to assess the influence of a test compound on the polypeptides of this invention. When the functional outcomes are determined using intact cells or animals, a variety of effects can be assessed such as, in the case of a cancer associated with solid tumors, tumor growth, tumor metastasis, neovascularization, hormone release, transcriptional changes to both known and uncharacterized genetic markers (e.g., by Northern blots), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as cGNIP.

[0536] Methods of Identifying Characterizing Cancer-Associated Sequences

[0537] Expression of various gene sequences is correlated with cancer. Accordingly, disorders based on mutant or variant cancer genes are determined. In one embodiment, the invention provides methods for identifying cells containing variant cancer genes, e.g., determining the presence of, all or part, the sequence of at least one endogenous cancer gene in a cell. This is accomplished using any number of sequencing techniques. The invention comprises methods of identifying the cancer genotype of an individual, e.g., determining all or part of the sequence of at least one gene of the invention in the individual. This is generally done in at least one tissue of the individual, e.g., a tissue set forth in Table I, and may include the evaluation of a number of tissues or different samples of the same tissue. The method may include comparing the sequence of the sequenced gene to a known cancer gene, i.e., a wild-type gene to determine the presence of family members, homologies, mutations or variants. The sequence of all or part of the gene can then be compared to the sequence of a known cancer gene to determine if any differences exist. This is done using any number of known homology programs, such as BLAST, Bestfit, etc. The presence of a difference in the sequence between the cancer gene of the patient and the known cancer gene correlates with a disease state or a propensity for a disease state, as outlined herein.

[0538] In a preferred embodiment, the cancer genes are used as probes to determine the number of copies of the cancer gene in the genome. The cancer genes are used as probes to determine the chromosomal localization of the cancer genes. Information such as chromosomal localization finds use in providing a diagnosis or prognosis in particular when chromosomal abnormalities such as translocations, and the like are identified in the cancer gene locus.

[0539] XIV.) Kits/Articles of Manufacture

[0540] For use in the laboratory, prognostic, prophylactic, diagnostic and therapeutic applications described herein, kits are within the scope of the invention. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in the method, along with a label or insert comprising instructions for use, such as a use described herein. For example, the container(s) can comprise a probe that is or can be detectably labeled. Such probe can be an antibody or polynucleotide specific for a protein or a gene or message of the invention, respectively. Where the method utilizes nucleic acid hybridization to detect the target nucleic acid, the kit can also have containers containing nucleotide(s) for amplification of the target nucleic acid sequence. Kits can comprise a container comprising a reporter, such as a biotin-binding protein, such as avidin or streptavidin, bound to a reporter molecule, such as an enzymatic, fluorescent, or radioisotope label; such a reporter can be used with, e.g., a nucleic acid or antibody. The kit can include all or part of the amino acid sequences in FIG. 2 or FIG. 3 or analogs thereof, or a nucleic acid molecule that encodes such amino acid sequences.

[0541] The kit of the invention will typically comprise the container described above and one or more other containers associated therewith that comprise materials desirable from

a commercial and user standpoint, including buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use.

[0542] A label can be present on or with the container to indicate that the composition is used for a specific therapy or non-therapeutic application, such as a prognostic, prophylactic, diagnostic or laboratory application, and can also indicate directions for either in vivo or in vitro use, such as those described herein. Directions and/or other information can also be included on an insert(s) or label(s) which is included with or on the kit. The label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. The label can indicate that the composition is used for diagnosing, treating, prophylaxing or prognosing a condition, such as a neoplasia of a tissue set forth in Table I.

[0543] The terms "kit" and "article of manufacture" can be used as synonyms.

[0544] In another embodiment of the invention, an article(s) of manufacture containing compositions, such as amino acid sequence(s), small molecule(s), nucleic acid sequence(s), and/or antibody(s), e.g., materials useful for the diagnosis, prognosis, prophylaxis and/or treatment of neoplasias of tissues such as those set forth in Table I is provided. The article of manufacture typically comprises at least one container and at least one label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass, metal or plastic. The container can hold amino acid sequence(s), small molecule(s), nucleic acid sequence(s), cell population(s) and/or antibody(s). In one embodiment, the container holds a polynucleotide for use in examining the mRNA expression profile of a cell, together with reagents used for this purpose. In another embodiment a container comprises an antibody, binding fragment thereof or specific binding protein for use in evaluating protein expression of 282P1 G3 in cells and tissues, or for relevant laboratory, prognostic, diagnostic, prophylactic and therapeutic purposes; indications and/or directions for such uses can be included on or with such container, as can reagents and other compositions or tools used for these purposes. In another embodiment, a container comprises materials for eliciting a cellular or humoral immune response, together with associated indications and/or directions. In another embodiment, a container comprises materials for adoptive immunotherapy, such as cytotoxic T cells (CTL) or helper T cells (HTL), together with associated indications and/or directions; reagents and other compositions or tools used for such purpose can also be included.

[0545] The container can alternatively hold a composition that is effective for treating, diagnosis, prognosing or prophylaxing a condition and can have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agents in the composition can be an antibody capable of specifically binding 282P1 G3 and modulating the function of 282P1 G3.

[0546] The article of manufacture can further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and/or dextrose solution. It can further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, stirrers, needles, syringes, and/or package inserts with indications and/or instructions for use.

EXAMPLES

[0547] Various aspects of the invention are further described and illustrated by way of the several examples that follow, none of which is intended to limit the scope of the invention.

Example 1

SSH-Generated Isolation of cDNA Fragment of the 273P4B7 Gene

[0548] To isolate genes that are over-expressed in lung cancer the Suppression Subtractive Hybridization (SSH) procedure was used using cDNA derived from lung cancer tissues. The 273P4B7 SSH cDNA sequence was derived from lung tumor minus cDNAs derived from normal lung. The 273P4B7 cDNA was identified as highly expressed in cancer.

[0549] Materials and Methods

[0550] Human Tissues:

[0551] The patient cancer and normal tissues were purchased from different sources such as the NDRI (Philadelphia, Pa.). mRNA for some normal tissues were purchased from Clontech, Palo Alto, Calif.

[0552] RNA Isolation:

[0553] Tissues were homogenized in TRIZOL reagent (Life Technologies, Gibco BRL) using 10 ml/g tissue isolate total RNA. Poly A RNA was purified from total RNA using Qiagen's Oligotex mRNA Mini and Midi kits. Total and mRNA were quantified by spectrophotometric analysis (O.D. 260/280 nm) and analyzed by gel electrophoresis.

[0554] Oligonucleotides:

[0555] The following HPLC purified oligonucleotides were used.

2 DPNCND (cDNA synthesis primer): (SEQ ID NO: 30)
 5' TTTTGATCAAGCTT3'-
 Adaptor 1: (SEQ ID NO: 31)
 5' CTAATACGACTCACTATAGGGCTCGAGCGGCCCGGGGAG3'
 (SEQ ID NO: 32)
 3' GGCCCGTCCTAG5'
 Adaptor 2: (SEQ ID NO: 33)
 5' GTAATACGACTCACTATAGGGCAGCGTGGTCGCGCCGAG3'
 (SEQ ID NO: 34)
 3' CGGCTCCTAG5'

-continued

PCR primer 1: (SEQ ID NO: 35)
 5' CTAATACGACTCACTATAGGGC3'
 Nested primer (NP)1: (SEQ ID NO: 36)
 5' TCGAGCGGCCCGCCGGGCGAGGA3'
 Nested primer (NP)2: (SEQ ID NO: 37)
 5' AGCGTGGTCGCGGCCGAGGA3'

[0556] Suppression Subtractive Hybridization:

[0557] Suppression Subtractive Hybridization (SSH) was used to identify cDNAs corresponding to genes that may be differentially expressed in cancer. The SSH reaction utilized cDNA from lung cancer and normal tissues.

[0558] The gene 273P4B7 sequence was derived from lung cancer minus normal lung and a mix of 9 normal tissues cDNA subtraction. The SSH DNA sequence (FIG. 1) was identified.

[0559] The cDNA derived from normal lung mixed with a pool of 9 normal tissues was used as the source of the "driver" cDNA, while the cDNA from lung cancer was used as the source of the "tester" cDNA. Double stranded cDNAs corresponding to tester and driver cDNAs were synthesized from 2 µg of poly(A)+RNA isolated from the relevant tissue, as described above, using CLONTECH's PCR-Select cDNA Subtraction Kit and 1 ng of oligonucleotide DPNCND as primer. First- and second-strand synthesis were carried out as described in the Kit's user manual protocol (CLONTECH Protocol No. PT1117-1, Catalog No. K1804-1). The resulting cDNA was digested with Dpn II for 3 hrs at 37° C. Digested cDNA was extracted with phenol/chloroform (1:1) and ethanol precipitated.

[0560] Driver cDNA was generated by combining in a 1:1 ratio Dpn II digested cDNA from normal lung with a mix of digested cDNAs derived from the nine normal tissues: stomach, skeletal muscle, lung, brain, liver, kidney, pancreas, small intestine, and heart.

[0561] Tester cDNA was generated by diluting 1 µl of Dpn II digested cDNA from the relevant tissue source (see above) (400 ng) in 511 of water. The diluted cDNA (2 µl, 160 ng) was then ligated to 2 µl of Adaptor 1 and Adaptor 2 (10 µM), in separate ligation reactions, in a total volume of 10 µl at 16° C. overnight, using 400 u of T4 DNA ligase (CLONTECH). Ligation was terminated with 1 µl of 0.2 M EDTA and heating at 72° C. for 5 min.

[0562] The first hybridization was performed by adding 1.5 µl (600 ng) of driver cDNA to each of two tubes containing 1.5 µl (20 ng) Adaptor 1- and Adaptor 2-ligated tester cDNA. In a final volume of 4 µl, the samples were overlaid with mineral oil, denatured in an MJ Research thermal cycler at 98° C. for 1.5 minutes, and then were allowed to hybridize for 8 hrs at 68° C. The two hybridizations were then mixed together with an additional 1 µl of fresh denatured driver cDNA and were allowed to hybridize overnight at 68° C. The second hybridization was then diluted in 200 µl of 20 mM Hepes, pH 8.3, 50 mM NaCl, 0.2 mM EDTA, heated at 70° C. for 7 min. and stored at -20° C.

[0563] PCR Amplification, Cloning and Sequencing of Gene Fragments Generated from SSH:

[0564] To amplify gene fragments resulting from SSH reactions, two PCR amplifications were performed. In the primary PCR reaction 1 μ l of the diluted final hybridization mix was added to 1 μ l of PCR primer 1 (10 pM), 0.5 μ l dNTP mix (10 μ M), 2.5 μ l 10 $\times$ reaction buffer (CLONTECH) and 0.5 μ l 50 $\times$ Advantage cDNA polymerase Mix (CLONTECH) in a final volume of 25 μ l. PCR 1 was conducted using the following conditions: 75° C. for 5 min., 94° C. for 25 sec., then 27 cycles of 94° C. for 10 sec, 66° C. for 30 sec, 72° C. for 1.5 min. Five separate primary PCR reactions were performed for each experiment. The products were pooled and diluted 1:10 with water. For the secondary PCR reaction, 1 μ l from the pooled and diluted primary PCR reaction was added to the same reaction mix as used for PCR 1, except that primers NP1 and NP2 (10 μ M) were used instead of PCR primer 1. PCR 2 was performed using 10-12 cycles of 94° C. for 10 sec, 68° C. for 30 sec, and 72° C. for 1.5 minutes. The PCR products were analyzed using 2% agarose gel electrophoresis.

[0565] The PCR products were inserted into pCR2.1 using the T/A vector cloning kit (Invitrogen). Transformed *E. coli* were subjected to blue/white and ampicillin selection. White colonies were picked and arrayed into 96 well plates and were grown in liquid culture overnight. To identify inserts, PCR amplification was performed on 1 μ l of bacterial culture using the conditions of PCR1 and NP1 and NP2 as primers. PCR products were analyzed using 2% agarose gel electrophoresis.

[0566] Bacterial clones were stored in 20% glycerol in a 96 well format. Plasmid DNA was prepared, sequenced, and subjected to nucleic acid homology searches of the GenBank, dBest, and NCI-CGAP databases.

[0567] RT-PCR Expression Analysis:

[0568] First strand cDNAs can be generated from 1 μ g of mRNA with oligo (dT)12-18 priming using the GIBCO-BRL SUPERSCRIPT PREAMPLIFICATION system. The manufacturer's protocol was used which included an incubation for 50 min at 42° C. with reverse transcriptase followed by RNase H treatment at 37° C. for 20 min. After completing the reaction, the volume can be increased to 200 μ l with water prior to normalization. First strand cDNAs from 16 different normal human tissues can be obtained from Clontech.

[0569] Normalization of the first strand cDNAs from multiple tissues was performed by using the primers 5'atategccgcgtcgtcgtcgacaa3' (SEQ ID NO: 38) and 5'agccacacgcagctcatttagaagg 3' (SEQ ID NO: 39) to amplify β -actin. First strand cDNA (5 μ l) were amplified in a total volume of 5011 containing 0.4 μ M primers, 0.2 μ M each dNTPs, 1 $\times$ PCR buffer (Clontech, 10 mM Tris-HCL, 1.5 mM MgCl₂, 50 mM KCl, pH8.3) and 1 $\times$ Klenaq DNA polymerase (Clontech). Five μ l of the PCR reaction can be removed at 18, 20, and 22 cycles and used for agarose gel electrophoresis. PCR was performed using an MJ Research thermal cycler under the following conditions: Initial denaturation can be at 94° C. for 15 sec, followed by a 18, 20, and 22 cycles of 94° C. for 15, 65° C. for 2 min, 72° C. for 5 sec. A final extension at 72° C. was carried out for 2 min. After agarose gel electrophoresis, the band intensities of the 283

b.p. β -actin bands from multiple tissues were compared by visual inspection. Dilution factors for the first strand cDNAs were calculated to result in equal M-actin band intensities in all tissues after 22 cycles of PCR. Three rounds of normalization can be required to achieve equal band intensities in all tissues after 22 cycles of PCR.

[0570] To determine expression levels of the 273P4B7 gene, 5 μ l of normalized first strand cDNA were analyzed by PCR using 26, and 30 cycles of amplification. Semi-quantitative expression analysis can be achieved by comparing the PCR products at cycle numbers that give light band intensities. The primers used for RT-PCR are listed below:

[0571] 3 273P4B7.1 5'-GCTAGTGCTCAGAATACCA-GACTATGG-3' (SEQ ID NO: 40) 272P4B7.2 5'-CGCT-TGACATAAAAAGTGCAGATCC-3' (SEQ ID NO: 41)

[0572] A typical RT-PCR expression analysis is shown in FIGS. 14(A) and 14(B). First strand cDNA was prepared from vital pool 1 (liver, lung and kidney), vital pool 2 (pancreas, colon and stomach), normal pancreas, ovary cancer pool, and pancreas cancer pool. Normalization was performed by PCR using primers to actin and GAPDH. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Expression of 273P4B7 was detected in ovary cancer pool, pancreas cancer pool vital pool 1, but not in vital pool 2 nor in normal pancreas.

Example 2

Full Length Cloning of 273P4B7

[0573] The 273P4B7 SSH cDNA sequence was derived from a subtraction consisting of lung cancer minus a normal tissues. The SSH cDNA sequence of 170 bp (FIG. 1) was designated 273P4B7.

[0574] 273P4B7 v.1 of 4194 bp was cloned from lung cancer, revealing an ORF of 1250 amino acids (FIG. 2 and FIG. 3). Other variants of 273P4B7 were also identified and these are listed in FIG. 2 and FIG. 3.

[0575] 273P4B7 v.1, v.3, v.7, and v.8 code for identical proteins of 1250 amino acids in length. 273P4B7 v.4, v.5 and v.6 differ from 273P4B7 v.1 by one amino acid as shown in FIG. 2. 273P4B7 v.2 is a splice variant of 273P4B7 v.1 and code for a protein of 1127 amino acids.

[0576] 273P4B7 v.1 shows 99% over only 1106 amino acids to the unnamed protein AK074719. The nucleic acid sequence of 273P4B7 v.1 aligns with 99% identity to the nucleotide position 159-4194, to cDNA FLJ31932 fis, clone NT2RP7006296, weakly similar to EXCISION REPAIR PROTEIN ERCC-6.

[0577] 273P4B7 v.1 shows 72% identity to the mouse protein BC004701 shown to be a member of the family of DEAD-like helicase superfamily. Members of this family include the DEAD and DEAH box helicases. Helicases are involved in unwinding nucleic acids. The DEAD box helicases are involved in various aspects of RNA metabolism, including nuclear transcription, pre mRNA splicing, ribosome biogenesis, nucleocytoplasmic transport, translation, RNA decay and organellar gene expression.

Example 3

Chromosomal Mapping of 273P4B7

[0578] Chromosomal localization can implicate genes in disease pathogenesis. Several chromosome mapping

approaches are available including fluorescent in situ hybridization (FISH), human/hamster radiation hybrid (RH) panels (Walter et al., 1994; Nature Genetics 7:22; Research Genetics, Huntsville Ala.), human-rodent somatic cell hybrid panels such as is available from the Coriell Institute (Camden, N.J.), and genomic viewers utilizing BLAST homologies to sequenced and mapped genomic clones (NCBI, Bethesda, Md.).

[0579] 273P4B7 maps to chromosome Xq13.1 using 273P4B7 sequence and the NCBI BLAST tool located on the World Wide Web.

Example 4

Expression Analysis of 273P4B7 in Normal Tissues and Patient Specimens

[0580] Expression analysis by RT-PCR demonstrated that 273P4B7 is strongly expressed in patient cancer specimens (FIG. 14). First strand cDNA was prepared from normal tissues (bladder, brain, heart, kidney, liver, lung, prostate, spleen, skeletal muscle, testis, pancreas, colon and stomach), and from pools of patient cancer specimens (pancreas cancer pool, bladder cancer pool, kidney cancer pool, colon cancer pool, lung cancer pool, ovary cancer pool, breast cancer pool, cancer metastasis pool, pancreas cancer pool, prostate cancer xenograft pool, prostate metastasis to lymph node, bone and melanoma cancer pool, cervical cancer pool, lymphoma cancer pool, stomach cancer pool, uterus cancer pool, and multi-xenograft pool). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 22, 26 and 30 cycles of amplification. In FIG. 14(A) picture of the RT-PCR agarose gel is shown. In FIG. 14(B) PCR products were quantitated using the ALPHALMAGER software. Results show strong expression of 273P4B7 in prostate cancer pool, bladder cancer pool, kidney cancer pool, colon cancer pool, lung cancer pool, ovary cancer pool, breast cancer pool, cancer metastasis pool, pancreas cancer pool, prostate cancer xenograft pool, prostate metastasis to lymph node, bone and melanoma cancer pool, cervical cancer pool, lymphoma cancer pool, stomach cancer pool, uterus cancer pool and multi-xenograft pool (prostate cancer, kidney cancer and bladder cancer xenograft pool). In normal tissues, 273P4B7 is predominantly expressed in testis and not in any other normal tissue tested.

[0581] Extensive expression of 273P4B7 in normal tissues is shown in FIG. 15. Two multiple tissue northern blots (Clontech) both with 2 µg of mRNA/lane were probed with the 273P4B7 sequence. Size standards in kilobases (kb) are indicated on the side. Results show expression of an approximately 7 kb 273P4B7 transcript in normal testis but not in the other normal tissues tested.

[0582] Expression of 273P4B7 in pancreas, ovary and testis cancer patient specimens is shown in FIG. 16. RNA was extracted from normal pancreas (NP_a), normal ovary (NO), normal testis (NT_e), pancreas cancer patient specimen (P1), ovary cancer patient specimen (P2, P3, P4), and testis cancer patient specimen (P5, P6, P7). Northern blot with 10 µg of total RNA/lane was probed with 273P4B7 SSH sequence. Size standards in kilobases (kb) are indicated on the side. 273P4B7 transcript was detected in the patient specimens, but not in the normal tissues.

[0583] FIG. 17 shows 273P4B7 expression in cervical cancer patient specimens. In FIG. 17(A), total RNA was extracted from cervical cancer patient specimens (T1-T7), and HeLa cell line. Northern blot with 10 µg of total RNA/lane was probed with 273P4B7 SSH sequence. Size standards in kilobases (kb) are indicated on the side. 273P4B7 transcript was detected in all patient specimens tested as well as in the HeLa cell line. In FIG. 17(B), first strand cDNA was prepared from a panel of cervical cancer patient specimens, normal cervix and HeLa cervical cell line. Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the ALPHALMAGER software. Expression was recorded as absent, low, medium or strong. Results show expression of 273P4B7 in most of the cervical cancer tissues tested.

[0584] Expression of 273P4B7 in bladder cancer patient specimens is shown in FIG. 18. First strand cDNA was prepared from a panel of bladder cancer patient specimens, normal bladder (N) and bladder cancer cell lines (UM-UC-3, TCCSUP, J82). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel FIG. 18(A), and PCR products were quantitated using the ALPHALMAGER software FIG. 18(B). Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in most of the bladder cancer tissues tested, but not in the normal bladder tissues.

[0585] Expression of 273P4B7 in colon cancer patient specimens is shown in FIG. 19. First strand cDNA was prepared from a panel of colon cancer patient specimens, normal colon, and colon cancer cell lines (LoVo, CaCo-2, SK-CO1, Colo205, and T284). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the ALPHALMAGER software. Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in the majority of the colon cancer tissues tested, but not in the normal colon tissues. Expression was also detected in the cell lines LoVo, CaCo-2, SK-CO1, Colo205, but not in the T284 cell line.

[0586] FIG. 20 shows 273P4B7 expression in ovary cancer patient specimens. First strand cDNA was prepared from a panel of ovarian cancer patient specimens, normal ovary and ovarian cancer cell lines (OV-1063, PA-1, SW626). Normalization was performed by PCR using primers to actin. Semi-quantitative PCR, using primers to 273P4B7, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the ALPHALMAGER software. Expression was recorded as absent, low, medium or high. Results show expression of 273P4B7 in the majority of ovary cancer tissues tested as well as in the cell lines, but not in normal ovary.

[0587] The restricted expression of 273P4B7 in normal tissues and the expression detected in cancer patient specimens suggest that 273P4B7 is a therapeutic target and a diagnostic marker for human cancers.

Example 5

Transcript Variants of 273P4B7

[0588] As used herein, the term variant comprises Transcript variants and Single Nucleotide Polymorphisms (SNPs). Transcript variants are variants of mature mRNA from the same gene which arise by alternative transcription or alternative splicing. Alternative transcripts are transcripts from the same gene but start transcription at different points. Splice variants are mRNA variants spliced differently from the same transcript. In eukaryotes, when a multi-exon gene is transcribed from genomic DNA, the initial RNA is spliced to produce functional mRNA, which has only exons and is used for translation into an amino acid sequence. Accordingly, a given gene can have zero to many alternative transcripts and each transcript can have zero to many splice variants. Each transcript variant has a unique exon makeup, and can have different coding and/or non-coding (5' or 3' end) portions, from the original transcript. Transcript variants can code for the same, similar or different proteins with the same or a similar function or can encode proteins with different functions, and can be expressed in the same tissue at the same time, or in different tissues at the same time, or in the same tissue at different times, or in different tissues at different times. Proteins encoded by transcript variants can have similar or different subcellular or extracellular localizations, e.g., secreted versus intracellular.

[0589] Transcript variants are identified by a variety of art-accepted methods. For example, alternative transcripts and splice variants are identified by full-length cloning experiments, or by use of full-length transcript and EST sequences. First, all human ESTs were grouped into clusters which show direct or indirect identity with each other. Second, ESTs in the same cluster were further grouped into sub-clusters and assembled into a consensus sequence. The original gene sequence is compared to the consensus sequence(s) or other full-length sequences. Each consensus sequence is a potential splice variant for that gene. Even when a variant is identified that is not yet a full-length clone, that portion of the variant is very useful as a research tool, e.g., for antigen generation and for further cloning of the full-length splice variant, using techniques known to those skilled in the art.

[0590] Moreover, computer programs are available to those skilled in the art that identify transcript variants based on genomic sequences. Genomic-based transcript variant identification programs include FgenesH (A. Salamov and V. Solovyev, "Ab initio gene finding in *Drosophila* genomic DNA," Genome Research. 2000 April; 10(4):516-22); Grail and Gen Scan. For a general discussion of splice variant identification protocols see., e.g., Southan, C., A genomic perspective on human proteases, FEBS Lett. 2001 Jun. 8; 498(2-3):214-8; de Souza, S. J., et al., Identification of human chromosome 22 transcribed sequences with ORF expressed sequence tags, Proc. Natl. Acad. Sci. USA. 2000 Nov. 7; 97(23):12690-3.

[0591] To further confirm the parameters of a transcript variant, a variety of techniques are available in the art, such as full-length cloning, proteomic validation, PCR-based validation, and 5'RACE validation, etc. (see e.g., Proteomic Validation: Brennan, S. O., et al., Albumin banks peninsula: a new termination variant characterized by electrospray

mass spectrometry, Biochem Biophys Acta. 1999 Aug. 17; 1433(1-2):321-6; Ferranti P, et al., Differential splicing of pre-messenger RNA produces multiple forms of mature caprine alpha(s1)-casein, Eur J. Biochem. 1997 Oct. 1; 249(1):1-7. For PCR-based Validation: Wellmann S, et al., Specific reverse transcription-PCR quantification of vascular endothelial growth factor (VEGF) splice variants by LightCycler technology, Clin Chem. 2001 April; 47(4):654-60; Jia, H. P., et al., Discovery of new human beta-defensins using a genomics-based approach, Gene. 2001 Jan. 24; 263(1-2):211-8. For PCR-based and 5'RACE Validation: Brigle, K. E., et al., Organization of the murine reduced folate carrier gene and identification of variant splice forms, Biochem Biophys Acta. 1997 Aug. 7; 1353(2): 191-8).

[0592] It is known in the art that genomic regions are modulated in cancers. When the genomic region to which a gene maps is modulated in a particular cancer, the alternative transcripts or splice variants of the gene are modulated as well. Disclosed herein is that 273P4B7 has a particular expression profile related to cancer (See, e.g., Table I). Alternative transcripts and splice variants of 273P4B7 are also be involved in cancers in the same or different tissues, thus serving as tumor-associated markers/antigens.

[0593] Using the full-length gene and EST sequences, four additional transcript variants were identified, designated as 273P4B7 v.2, v.9 and v.10. The boundaries of exons in the original transcript, 273P4B7 v.1 are shown in Table LI. The structures of the transcript variants are shown in FIG. 10. Variant 273P4B7 v.2 added 22 bases to the 5' end of exon1 and an additional exon in the first intron of variant v.1. Variants v.9 and v.10 were shorter and matched part of the last exon of v.1, with a few different base pairs. Tables LII(a)-(d) through LV(a)-(c) are set forth on a variant-by-variant bases. Tables LII(a)-(d) show nucleotide sequence of the transcript variants. Tables LIII(a)-(d) show the alignment of the transcript variant with nucleic acid sequence of 273P4B7 v.1. Table LIV(a)-(d) lay out amino acid translation of the transcript variant for the identified reading frame orientation. Table LV(a)-(d) display alignments of the amino acid sequence encoded by the splice variant with that of 273P4B7 v. 1.

Example 6

Single Nucleotide Polymorphisms of 273P4B7

[0594] A Single Nucleotide Polymorphism (SNP) is a single base pair variation in a nucleotide sequence at a specific location. At any given point of the genome, there are four possible nucleotide base pairs: A/T, C/G, G/C and T/A. Genotype refers to the specific base pair sequence of one or more locations in the genome of an individual. Haplotype refers to the base pair sequence of more than one location on the same DNA molecule (or the same chromosome in higher organisms), often in the context of one gene or in the context of several tightly linked genes. SNP that occurs on a cDNA is called cSNP. This cSNP may change amino acids of the protein encoded by the gene and thus change the functions of the protein. Some SNP cause inherited diseases; others contribute to quantitative variations in phenotype and reactions to environmental factors including diet and drugs among individuals. Therefore, SNP and/or combinations of alleles (called haplotypes) have many applications, including diagnosis of inherited diseases, determination of drug

reactions and dosage, identification of genes responsible for diseases, and analysis of the genetic relationship between individuals (P. Nowotny, J. M. Kwon and A. M. Goate, "SNP analysis to dissect human traits," *Curr. Opin. Neurobiol.* 2001 October; 11(5):637-641; M. Pirmohamed and B. K. Park, "Genetic susceptibility to adverse drug reactions," *Trends Pharmacol. Sci.* 2001 June; 22(6):298-305; J. H. Riley, C. J. Allan, E. Lai and A. Roses, "The use of single nucleotide polymorphisms in the isolation of common disease genes," *Pharmacogenomics*. 2000 February; 1(1):39-47; R. Judson, J. C. Stephens and A. Windemuth, "The predictive power of haplotypes in clinical response," *Pharmacogenomics*. 2000 February; 1(1): 15-26).

[0595] SNP are identified by a variety of art-accepted methods (P. Bean, "The promising voyage of SNP target discovery," *Am. Clin. Lab.* 2001 October-November; 20(9):18-20; K. M. Weiss, "In search of human variation," *Genome Res.* 1998 July; 8(7):691-697; M. M. She, "Enabling large-scale pharmacogenetic studies by high-throughput mutation detection and genotyping technologies," *Clin. Chem.* 2001 February; 47(2):164-172). For example, SNP can be identified by sequencing DNA fragments that show polymorphism by gel-based methods such as restriction fragment length polymorphism (RFLP) and denaturing gradient gel electrophoresis (DGGE). They can also be discovered by direct sequencing of DNA samples pooled from different individuals or by comparing sequences from different DNA samples. With the rapid accumulation of sequence data in public and private databases, one can discover SNP by comparing sequences using computer programs (Z. Gu, L. Hillier and P. Y. Kwok, "Single nucleotide polymorphism hunting in cyberspace," *Hum. Mutat.* 1998; 12(4):221-225). SNP can be verified and genotype or haplotype of an individual can be determined by a variety of methods including direct sequencing and high throughput microarrays (P. Y. Kwok, "Methods for genotyping single nucleotide polymorphisms," *Annu. Rev. Genomics Hum. Genet.* 2001; 2:235-258; M. Kokoris, K. Dix, K. Moynihan, J. Mathis, B. Erwin, P. Grass, B. Hines and A. Dueterhoeft, "High-throughput SNP genotyping with the Masscode system," *Mol. Diagn.* 2000 December; 5(4):329-340).

[0596] Using the methods described above, six SNP were identified in the transcript, 273P4B7 v. 1, as shown in Table LVI. The transcripts or proteins with alternative allele were designated as variant 273P4B7 v.3 through v.8, as shown in Table LVI and FIG. 12. These alleles of the SNP, though shown separately here, can occur in different combinations (haplotypes) and in any one of the transcript variants (such as 273P4B7 v.2, as listed in table LVI) that contains the site of the SNP, as laid out in FIGS. 11 and 12.

Example 7

Production of Recombinant 273P4B7 in Prokaryotic Systems

[0597] To express recombinant 273P4B7 and 273P4B7 variants in prokaryotic cells, the full or partial length 273P4B7 and 273P4B7 variant cDNA sequences are cloned into any one of a variety of expression vectors known in the art. One or more of the following regions of 273P4B7 variants are expressed: the full length sequence presented in FIGS. 2 and 3, or any 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,

19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more contiguous amino acids from 273P4B7, variants, or analogs thereof.

[0598] A. In Vitro Transcription and Translation Constructs:

[0599] pCRII: To generate 273P4B7 sense and anti-sense RNA probes for RNA in situ investigations, pCRII constructs (Invitrogen, Carlsbad Calif.) are generated encoding either all or fragments of the 273P4B7 cDNA. The pCRII vector has Sp6 and T7 promoters flanking the insert to drive the transcription of 273P4B7 RNA for use as probes in RNA in situ hybridization experiments. These probes are used to analyze the cell and tissue expression of 273P4B7 at the RNA level. Transcribed 273P4B7 RNA representing the cDNA amino acid coding region of the 273P4B7 gene is used in in vitro translation systems such as the TNT COUPLED RETICULOLYSATE SYSTEM (Promega, Corp., Madison, Wis.) to synthesize 273P4B7 protein.

[0600] B. Bacterial Constructs:

[0601] pGEX Constructs: To generate recombinant 273P4B7 proteins in bacteria that are fused to the Glutathione S-transferase (GST) protein, all or parts of the 273P4B7 cDNA protein coding sequence are cloned into the pGEX family of GST-fusion vectors (Amersham Pharmacia Biotech, Piscataway, N.J.). These constructs allow controlled expression of recombinant 273P4B7 protein sequences with GST fused at the amino-terminus and a six histidine epitope (6xHis) at the carboxyl-terminus. The GST and 6xHis tags permit purification of the recombinant fusion protein from induced bacteria with the appropriate affinity matrix and allow recognition of the fusion protein with anti-GST and anti-His antibodies. The 6xHis tag is generated by adding 6 histidine codons to the cloning primer at the 3' end, e.g., of the open reading frame (ORF). A proteolytic cleavage site, such as the PRECISION recognition site in pGEX-6P-1, may be employed such that it permits cleavage of the GST tag from 273P4B7-related protein. The ampicillin resistance gene and pBR322 origin permits selection and maintenance of the pGEX plasmids in *E. coli*.

[0602] pMAL Constructs: To generate, in bacteria, recombinant 273P4B7 proteins that are fused to maltose-binding protein (MBP), all or parts of the 273P4B7 cDNA protein coding sequence are fused to the MBP gene by cloning into the pMAL-c2x and pMAL-p2x vectors (New England Biolabs, Beverly, Mass.). These constructs allow controlled expression of recombinant 273P4B7 protein sequences with MBP fused at the amino-terminus and a 6xHis epitope tag at the carboxyl-terminus. The MBP and 6xHis tags permit purification of the recombinant protein from induced bacteria with the appropriate affinity matrix and allow recognition of the fusion protein with anti-MBP and anti-His antibodies. The 6xHis epitope tag is generated by adding 6 histidine codons to the 3' cloning primer. A Factor Xa recognition site permits cleavage of the pMAL tag from 273P4B7. The pMAL-c2x and pMAL-p2x vectors are optimized to express the recombinant protein in the cytoplasm or periplasm respectively. Periplasm expression enhances folding of proteins with disulfide bonds.

[0603] pET Constructs: To express 273P4B7 in bacterial cells, all or parts of the 273P4B7 cDNA protein coding sequence are cloned into the pET family of vectors

(Novagen, Madison, Wis.). These vectors allow tightly controlled expression of recombinant 273P4B7 protein in bacteria with and without fusion to proteins that enhance solubility, such as NusA and thioredoxin (Trx), and epitope tags, such as 6xHis and S-Tag™ that aid purification and detection of the recombinant protein. For example, constructs are made utilizing pET NusA fusion system 43.1 such that regions of the 273P4B7 protein are expressed as amino-terminal fusions to NusA.

[0604] C. Yeast Constructs:

[0605] pESC Constructs: To express 273P4B7 in the yeast species *Saccharomyces cerevisiae* for generation of recombinant protein and functional studies, all or parts of the 273P4B7 cDNA protein coding sequence are cloned into the pESC family of vectors each of which contain 1 of 4 selectable markers, HIS3, TRP1, LEU2, and URA3 (Stratagene, La Jolla, Calif.). These vectors allow controlled expression from the same plasmid of up to 2 different genes or cloned sequences containing either FLAG or Myc epitope tags in the same yeast cell. This system is useful to confirm protein-protein interactions of 273P4B7. In addition, expression in yeast yields similar post-translational modifications, such as glycosylations and phosphorylations that are found when expressed in eukaryotic cells.

[0606] pESP Constructs: To express 273P4B7 in the yeast species *Saccharomyces pombe*, all or parts of the 273P4B7 cDNA protein coding sequence are cloned into the pESP family of vectors. These vectors allow controlled high level of expression of a 273P4B7 protein sequence that is fused at either the amino terminus or at the carboxyl terminus to GST which aids purification of the recombinant protein. A FLAG epitope tag allows detection of the recombinant protein with anti-FLAG antibody.

Example 8

Production of Recombinant 273P4B7 in Higher Eukaryotic Systems

[0607] A. Mammalian Constructs:

[0608] To express recombinant 273P4B7 in eukaryotic cells, the full or partial length 273P4B7 cDNA sequences were cloned into any one of a variety of expression vectors known in the art. One or more of the following regions of 273P4B7 were expressed in these constructs, amino acids 1 to 1250 or any 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more contiguous amino acids from 273P4B7 v.1, v.4, v.5, and v.6; amino acids 1 to 1127 of v.2 or any 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more contiguous amino acids from 273P4B7 variants, or analogs thereof.

[0609] The constructs can be transfected into any one of a wide variety of mammalian cells such as 293T cells. Transfected 293T cell lysates can be probed with the anti-273P4B7 polyclonal serum, described herein.

[0610] pcDNA4/HisMax Constructs: To express 273P4B7 in mammalian cells, a 273P4B7 ORF, or portions thereof, of 273P4B7 are cloned into pcDNA4/HisMax Version A (Invitrogen, Carlsbad, Calif.). Protein expression is driven from the cytomegalovirus (CMV) promoter and the SP16 translational enhancer. The recombinant protein has Xpress™

and six histidine (6xHis) epitopes fused to the amino-terminus. The pcDNA4/HisMax vector also contains the bovine growth hormone (BGH) polyadenylation signal and transcription termination sequence to enhance mRNA stability along with the SV40 origin for episomal replication and simple vector rescue in cell lines expressing the large T antigen. The Zeocin resistance gene allows for selection of mammalian cells expressing the protein and the ampicillin resistance gene and ColE1 origin permits selection and maintenance of the plasmid in *E. coli*.

[0611] pcDNA3.1MycHis Constructs: To express 273P4B7 in mammalian cells, 273P4B7 ORF, or portions thereof, of 273P4B7 with a consensus Kozak translation initiation site was cloned into pcDNA3.1/MycHis Version A (Invitrogen, Carlsbad, Calif.). Protein expression is driven from the cytomegalovirus (CMV) promoter. The recombinant proteins have the myc epitope and 6xHis epitope fused to the carboxyl-terminus. The pcDNA3.1/MycHis vector also contains the bovine growth hormone (BGH) polyadenylation signal and transcription termination sequence to enhance mRNA stability, along with the SV40 origin for episomal replication and simple vector rescue in cell lines expressing the large T antigen. The Neomycin resistance gene can be used, as it allows for selection of mammalian cells expressing the protein and the ampicillin resistance gene and ColE1 origin permits selection and maintenance of the plasmid in *E. coli*.

[0612] pcDNA3.1CT-GFP-TOPO Construct: To express 273P4B7 in mammalian cells and to allow detection of the recombinant proteins using fluorescence, a 273P4B7 ORF, or portions thereof, with a consensus Kozak translation initiation site are cloned into pcDNA3.1/CT-GFP-TOPO (Invitrogen, CA). Protein expression is driven from the cytomegalovirus (CMV) promoter. The recombinant proteins have the Green Fluorescent Protein (GFP) fused to the carboxyl-terminus facilitating non-invasive, in vivo detection and cell biology studies. The pcDNA3.1CT-GFP-TOPO vector also contains the bovine growth hormone (BGH) polyadenylation signal and transcription termination sequence to enhance mRNA stability along with the SV40 origin for episomal replication and simple vector rescue in cell lines expressing the large T antigen. The Neomycin resistance gene allows for selection of mammalian cells that express the protein, and the ampicillin resistance gene and ColE1 origin permits selection and maintenance of the plasmid in *E. coli*. Additional constructs with an amino-terminal GFP fusion are made in pcDNA3.1/NT-GFP-TOPO spanning the entire length of a 273P4B7 protein.

[0613] PAPtag: A 273P4B7 ORF, or portions thereof, is cloned into pAPtag-5 (GenHunter Corp. Nashville, Tenn.). This construct generates an alkaline phosphatase fusion at the carboxyl-terminus of a 273P4B7 protein while fusing the IgG.kappa. signal sequence to the amino-terminus. Constructs are also generated in which alkaline phosphatase with an amino-terminal IgG.kappa. signal sequence is fused to the amino-terminus of a 273P4B7 protein. The resulting recombinant 273P4B7 proteins are optimized for secretion into the media of transfected mammalian cells and can be used to identify proteins such as ligands or receptors that interact with 273P4B7 proteins. Protein expression is driven from the CMV promoter and the recombinant proteins also contain myc and 6xHis epitopes fused at the carboxyl-terminus that facilitates detection and purification. The Zeo-

cin resistance gene present in the vector allows for selection of mammalian cells expressing the recombinant protein and the ampicillin resistance gene permits selection of the plasmid in *E. coli*.

[0614] pTag5: A 273P4B7 ORF, or portions thereof, is cloned into pTag-5. This vector is similar to pAptag but without the alkaline phosphatase fusion. This construct generates 273P4B7 protein with an amino-terminal IgG.kappa. signal sequence and myc and 6xHis epitope tags at the carboxyl-terminus that facilitate detection and affinity purification. The resulting recombinant 273P4B7 protein is optimized for secretion into the media of transfected mammalian cells, and is used as immunogen or ligand to identify proteins such as ligands or receptors that interact with the 273P4B7 proteins. Protein expression is driven from the CMV promoter. The Zeocin resistance gene present in the vector allows for selection of mammalian cells expressing the protein, and the ampicillin resistance gene permits selection of the plasmid in *E. coli*.

[0615] PsecFc: A 273P4B7 ORF, or portions thereof, is also cloned into psecFc. The psecFc vector was assembled by cloning the human immunoglobulin G1 (IgG) Fc (hinge, CH2, CH3 regions) into pSecTag2 (Invitrogen, California). This construct generates an IgG1 Fc fusion at the carboxyl-terminus of the 273P4B7 proteins, while fusing the IgGK signal sequence to N-terminus. 273P4B7 fusions utilizing the murine IgG1 Fc region are also used. The resulting recombinant 273P4B7 proteins are optimized for secretion into the media of transfected mammalian cells, and can be used as immunogens or to identify proteins such as ligands or receptors that interact with 273P4B7 protein. Protein expression is driven from the CMV promoter. The hygromycin resistance gene present in the vector allows for selection of mammalian cells that express the recombinant protein, and the ampicillin resistance gene permits selection of the plasmid in *E. coli*. 1

[0616] pSR.alpha. Constructs: To generate mammalian cell lines that express 273P4B7 constitutively, 273P4B7 ORF, or portions thereof, of 273P4B7 were cloned into pSR.alpha. constructs. Amphotropic and ecotropic retroviruses were generated by transfection of pSR.alpha. constructs into the 293T-10A1 packaging line or co-transfection of pSR.alpha. and a helper plasmid (containing deleted packaging sequences) into the 293 cells, respectively. The retrovirus is used to infect a variety of mammalian cell lines, resulting in the integration of the cloned gene, 273P4B7, into the host cell-lines. Protein expression is driven from a long terminal repeat (LTR). The Neomycin resistance gene present in the vector allows for selection of mammalian cells that express the protein, and the ampicillin resistance gene and ColE1 origin permit selection and maintenance of the plasmid in *E. coli*. The retroviral vectors can thereafter be used for infection and generation of various cell lines using, for example, PC3, NIH 3T3, TsuPr1, 293 or rat-1 cells.

[0617] Additional pSR.alpha. constructs were made that fuse an epitope tag such as the FLAG™ tag to the carboxyl-terminus of 273P4B7 sequences to allow detection using anti-Flag antibodies. For example, the FLAG™ sequence 5' gat tac aag gat gac gac gat aag 3' (SEQ ID NO: 42) is added to cloning primer at the 3' end of the ORF. Additional pSR.alpha. constructs are made to produce both amino-terminal and carboxyl-terminal GFP and myc/6xHis fusion proteins of the full-length 273P4B7 proteins.

[0618] Additional Viral Vectors: Additional constructs are made for viral-mediated delivery and expression of 273P4B7. High virus titer leading to high level expression of 273P4B7 is achieved in viral delivery systems such as adenoviral vectors and herpes amplicon vectors. A 273P4B7 coding sequences or fragments thereof are amplified by PCR and subcloned into the AdEasy shuttle vector (Stratagene). Recombination and virus packaging are performed according to the manufacturer's instructions to generate adenoviral vectors. Alternatively, 273P4B7 coding sequences or fragments thereof are cloned into the HSV-1 vector (Imgenex) to generate herpes viral vectors. The viral vectors are thereafter used for infection of various cell lines such as PC3, NIH 3T3, 293 or rat-1 cells.

[0619] Regulated Expression Systems: To control expression of 273P4B7 in mammalian cells, coding sequences of 273P4B7, or portions thereof, are cloned into regulated mammalian expression systems such as the T-Rex System (Invitrogen), the GeneSwitch System (Invitrogen) and the tightly-regulated Ecdysone System (Stratagene). These systems allow the study of the temporal and concentration dependent effects of recombinant 273P4B7. These vectors are thereafter used to control expression of 273P4B7 in various cell lines such as PC3, NIH 3T3, 293 or rat-1 cells.

[0620] B. Baculovirus Expression Systems

[0621] To generate recombinant 273P4B7 proteins in a baculovirus expression system, 273P4B7 ORF, or portions thereof, are cloned into the baculovirus transfer vector pBlueBac 4.5 (Invitrogen), which provides a His-tag at the N-terminus. Specifically, pBlueBac-273P4B7 is co-transfected with helper plasmid pBac-N-Blue (Invitrogen) into SF9 (*Spodoptera frugiperda*) insect cells to generate recombinant baculovirus (see Invitrogen instruction manual for details). Baculovirus is then collected from cell supernatant and purified by plaque assay.

[0622] Recombinant 273P4B7 protein is then generated by infection of HighFive insect cells (Invitrogen) with purified baculovirus. Recombinant 273P4B7 protein can be detected using anti-273P4B7 or anti-His-tag antibody. 273P4B7 protein can be purified and used in various cell-based assays or as immunogen to generate polyclonal and monoclonal antibodies specific for 273P4B7.

Example 9

Antigenicity Profiles and Secondary Structure

[0623] FIG. 5, FIG. 6, FIG. 7, FIG. 8, and FIG. 9 depict graphically five amino acid profiles of 273P4B7 variant 1, each assessment available by accessing the ProtScale website located on the World Wide Web at (www.expasy.ch/cgi-bin/protscale.pl) on the ExPasy molecular biology server.

[0624] These profiles: FIG. 5, Hydrophilicity, (Hopp T. P., Woods K. R., 1981. Proc. Natl. Acad. Sci. U.S.A. 78:3824-3828); FIG. 6, Hydropathicity, (Kyte J., Doolittle R. F., 1982. J. Mol. Biol. 157:105-132); FIG. 7, Percentage Accessible Residues (Janin J., 1979 Nature 277:491-492); FIG. 8, Average Flexibility, (Bhaskaran R., and Ponnuswamy P. K., 1988. Int. J. Pept. Protein Res. 32:242-255); FIG. 9, Beta-turn (Deleage, G., Roux B. 1987 Protein Engineering 1:289-294); and optionally others available in the art, such as on the ProtScale website, were used to identify antigenic

regions of each of the 273P4B7 variant proteins. Each of the above amino acid profiles of 273P4B7 variants were generated using the following ProtScale parameters for analysis: 1) A window size of 9; 2) 100% weight of the window edges compared to the window center; and, 3) amino acid profile values normalized to lie between 0 and 1.

[0625] Hydrophilicity (FIG. 5), Hydropathicity (FIG. 6) and Percentage Accessible Residues (FIG. 7) profiles were used to determine stretches of hydrophilic amino acids (i.e., values greater than 0.5 on the Hydrophilicity and Percentage Accessible Residues profile, and values less than 0.5 on the Hydropathicity profile). Such regions are likely to be exposed to the aqueous environment, be present on the surface of the protein, and thus available for immune recognition, such as by antibodies.

[0626] Average Flexibility (FIG. 8) and Beta-turn (FIG. 9) profiles determine stretches of amino acids (i.e., values greater than 0.5 on the Beta-turn profile and the Average Flexibility profile) that are not constrained in secondary structures such as beta sheets and alpha helices. Such regions are also more likely to be exposed on the protein and thus accessible to immune recognition, such as by antibodies.

[0627] Antigenic sequences of the 273P4B7 variant proteins indicated, e.g., by the profiles set forth in FIG. 5, FIG. 6, FIG. 7, FIG. 8, and/or FIG. 9 are used to prepare immunogens, either peptides or nucleic acids that encode them, to generate therapeutic and diagnostic anti-273P4B7 antibodies. The immunogen can be any 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50 or more than 50 contiguous amino acids, or the corresponding nucleic acids that encode them, from the 273P4B7 protein variants listed in FIGS. 2 and 3. In particular, peptide immunogens of the invention can comprise, a peptide region of at least 5 amino acids of FIGS. 2 and 3 in any whole number increment that includes an amino acid position having a value greater than 0.5 in the Hydrophilicity profiles of FIG. 5; a peptide region of at least 5 amino acids of FIGS. 2 and 3 in any whole number increment that includes an amino acid position having a value less than 0.5 in the Hydropathicity profile of FIG. 6; a peptide region of at least 5 amino acids of FIGS. 2 and 3 in any whole number increment that includes an amino acid position having a value greater than 0.5 in the Percent Accessible Residues profiles of FIG. 7; a peptide region of at least 5 amino acids of FIGS. 2 and 3 in any whole number increment that includes an amino acid position having a value greater than 0.5 in the Average Flexibility profiles on FIG. 8; and, a peptide region of at least 5 amino acids of FIGS. 2 and 3 in any whole number increment that includes an amino acid position having a value greater than 0.5 in the Beta-turn profile of FIG. 9. Peptide immunogens of the invention can also comprise nucleic acids that encode any of the foregoing.

[0628] All immunogens of the invention, peptide or nucleic acid, can be embodied in human unit dose form, or comprised by a composition that includes a pharmaceutical excipient compatible with human physiology.

[0629] The secondary structure of 273P4B7 protein variant 1, namely the predicted presence and location of alpha helices, extended strands, and random coils, is predicted from the primary amino acid sequence using the HNN-Hierarchical Neural Network method (NPS@: Network

Protein Sequence Analysis TIBS 2000 March Vol. 25, No 3 [291]:147-150 Combet C., Blanchet C., Geourjon C. and Delage G.), accessed from the ExPasy molecular biology server located on the World Wide Web. The analysis indicates that 273P4B7 variant 1 is composed of 41.60% alpha helix, 11.12% extended strand, and 47.28% random coil (FIG. 13A).

[0630] Analysis for the potential presence of transmembrane domains in the 273P4B7 variant protein 1 was carried out using a variety of transmembrane prediction algorithms accessed from the ExPasy molecular biology server located on the World Wide Web. Shown graphically in FIG. 13B and FIG. 13C are the results of analysis of variant 1 using the TMpred program (FIG. 13B) and TMHMM program (FIG. 13C). The TMpred program predicts the presence of 2 transmembrane domains, whereas the TMHMM program does not predict transmembrane domains. Taken together with analysis using other programs summarized in Table VI and Table L, the data suggest that 273P4B7 is most likely a soluble protein.

Example 10

Generation of 273P4B7 Polyclonal Antibodies

[0631] Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. In addition to immunizing with a full length 273P4B7 protein variant, computer algorithms are employed in design of immunogens that, based on amino acid sequence analysis contain characteristics of being antigenic and available for recognition by the immune system of the immunized host (see the Example entitled "Antigenicity Profiles and Secondary Structure"). Such regions would be predicted to be hydrophilic, flexible, in beta-turn conformations, and be exposed on the surface of the protein (see, e.g., FIG. 5, FIG. 6, FIG. 7, FIG. 8, or FIG. 9 for amino acid profiles that indicate such regions of 273P4B7 protein variant 1).

[0632] For example, recombinant bacterial fusion proteins or peptides containing hydrophilic, flexible, beta-turn regions of 273P4B7 protein variants are used as antigens to generate polyclonal antibodies in New Zealand White rabbits or monoclonal antibodies as described (see the Example entitled "Generation of 273P4B7 Monoclonal Antibodies (mAbs)"). For example, in 273P4B7 variant 1, such regions include, but are not limited to, amino acids 1-16, amino acids 23-43, amino acids 170-194, amino acids 324-368, amino acids 430-461, amino acids 735-753, amino acids 774-792, amino acids 1002-1043, and amino acids 1105-1158. It is useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to, keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. In one embodiment, a peptide encoding amino acids 1-16 of 273P4B7 variant 1 was conjugated to KLH and used to immunize a rabbit. Alternatively the immunizing agent may include all or portions of the 273P4B7 variant proteins, analogs or fusion proteins thereof. For example, the 273P4B7 variant 1 amino acid sequence can be fused using recombinant DNA techniques

to any one of a variety of fusion protein partners that are well known in the art, such as glutathione-S-transferase (GST) and HIS tagged fusion proteins. In another embodiment, amino acids 1000-1250 of 273P4B7 variant 1 is fused to GST using recombinant techniques and the pGEX expression vector, expressed, purified and used to immunize a rabbit. Such fusion proteins are purified from induced bacteria using the appropriate affinity matrix.

[0633] Other recombinant bacterial fusion proteins that may be employed include maltose binding protein, LacZ, thioredoxin, NusA, or an immunoglobulin constant region (see the Example entitled "Production of 273P4B7 in Prokaryotic Systems" and Current Protocols In Molecular Biology, Volume 2, Unit 16, Frederick M. Ausubul et al. eds., 1995; Linsley, P. S., Brady, W., Urnes, M., Grosmaire, L., Damle, N., and Ledbetter, L. (1991) J. Exp. Med. 174, 561-566).

[0634] In addition to bacterial derived fusion proteins, mammalian expressed protein antigens are also used. These antigens are expressed from mammalian expression vectors such as the Tag5 and Fc-fusion vectors (see the Example entitled "Production of Recombinant 273P4B7 in Eukaryotic Systems"), and retain post-translational modifications such as glycosylations found in native protein. In one embodiment, the complete cDNA of 273P4B7 variant 1 is cloned into the Tag5 mammalian secretion vector, and expressed in 293T cells. The recombinant protein is purified by metal chelate chromatography from tissue culture supernatants of 293T cells stably expressing the recombinant vector. The purified Tag5 273P4B7 protein is then used as immunogen.

[0635] During the immunization protocol, it is useful to mix or emulsify the antigen in adjuvants that enhance the immune response of the host animal. Examples of adjuvants include, but are not limited to, complete Freund's adjuvant (CFA) and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

[0636] In a typical protocol, rabbits are initially immunized subcutaneously with up to 200 μ g, typically 100-200 μ g, of fusion protein or peptide conjugated to KLH mixed in complete Freund's adjuvant (CFA). Rabbits are then injected subcutaneously every two weeks with up to 200 μ g, typically 100-200 μ g, of the immunogen in incomplete Freund's adjuvant (IFA). Test bleeds are taken approximately 7-10 days following each immunization and used to monitor the titer of the antiserum by ELISA.

[0637] To test reactivity and specificity of immune serum, such as the rabbit serum derived from immunization with the GST-fusion of 273P4B7 variant 1 protein, the full-length 273P4B7 variant 1 cDNA is cloned into pcDNA 3.1 myc-his expression vector (Invitrogen, see the Example entitled "Production of Recombinant 273P4B7 in Eukaryotic Systems"). After transfection of the constructs into 293T cells, cell lysates are probed with the anti-273P4B7 serum and with anti-His antibody (Santa Cruz Biotechnologies, Santa Cruz, Calif.) to determine specific reactivity to denatured 273P4B7 protein using the Western blot technique. In addition, the immune serum is tested by fluorescence microscopy, flow cytometry and immunoprecipitation against 293T and other recombinant 273P4B7-expressing cells to determine specific recognition of native protein. Western blot, immunoprecipitation, fluorescent microscopy, and flow

cytometric techniques using cells that endogenously express 273P4B7 are also carried out to test reactivity and specificity.

[0638] Anti-serum from rabbits immunized with 273P4B7 variant fusion proteins, such as GST and MBP fusion proteins, are purified by depletion of antibodies reactive to the fusion partner sequence by passage over an affinity column containing the fusion partner either alone or in the context of an irrelevant fusion protein. For example, anti-serum derived from a GST-273P4B7 variant 1 fusion protein is first purified by passage over a column of GST protein covalently coupled to AffiGel matrix (BioRad, Hercules, Calif.). The antiserum is then affinity purified by passage over a column composed of a MBP-273P4B7 fusion protein covalently coupled to Affigel matrix. The serum is then further purified by protein G affinity chromatography to isolate the IgG fraction. Sera from other His-tagged antigens and peptide immunized rabbits as well as fusion partner depleted sera are affinity purified by passage over a column matrix composed of the original protein immunogen or free peptide.

Example 11

Generation of 273P4B7 Monoclonal Antibodies (mAbs)

[0639] In one embodiment, therapeutic mAbs to 273P4B7 variants comprise those that react with epitopes specific for each variant protein or specific to sequences in common between the variants that would disrupt or modulate the biological function of the 273P4B7 variants, for example those that would disrupt the interaction with ligands and binding partners. Immunogens for generation of such mAbs include those designed to encode or contain the entire 273P4B7 protein variant sequence, regions predicted to contain functional motifs, and regions of the 273P4B7 protein variants predicted to be antigenic from computer analysis of the amino acid sequence (see, e.g., FIG. 5, FIG. 6, FIG. 7, FIG. 8, or FIG. 9, and the Example entitled "Antigenicity Profiles"). Immunogens include peptides, recombinant bacterial proteins, and mammalian expressed Tag 5 proteins and human and murine IgG FC fusion proteins. In addition, cells engineered to express high levels of a respective 273P4B7 variant, such as 293T-273P4B7 variant 1 or 300.19-273P4B7 variant 1 murine Pre-B cells, are used to immunize mice.

[0640] To generate mAbs to a 273P4B7 variant, mice are first immunized intraperitoneally (IP) with, typically, 10-50 μ g of protein immunogen or 10^7 273P4B7-expressing cells mixed in complete Freund's adjuvant. Mice are then subsequently immunized IP every 2-4 weeks with, typically, 10-50 μ g of protein immunogen or 10^7 cells mixed in incomplete Freund's adjuvant. Alternatively, MPL-TDM adjuvant is used in immunizations. In addition to the above protein and cell-based immunization strategies, a DNA-based immunization protocol is employed in which a mammalian expression vector encoding a 273P4B7 variant sequence is used to immunize mice by direct injection of the plasmid DNA. For example, the complete cDNA of 273P4B7 of variant 1 is cloned into the Tag5 mammalian secretion vector and the recombinant vector will then be used as immunogen. In another example the same amino acids are cloned into an Fc-fusion secretion vector in which

the 273P4B7 variant 2 sequence is fused at the amino-terminus to an IgK leader sequence and at the carboxyl-terminus to the coding sequence of the human or murine IgG Fc region. This recombinant vector is then used as immunogen. The plasmid immunization protocols are used in combination with purified proteins expressed from the same vector and with cells expressing the respective 273P4B7 variant.

[0641] During the immunization protocol, test bleeds are taken 7-10 days following an injection to monitor titer and specificity of the immune response. Once appropriate reactivity and specificity is obtained as determined by ELISA, Western blotting, immunoprecipitation, fluorescence microscopy, and flow cytometric analyses, fusion and hybridoma generation is then carried out with established procedures well known in the art (see, e.g., Harlow and Lane, 1988).

[0642] In one embodiment for generating 273P4B7 monoclonal antibodies, a GST-fusion of variant 1 antigen encoding amino acids 1000-1250 is expressed and purified from bacteria. Balb C mice are initially immunized intraperitoneally with 25 µg of the GST-273P4B7 variant 1 protein mixed in complete Freund's adjuvant. Mice are subsequently immunized every two weeks with 25 µg of the antigen mixed in incomplete Freund's adjuvant for a total of three immunizations. ELISA using the GST-fusion antigen and a cleavage product from which the GST portion is removed determines the titer of serum from immunized mice. Reactivity and specificity of serum to full length 273P4B7 variant 1 protein is monitored by Western blotting, immunoprecipitation and flow cytometry using 293T cells transfected with an expression vector encoding the 273P4B7 variant 1 cDNA (see e.g., the Example entitled "Production of Recombinant 273P4B7 in Eukaryotic Systems"). Other recombinant 273P4B7 variant 1-expressing cells or cells endogenously expressing 273P4B7 variant 1 are also used. Mice showing the strongest reactivity are rested and given a final injection of antigen in PBS and then sacrificed four days later. The spleens of the sacrificed mice are harvested and fused to SPO/2 myeloma cells using standard procedures (Harlow and Lane, 1988). Supernatants from HAT selected growth wells are screened by ELISA, Western blot, immunoprecipitation, fluorescent microscopy, and flow cytometry to identify 273P4B7 specific antibody-producing clones. The binding affinity of a 273P4B7 variant monoclonal antibody is determined using standard technologies. Affinity measurements quantify the strength of antibody to epitope binding and are used to help define which 273P4B7 variant monoclonal antibodies preferred for diagnostic or therapeutic use, as appreciated by one of skill in the art. The BIAcore system (Uppsala, Sweden) is a preferred method for determining binding affinity. The BIAcore system uses surface plasmon resonance (SPR, Welford K. 1991, Opt. Quant. Elect. 23:1; Morton and Myszk, 1998, Methods in Enzymology 295: 268) to monitor biomolecular interactions in real time. BIAcore analysis conveniently generates association rate constants, dissociation rate constants, equilibrium dissociation constants, and affinity constants.

Example 12

HLA Class I and Class II Binding Assays

[0643] HLA class I and class II binding assays using purified HLA molecules are performed in accordance with

disclosed protocols (e.g., PCT publications WO 94/20127 and WO 94/03205; Sidney et al., Current Protocols in Immunology 18.3.1 (1998); Sidney, et al., J. Immunol. 154:247 (1995); Sette, et al., Mol. Immunol. 31:813 (1994)). Briefly, purified MHC molecules (5 to 500 nM) are incubated with various unlabeled peptide inhibitors and 1-10 nM ¹²⁵I-radiolabeled probe peptides as described. Following incubation, MHC-peptide complexes are separated from free peptide by gel filtration and the fraction of peptide bound is determined. Typically, in preliminary experiments, each MHC preparation is titrated in the presence of fixed amounts of radiolabeled peptides to determine the concentration of HLA molecules necessary to bind 10-20% of the total radioactivity. All subsequent inhibition and direct binding assays are performed using these HLA concentrations.

[0644] Since under these conditions [label]<[HLA] and IC₅₀.50.gtoeq[HLA], the measured IC₅₀ values are reasonable approximations of the true KD values. Peptide inhibitors are typically tested at concentrations ranging from 120 µg/ml to 1.2 ng/ml, and are tested in two to four completely independent experiments. To allow comparison of the data obtained in different experiments, a relative binding figure is calculated for each peptide by dividing the IC₅₀ of a positive control for inhibition by the IC₅₀ for each tested peptide (typically unlabeled versions of the radiolabeled probe peptide). For database purposes, and inter-experiment comparisons, relative binding values are compiled. These values can subsequently be converted back into IC₅₀ nM values by dividing the IC₅₀ nM of the positive controls for inhibition by the relative binding of the peptide of interest. This method of data compilation is accurate and consistent for comparing peptides that have been tested on different days, or with different lots of purified MHC.

[0645] Binding assays as outlined above may be used to analyze HLA supermotif and/or HLA motif-bearing peptides (see Table IV).

Example 13

Identification of HLA Supermotif- and Motif-Bearing CTL Candidate Epitopes

[0646] HLA vaccine compositions of the invention can include multiple epitopes. The multiple epitopes can comprise multiple HLA supermotifs or motifs to achieve broad population coverage. This example illustrates the identification and confirmation of supermotif- and motif-bearing epitopes for the inclusion in such a vaccine composition. Calculation of population coverage is performed using the strategy described below.

[0647] Computer Searches and Algorithms for Identification of Supermotif and/or Motif-Bearing Epitopes

[0648] The searches performed to identify the motif-bearing peptide sequences in the Example entitled "Antigenicity Profiles" and Tables VIII-XXI and XXII-XLIX employ the protein sequence data from the gene product of 273P4B7 set forth in FIGS. 2 and 3, the specific search peptides used to generate the tables are listed in Table VII.

[0649] Computer searches for epitopes bearing HLA Class I or Class II supermotifs or motifs are performed as follows. All translated 273P4B7 protein sequences are analyzed using a text string search software program to identify

potential peptide sequences containing appropriate HLA binding motifs; such programs are readily produced in accordance with information in the art in view of known motif/supermotif disclosures. Furthermore, such calculations can be made mentally.

[0650] Identified A2-, A3-, and DR-supermotif sequences are scored using polynomial algorithms to predict their capacity to bind to specific HLA-Class I or Class II molecules. These polynomial algorithms account for the impact of different amino acids at different positions, and are essentially based on the premise that the overall affinity (or AG) of peptide-HLA molecule interactions can be approximated as a linear polynomial function of the type:

$$\Delta G' = a_1 x_1 + a_2 x_2 + \dots + a_n x_n$$

[0651] where a_{ji} is a coefficient which represents the effect of the presence of a given amino acid (j) at a given position (i) along the sequence of a peptide of n amino acids. The crucial assumption of this method is that the effects at each position are essentially independent of each other (i.e., independent binding of individual side-chains). When residue j occurs at position i in the peptide, it is assumed to contribute a constant amount j_i to the free energy of binding of the peptide irrespective of the sequence of the rest of the peptide.

[0652] The method of derivation of specific algorithm coefficients has been described in Gulukota et al., J. Mol. Biol. 267:1258-126, 1997; (see also Sidney et al., Human Immunol. 45:79-93, 1996; and Southwood et al., J. Immunol. 160:3363-3373, 1998). Briefly, for all i positions, anchor and non-anchor alike, the geometric mean of the average relative binding (ARB) of all peptides carrying j is calculated relative to the remainder of the group, and used as the estimate of j_i . For Class II peptides, if multiple alignments are possible, only the highest scoring alignment is utilized, following an iterative procedure. To calculate an algorithm score of a given peptide in a test set, the ARB values corresponding to the sequence of the peptide are multiplied. If this product exceeds a chosen threshold, the peptide is predicted to bind. Appropriate thresholds are chosen as a function of the degree of stringency of prediction desired.

Selection of HLA-A2 Supertype Cross-Reactive Peptides

[0653] Protein sequences from 273P4B7 are scanned utilizing motif identification software, to identify 8-, 9-10- and 11-mer sequences containing the HLA-A2-supermotif main anchor specificity. Typically, these sequences are then scored using the protocol described above and the peptides corresponding to the positive-scoring sequences are synthesized and tested for their capacity to bind purified HLA-A*0201 molecules in vitro (HLA-A*0201 is considered a prototype A2 supertype molecule).

[0654] These peptides are then tested for the capacity to bind to additional A2-supertype molecules (A*0202, A*0203, A*0206, and A*6802). Peptides that bind to at least three of the five A2-supertype alleles tested are typically deemed A2-supertype cross-reactive binders. Preferred peptides bind at an affinity equal to or less than 500 nM to three or more HLA-A2 supertype molecules.

Selection of HLA-A3 Supermotif-Bearing Epitopes

[0655] The 273P4B7 protein sequence(s) scanned above is also examined for the presence of peptides with the HLA-

A3-supermotif primary anchors. Peptides corresponding to the HLA A3 supermotif-bearing sequences are then synthesized and tested for binding to HLA-A*0301 and HLA-A*1101 molecules, the molecules encoded by the two most prevalent A3-supertype alleles. The peptides that bind at least one of the two alleles with binding affinities of ≤ 500 nM, often ≤ 200 nM, are then tested for binding cross-reactivity to the other common A3-supertype alleles (e.g., A*3101, A*3301, and A*6801) to identify those that can bind at least three of the five HLA-A3-supertype molecules tested.

[0656] Selection of HLA-B7 Supermotif Bearing Epitopes

[0657] The 273P4B7 protein(s) scanned above is also analyzed for the presence of 8-, 9-10-, or 11-mer peptides with the HLA-B7-supermotif. Corresponding peptides are synthesized and tested for binding to HLA-B*0702, the molecule encoded by the most common B7-supertype allele, (i.e., the prototype B7 supertype allele). Peptides binding B*0702 with IC₅₀ of ≤ 500 nM are identified using standard methods. These peptides are then tested for binding to other common B7-supertype molecules (e.g., B*3501, B*5101, B*5301, and B*5401). Peptides capable of binding to three or more of the five B7-supertype alleles tested are thereby identified.

Selection of A1 and A24 Motif-Bearing Epitopes

[0658] To further increase population coverage, HLA-A1 and -A24 epitopes can also be incorporated into vaccine compositions. An analysis of the 273P4B7 protein can also be performed to identify HLA-A1- and A24-motif-containing sequences.

[0659] High affinity and/or cross-reactive binding epitopes that bear other motif and/or supermotifs are identified using analogous methodology.

Example 14

Confirmation of Immunogenicity

[0660] Cross-reactive candidate CTL A2-supermotif-bearing peptides that are identified as described herein are selected to confirm in vitro immunogenicity. Confirmation is performed using the following methodology:

Target Cell Lines for Cellular Screening:

[0661] The 221A2.1 cell line, produced by transferring the HLA-A2.1 gene into the HLA-A, -B, -C null mutant human B-lymphoblastoid cell line 721.221, is used as the peptide-loaded target to measure activity of HLA-A2.1-restricted CTL. This cell line is grown in RPMI-1640 medium supplemented with antibiotics, sodium pyruvate, nonessential amino acids and 10% (v/v) heat inactivated FCS. Cells that express an antigen of interest, or transfectants comprising the gene encoding the antigen of interest, can be used as target cells to confirm the ability of peptide-specific CTLs to recognize endogenous antigen.

Primary CTL Induction Cultures:

[0662] Generation of Dendritic Cells (DC): PBMCs are thawed in RPMI with 30 μ g/ml DNase, washed twice and resuspended in complete medium (RPMI-1640 plus 5% AB human serum, non-essential amino acids, sodium pyruvate, L-glutamine and penicillin/streptomycin). The monocytes

are purified by plating 10×10^6 PBMC/well in a 6-well plate. After 2 hours at 37°C ., the non-adherent cells are removed by gently shaking the plates and aspirating the supernatants. The wells are washed a total of three times with 3 ml RPMI to remove most of the non-adherent and loosely adherent cells. Three ml of complete medium containing 50 ng/ml of GM-CSF and 1,000 U/ml of IL-4 are then added to each well. TNF.alpha. is added to the DCs on day 6 at 75 ng/ml and the cells are used for CTL induction cultures on day 7.

[0663] Induction of CTL with DC and Peptide: CD8+ T-cells are isolated by positive selection with Dynal immunomagnetic beads (DYNABEADS M-450) and the DETACHABEAD reagent. Typically about $200\text{--}250 \times 10^6$ PBMC are processed to obtain 24×10^6 CD8+ T-cells (enough for a 48-well plate culture). Briefly, the PBMCs are thawed in RPMI with 30 $\mu\text{g/ml}$ DNase, washed once with PBS containing 1% human AB serum and resuspended in PBS/1% AB serum at a concentration of 20×10^6 cells/ml. The magnetic beads are washed 3 times with PBS/AB serum, added to the cells (140 μl beads/ 20×10^6 cells) and incubated for 1 hour at 4°C . with continuous mixing. The beads and cells are washed 4 $\times$ with PBS/AB serum to remove the nonadherent cells and resuspended at 100×10^6 cells/ml (based on the original cell number) in PBS/AB serum containing 100 $\mu\text{l/ml}$ DETACHA-BEAD reagent and 30 $\mu\text{g/ml}$ DNase. The mixture is incubated for 1 hour at room temperature with continuous mixing. The beads are washed again with PBS/AB/DNase to collect the CD8+ T-cells. The DC are collected and centrifuged at 1300 rpm for 5-7 minutes, washed once with PBS with 1% BSA, counted and pulsed with 40 $\mu\text{g/ml}$ of peptide at a cell concentration of $1\text{--}2 \times 10^6/\text{ml}$ in the presence of 3 $\mu\text{g/ml}$ 92-microglobulin for 4 hours at 20°C . The DC are then irradiated (4,200 rads), washed 1 time with medium and counted again.

[0664] Setting up induction cultures: 0.25 ml cytokine-generated DC (at 1×10^5 cells/ml) are co-cultured with 0.25 ml of CD8+ T-cells (at 2×10^6 cell/ml) in each well of a 48-well plate in the presence of 10 ng/ml of IL-7. Recombinant human IL-10 is added the next day at a final concentration of 10 ng/ml and rhuman IL-2 is added 48 hours later at 10 IU/ml.

[0665] Restimulation of the induction cultures with peptide-pulsed adherent cells: Seven and fourteen days after the primary induction, the cells are restimulated with peptide-pulsed adherent cells. The PBMCs are thawed and washed twice with RPMI and DNase. The cells are resuspended at 5×10^6 cells/ml and irradiated at ~ 4200 rads. The PBMCs are plated at 2×10^6 in 0.5 ml complete medium per well and incubated for 2 hours at 37°C . The plates are washed twice with RPMI by tapping the plate gently to remove the nonadherent cells and the adherent cells pulsed with 10 $\mu\text{g/ml}$ of peptide in the presence of 3 $\mu\text{g/ml}$ β_2 microglobulin in 0.25 ml RPMI/5% AB per well for 2 hours at 37°C . Peptide solution from each well is aspirated and the wells are washed once with RPMI. Most of the media is aspirated from the induction cultures (CD8+ cells) and brought to 0.5 ml with fresh media. The cells are then transferred to the wells containing the peptide-pulsed adherent cells. Twenty four hours later recombinant human IL-10 is added at a final concentration of 10 ng/ml and recombinant human IL2 is added the next day and again 2-3 days later at 501 U/ml (Tsai et al., Critical Reviews in Immunology 18(1-2):65-75,

1998). Seven days later, the cultures are assayed for CTL activity in a ^{51}Cr release assay. In some experiments the cultures are assayed for peptide-specific recognition in the *in situ* IFN γ ELISA at the time of the second restimulation followed by assay of endogenous recognition 7 days later. After expansion, activity is measured in both assays for a side-by-side comparison.

Measurement of CTL Lytic Activity by ^{51}Cr Release.

[0666] Seven days after the second restimulation, cytotoxicity is determined in a standard (5 hr) ^{51}Cr release assay by assaying individual wells at a single E:T. Peptide-pulsed targets are prepared by incubating the cells with 10 $\mu\text{g/ml}$ peptide overnight at 37°C .

[0667] Adherent target cells are removed from culture flasks with trypsin-EDTA. Target cells are labeled with 200 μCi of ^{51}Cr sodium chromate (Dupont, Wilmington, Del.) for 1 hour at 37°C . Labeled target cells are resuspended at 10^6 per ml and diluted 1:10 with K562 cells at a concentration of $3.3 \times 10^6/\text{ml}$ (an NK-sensitive erythroblastoma cell line used to reduce non-specific lysis). Target cells (100 μl) and effectors (100 μl) are plated in 96 well round-bottom plates and incubated for 5 hours at 37°C . At that time, 100 μl of supernatant are collected from each well and percent lysis is determined according to the formula:

$$\frac{[(\text{cpm of the test sample} - \text{cpm of the spontaneous } ^{51}\text{Cr release sample}) / (\text{cpm of the maximal } ^{51}\text{Cr release sample} - \text{cpm of the spontaneous } ^{51}\text{Cr release sample})] \times 100}{100}$$

[0668] Maximum and spontaneous release are determined by incubating the labeled targets with 1% Triton X-100 and media alone, respectively. A positive culture is defined as one in which the specific lysis (sample-background) is 10% or higher in the case of individual wells and is 15% or more at the two highest E:T ratios when expanded cultures are assayed.

In Situ Measurement of Human IFN γ Production as an Indicator of Peptide-Specific and Endogenous Recognition

[0669] Immulon 2 plates are coated with mouse anti-human IFN γ monoclonal antibody (4 $\mu\text{g/ml}$ 0.1M NaHCO_3 , pH8.2) overnight at 4°C . The plates are washed with Ca^{2+} , Mg^{2+} -free PBS/0.05% Tween 20 and blocked with PBS/10% FCS for two hours, after which the CTLs (100 $\mu\text{l/well}$) and targets (100 $\mu\text{l/well}$) are added to each well, leaving empty wells for the standards and blanks (which received media only). The target cells, either peptide-pulsed or endogenous targets, are used at a concentration of 1×10^6 cells/ml. The plates are incubated for 48 hours at 37°C . with 5% CO_2 .

[0670] Recombinant human IFN-gamma is added to the standard wells starting at 400 μg or 1200 $\mu\text{g}/100$ microliter/well and the plate incubated for two hours at 37°C . The plates are washed and 100 μl of biotinylated mouse anti-human IFN-gamma monoclonal antibody (2 microgram/ml in PBS/3% FCS/0.05% Tween 20) are added and incubated for 2 hours at room temperature. After washing again, 100 microliter HRP-streptavidin (1:4000) are added and the plates incubated for one hour at room temperature. The plates are then washed 6 $\times$ with wash buffer, 100 microliter/well developing solution (TMB 1:1) are added, and the plates allowed to develop for 5-15 minutes. The reaction is stopped with 50 microliter/well 1M H_3PO_4 and read at

OD₄₅₀. A culture is considered positive if it measured at least 50 pg of IFN-gamma/well above background and is twice the background level of expression.

[0671] CTL Expansion.

[0672] Those cultures that demonstrate specific lytic activity against peptide-pulsed targets and/or tumor targets are expanded over a two week period with anti-CD3. Briefly, 5×10⁴ CD8⁺ cells are added to a T25 flask containing the following: 1×10⁶ irradiated (4,200 rad) PBMC (autologues or allogeneic) per ml, 2×10⁵ irradiated (8,000 rad) EBV-transformed cells per ml, and OKT3 (anti-CD3) at 30 ng per ml in RPMI-1640 containing 10% (v/v) human AB serum, non-essential amino acids, sodium pyruvate, 25 μM 2-mercaptoethanol, L-glutamine and penicillin/streptomycin. Recombinant human IL2 is added 24 hours later at a final concentration of 200 IU/ml and every three days thereafter with fresh media at 501 U/ml. The cells are split if the cell concentration exceeds 1×10⁶ ml and the cultures are assayed between days 13 and 15 at E:T ratios of 30, 10, 3 and 1:1 in the ⁵¹Cr release assay or at 1×10⁶/ml in the in situ IFNγ assay using the same targets as before the expansion.

[0673] Cultures are expanded in the absence of anti-CD3⁺ as follows. Those cultures that demonstrate specific lytic activity against peptide and endogenous targets are selected and 5×10⁴ CD8⁺ cells are added to a T25 flask containing the following: 1×10⁶ autologous PBMC per ml which have been peptide-pulsed with 10 μg/ml peptide for two hours at 37° C. and irradiated (4,200 rad); 2×10⁵ irradiated (8,000 rad) EBV-transformed cells per ml RPMI-1640 containing 10% (v/v) human AB serum, non-essential AA, sodium pyruvate, 25 mM 2-ME, L-glutamine and gentamicin.

Immunogenicity of A2 Supermotif-Bearing Peptides

[0674] A2-supermotif cross-reactive binding peptides are tested in the cellular assay for the ability to induce peptide-specific CTL in normal individuals. In this analysis, a peptide is typically considered to be an epitope if it induces peptide-specific CTLs in at least individuals, and preferably, also recognizes the endogenously expressed peptide.

[0675] Immunogenicity can also be confirmed using PBMCs isolated from patients bearing a tumor that expresses 273P4B7. Briefly, PBMCs are isolated from patients, re-stimulated with peptide-pulsed monocytes and assayed for the ability to recognize peptide-pulsed target cells as well as transfected cells endogenously expressing the antigen.

[0676] Evaluation of A*03/A11 Immunogenicity

[0677] HLA-A3 supermotif-bearing cross-reactive binding peptides are also evaluated for immunogenicity using methodology analogous for that used to evaluate the immunogenicity of the HLA-A2 supermotif peptides.

[0678] Evaluation of B7 Immunogenicity

[0679] Immunogenicity screening of the B7-supertype cross-reactive binding peptides identified as set forth herein are confirmed in a manner analogous to the confirmation of A2- and A3-supermotif-bearing peptides.

[0680] Peptides bearing other supermotifs/motifs, e.g., HLA-A1, HLA-A24 etc. are also confirmed using similar methodology

Example 15

Implementation of the Extended Supermotif to Improve the Binding Capacity of Native Epitopes by Creating Analogs

[0681] HLA motifs and supermotifs (comprising primary and/or secondary residues) are useful in the identification and preparation of highly cross-reactive native peptides, as demonstrated herein. Moreover, the definition of HLA motifs and supermotifs also allows one to engineer highly cross-reactive epitopes by identifying residues within a native peptide sequence which can be analoged to confer upon the peptide certain characteristics, e.g. greater cross-reactivity within the group of HLA molecules that comprise a supertype, and/or greater binding affinity for some or all of those HLA molecules. Examples of analoging peptides to exhibit modulated binding affinity are set forth in this example.

[0682] Analoging at Primary Anchor Residues

[0683] Peptide engineering strategies are implemented to further increase the cross-reactivity of the epitopes. For example, the main anchors of A2-supermotif-bearing peptides are altered, for example, to introduce a preferred L, I, V, or M at position 2, and I or V at the C-terminus.

[0684] To analyze the cross-reactivity of the analog peptides, each engineered analog is initially tested for binding to the prototype A2 supertype allele A*0201, then, if A*0201 binding capacity is maintained, for A2-supertype cross-reactivity.

[0685] Alternatively, a peptide is confirmed as binding one or all supertype members and then analoged to modulate binding affinity to any one (or more) of the supertype members to add population coverage.

[0686] The selection of analogs for immunogenicity in a cellular screening analysis is typically further restricted by the capacity of the parent wild type (WT) peptide to bind at least weakly, i.e., bind at an IC₅₀ of 5000 nM or less, to three or more A2 supertype alleles. The rationale for this requirement is that the WT peptides must be present endogenously in sufficient quantity to be biologically relevant. Analoged peptides have been shown to have increased immunogenicity and cross-reactivity by T cells specific for the parent epitope (see, e.g., Parkhurst et al., J. Immunol. 157:2539, 1996; and Pogue et al., Proc. Natl. Acad. Sci. USA 92:8166, 1995).

[0687] In the cellular screening of these peptide analogs, it is important to confirm that analog-specific CTLs are also able to recognize the wild-type peptide and, when possible, target cells that endogenously express the epitope.

[0688] Analoging of HLA-A3 and B7-Supermotif-Bearing Peptides

[0689] Analogs of HLA-A3 supermotif-bearing epitopes are generated using strategies similar to those employed in analoging HLA-A2 supermotif-bearing peptides. For example, peptides binding to 3/5 of the A3-supertype molecules are engineered at primary anchor residues to possess a preferred residue (V, S, M, or A) at position 2.

[0690] The analog peptides are then tested for the ability to bind A*03 and A*11 (prototype A3 supertype alleles).

Those peptides that demonstrate .ltoreq.500 nM binding capacity are then confirmed as having A3-supertype cross-reactivity.

[0691] Similarly to the A2- and A3-motif bearing peptides, peptides binding 3 or more B7-supertype alleles can be improved, where possible, to achieve increased cross-reactive binding or greater binding affinity or binding half life. B7 supermotif-bearing peptides are, for example, engineered to possess a preferred residue (V, I, L, or F) at the C-terminal primary anchor position, as demonstrated by Sidney et al. (J. Immunol. 157:3480-3490, 1996).

[0692] Analoging at primary anchor residues of other motif and/or supermotif-bearing epitopes is performed in a like manner.

[0693] The analog peptides are then be confirmed for immunogenicity, typically in a cellular screening assay. Again, it is generally important to demonstrate that analog-specific CTLs are also able to recognize the wild-type peptide and, when possible, targets that endogenously express the epitope.

[0694] Analoging at Secondary Anchor Residues

[0695] Moreover, HLA supermotifs are of value in engineering highly cross-reactive peptides and/or peptides that bind HLA molecules with increased affinity by identifying particular residues at secondary anchor positions that are associated with such properties. For example, the binding capacity of a B7 supermotif-bearing peptide with an F residue at position 1 is analyzed. The peptide is then analoged to, for example, substitute L for F at position 1. The analoged peptide is evaluated for increased binding affinity, binding half life and/or increased cross-reactivity. Such a procedure identifies analoged peptides with enhanced properties.

[0696] Engineered analogs with sufficiently improved binding capacity or cross-reactivity can also be tested for immunogenicity in HLA-B7-transgenic mice, following for example, IFA immunization or lipopeptide immunization. Analoged peptides are additionally tested for the ability to stimulate a recall response using PBMC from patients with 273P4B7-expressing tumors.

[0697] Other Analoging Strategies

[0698] Another form of peptide analoging, unrelated to anchor positions, involves the substitution of a cysteine with .alpha.-amino butyric acid. Due to its chemical nature, cysteine has the propensity to form disulfide bridges and sufficiently alter the peptide structurally so as to reduce binding capacity. Substitution of a-amino butyric acid for cysteine not only alleviates this problem, but has been shown to improve binding and crossbinding capabilities in some instances (see, e.g., the review by Sette et al., In: Persistent Viral Infections, Eds. R. Ahmed and I. Chen, John Wiley & Sons, England, 1999).

[0699] Thus, by the use of single amino acid substitutions, the binding properties and/or cross-reactivity of peptide ligands for HLA supertype molecules can be modulated.

Example 16

Identification and Confirmation of 273P4B7-Derived Sequences with HLA-DR Binding Motifs

[0700] Peptide epitopes bearing an HLA class II supermotif or motif are identified and confirmed as outlined below using methodology similar to that described for HLA Class I peptides.

[0701] Selection of HLA-DR-Supermotif-Bearing Epitopes.

[0702] To identify 273P4B7-derived, HLA class II HTL epitopes, a 273P4B7 antigen is analyzed for the presence of sequences bearing an HLA-DR-motif or supermotif. Specifically, 15-mer sequences are selected comprising a DR-supermotif, comprising a 9-mer core, and three-residue N- and C-terminal flanking regions (15 amino acids total).

[0703] Protocols for predicting peptide binding to DR molecules have been developed (Southwood et al., J. Immunol. 160:3363-3373, 1998). These protocols, specific for individual DR molecules, allow the scoring, and ranking, of 9-mer core regions. Each protocol not only scores peptide sequences for the presence of DR-supermotif primary anchors (i.e., at position 1 and position 6) within a 9-mer core, but additionally evaluates sequences for the presence of secondary anchors. Using allele-specific selection tables (see, e.g., Southwood et al., *ibid.*), it has been found that these protocols efficiently select peptide sequences with a high probability of binding a particular DR molecule. Additionally, it has been found that performing these protocols in tandem, specifically those for DR1, DR4w4, and DR7, can efficiently select DR cross-reactive peptides.

[0704] The 273P4B7-derived peptides identified above are tested for their binding capacity for various common HLA-DR molecules. All peptides are initially tested for binding to the DR molecules in the primary panel: DR1, DR4w4, and DR7. Peptides binding at least two of these three DR molecules are then tested for binding to DR2w2.beta.1, DR2w2.beta.2, DR6w19, and DR9 molecules in secondary assays. Finally, peptides binding at least two of the four secondary panel DR molecules, and thus cumulatively at least four of seven different DR molecules, are screened for binding to DR4w15, DR5w11, and DR8w2 molecules in tertiary assays. Peptides binding at least seven of the ten DR molecules comprising the primary, secondary, and tertiary screening assays are considered cross-reactive DR binders. 273P4B7-derived peptides found to bind common HLA-DR alleles are of particular interest.

[0705] Selection of DR3Motif Peptides

[0706] Because HLA-DR3 is an allele that is prevalent in Caucasian, Black, and Hispanic populations, DR3 binding capacity is a relevant criterion in the selection of HTL epitopes. Thus, peptides shown to be candidates may also be assayed for their DR3 binding capacity. However, in view of the binding specificity of the DR3 motif, peptides binding only to DR3 can also be considered as candidates for inclusion in a vaccine formulation.

[0707] To efficiently identify peptides that bind DR3, target 273P4B7 antigens are analyzed for sequences carrying one of the two DR3-specific binding motifs reported by

Geluk et al. (J. Immunol. 152:5742-5748, 1994). The corresponding peptides are then synthesized and confirmed as having the ability to bind DR3 with an affinity of 1 μ M or better, i.e., less than 1 μ M. Peptides are found that meet this binding criterion and qualify as HLA class II high affinity binders.

[0708] DR3 binding epitopes identified in this manner are included in vaccine compositions with DR supermotif-bearing peptide epitopes.

[0709] Similarly to the case of HLA class I motif-bearing peptides, the class II motif-bearing peptides are analogized to improve affinity or cross-reactivity. For example, aspartic acid at position 4 of the 9-mer core sequence is an optimal residue for DR3 binding, and substitution for that residue often improves DR 3 binding.

Example 17

Immunogenicity of 273P4B7-Derived HTL Epitopes

[0710] This example determines immunogenic DR supermotif- and DR3 motif-bearing epitopes among those identified using the methodology set forth herein.

[0711] Immunogenicity of HTL epitopes are confirmed in a manner analogous to the determination of immunogenicity of CTL epitopes, by assessing the ability to stimulate HTL responses and/or by using appropriate transgenic mouse models. Immunogenicity is determined by screening for: 1.) in vitro primary induction using normal PBMC or 2.) recall responses from patients who have 273P4B7-expressing tumors.

Example 18

Calculation of Phenotypic Frequencies of HLA-Supertypes in Various Ethnic Backgrounds to Determine Breadth of Population Coverage

[0712] This example illustrates the assessment of the breadth of population coverage of a vaccine composition comprised of multiple epitopes comprising multiple supermotifs and/or motifs.

[0713] In order to analyze population coverage, gene frequencies of HLA alleles are determined. Gene frequencies for each HLA allele are calculated from antigen or allele frequencies utilizing the binomial distribution formulae $gf=1-(SQRT(1-af))$ (see, e.g., Sidney et al., Human Immunol. 45:79-93, 1996). To obtain overall phenotypic frequencies, cumulative gene frequencies are calculated, and the cumulative antigen frequencies derived by the use of the inverse formula $[af=1-(1-Cgf)^2]$.

[0714] Where frequency data is not available at the level of DNA typing, correspondence to the serologically defined antigen frequencies is assumed. To obtain total potential supertype population coverage no linkage disequilibrium is assumed, and only alleles confirmed to belong to each of the superotypes are included (minimal estimates). Estimates of total potential coverage achieved by inter-loci combinations are made by adding to the A coverage the proportion of the non-A covered population that could be expected to be covered by the B alleles considered (e.g., $total=A+B*(1-A)$). Confirmed members of the A3-like supertype are A3,

A11, A31, A*3301, and A*6801. Although the A3-like supertype may also include A34, A66, and A*7401, these alleles were not included in overall frequency calculations. Likewise, confirmed members of the A2-like supertype family are A*0201, A*0202, A*0203, A*0204, A*0205, A*0206, A*0207, A*6802, and A*6901. Finally, the B7-like supertype-confirmed alleles are: 87, B*3501-03, B51, B*5301, B*5401, B*5501-2, B*5601, B*6701, and B*7801 (potentially also B*1401, B*3504-06, B*4201, and B*5602).

[0715] Population coverage achieved by combining the A2-, A3- and B7-supertypes is approximately 86% in five major ethnic groups. Coverage may be extended by including peptides bearing the A1 and A24 motifs. On average, A1 is present in 12% and A24 in 29% of the population across five different major ethnic groups (Caucasian, North American Black, Chinese, Japanese, and Hispanic). Together, these alleles are represented with an average frequency of 39% in these same ethnic populations. The total coverage across the major ethnicities when A1 and A24 are combined with the coverage of the A2-, A3- and B7-supertype alleles is >95%, see, e.g., Table IV (G). An analogous approach can be used to estimate population coverage achieved with combinations of class II motif-bearing epitopes.

[0716] Immunogenicity studies in humans (e.g., Bertoni et al., J. Clin. Invest. 100:503, 1997; Doolan et al., Immunity 7:97, 1997; and Threlkeld et al., J. Immunol. 159:1648, 1997) have shown that highly cross-reactive binding peptides are almost always recognized as epitopes. The use of highly cross-reactive binding peptides is an important selection criterion in identifying candidate epitopes for inclusion in a vaccine that is immunogenic in a diverse population.

[0717] With a sufficient number of epitopes (as disclosed herein and from the art), an average population coverage is predicted to be greater than 95% in each of five major ethnic populations. The game theory Monte Carlo simulation analysis, which is known in the art (see e.g., Osborne, M. J. and Rubinstein, A. "A course in game theory" MIT Press, 1994), can be used to estimate what percentage of the individuals in a population comprised of the Caucasian, North American Black, Japanese, Chinese, and Hispanic ethnic groups would recognize the vaccine epitopes described herein. A preferred percentage is 90%. A more preferred percentage is 95%.

Example 19

CTL Recognition of Endogenously Processed Antigens after Priming

[0718] This example confirms that CTL induced by native or analogized peptide epitopes identified and selected as described herein recognize endogenously synthesized, i.e., native antigens.

[0719] Effector cells isolated from transgenic mice that are immunized with peptide epitopes, for example HLA-A2 supermotif-bearing epitopes, are re-stimulated in vitro using peptide-coated stimulator cells. Six days later, effector cells are assayed for cytotoxicity and the cell lines that contain peptide-specific cytotoxic activity are further re-stimulated. An additional six days later, these cell lines are tested for cytotoxic activity on ^{51}Cr labeled Jurkat-A2.1/K^b target cells in the absence or presence of peptide, and also tested on ^{51}Cr

labeled target cells bearing the endogenously synthesized antigen, i.e. cells that are stably transfected with 273P4B7 expression vectors.

[0720] The results demonstrate that CTL lines obtained from animals primed with peptide epitope recognize endogenously synthesized 273P4B7 antigen. The choice of transgenic mouse model to be used for such an analysis depends upon the epitope(s) that are being evaluated. In addition to HLA-A*0201/K^b transgenic mice, several other transgenic mouse models including mice with human A11, which may also be used to evaluate A3 epitopes, and B7 alleles have been characterized and others (e.g., transgenic mice for HLA-A1 and A24) are being developed. HLA-DR1 and HLA-DR3 mouse models have also been developed, which may be used to evaluate HTL epitopes.

Example 20

Activity of CTL-HTL Conjugated Epitopes in Transgenic Mice

[0721] This example illustrates the induction of CTLs and HTLs in transgenic mice, by use of a 273P4B7-derived CTL and HTL peptide vaccine compositions. The vaccine composition used herein comprise peptides to be administered to a patient with a 273P4B7-expressing tumor. The peptide composition can comprise multiple CTL and/or HTL epitopes. The epitopes are identified using methodology as described herein. This example also illustrates that enhanced immunogenicity can be achieved by inclusion of one or more HTL epitopes in a CTL vaccine composition; such a peptide composition can comprise an HTL epitope conjugated to a CTL epitope. The CTL epitope can be one that binds to multiple HLA family members at an affinity of 500 nM or less, or analogs of that epitope. The peptides may be lipidated, if desired.

[0722] Immunization procedures: Immunization of transgenic mice is performed as described (Alexander et al., J. Immunol. 159:4753-4761, 1997). For example, A2/K^b mice, which are transgenic for the human HLA A2.1 allele and are used to confirm the immunogenicity of HLA-A*0201 motif or HLA-A2 supermotif-bearing epitopes, and are primed subcutaneously (base of the tail) with a 0.1 ml of peptide in Incomplete Freund's Adjuvant, or if the peptide composition is a lipidated CTUHTL conjugate, in DMSO/saline, or if the peptide composition is a polypeptide, in PBS or Incomplete Freund's Adjuvant. Seven days after priming, splenocytes obtained from these animals are restimulated with syngenic irradiated LPS-activated lymphoblasts coated with peptide.

[0723] Cell lines: Target cells for peptide-specific cytotoxicity assays are Jurkat cells transfected with the HLA-A2.1/K^b chimeric gene (e.g., Vitiello et al., J. Exp. Med. 173:1007, 1991)

[0724] In vitro CTL activation: One week after priming, spleen cells (30×10⁶ cells/flask) are co-cultured at 37° C. with syngenic, irradiated (3000 rads), peptide coated lymphoblasts (10×10⁶ cells/flask) in 10 ml of culture medium/T25 flask. After six days, effector cells are harvested and assayed for cytotoxic activity.

[0725] Assay for cytotoxic activity: Target cells (1.0 to 1.5×10⁶) are incubated at 37°C in the presence of 200 µl of ⁵¹Cr. After 60 minutes, cells are washed three times and

resuspended in R10 medium. Peptide is added where required at a concentration of 1 µg/ml. For the assay, 10⁴ ⁵¹Cr-labeled target cells are added to different concentrations of effector cells (final volume of 200 µl) in U-bottom 96-well plates. After a six hour incubation period at 37° C., a 0.1 ml aliquot of supernatant is removed from each well and radioactivity is determined in a Micromedic automatic gamma counter. The percent specific lysis is determined by the formula: percent specific release=100×(experimental release-spontaneous release)/(maximum release-spontaneous release). To facilitate comparison between separate CTL assays run under the same conditions, % ⁵¹Cr release data is expressed as lytic units/10⁶ cells. One lytic unit is arbitrarily defined as the number of effector cells required to achieve 30% lysis of 10,000 target cells in a six hour ⁵¹Cr release assay. To obtain specific lytic units/10, the lytic units/10⁶ obtained in the absence of peptide is subtracted from the lytic units/10⁶ obtained in the presence of peptide. For example, if 30% ⁵¹Cr release is obtained at the effector (E): target (T) ratio of 50:1 (i.e., 5×10⁵ effector cells for 10,000 targets) in the absence of peptide and 5:1 (i.e., 5×10⁴ effector cells for 10,000 targets) in the presence of peptide, the specific lytic units would be: [(1/50,000)–(1/500,000)]10⁶= 18 LU.

[0726] The results are analyzed to assess the magnitude of the CTL responses of animals injected with the immunogenic CTL/HTL conjugate vaccine preparation and are compared to the magnitude of the CTL response achieved using, for example, CTL epitopes as outlined above in the Example entitled "Confirmation of Immunogenicity." Analyses similar to this may be performed to confirm the immunogenicity of peptide conjugates containing multiple CTL epitopes and/or multiple HTL epitopes. In accordance with these procedures, it is found that a CTL response is induced, and concomitantly that an HTL response is induced upon administration of such compositions.

Example 21

Selection of CTL and HTL Epitopes for Inclusion in a 273P4B7-Specific Vaccine

[0727] This example illustrates a procedure for selecting peptide epitopes for vaccine compositions of the invention. The peptides in the composition can be in the form of a nucleic acid sequence, either single or one or more sequences (i.e., minigene) that encodes peptide(s), or can be single and/or polyepitopic peptides.

[0728] The following principles are utilized when selecting a plurality of epitopes for inclusion in a vaccine composition. Each of the following principles is balanced in order to make the selection.

[0729] Epitopes are selected which, upon administration, mimic immune responses that are correlated with 273P4B7 clearance. The number of epitopes used depends on observations of patients who spontaneously clear 273P4B7. For example, if it has been observed that patients who spontaneously clear 273P4B7-expressing cells generate an immune response to at least three (3) epitopes from 273P4B7 antigen, then at least three epitopes should be included for HLA class I. A similar rationale is used to determine HLA class II epitopes.

[0730] Epitopes are often selected that have a binding affinity of an IC₅₀ of 500 nM or less for an HLA class

I molecule, or for class II, an IC_{50} of 1000 nM or less; or HLA Class I peptides with high binding scores from the BIMAS web site.

[0731] In order to achieve broad coverage of the vaccine through out a diverse population, sufficient supermotif bearing peptides, or a sufficient array of allele-specific motif bearing peptides, are selected to give broad population coverage. In one embodiment, epitopes are selected to provide at least 80% population coverage. A Monte Carlo analysis, a statistical evaluation known in the art, can be employed to assess breadth, or redundancy, of population coverage.

[0732] When creating polyepitopic compositions, or a minigene that encodes same, it is typically desirable to generate the smallest peptide possible that encompasses the epitopes of interest. The principles employed are similar, if not the same, as those employed when selecting a peptide comprising nested epitopes. For example, a protein sequence for the vaccine composition is selected because it has maximal number of epitopes contained within the sequence, i.e., it has a high concentration of epitopes. Epitopes may be nested or overlapping (i.e., frame shifted relative to one another). For example, with overlapping epitopes, two 9-mer epitopes and one 10-mer epitope can be present in a 10 amino acid peptide. Each epitope can be exposed and bound by an HLA molecule upon administration of such a peptide. A multi-epitopic, peptide can be generated synthetically, recombinantly, or via cleavage from the native source. Alternatively, an analog can be made of this native sequence, whereby one or more of the epitopes comprise substitutions that alter the cross-reactivity and/or binding affinity properties of the polyepitopic peptide. Such a vaccine composition is administered for therapeutic or prophylactic purposes. This embodiment provides for the possibility that an as yet undiscovered aspect of immune system processing will apply to the native nested sequence and thereby facilitate the production of therapeutic or prophylactic immune response-inducing vaccine compositions. Additionally such an embodiment provides for the possibility of motif-bearing epitopes for an HLA makeup that is presently unknown. Furthermore, this embodiment (absent the creating of any analogs) directs the immune response to multiple peptide sequences that are actually present in 273P4B7, thus avoiding the need to evaluate any junctional epitopes. Lastly, the embodiment provides an economy of scale when producing nucleic acid vaccine compositions. Related to this embodiment, computer programs can be derived in accordance with principles in the art, which identify in a target sequence, the greatest number of epitopes per sequence length.

[0733] A vaccine composition comprised of selected peptides, when administered, is safe, efficacious, and elicits an immune response similar in magnitude to an immune response that controls or clears cells that bear or overexpress 273P4B7.

Example 22

Construction of "Minigene" Multi-Epitope DNA Plasmids

[0734] This example discusses the construction of a minigene expression plasmid. Minigene plasmids may, of course, contain various configurations of B cell, CTL and/or HTL epitopes or epitope analogs as described herein.

[0735] A minigene expression plasmid typically includes multiple CTL and HTL peptide epitopes. In the present example, HLA-A2, -A3, -B7 supermotif-bearing peptide epitopes and HLA-A1 and -A24 motif-bearing peptide epitopes are used in conjunction with DR supermotif-bearing epitopes and/or DR3 epitopes. HLA class I supermotif or motif-bearing peptide epitopes derived 273P4B7, are selected such that multiple supermotifs/motifs are represented to ensure broad population coverage. Similarly, HLA class II epitopes are selected from 273P4B7 to provide broad population coverage, i.e. both HLA DR-1-4-7 supermotif-bearing epitopes and HLA DR-3 motif-bearing epitopes are selected for inclusion in the minigene construct. The selected CTL and HTL epitopes are then incorporated into a minigene for expression in an expression vector.

[0736] Such a construct may additionally include sequences that direct the HTL epitopes to the endoplasmic reticulum. For example, the II protein may be fused to one or more HTL epitopes as described in the art, wherein the CLIP sequence of the II protein is removed and replaced with an HLA class II epitope sequence so that HLA class II epitope is directed to the endoplasmic reticulum, where the epitope binds to an HLA class II molecules.

[0737] This example illustrates the methods to be used for construction of a minigene-bearing expression plasmid. Other expression vectors that may be used for minigene compositions are available and known to those of skill in the art.

[0738] The minigene DNA plasmid of this example contains a consensus Kozak sequence and a consensus murine kappa Ig-light chain signal sequence followed by CTL and/or HTL epitopes selected in accordance with principles disclosed herein. The sequence encodes an open reading frame fused to the Myc and H is antibody epitope tag coded for by the pcDNA 3.1 Myc-His vector.

[0739] Overlapping oligonucleotides that can, for example, average about 70 nucleotides in length with 15 nucleotide overlaps, are synthesized and HPLC-purified. The oligonucleotides encode the selected peptide epitopes as well as appropriate linker nucleotides, Kozak sequence, and signal sequence. The final multi-epitope minigene is assembled by extending the overlapping oligonucleotides in three sets of reactions using PCR. A Perkin/Elmer 9600 PCR machine is used and a total of 30 cycles are performed using the following conditions: 95° C. for 15 sec. annealing temperature (5° below the lowest calculated T_m of each primer pair) for 30 sec, and 72° C. for 1 min.

[0740] For example, a minigene is prepared as follows. For a first PCR reaction, 5 µg of each of two oligonucleotides are annealed and extended: In an example using eight oligonucleotides, i.e., four pairs of primers, oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined in 100 µl reactions containing Pfu polymerase buffer (1x=10 mM KCL, 10 mM $(NH_4)_2SO_4$, 20 mM Tris-chloride, pH 8.75, 2 mM $MgSO_4$, 0.1% Triton X-100, 100 µg/ml BSA), 0.25 mM each dNTP, and 2.5 U of Pfu polymerase. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended for 10 cycles. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product. The full-length product is

gel-purified and cloned into pCR-blunt (Invitrogen) and individual clones are screened by sequencing.

Example 23

The Plasmid Construct and the Degree to which it Induces Immunogenicity

[0741] The degree to which a plasmid construct, for example a plasmid constructed in accordance with the previous Example, is able to induce immunogenicity is confirmed *in vitro* by determining epitope presentation by APC following transduction or transfection of the APC with an epitope-expressing nucleic acid construct. Such a study determines “antigenicity” and allows the use of human APC. The assay determines the ability of the epitope to be presented by the APC in a context that is recognized by a T cell by quantifying the density of epitope-HLA class I complexes on the cell surface. Quantitation can be performed by directly measuring the amount of peptide eluted from the APC (see, e.g., Sijts et al., *J. Immunol.* 156:683692, 1996; Demotz et al., *Nature* 342:682-684, 1989); or the number of peptide-HLA class I complexes can be estimated by measuring the amount of lysis or lymphokine release induced by diseased or transfected target cells, and then determining the concentration of peptide necessary to obtain equivalent levels of lysis or lymphokine release (see, e.g., Kageyama et al., *J. Immunol.* 154:567-576, 1995).

[0742] Alternatively, immunogenicity is confirmed through *in vivo* injections into mice and subsequent *in vitro* assessment of CTL and HTL activity, which are analyzed using cytotoxicity and proliferation assays, respectively, as detailed e.g., in Alexander et al., *Immunity* 1:751-761, 1994.

[0743] For example, to confirm the capacity of a DNA minigene construct containing at least one HLA-A2 supermotif peptide to induce CTLs *in vivo*, HLA-A2.1/K^b transgenic mice, for example, are immunized intramuscularly with 100 µg of naked cDNA. As a means of comparing the level of CTLs induced by cDNA immunization, a control group of animals is also immunized with an actual peptide composition that comprises multiple epitopes synthesized as a single polypeptide as they would be encoded by the minigene.

[0744] Splenocytes from immunized animals are stimulated twice with each of the respective compositions (peptide epitopes encoded in the minigene or the polypeptidic peptide), then assayed for peptide-specific cytotoxic activity in a ⁵¹Cr release assay. The results indicate the magnitude of the CTL response directed against the A2-restricted epitope, thus indicating the *in vivo* immunogenicity of the minigene vaccine and polypeptidic vaccine.

[0745] It is, therefore, found that the minigene elicits immune responses directed toward the HLA-A2 supermotif peptide epitopes as does the polypeptidic peptide vaccine. A similar analysis is also performed using other HLA-A3 and HLA-B7 transgenic mouse models to assess CTL induction by HLA-A3 and HLA-B7 motif or supermotif epitopes, whereby it is also found that the minigene elicits appropriate immune responses directed toward the provided epitopes.

[0746] To confirm the capacity of a class II epitope-encoding minigene to induce HTLs *in vivo*, DR transgenic mice, or for those epitopes that cross react with the appro-

priate mouse MHC molecule, I-Ab-restricted mice, for example, are immunized intramuscularly with 100 µg of plasmid DNA. As a means of comparing the level of HTLs induced by DNA immunization, a group of control animals is also immunized with an actual peptide composition emulsified in complete Freund's adjuvant. CD4⁺ T cells, i.e. HTLs, are purified from splenocytes of immunized animals and stimulated with each of the respective compositions (peptides encoded in the minigene). The HTL response is measured using a ³H-thymidine incorporation proliferation assay, (see, e.g., Alexander et al. *Immunity* 1:751-761, 1994). The results indicate the magnitude of the HTL response, thus demonstrating the *in vivo* immunogenicity of the minigene.

[0747] DNA minigenes, constructed as described in the previous Example, can also be confirmed as a vaccine in combination with a boosting agent using a prime boost protocol. The boosting agent can consist of recombinant protein (e.g., Barnett et al., *Aids Res. and Human Retroviruses* 14, Supplement 3:S299-S309, 1998) or recombinant vaccinia, for example, expressing a minigene or DNA encoding the complete protein of interest (see, e.g., Hanke et al., *Vaccine* 16:439-445, 1998; Sedegah et al., *Proc. Natl. Acad. Sci USA* 95:7648-53, 1998; Hanke and McMichael, *Immunol. Letters* 66:177-181, 1999; and Robinson et al., *Nature Med.* 5:526-34, 1999).

[0748] For example, the efficacy of the DNA minigene used in a prime boost protocol is initially evaluated in transgenic mice. In this example, A2.1/K^b transgenic mice are immunized IM with 100 µg of a DNA minigene encoding the immunogenic peptides including at least one HLA-A2 supermotif-bearing peptide. After an incubation period (ranging from 3-9 weeks), the mice are boosted IP with 10⁷ pfu/mouse of a recombinant vaccinia virus expressing the same sequence encoded by the DNA minigene. Control mice are immunized with 100 µg of DNA or recombinant vaccinia without the minigene sequence, or with DNA encoding the minigene, but without the vaccinia boost. After an additional incubation period of two weeks, splenocytes from the mice are immediately assayed for peptide-specific activity in an ELISPOT assay. Additionally, splenocytes are stimulated *in vitro* with the A2-restricted peptide epitopes encoded in the minigene and recombinant vaccinia, then assayed for peptide-specific activity in an alpha, beta and/or gamma IFN ELISA.

[0749] It is found that the minigene utilized in a prime-boost protocol elicits greater immune responses toward the HLA-A2 supermotif peptides than with DNA alone. Such an analysis can also be performed using HLA-A11 or HLA-B7 transgenic mouse models to assess CTL induction by HLA-A3 or HLA-B7 motif or supermotif epitopes. The use of prime boost protocols in humans is described below in the Example entitled “Induction of CTL Responses Using a Prime Boost Protocol.”

Example 24

Peptide Compositions for Prophylactic Uses

[0750] Vaccine compositions of the present invention can be used to prevent 273P4B7 expression in persons who are at risk for tumors that bear this antigen. For example, a polypeptidic peptide epitope composition (or a nucleic acid

comprising the same) containing multiple CTL and HTL epitopes such as those selected in the above Examples, which are also selected to target greater than 80% of the population, is administered to individuals at risk for a 273P4B7-associated tumor.

[0751] For example, a peptide-based composition is provided as a single polypeptide that encompasses multiple epitopes. The vaccine is typically administered in a physiological solution that comprises an adjuvant, such as Incomplete Freund's Adjuvant. The dose of peptide for the initial immunization is from about 1 to about 50,000 µg, generally 100-5,000 µg, for a 70 kg patient. The initial administration of vaccine is followed by booster dosages at 4 weeks followed by evaluation of the magnitude of the immune response in the patient, by techniques that determine the presence of epitope-specific CTL populations in a PBMC sample. Additional booster doses are administered as required. The composition is found to be both safe and efficacious as a prophylaxis against 273P4B7-associated disease.

[0752] Alternatively, a composition typically comprising transfecting agents is used for the administration of a nucleic acid-based vaccine in accordance with methodologies known in the art and disclosed herein.

Example 25

Polyepitopic Vaccine Compositions Derived from Native 273P4B7 Sequences

[0753] A native 273P4B7 polypeptide sequence is analyzed, preferably using computer algorithms defined for each class I and/or class II supermotif or motif, to identify "relatively short" regions of the polypeptide that comprise multiple epitopes. The "relatively short" regions are preferably less in length than an entire native antigen. This relatively short sequence that contains multiple distinct or overlapping, "nested" epitopes can be used to generate a minigene construct. The construct is engineered to express the peptide, which corresponds to the native protein sequence. The "relatively short" peptide is generally less than 250 amino acids in length, often less than 100 amino acids in length, preferably less than 75 amino acids in length, and more preferably less than 50 amino acids in length. The protein sequence of the vaccine composition is selected because it has maximal number of epitopes contained within the sequence, i.e., it has a high concentration of epitopes. As noted herein, epitope motifs may be nested or overlapping (i.e., frame shifted relative to one another). For example, with overlapping epitopes, two 9-mer epitopes and one 10-mer epitope can be present in a 10 amino acid peptide. Such a vaccine composition is administered for therapeutic or prophylactic purposes.

[0754] The vaccine composition will include, for example, multiple CTL epitopes from 273P4B7 antigen and at least one HTL epitope. This polyepitopic native sequence is administered either as a peptide or as a nucleic acid sequence which encodes the peptide. Alternatively, an analog can be made of this native sequence, whereby one or more of the epitopes comprise substitutions that alter the cross-reactivity and/or binding affinity properties of the polyepitopic peptide.

[0755] The embodiment of this example provides for the possibility that an as yet undiscovered aspect of immune

system processing will apply to the native nested sequence and thereby facilitate the production of therapeutic or prophylactic immune response-inducing vaccine compositions. Additionally, such an embodiment provides for the possibility of motif-bearing epitopes for an HLA makeup(s) that is presently unknown. Furthermore, this embodiment (excluding an analogized embodiment) directs the immune response to multiple peptide sequences that are actually present in native 273P4B7, thus avoiding the need to evaluate any junctional epitopes. Lastly, the embodiment provides an economy of scale when producing peptide or nucleic acid vaccine compositions.

[0756] Related to this embodiment, computer programs are available in the art which can be used to identify in a target sequence, the greatest number of epitopes per sequence length.

Example 26

Polyepitopic Vaccine Compositions from Multiple Antigens

[0757] The 273P4B7 peptide epitopes of the present invention are used in conjunction with epitopes from other target tumor-associated antigens, to create a vaccine composition that is useful for the prevention or treatment of cancer that expresses 273P4B7 and such other antigens. For example, a vaccine composition can be provided as a single polypeptide that incorporates multiple epitopes from 273P4B7 as well as tumor-associated antigens that are often expressed with a target cancer associated with 273P4B7 expression, or can be administered as a composition comprising a cocktail of one or more discrete epitopes. Alternatively, the vaccine can be administered as a minigene construct or as dendritic cells which have been loaded with the peptide epitopes in vitro.

Example 27

Use of Peptides to Evaluate an Immune Response

[0758] Peptides of the invention may be used to analyze an immune response for the presence of specific antibodies, CTL or HTL directed to 273P4B7. Such an analysis can be performed in a manner described by Ogg et al., *Science* 279:2103-2106, 1998. In this Example, peptides in accordance with the invention are used as a reagent for diagnostic or prognostic purposes, not as an immunogen.

[0759] In this example highly sensitive human leukocyte antigen tetrameric complexes ("tetramers") are used for a cross-sectional analysis of, for example, 273P4B7 HLA-A*0201-specific CTL frequencies from HLA A*0201-positive individuals at different stages of disease or following immunization comprising a 273P4B7 peptide containing an A*0201 motif. Tetrameric complexes are synthesized as described (Musey et al., *N. Engl. J. Med.* 337:1267, 1997). Briefly, purified HLA heavy chain (A*0201 in this example) and P2-microglobulin are synthesized by means of a prokaryotic expression system. The heavy chain is modified by deletion of the transmembrane-cytosolic tail and COOH-terminal addition of a sequence containing a BirA enzymatic biotinylation site. The heavy chain, P2-microglobulin, and peptide are refolded by dilution. The 45-kD refolded product is isolated by fast protein liquid chromatography and then biotinylated by BirA in the presence of biotin (Sigma, St.

Louis, Mo.), adenosine 5' triphosphate and magnesium. Streptavidin-phycoerythrin conjugate is added in a 1:4 molar ratio, and the tetrameric product is concentrated to 1 mg/ml. The resulting product is referred to as tetramer-phycoerythrin.

[0760] For the analysis of patient blood samples, approximately one million PBMCs are centrifuged at 300 g for 5 minutes and resuspended in 50 μ l of cold phosphate-buffered saline. Tri-color analysis is performed with the tetramer-phycoerythrin, along with anti-CD8-Tricolor, and anti-CD38. The PBMCs are incubated with tetramer and antibodies on ice for 30 to 60 min and then washed twice before formaldehyde fixation. Gates are applied to contain >99.98% of control samples. Controls for the tetramers include both A*0201-negative individuals and A*0201-positive non-diseased donors. The percentage of cells stained with the tetramer is then determined by flow cytometry. The results indicate the number of cells in the PBMC sample that contain epitope-restricted CTLs, thereby readily indicating the extent of immune response to the 273P4B7 epitope, and thus the status of exposure to 273P4B7, or exposure to a vaccine that elicits a protective or therapeutic response.

Example 28

Use of Peptide Epitopes to Evaluate Recall Responses

[0761] The peptide epitopes of the invention are used as reagents to evaluate T cell responses, such as acute or recall responses, in patients. Such an analysis may be performed on patients who have recovered from 273P4B7-associated disease or who have been vaccinated with a 273P4B7 vaccine.

[0762] For example, the class I restricted CTL response of persons who have been vaccinated may be analyzed. The vaccine may be any 273P4B7 vaccine. PBMC are collected from vaccinated individuals and HLA typed. Appropriate peptide epitopes of the invention that, optimally, bear supermotifs to provide cross-reactivity with multiple HLA super-type family members, are then used for analysis of samples derived from individuals who bear that HLA type.

[0763] PBMC from vaccinated individuals are separated on Ficoll-Histopaque density gradients (Sigma Chemical Co., St. Louis, Mo.), washed three times in HBSS (GIBCO Laboratories), resuspended in RPMI-1640 (GIBCO Laboratories) supplemented with L-glutamine (2 mM), penicillin (50 U/ml), streptomycin (50 μ g/ml), and Hepes (10 mM) containing 10% heat-inactivated human AB serum (complete RPMI) and plated using microculture formats. A synthetic peptide comprising an epitope of the invention is added at 10 μ g/ml to each well and HBV core 128-140 epitope is added at 1 μ g/ml to each well as a source of T cell help during the first week of stimulation.

[0764] In the microculture format, 4×10^5 PBMC are stimulated with peptide in 8 replicate cultures in 96-well round bottom plate in 100 μ l/well of complete RPMI. On days 3 and 10, 100 μ l of complete RPMI and 20 U/ml final concentration of rIL-2 are added to each well. On day 7 the cultures are transferred into a 96-well flat-bottom plate and restimulated with peptide, rIL-2 and 10^5 irradiated (3,000 rad) autologous feeder cells. The cultures are tested for cytotoxic activity on day 14. A positive CTL response

requires two or more of the eight replicate cultures to display greater than 10% specific ^{51}Cr release, based on comparison with non-diseased control subjects as previously described (Rehermann, et al., *Nature Med.* 2:1104, 1108, 1996; Rehermann et al., *J. Clin. Invest.* 97:1655-1665, 1996; and Rehermann et al *J. Clin. Invest.* 98:1432-1440, 1996).

[0765] Target cell lines are autologous and allogeneic EBV-transformed B-LCL that are either purchased from the American Society for Histocompatibility and Immunogenetics (ASHI, Boston, Mass.) or established from the pool of patients as described (Guilhot, et al. *J. Virol.* 66:2670-2678, 1992).

[0766] Cytotoxicity assays are performed in the following manner. Target cells consist of either allogeneic HLA-matched or autologous EBV-transformed B lymphoblastoid cell line that are incubated overnight with the synthetic peptide epitope of the invention at 10 μ M, and labeled with 100 μ Ci of ^{51}Cr (Amersham Corp., Arlington Heights, Ill.) for 1 hour after which they are washed four times with HBSS.

[0767] Cytolytic activity is determined in a standard 4-h, split well ^{51}Cr release assay using U-bottomed 96 well plates containing 3,000 targets/well. Stimulated PBMC are tested at effector/target (E/T) ratios of 20:50:1 on day 14. Percent cytotoxicity is determined from the formula: $100 \times [(\text{experimental release} - \text{spontaneous release}) / \text{maximum release} - \text{spontaneous release}]$. Maximum release is determined by lysis of targets by detergent (2% Triton X-100; Sigma Chemical Co., St. Louis, Mo.). Spontaneous release is <25% of maximum release for all experiments.

[0768] The results of such an analysis indicate the extent to which HLA-restricted CTL populations have been stimulated by previous exposure to 273P4B7 or a 273P4B7 vaccine.

[0769] Similarly, Class II restricted HTL responses may also be analyzed. Purified PBMC are cultured in a 96-well flat bottom plate at a density of 1.5×10^5 cells/well and are stimulated with 10 μ g/ml synthetic peptide of the invention, whole 273P4B7 antigen, or PHA. Cells are routinely plated in replicates of 4-6 wells for each condition. After seven days of culture, the medium is removed and replaced with fresh medium containing 10 U/ml IL-2. Two days later, 1 μ Ci ^3H -thymidine is added to each well and incubation is continued for an additional 18 hours. Cellular DNA is then harvested on glass fiber mats and analyzed for ^3H -thymidine incorporation. Antigen-specific T cell proliferation is calculated as the ratio of ^3H -thymidine incorporation in the presence of antigen divided by the ^3H -thymidine incorporation in the absence of antigen.

Example 29

Induction of Specific CTL Response in Humans

[0770] A human clinical trial for an immunogenic composition comprising CTL and HTL epitopes of the invention is set up as an IND Phase I, dose escalation study and carried out as a randomized, double-blind, placebo-controlled trial. Such a trial is designed, for example, as follows:

[0771] A total of about 27 individuals are enrolled and divided into 3 groups:

Group I: 3 subjects are injected with placebo and 6 subjects are injected with 5 μ g of peptide composition;

Group II: 3 subjects are injected with placebo and 6 subjects are injected with 50 µg peptide composition;

Group III: 3 subjects are injected with placebo and 6 subjects are injected with 500 µg of peptide composition.

[0772] After 4 weeks following the first injection, all subjects receive a booster inoculation at the same dosage.

[0773] The endpoints measured in this study relate to the safety and tolerability of the peptide composition as well as its immunogenicity. Cellular immune responses to the peptide composition are an index of the intrinsic activity of this the peptide composition, and can therefore be viewed as a measure of biological efficacy. The following summarize the clinical and laboratory data that relate to safety and efficacy endpoints.

[0774] Safety: The incidence of adverse events is monitored in the placebo and drug treatment group and assessed in terms of degree and reversibility.

[0775] Evaluation of Vaccine Efficacy: For evaluation of vaccine efficacy, subjects are bled before and after injection. Peripheral blood mononuclear cells are isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation, aliquoted in freezing media and stored frozen. Samples are assayed for CTL and HTL activity.

[0776] The vaccine is found to be both safe and efficacious.

Example 30

Phase II Trials in Patients Expressing 273P4B7

[0777] Phase II trials are performed to study the effect of administering the CTL-HTL peptide compositions to patients having cancer that expresses 273P4B7. The main objectives of the trial are to determine an effective dose and regimen for inducing CTLs in cancer patients that express 273P4B7, to establish the safety of inducing a CTL and HTL response in these patients, and to see to what extent activation of CTLs improves the clinical picture of these patients, as manifested, e.g., by the reduction and/or shrinking of lesions. Such a study is designed, for example, as follows:

[0778] The studies are performed in multiple centers. The trial design is an open-label, uncontrolled, dose escalation protocol wherein the peptide composition is administered as a single dose followed six weeks later by a single booster shot of the same dose. The dosages are 50, 500 and 5,000 micrograms per injection. Drug-associated adverse effects (severity and reversibility) are recorded.

[0779] There are three patient groupings. The first group is injected with 50 micrograms of the peptide composition and the second and third groups with 500 and 5,000 micrograms of peptide composition, respectively. The patients within each group range in age from 21-65 and represent diverse ethnic backgrounds. All of them have a tumor that expresses 273P4B7.

[0780] Clinical manifestations or antigen-specific T-cell responses are monitored to assess the effects of administering the peptide compositions. The vaccine composition is found to be both safe and efficacious in the treatment of 273P4B7-associated disease.

Example 31

Induction of CTL Responses Using a Prime Boost Protocol

[0781] A prime boost protocol similar in its underlying principle to that used to confirm the efficacy of a DNA vaccine in transgenic mice, such as described above in the Example entitled "The Plasmid Construct and the Degree to Which It Induces Immunogenicity," can also be used for the administration of the vaccine to humans. Such a vaccine regimen can include an initial administration of, for example, naked DNA followed by a boost using recombinant virus encoding the vaccine, or recombinant protein/polypeptide or a peptide mixture administered in an adjuvant.

[0782] For example, the initial immunization may be performed using an expression vector, such as that constructed in the Example entitled "Construction of "Mini-gene" Multi-Epitope DNA Plasmids" in the form of naked nucleic acid administered IM (or SC or ID) in the amounts of 0.5-5 mg at multiple sites. The nucleic acid (0.1 to 1000 µg) can also be administered using a gene gun. Following an incubation period of 3-4 weeks, a booster dose is then administered. The booster can be recombinant fowlpox virus administered at a dose of $5 \cdot 10^7$ to $5 \cdot 10^9$ pfu. An alternative recombinant virus, such as an MVA, canarypox, adenovirus, or adeno-associated virus, can also be used for the booster, or the polypeptidic protein or a mixture of the peptides can be administered. For evaluation of vaccine efficacy, patient blood samples are obtained before immunization as well as at intervals following administration of the initial vaccine and booster doses of the vaccine. Peripheral blood mononuclear cells are isolated from fresh heparinized blood by Ficoll-1-Hypaque density gradient centrifugation, aliquoted in freezing media and stored frozen. Samples are assayed for CTL and HTL activity.

[0783] Analysis of the results indicates that a magnitude of response sufficient to achieve a therapeutic or protective immunity against 273P4B7 is generated.

Example 32

Administration of Vaccine Compositions Using Dendritic Cells (DC)

[0784] Vaccines comprising peptide epitopes of the invention can be administered using APCs, or "professional" APCs such as DC. In this example, peptide-pulsed DC are administered to a patient to stimulate a CTL response in vivo. In this method, dendritic cells are isolated, expanded, and pulsed with a vaccine comprising peptide CTL and HTL epitopes of the invention. The dendritic cells are infused back into the patient to elicit CTL and HTL responses in vivo. The induced CTL and HTL then destroy or facilitate destruction, respectively, of the target cells that bear the 273P4B7 protein from which the epitopes in the vaccine are derived.

[0785] For example, a cocktail of epitope-comprising peptides is administered ex vivo to PBMC, or isolated DC therefrom. A pharmaceutical to facilitate harvesting of DC can be used, such as PROGENIPOIETIN (Monsanto, St. Louis, Mo.) or GM-CSF/IL-4. After pulsing the DC with

peptides, and prior to reinfusion into patients, the DC are washed to remove unbound peptides.

[0786] As appreciated clinically, and readily determined by one of skill based on clinical outcomes, the number of DC reinfused into the patient can vary (see, e.g., *Nature Med.* 4:328, 1998; *Nature Med.* 2:52, 1996 and *Prostate* 32:272, 1997). Although $2\text{--}50 \times 10^6$ DC per patient are typically administered, larger number of DC, such as 10^7 or 10^8 can also be provided. Such cell populations typically contain between 50-90% DC.

[0787] In some embodiments, peptide-loaded PBMC are injected into patients without purification of the DC. For example, PBMC generated after treatment with an agent such as PROGENIPOIETIN are injected into patients without purification of the DC. The total number of PBMC that are administered often ranges from 10^8 to 10^{10} . Generally, the cell doses injected into patients is based on the percentage of DC in the blood of each patient, as determined, for example, by immunofluorescence analysis with specific anti-DC antibodies. Thus, for example, if PROGENIPOIETIN mobilizes 2% DC in the peripheral blood of a given patient, and that patient is to receive 5×10^6 DC, then the patient will be injected with a total of 2.5×10^8 peptide-loaded PBMC. The percent DC mobilized by an agent such as PROGENIPOIETIN is typically estimated to be between 2-10%, but can vary as appreciated by one of skill in the art.

[0788] Ex Vivo Activation of CTL/HTL Responses

[0789] Alternatively, ex vivo CTL or HTL responses to 273P4B7 antigens can be induced by incubating, in tissue culture, the patient's, or genetically compatible, CTL or HTL precursor cells together with a source of APC, such as DC, and immunogenic peptides. After an appropriate incubation time (typically about 7-28 days), in which the precursor cells are activated and expanded into effector cells, the cells are infused into the patient, where they will destroy (CTL) or facilitate destruction (HTL) of their specific target cells, i.e., tumor cells.

Example 33

An Alternative Method of Identifying and Confirming Motif-Bearing Peptides

[0790] Another method of identifying and confirming motif-bearing peptides is to elute them from cells bearing defined MHC molecules. For example, EBV transformed B cell lines used for tissue typing have been extensively characterized to determine which HLA molecules they express. In certain cases these cells express only a single type of HLA molecule. These cells can be transfected with nucleic acids that express the antigen of interest, e.g. 273P4B7. Peptides produced by endogenous antigen processing of peptides produced as a result of transfection will then bind to HLA molecules within the cell and be transported and displayed on the cell's surface. Peptides are then eluted from the HLA molecules by exposure to mild acid conditions and their amino acid sequence determined, e.g., by mass spectral analysis (e.g., Kubo et al., *J. Immunol.* 152:3913, 1994). Because the majority of peptides that bind a particular HLA molecule are motif-bearing, this is an alternative modality for obtaining the motif-bearing peptides correlated with the particular HLA molecule expressed on the cell.

[0791] Alternatively, cell lines that do not express endogenous HLA molecules can be transfected with an expression construct encoding a single HLA allele. These cells can then be used as described, i.e., they can then be transfected with nucleic acids that encode 273P4B7 to isolate peptides corresponding to 273P4B7 that have been presented on the cell surface. Peptides obtained from such an analysis will bear motif(s) that correspond to binding to the single HLA allele that is expressed in the cell.

[0792] As appreciated by one in the art, one can perform a similar analysis on a cell bearing more than one HLA allele and subsequently determine peptides specific for each HLA allele expressed. Moreover, one of skill would also recognize that means other than transfection, such as loading with a protein antigen, can be used to provide a source of antigen to the cell.

Example 34

Complementary Polynucleotides

[0793] Sequences complementary to the 273P4B7-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring 273P4B7. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using, e.g., OLIGO 4.06 software (National Biosciences) and the coding sequence of 273P4B7. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to a 273P4B7-encoding transcript.

Example 35

Purification of Naturally-Occurring or Recombinant 273P4B7 Using 273P4B7-Specific Antibodies

[0794] Naturally occurring or recombinant 273P4B7 is substantially purified by immunoaffinity chromatography using antibodies specific for 273P4B7. An immunoaffinity column is constructed by covalently coupling anti-273P4B7 antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

[0795] Media containing 273P4B7 are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of 273P4B7 (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/273P4B7 binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and GCRP is collected.

Example 36

Identification of Molecules which Interact with 273P4B7

[0796] 273P4B7, or biologically active fragments thereof, are labeled with 121 I Bolton-Hunter reagent. (See, e.g.,

Bolton et al. (1973) *Biochem. J.* 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled 273P4B7, washed, and any wells with labeled 273P4B7 complex are assayed. Data obtained using different concentrations of 273P4B7 are used to calculate values for the number, affinity, and association of 273P4B7 with the candidate molecules.

Example 37

In Vivo Assay for 273P4B7 Tumor Growth Promotion

[0797] The effect of the 273P4B7 protein on tumor cell growth is evaluated in vivo by evaluating tumor development and growth of cells expressing or lacking 273P4B7. For example, SCID mice are injected subcutaneously on each flank with 1×10^6 of either 3T3, cancer cell lines expressing 273P4B7 (Table I), or cancer cell lines containing tkNeo empty vector. At least two strategies may be used: (1) Constitutive 273P4B7 expression under regulation of a promoter such as a constitutive promoter obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 Jul. 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), or from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, provided such promoters are compatible with the host cell systems, and (2) Regulated expression under control of an inducible vector system, such as ecodyson, tetracycline, etc., provided such promoters are compatible with the host cell systems. Tumor volume is then monitored by caliper measurement at the appearance of palpable tumors and followed over time to determine if 273P4B7-expressing cells grow at a faster rate and whether tumors produced by 273P4B7-expressing cells demonstrate characteristics of altered aggressiveness (e.g. enhanced metastasis, vascularization, reduced responsiveness to chemotherapeutic drugs).

[0798] Additionally, mice can be implanted with 1×10^5 of the same cells orthotopically to determine if 273P4B7 has an effect on local growth, and whether 273P4B7 affects the ability of the cells to metastasize, specifically to lymph nodes, and bone (Azuma H et al., *J. Urol.* 2003, 169:2372; Fu X et al., *Int J. Cancer.* 1991, 49:938). The effect of 273P4B7 on bone tumor formation and growth may be assessed by injecting tumor cells intratibially. The assay is also useful to determine the 273P4B7 inhibitory effect of candidate therapeutic compositions, such as for example, 273P4B7 intrabodies, 273P4B7 antisense molecules and ribozymes.

Example 38

273P4B7 Monoclonal Antibody-Mediated Inhibition of Tumors In Vivo

[0799] The significant expression of 273P4B7 in cancer tissues, together with its restricted expression in normal tissues, makes 273P4B7 an excellent target for antibody therapy. In cases where the monoclonal antibody target is a cell surface protein, antibodies have been shown to be efficacious at inhibiting tumor growth (See, e.g., (Saffran, D., et al., *PNAS* 10:1073-1078 or on the World Wide Web. In cases where the target is not on the cell surface, such as

for 273P4B7, and including PSA and PAP in prostate cancer, antibodies have still been shown to recognize and inhibit growth of cells expressing those proteins (Saffran, D. C., et al., *Cancer and Metastasis Reviews*, 1999, 18: p. 437-449). As with any cellular protein with a restricted expression profile, 273P4B7 is a target for T cell-based immunotherapy.

[0800] Accordingly, the therapeutic efficacy of anti-273P4B7 mAbs in human xenograft mouse models, including bladder, pancreas, cervix, lung and the other cancers set forth in Table I, is modeled in 273P4B7-expressing cancer xenografts or cancer cell lines, such as those described in the Example entitled "In Vivo Assay for 273P4B7 Tumor Growth Promotion", that endogenously express 273P4B7 or that have been engineered to express 273P4B7.

[0801] Antibody efficacy on tumor growth and metastasis formation is confirmed, e.g., in a mouse orthotopic cancer xenograft model. The antibodies can be unconjugated, as discussed in this Example, or can be conjugated to a therapeutic modality, as appreciated in the art. It is confirmed that anti-273P4B7 mAbs inhibit formation of 273P4B7-expressing tumors. Anti-273P4B7 mAbs also retard the growth of established orthotopic tumors and prolong survival of tumor-bearing mice. These results indicate the utility of anti-273P4B7 mAbs in the treatment of local and advanced stages of cancer. (See, e.g., Saffran, D., et al., *PNAS* 10:1073-1078 or on the World Wide Web.

[0802] Administration of anti-273P4B7 mAbs retard established orthotopic tumor growth and inhibit metastasis to distant sites, resulting in a significant prolongation in the survival of tumor-bearing mice. These studies indicate that 273P4B7 is an attractive target for immunotherapy and demonstrate the therapeutic potential of anti-273P4B7 mAbs for the treatment of local and metastatic cancer.

[0803] This example demonstrates that unconjugated 273P4B7 monoclonal antibodies effectively to inhibit the growth of human bladder tumors grown in SCID mice; accordingly a combination of such efficacious monoclonal antibodies is also effective.

Tumor Inhibition Using Multiple Unconjugated 273P4B7 mAbs Materials and Methods

[0804] 273P4B7 Monoclonal Antibodies

[0805] Monoclonal antibodies are raised against 273P4B7 as described in the Example entitled "Generation of 273P4B7 Monoclonal Antibodies (mAbs)." The antibodies are characterized by ELISA, Western blot, FACS, and immunoprecipitation, in accordance with techniques known in the art, for their capacity to bind 273P4B7. Epitope mapping data for the anti-273P4B7 mAbs, as determined by ELISA and Western analysis, recognize epitopes on the 273P4B7 protein. Immunohistochemical analysis of cancer tissues and cells with these antibodies is performed.

[0806] The monoclonal antibodies are purified from ascites or hybridoma tissue culture supernatants by Protein-G Sepharose chromatography, dialyzed against PBS, filter sterilized, and stored at -20°C . Protein determinations are performed by a Bradford assay (Bio-Rad, Hercules, Calif.). A therapeutic monoclonal antibody or a cocktail comprising a mixture of individual monoclonal antibodies is prepared and used for the treatment of mice receiving subcutaneous or orthotopic injections of bladder tumor xenografts.

[0807] Cancer Cell Lines

[0808] Cancer cell lines expressing 273P4B7 are generated by retroviral gene transfer as described in Hubert, R. S., et al., STEAP: a prostate-specific cell-surface antigen highly expressed in human prostate tumors. *Proc Natl Acad Sci USA*, 1999. 96(25):14523-8. Cancer cell lines endogenously expressing 273P4B7, including prostate, bladder, kidney, and the other tissues set forth in Table I are also used for in vivo and in vitro models. Anti-273P4B7 staining is detected by using an FITC-conjugated goat anti-mouse antibody (Southern Biotechnology Associates) followed by analysis on a Coulter Epics-XL flow cytometer.

[0809] In Vivo Mouse Models

[0810] Subcutaneous (s.c.) tumors are generated by injection of 1×10^6 273P4B7-expressing cancer cells, mixed at a 1:1 dilution with Matrigel (Collaborative Research) in the right flank of male SCID mice. To test antibody efficacy on tumor formation, i.p. antibody injections are started on the same day as tumor-cell injections. As a control, mice are injected with either purified mouse IgG (ICN) or PBS; or a purified monoclonal antibody that recognizes an irrelevant antigen not expressed in human cells. In preliminary studies, no difference is found between mouse IgG or PBS on tumor growth. Tumor sizes are determined by vernier caliper measurements, and the tumor volume is calculated as length $\times$ width $\times$ height. Mice with s.c. tumors greater than 1.5 cm in diameter are sacrificed. Circulating levels of anti-273P4B7 mAbs are determined by a capture ELISA kit (Bethyl Laboratories, Montgomery, Tex.). (See, e.g., (Saffran, D., et al., *PNAS* 10:1073-1078)

[0811] Orthotopic injections are performed, for example, in two alternative embodiments, under anesthesia by, for example, use of ketamine/xylazine. In a first embodiment, an intravesicular injection of cancer cells is administered directly (Peralta, E. A., et al., *J. Urol.*, 1999. 162:1806-1811). In a second embodiment, an incision is made through the abdominal wall, the tissue is exposed, and tumor tissue pieces (1-2 mm in size) derived from a s.c. tumor are surgically glued onto the exterior wall, termed "onplantation" (Fu, X., et al., *Int. J. Cancer*, 1991. 49: 938-939; Chang, S., et al., *Anticancer Res.*, 1997. 17: p. 3239-3242). Antibodies can be administered to groups of mice at the time of tumor injection or onplantation, or after 1-2 weeks to allow tumor establishment.

[0812] Anti-273P4B7 mAbs Inhibit Growth of 273P4B7-Expressing Tumors

[0813] In one embodiment, the effect of anti-273P4B7 mAbs on tumor formation is investigated in subcutaneous models of the cancers listed in Table I, by inoculating the right flank of SCID mice with the appropriate 273P4B7-expressing cell line, and comparing its growth in the presence or absence of anti-273P4B7 mAb, as described below.

[0814] In another embodiment, the effect of anti-273P4B7 mAbs on tumor formation is tested by using the orthotopic model. As compared with the s.c. tumor model, the orthotopic model, which requires surgical attachment of tumor tissue directly, results in a local tumor growth, development of metastasis in distal sites, and subsequent death (Fu, X., et al., *Int. J. Cancer*, 1991. 49: p. 938-939; Chang, S., et al., *Anticancer Res.*, 1997. 17: p. 3239-3242). This feature make the orthotopic model more representative of human disease

progression and allows one to follow the therapeutic effect of mAbs, as well as other therapeutic modalities, on clinically relevant end points.

[0815] Accordingly, 273P4B7-expressing tumor cells are onplanted orthotopically, and 2 days later, the mice are segregated into two groups and treated with either: a) 50-2000 gp, usually 200-500 μ g, of anti-273P4B7 Ab, or b) PBS, three times per week for two to five weeks. Mice are monitored weekly for indications of tumor growth.

[0816] As noted, a major advantage of the orthotopic cancer model is the ability to study the development of metastases. Formation of metastasis in mice bearing established orthotopic tumors is studied by histological analysis of tissue sections, including lung and lymph nodes (Fu, X., et al., *Int. J. Cancer*, 1991. 49:938-939; Chang, S., et al., *Anticancer Res.*, 1997. 17:3239-3242). Additionally, IHC analysis using anti-273P4B7 antibodies can be performed on the tissue sections.

[0817] Mice bearing established orthotopic 273P4B7-expressing tumors are administered 1 OOp_g injections of either anti-273P4B7 mAb or PBS over a 4-week period. Mice in both groups are allowed to establish a high tumor burden (1-2 weeks growth), to ensure a high frequency of metastasis formation in mouse lungs and lymph nodes. Mice are then sacrificed and their local tumor and lung and lymph node tissue are analyzed for the presence of tumor cells by histology and IHC analysis.

[0818] These studies demonstrate a broad anti-tumor efficacy of anti-273P4B7 antibodies on initiation and progression of cancers in mouse models. Anti-273P4B7 antibodies inhibit tumor formation and retard the growth of already established tumors and prolong the survival of treated mice. Moreover, anti-273P4B7 mAbs demonstrate a dramatic inhibitory effect on the spread of local tumor to distal sites, even in the presence of a large tumor burden. Thus, anti-273P4B7 mAbs are efficacious on major clinically relevant end points including lessened tumor growth, lessened metastasis, and prolongation of survival.

Example 39**Therapeutic and Diagnostic use of Anti-273P4B7 Antibodies in Humans**

[0819] Anti-273P4B7 monoclonal antibodies are safely and effectively used for diagnostic, prophylactic, prognostic and/or therapeutic purposes in humans. Western blot and immunohistochemical analysis of cancer tissues and cancer xenografts with anti-273P4B7 mAb show strong extensive staining in carcinoma but significantly lower or undetectable levels in normal tissues. Detection of 273P4B7 in carcinoma and in metastatic disease demonstrates the usefulness of the mAb as a diagnostic and/or prognostic indicator. Anti-273P4B7 antibodies are therefore used in diagnostic applications such as immunohistochemistry of kidney biopsy specimens to detect cancer from suspect patients.

[0820] As determined by flow cytometry, anti-273P4B7 mAb specifically binds to carcinoma cells. Thus, anti-273P4B7 antibodies are used in diagnostic whole body imaging applications, such as radioimmunoscinigraphy and radioimmunotherapy, (see, e.g., Potamianos S., et. al. *Anticancer Res* 20(2A):925-948 (2000)) for the detection of

localized and metastatic cancers that exhibit expression of 273P4B7. Shedding or release of an extracellular domain of 273P4B7 into the extracellular milieu, such as that seen for alkaline phosphodiesterase B10 (Meerson, N. R., *Hepatology* 27:563-568 (1998)), allows diagnostic detection of 273P4B7 by anti-273P4B7 antibodies in serum and/or urine samples from suspect patients.

[0821] Anti-273P4B7 antibodies that specifically bind 273P4B7 are used in therapeutic applications for the treatment of cancers that express 273P4B7. Anti-273P4B7 antibodies are used as an unconjugated modality and as conjugated form in which the antibodies are attached to one of various therapeutic or imaging modalities well known in the art, such as a prodrugs, enzymes or radioisotopes. In pre-clinical studies, unconjugated and conjugated anti-273P4B7 antibodies are tested for efficacy of tumor prevention and growth inhibition in the SCID mouse cancer xenograft models, e.g., kidney cancer models AGS-K3 and AGS-K6, (see, e.g., the Example entitled "273P4B7 Monoclonal Antibody-mediated Inhibition of Bladder and Lung Tumors In Vivo"). Either conjugated and unconjugated anti-273P4B7 antibodies are used as a therapeutic modality in human clinical trials either alone or in combination with other treatments as described in following Examples.

Example 40

Human Clinical Trials for the Treatment and Diagnosis of Human Carcinomas Through Use of Human Anti-273P4B7 Antibodies In Vivo

[0822] Antibodies are used in accordance with the present invention which recognize an epitope on 273P4B7, and are used in the treatment of certain tumors such as those listed in Table I. Based upon a number of factors, including 273P4B7 expression levels, tumors such as those listed in Table I are presently preferred indications. In connection with each of these indications, three clinical approaches are successfully pursued.

[0823] I.) Adjunctive therapy: In adjunctive therapy, patients are treated with anti-273P4B7 antibodies in combination with a chemotherapeutic or antineoplastic agent and/or radiation therapy. Primary cancer targets, such as those listed in Table I, are treated under standard protocols by the addition anti-273P4B7 antibodies to standard first and second line therapy. Protocol designs address effectiveness as assessed by reduction in tumor mass as well as the ability to reduce usual doses of standard chemotherapy. These dosage reductions allow additional and/or prolonged therapy by reducing dose-related toxicity of the chemotherapeutic agent. Anti-273P4B7 antibodies are utilized in several adjunctive clinical trials in combination with the chemotherapeutic or antineoplastic agents adriamycin (advanced prostate carcinoma), cisplatin (advanced head and neck and lung carcinomas), taxol (breast cancer), and doxorubicin (preclinical).

[0824] II.) Monotherapy: In connection with the use of the anti-273P4B7 antibodies in monotherapy of tumors, the antibodies are administered to patients without a chemotherapeutic or antineoplastic agent. In one embodiment, monotherapy is conducted clinically in end stage cancer patients with extensive metastatic disease. Patients show some disease stabilization. Trials demonstrate an effect in refractory patients with cancerous tumors.

[0825] III.) Imaging Agent: Through binding a radionuclide (e.g., iodine or yttrium (^{113}I , ^{90}Y) to anti-273P4B7 antibodies, the radiolabeled antibodies are utilized as a diagnostic and/or imaging agent. In such a role, the labeled antibodies localize to both solid tumors, as well as, metastatic lesions of cells expressing 273P4B7. In connection with the use of the anti-273P4B7 antibodies as imaging agents, the antibodies are used as an adjunct to surgical treatment of solid tumors, as both a pre-surgical screen as well as a post-operative follow-up to determine what tumor remains and/or returns. In one embodiment, a (^{111}In)-273P4B7 antibody is used as an imaging agent in a Phase I human clinical trial in patients having a carcinoma that expresses 273P4B7 (by analogy see, e.g., Divgi et al. *J. Natl. Cancer Inst.* 83:97-104 (1991)). Patients are followed with standard anterior and posterior gamma camera. The results indicate that primary lesions and metastatic lesions are identified.

[0826] Dose and Route of Administration

[0827] As appreciated by those of ordinary skill in the art, dosing considerations can be determined through comparison with the analogous products that are in the clinic. Thus, anti-273P4B7 antibodies can be administered with doses in the range of 5 to 400 mg/m², with the lower doses used, e.g., in connection with safety studies. The affinity of anti-273P4B7 antibodies relative to the affinity of a known antibody for its target is one parameter used by those of skill in the art for determining analogous dose regimens. Further, anti-273P4B7 antibodies that are fully human antibodies, as compared to the chimeric antibody, have slower clearance; accordingly, dosing in patients with such fully human anti-273P4B7 antibodies can be lower, perhaps in the range of 50 to 300 mg/m², and still remain efficacious. Dosing in mg/m², as opposed to the conventional measurement of dose in mg/kg, is a measurement based on surface area and is a convenient dosing measurement that is designed to include patients of all sizes from infants to adults.

[0828] Three distinct delivery approaches are useful for delivery of anti-273P4B7 antibodies. Conventional intravenous delivery is one standard delivery technique for many tumors. However, in connection with tumors in the peritoneal cavity, such as tumors of the ovaries, biliary duct, other ducts, and the like, intraperitoneal administration may prove favorable for obtaining high dose of antibody at the tumor and to also minimize antibody clearance. In a similar manner, certain solid tumors possess vasculature that is appropriate for regional perfusion. Regional perfusion allows for a high dose of antibody at the site of a tumor and minimizes short term clearance of the antibody.

[0829] Clinical Development Plan (CDP)

[0830] Overview: The CDP follows and develops treatments of anti-273P4B7 antibodies in connection with adjunctive therapy, monotherapy, and as an imaging agent. Trials initially demonstrate safety and thereafter confirm efficacy in repeat doses. Trials are open label comparing standard chemotherapy with standard therapy plus anti-273P4B7 antibodies. As will be appreciated, one criteria that can be utilized in connection with enrollment of patients is 273P4B7 expression levels in their tumors as determined by biopsy.

[0831] As with any protein or antibody infusion-based therapeutic, safety concerns are related primarily to (i)

cytokine release syndrome, i.e., hypotension, fever, shaking, chills; (ii) the development of an immunogenic response to the material (i.e., development of human antibodies by the patient to the antibody therapeutic, or HAHA response); and, (iii) toxicity to normal cells that express 273P4B7. Standard tests and follow-up are utilized to monitor each of these safety concerns. Anti-273P4B7 antibodies are found to be safe upon human administration.

Example 41

Human Clinical Trial Adjunctive Therapy with Human Anti-273P4B7 Antibody and Chemotherapeutic Agent

[0832] A phase I human clinical trial is initiated to assess the safety of six intravenous doses of a human anti-273P4B7 antibody in connection with the treatment of a solid tumor, e.g., a cancer of a tissue listed in Table I. In the study, the safety of single doses of anti-273P4B7 antibodies when utilized as an adjunctive therapy to an antineoplastic or chemotherapeutic agent as defined herein, such as, without limitation: cisplatin, topotecan, doxorubicin, adriamycin, taxol, or the like, is assessed. The trial design includes delivery of six single doses of an anti-273P4B7 antibody with dosage of antibody escalating from approximately about 25 mg/m² to about 275 mg/m² over the course of the treatment in accordance with the following schedule:

	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
mAb	25	75	125	175	225	275
Dose	mg/m ²	mg/m ²	mg/m ²	mg/m ²	mg/m ²	mg/m ²
Chemotherapy	+	+	+	+	+	+
(standard dose)						

[0833] Patients are closely followed for one-week following each administration of antibody and chemotherapy. In particular, patients are assessed for the safety concerns mentioned above: (i) cytokine release syndrome, i.e., hypotension, fever, shaking, chills; (ii) the development of an immunogenic response to the material (i.e., development of human antibodies by the patient to the human antibody therapeutic, or HAHA response); and, (iii) toxicity to normal cells that express 273P4B7. Standard tests and follow-up are utilized to monitor each of these safety concerns. Patients are also assessed for clinical outcome, and particularly reduction in tumor mass as evidenced by MRI or other imaging.

[0834] The anti-273P4B7 antibodies are demonstrated to be safe and efficacious, Phase II trials confirm the efficacy and refine optimum dosing.

Example 42

Human Clinical Trial: Monotherapy with Human Anti-273P4B7 Antibody

[0835] Anti-273P4B7 antibodies are safe in connection with the above-discussed adjunctive trial, a Phase II human clinical trial confirms the efficacy and optimum dosing for monotherapy. Such trial is accomplished, and entails the same safety and outcome analyses, to the above-described

adjunctive trial with the exception being that patients do not receive chemotherapy concurrently with the receipt of doses of anti-273P4B7 antibodies.

Example 43

Human Clinical Trial: Diagnostic Imaging with Anti-273P4B7 Antibody

[0836] Once again, as the adjunctive therapy discussed above is safe within the safety criteria discussed above, a human clinical trial is conducted concerning the use of anti-273P4B7 antibodies as a diagnostic imaging agent. The protocol is designed in a substantially similar manner to those described in the art, such as in Divgi et al. J. Natl Cancer Inst. 83:97-104 (1991). The antibodies are found to be both safe and efficacious when used as a diagnostic modality.

Example 44

Homology Comparison of 273P4B7 to Known Sequences

[0837] The 273P4B7 protein of FIG. 3 has 1250 amino acids with calculated molecular weight of 141.1 kDa, and pI of 5.19. 273P4B7 is predicted to be a nuclear protein (65% by PSORT) with a possibility of being a cytoplasmic protein (50% PSORT). Although some prediction programs indicate that 273P4B7 may have a transmembrane domain, it is equally likely that the 273P4B7 protein is a soluble intracellular protein.

[0838] By use of the PubMed website of the N.C.B.I. available on the World Wide Web, it was found at the protein level that 273P4B7 shows best homology to an un-named protein (gi.vertline.22760345) of unknown function, with 99% identity and 99% homology over the entire length of the protein (FIG. 4A). The 273P4B7 protein demonstrates similarity to a hypothetical human protein named BJ-HCC-15 tumor antigen (gi.vertline.22002580) with 99% identity and 100% homology over the last 419aa of the 273P4B7 protein (FIG. 4B). The mouse ortholog of 273P4B7 has been identified showing 72% identity and 81% homology to 273P4B7 (FIG. 4C). Bioinformatic analysis revealed the presence of a SNF2 motif at aa 99-417 and a helicase motif at aa 490-574 of the 273P4B7 protein. These motifs are also found in the mouse SNF2/RAD54 family protein (gi.vertline.27414501) which carries 72% identity to 273P4B7.

[0839] The SNF2 domain is often found in proteins involved in transcription regulation, DNA repair, DNA recombination, and chromatin unwinding (Alexeev A, Mazin A, Kowalczykowski S C. Nat Struct Biol. 2003, 10:182; Solinger J A, Kiianitsa K, Heyer W D. Mol. Cell. 2002, 10:1175; Martens J A, Winston F. Genes Dev. 2002, 16:2231). By remodeling DNA complexes, SNF2 makes nucleosomal DNA accessible to regulatory factors, thereby regulating gene expression (Fan H Y et al., Mol. Cell. 2003, 11:1311). Evidence in *Saccharomyces cerevisiae* indicates that SNF2 regulates transcription in these organisms. It has been shown that SNF complexes with SWI and the SWI/SNF is recruited to the promoter of specific genes inducing their transcriptional activation (Kingston, R. E. and Narlikar, G. J. Genes & Dev. 1999, 13: 2339-2352). A similar chromatin remodeling complex has been identified in mammalian cells, known as Brm/Brg1. This complex was found to

regulate gene expression as well as cell cycle (Muchardt C and Yaniv M, *Oncogene* 2001, 20:3067). Finally, a "proliferation-associated SNF2-like genes which contains SNF2 motifs has been associated with AML (Lee D et al., *Cancer Res.* 2000, 60:3612).

[0840] Our findings that 273P4B7 is highly expressed in several cancers while showing a restricted expression pattern in normal tissues suggests that the 273P4B7 gene may play an important role in various cancers, including the cancers set forth in Table I. It is provided by the present invention that 273P4B7 controls tumor growth and progression by regulating proliferation, cell cycle, gene expression as well as cell survival. Accordingly, when 273P4B7 functions as a regulator of proliferation, cell cycle, gene expression, and cell survival, 273P4B7 is used for therapeutic, diagnostic, prognostic or preventative purposes.

Example 45

Identification and Confirmation of Signal Transduction Pathways

[0841] Many mammalian proteins have been reported to interact with signaling molecules and to participate in regulating signaling pathways. (*J Neurochem.* 2001; 76:217-223). In particular, transcription factors have been shown to regulate mitogenic and survival pathways (Neeley K, *Biochim Biophys Acta.* 2002, 1603:19). Using immunoprecipitation and Western blotting techniques, proteins are identified that associate with 273P4B7 and mediate signaling events. Several pathways known to play a role in cancer biology can be regulated by 273P4B7, including phospholipid pathways such as P13K, AKT, etc, adhesion and migration pathways, including FAK, Rho, Rac-1, etc, as well as mitogenic/survival cascades such as ERK, p38, etc (*Cell Growth Differ.* 2000, 11:279; *J Biol Chem.* 1999, 274:801; *Oncogene.* 2000, 19:3003, *J. Cell Biol.* 1997, 138:913). Bioinformatic analysis revealed that 273P4B7 can become phosphorylated by serine/threonine as well as tyrosine kinases. Thus, the phosphorylation of 273P4B7 is provided by the present invention to lead to activation of the above listed pathways.

[0842] Using, e.g., Western blotting techniques the ability of 273P4B7 to regulate these pathways is confirmed. Cells expressing or lacking 273P4B7 are left untreated or stimulated with cytokines, hormones and anti-integrin antibodies. Cell lysates are analyzed using anti-phospho-specific antibodies (*Cell Signaling, Santa Cruz Biotechnology*) in order to detect phosphorylation and regulation of ERK, p38, AKT, P13K, PLC and other signaling molecules.

[0843] To confirm that 273P4B7 directly or indirectly activates known signal transduction pathways in cells, luciferase (luc) based transcriptional reporter assays are carried out in cells expressing individual genes. These transcriptional reporters contain consensus-binding sites for known transcription factors that lie downstream of well-characterized signal transduction pathways. The reporters and examples of these associated transcription factors, signal transduction pathways, and activation stimuli are listed below.

[0844] 1. NFkB-luc, NFkB/Rel; Ik-kinase/SAPK; growth/apoptosis/stress

[0845] 2. SRE-luc, SRF/TCF/ELK1; MAPK/SAPK; growth/differentiation

[0846] 3. AP-1-luc, FOS/JUN; MAPK/SAPK/PKC; growth/apoptosis/stress

[0847] 4. ARE-luc, androgen receptor; steroids/MAPK; growth/differentiation/apoptosis

[0848] 5. p53-luc, p53; SAPK; growth/differentiation/apoptosis

[0849] 6. CRE-luc, CREB/ATF2; PKA/p38; growth/apoptosis/stress

[0850] Gene-mediated effects can be assayed in cells showing mRNA expression. Luciferase reporter plasmids can be introduced by lipid-mediated transfection (TFX-50, Promega). Luciferase activity, an indicator of relative transcriptional activity, is measured by incubation of cell extracts with luciferin substrate and luminescence of the reaction is monitored in a luminometer.

[0851] Signaling pathways activated by 273P4B7 are mapped and used for the identification and validation of therapeutic targets. When 273P4B7 plays a role in the regulation of signaling pathways, mitogenic and survival pathways, phospholipid pathways and adhesion and migration pathways whether individually or communally, it is used as a target for diagnostic, prognostic, preventative and therapeutic purposes. Additionally, when 273P4B7 is involved in cell signaling, it is used as target for diagnostic, prognostic, preventative and therapeutic purposes.

Example 46

Involvement in Tumor Progression

[0852] The 273P4B7 gene can contribute to the growth of cancer cells. The role of 273P4B7 in tumor growth is confirmed in a variety of primary and transfected cell lines including pancreas, cervix, bladder, lung, prostate, kidney, colon, ovary, breast, bone, skin, lymph node, stomach, and uterus cell lines as well as NIH 3T3 cells engineered to stably express 273P4B7. Parental cells lacking 273P4B7 and cells expressing 273P4B7 are evaluated for cell growth using a well-documented proliferation assay (Fraser S P, Grimes J A, Djamgoz M B. *Prostate.* 2000; 44:61, Johnson D E, Ochieng J, Evans S L. *Anticancer Drugs.* 1996, 7:288).

[0853] To confirm the role of 273P4B7 in the transformation process, its effect in colony forming assays is investigated. Parental NIH3T3 cells lacking 273P4B7 are compared to NIH3T3 cells expressing 273P4B7, using a soft agar assay under stringent and more permissive conditions (Song Z. et al. *Cancer Res.* 2000, 60:6730).

[0854] To confirm the role of 273P4B7 in invasion and metastasis of cancer cells, a well-established assay is used, e.g., a Transwell Insert System assay (Becton Dickinson) (*Cancer Res.* 1999, 59:6010). Control cells, including, but not limited to prostate, colon, bladder and kidney cell lines lacking 273P4B7 are compared to cells expressing 273P4B7. Cells are loaded with the fluorescent dye, calcein, and plated in the top well of the Transwell insert coated with a basement membrane analog. Invasion is determined by fluorescence of cells in the lower chamber relative to the fluorescence of the entire cell population. 273P4B7 can also play a role in cell cycle and apoptosis. Parental cells and cells expressing 273P4B7 are compared for differences in cell cycle regulation using a well-established BrdU assay

(Abdel-Malek Z A. *J Cell Physiol.* 1988, 136:247). In short, cells are grown under both optimal (full serum) and limiting (low serum) conditions are labeled with BrdU and stained with anti-BrdU Ab and propidium iodide. Cells are analyzed for entry into the G1, S, and G2M phases of the cell cycle. Alternatively, the effect of stress on apoptosis is evaluated in control parental cells and cells expressing 273P4B7. Engineered and parental cells are treated with various chemotherapeutic agents, such as paclitaxel, gemcitabine, etc, and protein synthesis inhibitors, such as cycloheximide. Cells are stained with annexin V-FITC and cell death is measured by FACS analysis. The modulation of cell death by 273P4B7 can play a critical role in regulating tumor progression and tumor load.

[0855] When 273P4B7 plays a role in cell growth, transformation, invasion and metastasis, and cell cycle and apoptosis, it is used as a target for diagnostic, prognostic, preventative and therapeutic purposes.

Example 47

Involvement in Angiogenesis

[0856] Angiogenesis or new capillary blood vessel formation is necessary for tumor growth (Hanahan D, Folkman J. *Cell.* 1996, 86:353; Folkman J. *Endocrinology.* 1998 139:441). Several assays have been developed to measure angiogenesis in vitro and in vivo, such as the tissue culture assays, endothelial cell tube formation, and endothelial cell proliferation. Using these assays as well as in vitro neo-vascularization, the effect of 273P4B7 on angiogenesis is confirmed.

[0857] For example, endothelial cells engineered to express 273P4B7 are evaluated using tube formation and proliferation assays. The effect of 273P4B7 is also confirmed in animal models in vivo. For example, cells either expressing or lacking 273P4B7 are implanted subcutaneously in immunocompromised mice. Endothelial cell migration and angiogenesis are evaluated 5-15 days later using immunohistochemistry techniques.

[0858] When 273P4B7 affects angiogenesis, it is used as a target for diagnostic, prognostic, preventative and therapeutic purposes.

Example 48

Regulation of Transcription

[0859] The localization of 273P4B7 to the nucleus and its similarity to SNF2 containing proteins known to regulate gene expression and chromatin structure, support the present invention use of 273P4B7 based on its role in the transcriptional regulation of eukaryotic genes. Regulation of gene expression is confirmed, e.g., by studying gene expression in cells expressing or lacking 273P4B7. For this purpose, two types of experiments are performed.

[0860] In the first set of experiments, RNA from parental and 273P4B7-expressing cells are extracted and hybridized to commercially available gene arrays (Clontech) (Smid-Koopman E et al. *Br J Cancer.* 2000, 83:246). Resting cells as well as cells treated with FBS or androgen are compared. Differentially expressed genes are identified in accordance with procedures known in the art. The differentially

expressed genes are then mapped to biological pathways (Chen K et al., *Thyroid.* 2001, 11:41).

[0861] In the second set of experiments, specific transcriptional pathway activation is evaluated using commercially available (Stratagene) luciferase reporter constructs including: NFkB-luc, SRE-luc, ELK1-luc, ARE-luc, p53-luc, and CRE-luc. These transcriptional reporters contain consensus binding sites for known transcription factors that lie downstream of well-characterized signal transduction pathways, and represent a good tool to ascertain pathway activation and screen for positive and negative modulators of pathway activation.

[0862] Thus, when 273P4B7 plays a role in gene regulation, it is used as a target for diagnostic, prognostic, preventative and therapeutic purposes.

Example 49

Protein-Protein Association

[0863] SNF2 containing proteins have been shown to interact with other proteins, thereby forming protein complexes that can regulate protein localization, chromatin structure, gene transcription, and cell transformation (Papoulas et al., *Development,* 1998, 125:3955; Cao et al., *Mol. Cell. Biol.* 1997, 17:3323). Using immunoprecipitation techniques as well as two yeast hybrid systems, proteins are identified that associate with 273P4B7. Immunoprecipitates from cells expressing 273P4B7 and cells lacking 273P4B7 are compared for specific protein-protein associations.

[0864] Studies are performed to determine the extent of the association of 273P4B7 with receptors, such as the EGF and IGF receptors, and with intracellular proteins, such as IGF-BP, cytoskeletal proteins etc. Studies comparing 273P4B7 positive and 273P4B7 negative cells, as well as studies comparing unstimulated/resting cells and cells treated with epithelial cell activators, such as cytokines, growth factors and anti-integrin Ab reveal unique interactions.

[0865] In addition, protein-protein interactions are confirmed using two yeast hybrid methodology (Curr Opin Chem. Biol. 1999, 3:64). A vector carrying a library of proteins fused to the activation domain of a transcription factor is introduced into yeast expressing a 273P4B7-DNA-binding domain fusion protein and a reporter construct. Protein-protein interaction is detected by colorimetric reporter activity. Specific association with surface receptors and effector molecules directs one of skill to the mode of action of 273P4B7, and thus identifies therapeutic, prognostic, preventative and/or diagnostic targets for cancer. This and similar assays are also used to identify and screen for small molecules that interact with 273P4B7. When 273P4B7 associates with proteins to regulate protein localization, chromatin structure, gene transcription, and cell transformation or associates with small molecules it is used as a target for diagnostic, prognostic, preventative and therapeutic purposes.

[0866] Throughout this application, various website data content, publications, patent applications and patents are referenced. The disclosures of each of these references are hereby incorporated by reference herein in their entireties.

[0867] The present invention is not to be limited in scope by the embodiments disclosed herein, which are intended as single illustrations of individual aspects of the invention,

and any that are functionally equivalent are within the scope of the invention. Various modifications to the models and methods of the invention, in addition to those described herein, will become apparent to those skilled in the art from

the foregoing description and teachings, and are similarly intended to fall within the scope of the invention. Such modifications or other embodiments can be practiced without departing from the true scope and spirit of the invention.

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caattgagaa tgtaacctgt ttattgtatt ttaaagttaa actgaatatg agggaatttt 3900
tgttcccata attggattct ttgggaacat gaagcattca ggcttaaggc aagaaagatc 3960
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<210> SEQ ID NO 3

<211> LENGTH: 1250

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 3

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 1             5             10            15

Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
      20             25            30

Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
      35             40            45

Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
      50             55            60

Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
      65             70            75            80

Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
      85             90            95

Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
      100            105           110

Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
      115            120           125

Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
      130            135           140

Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
      145            150           155           160

Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe
      165            170           175

His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
      180            185           190

Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
      195            200           205

Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
      210            215           220

Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
      225            230           235           240

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Ala	Ile	Cys	Ala	Arg	Ala	Ile	Pro	Ala	Ser	Asn	Arg	Leu	Leu	Leu	Thr	245	250	255
Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu	Trp	Ser	Leu	Phe	Asp	260	265	270
Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu	Lys	Thr	Phe	Lys	Met	275	280	285
Glu	Tyr	Glu	Asn	Pro	Ile	Thr	Arg	Ala	Arg	Glu	Lys	Asp	Ala	Thr	Pro	290	295	300
Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Ile	Ser	Glu	Asn	Leu	Met	Ala	Ile	305	310	315
Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu	Asp	Val	Gln	Lys	Lys	325	330	335
Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu	Lys	Asn	Pro	Asp	Val	340	345	350
Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Lys	Asn	Asp	Leu	Ile	355	360	365
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe	370	375	380
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro	385	390	395
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu	405	410	415
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala	420	425	430
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp	435	440	445
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe	450	455	460
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu	465	470	475
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu	485	490	495
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His	500	505	510
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp	515	520	525
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr	530	535	540
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro	545	550	555
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys	565	570	575
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu	580	585	590
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr	595	600	605
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu	610	615	620
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu	625	630	635

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Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu	645	650	655	
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser	660	665	670	
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu	675	680	685	
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala	690	695	700	
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu	705	710	715	720
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe	725	730	735	
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro	740	745	750	
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile	755	760	765	
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly	770	775	780	
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln	785	790	795	800
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys	805	810	815	
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met	820	825	830	
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu	835	840	845	
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser	850	855	860	
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn	865	870	875	880
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro	Trp	885	890	895	
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val	900	905	910	
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu	915	920	925	
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala	930	935	940	
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser	945	950	955	960
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu	965	970	975	
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe	980	985	990	
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp	995	1000	1005	
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg	1010	1015	1020	
Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	Ser	Phe	Lys	Asp	Thr	1025	1030	1035	1040
Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser	Val				

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1045	1050	1055
Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly		
1060	1065	1070
Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn		
1075	1080	1085
Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu		
1090	1095	1100
Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala		
1105	1110	1115
Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly		
1125	1130	1135
Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser		
1140	1145	1150
Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu		
1155	1160	1165
Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln		
1170	1175	1180
Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr		
1185	1190	1195
Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile		
1205	1210	1215
Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala		
1220	1225	1230
Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn		
1235	1240	1245
Asn Asn		
1250		

<210> SEQ ID NO 4

<211> LENGTH: 4334

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 4

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aggcatcccg aaggtttccg gaagccgagg ccttgagccc agagcaggct gctcattacc	180
taagggtctt gctgtgtcgc ccagactgga attcagtggc ctgatcatag ttcactgcag	240
cctcgaactc ctgggctcaa gcagtcctcc tgccccagcc tccctagtag ctgggactta	300
agatatgtga aagaggccaa agaagcaact aagaatggag acctggaaga agcatttaaa	360
cttttcaatt tggcaaaagg catttttccc aatgaaaaag tgctgagcag aatccaaaaa	420
atacaggaag ccttgaggga gttggcagaa caggagatg atgaatttac agatgtgtgc	480
aactctggct tgctacttta tcgagaactg cacaaccaac tctttgagca ccagaaggaa	540
ggcatagctt tcctctatag cctgtatagg gatggaagaa aaggtggat attggctgat	600
gatatgggat tagggaagac tgttcaaact attgctttcc tttccggtat gtttgatgca	660
tcacttgtga atcatgtgct gctgatcatg ccaaccaatc ttattaacac atgggtaaaa	720
gaattcatca agtggaactcc aggaatgaga gtcaaaacct ttcattgtcc tagcaaggat	780
gaacggacca gaaacctcaa tcggattcag caaaggaatg gtgttattat cactacatac	840

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gactatgtca tcctcgtatga agcacataaa ataaaaacct catctactaa gtcagcaata	960
tgtgctcgtg ctattcctgc aagtaatcgc ctccctcctca caggaaacccc aatccagaat	1020
aatttacaag aactatgggc cctatttgat tttgcttgtc aagggtcctt gctgggaaca	1080
ttaaaaaactt ttaagatgga gtatgaaaaa cctattacta gagcaagaga gaaggatgct	1140
acccagggag aaaaagcctt gggatttaaa atatctgaaa acttaatggc aatcataaaa	1200
ccctattttc tcaggaggac taaagaagac gtacagaaga aaaagtcaag caacccagag	1260
gccagactta atgaaaagaa tccagatggt gatgccattt gtgaaatgcc ttccctttcc	1320
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gaaagtttta attatgtact tagcaaatca accaaagctg atattgggac aaatttagat	2880
caactaaagg atgatgagat ttacgtcat tgcaatcctt ggccattat ttccataaca	2940
aatgaaagtc aaaatgcaga atcaaatgta tccattattg aaatagctga tgacctttca	3000
gcattccata gtgcactgca gtagtctcaa gcaagtgagg ccaagttgga agaggaaact	3060
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gtaaataagt ctatgaactc tagaagatct ctggcttcta ggaggctctt tattaatatg 3540
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catattctat aaatttaact gtgttgtttc ttggaaagtt ttgtaaaatt attctggtca 4260
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<210> SEQ ID NO 5

<211> LENGTH: 1127

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 5

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  20             25             30
Leu Ile Asn Thr Trp Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met
  35             40             45
Arg Val Lys Thr Phe His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn
  50             55             60
Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln
  65             70             75             80
Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu
  85             90             95
Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr
  100            105            110
Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn
  115            120            125
Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu

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130					135					140					
Trp 145	Ser	Leu	Phe	Asp	Phe 150	Ala	Cys	Gln	Gly	Ser 155	Leu	Leu	Gly	Thr	Leu 160
Lys	Thr	Phe	Lys	Met 165	Glu	Tyr	Glu	Asn	Pro 170	Ile	Thr	Arg	Ala	Arg 175	Glu
Lys	Asp	Ala	Thr	Pro 180	Gly	Glu	Lys	Ala 185	Leu	Gly	Phe	Lys	Ile 190	Ser	Glu
Asn	Leu	Met	Ala	Ile	Ile	Lys	Pro 200	Tyr	Phe	Leu	Arg	Arg 205	Thr	Lys	Glu
Asp	Val	Gln	Lys	Lys	Lys 215	Ser	Asn	Pro	Glu	Ala 220	Arg	Leu	Asn	Glu	
Lys	Asn	Pro	Asp	Val 230	Asp	Ala	Ile	Cys	Glu	Met 235	Pro	Ser	Leu	Ser	Arg 240
Lys	Asn	Asp	Leu	Ile 245	Ile	Trp	Ile	Arg	Leu 250	Val	Pro	Leu	Gln	Glu	Glu 255
Ile	Tyr	Arg	Lys	Phe 260	Val	Ser	Leu	Asp 265	His	Ile	Lys	Glu	Leu 270	Leu	Met
Glu	Thr	Arg	Ser	Pro	Leu	Ala	Glu 280	Leu	Gly	Val	Leu	Lys 285	Lys	Leu	Cys
Asp	His	Pro	Arg	Leu	Leu 295	Ser	Ala	Arg	Ala	Cys 300	Cys	Leu	Leu	Asn	Leu
Gly	Thr	Phe	Ser	Ala 310	Gln	Asp	Gly	Asn	Glu	Gly 315	Glu	Asp	Ser	Pro	Asp 320
Val	Asp	His	Ile	Asp 325	Gln	Val	Thr	Asp	Asp 330	Thr	Leu	Met	Glu	Glu	Ser 335
Gly	Lys	Met	Ile 340	Phe	Leu	Met	Asp	Leu 345	Leu	Lys	Arg	Leu 350	Asp	Glu	
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Ile	Glu	Arg	Leu	Leu	Lys 375	Asn	Arg	His	Phe	Lys	Thr 380	Leu	Arg	Ile	Asp
Gly	Thr	Val	Thr	His 390	Leu	Leu	Glu	Arg	Glu	Lys 395	Arg	Ile	Asn	Leu	Phe 400
Gln	Gln	Asn	Lys	Asp 405	Tyr	Ser	Val	Phe	Leu 410	Leu	Thr	Thr	Gln	Val	Gly 415
Gly	Val	Gly	Leu	Thr 420	Leu	Thr	Ala	Ala 425	Thr	Arg	Val	Val 430	Ile	Phe	Asp
Pro	Ser	Trp	Asn	Pro	Ala	Thr	Asp 440	Ala	Gln	Ala	Val	Asp 445	Arg	Val	Tyr
Arg	Ile	Gly	Gln	Lys	Glu	Asn 455	Val	Val	Val	Tyr	Arg 460	Leu	Ile	Thr	Cys
Gly	Thr	Val	Glu	Glu 470	Lys	Ile	Tyr	Arg	Arg	Gln 475	Val	Phe	Lys	Asp	Ser 480
Leu	Ile	Arg	Gln	Thr 485	Thr	Gly	Glu	Lys	Lys 490	Asn	Pro	Phe	Arg	Tyr	Phe 495
Ser	Lys	Gln	Glu	Leu 500	Arg	Glu	Leu	Phe 505	Thr	Ile	Glu	Asp 510	Leu	Gln	Asn
Ser	Val	Thr	Gln	Leu 515	Gln	Leu	Gln 520	Ser	Leu	His	Ala 525	Ala	Gln	Arg	Lys
Ser	Asp	Ile	Lys	Leu 530	Asp	Glu 535	His	Ile	Ala	Tyr	Leu 540	Gln	Ser	Leu	Gly

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Ile	Ala	Gly	Ile	Ser	Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser
545					550					555					560
Val	Lys	Glu	Glu	Leu	Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln
				565					570					575	
Arg	Val	Gln	Lys	Ala	Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys
			580					585					590		
Glu	Phe	Leu	Met	Glu	Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu
		595					600					605			
Arg	Glu	Pro	Val	Phe	Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu
	610					615					620				
Asn	Lys	Pro	Gln	Pro	Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr
625					630					635					640
Gln	Glu	Glu	Asp	Ile	Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp
			645						650					655	
Leu	Pro	Lys	Glu	Gly	Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn
		660						665					670		
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His	Cys	Asn	Pro	Trp	Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn
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Gln	Phe	Ser	Ser	Val	Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp
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<211> LENGTH: 3671

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 6

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<210> SEQ ID NO 7

<211> LENGTH: 1106

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 7

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His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
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Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
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Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
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Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
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        180            185            190
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Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile
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Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe
225            230            235            240
Val Ser Leu Asp His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro
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 <211> LENGTH: 2312
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gtaaataagt ctatgaactc tagaagatct ctggcttcta ggaggctctt tattaatatg    1500
gttttagacc acgtggagga catggaggaa agacttgacg acagcagtgga agcaaagggt    1560
cctgaagatt atccagaaga aggggtggag gaaagcagtg gcgaagcctc caagtataca    1620
gaagaggatc cttccggaga aacactgtct tcagaaaaca agtccagctg gttaatgacg    1680
tctaagccta gtgctctagc tcaagagacc tctcttggtg cccctgagcc tttgtctggt    1740
gaacagttgg ttggttctcc ccaggataag ggggcagagg ctacaaatga ctatgagact    1800
cttgtaaagc gtggaaaaga actaaaagag tgtggaaaaa tccaggaggc cctaaactgc    1860

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ttagttaag cgcttgacat aaaaagtga gatcctgaag ttatgctctt gactttaagt 1920
ttgtataagc aacttaataa caattgagaa tgtaacctgt ttattgtatt ttaaagtga 1980
actgaatatg agggaatfff tggtcccata attggattct ttgggaacat gaagcattca 2040
ggcttaaggc aagaaagatc tcaaaaagca acttctgccc tgcaacgccc cccactccat 2100
agtctgggat tctgagcact agcttaatat ttcttcactt gaatattctt atattttagg 2160
catattctat aaatttaact gtgtgtgttc ttggaaagtt ttgtaaaatt attctgggtca 2220
ttcttaattt tactctgaaa gtgatcatct ttgtatataa cagttcagat aagaaaatta 2280
aagttacttt tctcaaaaaa aaaaaaaaaa aa 2312

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<210> SEQ ID NO 9

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 9

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Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
  1             5             10            15
Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
          20            25            30
Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
          35            40            45
Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
          50            55            60
Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
          65            70            75            80
Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
          85            90            95
Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
          100           105           110
Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
          115           120           125
Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
          130           135           140
Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Lys Ala Gly
          145           150           155           160
Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
          165           170           175
Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
          180           185           190
Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
          195           200           205
Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
          210           215           220
Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
          225           230           235           240
Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met
          245           250           255
Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val
          260           265           270
Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu

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275	280	285
Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser		
290	295	300
Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu		
305	310	315
Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala		
	325	330
Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu		
	340	345
Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp		
	355	360
Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys		
	370	375
Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser		
	385	390
Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu		
	405	410

Asn Asn Asn

<210> SEQ ID NO 10

<211> LENGTH: 1720

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 10

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ggcacgaggc caccttgcaa gatggtaaag gtacaggtag tgctgactct atagctactt    60
taccaaaggg gtttgaagt gtagaagaac tttgtactaa ctcttcattg ggaatggaaa    120
aaagctttgc aactaaaat gaagctgtac aaaaagagac attacaagag gggcctaagc    180
aagaggcact gcaagaggat cctctggaaa gttttaatta tgtacttagc aaatcaacca    240
aagctgatat tgggccaaat ttagatcaac taaaggatga tgagatttta cgtcattgca    300
atccttggcc cattatttcc ataacaaatg aaagtcaaaa tgcagaatca aatgtatcca    360
ttattgaaat agctgatgac ctttcagcat cccatagtgc actgcaggat gctcaagcaa    420
gtgaggccaa gttggaagag gaaccttcag catcttcacc acagtatgca tgtgatttca    480
atcttttctt ggaagactca gcagacaaca gacaaaatth ttccagtcag tctttagagc    540
atgttgagaa agaaaatagc ttgtgtggct ctgcacctaa ttccagagca gggtttgtgc    600
atagcaaaac atgtctcagt tgggagtttt ctgagaaaga cgatgaacca gaagaagtag    660
tagttaaagc aaaaatcaga agtaaagcta gaaggattgt ttcagatggc gaagatgaag    720
atgattcttt taaagatacc tcaagcataa atccattcaa cacatctctc ttcaattct    780
catctgtgaa acaatttgat gcttcaactc ccaaaaatga catcagtcca ccaggaaggt    840
tcttttcata tcaaatatcc agtagtgtaa ataagtctat gaactctaga agatctctgg    900
cttctaggag gtctcttatt aatatggttt tagaccacgt ggaggacatg gaggaaagac    960
ttgacgacag cagtgaagca aagggtcctg aagattatcc agaagaaggg gtggaggaaa   1020
gcagtggcga agcctccaag tatacagaag aggatccttc cggagaaaca ctgtcttcag   1080
aaaacaagtc cagctgggta atgacgtcta agcctagtgc tctagctcaa gagacctctc   1140
ttggtgcccc tgagcctttg tctgggtgaa agttgggttg ttctccccag gataaggcgg   1200

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cagaggctac aaatgactat gagactcttg taaagcgtgg aaaagaacta aaagagtgtg 1260
gaaaaatcca ggaggcccta aactgcttag ttaaagcgct tgacataaaa agtgcagatc 1320
ctgaagttat gctcttgact ttaagtttgt ataagcaact taataacaat tgagaatgta 1380
acctgtttat tgtattttaa agtgaaactg aatatgaggg aatttttgtt cccataattg 1440
gattcttttg gaacatgaag cattcaggct taaggcaaga aagatctcaa aaagcaactt 1500
ctgccctgca acgcccccca ctccatagtc tgggtattctg agcactagct taatatttct 1560
tcacttgaat attcttatat tttaggcata ttctataaat ttaactgtgt tgtttcttgg 1620
aaagttttgt aaaattattc tggtcattct taattttact ctgaaagtga tcatctttgt 1680
atataacagt tcagataaga aaattaaagt tactttttctc 1720

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<210> SEQ ID NO 11

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 11

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Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
  1             5             10            15
Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
      20            25            30
Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
      35            40            45
Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
      50            55            60
Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
      65            70            75            80
Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
      85            90            95
Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
      100           105           110
Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
      115           120           125
Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
      130           135           140
Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly
      145           150           155           160
Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
      165           170           175
Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
      180           185           190
Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
      195           200           205
Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
      210           215           220
Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
      225           230           235           240
Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met
      245           250           255
Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val
      260           265           270

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Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu
275 280 285
Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser
290 295 300
Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu
305 310 315 320
Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala
325 330 335
Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu
340 345 350
Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp
355 360 365
Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys
370 375 380
Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser
385 390 395 400
Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
405 410 415
Asn Asn Asn

<210> SEQ ID NO 12

<211> LENGTH: 1250

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 12

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
1 5 10 15
Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
20 25 30
Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
35 40 45
Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
50 55 60
Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
65 70 75 80
Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
85 90 95
Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
100 105 110
Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
115 120 125
Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
130 135 140
Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
145 150 155 160
Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe
165 170 175
His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
180 185 190
Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
195 200 205

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Trp	Gln	Gln	Leu	Ser	Ser	Phe	Arg	Gly	Gln	Glu	Phe	Val	Trp	Asp	Tyr	210	215	220
Val	Ile	Leu	Asp	Glu	Ala	His	Lys	Ile	Lys	Thr	Ser	Ser	Thr	Lys	Ser	225	230	235
Ala	Ile	Cys	Ala	Arg	Ala	Ile	Pro	Ala	Ser	Asn	Arg	Leu	Leu	Leu	Thr	245	250	255
Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu	Trp	Ser	Leu	Phe	Asp	260	265	270
Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu	Lys	Thr	Phe	Lys	Met	275	280	285
Glu	Tyr	Glu	Asn	Pro	Ile	Thr	Arg	Ala	Arg	Glu	Lys	Asp	Ala	Thr	Pro	290	295	300
Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Ile	Ser	Glu	Asn	Leu	Met	Ala	Ile	305	310	315
Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu	Asp	Val	Gln	Lys	Lys	325	330	335
Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu	Lys	Asn	Pro	Asp	Val	340	345	350
Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Lys	Asn	Asp	Leu	Ile	355	360	365
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe	370	375	380
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro	385	390	395
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu	405	410	415
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala	420	425	430
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp	435	440	445
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe	450	455	460
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu	465	470	475
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu	485	490	495
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His	500	505	510
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp	515	520	525
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr	530	535	540
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro	545	550	555
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys	565	570	575
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu	580	585	590
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr	595	600	605

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Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu
610						615					620				
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu
625					630					635					640
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu
				645					650					655	
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser
			660					665					670		
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu
		675					680					685			
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala
	690					695					700				
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu
705					710					715					720
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe
				725					730					735	
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro
			740					745					750		
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile
			755				760					765			
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly
	770					775					780				
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln
785					790					795					800
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys
				805					810					815	
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met
			820					825					830		
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu
		835					840					845			
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser
	850					855					860				
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn
865					870					875					880
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro	Trp
				885					890					895	
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val
			900					905						910	
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu
		915					920					925			
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala
	930					935						940			
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser
945					950					955					960
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu
				965					970					975	
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe
		980						985					990		
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp
		995					1000					1005			
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg

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1010	1015	1020
Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr		
1025	1030	1035 1040
Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val		
	1045	1050 1055
Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly		
	1060	1065 1070
Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn		
	1075	1080 1085
Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu		
	1090	1095 1100
Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala		
	1105	1110 1115 1120
Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly		
	1125	1130 1135
Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser		
	1140	1145 1150
Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu		
	1155	1160 1165
Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln		
	1170	1175 1180
Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr		
	1185	1190 1195 1200
Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile		
	1205	1210 1215
Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala		
	1220	1225 1230
Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn		
	1235	1240 1245
Asn Asn		
1250		

<210> SEQ ID NO 13

<211> LENGTH: 1127

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 13

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

Ser	Ser	Thr	Lys	Ser	Ala	Ile	Cys	Ala	Arg	Ala	Ile	Pro	Ala	Ser	Asn
		115					120					125			
Arg	Leu	Leu	Leu	Thr	Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu
	130					135					140				
Trp	Ser	Leu	Phe	Asp	Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu
145					150					155					160
Lys	Thr	Phe	Lys	Met	Glu	Tyr	Glu	Asn	Pro	Ile	Thr	Arg	Ala	Arg	Glu
				165					170					175	
Lys	Asp	Ala	Thr	Pro	Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Ile	Ser	Glu
			180					185					190		
Asn	Leu	Met	Ala	Ile	Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu
		195					200					205			
Asp	Val	Gln	Lys	Lys	Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu
	210					215					220				
Lys	Asn	Pro	Asp	Val	Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg
225					230					235					240
Lys	Asn	Asp	Leu	Ile	Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu
			245						250					255	
Ile	Tyr	Arg	Lys	Phe	Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met
			260					265					270		
Glu	Thr	Arg	Ser	Pro	Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys
		275					280					285			
Asp	His	Pro	Arg	Leu	Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu
	290					295					300				
Gly	Thr	Phe	Ser	Ala	Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp
305					310					315					320
Val	Asp	His	Ile	Asp	Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser
			325						330					335	
Gly	Lys	Met	Ile	Phe	Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu
			340					345					350		
Gly	His	Gln	Thr	Leu	Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile
		355					360					365			
Ile	Glu	Arg	Leu	Leu	Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp
	370					375					380				
Gly	Thr	Val	Thr	His	Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe
385					390					395					400
Gln	Gln	Asn	Lys	Asp	Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly
			405						410					415	
Gly	Val	Gly	Leu	Thr	Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp
			420					425					430		
Pro	Ser	Trp	Asn	Pro	Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr
		435					440					445			
Arg	Ile	Gly	Gln	Lys	Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys
						455					460				
Gly	Thr														

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515					520					525					
Ser	Asp	Ile	Lys	Leu	Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly
530					535						540				
Ile	Ala	Gly	Ile	Ser	Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser
545					550					555				560	
Val	Lys	Glu	Glu	Leu	Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln
				565					570					575	
Arg	Val	Gln	Lys	Ala	Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys
			580					585					590		
Glu	Phe	Leu	Met	Glu	Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu
	595						600					605			
Arg	Glu	Pro	Val	Phe	Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu
610						615					620				
Asn	Lys	Pro	Gln	Pro	Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr
625					630					635					640
Gln	Glu	Glu	Asp	Ile	Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp
				645					650					655	
Leu	Pro	Lys	Glu	Gly	Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn
			660					665					670		
Val	Thr	Thr	Leu	Gln	Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile
		675					680					685			
Ala	Thr	Leu	Pro	Lys	Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn
	690					695					700				
Ser	Ser	Leu	Gly	Met	Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val
705					710					715					720
Gln	Lys	Glu	Thr	Leu	Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu
				725					730					735	
Asp	Pro	Leu	Glu	Ser	Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala
			740					745					750		
Asp	Ile	Gly	Pro	Asn	Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg
		755					760					765			
His	Cys	Asn	Pro	Trp	Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn
	770					775					780				
Ala	Glu	Ser	Asn	Val	Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala
785					790					795					800
Ser	His	Ser	Ala	Leu	Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu
				805					810					815	
Glu	Glu	Pro	Ser	Ala	Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu
			820					825					830		
Phe	Leu	Glu	Asp	Ser	Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser
		835					840					845			
Leu	Glu	His	Val	Glu	Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn
		850				855					860				
Ser	Arg	Ala	Gly	Phe	Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe
865					870					875					880
Ser	Glu	Lys	Asp	Asp	Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile
				885					890					895	
Arg	Ser	Lys	Ala	Arg	Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp
			900					905					910		
Ser	Phe	Lys	Asp	Thr	Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe
		915					920					925			

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Gln Phe Ser Ser Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp
 930 935 940
 Ile Ser Pro Pro Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val
 945 950 955 960
 Asn Lys Ser Met Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu
 965 970 975
 Ile Asn Met Val Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp
 980 985 990
 Asp Ser Ser Glu Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val
 995 1000 1005
 Glu Glu Ser Ser Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser
 1010 1015 1020
 Gly Glu Thr Leu Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser
 1025 1030 1035 1040
 Lys Pro Ser Ala Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro
 1045 1050 1055
 Leu Ser Gly Glu Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu
 1060 1065 1070
 Ala Thr Asn Asp Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys
 1075 1080 1085
 Glu Cys Gly Lys Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu
 1090 1095 1100
 Asp Ile Lys Ser Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu
 1105 1110 1115 1120
 Tyr Lys Gln Leu Asn Asn Asn
 1125

<210> SEQ ID NO 14
 <211> LENGTH: 1250
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 14

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
 1 5 10 15
 Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
 20 25 30
 Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
 35 40 45
 Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
 50 55 60
 Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
 65 70 75 80
 Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
 85 90 95
 Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
 100 105 110
 Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
 115 120 125
 Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
 130 135 140
 Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp

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145	150	155	160
Val Lys Glu Phe Ile	Lys Trp Thr Pro Gly Met Gly Val Lys Thr Phe		
	165	170	175
His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln			
	180	185	190
Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn			
	195	200	205
Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr			
	210	215	220
Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser			
	225	230	235
Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr			
	245	250	255
Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp			
	260	265	270
Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met			
	275	280	285
Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro			
	290	295	300
Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile			
	305	310	315
Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys			
	325	330	335
Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val			
	340	345	350
Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile			
	355	360	365
Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe			
	370	375	380
Val Ser Leu Asp His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro			
	385	390	395
Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys Asp His Pro Arg Leu			
	405	410	415
Leu Ser Ala Arg Ala Cys Cys Leu Leu Asn Leu Gly Thr Phe Ser Ala			
	420	425	430
Gln Asp Gly Asn Glu Gly Glu Asp Ser Pro Asp Val Asp His Ile Asp			
	435	440	445
Gln Val Thr Asp Asp Thr Leu Met Glu Glu Ser Gly Lys Met Ile Phe			
	450	455	460
Leu Met Asp Leu Leu Lys Arg Leu Arg Asp Glu Gly His Gln Thr Leu			
	465	470	475
Val Phe Ser Gln Ser Arg Gln Ile Leu Asn Ile Ile Glu Arg Leu Leu			
	485	490	495
Lys Asn Arg His Phe Lys Thr Leu Arg Ile Asp Gly Thr Val Thr His			
	500	505	510
Leu Leu Glu Arg Glu Lys Arg Ile Asn Leu Phe Gln Gln Asn Lys Asp			
	515	520	525
Tyr Ser Val Phe Leu Leu Thr Thr Gln Val Gly Gly Val Gly Leu Thr			
	530	535	540
Leu Thr Ala Ala Thr Arg Val Val Ile Phe Asp Pro Ser Trp Asn Pro			
	545	550	555
			560

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Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys	565	570	575
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu	580	585	590
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr	595	600	605
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu	610	615	620
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu	625	630	635
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu	645	650	655
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser	660	665	670
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu	675	680	685
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala	690	695	700
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu	705	710	715
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe	725	730	735
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro	740	745	750
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile	755	760	765
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly	770	775	780
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln	785	790	795
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys	805	810	815
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met	820	825	830
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu	835	840	845
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser	850	855	860
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn	865	870	875
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro	Trp	885	890	895
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val	900	905	910
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu	915	920	925
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala	930	935	940
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser	945	950	955

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Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu
965 970 975

Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe
980 985 990

Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp
995 1000 1005

Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg
1010 1015 1020

Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr
1025 1030 1035 1040

Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val
1045 1050 1055

Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly
1060 1065 1070

Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn
1075 1080 1085

Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu
1090 1095 1100

Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala
1105 1110 1115 1120

Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly
1125 1130 1135

Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser
1140 1145 1150

Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu
1155 1160 1165

Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln
1170 1175 1180

Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr
1185 1190 1195 1200

Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile
1205 1210 1215

Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
1220 1225 1230

Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
1235 1240 1245

Asn Asn
1250

<210> SEQ ID NO 15

<211> LENGTH: 1250

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 15

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
1 5 10 15

Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
20 25 30

Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
35 40 45

Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
50 55 60

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Glu	Ala	Leu	Glu	Glu	Leu	Ala	Glu	Gln	Gly	Asp	Asp	Glu	Phe	Thr	Asp	
65					70					75					80	
Val	Cys	Asn	Ser	Gly	Leu	Leu	Leu	Tyr	Arg	Glu	Leu	His	Asn	Gln	Leu	
				85					90					95		
Phe	Glu	His	Gln	Lys	Glu	Gly	Ile	Ala	Phe	Leu	Tyr	Ser	Leu	Tyr	Arg	
			100					105					110			
Asp	Gly	Arg	Lys	Gly	Gly	Ile	Leu	Ala	Asp	Asp	Met	Gly	Leu	Gly	Lys	
			115				120						125			
Thr	Val	Gln	Ile	Ile	Ala	Phe	Leu	Ser	Gly	Met	Phe	Asp	Ala	Ser	Leu	
			130				135					140				
Val	Asn	His	Val	Leu	Leu	Ile	Met	Pro	Thr	Asn	Leu	Ile	Asn	Thr	Trp	
145				150						155					160	
Val	Lys	Glu	Phe	Ile	Lys	Trp	Thr	Pro	Gly	Met	Arg	Val	Lys	Thr	Phe	
				165					170					175		
His	Gly	Pro	Ser	Lys	Asp	Glu	Arg	Thr	Arg	Asn	Leu	Asn	Arg	Ile	Gln	
			180					185					190			
Gln	Arg	Asn	Gly	Val	Ile	Ile	Thr	Thr	Tyr	Gln	Met	Leu	Ile	Asn	Asn	
		195					200					205				
Trp	Gln	Gln	Leu	Ser	Ser	Phe	Arg	Gly	Gln	Glu	Phe	Val	Trp	Asp	Tyr	
		210					215					220				
Val	Ile	Leu	Asp	Glu	Ala	His	Lys	Ile	Lys	Thr	Ser	Ser	Thr	Lys	Ser	
225					230					235					240	
Ala	Ile	Cys	Ala	Arg	Ala	Ile	Pro	Ala	Ser	Asn	Arg	Leu	Leu	Leu	Thr	
				245					250					255		
Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu	Trp	Ser	Leu	Phe	Asp	
			260				265						270			
Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu	Lys	Thr	Phe	Lys	Met	
		275					280					285				
Glu	Tyr	Glu	Asn	Pro	Ile	Thr	Arg	Ala	Arg	Glu	Lys	Asp	Ala	Thr	Pro	
		290				295					300					
Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Ile	Ser	Glu	Asn	Leu	Met	Ala	Ile	
305					310					315					320	
Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu	Asp	Val	Gln	Lys	Lys	
				325					330					335		
Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu	Lys	Asn	Pro	Asp	Val	
			340					345					350			
Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Arg	Asn	Asp	Leu	Ile	
		355					360					365				
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe	
		370				375					380					
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro	
385					390					395					400	
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu	
				405					410					415		
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala	
			420					425					430			
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp	
		435					440					445				
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe	
		450				455					460					

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Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu	465	470	475	480
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu	485	490	495	
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His	500	505	510	
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp	515	520	525	
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr	530	535	540	
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro	545	550	555	560
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys	565	570	575	
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu	580	585	590	
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr	595	600	605	
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu	610	615	620	
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu	625	630	635	640
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu	645	650	655	
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser	660	665	670	
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu	675	680	685	
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala	690	695	700	
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu	705	710	715	720
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe	725	730	735	
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro	740	745	750	
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile	755	760	765	
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly	770	775	780	
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln	785	790	795	800
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys	805	810	815	
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met	820	825	830	
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu	835	840	845	
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser	850	855	860	
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn				

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865	870	875	880
Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro Trp	885	890	895
Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn Val	900	905	910
Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala Leu	915	920	925
Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser Ala	930	935	940
Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp Ser	945	950	955
Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu	965	970	975
Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe	980	985	990
Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp	995	1000	1005
Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg	1010	1015	1020
Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr	1025	1030	1035
Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val	1045	1050	1055
Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly	1060	1065	1070
Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn	1075	1080	1085
Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu	1090	1095	1100
Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala	1105	1110	1115
Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly	1125	1130	1135
Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser	1140	1145	1150
Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu	1155	1160	1165
Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln	1170	1175	1180
Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr	1185	1190	1195
Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile	1205	1210	1215
Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala	1220	1225	1230
Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn	1235	1240	1245
Asn Asn	1250		

-continued

<211> LENGTH: 1250

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 16

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
1 5 10 15

Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
20 25 30

Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
35 40 45

Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
50 55 60

Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
65 70 75 80

Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
85 90 95

Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
100 105 110

Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
115 120 125

Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
130 135 140

Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
145 150 155 160

Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe
165 170 175

His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
180 185 190

Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
195 200 205

Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
210 215 220

Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
225 230 235 240

Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
245 250 255

Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
260 265 270

Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
275 280 285

Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
290 295 300

Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
305 310 315 320

Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
325 330 335

Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val
340 345 350

Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile
355 360 365

Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe

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370					375					380					
Val 385	Ser	Leu	Asp	His	Ile 390	Lys	Glu	Leu	Leu	Met 395	Glu	Thr	Arg	Ser	Pro 400
Leu	Ala	Glu	Leu	Gly 405	Val	Leu	Lys	Lys	Leu 410	Cys	Asp	His	Pro	Arg	Leu 415
Leu	Ser	Ala	Arg	Ala 420	Cys	Cys	Leu	Leu 425	Asn	Leu	Gly	Thr	Phe 430	Ser	Ala
Gln	Asp	Gly 435	Asn	Glu	Gly	Glu	Asp 440	Ser	Pro	Asp	Val	Asp 445	His	Ile	Asp
Gln	Val	Thr	Asp	Asp	Thr 455	Leu	Met	Glu	Glu	Ser	Gly 460	Lys	Met	Ile	Phe
Leu 465	Met	Asp	Leu	Leu 470	Lys	Arg	Leu	Arg	Asp	Glu 475	Gly	His	Gln	Thr	Leu 480
Val	Phe	Ser	Gln	Ser 485	Arg	Gln	Ile	Leu	Asn 490	Ile	Ile	Glu	Arg	Leu 495	Leu
Lys	Asn	Arg	His 500	Phe	Lys	Thr	Leu	Arg 505	Ile	Asp	Gly	Thr	Val 510	Thr	His
Leu	Leu	Glu 515	Arg	Glu	Lys	Arg	Ile 520	Asn	Leu	Phe	Gln	Gln 525	Asn	Lys	Asp
Tyr 530	Ser	Val	Phe	Leu	Leu 535	Thr	Gln	Val	Gly 540	Gly	Val	Gly	Leu	Thr	
Leu 545	Thr	Ala	Ala	Thr 550	Arg	Val	Val	Ile	Phe 555	Asp	Pro	Ser	Trp	Asn	Pro 560
Ala	Thr	Asp	Ala 565	Gln	Ala	Val	Asp	Arg 570	Val	Tyr	Arg	Ile	Gly	Gln	Lys
Glu	Asn	Val 580	Val	Val	Tyr	Arg	Leu 585	Ile	Thr	Cys	Gly	Thr 590	Val	Glu	Glu
Lys	Ile 595	Tyr	Arg	Arg	Gln	Val	Phe 600	Lys	Asp	Ser	Leu	Ile 605	Arg	Gln	Thr
Thr 610	Gly	Glu	Lys	Lys	Asn 615	Pro	Phe	Arg	Tyr	Phe 620	Ser	Lys	Gln	Glu	Leu
Arg 625	Glu	Leu	Phe	Thr 630	Ile	Glu	Asp	Leu	Gln	Asn 635	Ser	Val	Thr	Gln	Leu 640
Gln	Leu	Gln	Ser 645	Leu	His	Ala	Ala	Gln	Arg 650	Lys	Ser	Asp	Ile	Lys	Leu 655
Asp	Glu	His 660	Ile	Ala	Tyr	Leu	Gln 665	Ser	Leu	Gly	Ile	Ala 670	Gly	Ile	Ser
Asp	His 675	Asp	Leu	Met	Tyr	Thr	Cys 680	Asp	Leu	Ser	Val	Lys 685	Glu	Glu	Leu
Asp 690	Val	Val	Glu	Glu	Ser	His 695	Tyr	Ile	Gln	Gln 700	Arg	Val	Gln	Lys	Ala
Gln 705	Phe	Leu	Val	Glu	Phe 710	Glu	Ser	Gln	Asn	Lys 715	Glu	Phe	Leu	Met	Glu 720
Gln	Gln	Arg	Thr 725	Arg	Asn	Glu	Gly	Ala 730	Trp	Leu	Arg	Glu	Pro	Val	Phe
Pro	Ser	Ser 740	Thr	Lys	Lys	Lys	Cys	Pro 745	Lys	Leu	Asn	Lys	Pro 750	Gln	Pro
Gln 755	Pro	Ser	Pro	Leu	Leu	Ser	Thr 760	His	His	Thr	Gln 765	Glu	Glu	Asp	Ile
Ser 770	Ser	Lys	Met	Ala	Ser 775	Val	Val	Ile	Asp	Asp 780	Leu	Pro	Lys	Glu	Gly

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Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln	785	790	795	800
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys	805	810	815	
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met	820	825	830	
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu	835	840	845	
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser	850	855	860	
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn	865	870	875	880
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Val	Leu	Arg	His	Cys	Asn	Pro	Trp	885	890	895	
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val	900	905	910	
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu	915	920	925	
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Pro	Ser	Ala		930	935	940	
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser	945	950	955	960
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu	965	970	975	
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe	980	985	990	
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp	995	1000	1005	
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg	1010	1015	1020	
Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Asp	Ser	Phe	Lys	Asp	Thr			1025	1030	1035	1040
Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser	Val	1045	1050	1055	
Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	Ile	Ser	Pro	Pro	Gly	1060	1065	1070	
Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	Asn	Lys	Ser	Met	Asn	1075	1080	1085	
Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	Ile	Asn	Met	Val	Leu	1090	1095	1100	
Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	Asp	Ser	Ser	Glu	Ala	1105	1110	1115	1120
Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	Glu	Glu	Ser	Ser	Gly	1125	1130	1135	
Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	Gly	Glu	Thr	Leu	Ser	1140	1145	1150	
Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	Lys	Pro	Ser	Ala	Leu	1155	1160	1165	
Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	Leu	Ser	Gly	Glu	Gln	1170	1175	1180	

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Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr
 1185 1190 1195 1200

Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile
 1205 1210 1215

Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
 1220 1225 1230

Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
 1235 1240 1245

Asn Asn
 1250

<210> SEQ ID NO 17
 <211> LENGTH: 1106
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 17

Met Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
 1 5 10 15

Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Gly Val Lys Thr Phe
 20 25 30

His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
 35 40 45

Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
 50 55 60

Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
 65 70 75 80

Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
 85 90 95

Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
 100 105 110

Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
 115 120 125

Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
 130 135 140

Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
 145 150 155 160

Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
 165 170 175

Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
 180 185 190

Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val
 195 200 205

Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile
 210 215 220

Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe
 225 230 235 240

Val Ser Leu Asp His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro
 245 250 255

Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys Asp His Pro Arg Leu
 260 265 270

Leu Ser Ala Arg Ala Cys Cys Leu Leu Asn Leu Gly Thr Phe Ser Ala
 275 280 285

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Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp
290						295					300				
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe
305					310					315					320
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu
			325						330					335	
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu
			340					345					350		
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His
	355						360					365			
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp
370						375					380				
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr
385					390					395					400
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro
				405					410					415	
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys
			420					425					430		
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu
	435						440					445			
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr
450						455					460				
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu
465					470					475					480
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu
			485						490					495	
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu
			500					505					510		
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser
	515						520				525				
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu
530						535					540				
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala
545						550				555					560
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu
			565						570					575	
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe
			580					585					590		
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro
	595						600					605			
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile
610						615					620				
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly
625					630					635					640
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln
			645						650					655	
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys
	660							665					670		
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met
675							680						685		

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Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu
690						695					700				
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser
705					710					715					720
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn
				725					730					735	
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Val	Leu	Arg	His	Cys	Asn	Pro	Trp
			740					745					750		
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val
	755						760					765			
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu
	770					775						780			
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala
785					790					795					800
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser
				805					810					815	
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu
				820				825					830		
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe
		835					840					845			
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp
	850					855					860				
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg
865					870					875					880
Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	Ser	Phe	Lys	Asp	Thr
				885					890					895	
Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser	Val
			900					905					910		
Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	Ile	Ser	Pro	Pro	Gly
		915					920					925			
Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	Asn	Lys	Ser	Met	Asn
	930					935					940				
Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	Ile	Asn	Met	Val	Leu
945					950					955					960
Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	Asp	Ser	Ser	Glu	Ala
				965					970					975	
Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	Glu	Glu	Ser	Ser	Gly
		980						985					990		
Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	Gly	Glu	Thr	Leu	Ser
		995					1000					1005			
Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	Lys	Pro	Ser	Ala	Leu
	1010					1015					1020				
Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	Leu	Ser	Gly	Glu	Gln
1025					1030					1035					1040
Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu	Ala	Thr	Asn	Asp	Tyr
				1045					1050					1055	
Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys	Glu	Cys	Gly	Lys	Ile
		1060						1065					1070		
Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu	Asp	Ile	Lys	Ser	Ala
	1075						1080					1085			
Asp	Pro	Glu	Val	Met	Leu	Leu	Thr	Leu	Ser	Leu	Tyr	Lys	Gln	Leu	Asn

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1090	1095	1100
Asn Asn		
1105		
<210> SEQ ID NO 18		
<211> LENGTH: 419		
<212> TYPE: PRT		
<213> ORGANISM: Homo Sapiens		
<400> SEQUENCE: 18		
Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr		
1 5 10 15		
Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu		
20 25 30		
Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro		
35 40 45		
Asn Leu Asp Gln Leu Lys Asp Glu Ile Leu Arg His Cys Asn Pro		
50 55 60		
Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn		
65 70 75 80		
Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala		
85 90 95		
Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser		
100 105 110		
Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp		
115 120 125		
Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val		
130 135 140		
Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Lys Ala Gly		
145 150 155 160		
Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp		
165 170 175		
Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala		
180 185 190		
Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp		
195 200 205		
Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser		
210 215 220		
Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro		
225 230 235 240		
Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met		
245 250 255		
Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val		
260 265 270		
Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu		
275 280 285		
Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser		
290 295 300		
Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu		
305 310 315 320		
Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala		
325 330 335		

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Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu
      340                      345                      350

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

Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys
      370                      375                      380

Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser
      385                      390                      395                      400

Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
      405                      410                      415

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Asn Asn Asn

<210> SEQ ID NO 19

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 19

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Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
  1           5           10           15

Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
      20           25           30

Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
      35           40           45

Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
      50           55           60

Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
      65           70           75           80

Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
      85           90           95

Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
      100          105          110

Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
      115          120          125

Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
      130          135          140

Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly
      145          150          155          160

Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
      165          170          175

Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
      180          185          190

Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
      195          200          205

Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
      210          215          220

Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
      225          230          235          240

Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met
      245          250          255

Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val
      260          265          270

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Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu
 275 280 285
 Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser
 290 295 300
 Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu
 305 310 315 320
 Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala
 325 330 335
 Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu
 340 345 350
 Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp
 355 360 365
 Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys
 370 375 380
 Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser
 385 390 395 400
 Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
 405 410 415
 Asn Asn Asn

<210> SEQ ID NO 20
 <211> LENGTH: 1106
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 20

Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
 1 5 10 15
 Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe
 20 25 30
 His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
 35 40 45
 Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
 50 55 60
 Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
 65 70 75 80
 Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
 85 90 95
 Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
 100 105 110
 Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
 115 120 125
 Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
 130 135 140
 Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
 145 150 155 160
 Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
 165 170 175
 Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
 180 185 190
 Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val
 195 200 205

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Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Lys	Asn	Asp	Leu	Ile
210						215					220				
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe
225					230					235					240
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro
				245						250				255	
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu
			260					265					270		
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala
		275					280					285			
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp
	290					295					300				
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe
305					310					315					320
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu
				325					330					335	
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu
			340					345					350		
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His
		355					360					365			
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp
	370					375					380				
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr
385					390					395					400
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro
				405					410					415	
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys
			420				425						430		
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu
		435					440					445			
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr
	450				455						460				
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu
465					470					475					480
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu
				485					490					495	
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu
			500					505					510		
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser
		515					520					525			
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu
	530					535					540				
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala
545					550					555					560
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu
				565					570					575	
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe
			580					585					590		
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro
		595					600					605			
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile

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610	615	620
Ser Ser Lys Met Ala	Ser Val Val Ile Asp Asp	Leu Pro Lys Glu Gly
625	630	635 640
Glu Lys Gln Asp Leu	Ser Ser Ile Lys Val Asn Val Thr Thr Leu Gln	
	645	650 655
Asp Gly Lys Gly Thr	Gly Ser Ala Asp Ser Ile Ala Thr Leu Pro Lys	
	660	665 670
Gly Phe Gly Ser Val	Glu Glu Leu Cys Thr Asn Ser Ser Leu Gly Met	
	675	680 685
Glu Lys Ser Phe Ala Thr	Lys Asn Glu Ala Val Gln Lys Glu Thr Leu	
	690	695 700
Gln Glu Gly Pro Lys	Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu Ser	
	705	710 715 720
Phe Asn Tyr Val Leu	Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro Asn	
	725	730 735
Leu Asp Gln Leu Lys	Asp Asp Glu Ile Leu Arg His Cys Asn Pro Trp	
	740	745 750
Pro Ile Ile Ser Ile Thr	Asn Glu Ser Gln Asn Ala Glu Ser Asn Val	
	755	760 765
Ser Ile Ile Glu Ile Ala	Asp Asp Leu Ser Ala Ser His Ser Ala Leu	
	770	775 780
Gln Asp Ala Gln Ala	Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser Ala	
	785	790 795 800
Ser Ser Pro Gln Tyr	Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp Ser	
	805	810 815
Ala Asp Asn Arg Gln	Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu	
	820	825 830
Lys Glu Asn Ser Leu Cys	Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe	
	835	840 845
Val His Ser Lys Thr Cys	Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp	
	850	855 860
Glu Pro Glu Glu Val Val	Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg	
	865	870 875 880
Arg Ile Val Ser Asp	Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr	
	885	890 895
Ser Ser Ile Asn Pro Phe	Asn Thr Ser Leu Phe Gln Phe Ser Ser Val	
	900	905 910
Lys Gln Phe Asp Ala	Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly	
	915	920 925
Arg Phe Phe Ser Ser Gln	Ile Pro Ser Ser Val Asn Lys Ser Met Asn	
	930	935 940
Ser Arg Arg Ser Leu Ala	Ser Arg Arg Ser Leu Ile Asn Met Val Leu	
	945	950 955 960
Asp His Val Glu Asp	Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala	
	965	970 975
Lys Gly Pro Glu Asp Tyr	Pro Glu Glu Gly Val Glu Glu Ser Ser Gly	
	980	985 990
Glu Ala Ser Lys Tyr Thr	Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser	
	995	1000 1005
Ser Glu Asn Lys Ser Ser	Trp Leu Met Thr Ser Lys Pro Ser Ala Leu	
	1010	1015 1020

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Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln
 1025 1030 1035 1040

Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr
 1045 1050 1055

Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile
 1060 1065 1070

Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
 1075 1080 1085

Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
 1090 1095 1100

Asn Asn
 1105

<210> SEQ ID NO 21
 <211> LENGTH: 1106
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 21

Met Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
 1 5 10 15

Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Gly Val Lys Thr Phe
 20 25 30

His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
 35 40 45

Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
 50 55 60

Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
 65 70 75 80

Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
 85 90 95

Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
 100 105 110

Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
 115 120 125

Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
 130 135 140

Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
 145 150 155 160

Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
 165 170 175

Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
 180 185 190

Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val
 195 200 205

Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile
 210 215 220

Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe
 225 230 235 240

Val Ser Leu Asp His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro
 245 250 255

Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys Asp His Pro Arg Leu

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260							265					270				
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala	
		275					280					285				
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp	
	290					295					300					
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe	
305					310					315					320	
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu	
			325						330					335		
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu	
			340					345					350			
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His	
		355					360					365				
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp	
	370					375					380					
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr	
385					390					395					400	
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro	
				405					410					415		
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys	
			420					425					430			
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu	
		435					440					445				
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr	
	450					455					460					
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu	
465					470					475					480	
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu	
				485					490					495		
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu	
			500					505					510			
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser	
		515					520					525				
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu	
	530					535					540					
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala	
545					550					555					560	
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu	
				565					570					575		
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe	
			580					585					590			
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro	
		595					600					605				
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile	
	610					615					620					
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly	
625					630					635					640	
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln	
				645					650					655		
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys	
			660				665						670			

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Gly Phe Gly Ser Val Glu Glu Leu Cys Thr Asn Ser Ser Leu Gly Met	
675	680 685
Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr Leu	
690	695 700
Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu Ser	
705	710 715 720
Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro Asn	
725	730 735
Leu Asp Gln Leu Lys Asp Asp Glu Val Leu Arg His Cys Asn Pro Trp	
740	745 750
Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn Val	
755	760 765
Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala Leu	
770	775 780
Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser Ala	
785	790 795 800
Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp Ser	
805	810 815
Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu	
820	825 830
Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe	
835	840 845
Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp	
850	855 860
Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg	
865	870 875 880
Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Ser Phe Lys Asp Thr	
885	890 895
Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val	
900	905 910
Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly	
915	920 925
Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn	
930	935 940
Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu	
945	950 955 960
Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala	
965	970 975
Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly	
980	985 990
Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser	
995	1000 1005
Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu	
1010	1015 1020
Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln	
1025	1030 1035 1040
Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr	
1045	1050 1055
Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile	
1060	1065 1070

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Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
 1075 1080 1085
 Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
 1090 1095 1100
 Asn Asn
 1105

 <210> SEQ ID NO 22
 <211> LENGTH: 419
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

 <400> SEQUENCE: 22

 Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
 1 5 10 15
 Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
 20 25 30
 Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
 35 40 45
 Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
 50 55 60
 Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
 65 70 75 80
 Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
 85 90 95
 Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
 100 105 110
 Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
 115 120 125
 Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
 130 135 140
 Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly
 145 150 155 160
 Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
 165 170 175
 Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
 180 185 190
 Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
 195 200 205
 Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
 210 215 220
 Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
 225 230 235 240
 Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met
 245 250 255
 Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val
 260 265 270
 Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu
 275 280 285
 Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser
 290 295 300
 Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu
 305 310 315 320

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Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala
 325 330 335

Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu
 340 345 350

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

Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys
 370 375 380

Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser
 385 390 395 400

Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
 405 410 415

Asn Asn Asn

<210> SEQ ID NO 23
 <211> LENGTH: 419
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 23

Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
 1 5 10 15

Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
 20 25 30

Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
 35 40 45

Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
 50 55 60

Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
 65 70 75 80

Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
 85 90 95

Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
 100 105 110

Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
 115 120 125

Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
 130 135 140

Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Lys Ala Gly
 145 150 155 160

Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
 165 170 175

Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
 180 185 190

Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
 195 200 205

Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
 210 215 220

Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
 225 230 235 240

Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met
 245 250 255

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Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val
 260 265 270
 Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu
 275 280 285
 Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser
 290 295 300
 Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu
 305 310 315 320
 Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala
 325 330 335
 Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu
 340 345 350
 Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp
 355 360 365
 Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys
 370 375 380
 Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser
 385 390 395 400
 Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
 405 410 415
 Asn Asn Asn

<210> SEQ ID NO 24
 <211> LENGTH: 1248
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens
 <400> SEQUENCE: 24

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
 1 5 10 15
 Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
 20 25 30
 Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
 35 40 45
 Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
 50 55 60
 Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
 65 70 75 80
 Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
 85 90 95
 Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
 100 105 110
 Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
 115 120 125
 Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
 130 135 140
 Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
 145 150 155 160
 Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe
 165 170 175
 His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
 180 185 190

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Gln	Arg	Asn	Gly	Val	Ile	Ile	Thr	Thr	Tyr	Gln	Met	Leu	Ile	Asn	Asn
	195						200					205			
Trp	Gln	Gln	Leu	Ser	Ser	Phe	Arg	Gly	Gln	Glu	Phe	Val	Trp	Asp	Tyr
	210					215					220				
Val	Ile	Leu	Asp	Glu	Ala	His	Lys	Ile	Lys	Thr	Ser	Ser	Thr	Lys	Ser
	225				230					235					240
Ala	Ile	Cys	Ala	Arg	Ala	Ile	Pro	Ala	Ser	Asn	Arg	Leu	Leu	Leu	Thr
				245					250					255	
Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu	Trp	Ser	Leu	Phe	Asp
			260					265					270		
Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu	Lys	Thr	Phe	Lys	Met
	275					280						285			
Glu	Tyr	Glu	Asn	Pro	Ile	Thr	Arg	Ala	Arg	Glu	Lys	Asp	Ala	Thr	Pro
	290					295					300				
Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Ile	Ser	Glu	Asn	Leu	Met	Ala	Ile
	305				310					315					320
Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu	Asp	Val	Gln	Lys	Lys
				325					330					335	
Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu	Lys	Asn	Pro	Asp	Val
			340					345					350		
Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Lys	Asn	Asp	Leu	Ile
	355						360					365			
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe
	370					375					380				
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro
	385				390					395					400
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu
			405						410					415	
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala
			420					425					430		
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp
	435						440					445			
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe
	450					455					460				
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu
	465				470					475					480
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu
			485					490						495	
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His
			500					505					510		
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp
	515						520					525			
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr
	530					535					540				
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro
	545				550					555					560
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys
			565						570					575	
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu
			580					585					590		

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Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr
	595						600					605			
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu
	610					615					620				
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu
625					630					635					640
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu
				645					650					655	
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser
		660						665					670		
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu
		675					680					685			
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala
	690					695					700				
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu
705					710					715					720
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe
				725					730						735
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro
			740					745					750		
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile
		755					760					765			
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly
	770					775					780				
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln
785					790					795					800
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys
				805					810					815	
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met
			820					825					830		
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu
		835					840					845			
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser
	850					855					860				
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn
865					870					875					880
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro	Trp
				885					890					895	
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val
			900					905					910		
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu
		915					920					925			
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala
	930					935					940				
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser
945					950					955					960
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu
				965					970					975	
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe
		980						985					990		
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp

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995	1000	1005
Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg		
1010	1015	1020
Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Ser Phe Lys Asp Thr		
1025	1030	1035 1040
Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val		
	1045	1050 1055
Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly		
	1060	1065 1070
Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn		
	1075	1080 1085
Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu		
	1090	1095 1100
Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala		
1105	1110	1115 1120
Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly		
	1125	1130 1135
Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser		
	1140	1145 1150
Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu		
	1155	1160 1165
Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln		
	1170	1175 1180
Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr		
1185	1190	1195 1200
Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile		
	1205	1210 1215
Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala		
	1220	1225 1230
Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn		
	1235	1240 1245
<210> SEQ ID NO 25		
<211> LENGTH: 1229		
<212> TYPE: PRT		
<213> ORGANISM: Homo Sapiens		
<400> SEQUENCE: 25		
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Leu Ala Glu Ser Tyr Leu Arg Tyr Ser Gln Glu Ala Lys Glu Ala Ala		
	20	25 30
Lys Asn Gly Asp Leu Glu Glu Ala Leu Lys Leu Phe Asn Leu Ala Lys		
	35	40 45
Asp Ile Phe Pro Thr Lys Lys Val Ile Ser Arg Ile Gln Lys Leu Gln		
	50	55 60
Glu Ala Leu Glu Gln Leu Ala Glu Glu Glu Asp Glu Phe Thr Asp		
65	70	75 80
Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu Tyr Glu Lys Leu		
	85	90 95
Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Lys		
	100	105 110

Asn	Gly	Arg	Lys	Gly	Gly	Ile	Leu	Ala	Asp	Asp	Met	Gly	Leu	Gly	Lys
115						120						125			
Thr	Val	Gln	Ile	Ile	Ala	Phe	Leu	Ser	Gly	Met	Phe	Asp	Ala	Ser	Leu
130						135				140					
Val	Asn	His	Val	Leu	Leu	Ile	Met	Pro	Thr	Asn	Leu	Ile	Asn	Thr	Trp
145				150						155				160	
Val	Lys	Glu	Phe	Ala	Lys	Trp	Thr	Pro	Gly	Met	Arg	Val	Lys	Thr	Phe
				165				170						175	
His	Gly	Ser	Ser	Lys	Asn	Glu	Arg	Ile	Arg	Asn	Leu	Thr	Arg	Ile	Gln
		180						185				190			
Gln	Arg	Asn	Gly	Val	Val	Ile	Thr	Thr	Tyr	Gln	Met	Leu	Leu	Asn	Asn
		195				200						205			
Trp	Gln	Gln	Leu	Ala	Ser	Phe	Asn	Gly	Gln	Ala	Phe	Val	Trp	Asp	Tyr
210						215				220					
Val	Ile	Leu	Asp	Glu	Ala	His	Lys	Ile	Lys	Ser	Ala	Ser	Thr	Lys	Ser
225				230						235				240	
Ala	Val	Cys	Ala	Arg	Ala	Val	Pro	Ala	Ser	Asn	Arg	Leu	Leu	Leu	Thr
				245				250						255	
Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu	Trp	Ser	Leu	Phe	Asp
		260						265				270			
Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu	Lys	Thr	Phe	Lys	Met
		275				280						285			
Glu	Tyr	Glu	Asn	Pro	Ile	Ile	Arg	Ala	Arg	Glu	Lys	Asp	Ala	Thr	Pro
290						295				300					
Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Met	Ser	Glu	Asn	Leu	Met	Glu	Ile
305				310						315				320	
Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu	Glu	Val	His	Met	Lys
				325				330						335	
Lys	Ala	Asp	Lys	Pro	Glu	Val	Arg	Pro	Gly	Glu	Lys	Asn	Ser	Gly	Val
		340						345				350			
Glu	Asp	Ile	Cys	Glu	Met	Leu	Ser	Leu	Thr	Arg	Lys	Asn	Asp	Leu	Ile
		355				360						365			
Val	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe
370						375				380					
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro
385				390						395				400	
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu
				405				410						415	
Leu	Ser	Ala	Arg	Ala	Cys	His	Leu	Leu	Asn	Leu	Gly	Thr	Val	Thr	Phe
		420						425				430			
Ser	Ala	Glu	Asp	Glu	Asn	Glu	Gln	Glu	Asp	Ala	Ser	Asn	Met	Gly	Ser
		435				440						445			
Ile	Asp	His	Leu	Ser	Asp	Asn	Ala	Leu	Met	Gln	Glu	Ser	Gly	Lys	Met
450						455				460					
Ile	Phe	Leu	Met	Ala	Leu	Leu	Glu	Arg	Leu	Gln	Asp	Glu	Gly	His	Gln
465				470						475				480	

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515					520					525					
Lys	Glu	Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly
530						535					540				
Leu	Thr	Leu	Thr	Ala	Ala	Ser	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp
545					550					555					560
Asn	Pro	Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly
				565					570					575	
Gln	Lys	Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val
			580					585					590		
Glu	Glu	Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg
		595					600					605			
Gln	Thr	Thr	Gly	Asp	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Thr	Lys	Gln
	610					615					620				
Glu	Leu	Lys	Glu	Leu	Phe	Thr	Val	Gly	Asp	Leu	Leu	Asn	Ser	Ala	Thr
625					630					635					640
Gln	Met	Gln	Leu	Gln	Cys	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Glu
				645					650					655	
Lys	Leu	Asp	Glu	His	Ile	Ala	Tyr	Leu	His	Ser	Leu	Gly	Ile	Ala	Gly
			660					665					670		
Ile	Ser	Asp	His	Asp	Leu	Met	Phe	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu
		675					680					685			
Glu	Leu	Asp	Met	Leu	Glu	Asp	Ala	Gln	Tyr	Ile	Gln	His	Arg	Val	Gln
	690					695					700				
Lys	Ala	Gln	Phe	Leu	Val	Glu	Ser	Glu	Ser	Gln	Asn	Thr	Lys	Glu	Arg
705					710					715					720
Pro	Ser	Glu	Glu	Asn	Trp	Leu	Lys	Ala	Gln	Glu	Phe	Pro	Ser	Gln	Gln
				725					730					735	
Arg	Lys	Lys	Gly	Asn	Lys	Pro	Gln	Pro	Gln	Pro	Ser	Arg	Leu	Leu	Ala
			740					745					750		
Asn	Pro	Thr	Gln	Val	Glu	Ala	Ile	Ser	Ser	Gln	Met	Ala	Ser	Ile	Ser
		755					760					765			
Ile	Tyr	Asp	Gln	Ser	Thr	Glu	Ser	Glu	Pro	Gln	Glu	Leu	Ser	Glu	Ala
	770					775					780				
His	Asp	Val	Thr	Ser	Leu	Gln	Gly	Asp	Gln	His	His	Phe	Glu	Ser	Thr
785					790					795					800
Ser	Asp	Ala	Gly	Thr	Ile	Ala	Ser	Leu	Pro	Gln	Gly	Ala	Glu	Ser	Ile
				805					810					815	
Gly	Gly	Val	Trp	Thr	Asp	Ser	Leu	Leu	Ser	Pro	Ala	Lys	Gly	Phe	Ala
			820					825					830		
Ala	Asp	Asn	Glu	Ala	Val	Gln	Lys	Asn	Glu	Leu	Gln	Ala	Ser	Pro	Gly
		835					840					845			
Gln	Glu	Ala	Leu	Ser	Glu	Asn	Leu	Gly	Ser	Phe	His	Tyr	Leu	Pro	Arg
	850					855					860				
Gln	Ser	Ser	Lys	Ala	Asp	Leu	Glu	Pro	Asn	Leu	Asp	Val	Gln	Asp	Ser
865					870					875					880
Val	Val	Leu	Tyr	His	Gln	Ser	Pro	Thr	Ala	Asn	Glu	Asn	Gln	Asn	Leu
				885					890					895	
Glu	Ser	Asn	Glu	Pro	Met	Ile	Glu	Ile	Ser	Asp	Asp	Leu	Ser	Ala	Ser
		900						905					910		
Pro	Ser	Ala	Leu	Gln	Gly	Ala	Gln	Ala	Met	Glu	Ala	Gln	Leu	Glu	Leu
		915					920					925			

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Lys Lys Asp Pro Leu Glu Ser Pro Pro Gln Tyr Glu Cys Asp Phe Asn
 930 935 940
 Leu Phe Leu Glu Asp Ser Ala Asp Thr Arg Gln Asn Leu Ser Ser Lys
 945 950 955 960
 Phe Leu Glu His Val Glu Lys Glu Asn Ser Leu Gln Arg Pro Ala Gly
 965 970 975
 Asn Ser Gly Glu Glu Ser Ala His Asn Leu Ser Leu Asp Ser Ser Asn
 980 985 990
 Lys Ile Asp Glu Glu Ser Glu Val Ile Thr Val Lys Thr Lys Asn Lys
 995 1000 1005
 Ala Arg Arg Ile Leu Ser Asp Asp Glu Asp Glu Glu Asp Ala Phe Lys
 1010 1015 1020
 Asp Thr Ser Thr Asn Ser Phe Ser Val Ser Pro Leu Thr Phe Ser Ser
 1025 1030 1035 1040
 Val Lys His Phe Asp Ala Ser Thr Pro Gln Asn Asp Ser Asn Pro Ser
 1045 1050 1055
 Arg Arg Phe Phe Ser Pro Lys Ile Pro Asp Asp Val Asn Thr Ser Leu
 1060 1065 1070
 His Pro Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Val Val
 1075 1080 1085
 Leu Asp Asp Met Glu Asp Met Glu Glu Arg Leu Asp Thr Ser Ser Glu
 1090 1095 1100
 Glu Glu Ser Glu Pro Glu Leu Ser Glu Asp Ser Asn Glu Glu Ala Val
 1105 1110 1115 1120
 Ala Cys Thr Glu Glu Gln Arg Ser Gly Ala Thr Leu Ala Ser Gly Asn
 1125 1130 1135
 Lys His Ser Ser Leu Thr Glu Ser Glu Pro Thr Ser Pro Ala Pro Gln
 1140 1145 1150
 Ser Ser Pro Cys Ala Pro Glu Pro Ser Ser Ser Asp Pro Leu Leu Asp
 1155 1160 1165
 Pro Pro Gln Asp Pro Ala Val Glu Ala Ala Asn Asp Tyr Glu Ser Leu
 1170 1175 1180
 Val Ala Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Thr Gln Glu Ala
 1185 1190 1195 1200
 Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala Asp Pro Glu
 1205 1210 1215
 Val Met Arg Met Thr Leu Ser Leu Tyr Lys Gln Leu Asn
 1220 1225

<210> SEQ ID NO 26
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Clostridium tetani

<400> SEQUENCE: 26

Gln Tyr Ile Lys Ala Asn Ser Lys Phe Ile Gly Ile Thr Glu
 1 5 10

<210> SEQ ID NO 27
 <211> LENGTH: 21
 <212> TYPE: PRT
 <213> ORGANISM: Plasmodium falciparum

<400> SEQUENCE: 27

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Asp Ile Glu Lys Lys Ile Ala Lys Met Glu Lys Ala Ser Ser Val Phe
1 5 10 15

Asn Val Val Asn Ser
20

<210> SEQ ID NO 28
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Streptococcus aureus

<400> SEQUENCE: 28

Gly Ala Val Asp Ser Ile Leu Gly Gly Val Ala Thr Tyr Gly Ala Ala
1 5 10 15

<210> SEQ ID NO 29
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 3
<223> OTHER INFORMATION: Xaa is either cyclohexylalanine, phenylalanine,
or tyrosine
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 1, 13
<223> OTHER INFORMATION: Xaa is is either D-alanine or L-alanine
<220> FEATURE:
<223> OTHER INFORMATION: Artificially Synthesized Peptide

<400> SEQUENCE: 29

Xaa Lys Xaa Val Ala Ala Trp Thr Leu Lys Ala Xaa
1 5 10

<210> SEQ ID NO 30
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 30

ttttgatcaa gctt 14

<210> SEQ ID NO 31
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 31

ctaatacgcac tcactatagg gctcgagcgg ccgcccgggc ag 42

<210> SEQ ID NO 32
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 32

gatacctgccc gg 12

<210> SEQ ID NO 33
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

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<400> SEQUENCE: 33

gtaatacgcac tcactatagg gcagcgtggt cgcggccgag 40

<210> SEQ ID NO 34

<211> LENGTH: 10

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 34

gatacctcggc 10

<210> SEQ ID NO 35

<211> LENGTH: 22

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 35

ctaatacgcac tcactatagg gc 22

<210> SEQ ID NO 36

<211> LENGTH: 22

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 36

tcgagcggcc gcccgggcag ga 22

<210> SEQ ID NO 37

<211> LENGTH: 20

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 37

agcgtggtcg cggccgagga 20

<210> SEQ ID NO 38

<211> LENGTH: 25

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 38

atatcgccgc gctcgtcgtc gacaa 25

<210> SEQ ID NO 39

<211> LENGTH: 26

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 39

agccacacgc agtcattgt agaagg 26

<210> SEQ ID NO 40

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 40

gctagtgtctc agaataccag actatgg 27

<210> SEQ ID NO 41

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<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 41

cgcttgacat aaaaagtgca gatcc

25

<210> SEQ ID NO 42
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 42

gattacaagg atgacgacga taag

24

<210> SEQ ID NO 43
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 43

Asn Val Thr Thr

1

<210> SEQ ID NO 44
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 44

Asn Ser Ser Leu

1

<210> SEQ ID NO 45
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 45

Asn Glu Ser Gln

1

<210> SEQ ID NO 46
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 46

Asn Val Ser Ile

1

<210> SEQ ID NO 47
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 47

Asn Phe Ser Ser

1

<210> SEQ ID NO 48
<211> LENGTH: 4

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<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 48

Asn Thr Ser Leu
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<210> SEQ ID NO 49
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 49

Asn Lys Ser Met
1

<210> SEQ ID NO 50
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 50

Asn Lys Ser Ser
1

<210> SEQ ID NO 51
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 51

Glu Ala Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu
1 5 10 15

<210> SEQ ID NO 52
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 52

Ser Ser Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly
1 5 10 15

<210> SEQ ID NO 53
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 53

Ala Ala Glu Ala Thr Asn Asp Tyr Glu Thr Leu Val Lys Arg Gly Lys
1 5 10 15

Lys Lys Ser

<210> SEQ ID NO 54
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 54

Lys Lys Lys Ser
1

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<210> SEQ ID NO 55
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 55

Lys Lys Ser Ser
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<210> SEQ ID NO 56
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 56

Ser Lys Asp Glu
1

<210> SEQ ID NO 57
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 57

Ser Leu Phe Asp
1

<210> SEQ ID NO 58
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 58

Thr Pro Gly Glu
1

<210> SEQ ID NO 59
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 59

Thr Lys Glu Asp
1

<210> SEQ ID NO 60
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 60

Ser Asn Pro Glu
1

<210> SEQ ID NO 61
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 61

Ser Ala Gln Asp
1

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<210> SEQ ID NO 62
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 62

Thr Leu Met Glu
1

<210> SEQ ID NO 63
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 63

Thr Val Glu Glu
1

<210> SEQ ID NO 64
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 64

Thr Thr Gly Glu
1

<210> SEQ ID NO 65
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 65

Ser Lys Gln Glu
1

<210> SEQ ID NO 66
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 66

Thr Ile Glu Asp
1

<210> SEQ ID NO 67
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 67

Ser Asp His Asp
1

<210> SEQ ID NO 68
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 68

Ser Val Lys Glu

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1

<210> SEQ ID NO 69
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 69

Thr Arg Asn Glu
1

<210> SEQ ID NO 70
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 70

Thr Gln Glu Glu
1

<210> SEQ ID NO 71
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 71

Thr Leu Gln Asp
1

<210> SEQ ID NO 72
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 72

Ser Val Glu Glu
1

<210> SEQ ID NO 73
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 73

Thr Lys Asn Glu
1

<210> SEQ ID NO 74
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 74

Thr Leu Gln Glu
1

<210> SEQ ID NO 75
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 75

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Thr Lys Ala Asp
1

<210> SEQ ID NO 76
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 76

Ser Ile Ile Glu
1

<210> SEQ ID NO 77
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 77

Ser Glu Lys Asp
1

<210> SEQ ID NO 78
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 78

Ser Asp Gly Glu
1

<210> SEQ ID NO 79
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 79

Ser Phe Lys Asp
1

<210> SEQ ID NO 80
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 80

Ser Ser Gly Glu
1

<210> SEQ ID NO 81
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 81

Thr Glu Glu Asp
1

<210> SEQ ID NO 82
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 82

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Ser Pro Gln Asp
1

<210> SEQ ID NO 83
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 83

Lys Leu Asp Glu His Ile Ala Tyr
1 5

<210> SEQ ID NO 84
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 84

Gly Gly Ile Leu Ala Asp
1 5

<210> SEQ ID NO 85
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 85

Gly Leu Gly Lys Thr Val
1 5

<210> SEQ ID NO 86
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 86

Gly Met Phe Asp Ala Ser
1 5

<210> SEQ ID NO 87
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 87

Gly Val Ile Ile Thr Thr
1 5

<210> SEQ ID NO 88
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 88

Gly Ser Leu Leu Gly Thr
1 5

<210> SEQ ID NO 89
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

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<400> SEQUENCE: 89

Gly Thr Leu Lys Thr Phe
1 5

<210> SEQ ID NO 90

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 90

Gly Thr Phe Ser Ala Gln
1 5

<210> SEQ ID NO 91

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 91

Gly Val Gly Leu Thr Leu
1 5

<210> SEQ ID NO 92

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 92

Gly Leu Thr Leu Thr Ala
1 5

<210> SEQ ID NO 93

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 93

Gly Gln Lys Glu Asn Val
1 5

<210> SEQ ID NO 94

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 94

Gly Thr Gly Ser Ala Asp
1 5

<210> SEQ ID NO 95

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 95

Gly Ser Ala Asp Ser Ile
1 5

<210> SEQ ID NO 96

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

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<400> SEQUENCE: 96

Gly Met Glu Lys Ser Phe
1 5

<210> SEQ ID NO 97

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 97

Gly Ser Ala Pro Asn Ser
1 5

<210> SEQ ID NO 98

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 98

Gly Val Glu Glu Ser Ser
1 5

<210> SEQ ID NO 99

<211> LENGTH: 4

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 99

Asp Gly Arg Lys
1

<210> SEQ ID NO 100

<211> LENGTH: 1250

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 100

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
1 5 10 15Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
20 25 30Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
35 40 45Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
50 55 60Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
65 70 75 80Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
85 90 95Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
100 105 110Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
115 120 125Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
130 135 140Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
145 150 155 160

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Val	Lys	Glu	Phe	Ile	Lys	Trp	Thr	Pro	Gly	Met	Arg	Val	Lys	Thr	Phe	165	170	175
His	Gly	Pro	Ser	Lys	Asp	Glu	Arg	Thr	Arg	Asn	Leu	Asn	Arg	Ile	Gln	180	185	190
Gln	Arg	Asn	Gly	Val	Ile	Ile	Thr	Thr	Tyr	Gln	Met	Leu	Ile	Asn	Asn	195	200	205
Trp	Gln	Gln	Leu	Ser	Ser	Phe	Arg	Gly	Gln	Glu	Phe	Val	Trp	Asp	Tyr	210	215	220
Val	Ile	Leu	Asp	Glu	Ala	His	Lys	Ile	Lys	Thr	Ser	Ser	Thr	Lys	Ser	225	230	235
Ala	Ile	Cys	Ala	Arg	Ala	Ile	Pro	Ala	Ser	Asn	Arg	Leu	Leu	Leu	Thr	245	250	255
Gly	Thr	Pro	Ile	Gln	Asn	Asn	Leu	Gln	Glu	Leu	Trp	Ser	Leu	Phe	Asp	260	265	270
Phe	Ala	Cys	Gln	Gly	Ser	Leu	Leu	Gly	Thr	Leu	Lys	Thr	Phe	Lys	Met	275	280	285
Glu	Tyr	Glu	Asn	Pro	Ile	Thr	Arg	Ala	Arg	Glu	Lys	Asp	Ala	Thr	Pro	290	295	300
Gly	Glu	Lys	Ala	Leu	Gly	Phe	Lys	Ile	Ser	Glu	Asn	Leu	Met	Ala	Ile	305	310	315
Ile	Lys	Pro	Tyr	Phe	Leu	Arg	Arg	Thr	Lys	Glu	Asp	Val	Gln	Lys	Lys	325	330	335
Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu	Lys	Asn	Pro	Asp	Val	340	345	350
Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Lys	Asn	Asp	Leu	Ile	355	360	365
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe	370	375	380
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro	385	390	395
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu	405	410	415
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala	420	425	430
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp	435	440	445
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe	450	455	460
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu	465	470	475
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu	485	490	495
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His	500	505	510
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp	515	520	525
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr	530	535	540
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro	545	550	555

Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys		
				565						570		575					
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu		
				580						585		590					
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr		
				595						600		605					
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu		
						615						620					
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu		
						630						635		640			
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu		
				645						650		655					
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser		
				660						665		670					
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu		
				675						680		685					
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala		
				690						695		700					
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu		
				705						710		715					
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe		
				725						730		735					
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro		
				740						745		750					
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile		
				755						760		765					
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly		
				770						775		780					
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln		
				785						790		795					
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys		
				805						810		815					
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met		
				820						825		830					
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu		
				835						840		845					
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser		
				850						855		860					
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn		
				865						870		875					
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro	Trp		
				885						890		895					
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val		
				900						905		910					
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu		
				915						920		925					
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala		
				930						935		940					
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser		
				945						950		955					
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Gln		

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965				970				975							
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe
		980						985					990		
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp
		995					1000					1005			
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg
	1010					1015					1020				
Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	Ser	Phe	Lys	Asp	Thr
1025				1030					1035						1040
Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser	Val
			1045					1050						1055	
Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	Ile	Ser	Pro	Pro	Gly
		1060						1065					1070		
Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	Asn	Lys	Ser	Met	Asn
	1075					1080					1085				
Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	Ile	Asn	Met	Val	Leu
	1090				1095						1100				
Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	Asp	Ser	Ser	Glu	Ala
1105				1110						1115				1120	
Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	Glu	Glu	Ser	Ser	Gly
		1125							1130					1135	
Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	Gly	Glu	Thr	Leu	Ser
		1140						1145					1150		
Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	Lys	Pro	Ser	Ala	Leu
	1155					1160					1165				
Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	Leu	Ser	Gly	Glu	Gln
	1170				1175						1180				
Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu	Ala	Thr	Asn	Asp	Tyr
1185				1190						1195				1200	
Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys	Glu	Cys	Gly	Lys	Ile
		1205							1210					1215	
Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu	Asp	Ile	Lys	Ser	Ala
		1220						1225					1230		
Asp	Pro	Glu	Val	Met	Leu	Leu	Thr	Leu	Ser	Leu	Tyr	Lys	Gln	Leu	Asn
	1235					1240					1245				
Asn	Asn														
	1250														

<210> SEQ ID NO 101
 <211> LENGTH: 17
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 101

Phe	Ile	Lys	Trp	Thr	Pro	Gly	Met	Gly	Val	Lys	Thr	Phe	His	Gly	Pro
1				5					10					15	

Ser

<210> SEQ ID NO 102
 <211> LENGTH: 19
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 102

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Glu Phe Ile Lys Trp Thr Pro Gly Met Gly Val Lys Thr Phe His Gly
1 5 10 15

Pro Ser Lys

<210> SEQ ID NO 103
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 103

Asn Thr Trp Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Gly Val
1 5 10 15

Lys Thr Phe His Gly Pro Ser Lys Asp Glu Arg Thr Arg
20 25

<210> SEQ ID NO 104
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 104

Cys Glu Met Pro Ser Leu Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile
1 5 10 15

Arg

<210> SEQ ID NO 105
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 105

Ile Cys Glu Met Pro Ser Leu Ser Arg Arg Asn Asp Leu Ile Ile Trp
1 5 10 15

Ile Arg Leu

<210> SEQ ID NO 106
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 106

Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Arg Asn
1 5 10 15

Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln Glu
20 25

<210> SEQ ID NO 107
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 107

Leu Asp Gln Leu Lys Asp Asp Glu Val Leu Arg His Cys Asn Pro Trp
1 5 10 15

Pro

<210> SEQ ID NO 108
<211> LENGTH: 19

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<212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 108

Asn Leu Asp Gln Leu Lys Asp Asp Glu Val Leu Arg His Cys Asn Pro
 1 5 10 15

Trp Pro Ile

<210> SEQ ID NO 109
 <211> LENGTH: 29
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 109

Ala Asp Ile Gly Pro Asn Leu Asp Gln Leu Lys Asp Asp Glu Val Leu
 1 5 10 15

Arg His Cys Asn Pro Trp Pro Ile Ile Ser Ile Thr Asn
 20 25

<210> SEQ ID NO 110
 <211> LENGTH: 4334
 <212> TYPE: DNA
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 110

atgcgcgggg cgaggagtgc cgaaattcaa gctccaaact ctaagctcca agctccaagc 60
 tccaagctcc aagctccaaa ctcccgccgg ggtaactgga acccaatccg agggcatgag 120
 aggcattccc aaggtttccg gaagccgagg ccttgagccc agagcaggct gctcattacc 180
 taagggtctt gctgtgtcgc ccagactgga attcagtggc ctgatcatag ttcactgcag 240
 cctcgaactc ctgggctcaa gcagtcctcc tgcccagacc tcctagtag ctgggactta 300
 agatatgtga aagaggccaa agaagcaact aagaatggag acctggaaga agcattttaa 360
 cttttcaatt tggcaaagga catttttccc aatgaaaaag tgctgagcag aatccaaaaa 420
 atacaggaag ccttgaggga gttggcagaa caggagatg atgaatttac agatgtgtgc 480
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<210> SEQ ID NO 111

<211> LENGTH: 4312

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 111

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<210> SEQ ID NO 112

<211> LENGTH: 4194

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 112

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<210> SEQ ID NO 113

<211> LENGTH: 1127

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 113

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Arg Val Lys Thr Phe His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn
      50             55             60
Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln
      65             70             75             80
Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu
      85             90             95
Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr
      100            105            110
Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn
      115            120            125
Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu
      130            135            140
Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu
      145            150            155            160
Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu
      165            170            175
Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu
      180            185            190
Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu
      195            200            205
Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu
      210            215            220
Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg
      225            230            235            240
Lys Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu

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245								250				255			
Ile	Tyr	Arg	Lys	Phe	Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met
260								265					270		
Glu	Thr	Arg	Ser	Pro	Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys
275								280					285		
Asp	His	Pro	Arg	Leu	Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu
290								295					300		
Gly	Thr	Phe	Ser	Ala	Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp
305								310					315		
Val	Asp	His	Ile	Asp	Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser
325								330					335		
Gly	Lys	Met	Ile	Phe	Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu
340								345					350		
Gly	His	Gln	Thr	Leu	Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile
355								360					365		
Ile	Glu	Arg	Leu	Leu	Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp
370								375					380		
Gly	Thr	Val	Thr	His	Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe
385								390					395		
Gln	Gln	Asn	Lys	Asp	Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly
405								410					415		
Gly	Val	Gly	Leu	Thr	Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp
420								425					430		
Pro	Ser	Trp	Asn	Pro	Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr
435								440					445		
Arg	Ile	Gly	Gln	Lys	Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys
450								455					460		
Gly	Thr	Val	Glu	Glu	Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser
465								470					475		
Leu	Ile	Arg	Gln	Thr	Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe
485								490					495		
Ser	Lys	Gln	Glu	Leu	Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn
500								505					510		
Ser	Val	Thr	Gln	Leu	Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys
515								520					525		
Ser	Asp	Ile	Lys	Leu	Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly
530								535					540		
Ile	Ala	Gly	Ile	Ser	Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser
545								550					555		
Val	Lys	Glu	Glu	Leu	Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln
565								570					575		
Arg	Val	Gln	Lys	Ala	Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys
580								585					590		
Glu	Phe	Leu	Met	Glu	Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu
595								600					605		
Arg	Glu	Pro	Val	Phe	Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu
610								615					620		
Asn	Lys	Pro	Gln	Pro	Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr
625								630					635		
Gln	Glu	Glu	Asp	Ile	Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp
645								650					655		

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Leu	Pro	Lys	Glu	Gly	Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn
			660					665					670		
Val	Thr	Thr	Leu	Gln	Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile
	675						680					685			
Ala	Thr	Leu	Pro	Lys	Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn
	690					695					700				
Ser	Ser	Leu	Gly	Met	Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val
705				710						715				720	
Gln	Lys	Glu	Thr	Leu	Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu
			725					730						735	
Asp	Pro	Leu	Glu	Ser	Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala
		740						745					750		
Asp	Ile	Gly	Pro	Asn	Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg
	755						760					765			
His	Cys	Asn	Pro	Trp	Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn
	770					775					780				
Ala	Glu	Ser	Asn	Val	Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala
785				790						795					800
Ser	His	Ser	Ala	Leu	Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu
			805					810						815	
Glu	Glu	Pro	Ser	Ala	Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu
		820						825					830		
Phe	Leu	Glu	Asp	Ser	Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser
	835						840					845			
Leu	Glu	His	Val	Glu	Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn
	850					855					860				
Ser	Arg	Ala	Gly	Phe	Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe
865				870						875					880
Ser	Glu	Lys	Asp	Asp	Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile
			885						890					895	
Arg	Ser	Lys	Ala	Arg	Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp
		900						905					910		
Ser	Phe	Lys	Asp	Thr	Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe
	915						920					925			
Gln	Phe	Ser	Ser	Val	Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp
	930					935						940			
Ile	Ser	Pro	Pro	Gly	Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val
945				950						955					960
Asn	Lys	Ser	Met	Asn	Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu
			965						970					975	
Ile	Asn	Met	Val	Leu	Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp
		980						985					990		
Asp	Ser	Ser	Glu	Ala	Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val
		995					1000					1005			
Glu	Glu	Ser	Ser	Gly	Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser
	1010					1015						1020			
Gly	Glu	Thr	Leu	Ser	Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser
1025				1030						1035					1040
Lys	Pro	Ser	Ala	Leu	Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro
			1045						1050					1055	

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Leu Ser Gly Glu Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu
 1060 1065 1070

Ala Thr Asn Asp Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys
 1075 1080 1085

Glu Cys Gly Lys Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu
 1090 1095 1100

Asp Ile Lys Ser Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu
 1105 1110 1115 1120

Tyr Lys Gln Leu Asn Asn Asn
 1125

<210> SEQ ID NO 114

<211> LENGTH: 1127

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 114

Met Gly Leu Gly Lys Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met
 1 5 10 15

Phe Asp Ala Ser Leu Val Asn His Val Leu Leu Ile Met Pro Thr Asn
 20 25 30

Leu Ile Asn Thr Trp Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met
 35 40 45

Arg Val Lys Thr Phe His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn
 50 55 60

Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln
 65 70 75 80

Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu
 85 90 95

Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr
 100 105 110

Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn
 115 120 125

Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu
 130 135 140

Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu
 145 150 155 160

Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu
 165 170 175

Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu
 180 185 190

Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu
 195 200 205

Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu
 210 215 220

Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg
 225 230 235 240

Lys Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu
 245 250 255

Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu Leu Met
 260 265 270

Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys
 275 280 285

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Asp	His	Pro	Arg	Leu	Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu
290						295					300				
Gly	Thr	Phe	Ser	Ala	Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp
305					310					315					320
Val	Asp	His	Ile	Asp	Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser
				325					330					335	
Gly	Lys	Met	Ile	Phe	Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu
			340					345					350		
Gly	His	Gln	Thr	Leu	Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile
	355						360					365			
Ile	Glu	Arg	Leu	Leu	Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp
370						375					380				
Gly	Thr	Val	Thr	His	Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe
385					390					395					400
Gln	Gln	Asn	Lys	Asp	Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly
			405						410					415	
Gly	Val	Gly	Leu	Thr	Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp
			420					425					430		
Pro	Ser	Trp	Asn	Pro	Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr
		435					440					445			
Arg	Ile	Gly	Gln	Lys	Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys
450						455					460				
Gly	Thr	Val	Glu	Glu	Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser
465					470					475					480
Leu	Ile	Arg	Gln	Thr	Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe
			485					490						495	
Ser	Lys	Gln	Glu	Leu	Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn
		500						505					510		
Ser	Val	Thr	Gln	Leu	Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys
		515					520					525			
Ser	Asp	Ile	Lys	Leu	Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly
	530					535					540				
Ile	Ala	Gly	Ile	Ser	Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser
545					550					555					560
Val	Lys	Glu	Glu	Leu	Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln
			565					570						575	
Arg	Val	Gln	Lys	Ala	Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys
		580						585					590		
Glu	Phe	Leu	Met	Glu	Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu
	595						600					605			
Arg	Glu	Pro	Val	Phe	Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu
	610					615					620				
Asn	Lys	Pro	Gln	Pro	Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr
625					630					635					640
Gln	Glu	Glu	Asp	Ile	Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp
			645						650					655	
Leu	Pro	Lys	Glu	Gly	Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn
		660						665					670		
Val	Thr	Thr	Leu	Gln	Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile
	675						680					685			

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Ala	Thr	Leu	Pro	Lys	Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	690	695	700
Ser	Ser	Leu	Gly	Met	Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	705	710	715
Gln	Lys	Glu	Thr	Leu	Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	725	730	735
Asp	Pro	Leu	Glu	Ser	Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	740	745	750
Asp	Ile	Gly	Pro	Asn	Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	755	760	765
His	Cys	Asn	Pro	Trp	Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	770	775	780
Ala	Glu	Ser	Asn	Val	Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	785	790	795
Ser	His	Ser	Ala	Leu	Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	805	810	815
Glu	Glu	Pro	Ser	Ala	Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	820	825	830
Phe	Leu	Glu	Asp	Ser	Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	835	840	845
Leu	Glu	His	Val	Glu	Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	850	855	860
Ser	Arg	Ala	Gly	Phe	Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	865	870	875
Ser	Glu	Lys	Asp	Asp	Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	885	890	895
Arg	Ser	Lys	Ala	Arg	Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	900	905	910
Ser	Phe	Lys	Asp	Thr	Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	915	920	925
Gln	Phe	Ser	Ser	Val	Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	930	935	940
Ile	Ser	Pro	Pro	Gly	Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	945	950	955
Asn	Lys	Ser	Met	Asn	Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	965	970	975
Ile	Asn	Met	Val	Leu	Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	980	985	990
Asp	Ser	Ser	Glu	Ala	Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	995	1000	1005
Glu	Glu	Ser	Ser	Gly	Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	1010	1015	1020
Gly	Glu	Thr	Leu	Ser	Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	1025	1030	1035
Lys	Pro	Ser	Ala	Leu	Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	1045	1050	1055
Leu	Ser	Gly	Glu	Gln	Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu	1060	1065	1070
Ala	Thr	Asn	Asp	Tyr	Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys	1075	1080	1085
Glu	Cys	Gly	Lys	Ile	Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu			

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1090	1095	1100
Asp Ile Lys Ser Ala	Asp Pro Glu Val Met	Leu Leu Thr Leu Ser Leu
1105	1110	1115 1120
Tyr Lys Gln Leu Asn Asn Asn		
	1125	
<210> SEQ ID NO 115		
<211> LENGTH: 1127		
<212> TYPE: PRT		
<213> ORGANISM: Homo Sapiens		
<400> SEQUENCE: 115		
Met Gly Leu Gly Lys Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met		
1 5 10 15		
Phe Asp Ala Ser Leu Val Asn His Val Leu Leu Ile Met Pro Thr Asn		
20 25 30		
Leu Ile Asn Thr Trp Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met		
35 40 45		
Arg Val Lys Thr Phe His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn		
50 55 60		
Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln		
65 70 75 80		
Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu		
85 90 95		
Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr		
100 105 110		
Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn		
115 120 125		
Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu		
130 135 140		
Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu		
145 150 155 160		
Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu		
165 170 175		
Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu		
180 185 190		
Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu		
195 200 205		
Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu		
210 215 220		
Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg		
225 230 235 240		
Lys Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu		
245 250 255		
Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu Leu Met		
260 265 270		
Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys		
275 280 285		
Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu Asn Leu		
290 295 300		
Gly Thr Phe Ser Ala Gln Asp Gly Asn Glu Gly Glu Asp Ser Pro Asp		
305 310 315 320		

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Val	Asp	His	Ile	Asp	Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser
			325						330					335	
Gly	Lys	Met	Ile	Phe	Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu
			340					345					350		
Gly	His	Gln	Thr	Leu	Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile
		355					360					365			
Ile	Glu	Arg	Leu	Leu	Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp
	370					375					380				
Gly	Thr	Val	Thr	His	Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe
385					390					395					400
Gln	Gln	Asn	Lys	Asp	Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly
				405					410					415	
Gly	Val	Gly	Leu	Thr	Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp
			420					425					430		
Pro	Ser	Trp	Asn	Pro	Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr
		435					440					445			
Arg	Ile	Gly	Gln	Lys	Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys
	450					455					460				
Gly	Thr	Val	Glu	Glu	Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser
465					470					475					480
Leu	Ile	Arg	Gln	Thr	Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe
				485					490					495	
Ser	Lys	Gln	Glu	Leu	Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn
			500					505					510		
Ser	Val	Thr	Gln	Leu	Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys
		515					520					525			
Ser	Asp	Ile	Lys	Leu	Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly
	530					535					540				
Ile	Ala	Gly	Ile	Ser	Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser
545					550					555					560
Val	Lys	Glu	Glu	Leu	Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln
				565					570					575	
Arg	Val	Gln	Lys	Ala	Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys
			580					585						590	
Glu	Phe	Leu	Met	Glu	Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu
	595						600					605			
Arg	Glu	Pro	Val	Phe	Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu
	610					615					620				
Asn	Lys	Pro	Gln	Pro	Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr
625					630					635					640
Gln	Glu	Glu	Asp	Ile	Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp
			645						650					655	
Leu	Pro	Lys	Glu	Gly	Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn
			660					665					670		
Val	Thr	Thr	Leu	Gln	Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile
		675					680					685			
Ala	Thr	Leu	Pro	Lys	Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn
	690					695					700				
Ser	Ser	Leu	Gly	Met	Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val
705					710					715					720
Gln	Lys	Glu	Thr	Leu	Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu

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725					730					735					
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			740					745					750		
Asp	Ile	Gly	Pro	Asn	Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg
		755					760					765			
His	Cys	Asn	Pro	Trp	Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn
	770					775					780				
Ala	Glu	Ser	Asn	Val	Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala
	785					790					795				800
Ser	His	Ser	Ala	Leu	Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu
				805					810					815	
Glu	Glu	Pro	Ser	Ala	Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu
			820					825						830	
Phe	Leu	Glu	Asp	Ser	Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser
		835					840					845			
Leu	Glu	His	Val	Glu	Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn
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Ser	Arg	Ala	Gly	Phe	Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe
	865					870					875				880
Ser	Glu	Lys	Asp	Asp	Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile
				885					890					895	
Arg	Ser	Lys	Ala	Arg	Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp
			900					905					910		
Ser	Phe	Lys	Asp	Thr	Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe
		915					920					925			
Gln	Phe	Ser	Ser	Val	Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp
	930					935						940			
Ile	Ser	Pro	Pro	Gly	Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val
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Asn	Lys	Ser	Met	Asn	Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu
				965					970					975	
Ile	Asn	Met	Val	Leu	Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp
		980						985					990		
Asp	Ser	Ser	Glu	Ala	Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val
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Glu	Glu	Ser	Ser	Gly	Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser
	1010					1015					1020				
Gly	Glu	Thr	Leu	Ser	Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser
	1025					1030					1035				1040
Lys	Pro	Ser	Ala	Leu	Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro
				1045					1050					1055	
Leu	Ser	Gly	Glu	Gln	Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu
			1060					1065					1070		
Ala	Thr	Asn	Asp	Tyr	Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys
		1075					1080					1085			
Glu	Cys	Gly	Lys	Ile	Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu
	1090					1095					1100				
Asp	Ile	Lys	Ser	Ala	Asp	Pro	Glu	Val	Met	Leu	Leu	Thr	Leu	Ser	Leu
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<210> SEQ ID NO 116

<211> LENGTH: 3671

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 116

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cggaccagaa acctcaatcg gattcagcaa aggaatggtg ttattatcac tacataccaa   180
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ttaagagagc tctttacaat cgaggatctt cagaactctg taaccagct gcagcttcag   1500
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<210> SEQ ID NO 117

<211> LENGTH: 3694

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 117

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ggggccaaga gtttgtgtgg gactatgtca tcctcgatga agcacataaa ataaaaacct 300
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<210> SEQ ID NO 118

<211> LENGTH: 3671

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 118

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aataagtcta	tgaactctag	aagatctctg	gottctagga	ggtctcttat	taatatggtt	2880
ttagaccacg	tgaggacat	ggaggaaaga	cttgacgaca	gcagtgaagc	aaagggtcct	2940
gaagattatc	cagaagaagg	ggtggaggaa	agcagtggcg	aagcctcaa	gtatacagaa	3000
gaggatcctt	ccggagaaac	actgtcttca	gaaaacaagt	ccagctgggt	aatgacgtct	3060
aagcctagtg	ctctagctca	agagacctct	cttggtgccc	ctgagccttt	gtctggtgaa	3120
cagttgggtg	gttcccccca	ggataaggcg	gcagaggcta	caaatgacta	tgagactctt	3180
gtaaagcgtg	gaaaagaact	aaaagagtgt	ggaaaaatcc	aggaggccct	aaactgctta	3240

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gttaaagcgc ttgacataaa aagtgcagat cctgaagtta tgctcttgac ttttaagtttg 3300
tataagcaac ttaataacaa ttgagaatgt aacctgttta ttgtatttta aagtgaact 3360
gaatatgagg gaatttttgt tcccataatt ggattctttg ggaacatgaa gcattcaggc 3420
ttaaggcaag aaagatctca aaaagcaact tctgccctgc aacgcccccc actccatagt 3480
ctgggtattct gagcactagc ttaatatattc ttactttgaa tttctttata ttttaggcac 3540
attctataaa ttttaactgtg ttgtttcttg gaaagttttg taaaattatt ctgggtcattc 3600
ttaattttac tctgaaagtg atcatctttg tatataacag ttcagataag aaaattaaag 3660
ttacttttct c 3671

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<210> SEQ ID NO 119

<211> LENGTH: 1106

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 119

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Met Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
 1           5           10           15
Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Gly Val Lys Thr Phe
 20           25           30
His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
 35           40           45
Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
 50           55           60
Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
 65           70           75           80
Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
 85           90           95
Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
100          105          110
Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
115          120          125
Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
130          135          140
Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
145          150          155          160
Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
165          170          175
Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
180          185          190
Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val
195          200          205
Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile
210          215          220
Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe
225          230          235          240
Val Ser Leu Asp His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro
245          250          255
Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys Asp His Pro Arg Leu
260          265          270

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Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala
		275					280					285			
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp
		290				295					300				
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe
305					310					315					320
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu
			325						330					335	
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu
			340					345					350		
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His
		355					360					365			
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp
		370				375					380				
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr
385					390					395					400
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro
				405					410					415	
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys
			420					425					430		
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu
		435					440					445			
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr
	450					455					460				
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu
465					470					475					480
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu
				485					490					495	
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu
			500					505					510		
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser
		515					520					525			
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu
	530					535					540				
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala
545					550					555					560
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu
				565					570					575	
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe
			580					585					590		
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro
		595					600					605			
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Glu	Asp	Ile
	610					615					620				
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly
625					630					635					640
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln
				645					650					655	
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys
			660					665					670		
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met

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675						680					685				
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu
690						695					700				
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser
705					710					715					720
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn
				725					730					735	
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Val	Leu	Arg	His	Cys	Asn	Pro	Trp
			740					745					750		
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val
	755						760					765			
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu
	770					775					780				
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala
785					790					795					800
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser
				805					810					815	
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu
			820						825				830		
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe
		835					840					845			
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp
	850					855						860			
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg
865					870					875					880
Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	Ser	Phe	Lys	Asp	Thr
				885					890					895	
Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser	Val
			900						905				910		
Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	Ile	Ser	Pro	Pro	Gly
		915					920					925			
Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	Asn	Lys	Ser	Met	Asn
	930					935						940			
Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	Ile	Asn	Met	Val	Leu
945					950					955					960
Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	Asp	Ser	Ser	Glu	Ala
				965					970					975	
Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	Glu	Glu	Ser	Ser	Gly
			980					985					990		
Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	Gly	Glu	Thr	Leu	Ser
		995						1000				1005			
Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	Lys	Pro	Ser	Ala	Leu
	1010					1015						1020			
Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	Leu	Ser	Gly	Glu	Gln
1025					1030					1035					1040
Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu	Ala	Thr	Asn	Asp	Tyr
				1045					1050					1055	
Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys	Glu	Cys	Gly	Lys	Ile
			1060					1065					1070		
Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu	Asp	Ile	Lys	Ser	Ala
	1075						1080					1085			

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Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
 1090 1095 1100

Asn Asn
 1105

<210> SEQ ID NO 120
 <211> LENGTH: 1150
 <212> TYPE: PRT
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 120

Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg Asp Gly Arg Lys
 1 5 10 15

Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys Thr Val Gln Ile
 20 25 30

Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu Val Asn His Val
 35 40 45

Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp Val Lys Glu Phe
 50 55 60

Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe His Gly Pro Ser
 65 70 75 80

Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly
 85 90 95

Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu
 100 105 110

Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp
 115 120 125

Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala
 130 135 140

Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile
 145 150 155 160

Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln
 165 170 175

Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn
 180 185 190

Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala
 195 200 205

Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr
 210 215 220

Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn
 225 230 235 240

Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys
 245 250 255

Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile Ile Trp Ile Arg
 260 265 270

Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp
 275 280 285

His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu
 290 295 300

Gly Val Leu Lys Lys Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg
 305 310 315 320

Ala Cys Cys Leu Leu Asn Leu Gly Thr Phe Ser Ala Gln Asp Gly Asn

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325					330					335				
Glu Gly Glu Asp Ser Pro Asp Val Asp His Ile Asp Gln Val Thr Asp	340							345					350	
Asp Thr Leu Met Glu Glu Ser Gly Lys Met Ile Phe Leu Met Asp Leu	355						360					365		
Leu Lys Arg Leu Arg Asp Glu Gly His Gln Thr Leu Val Phe Ser Gln	370					375					380			
Ser Arg Gln Ile Leu Asn Ile Ile Glu Arg Leu Leu Lys Asn Arg His	385				390				395				400	
Phe Lys Thr Leu Arg Ile Asp Gly Thr Val Thr His Leu Leu Glu Arg		405						410				415		
Glu Lys Arg Ile Asn Leu Phe Gln Gln Asn Lys Asp Tyr Ser Val Phe		420					425				430			
Leu Leu Thr Thr Gln Val Gly Gly Val Gly Leu Thr Leu Thr Ala Ala		435					440				445			
Thr Arg Val Val Ile Phe Asp Pro Ser Trp Asn Pro Ala Thr Asp Ala		450				455				460				
Gln Ala Val Asp Arg Val Tyr Arg Ile Gly Gln Lys Glu Asn Val Val		465			470				475				480	
Val Tyr Arg Leu Ile Thr Cys Gly Thr Val Glu Glu Lys Ile Tyr Arg			485					490				495		
Arg Gln Val Phe Lys Asp Ser Leu Ile Arg Gln Thr Thr Gly Glu Lys		500					505				510			
Lys Asn Pro Phe Arg Tyr Phe Ser Lys Gln Glu Leu Arg Glu Leu Phe		515				520				525				
Thr Ile Glu Asp Leu Gln Asn Ser Val Thr Gln Leu Gln Leu Gln Ser		530				535				540				
Leu His Ala Ala Gln Arg Lys Ser Asp Ile Lys Leu Asp Glu His Ile		545			550				555				560	
Ala Tyr Leu Gln Ser Leu Gly Ile Ala Gly Ile Ser Asp His Asp Leu			565				570					575		
Met Tyr Thr Cys Asp Leu Ser Val Lys Glu Glu Leu Asp Val Val Glu		580					585				590			
Glu Ser His Tyr Ile Gln Gln Arg Val Gln Lys Ala Gln Phe Leu Val		595				600				605				
Glu Phe Glu Ser Gln Asn Lys Glu Phe Leu Met Glu Gln Gln Arg Thr		610				615				620				
Arg Asn Glu Gly Ala Trp Leu Arg Glu Pro Val Phe Pro Ser Ser Thr		625			630				635				640	
Lys Lys Lys Cys Pro Lys Leu Asn Lys Pro Gln Pro Gln Pro Ser Pro			645					650				655		
Leu Leu Ser Thr His His Thr Gln Glu Glu Asp Ile Ser Ser Lys Met			660				665				670			
Ala Ser Val Val Ile Asp Asp Leu Pro Lys Glu Gly Glu Lys Gln Asp		675				680				685				
Leu Ser Ser Ile Lys Val Asn Val Thr Thr Leu Gln Asp Gly Lys Gly		690				695				700				
Thr Gly Ser Ala Asp Ser Ile Ala Thr Leu Pro Lys Gly Phe Gly Ser		705			710				715				720	
Val Glu Glu Leu Cys Thr Asn Ser Ser Leu Gly Met Glu Lys Ser Phe			725				730					735		

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Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr Leu Gln Glu Gly Pro	740	745	750
Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu Ser Phe Asn Tyr Val	755	760	765
Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro Asn Leu Asp Gln Leu	770	775	780
Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro Trp Pro Ile Ile Ser	785	790	795
Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn Val Ser Ile Ile Glu	805	810	815
Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala Leu Gln Asp Ala Gln	820	825	830
Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser Ala Ser Ser Pro Gln	835	840	845
Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp Ser Ala Asp Asn Arg	850	855	860
Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu Lys Glu Asn Ser	865	870	875
Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe Val His Ser Lys	885	890	895
Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp Glu Pro Glu Glu	900	905	910
Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg Arg Ile Val Ser	915	920	925
Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr Ser Ser Ile Asn	930	935	940
Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val Lys Gln Phe Asp	945	950	955
Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly Arg Phe Phe Ser	965	970	975
Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn Ser Arg Arg Ser	980	985	990
Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu Asp His Val Glu	995	1000	1005
Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala Lys Gly Pro Glu	1010	1015	1020
Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly Glu Ala Ser Lys	1025	1030	1035
Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser Ser Glu Asn Lys	1045	1050	1055
Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu Ala Gln Glu Thr	1060	1065	1070
Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln Leu Val Gly Ser	1075	1080	1085
Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr Glu Thr Leu Val	1090	1095	1100
Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile Gln Glu Ala Leu	1105	1110	1115
Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala Asp Pro Glu Val	1125	1130	1135

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Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn Asn Asn
 1140 1145 1150

<210> SEQ ID NO 121

<211> LENGTH: 1106

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 121

Met Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
 1 5 10 15

Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Gly Val Lys Thr Phe
 20 25 30

His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
 35 40 45

Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
 50 55 60

Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
 65 70 75 80

Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
 85 90 95

Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
 100 105 110

Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
 115 120 125

Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
 130 135 140

Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
 145 150 155 160

Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
 165 170 175

Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
 180 185 190

Lys Ser Ser Asn Pro Glu Ala Arg Leu Asn Glu Lys Asn Pro Asp Val
 195 200 205

Asp Ala Ile Cys Glu Met Pro Ser Leu Ser Arg Lys Asn Asp Leu Ile
 210 215 220

Ile Trp Ile Arg Leu Val Pro Leu Gln Glu Glu Ile Tyr Arg Lys Phe
 225 230 235 240

Val Ser Leu Asp His Ile Lys Glu Leu Leu Met Glu Thr Arg Ser Pro
 245 250 255

Leu Ala Glu Leu Gly Val Leu Lys Lys Leu Cys Asp His Pro Arg Leu
 260 265 270

Leu Ser Ala Arg Ala Cys Cys Leu Leu Asn Leu Gly Thr Phe Ser Ala
 275 280 285

Gln Asp Gly Asn Glu Gly Glu Asp Ser Pro Asp Val Asp His Ile Asp
 290 295 300

Gln Val Thr Asp Asp Thr Leu Met Glu Glu Ser Gly Lys Met Ile Phe
 305 310 315 320

Leu Met Asp Leu Leu Lys Arg Leu Arg Asp Glu Gly His Gln Thr Leu
 325 330 335

Val Phe Ser Gln Ser Arg Gln Ile Leu Asn Ile Ile Glu Arg Leu Leu
 340 345 350

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Lys Asn Arg His Phe Lys Thr Leu Arg Ile Asp Gly Thr Val Thr His
 355 360 365
 Leu Leu Glu Arg Glu Lys Arg Ile Asn Leu Phe Gln Gln Asn Lys Asp
 370 375 380
 Tyr Ser Val Phe Leu Leu Thr Thr Gln Val Gly Gly Val Gly Leu Thr
 385 390 395 400
 Leu Thr Ala Ala Thr Arg Val Val Ile Phe Asp Pro Ser Trp Asn Pro
 405 410 415
 Ala Thr Asp Ala Gln Ala Val Asp Arg Val Tyr Arg Ile Gly Gln Lys
 420 425 430
 Glu Asn Val Val Val Tyr Arg Leu Ile Thr Cys Gly Thr Val Glu Glu
 435 440 445
 Lys Ile Tyr Arg Arg Gln Val Phe Lys Asp Ser Leu Ile Arg Gln Thr
 450 455 460
 Thr Gly Glu Lys Lys Asn Pro Phe Arg Tyr Phe Ser Lys Gln Glu Leu
 465 470 475 480
 Arg Glu Leu Phe Thr Ile Glu Asp Leu Gln Asn Ser Val Thr Gln Leu
 485 490 495
 Gln Leu Gln Ser Leu His Ala Ala Gln Arg Lys Ser Asp Ile Lys Leu
 500 505 510
 Asp Glu His Ile Ala Tyr Leu Gln Ser Leu Gly Ile Ala Gly Ile Ser
 515 520 525
 Asp His Asp Leu Met Tyr Thr Cys Asp Leu Ser Val Lys Glu Glu Leu
 530 535 540
 Asp Val Val Glu Glu Ser His Tyr Ile Gln Gln Arg Val Gln Lys Ala
 545 550 555 560
 Gln Phe Leu Val Glu Phe Glu Ser Gln Asn Lys Glu Phe Leu Met Glu
 565 570 575
 Gln Gln Arg Thr Arg Asn Glu Gly Ala Trp Leu Arg Glu Pro Val Phe
 580 585 590
 Pro Ser Ser Thr Lys Lys Lys Cys Pro Lys Leu Asn Lys Pro Gln Pro
 595 600 605
 Gln Pro Ser Pro Leu Leu Ser Thr His His Thr Gln Glu Glu Asp Ile
 610 615 620
 Ser Ser Lys Met Ala Ser Val Val Ile Asp Asp Leu Pro Lys Glu Gly
 625 630 635 640
 Glu Lys Gln Asp Leu Ser Ser Ile Lys Val Asn Val Thr Thr Leu Gln
 645 650 655
 Asp Gly Lys Gly Thr Gly Ser Ala Asp Ser Ile Ala Thr Leu Pro Lys
 660 665 670
 Gly Phe Gly Ser Val Glu Glu Leu Cys Thr Asn Ser Ser Leu Gly Met
 675 680 685
 Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr Leu
 690 695 700
 Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu Ser
 705 710 715 720
 Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro Asn
 725 730 735
 Leu Asp Gln Leu Lys Asp Asp Glu Val Leu Arg His Cys Asn Pro Trp
 740 745 750

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Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn Val
   755                               760                               765

Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala Leu
   770                               775                               780

Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser Ala
  785                               790                               795                               800

Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp Ser
   805                               810                               815

Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu
   820                               825                               830

Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe
   835                               840                               845

Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp
   850                               855                               860

Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg
  865                               870                               875                               880

Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr
   885                               890                               895

Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val
   900                               905                               910

Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly
   915                               920                               925

Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn
   930                               935                               940

Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu
  945                               950                               955                               960

Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala
   965                               970                               975

Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly
   980                               985                               990

Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser
   995                               1000                               1005

Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu
  1010                               1015                               1020

Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln
  1025                               1030                               1035                               1040

Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr
   1045                               1050                               1055

Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile
  1060                               1065                               1070

Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
  1075                               1080                               1085

Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
  1090                               1095                               1100

Asn Asn
1105

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<210> SEQ ID NO 122

<211> LENGTH: 2294

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 122

-continued

tcattaataa gacaaactac tgggtgaaaaa aagaaccctt tccgatatatt tagtaaacaa	60
gaattaagag agctctttac aatcgaggat cttcagaact ctgtaaccca gctgcagctt	120
cagtctttgc atgctgctca gaggaaatct gatataaac tagatgaaca tattgcctac	180
ctgcagctctt tggggatagc tggaatctca gaccatgatt tgatgtacac atgtgatctg	240
tctgttaaaag aagagcttga tgtggtagaa gaatctcact atattcaaca aagggttcag	300
aaagctcaat tcctcgttga attcgagtct caaaataaag agttcctgat ggaacaacaa	360
agaactagaa atgagggggc ctggctaaga gaacctgtat ttccttcttc aacaaagaag	420
aatgcccta aattgaataa accacagcct cagccttcac ctcttctaag tactcatcat	480
actcaggaag aagatatcag ttccaaaatg gcaagtgtag tcattgatga tctgccccaa	540
gagggtgaga aacaagatct ctccagtata aaggtgaatg ttaccacctt gcaagatggg	600
taaggtacag gtagtgctga ctctataact actttaccaa aggggtttgg aagtgtagaa	660
gaactttgta ctaactcttc attgggaatg gaaaaaagct ttgcaactaa aaatgaagct	720
gtacaaaaag agacattaca agaggggcct aagcaggagg cactgcaaga ggatcctctg	780
gaaagtttta attatgtact tagcaaatca accaaagctg atattggggc aaatttagat	840
caactaaagg atgatgagat ttacgtcat tgcaatcctt ggccattat ttccataaca	900
aatgaaagtc aaaatgcaga atcaaatgta tccattattg aaatagctga tgacctttca	960
gcatcccata gtgactgca ggatgctcaa gcaagtgagg ccaagttgga agaggaaacct	1020
tcagcatctt caccacagta tgcagtgtat ttcaatcttt tcttgaaga ctcagcagac	1080
aacagacaaa atttttccag tcagtcttta gagcatgttg agaagaaaa tagcttgtgt	1140
ggctctgcac ctaattccaa agcaggggtt gtgcatagca aaacatgtct cagttgggag	1200
ttttctgaga aagacgatga accagaagaa gtagtagtta aagcaaaaat cagaagtaaa	1260
gctagaagga ttgtttcaga tggcgaagat gaagatgatt cttttaaaga tacctcaagc	1320
ataaatccat tcaacacatc tctctttcaa ttctcatctg tgaacaatt tgatgcttca	1380
actcccaaaa atgacatcag tccaccagga aggttctttt catctcaaat acccagtagt	1440
gtaataaagt ctatgaatc tagaagatct ctggcttcta ggaggtctct tattaatatg	1500
gttttagacc acgtggagga catggaggaa agacttgacg acagcagtga agcaaaggg	1560
cctgaagatt atccagaaga aggggtggag gaaagcagtg gcgaagcctc caagtataca	1620
gaagaggatc cttccggaga aacactgtct tcagaaaaca agtccagctg gttaatgacg	1680
tctaagccta gtgctctagc tcaagagacc tctcttggtg cccctgagcc ttgtctggt	1740
gaacagttgg ttggttctcc ccaggataag gcggcagagg ctacaaatga ctatgagact	1800
cttgtaaaagc gtggaagaaga actaaaagag tgtggaaaaa tccaggaggc cctaaactgc	1860
ttagttaaaag cgcttgacat aaaaagtgc gatcctgaag ttatgctctt gactttaagt	1920
ttgtataagc aacttaataa caattgagaa tgtaacctgt ttattgtatt ttaaagtga	1980
actgaatatg agggaatatt tgttcccata attggattct ttgggaacat gaagcattca	2040
ggcttaaggc aagaaagatc tcaaaaagca acttctgccc tgcaacgccc cccactccat	2100
agtctggtat tctgagcact agcttaatat ttcttcactt gaatattctt atattttagg	2160
catattctat aaatttaact gtgtgttttc ttggaaagtt ttgtaaaatt attctgggtca	2220
ttcttaattt tactctgaaa gtgatcatct ttgtatataa cagttcagat aagaaaatta	2280

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aagttacttt tctc 2294

<210> SEQ ID NO 123

<211> LENGTH: 2294

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 123

tcattaataa gacaaactac tggtgaaaaa aagaaccctt tccgatat	60
ttt tagtaaacaa gaattaagag agctctttac aatcgaggat cttcagaact	120
ctgtaaccca gctgcagctt cagtctttgc atgctgctca gaggaaatct gatataaaac	180
tagatgaaca tattgcctac ctgcagtcctt tggggatagc tggaatctca	240
gaccatgatt tgatgtacac atgtgatctg tctgttaaag aagagcttga	300
tgtggtagaa gaatctcact atattcaaca aagggttcag aaagctcaat	360
tcctcgttga attcagagtct caaaaataag agttcctgat ggaacaacaa	420
agaactagaa atgagggggc ctggctaaga gaacctgtat ttccttcttc	480
aacaaagaag aaatgcccta aattgaataa accacagcct cagccttcac	540
ctcttctaag tactcatcat actcaggaag aagatatcag ttccaaaatg	600
gcaagtgtag tcattgatga tctgccc aaa gagggtgaga aacaagatct	660
ctccagtata aagggtgaatg ttaccacctt gcaagatggt aaaggtacag	720
gtagtctga ctctatagct actttaccaa aggggttttg aagtgtagaa	780
gaactttgta ctaactcttc attgggaatg gaaaaaagct ttgcaactaa	840
aatgaagct gtacaaaaag agacattaca agaggggcct aagcaagagg	900
cactgcaaga ggatcctctg gaaagtttta attatgtact tagcaaatca	960
accaaagctg atattgggcc aaatttagat caactaaagg atgatgagat	1020
tttacgtcat tgcaatcctt ggcccattat ttccataaca aatgaaagtc	1080
aaaatgcaga atcaaatgta tccattattg aaatagctga tgacctttca	1140
gcatcccata gtgcactgca ggatgctcaa gcaagtgagg ccaagttgga	1200
agaggaacct tcagcatctt caccacagta tgcagtgtgat ttcaatcttt	1260
tcttggaga ctcagcagac aacagacaaa atttttccag tcagtcttta	1320
gagcatgttg agaagaaaa tagcttgtgt ggctctgcac ctaattccag	1380
agcagggttt gtgcatagca aaacatgtct cagttgggag ttttctgaga	1440
aagacgatga accagaagaa gtagtagtta aagcaaaaat cagaagtaaa	1500
gctagaagga ttgtttcaga tggcgaagat gaagatgatt cttttaaaga	1560
tacctcaagc ataaatccat tcaacacatc tctctttcaa ttctcatctg	1620
tgaacaatt tgatgcttca actcccaaaa atgacatcag tccaccagga	1680
aggttctttt catctcaa at acccagtagt gtaaataagt ctatgaactc	1740
tagaagatct ctggcttcta ggaggctctt tattaatatg gttttagacc	1800
acgtggagga catggaggaa agacttgacg acagcagtg aacaaagggt	1860
cctgaagatt atccagaaga aggggtggag gaaagcagtg gcgaagcctc	1920
caagtataca gaagaggatc cttccggaga aacactgtct tcagaaaaca	1980
agtccagctg gttaatgacg tctaagccta gtgctctagc tcaagagacc	
tctcttggtg cccctgagcc tttgtctggt gaacagttgg ttggttctcc	
ccaggataag gggcagagg ctacaaatga ctatgagact cttgtaaagc	
gtggaaaaga actaaaagag tgtggaaaaa tccaggaggc cctaaactgc	
ttagttaaag cgcttgacat aaaaagtgca gatcctgaag ttatgctctt	
gactttaagt ttgtataagc aacttaataa caattgagaa tgtaacctgt	
ttattgtatt ttaaagtgaa	

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actgaatatg agggaat tttt tgttccata attggattct ttgggaacat gaagcattca 2040
ggcttaaggc aagaaagatc tcaaaaagca acttctgccc tgcaacgccc cccactccat 2100
agtctgggat tctgagcact agcttaatat ttcttcactt gaatattctt atattttagg 2160
catattctat aaatttaact gtgtgttttc ttggaaagtt ttgtaaaatt attctgggtca 2220
ttcttaat tttt tactctgaaa gtgatcatct ttgtatataa cagttcagat aagaaaatta 2280
aagttact tttt tctc 2294

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<210> SEQ ID NO 124

<211> LENGTH: 2294

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 124

```

tcattaataa gacaaactac tgggtgaaaa aagaaccctt tccgatattt tagtaaacaa 60
gaattaagag agctctttac aatcgaggat cttcagaact ctgtaaccca gctgcagctt 120
cagtctttgc atgctgctca gaggaatctt gatataaaac tagatgaaca tattgcctac 180
ctgcagctct tggggatagc tggaatctca gaccatgatt tgatgtacac atgtgatctg 240
tctgttaaa aagagcttga tgtggtagaa gaatctcact atattcaaca aagggttcag 300
aaagctcaat tcctcgttga attcagctct caaaaataag agttcctgat ggaacaacaa 360
agaactagaa atgagggggc ctggctaaga gaacctgtat ttccttcttc aacaaagaag 420
aaatgcccta aattgaataa accacagcct cagccttcac ctcttctaag tactcatcat 480
actcaggaag aagatatcag ttccaaaatg gcaagtgtag tcattgatga tctgccc aaa 540
gagggtgaga aacaagatct ctccagtata aaggtgaatg ttaccacctt gcaagatggg 600
taaggtagag gtagtgctga ctctataact actttaccaa aggggttttg aagtgtagaa 660
gaacttttga ctaactcttc attgggaatg gaaaaaagct ttgcaactaa aaatgaagct 720
gtacaaaaag agacattaca agaggggcct aagcaggagg cactgcaaga ggatcctctg 780
gaaagt tttt attatgtact tagcaaatca accaaagctg atattgggcc aaatttagat 840
caactaaagg atgatgagat tttacgtcat tgcaatcctt ggcccattat ttccataaca 900
aatgaaagtc aaaatgcaga atcaaatgta tccattattg aaatagctga tgacctttca 960
gcatcccata gtgactgca ggatgctcaa gcaagtgagg ccaagttgga agaggaacct 1020
tcagcatctt caccacagta tgcattgtat ttcaatcttt tcttggaaga ctacagcagac 1080
aacagacaaa atttttccag tcagctctta gagcatgttg agaagaaaa tagcttgtgt 1140
ggctctgcac ctaattccaa agcaggggtt gtgcatagca aaacatgtct cagttgggag 1200
ttttctgaga aagacgatga accagaagaa gtagtagtta aagcaaaaat cagaagtaaa 1260
gctagaagga ttgtttcaga tggcgaagat gaagatgatt cttttaaaga tacctcaagc 1320
ataaatccat tcaacacatc tctctttcaa ttctcatctg tgaacaatt tgatgcttca 1380
actccaaaa atgacatcag tccaccagga aggttctttt catctcaaat acccagtagt 1440
gtaaataagt ctatgaactc tagaagatct ctggcttcta ggaggtctct tattaatatg 1500
gttttagacc acgtggagga catggaggaa agacttgacg acagcagtgag agcaaagggt 1560
cctgaagatt atccagaaga aggggtggag gaaagcagtg gcgaagcctc caagtataca 1620
gaagaggatc cttccggaga aacactgtct tcagaaaaca agtccagctg gttaatgacg 1680

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tctaagccta gtgctctagc tcaagagacc tctcttggtg cccctgagcc ttgtctggt 1740
gaacagttagg ttggttctcc ccaggataag gcggcagagg ctacaaatga ctatgagact 1800
cttgtaaagc gtggaaaaga actaaaagag tgtggaaaaa tccaggaggc cctaaactgc 1860
ttagttaaag cgcttgacat aaaaagtga gatcctgaag ttatgctctt gactttaagt 1920
ttgtataagc aacttaataa caattgagaa tgtaacctgt ttattgtatt ttaaagtga 1980
actgaatatg agggaaattht tgttcccata attggattct ttgggaacat gaagcattca 2040
ggcttaaggc aagaaagatc tcaaaaagca acttctgccc tgcaacgccc cccactccat 2100
agtctggtat tctgagcact agcttaatat ttcttcactt gaatattctt atattttagg 2160
catattctat aaatttaact gtgtgtgttc ttggaaagtt ttgtaaaatt attctggtca 2220
ttcttaattht tactctgaaa gtgatcatct ttgtatataa cagttcagat aagaaaatta 2280
aagttacttht tctc 2294
```

<210> SEQ ID NO 125

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 125

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Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
 1           5           10          15
Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
 20          25          30
Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
 35          40          45
Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
 50          55          60
Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
 65          70          75          80
Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
 85          90          95
Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
100         105         110
Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
115         120         125
Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
130         135         140
Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Lys Ala Gly
145         150         155         160
Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
165         170         175
Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
180         185         190
Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
195         200         205
Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
210         215         220
Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
225         230         235         240
```

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<210> SEQ ID NO 126
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 126
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Asp 1	Gly	Lys	Gly	Thr 5	Gly	Ser	Ala	Asp 10	Ser	Ile	Ala	Thr	Leu	Pro 15	Lys
Gly	Phe	Gly 20	Ser	Val	Glu	Glu	Leu	Cys 25	Thr	Asn	Ser	Ser	Leu 30	Gly	Met
Glu	Lys	Ser 35	Phe	Ala	Thr	Lys	Asn 40	Glu	Ala	Val	Gln	Lys 45	Glu	Thr	Leu
Gln	Glu 50	Gly	Pro	Lys	Gln	Glu 55	Ala	Leu	Gln	Glu	Asp 60	Pro	Leu	Glu	Ser
Phe 65	Asn	Tyr	Val	Leu	Ser 70	Lys	Ser	Thr	Lys	Ala 75	Asp	Ile	Gly	Pro 80	Asn
Leu	Asp	Gln	Leu	Lys 85	Asp	Asp	Glu	Ile	Leu 90	Arg	His	Cys	Asn 95	Pro	Trp
Pro	Ile	Ile	Ser 100	Ile	Thr	Asn	Glu	Ser 105	Gln	Asn	Ala	Glu	Ser 110	Asn	Val
Ser	Ile	Ile 115	Glu	Ile	Ala	Asp	Asp 120	Leu	Ser	Ala	Ser	His 125	Ser	Ala	Leu
Gln	Asp 130	Ala	Gln	Ala	Ser	Glu 135	Ala	Lys	Leu	Glu	Glu 140	Glu	Pro	Ser	Ala
Ser 145	Ser	Pro	Gln	Tyr 150	Ala	Cys	Asp	Phe	Asn 155	Leu	Phe	Leu	Glu	Asp 160	Ser
Ala	Asp	Asn	Arg	Gln 165	Asn	Phe	Ser	Ser	Gln 170	Ser	Leu	Glu	His 175	Val	Glu

-continued

Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe
 180 185 190
 Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp
 195 200 205
 Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg
 210 215 220
 Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr
 225 230 235 240
 Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val
 245 250 255
 Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly
 260 265 270
 Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn
 275 280 285
 Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu
 290 295 300
 Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala
 305 310 315 320
 Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly
 325 330 335
 Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser
 340 345 350
 Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu
 355 360 365
 Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln
 370 375 380
 Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp Tyr
 385 390 395 400
 Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile
 405 410 415
 Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
 420 425 430
 Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
 435 440 445
 Asn Asn
 450

<210> SEQ ID NO 127

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 127

Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
 1 5 10 15
 Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
 20 25 30
 Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
 35 40 45
 Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
 50 55 60
 Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
 65 70 75 80

-continued

Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
 85 90 95
 Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
 100 105 110
 Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
 115 120 125
 Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
 130 135 140
 Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Lys Ala Gly
 145 150 155 160
 Phe Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp
 165 170 175
 Asp Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala
 180 185 190
 Arg Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp
 195 200 205
 Thr Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser
 210 215 220
 Val Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro
 225 230 235 240
 Gly Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met
 245 250 255
 Asn Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val
 260 265 270
 Leu Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu
 275 280 285
 Ala Lys Gly Pro Glu Asp Tyr Thr Glu Glu Gly Val Glu Glu Ser Ser
 290 295 300
 Gly Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu
 305 310 315 320
 Ser Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala
 325 330 335
 Leu Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu
 340 345 350
 Gln Leu Val Gly Ser Pro Gln Asp Lys Ala Ala Glu Ala Thr Asn Asp
 355 360 365
 Tyr Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys
 370 375 380
 Ile Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser
 385 390 395 400
 Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
 405 410 415
 Asn Asn Asn

<210> SEQ ID NO 128
 <211> LENGTH: 1720
 <212> TYPE: DNA
 <213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 128

ggcacgaggc caccttgcaa gatggtaaag gtacaggtag tgctgactct atagctactt

60

-continued

taccaaaagg	gtttggaagt	gtagaagaac	tttgtactaa	ctcttcattg	ggaatggaaa	120
aaagctttgc	aactaaaaat	gaagctgtac	aaaaagagac	attacaagag	gggcctaagc	180
aagaggcact	gcaagaggat	cctctggaaa	gttttaatta	tgtacttagc	aaatcaacca	240
aagctgatat	tgggccaaat	ttagatcaac	taaaggatga	tgagatttta	cgctcattgca	300
atccttgccc	cattattttcc	ataacaaatg	aaagtcaaaa	tgacagaatca	aatgtatcca	360
ttattgaaat	agctgatgac	ctttcagcat	cccatagtgc	actgcaggat	gctcaagcaa	420
gtgaggccaa	gttggaagag	gaaccttcag	catcttcacc	acagtatgca	tgtgatttca	480
atcttttctt	ggaagactca	gcagacaaca	gacaaaatth	ttccagtcag	tcttttagagc	540
atgttgagaa	agaaaatagc	ttgtgtggct	ctgcacctaa	ttccagagca	gggtttgtgc	600
atagcaaaac	atgtctcagt	tgggagtttt	ctgagaaaga	cgatgaacca	gaagaagtag	660
tagttaaaagc	aaaaatcaga	agtaaagcta	gaaggattgt	ttcagatggc	gaagatgaag	720
atgattcttt	taaagatacc	tcaagcataa	atccattcaa	cacatctctc	tttcaattct	780
catctgtgaa	acaatttgat	gcttcaactc	ccaaaaatga	catcagtcga	ccaggaaggt	840
tcttttcatc	tcaaataccc	agtagtgtaa	ataagtctat	gaactctaga	agatctcttg	900
cttctaggag	gtctcttatt	aatatgggtt	tagaccacgt	ggaggacatg	gaggaaagac	960
ttgacgacag	cagtgaagca	aagggtcctg	aagattatcc	agaagaaggg	gtggaggaaa	1020
gcagtggcga	agcctccaag	tatacagaag	aggatccttc	cggagaaaca	ctgtcttcag	1080
aaaaaagtc	cagctgggta	atgacgtcta	agcctagtgc	tctagctcaa	gagacctctc	1140
ttggtgcccc	tgagcctttg	tctggtgaac	agttggttgg	ttctccccag	gataaggcgg	1200
cagaggctac	aaatgactat	gagactcttg	taaagcgtgg	aaaagaacta	aaagagtgtg	1260
gaaaaatcca	ggaggcccta	aactgcttag	ttaaagcgct	tgacataaaa	agtgcagatc	1320
ctgaagttaa	gtctcttgact	ttaagtttgt	ataagcaact	taataacaat	tgagaatgta	1380
acctgtttat	tgtattttta	agtgaactg	aatatgaggg	aatttttgtt	cccataattg	1440
gattcttttg	gaactgaag	cattcaggct	taaggcaaga	aagatctcaa	aaagcaactt	1500
ctgccctgca	acgcccccca	ctccatagtc	tggtattctg	agcactagct	taatatttct	1560
tcacttgaat	attcttatat	tttaggcata	ttctataaat	ttaactgtgt	tgtttcttg	1620
aaagttttgt	aaaattattc	tggctattct	taatttttact	ctgaaagtga	tcattctttgt	1680
atataacagt	tcagataaga	aaattaaagt	tactttttctc			1720

<210> SEQ ID NO 129

<211> LENGTH: 1744

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 129

aaacagatct	ctccagtata	aaggatgaatg	ttaccacett	gcaagatggg	aaaggtagac	60
gtagtgctga	ctctatagct	actttaccaa	aggggttttg	aagtgtagaa	gaactttgta	120
ctaactcttc	attgggaatg	gaaaaaagct	ttgcaactaa	aatgaagct	gtacaaaaag	180
agacattaca	agaggggcct	aagcaagagg	cactgcaaga	ggatcctctg	gaaagtttta	240
attatgtact	tagcaaatca	accaaagctg	atattgggac	aaatttagat	caactaaagg	300
atgatgagat	tttacgtcat	tgcaatcctt	ggccatttat	ttccataaca	aatgaaagtc	360

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aaaaatgcaga atcaaatgta tccattattg aaatagctga tgacctttca gcatcccata	420
gtgcactgca ggatgctcaa gcaagtggag ccaagttgga agaggaaacct tcagcatctt	480
caccacagta tgcattgtat ttcaatcttt tcttggaaga ctcagcagac aacagacaaa	540
atthttccag tcagtcttta gagcatgttg agaaagaaaa tagcttgtgt ggctctgcac	600
ctaattccag agcagggttt gtgcatagca aaacatgtct cagttgggag ttttctgaga	660
aagacgatga accagaagaa gtagtagtta aagcaaaaat cagaagtaaa gctagaagga	720
ttgtttcaga tggcgaagat gaagatgatt cttttaaaga tacctcaagc ataaatccat	780
tcaacacatc tctctttcaa ttctcatctg tgaacaatt tgatgcttca actcccaaaa	840
atgacatcag tccaccagga aggttctttt catctcaaat acccagtagt gtaaataagt	900
ctatgaactc tagaagatct ctggcttcta ggaggtctct tattaatatg gtttagacc	960
acgtggagga catggaggaa agacttgacg acagcagtga agcaaagggt cctgaagatt	1020
atccagaaga aggggtggag gaaagcagtg gcgaagcctc caagtataca gaagaggatc	1080
cttcgagga aacactgtct tcagaaaaca agtccagctg gttaatgacg tctaagccta	1140
gtgctctagc tcaagagacc tctcttggtg cccctgagcc tttgtctggt gaacagttgg	1200
ttggttctcc ccaggataag gcggcagagg ctacaaatga ctatgagact cttgtaaagc	1260
gtggaaaaga actaaaagag tgtggaaaaa tccaggaggc cctaaactgc ttagttaag	1320
cgcttgacat aaaaagtgca gatcctgaag ttatgctctt gactttaagt ttgtataagc	1380
aacttaataa caattgagaa tgtaacctgt ttattgtatt ttaaagtga actgaatatg	1440
agggaaatth ttgtcccata attggattct ttgggaacat gaagcattca ggcttaaggc	1500
aagaaagatc tcaaaaagca acttctgccc tgcaacgccc cccactccat agtctggtat	1560
tctgagcact agcttaatat ttcttcactt gaatattctt atattttagg catattctat	1620
aaatttaact gtgtgttttc ttggaaagt ttgtaaaatt attctggtca ttcttaattt	1680
tactctgaaa gtgatcatct ttgtatataa cagttcagat aagaaaatta aagttacttt	1740
tctc	1744

<210> SEQ ID NO 130

<211> LENGTH: 1711

<212> TYPE: DNA

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 130

ccaccttgca agatggtaaa ggtacaggtg gtgctgactc tatagctact ttaccaaaag	60
ggtttggaag tgtagaagaa ctttgtacta actcttcatt gggaatggaa aaaagctttg	120
caactaaaaa tgaagctgta caaaaagaga cattacaaga ggggcctaag caagaggcac	180
tgcaagagga tcctctggaa agttttaatt atgtacttag caaatcaacc aaagctgata	240
ttgggcaaaa tttagatcaa ctaaaggatg atgagatttt acgtcattgc aatccttggc	300
ccattatttc cataacaat gaaagtcaaa atgcagaatc aaatgtatcc attattgaaa	360
tagctgatga cttttcagca tcccatagtg cactgcagga tgctcaagca agtgaggcca	420
agttggaaga ggaaccttca gcatcttcac cacagtatgc atgtgatttc aatcttttct	480
tggaagactc agcagacaac agacaaaatt tttccagtca gtctttagag catgttgaga	540
aagaaaatag cttgtgtggc tctgcaccta attccagagc agggtttgtg catagcaaaa	600

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catgtctcag ttgggagttt tctgagaaa acgatgaacc agaagaagta gtagttaaag 660
caaaaatcag aagtaaagct agaaggattg tttcagatgg cgaagatgaa gatgattctt 720
ttaagatac ctcaagcata aatccattca acacatctct ctttcaattc tcactctgtga 780
aacaatttga tgcttcaact cccaaaaatg acatcagtc accaggaagg ttcttttcat 840
ctcaaatacc cagtagtgta aataagtcta tgaactctag aagatctctg gcttctagga 900
ggtctcttat taatatggtt ttagaccacg tggaggacat ggaggaaaga cttgacgaca 960
gcagtgaagc aaagggtcct gaagattatc cagaagaagg ggtggaggaa agcagtggcg 1020
aagcctccaa gtatacagaa gaggatcctt ccggagaaac actgtcttca gaaaacaagt 1080
ccagctggtt aatgacgtct aagcctagtg ctctagctca agagacctct cttggtgccc 1140
ctgagccttt gtctggtgaa cagttggttg gttctcccca ggataaggcg gcagaggcta 1200
caaatgacta tgagactcct gtaaagcgtg gaaaagaact aaaagagtgt gaaaaaatcc 1260
aggaggccct aaactgctta gttaaagcgc ttgacataaa aagtgcagat cctgaagtta 1320
tgctcttgac tttaagtttg tataagcaac ttaataacaa ttgagaatgt aacctgttta 1380
ttgtatttta aagtgaact gaatatgagg gaatttttgt tcccataatt ggattctttg 1440
ggaacatgaa gcattcaggc ttaaggcaag aaagatctca aaaagcaact tctgccctgc 1500
aacgcccccc actccatagt ctggtattct gagcactagc ttaatatattc ttcacttgaa 1560
tattcttata ttttaggcac attctataaa tttactgtg ttgtttcttg gaaagttttg 1620
taaaattatt ctggtcattc ttaattttac tctgaaagt atcatctttg tatataacag 1680
ttcagataag aaaattaaag ttacttttct c 1711

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<210> SEQ ID NO 131

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 131

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Met Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr
 1           5           10          15
Leu Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu
 20          25          30
Ser Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro
 35          40          45
Asn Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro
 50          55          60
Trp Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn
 65          70          75          80
Val Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala
 85          90          95
Leu Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser
100         105         110
Ala Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp
115         120         125
Ser Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val
130         135         140
Glu Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly
145         150         155         160

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<210> SEQ ID NO 132
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 132

Asp Gly Lys Gly Thr Gly Ser Ala Asp Ser Ile Ala Thr Leu Pro Lys
 1             5             10             15

Gly Phe Gly Ser Val Glu Glu Leu Cys Thr Asn Ser Ser Leu Gly Met
 20             25             30

Glu Lys Ser Phe Ala Thr Lys Asn Glu Ala Val Gln Lys Glu Thr Leu
 35             40             45

Gln Glu Gly Pro Lys Gln Glu Ala Leu Gln Glu Asp Pro Leu Glu Ser
 50             55             60

Phe Asn Tyr Val Leu Ser Lys Ser Thr Lys Ala Asp Ile Gly Pro Asn
 65             70             75             80

Leu Asp Gln Leu Lys Asp Asp Glu Ile Leu Arg His Cys Asn Pro Trp
 85             90             95

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Pro Ile Ile Ser Ile Thr Asn Glu Ser Gln Asn Ala Glu Ser Asn Val
      100                      105                      110

Ser Ile Ile Glu Ile Ala Asp Asp Leu Ser Ala Ser His Ser Ala Leu
      115                      120                      125

Gln Asp Ala Gln Ala Ser Glu Ala Lys Leu Glu Glu Glu Pro Ser Ala
      130                      135                      140

Ser Ser Pro Gln Tyr Ala Cys Asp Phe Asn Leu Phe Leu Glu Asp Ser
145                      150                      155                      160

Ala Asp Asn Arg Gln Asn Phe Ser Ser Gln Ser Leu Glu His Val Glu
      165                      170                      175

Lys Glu Asn Ser Leu Cys Gly Ser Ala Pro Asn Ser Arg Ala Gly Phe
      180                      185                      190

Val His Ser Lys Thr Cys Leu Ser Trp Glu Phe Ser Glu Lys Asp Asp
      195                      200                      205

Glu Pro Glu Glu Val Val Val Lys Ala Lys Ile Arg Ser Lys Ala Arg
      210                      215                      220

Arg Ile Val Ser Asp Gly Glu Asp Glu Asp Asp Ser Phe Lys Asp Thr
225                      230                      235                      240

Ser Ser Ile Asn Pro Phe Asn Thr Ser Leu Phe Gln Phe Ser Ser Val
      245                      250                      255

Lys Gln Phe Asp Ala Ser Thr Pro Lys Asn Asp Ile Ser Pro Pro Gly
      260                      265                      270

Arg Phe Phe Ser Ser Gln Ile Pro Ser Ser Val Asn Lys Ser Met Asn
      275                      280                      285

Ser Arg Arg Ser Leu Ala Ser Arg Arg Ser Leu Ile Asn Met Val Leu
      290                      295                      300

Asp His Val Glu Asp Met Glu Glu Arg Leu Asp Asp Ser Ser Glu Ala
305                      310                      315                      320

Lys Gly Pro Glu Asp Tyr Pro Glu Glu Gly Val Glu Glu Ser Ser Gly
      325                      330                      335

Glu Ala Ser Lys Tyr Thr Glu Glu Asp Pro Ser Gly Glu Thr Leu Ser
      340                      345                      350

Ser Glu Asn Lys Ser Ser Trp Leu Met Thr Ser Lys Pro Ser Ala Leu
      355                      360                      365

Ala Gln Glu Thr Ser Leu Gly Ala Pro Glu Pro Leu Ser Gly Glu Gln
      370                      375                      380

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

Glu Thr Leu Val Lys Arg Gly Lys Glu Leu Lys Glu Cys Gly Lys Ile
      405                      410                      415

Gln Glu Ala Leu Asn Cys Leu Val Lys Ala Leu Asp Ile Lys Ser Ala
      420                      425                      430

Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu Asn
      435                      440                      445

Asn Asn
      450

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<210> SEQ ID NO 133

<211> LENGTH: 419

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 133

-continued

Met	Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr
1				5					10					15	
Leu	Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu
			20					25					30		
Ser	Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro
		35					40					45			
Asn	Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro
	50					55					60				
Trp	Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn
65					70					75					80
Val	Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala
				85					90					95	
Leu	Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser
			100					105					110		
Ala	Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp
		115					120					125			
Ser	Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val
	130					135					140				
Glu	Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly
145					150					155					160
Phe	Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp
				165					170					175	
Asp	Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala
			180					185					190		
Arg	Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	Ser	Phe	Lys	Asp
	195					200						205			
Thr	Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser
	210					215					220				
Val	Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	Ile	Ser	Pro	Pro
225					230					235					240
Gly	Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	Asn	Lys	Ser	Met
				245					250					255	
Asn	Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	Ile	Asn	Met	Val
		260						265					270		
Leu	Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	Asp	Ser	Ser	Glu
	275					280					285				
Ala	Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	Glu	Glu	Ser	Ser
	290					295					300				
Gly	Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	Gly	Glu	Thr	Leu
305					310					315					320
Ser	Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	Lys	Pro	Ser	Ala
			325						330					335	
Leu	Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	Leu	Ser	Gly	Glu
			340					345					350		
Gln	Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu	Ala	Thr	Asn	Asp
		355					360					365			
Tyr	Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys	Glu	Cys	Gly	Lys
	370					375					380				
Ile	Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu	Asp	Ile	Lys	Ser
385					390					395					400

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Ala Asp Pro Glu Val Met Leu Leu Thr Leu Ser Leu Tyr Lys Gln Leu
405 410 415

Asn Asn Asn

<210> SEQ ID NO 134

<211> LENGTH: 1250

<212> TYPE: PRT

<213> ORGANISM: Homo Sapiens

<400> SEQUENCE: 134

Met Glu Ala Ser Arg Arg Phe Pro Glu Ala Glu Ala Leu Ser Pro Glu
1 5 10 15

Gln Ala Ala His Tyr Leu Arg Tyr Val Lys Glu Ala Lys Glu Ala Thr
20 25 30

Lys Asn Gly Asp Leu Glu Glu Ala Phe Lys Leu Phe Asn Leu Ala Lys
35 40 45

Asp Ile Phe Pro Asn Glu Lys Val Leu Ser Arg Ile Gln Lys Ile Gln
50 55 60

Glu Ala Leu Glu Glu Leu Ala Glu Gln Gly Asp Asp Glu Phe Thr Asp
65 70 75 80

Val Cys Asn Ser Gly Leu Leu Leu Tyr Arg Glu Leu His Asn Gln Leu
85 90 95

Phe Glu His Gln Lys Glu Gly Ile Ala Phe Leu Tyr Ser Leu Tyr Arg
100 105 110

Asp Gly Arg Lys Gly Gly Ile Leu Ala Asp Asp Met Gly Leu Gly Lys
115 120 125

Thr Val Gln Ile Ile Ala Phe Leu Ser Gly Met Phe Asp Ala Ser Leu
130 135 140

Val Asn His Val Leu Leu Ile Met Pro Thr Asn Leu Ile Asn Thr Trp
145 150 155 160

Val Lys Glu Phe Ile Lys Trp Thr Pro Gly Met Arg Val Lys Thr Phe
165 170 175

His Gly Pro Ser Lys Asp Glu Arg Thr Arg Asn Leu Asn Arg Ile Gln
180 185 190

Gln Arg Asn Gly Val Ile Ile Thr Thr Tyr Gln Met Leu Ile Asn Asn
195 200 205

Trp Gln Gln Leu Ser Ser Phe Arg Gly Gln Glu Phe Val Trp Asp Tyr
210 215 220

Val Ile Leu Asp Glu Ala His Lys Ile Lys Thr Ser Ser Thr Lys Ser
225 230 235 240

Ala Ile Cys Ala Arg Ala Ile Pro Ala Ser Asn Arg Leu Leu Leu Thr
245 250 255

Gly Thr Pro Ile Gln Asn Asn Leu Gln Glu Leu Trp Ser Leu Phe Asp
260 265 270

Phe Ala Cys Gln Gly Ser Leu Leu Gly Thr Leu Lys Thr Phe Lys Met
275 280 285

Glu Tyr Glu Asn Pro Ile Thr Arg Ala Arg Glu Lys Asp Ala Thr Pro
290 295 300

Gly Glu Lys Ala Leu Gly Phe Lys Ile Ser Glu Asn Leu Met Ala Ile
305 310 315 320

Ile Lys Pro Tyr Phe Leu Arg Arg Thr Lys Glu Asp Val Gln Lys Lys
325 330 335

-continued

Lys	Ser	Ser	Asn	Pro	Glu	Ala	Arg	Leu	Asn	Glu	Lys	Asn	Pro	Asp	Val
			340					345					350		
Asp	Ala	Ile	Cys	Glu	Met	Pro	Ser	Leu	Ser	Arg	Lys	Asn	Asp	Leu	Ile
		355					360					365			
Ile	Trp	Ile	Arg	Leu	Val	Pro	Leu	Gln	Glu	Glu	Ile	Tyr	Arg	Lys	Phe
	370					375					380				
Val	Ser	Leu	Asp	His	Ile	Lys	Glu	Leu	Leu	Met	Glu	Thr	Arg	Ser	Pro
385					390					395					400
Leu	Ala	Glu	Leu	Gly	Val	Leu	Lys	Lys	Leu	Cys	Asp	His	Pro	Arg	Leu
				405					410					415	
Leu	Ser	Ala	Arg	Ala	Cys	Cys	Leu	Leu	Asn	Leu	Gly	Thr	Phe	Ser	Ala
		420						425					430		
Gln	Asp	Gly	Asn	Glu	Gly	Glu	Asp	Ser	Pro	Asp	Val	Asp	His	Ile	Asp
		435					440					445			
Gln	Val	Thr	Asp	Asp	Thr	Leu	Met	Glu	Glu	Ser	Gly	Lys	Met	Ile	Phe
	450					455					460				
Leu	Met	Asp	Leu	Leu	Lys	Arg	Leu	Arg	Asp	Glu	Gly	His	Gln	Thr	Leu
465					470				475						480
Val	Phe	Ser	Gln	Ser	Arg	Gln	Ile	Leu	Asn	Ile	Ile	Glu	Arg	Leu	Leu
				485					490					495	
Lys	Asn	Arg	His	Phe	Lys	Thr	Leu	Arg	Ile	Asp	Gly	Thr	Val	Thr	His
			500					505					510		
Leu	Leu	Glu	Arg	Glu	Lys	Arg	Ile	Asn	Leu	Phe	Gln	Gln	Asn	Lys	Asp
		515					520					525			
Tyr	Ser	Val	Phe	Leu	Leu	Thr	Thr	Gln	Val	Gly	Gly	Val	Gly	Leu	Thr
	530					535					540				
Leu	Thr	Ala	Ala	Thr	Arg	Val	Val	Ile	Phe	Asp	Pro	Ser	Trp	Asn	Pro
545					550					555					560
Ala	Thr	Asp	Ala	Gln	Ala	Val	Asp	Arg	Val	Tyr	Arg	Ile	Gly	Gln	Lys
				565					570					575	
Glu	Asn	Val	Val	Val	Tyr	Arg	Leu	Ile	Thr	Cys	Gly	Thr	Val	Glu	Glu
			580				585						590		
Lys	Ile	Tyr	Arg	Arg	Gln	Val	Phe	Lys	Asp	Ser	Leu	Ile	Arg	Gln	Thr
		595					600					605			
Thr	Gly	Glu	Lys	Lys	Asn	Pro	Phe	Arg	Tyr	Phe	Ser	Lys	Gln	Glu	Leu
	610					615					620				
Arg	Glu	Leu	Phe	Thr	Ile	Glu	Asp	Leu	Gln	Asn	Ser	Val	Thr	Gln	Leu
625					630					635					640
Gln	Leu	Gln	Ser	Leu	His	Ala	Ala	Gln	Arg	Lys	Ser	Asp	Ile	Lys	Leu
				645					650					655	
Asp	Glu	His	Ile	Ala	Tyr	Leu	Gln	Ser	Leu	Gly	Ile	Ala	Gly	Ile	Ser
			660					665				670			
Asp	His	Asp	Leu	Met	Tyr	Thr	Cys	Asp	Leu	Ser	Val	Lys	Glu	Glu	Leu
		675					680					685			
Asp	Val	Val	Glu	Glu	Ser	His	Tyr	Ile	Gln	Gln	Arg	Val	Gln	Lys	Ala
	690					695					700				
Gln	Phe	Leu	Val	Glu	Phe	Glu	Ser	Gln	Asn	Lys	Glu	Phe	Leu	Met	Glu
705					710					715					720
Gln	Gln	Arg	Thr	Arg	Asn	Glu	Gly	Ala	Trp	Leu	Arg	Glu	Pro	Val	Phe
			725					730						735	
Pro	Ser	Ser	Thr	Lys	Lys	Lys	Cys	Pro	Lys	Leu	Asn	Lys	Pro	Gln	Pro

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740							745				750				
Gln	Pro	Ser	Pro	Leu	Leu	Ser	Thr	His	His	Thr	Gln	Glu	Asp	Ile	
755							760				765				
Ser	Ser	Lys	Met	Ala	Ser	Val	Val	Ile	Asp	Asp	Leu	Pro	Lys	Glu	Gly
770							775				780				
Glu	Lys	Gln	Asp	Leu	Ser	Ser	Ile	Lys	Val	Asn	Val	Thr	Thr	Leu	Gln
785							790				795				
Asp	Gly	Lys	Gly	Thr	Gly	Ser	Ala	Asp	Ser	Ile	Ala	Thr	Leu	Pro	Lys
805							810				815				
Gly	Phe	Gly	Ser	Val	Glu	Glu	Leu	Cys	Thr	Asn	Ser	Ser	Leu	Gly	Met
820							825				830				
Glu	Lys	Ser	Phe	Ala	Thr	Lys	Asn	Glu	Ala	Val	Gln	Lys	Glu	Thr	Leu
835							840				845				
Gln	Glu	Gly	Pro	Lys	Gln	Glu	Ala	Leu	Gln	Glu	Asp	Pro	Leu	Glu	Ser
850							855				860				
Phe	Asn	Tyr	Val	Leu	Ser	Lys	Ser	Thr	Lys	Ala	Asp	Ile	Gly	Pro	Asn
865							870				875				
Leu	Asp	Gln	Leu	Lys	Asp	Asp	Glu	Ile	Leu	Arg	His	Cys	Asn	Pro	Trp
885							890				895				
Pro	Ile	Ile	Ser	Ile	Thr	Asn	Glu	Ser	Gln	Asn	Ala	Glu	Ser	Asn	Val
900							905				910				
Ser	Ile	Ile	Glu	Ile	Ala	Asp	Asp	Leu	Ser	Ala	Ser	His	Ser	Ala	Leu
915							920				925				
Gln	Asp	Ala	Gln	Ala	Ser	Glu	Ala	Lys	Leu	Glu	Glu	Glu	Pro	Ser	Ala
930							935				940				
Ser	Ser	Pro	Gln	Tyr	Ala	Cys	Asp	Phe	Asn	Leu	Phe	Leu	Glu	Asp	Ser
945							950				955				
Ala	Asp	Asn	Arg	Gln	Asn	Phe	Ser	Ser	Gln	Ser	Leu	Glu	His	Val	Glu
965							970				975				
Lys	Glu	Asn	Ser	Leu	Cys	Gly	Ser	Ala	Pro	Asn	Ser	Arg	Ala	Gly	Phe
980							985				990				
Val	His	Ser	Lys	Thr	Cys	Leu	Ser	Trp	Glu	Phe	Ser	Glu	Lys	Asp	Asp
995							1000				1005				
Glu	Pro	Glu	Glu	Val	Val	Val	Lys	Ala	Lys	Ile	Arg	Ser	Lys	Ala	Arg
1010							1015				1020				
Arg	Ile	Val	Ser	Asp	Gly	Glu	Asp	Glu	Asp	Asp	Ser	Phe	Lys	Asp	Thr
1025							1030				1035				
Ser	Ser	Ile	Asn	Pro	Phe	Asn	Thr	Ser	Leu	Phe	Gln	Phe	Ser	Ser	Val
1045							1050				1055				
Lys	Gln	Phe	Asp	Ala	Ser	Thr	Pro	Lys	Asn	Asp	Ile	Ser	Pro	Pro	Gly
1060							1065				1070				
Arg	Phe	Phe	Ser	Ser	Gln	Ile	Pro	Ser	Ser	Val	Asn	Lys	Ser	Met	Asn
1075							1080				1085				
Ser	Arg	Arg	Ser	Leu	Ala	Ser	Arg	Arg	Ser	Leu	Ile	Asn	Met	Val	Leu
1090							1095				1100				
Asp	His	Val	Glu	Asp	Met	Glu	Glu	Arg	Leu	Asp	Asp	Ser	Ser	Glu	Ala
1105							1110				1115				
Lys	Gly	Pro	Glu	Asp	Tyr	Pro	Glu	Glu	Gly	Val	Glu	Glu	Ser	Ser	Gly
1125							1130				1135				
Glu	Ala	Ser	Lys	Tyr	Thr	Glu	Glu	Asp	Pro	Ser	Gly	Glu	Thr	Leu	Ser
1140							1145				1150				

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Ser	Glu	Asn	Lys	Ser	Ser	Trp	Leu	Met	Thr	Ser	Lys	Pro	Ser	Ala	Leu
1155							1160					1165			
Ala	Gln	Glu	Thr	Ser	Leu	Gly	Ala	Pro	Glu	Pro	Leu	Ser	Gly	Glu	Gln
1170						1175					1180				
Leu	Val	Gly	Ser	Pro	Gln	Asp	Lys	Ala	Ala	Glu	Ala	Thr	Asn	Asp	Tyr
1185					1190					1195					1200
Glu	Thr	Leu	Val	Lys	Arg	Gly	Lys	Glu	Leu	Lys	Glu	Cys	Gly	Lys	Ile
				1205					1210						1215
Gln	Glu	Ala	Leu	Asn	Cys	Leu	Val	Lys	Ala	Leu	Asp	Ile	Lys	Ser	Ala
				1220					1225						1230
Asp	Pro	Glu	Val	Met	Leu	Leu	Thr	Leu	Ser	Leu	Tyr	Lys	Gln	Leu	Asn
		1235					1240					1245			
Asn	Asn														
1250															

1. A method for detecting a 273P4B7 gene product in a sample, comprising:

providing the sample and a probe that specifically binds to the 273P4B7 gene product, wherein the gene product is encoded directly or indirectly by the nucleotide sequence of SEQ ID NO:2, and wherein the gene product is selected from the group consisting of a protein or an mRNA;

contacting the sample with the probe; and

determining if the probe is bound specifically to the 273P4B7 gene product, wherein specific probe binding is evidence of the gene product in the sample.

2. The method of claim 1, wherein the protein comprising the amino acid sequence of SEQ ID NO:3.

3. The method of claim 2, wherein the probe is an antibody or antigen-binding fragment thereof that specifically binds to the protein.

4. The method of claim 1, wherein the mRNA complementary to SEQ ID NO:2.

5. The method of claim 4, wherein the probe is a nucleotide sequence derived from SEQ ID NO:2, which specifically binds to the mRNA.

6. The method of claim 1, wherein the probe is labeled with a detectable marker.

7. The method of claim 6, wherein the detectable marker is selected from the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator and an enzyme.

8. The method of claim 1, wherein the sample is selected from the group consisting of serum, blood, urine and tissue.

9. The method of claim 1, wherein the sample is a tissue sample.

10. The method of claim 9, wherein the tissue sample is obtained from a source selected from the group consisting of prostate, testis, kidney, brain, bone, skin, ovary, breast, pancreas, colon, and lung.

11. A method for determining relative levels of a 273P4B7 gene product in a test sample and a normal sample from a corresponding source, comprising:

providing the test sample and the normal sample;

contacting the test sample and the normal sample with a probe that specifically binds to the 273P4B7 gene product, wherein the gene product is encoded directly or indirectly by the nucleotide sequence of SEQ ID NO:2, and wherein the gene product is selected from the group consisting of a protein or an mRNA;

measuring binding of the probe bound specifically to the 273P4B7 gene product in the test sample and the normal sample; and

comparing the measurements of bind in the test sample and the normal sample to, determining relative levels of the 273P4B7 gene product in each sample.

12. The method of claim 11, wherein the protein comprising the amino acid sequence of SEQ ID NO:3.

13. The method of claim 12, wherein the probe is an antibody or antigen-binding fragment thereof that specifically binds to the protein.

14. The method of claim 13, wherein the mRNA complementary to SEQ ID NO:2.

15. The method of claim 13, wherein the probe is a nucleotide sequence derived from SEQ ID NO:2, which specifically binds to the mRNA.

16. The method of claim 11, wherein the probe is labeled with a detectable marker.

17. The method of claim 16, wherein the detectable marker is selected from the group consisting of a radioisotope, a fluorescent compound, a bioluminescent compound, a chemiluminescent compound, a metal chelator and an enzyme.

18. The method of claim 11, wherein the sample is selected from the group consisting of serum, blood, urine and tissue.

19. The method of claim 11, wherein the test sample and the normal sample is a tissue sample.

20. The method of claim 19, wherein the tissue sample is obtained from a source selected from the group consisting of prostate, testis, kidney, brain, bone, skin, ovary, breast, pancreas, colon, and lung.

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