Description

PEPTIDE VACCINES FOR CANCERS EXPRESSING MPHOSPH1 OR DEPDC1 POLYPEPTIDES

Technical Field

[0001] The present application claims the benefit of U.S. Provisional Application No. 60/852,575, filed October 17, 2006, the entire contents of which are incorporated by reference herein.

[0002] The present invention relates to the field of biological science, more specifically to the field of cancer therapy. In particular, the present invention relates to novel peptides that serve as extremely effective cancer vaccines, and drugs for treating and preventing tumors containing such peptides.

Background Art

[0003] It has been demonstrated that $CD8^+$ cytotoxic T lymphocytes (CTLs) recognize epitope peptides derived from tumor-associated antigens (TAAs) presented on MHC class I molecules, and lyse the tumor cells. Since the discovery of the MAGE family as the first example of TAAs, many other TAAs have been discovered using immunological approaches (Boon T. (1993) Int J Cancer 54: 177-80.; Boon T. et al., (1996) J Exp Med 183: 725-9.; van der Bruggen P et al., (1991) Science 254: 1643-7.; Brichard V et al., (1993) J Exp Med 178: 489-95.; Kawakami Y et al., (1994) J Exp Med 180: 347-52.). Some of them are now in clinical development as targets of immunotherapy. TAAs discovered so far include MAGE (van der Bruggen P et al., (1991) Science 254: 1643-7.), gp100 (Kawakami Y et al., (1994) J Exp Med 180: 347-52.), SART (Shichijo S et al., (1998) J Exp Med 187:277-88.), and NY-ESO-1 (Chen Y.T. et al., (1997) Proc. Natl. Acd. Sci. USA, 94: 1914-8.). On the other hand, certain gene products demonstrated to be somewhat specifically over-expressed in tumor cells have been shown to be recognized as targets for inducing cellular immune responses. Such gene products include p53 (Umano Y et al., (2001) Br J Cancer, 84:1052-7.), HER2/neu (Tanaka H et al., (2001) Br J Cancer, 84: 94-9.), CEA (Nukaya I et al., (1999) Int. J. Cancer 80, 92-7.) and the like.

[0004] Despite significant progress in basic and clinical research concerning TAAs (Rosenberg SA et al., (1998) Nature Med, 4: 321-7.; Mukherji B. et al., (1995) Proc Natl Acad Sci USA, 92: 8078-82.: Hu X et al., (1996) Cancer Res, 56: 2479-83.), only a very limited number of candidate TAAs suitable for treatment of cancers are presently available. TAAs that are abundantly expressed in cancer cells, and whose expression is restricted to cancer cells, would be promising candidates as immunotherapeutic targets.

[0005] Both HLA-A24 and HLA-A0201 are common HLA alleles in the Japanese and Caucasian populations (Date Y et al., (1996) Tissue Antigens 47: 93-101.; Kondo A et al., (1995) J Immunol 155: 4307-12.; Kubo RT et al., (1994) J Immunol 152: 3913-24.; Imanishi et al., Proceeding of the eleventh International Histocompatibility Workshop and Conference Oxford University Press, Oxford, 1065 (1992); Williams F et al., (1997) Tissue Antigen 49: 129-33.). Thus, antigenic peptides of cancers presented by these HLA alleles may find particular utility in the treatment of cancers among Japanese and Caucasian patients. Further, it is known that the induction of low-affinity CTL in vitro usually results from exposure to high concentrations of peptide, generating a high level of specific peptide/MHC complexes on antigen-presenting cells (APCs), which can effectively activate these CTL (Alexander-Miller et al., (1996) Proc Natl Acad Sci USA 93: 4102-7.).

[0006] Recent developments in cDNA microarray technologies have enabled the construction of comprehensive profiles of gene expression of malignant cells as compared to normal cells (Okabe, H. et al., (2001) Cancer Res., 61, 2129-37.; Lin YM. et al., (2002) Oncogene, 21;4120-8.; Hasegawa S. et al., (2002) Cancer Res 62:7012-7.). This approach enables an understanding of the complex nature of cancer cells and the mechanisms of carcinogenesis and facilitates the identification of genes whose expression is deregulated in tumors (Bienz M. et al., (2000) Cell 103, 311-20.). Among the transcripts identified as up-regulated in cancers, MPHOSPH1 (M-phase phosphoprotein 1; GenBank Accession No. NM_016195; SEQ ID Nos.1, 2), and DEPDC1 (DEP domain containing 1; GenBank Accession No. BM683578) have been recently discovered. See WO 2004/031413, WO 2006/085684 and WO 2007/013,665, the entire contents of which are incorporated by reference herein. DEPDC1 has been described in the context of two different transcriptional variants - DEPDC1 V1 (SEQ ID Nos.3, 4) and DEPDC1 V2 (SEQ ID Nos: 5, 6). These genes have been shown to be specifically up-regulated in tumor cells of the various cancer tissues of the cases analyzed (see below); however, Northern blot analyses demonstrate that these gene products are not found in normal vital organs (see PCT/JP2006/302684). In that immunogenic peptides derived from MPHOSPH1, and DEPDC1 may find utility in killing tumor cells expressing those antigens, these genes are of particular interest to the present inventors.

[0007] Since cytotoxic drugs, such as M-VAC, often cause severe adverse reactions, it is clear that thoughtful selection of novel target molecules on the basis of well-characterized mechanisms of action is important in the development of effective anti-cancer drugs having a minimized risk of negative side effects. Toward this goal, the inventors previously performed expression profile analysis on various cancers and normal human tissue, and discovered multiple genes that are specifically over-

expressed in cancer (Lin YM, et al., Oncogene. 2002 Jun 13;21:4120-8.; Kitahara O, et al., Cancer Res. 2001 May 1;61:3544-9.; Suzuki C, et al., Cancer Res. 2003 Nov 1;63:7038-41.; Ashida S, Cancer Res. 2004 Sep 1;64:5963-72.; Ochi K, et al., Int J Oncol. 2004 Mar;24(3):647-55.; Kaneta Y, et al., Int J Oncol. 2003 Sep;23:681-91.; Obama K, Hepatology. 2005 Jun;41:1339-48.; Kato T, et al., Cancer Res. 2005 Jul 1;65:5638-46.; Kitahara O, et al., Neoplasia. 2002 Jul-Aug;4:295-303.; Saito-Hisaminato A et al., DNA Res 2002, 9: 35-45.). Of these, MPHOSPH1 (in house No. C2093) and DEPDC1 (in house No. B5860N) were identified genes over-expressed in various cancers. In particular, MPHOSPH1 was identified as over-expressed in bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, soft tissue tumor. Similarly, DEPDC1 was identified as over-expressed in bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, NSCLC, lymphoma, osteosarcoma, prostate cancer, SCLC, soft tissue tumor

[0008] MPHOSPH1 was previously identified as one of the proteins specifically phosphorylated at the G2/M transition and characterized as a plus-end-directed kinesin related protein (Abaza A et al., J Biol Chem 2003, 278: 27844-52.). More particularly, MPHOSPH1 has been previously documented to be a plus-end-directed molecular motor that plays a crucial role in cytokinesis, and accumulates in the midzone of the spindle during anaphase to telophase in HeLa cells (Abaza A et al., J Biol Chem 2003, 278: 27844-52; Kamimoto T et al., J Biol Chem 2001, 276: 37520-8). The MPHOSPH1 cDNA encodes a 1780-amino acid protein that is composed of three domains: an NH2-kinasin motor domain, a central coiled coil-stalk domain, and a C-globular tail domain. Together, this data suggests that MPHOSPH1 is an NH2-type kinesin-related protein.

[0009] As for DEPDC1, its function remains unclear. The DEP domain contained in this protein is also found in Dishevelled, Egl-10, and Pleckstrin. The DEP domain in Drosophila dishevelled plays an essential role in rescue planar polarity defects and induces JNK signaling; nevertheless, its function in Humans has not yet been clarified. However, as disclosed in PCT/JP2006/302684, DEPDC1 siRNAs can suppress the growth of cancer cells. These results demonstrate that DEPDC1 plays an important role in growth of most cancer cells.

[0010] Summary of the Invention

As noted above, MPHOSPH1 (M-phase phosphoprotein 1), and DEPDC1 (DEP domain containing 1) have been identified as up-regulated in various cancers. More particularly, the genes were identified using gene expression profiling with a genome-wide cDNA microarray. As discussed above, expression of MPHOSPH1 and DEPDC1 has been shown to be specifically up-regulated in various tumor cells, including lung

cancer and bladder cancer. As described in Table 1, MPHOSPH1 expression was shown to be validly elevated in 30 out of 31 bladder cancers, 8 out of 36 breast cancers, 18 out of 18 cervical cancers, 5 out of 17 cholangincellular carcinomas, 25 out of 31 CMLs, 6 out of 11 colorectal cancers, 6 out of 14 gastric cancers, 5 out of 5 NSCLCs, 7 out of 7 lymphomas, 6 out of 10 osteosarcomas, 7 out of 22 prostate cancers, 10 out of 18 renal carcinomas and 15 out of 21soft tissue tumors. At the same time, DEPDC1 expression was shown to be validly elevated in 23 out of 25 bladder cancers, 6 out of 13 breast cancers, 12 out of 12 cervical cancers, 6 out of 6 cholangincellular carcinomas, 3 out of 4 CMLs 2 out of 4 colorectal cancers, 6 out of 6 NSCLCs, 7 out of 7 lymphomas, 10 out of 14 osteosarcomas, 11 out of 24 prostate cancers, 14 out of 14 SCLCs and 22 out of 31 soft tissue tumors as described in Table 1.

[0011] The present invention is based, at least in part, on the identification of specific epitope peptides of the gene products of these genes (MPHOSPH1 and DEPDC1) which possess the ability to induce cytotoxic T lymphocytes (CTLs) specific to the corresponding molecules. As discussed in detail below, Peripheral Blood Mononuclear Cells (PBMC) of healthy donor were stimulated using HLA-A*2402 and HLA-A*0201 binding candidate peptides derived from MPHOSPH1 or DEPDC1. CTL clones and/or lines were then established with specific cytotoxicity against the HLA-A24 or HLA-A2 positive target cells pulsed with each of the candidate peptides. These results demonstrate that these peptides are HLA-A24 or HLA-A2 restricted epitope peptides that can induce potent and specific immune responses against cells expressing MPHOSPH1 or DEPDC1.

[0012] Accordingly, the present invention provides methods for treating or preventing a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancer. Such methods involves the step of administering to a subject in need thereof a MPHOSPH1 and/or DEPDC1 polypeptide of the invention. Administration of such peptide(s) results in the induction of anti-tumor immunity. Thus, the present invention provides methods for inducing anti-tumor immunity in a subject, such methods involving the step of administering to the subject a MPHOSPH1 and/or DEPDC1 polypeptide, as well as pharmaceutical compositions for treating or preventing a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g cancer, that include the MPHOSPH1 and/or DEPDC1 polypeptides. Exemplary cancers include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, and soft tissue tumor.

[0013] That is, the present application includes following embodiments, and any combinations thereof.

[1] An isolated peptide having cytotoxic T cell inducibility, wherein said peptide derived from amino acid sequence of SEQ ID NO: 2, 4, or 6.

[2] An isolated peptide of less than about 15 amino acids selected from the group consisting of peptides comprising the amino acid sequences of SEQ ID NO: 7, 8 and 12, or a peptide having cytotoxic T cell inducibility, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 7, 8 and 12, wherein 1, 2, or several amino acids are substituted, deleted, or added.

[3] The peptide having cytotoxic T cell inducibility of [2] , wherein the second amino acid from the N-terminus is phenylalanine, tyrosine, methionine, or tryptophan.

[4] The peptide having cytotoxic T cell inducibility of [2] , wherein the C-terminal amino acid is phenylalanine, leucine, isoleucine, tryptophan, or methionine.

[5] An isolated peptide of less than about 15 amino acids selected from the group consisting of peptides comprising the amino acid sequences of SEQ ID NO: 9, 10, 11, 192, 195, 197, 209, 225, 226, 228, 230, 240, 241, 243, 244, 253, 254 and 255, or a peptide having cytotoxic T cell inducibility, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9, 10, 11, 192, 195, 197, 209, 225, 226, 228, 230, 240, 241, 243, 244, 253, 254 and 255, wherein 1, 2, or several amino acids are substituted, deleted, or added.

[6] The peptide having cytotoxic T cell inducibility of [5], wherein the second amino acid from the N-terminus is leucine or methionine.

[7] The peptide having cytotoxic T cell inducibility of [5], wherein the C-terminal amino acid is valine or leucine.

[8] A vector in which the DNA encodes peptides of any one of [1] to [7].

[9] A pharmaceutical composition for treating or preventing a disease associated with over-expression of the genes of SEQ ID NO: 1, 3 and/or 5, said composition comprising one or more peptides of any one of [1] to [7].

[10] The pharmaceutical composition of [9], wherein the disease is cancer.

[11] The pharmaceutical composition of [10], wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC and soft tissue tumor.

[12]. An exosome that presents on its surface a complex comprising a peptide of any one of [1] to[7] and an HLA antigen.

[13] The exosome of [12], wherein the HLA antigen is HLA-A24.

[14] The exosome of [13], wherein the HLA antigen is HLA-A2402.

[15]. The exosome of [12], wherein the HLA antigen is HLA-A2.

[16]. The exosome of [13], wherein the HLA antigen is HLA-A0201.

[17] A method of inducing antigen-presenting cells having a high cytotoxic T cell in-

ducibility comprising the step of contacting an antigen-presenting cell with a peptide of any one of [1] to [7].

[18] A method of inducing cytotoxic T cells by contacting a T cell with a peptide of any one of [1] to [7].

[19] A method of inducing antigen-presenting cells having high cytotoxic T cell inducibility, said method comprising the step of transferring a gene comprising a polynucleotide encoding a peptide of any one of [1] to [7] to an antigen-presenting cell.

[20] An isolated cytotoxic T cell, which is induced by contacting a T cell with a peptide of any one of claims 1 to 7 or which is transduced with the nucleic acids encoding the TCR subunits polypeptides binding with a peptide of any one claims 1 to 7 in the context of HLA-A24 or HLA-A2.

[21] An antigen-presenting cell, which comprises a complex formed between an HLA antigen and a peptide of any one of [1] to [7].

[22] The antigen-presenting cell of [21], induced by the method of [17].

[23] A vaccine for inhibiting proliferation of cells expressing genes of SEQ ID NO: 1, 3 and/or 5, wherein the vaccine comprises a peptide of any one of [1] to [7] as the active ingredient.

[24] The vaccine of [23], wherein the cell is a cancer cell.

[25] The vaccine of [24], wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC and soft tissue tumor.

[26] The vaccine of [23], formulated for administration to a subject whose HLA antigen is HLA-A24 or HLA-A2.

[27] A method of treating or preventing a disease associated with the over-expression of the genes of SEQ ID NO: 1, 3 and/or 5 in a subject comprising administering to said subject a vaccine comprising one or more peptide of any one of [1] to [7], an immunologically active fragment thereof, or a polynucleotide encoding said peptide or immunologically active fragment.

[28] The method of [27], wherein the disease is cancer.

[29] The method of [28], wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC and soft tissue tumor.

[0014] Alternatively, the present invention also relates to a method of inducing cytotoxic T cells comprising the step of contacting a T-cell with the antigen-presenting cell produced by the method of [19].

[0015] These and other objects and features of the invention will become more fully

apparent when the following detailed description is read in conjunction with the accompanying figures and examples. However, it is to be understood that both the foregoing summary of the invention and the following detailed description are of preferred embodiments, and not restrictive of the invention or other alternate embodiments of the invention.

Brief Description of the Drawings

[0016] [fig.1]Figure 1A depicts the results of an IFN-gamma ELISPOT assay for the screening of epitope peptides which, in turn, demonstrate that MPHOSPH1-A24-9-278 (SEQ ID NO: 7) is a potent producer of IFN-gamma. CTLs for those peptides derived from MPHOSHP1 were generated according to the protocols described in "Materials and Methods" section of the examples below. Resulting CTLs having detectable specific CTL activity are shown. In particular, the cells in the well number #4 stimulated with MPHOSPH1-A24-9-278 showed potent IFN-gamma production to recognize peptide pulsed target cells, as compared to the control. Figure 1B depicts the results of the IFN-gamma ELISPOT assay for the screening of CTL clones after limiting dilution (MPHOSPH1-A24-9-278 CTL clone). The cells in the positive well were expanded and limiting dilution was performed. As the depicted results demonstrate, CTL clones having higher specific CTL activities against the peptide-pulsed target as compared to the activities against target without peptide pulse were established.

[fig.2]Figure 2A depicts the results of an IFN-gamma ELISPOT assay for the screening of epitope peptides cytotoxicity, which, in turn, demonstrate that MPHOSPH1-A24-10-278 (SEQ ID NO: 8) is a potent producer of IFN-gamma . CTLs for those peptides derived from MPHOSHP1 were generated according to the protocols described in "Materials and Methods" section of the examples below. Resulting CTLs having detectable specific CTL activity are shown. In particular, the cells in the well number #8 stimulated with MPHOSPH1-A24-10-278 showed potent IFN-gamma production as compared to the control. Figure 2B depicts the results of an IFN-gamma ELISPOT assay for the screening of CTL clones after limiting dilution (MPHOSPH1-A24-10-278 CTL clone). The cells in the positive well were expanded and limiting dilution was performed. As the depicted results demonstrate, CTL clones having higher specific CTL activities against the MPHOSPH1-A24-10-278-pulsed target as compared to the activities against target without peptide pulse as shown were established.

[fig.3]Figure 3A depicts the establishment of CTL clones stimulated with MPHOSPH1-A24-9-278. (SEQ ID NO: 7). This CTL clone demonstrated high specific CTL activity against target cells (A24LCL) pulsed with MPHOSPH1-A24-9-278, but

did not show significant CTL activity against the same target cells (A24LCL) pulsed with no peptides. Figure 3B depicts the establishment of CTL clones stimulated with MPHOSPH1-A24-10-278 (SEQ ID NO: 8). This CTL clone demonstrated high specific CTL activity against target cells (A24LCL) pulsed with MPHOSPH1-A24-10-278, whereas it did not show significant CTL activity against the same target cells (A24LCL) pulsed with no peptides. R means Responder: CTL clone. S means Stimulator: peptide-pulsed A24-LCL ($1x10^4$/well).

[fig.4]Figure 4 depicts the expression of MPHOSPH1-A24-9-278 (SEQ ID NO: 7) on the target cell surface with HLA-A24. Specific CTL activity against COS7 transfected both with the full length MPHOSPH1 gene and the HLA-A*2402 molecule was assayed using as effector cells the CTL clone raised by MPHOSPH1-A24-9-278. COS7 transfected with full length MPHOSPH1 but not HLA-A*2402 and COS7 transfected with HLA-A*2402 but not full length MPHOSPH1 were prepared as controls. The CTL clone demonstrated high specific CTL activity against COS7 transfected with both MPHOSPH1 and HLA-A24. However, it did not show significant specific CTL activity against COS7 transfected neither MPHOSPH1 nor HLA-A24. R means Responder: CTL clone. S means Stimulator: COS7 transfectant ($1x10^4$ / well).

[fig.5]Figure 5 depicts the CTL activity against bladder cancer cell lines endogenously expressing MPHOSPH1. The established CTL clone induced with MPHOSPH1-A24-9-278 peptide recognized tumor cells endogenously expressing MPHOSPH1. HT1376, RT-4 and J82 cells expressed MPHOSPH1 endogenously, respectively. CTL clone showed IFN-gamma production against HT1376 which have HLA-A*2402 genotype, but no showing response against RT-4 and J82, does not have HLA-A*2402 genotype.

[fig.6]Figure 6 depicts in vivo immunogenicity analysis using MPHOSPH1-A24-9-278 peptide. IFA-conjugated peptide was injected subcutaneously into BALB/c mice on days 0 and 7. On day 14, splenocytes of vaccinated mice were harvested and used as responder cells, and $1x10^4$ RLmale1 cells pulsed MPHOSPH1-A24-9-278 peptide were used as stimulator cells for IFN-gamma ELISPOT assay. Spot forming counts (SFC) were indicated in cases of each mice; five mice (Ani1~Ani5) were vaccinated epitope peptide and three mice (nega1~nega3) were injected Mock IFA emulsion as a negative control.

[fig.7]Figure 7 depicts the results of an IFN-gamma ELISPOT assay for the screening of epitope peptides, which, in turn, demonstrate that MPHOSPH1-A2-9-282 (SEQ ID NO: 9), MPHOSPH1-A2-9-638 (SEQ ID NO: 10) and MPHOSPH1-A2-10-1714 (SEQ ID NO: 11) possess potent IFN-gamma production activity. CTLs for those peptides derived from MPHOSHP1 were generated according to the protocols described in

"Materials and Methods" section of the examples set forth below. Resulting CTLs having detectable specific CTL activity are shown. In particular, Figure 7A demonstrates that the cells in the well number #1 and #5, stimulated with MPHOSPH1-A2-9-282, showed potent IFN-gamma production sufficient to recognize peptide pulsed target cells, as compared to the control. Figure 7B demonstrates that the cells in the well number #8 stimulated with MPHOSPH1-A2-9-638 showed potent IFN-gamma production sufficient to recognize peptide pulsed target cells, as compared to the control. Figure 7C demonstrates that the cells in the well number #4 stimulated with MPHOSPH1-A2-10-1714 showed potent IFN-gamma production to recognize peptide pulsed target cells, as compared to the control.

[fig.8]Figure 8 depicts the establishment for CTL lines stimulated with MPHOSPH1-A02-9-282, (SEQ ID NO: 9) MPHOSPH1-A02-9-638 (SEQ ID NO: 10) and MPHOSPH1-A02-10-1714 (SEQ ID NO: 11). The cells in the positive well were expanded, and, as the depicted results demonstrate, CTL lines having higher specific CTL activities against the MPHOSPH1-A02-9-282-pulsed target (A), MPHOSPH1-A02-9-638-pulsed target (B) or MPHOSPH1-A02-10-1714-pulsed target (C) compared to the activities against target without peptide pulse were established.R means Responder: CTL lines. S means Stimulator: peptide-pulsed T2 ($1x10^4$/well).

[fig.9]Figure 9A depicts the results of an IFN-gamma ELISPOT assay for the screening of CTL clones after limiting dilution (MPHOSPH1-A2-9-282 CTL clone). The cells in the positive well were expanded and limiting dilution was performed. As the depicted results demonstrate CTL clones having higher specific CTL activities against the MPHOSPH1-A2-9-282 (SEQ ID NO: 9) pulsed target as compared to the activities against target without peptide pulse were established. Figure 9B depicts the establishment of CTL clones stimulated with MPHOSPH1-A02-9-282. The CTL clone demonstrated high specific CTL activity against target cells (T2) pulsed with MPHOSPH1-A2-9-282, but did not possess significant CTL activity against the same target cells (T2) pulsed with no peptides. R means Responder: CTL clone. S means Stimulator: peptide-pulsed T2 ($1x10^4$/well).

[fig.10]Figure 10A depicts the results of an IFN-gamma ELISPOT assay for the screening of epitope peptides, which, in turn, demonstrate that DEPDC1-A24-9-294 (SEQ ID NO: 12) is a potent producer of IFN-gamma . CTLs for those peptides derived from DEPDC1 were generated according to the protocols described in "Materials and Methods" section of the examples set forth below. Resulting CTLs showing detectable specific CTL activity are shown. The cells in the well number #10 stimulated with DEPDC1-A24-9-294 showed potent IFN-gamma production to recognize peptide pulsed target cells, compared with the control. Figure 10B depicts the results of an IFN-gamma ELISPOT assay for the screening of CTL clones after

limiting dilution (DEPDC1-A24-9-294 CTL clone). The cells in the positive well were expanded and limiting dilution performed. As the depicted results demonstrate, CTL clones having higher specific CTL activities against the DEPDC1-A24-9-294-pulsed target compared to the activities against target without peptide pulse were established.

[fig.11]Figure 11 depicts the establishment for CTL clones stimulated with DEPDC1-A24-9-294 (SEQ ID NO: 12). The CTL clone showed high specific CTL activity against target cells (A24LCL) pulsed with DEPDC1-A24-9-294, whereas it did not show significant CTL activity against the same target cells (A24LCL) pulsed with no peptides. R means Responder: DEPDC-A24-9-294 CTL clone. S means Stimulator: peptide-pulsed A24-LCL ($1x10^4$/well).

[fig.12]Figure 12 depicts the expression of DEPDC1-A24-9-294 (SEQ ID NO: 12) on the target cell surface with HLA-A24. Specific CTL activity against COS7 transfected with both the full length DEPDC1 gene and the HLA-A*2402 molecule was assayed using as effector cells the CTL clone raised by DEPDC1-A24-9-294. COS7 transfected with full length DEPDC1 but not HLA-A*2402 and COS7 transfected HLA-A*2402 but not full length DEPDC1 were prepared as controls. The CTL clone established demonstrated high specific CTL activity against COS7 transfected with both DEPDC1 and HLA-A24. However, it did not show significant specific CTL activity against COS7 transfected with neither DEPDC1 nor HLA-A24. R means Responder: DEP-A24-9-294 CTL clone. S means Stimulator: COS7 transfectant ($1x10^4$/well).

[fig.13]Figure 13 depicts the CTL activity against bladder cancer cell lines endogenously expressing DEPDC1. The established CTL clone induced with DEPDC1-A24-9-294 peptide recognized tumor cells endogenously expressing DEPDC1. HT1376, RT-4 and J82 cells expressed DEPDC1 endogenously, respectively. CTL clone showed IFN-gamma production against HT1376 which have HLA-A*2402 genotype, but no showing response against RT-4 and J82, does not have HLA-A*2402 genotype.

[fig.14]Figure 14 depicts the in vivo immunogenicity analysis using DEPDC1-A24-9-294 peptide. IFA-conjugated peptide was injected subcutaneously into BALB/c mice on days 0 and 7. On day 14, splenocytes of vaccinated mice were harvested and used as responder cells, and $1x10^4$ RLmale1 cells pulsed DEPDC1-A24-9-294 peptide were used as stimulator cells for IFN-gamma ELISPOT assay. Spot forming counts (SFC) were indicated in cases of each mice; five mice (Ani1~Ani5) were vaccinated epitope peptide and two mice (nega1 and nega2) were injected Mock IFA emulsion as a negative control.

[fig.15]Figure 15 depicts potent IFN-gamma production of DEPDC1-A02-10-644, -10-575, -10-506, -10-765, -10-395, -10-224, -9-297, -10-296 and -10-302 by IFN-gamma ELISPOT assay for the screening of epitope peptides. CTLs for those peptides

derived from DEPDC1 were generated in the way described in "Materials and Methods". The cells in the well number #4 and #7 stimulated with DEPDC1-A02-10-644, #2 with DEPDC1-A02-10-575, #7 with DEPDC1-A02-10-506, #1 with DEPDC1-A02-10-765 and #1 with DEPDC1-A02-10-395, #1 and #2 with DEPDC1-A02-10-224, #4 with DEPDC1-A02-9-297, #3-and #4 with DEPDC1-A02-10-296 and #2, #3, #5 and #7 with DEPDC1-A02-10-302 showed potent IFN-gamma production compared with the control.

[fig.16]Figure 16 depicts IFN-gamma production of CTL line generated with DEPDC1-A02-10-296 peptide. The established CTL lines raised by DEPDC1-A02-10-296 peptide have potent IFN-gamma production activity. It was shown IFN-gamma production against peptide-pulsed target cells, but not shown that against target cells without peptide pulse. Target cells were used T2 cells, expressed HLA-A2 molecule at cell surface.

[fig.17]Figure 17 depicts CTL activity against targets endogenously expressing DEPDC1 and HLA-A2 molecule. It was shown in upper panel that the established CTL line generated with DEPDC1-A02-10-296 peptide possessed IFN-gamma production activity against target cells which endogenously expressed DEPDC1V2 and HLA-A2. The case of using DEPDC1-A02-10-296 peptide was shown in lower panel. The target cells expressing only DEPDC1V2 and expressing only HLA-A2 with treatment of DEPDC1V1-9-674 or DEP-9-462 peptide pulse were prepared as the negative control. The target cells were prepared from HEK293 transfectant which stable expressed HLA-A2 or mock.

[fig.18]Figure 18 depicts antigen expression in Case 2. In Case 2, both MPHOSPH1 and DEPDC1 were expressed strongly. Therefore, two kinds of epitope peptides derived from MPHOSPH1 and DEPDC1 have been vaccinated.

[fig.19]Figure 19 depicts the clinical evaluation for local recurrence of bladder cancer in Case 2. Case 2 were evaluated SD in accordance with RECIST criteria.

[fig.20]Figure 20 depicts antigen expression in Case 3. In Case 3, DEPDC1 was expressed strongly. Therefore, we have vaccinated the epitope peptide derived from DEPDC1 alone.

[fig.21]Figure 21 depicts clinical evaluation for right lobe of metastatic lung in Case 3. The progression rate was decreased after vaccination. Especially, the size of the tumor was decreased after 3rd courses.

[fig.22]Figure 22 depicts clinical evaluation for left lobe of metastatic lung in Case 3. The progression rate was decreased after vaccination. Especially, the size of the tumor was decreased after 3rd courses.

[fig.23]Figure 23 depicts the Anti-tumor effect in Case 3. The progression rate of metastatic tumor was decreased after vaccination.

[fig.24]Figure 24 depicts specific CTL response in Case 3. Specific CTL response was strongly shown after vaccination.

[fig.25]Figure 25 depicts antigen expression in Case 4. In Case 4, MPHOSPH1 and DEPDC1 were expressed. Therefore, two kinds of epitope peptides derived from MPHOSPH1 and DEPDC1 have been vaccinated.

[fig.26]Figure 26 depicts the clinical evaluation for local recurrence of bladder cancer in Case 4. The size of the tumor was reduced 20% in accordance with RECIST criteria after 1st course vaccination.

[0017] Detailed Description of the Invention

The words "a", "an", and "the" as used herein mean "at least one" unless otherwise specifically indicated.

[0018] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0019] Identification of new TAAs, particularly those that induce potent and specific anti-tumor immune responses, warrants further development of the clinical application of the peptide vaccination strategy in various types of cancer (Boon T et al., (1996) J Exp Med 183: 725-9.; van der Bruggen P et al., (1991) Science 254: 1643-7.; Brichard V et al., (1993) J Exp Med 178: 489-95.; Kawakami Y et al., (1994) J Exp Med 180: 347-52.; Shichijo S et al., (1998) J Exp Med 187:277-88.; Chen YT et al., (1997) Proc.Natl.Acd. Sci.USA, 94: 1914-8.; Harris CC, (1996) J Natl Cancer Inst 88:1442-55.; Butterfield LH et al., (1999) Cancer Res 59:3134-42.; Vissers JL et al., (1999) Cancer Res 59: 5554-9.; van der Burg SH et al., (1996) J. Immunol 156:3308-14.; Tanaka F et al., (1997) Cancer Res 57:4465-8.; Fujie T et al., (1999) Int J Cancer 80:169-72.; Kikuchi M et al., (1999) Int J Cancer 81 : 459-66.; Oiso M et al., (1999) Int J Cancer 81:387-94.). As noted above, MPHOSPH1 (M-phase phosphoprotein 1; GenBank Accession No. NM_016195; SEQ ID Nos.1, 2) and DEPDC1 (DEP domain containing 1; GenBank Accession No. BM683578), more particularly its two variants, DEPDC1V1 (SEQ ID Nos.3, 4) and DEPDC1V2 (SEQ ID No. 5, 6), were previously identified using cDNA microarray technologies as over-expressed in various cancers. MPHOSPH1 was previously identified as one of the proteins specifically phosphorylated at the G2/M transition, and characterized as a plus-end-directed kinesin related protein (Abaza A et al., J Biol Chem 2003, 278: 27844-52.). More particularly, MPHOSPH1 was previously documented to be plus-end-directed molecular motor that plays a crucial role in cytokinesis, and accumulates in the midzone of the spindle during anaphase to telophase in HeLa cells (Abaza A et al., J Biol Chem 2003, 278: 27844-52; Kamimoto T et al., J Biol Chem 2001, 276: 37520-8.).The MPHOSPH1 cDNA encodes a 1780-amino acid protein that is

composed of three domains: an NH2-kinasin motor domain, a central coiled coil-stalk domain, and a C-globular tail domain. These data suggest that MPHOSPH1 is an NH2-type kinesin-related protein.

[0020] The function of DEPDC1 protein remains unclear. The DEP domain included this protein is found in Dishevelled, Egl-10, and Pleckstrin. In particular, the DEP domain in Drosophila dishevelled is essential to rescue planar polarity defects and induces JNK signaling; nevertheless, its function in Human has not yet been clarified. However, as disclosed in PCT/JP2006/302684, DEPDC1 (in house No. B5860N) has two different transcriptional variants consisting of 12 and 11 exons, corresponding to DEPDC1 V1 and V2, respectively. Alternative variations in exon 8 of V1 were noted, and the other remaining exons were found to be common to both variants. V2 variant has no exon 8 of the V1, but generates the same stop codon within last exon. The full-length cDNA sequences of the B5860NV1 and B5860NV2 variants consist of 5318 and 4466 nucleotides, respectively. The ORF of these variants start at within each exon 1. Eventually, V1 and V2 transcripts encode 811 and 527 amino acids, respectively. siRNAs suppressed the growth of cancer cells. These results demonstrate that DEPDC1 plays important roles in growth of most cancer cells.

[0021] As disclosed in PCT/JP2006/302684, MPHOSPH1 and DEPDC1 are over-expressed in bladder cancer but show minimal expression in normal tissues. In addition, these genes were found to have a significant function related to cell proliferation.

[0022] In the present invention, peptides derived from MPHOSPH1 or DEPDC1 are shown to be TAA epitopes restricted by HLA-A24 and HLA-A2, an HLA allele commonly found in the Japanese and Caucasian populations. Specifically, using their binding affinities to HLA-A24 and HLA-A2, candidates of HLA-A24 and HLA-A2 binding peptides derived from MPHOSPH1 or DEPDC1 were identified. After the in vitro stimulation of T-cells by dendritic cells (DCs) loaded with these peptides, CTLs were successfully established using MPHOSPH1-A24-9-278 (IYNEYIYDL (SEQ ID NO: 7)), MPHOSPH1-A24-10-278 (IYNEyIYDLF (SEQ ID NO: 8)), MPHOSPH1-A2-9-282 (YIYDLFVPV (SEQ ID NO: 9)), MPHOSPH1-A2-9-638 (RLAIFKDLV (SEQ ID NO: 10)), MPHOSPH1-A2-10-1714 (TMSSsKLSNV (SEQ ID NO: 11)), DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)), DEPDC1-A02-10-644 (SLMIhTFSRC (SEQ ID NO: 240)), DEPDC1-A02-10-575 (SLLPaSSMLT (SEQ ID NO: 241)), DEPDC1-A02-10-506 (QLCRsQSLLL (SEQ ID NO: 243)), DEPDC1-A02-10-765 (KQFQkEYPLI (SEQ ID NO: 244)), DEPDC1-A02-10-395 (IMGGSCHNLI (SEQ ID NO: 249), DEPDC1-A02-10-224 (NMANtSKRGV (SEQ ID NO: 253)), DEPDC1- A02-9-297 (ELFVNILGL (SEQ ID NO: 226)), DEPDC1-A02-10-296 (YELFvNILGL (SEQ ID NO: 254)), DEPDC1-A02-10-301 (NILGlLQPHL (SEQ ID NO: 255)), DEPDC1-A2-9-589

(LLQPHLERV (SEQ ID NO: 192)), DEPDC1-A2-9-619 (LLMRMISRM (SEQ ID NO: 195)), DEPDC1-A2-9-290 (LLTFEYYEL (SEQ ID NO: 197)), DEPDC1-A2-9-563 (RLCKSTIEL (SEQ ID NO: 209)), DEPDC1-A2-9-653 (CVLCCAEEV (SEQ ID NO: 225)), DEPDC1-A2-10-674 (FLMDhHQEIL (SEQ ID NO: 228)) and DEPDC1-A2-10-302 (ILVVcGYITV (SEQ ID NO: 230)). These CTLs demonstrated potent cytotoxic activity against the peptide-pulsed A24LCL and T2 cells. Furthermore, CTL clones derived from these cells also demonstrated specific cytotoxicity against HLA-A24 or HLA-A2 positive cells expressing MPHOSPH1 or DEPDC1, respectively.. However, these CTL clones did not express cytotoxic activity against cells having expression of only one of peptides, including HLA-A24, HLA-A2, MPHOSPH1 and DEPDC1. Together these results suggest the utility of MPHOSPH1 and DEPDC1 as TAAs for cancer cells and that MPHOSPH1-A24-9-278 (IYNEYIYDL (SEQ ID NO: 7)), MPHOSPH1-A24-10-278 (IYNEyIYDLF (SEQ ID NO: 8)), MPHOSPH1-A2-9-282 (YIYDLFVPV (SEQ ID NO: 9)), MPHOSPH1-A2-9-638 (RLAIFKDLV (SEQ ID NO: 10)), MPHOSPH1-A2-10-1714 (TMSSsKLSNV (SEQ ID NO: 11)), DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)), DEPDC1-A02-10-644 (SLMIhTFSRC (SEQ ID NO: 240)), DEPDC1-A02-10-575 (SLLPaSSMLT (SEQ ID NO: 241)), DEPDC1-A02-10-506 (QLCRsQSLLL (SEQ ID NO: 243)), DEPDC1-A02-10-765 (KQFQkEYPLI (SEQ ID NO: 244)), DEPDC1- A02-10-395 (IMGGSCHNLI (SEQ ID NO: 249), DEPDC1-A02-10-224 (NMANtSKRGV (SEQ ID NO: 253)), DEPDC1- A02-9-297 (ELFVNILGL (SEQ ID NO: 226)), DEPDC1-A02-10-296 (YELFvNILGL (SEQ ID NO: 254)), DEPDC1-A02-10-301 (NILGlLQPHL (SEQ ID NO: 255)), DEPDC1-A2-9-589 (LLQPHLERV (SEQ ID NO: 192)), DEPDC1-A2-9-619 (LLMRMISRM (SEQ ID NO: 195)), DEPDC1-A2-9-290 (LLTFEYYEL (SEQ ID NO: 197)), DEPDC1-A2-9-563 (RLCKSTIEL (SEQ ID NO: 209)), DEPDC1-A2-9-653 (CVLCCAEEV (SEQ ID NO: 225)), DEPDC1-A2-10-674 (FLMDhHQEIL (SEQ ID NO: 228)) and DEPDC1-A2-10-302 (ILVVcGYITV (SEQ ID NO: 230)) are epitope peptides of each TAA restricted by HLA-A24 or HLA-A2. Since these antigens are over-expressed in most cancers and are associated with tumor cell proliferation, they find utility as immunotherapeutic targets against cancers. Exemplary cancers include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0023] Accordingly, the present invention further provides methods of treating or preventing a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, in a subject, such methods including the steps of administering to a subject in

need thereof an immunogenic peptide of less than about 40 amino acids, often less than about 20 amino acids, usually less than about 15 amino acids and having the amino acid sequence of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 or 255. Alternatively, the immunogenic peptide may be composed of a sequence of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 or 255 in which 1, 2, or several (e.g., up to 5) amino acids are substituted, deleted or added, provided the resulting variant peptide retains the immunogenic activity (i.e., the ability to induce CTLs specific to cells expressing MPHOSPH1 and/or DEPDC1, e.g. cancers). The number of residues to be substituted, deleted, or added is generally 5 amino acids or less, preferably 4 amino acids or less, more preferably 3 amino acids or less, even more preferably one or two amino acids. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0024] Variant peptides (i.e., peptides having an amino acid sequence modified by substituting, deleting, or adding one, two or several amino acid residues to an original amino acid sequence) are known to retain the original biological activity (Mark DF et al., (1984) Proc Natl Acad Sci USA 81: 5662-6.; Zoller MJ and Smith M, (1982) Nucleic Acids Res 10:6487-500.; Dalbadie-McFarland G et al., (1982) Proc Natl Acad Sci USA 79: 6409-13.). In the context of the present invention, it is preferable that the amino acid modification results in conservation of the properties of the original amino acid side-chain (a process known as conservative amino acid substitution). Examples of properties of amino acid side chains include hydrophobic amino acids (A, I, L, M, F, P, W, Y, V), hydrophilic amino acids (R, D, N, C, E, Q, G, H, K, S, T), and side chains having the following functional groups or characteristics in common: an aliphatic side-chain (G, A, V, L, I, P); a hydroxyl group containing side-chain (S, T, Y); a sulfur atom containing side-chain (C, M); a carboxylic acid and amide containing side-chain (D, N, E, Q); a base containing side-chain (R, K, H); and an aromatic containing side-chain (H, F, Y, W). Note, the parenthetic letters indicate the one-letter codes of amino acids.

[0025] In preferred embodiments, the immunogenic peptide is a nonapeptide (9-mer) or a decapeptide (10-mer).

[0026] The present invention further provides a method of inducing anti-tumor immunity for a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, in a subject, such a method including the steps of administering to a subject in need thereof an immunogenic peptide of the present invention, namely one having the amino acid sequence of S SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225,

226 228, 230, 240, 241, 243, 244, 249, 253, 254 or 255 or a variant thereof (i.e., including 1, 2, or several amino acid substitutions, deletions, or additions). The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0027] In the context of the present invention, the subject is preferably a mammal. Exemplary mammals include, but are not limited to, e.g., a human, non-human primate, mouse, rat, dog, cat, horse, or cow.

[0028] In the present invention, the peptide can be administered to a subject via an in vivo or ex vivo protocol. Furthermore, the present invention also provides use of nonapeptide or decapeptide selected from peptides having the amino acid sequence of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 and 255 (and variants thereof) for manufacturing an immunogenic composition for treating or preventing a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0029] Homology analyses of MPHOSPH1-A24-9-278 (IYNEYIYDL (SEQ ID NO: 7)), MPHOSPH1-A24-10-278 (IYNEyIYDLF (SEQ ID NO: 8)), MPHOSPH1-A2-9-282 (YIYDLFVPV (SEQ ID NO: 9)), MPHOSPH1-A2-9-638 (RLAIFKDLV (SEQ ID NO: 10)), MPHOSPH1-A2-10-1714 (TMSSsKLSNV (SEQ ID NO: 11)), DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)), DEPDC1-A2-9-589 (LLQPHLERV (SEQ ID NO: 192)), DEPDC1-A2-9-619 (LLMRMISRM (SEQ ID NO: 195)), DEPDC1-A2-9-290 (LLTFEYYEL (SEQ ID NO: 197)), DEPDC1-A2-9-563 (RLCKSTIEL (SEQ ID NO: 209)), DEPDC1-A2-9-653 (CVLCCAEEV (SEQ ID NO: 225)), DEPDC1-A2-10-674 (FLMDhHQEIL (SEQ ID NO: 228)), DEPDC1-A2-10-302 (ILVVcGYITV (SEQ ID NO: 230)) DEPDC1-A02-10-644 (SLMIhTFSRC (SEQ ID NO: 240)), DEPDC1-A02-10-575 (SLLPaSSMLT (SEQ ID NO: 241)), DEPDC1-A02-10-506 (QLCRsQSLLL (SEQ ID NO: 243)), DEPDC1-A02-10-765 (KQFQkEYPLI (SEQ ID NO: 244)), DEPDC1-A02-10-395 (IMGGSCHNLI (SEQ ID NO: 249), DEPDC1-A02-10-224 (NMANtSKRGV (SEQ ID NO: 253)), DEPDC1- A02-9-297 (ELFVNILGL (SEQ ID NO: 226)), DEPDC1-A02-10-296 (YELFvNILGL (SEQ ID NO: 254)) and DEPDC1-A02-10-301 (NILGlLQPHL (SEQ ID NO: 255)) demonstrate that they do not have significant homology with the peptides derived from any known human gene products. Accordingly, the possibility of unknown or undesirable immune responses with immunotherapy against these molecules is significantly reduced.

[0030] Regarding HLA antigens, the data presented here demonstrate that the uses of A-24 type or A-2 type antigens (which are said to be highly expressed among the Japanese) are favorable for obtaining effective results. The uses of subtypes such as A-2402 and A-0201 are even more preferable. Typically, in the clinic, the type of HLA antigen of the patient requiring treatment is investigated in advance, which, in turn, enables the selection of appropriate peptides having high levels of binding affinity to the patient antigen, or having cytotoxic T cell (CTL) inducibility by antigen presentation. Furthermore, in order to obtain peptides having high binding affinity and CTL inducibility, substitution, deletion, or addition of 1, 2, or several amino acids may be performed based on the amino acid sequence of the naturally occurring MPHOSPH1 and DEPDC1 partial peptide. Herein, the term "several" means refers to 5 or less, more preferably 3 or less. Furthermore, in addition to peptides that are naturally displayed, since the regularity of the sequences of peptides displayed by binding to HLA antigens is already known (Kubo RT, et al., (1994) J. Immunol., 152, 3913-24.; Rammensee HG, et al., (1995) Immunogenetics. 41:178-228.; Kondo A, et al., (1995) J. Immunol. 155:4307-12.), modifications based on such regularity can be performed on the immunogenic peptides of the invention. For example, peptides possessing high HLA-24 binding affinity in which the second amino acid from the N terminus substituted with phenylalanine, tyrosine, methionine, or tryptophan may be favorably used. Likewise, peptides whose C-terminal amino acid is substituted with phenylalanine, leucine, isoleucine, tryptophan, or methionine may also be used favorably. On the other hand, peptides possessing high HLA-A2 binding affinity having their second amino acid from the N terminus substituted with leucine or methionine, and peptides whose C-terminal amino acid is substituted with valine or leucine may be used favorably. Furthermore, 1 to 2 amino acids may be added to the N terminus and/or C terminus of the peptide.

[0031] However, when the peptide sequence is identical to a portion of the amino acid sequence of an endogenous or exogenous protein having a different function, side effects such as autoimmune disorders or allergic symptoms against specific substances may be induced. Therefore, it is preferable to avoid the situation wherein the immunogenic sequence matches the amino acid sequence of a known protein. This situation may be avoided by performing a homology search using available databases. If homology searches confirm that peptides in which 1, 2 or several different amino acids do not exist in nature, then the danger that modifications of the above-mentioned amino acid sequence that, for example, increase the binding affinity with HLA antigens, and/or increase the CTL inducibility can be avoided.

[0032] Although peptides having high binding affinity to the HLA antigens as described above are expected to be highly effective as cancer vaccines, the candidate peptides,

which are selected according to the presence of high binding affinity as an indicator, must be examined for the actual presence of CTL inducibility. CTL inducibility may be routinely confirmed by inducing antigen-presenting cells carrying human MHC antigens (for example, B-lymphocytes, macrophages, and dendritic cells), or more specifically dendritic cells derived from human peripheral blood mononuclear leukocytes, and, after stimulation with the peptide of interest, mixing with CD8-positive cells and measuring the cytotoxic activity against the target cells. As the reaction system, transgenic animals produced to express a human HLA antigen (for example, those described in BenMohamed L, et al., (2000) Hum. Immunol.; 61(8):764-79 Related Articles, Books, Linkout.) may be used. For example, the target cells can be radiolabeled with ^{51}Cr and such, and cytotoxic activity can be calculated from radioactivity released from the target cells. Alternatively, it can be examined by measuring IFN-gamma produced and released by CTL in the presence of antigen-presenting cells that carry immobilized peptides, and visualizing the inhibition zone on the media using anti-IFN-gamma monoclonal antibodies.

[0033] As a result of examining the CTL inducibility of peptides as described above, it was discovered that those peptides having high binding affinity to an HLA antigen did not necessarily have high inducibility. However, nonapeptides or decapeptides selected from the group of peptides having the amino acid sequences indicated by IYNEYIYDL (SEQ ID NO: 7), IYNEyIYDLF (SEQ ID NO: 8), YIYDLFVPV (SEQ ID NO: 9), RLAIFKDLV (SEQ ID NO: 10), TMSSsKLSNV (SEQ ID NO: 11), EYYELFVNI (SEQ ID NO: 12), LLQPHLERV (SEQ ID NO: 192), LLMRMISRM (SEQ ID NO: 195), LLTFEYYEL (SEQ ID NO: 197), RLCKSTIEL (SEQ ID NO: 209), CVLCCAEEV (SEQ ID NO: 225), FLMDhHQEIL (SEQ ID NO: 228), ILVVcGYITV (SEQ ID NO: 230) DEPDC1-A02-10-644 (SLMIhTFSRC (SEQ ID NO: 240)), DEPDC1-A02-10-575 (SLLPaSSMLT (SEQ ID NO: 241)), DEPDC1-A02-10-506 (QLCRsQSLLL (SEQ ID NO: 243)), DEPDC1-A02-10-765 (KQFQkEYPLI (SEQ ID NO: 244)), DEPDC1- A02-10-395 (IMGGSCHNLI (SEQ ID NO: 249), DEPDC1-A02-10-224 (NMANtSKRGV (SEQ ID NO: 253)), DEPDC1- A02-9-297 (ELFVNILGL (SEQ ID NO: 226)), DEPDC1-A02-10-296 (YELFvNILGL (SEQ ID NO: 254)) and DEPDC1-A02-10-301 (NILGlLQPHL (SEQ ID NO: 255)) showed particularly high CTL inducibility.

[0034] As noted above, the present invention provides peptides having cytotoxic T cell inducibility, namely those having the amino acid sequence of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 or 255 or a variant thereof (i.e., those in which 1, 2, or several amino acids are substituted, deleted, or added). It is preferable that the amino acid sequences composed of 9 or 10 amino acids indicated in SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226

228, 230, 240, 241, 243, 244, 249, 253, 254 or 255 or a variant thereof do not match an amino acid sequence associated with another endogenous protein. In particular, amino acid substitution to leucine or methionine at the second amino acid from the N terminus, amino acid substitution to valine or leucine at the C-terminal amino acid, and amino acid addition of 1 to 2 amino acids at the N terminus and/or C terminus are examples of preferred variants. One of skill in the art will recognize that in addition to amino acid substitutions and additions, immunologically active fragments of the peptides may also be used in the methods of the invention. Methods for determining active fragments are well known in the art. CTL clones obtained by stimulation by these modified peptides can recognize the original peptides and cause damage for cells expressing the original peptides.

[0035] Peptides of the present invention can be prepared using well known techniques. For example, the peptides can be prepared synthetically, using either recombinant DNA technology or chemical synthesis. Peptides of the present invention may be synthesized individually or as longer polypeptides comprising two or more peptides. The peptides of the present invention are preferably isolated, i.e., substantially free of other naturally occurring host cell proteins and fragments thereof.

[0036] The peptides of the present invention may contain modifications, such as glyc-osylation, side chain oxidation, or phosphorylation; so long as the modifications do not destroy the biological activity of the peptides as described herein, namely the ability to binding to an HLA antigen and induce CTL. Other modifications include incorporation of D-amino acids or other amino acid mimetics that can be used, for example, to increase the serum half life of the peptides.

[0037] The peptides of this invention can be prepared as a combination, which includes two or more of peptides of the invention, for use as a vaccine for a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, such a vaccine inducing CTL in vivo. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor. The peptides may be in a cocktail or may be conjugated to each other using standard techniques. For example, the peptides can be expressed as a single polypeptide sequence. The peptides in the combination may be the same or different. By administering the peptides of this invention, the peptides are presented at a high density on the HLA antigens of antigen-presenting cells, which, in turn, induces CTLs that specifically react toward the complex formed between the displayed peptide and the HLA antigen. Alternatively, antigen-presenting cells having immobilized the peptides of this invention on their cell surface, obtained by removing dendritic cells from the subjects, may be stimulated by the peptides of this invention.

Re-administration of these cells to the respective subjects induces CTL, and, as a result, aggressiveness towards the target cells can be increased.

[0038] More specifically, the present invention provides drugs for treating and/or preventing proliferation, metastasis, and such of a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, which include one or more of peptides of this invention. The peptides of this invention find particular utility in the treatment of a disease associating MPHOSPH1 and/or DEPDC1, e.g. cancers. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0039] The peptides of this invention can be administered to a subject directly, as a pharmaceutical composition that has been formulated by conventional formulation methods. In such cases, in addition to the peptides of this invention, carriers, excipients, and such that are ordinarily used for drugs can be included as appropriate, without particular limitations. The immunogenic compositions of this invention may be used for treatment and prevention of a disease associating MPHOSPH1 and/or DEPDC1, e.g. cancers. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0040] The immunogenic compositions for treatment and/or prevention of a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, which comprise as the active ingredient one or more peptides of the present invention, can further include an adjuvant so that cellular immunity will be established effectively. Alternatively, they may be administered with other active ingredients, such as anti-cancer agents. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor. Suitable formulations include granules. Suitable adjuvants are described in the literature (Johnson AG. (1994) Clin. Microbiol. Rev., 7:277-89.). Exemplary adjuvants include, but are not limited to, aluminum phosphate, aluminum hydroxide, and alum. Furthermore, liposome formulations, granular formulations in which the drug is bound to few-micrometer diameter beads, and formulations in which a lipid is bound to the peptide may be conveniently used. The method of administration may be oral, intradermal, subcutaneous, intravenous injection, or such, and may include systemic administration or local administration to the vicinity of the targeted tumor. The dose of the peptide(s) of this invention can be adjusted appropriately according to the disease to be treated, age of the patient, weight,

method of administration, and such. Though the dosage is ordinarily 0.001 mg to 1000 mg, preferably 0.01 mg to 100 mg, more preferably 0.1 mg to 10 mg, preferably administered once in a few days to few months, one skilled in the art can readily select the appropriate dose and method of administration, as, the selection and optimization of these parameters is well within routine skill.

[0041] The present invention further provides intracellular vesicles called exosomes, which present complexes formed between the peptides of this invention and HLA antigens on their surface. Exosomes can be prepared, for example, by using the methods described in detail in Published Japanese Translation of International Publication Nos. Hei 11-510507 and 2000-512161, and are preferably prepared using antigen-presenting cells obtained from subjects who are targets of treatment and/or prevention. The exosomes of this invention can be inoculated as cancer vaccines, similarly to the peptides of this invention.

[0042] The type of HLA antigens used must match that of the subject requiring treatment and/or prevention. For example, in the Japanese population, HLA-A24 or HLA-A2, particularly HLA-A2402 or HLA-A0201, is often appropriate.

[0043] In some embodiments, the vaccine compositions of the present invention include a component which primes cytotoxic T lymphocytes. Lipids have been identified as agents capable of priming CTL in vivo against viral antigens. For example, palmitic acid residues can be attached to the epsilon-and alpha-amino groups of a lysine residue and then linked to an immunogenic peptide of the invention. The lipidated peptide can then be administered either directly, in a micelle or particle, incorporated into a liposome, or emulsified in an adjuvant. As another example of a lipid priming of CTL responses, E. coli lipoproteins, such as tripalmitoyl-S-glycerylcysteinlyseryl- serine (P3CSS), can be used to prime CTL when covalently attached to an appropriate peptide (see, e.g., Deres K, et al., (1989) Nature 342:561-4.).

[0044] The immunogenic compositions of the present invention may also include nucleic acids encoding one or more of the immunogenic peptides disclosed here. See, e.g., Wolff JA et al., (1990) Science 247:1465-8; U.S. Patent Nos. 5,580,859; 5,589,466; 5,804,566; 5,739,118; 5,736,524; 5,679,647; and WO 98/04720. Examples of DNA-based delivery technologies include "naked DNA", facilitated (bupivicaine, polymers, peptide-mediated) delivery, cationic lipid complexes, and particle-mediated ("gene gun") or pressure-mediated delivery (see, e.g., U.S. Patent No. 5,922,687).

[0045] The immunogenic peptides of the invention can also be expressed by viral or bacterial vectors. Examples of suitable expression vectors include attenuated viral hosts, such as vaccinia or fowlpox. This approach involves the use of vaccinia virus, e.g., as a vector to express nucleotide sequences that encode the peptide. Upon introduction into a host, the recombinant vaccinia virus expresses the immunogenic

peptide, and thereby elicits an immune response. Vaccinia vectors and methods useful in immunization protocols are described in, e.g., U.S. Patent No. 4,722,848. Another suitable vector is BCG (Bacille Calmette Guerin). BCG vectors are described in Stover CK, et al., (1991) Nature 351:456-60. A wide variety of other vectors useful for therapeutic administration or immunization e.g., adeno and adeno-associated virus vectors, retroviral vectors, Salmonella typhi vectors, detoxified anthrax toxin vectors, and the like, are known in the art. See, e.g., Shata MT, et al., (2000) Mol. Med. Today 6:66-71; Shedlock DJ and Weiner DB., et al., (2000) J. Leukoc. Biol. 68:793-806; and Hipp JD, et al., (2000) In Vivo 14:571-85.

[0046] The present invention also provides methods of inducing antigen-presenting cells using one or more peptides of this invention. The antigen-presenting cells can be induced by inducing dendritic cells from the peripheral blood monocytes and then contacting (stimulating) them with one or more peptides of this invention in vitro, ex vivo or in vivo. When peptides of the present invention are administered to the subjects, antigen-presenting cells that have the peptides of this invention immobilized to them are induced in the body of the subject. Alternatively, after immobilizing the peptides of this invention to the antigen-presenting cells, the cells can be administered to the subject as a vaccine. For example, the ex vivo administration may include the steps of:

a: collecting antigen-presenting cells from a subject, and

b: contacting the antigen-presenting cells of step a with a peptide of the present invention.

[0047] The antigen-presenting cells obtained by step b can be administered to the subject as a vaccine.

[0048] This invention also provides a method for inducing antigen-presenting cells having a high level of cytotoxic T cell inducibility, in which the method includes the step of transferring genes composed of polynucleotide(s) encoding one or more peptides of this invention to antigen-presenting cells in vitro. The introduced genes may be in the form of DNAs or RNAs. For the method of introduction, without particular limitations, various methods conventionally performed in this field, such as lipofection, electroporation, and calcium phosphate method may be suitably used. More specifically, transfection may be performed as described in Reeves ME, et al., (1996) Cancer Res., 56:5672-7.; Butterfield LH, et al., (1998) J. Immunol., 161:5607-13.; Boczkowski D, et al., (1996) J. Exp. Med., 184:465-72.; Published Japanese Translation of International Publication No. 2000-509281. By transferring the gene into antigen-presenting cells, the gene undergoes transcription, translation, and such in the cell, and then the obtained protein is processed by MHC Class I or Class II, and proceeds through a presentation pathway to present partial peptides.

[0049] The present invention further provides methods for inducing CTL using one or more peptides of this invention. When the peptides of this invention are administered to a subject, CTL are induced in the body of the subject, and the strength of the immune system targeting the cells expressing MPHOSPH1 and/or DEPDC1, e.g. cancer cells in the tumor tissues is thereby enhanced. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor. Alternatively, the peptides of the present invention may be used in the context of an ex vivo therapeutic method, in which subject-derived antigen-presenting cells and CD8-positive cells or peripheral blood mononuclear leukocytes are contacted (stimulated) with one or more peptides of this invention in vitro, and, after inducing CTL, the cells are returned to the subject. For example, the method may include the steps of:

a: collecting antigen-presenting cells from a subject,

b: contacting the antigen-presenting cells of step a with a peptide of the present invention,

c: mixing the antigen-presenting cells of step b with CD^{8+} T cells and co-culturing so as to induce cytotoxic T-cells:, and

d: collecting CD^{8+} T cells from the co-culture of step c.

The CD^{8+} T cells having cytotoxic activity obtained by step d can be administered to the subject as a vaccine.

[0050] The present invention further provides methods for producing activated cytotoxic T cell using the peptides of this invention. For example, the method may include the following steps of:

a: collecting T cells from a subject, and

b: contacting T cells with following peptides.

(1) An isolated peptide of less than about 15 amino acids selected from the group consisting of peptides having the amino acid sequences of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 and 255.

(2) A peptide having cytotoxic T cell inducibility, wherein said peptide has an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 and 255, wherein 1, 2, or several amino acids are substituted, deleted, or added.

[0051] The present invention also provides method for producing APC having activated T-cell inducibility using the peptides of the present invention. For instance, the method may include the step of contacting antigen presenting cells with the peptides to produce antigen presenting cells presenting the peptide and HLA antigen on the

surface.

In the context of the present invention, "activated cytotoxic T cell" induces IFN-gamma producing, IFN-gamma releasing, and death of tumor cells.

[0052] The present invention further provides isolated cytotoxic T cells induced using the peptides of this invention. The cytotoxic T cells, induced by stimulation with an antigen-presenting cell presenting one or more peptides of this invention, are preferably derived from subjects who are the target of treatment and/or prevention, and can be administered alone or in combination with other drugs, including one or more peptides of this invention or exosomes having anti-tumor activity. The obtained cytotoxic T cells act specifically against target cells presenting the peptides of this invention, or preferably the same peptide(s) used for induction. The target cells may be cells that express MPHOSPH1 and/or DEPDC1 endogenously, or cells that are transfected with MPHOSPH1 and/or DEPDC1 genes. Cells that present the peptides of this invention on the cell surface, due to stimulation with these peptides, can also become targets of attack.

[0053] The present invention also provides antigen-presenting cells presenting complexes formed between HLA antigens and one or more peptides of this invention. The antigen-presenting cells, obtained through contact with the peptides of this invention or the nucleotides encoding such peptides, are preferably derived from subjects who are the target of treatment and/or prevention, and can be administered as vaccines, alone or in combination with other drugs, including the peptides, exosomes, or cytotoxic T cells of the present invention.

[0054] The present invention also provides a composition comprising nucleic acids encoding polypeptides that are capable of forming a subunit of a T cell receptor (TCR), and methods of using the same. The TCR subunits have the ability to form TCRs that confer specificity to T cells for tumor cells presenting MPHOSPH1 or DEPDC1. By using the known method in the art, the nucleic acids of alpha- and beta-chain as the TCR subunits of the CTL induced with one or more peptides of this invention may be identified (WO2007/032255 and Morgan et al., J Immunol, 171, 3288 (2003)). The derivative TCRs preferably bind target cells displaying the MPHOSPH1 or DEPDC1 peptide with high avidity, and optionally mediate efficient killing of target cells presenting the MPHOSPH1 or DEPDC1 peptide in vivo and in vitro.

[0055] The nucleic acids encoding the TCR subunits can be incorporated into suitable vectors e.g. retroviral vectors. These vectors are well known in the art. The nucleic acids or the vectors comprising them usefully can be transferred into a T cell, which T cell is preferably from a patient. Advantageously, the invention provides an off-the-shelf composition allowing rapid modification of a patient's own T cells (or those of another mammal) to rapidly and easily produce modified T cells having excellent

cancer cell killing properties.

[0056] Also, the present invention provides CTLs which are prepared by transduction with the nucleic acids encoding the TCR subunits polypeptides binding with MPHOSPH1 or DEPDC1 peptide e.g. SEQ ID NOs: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226 228, 230, 240, 241, 243, 244, 249, 253, 254 or 255 in the context of HLA-A24 or HLA-A2. The transduced CTLs are capable of homing to cancer cells in vivo, and expanded by well known culturing method in vitro (e.g., Kawakami et al., J Immunol., 142, 3452-3461 (1989)). The T cells of the invention can be used to form an immunogenic composition useful in treating or preventing cancer in a patient in need of therapy or protection (WO2006/031221).

[0057] In the context of the present invention, the term "vaccine" (also referred to as an immunogenic composition) refers to a substance that induces anti-tumor immunity or suppresses cancers upon inoculation into animals. According to the present invention, polypeptides having the amino acid sequence of SEQ ID NO: 7, 8 or 12 were suggested to be HLA-A24 restricted epitope peptides and those of SEQ ID NO: 9, 10, 11, 192, 195, 197, 209, 225, 226, 228 230, 240, 241, 243, 244, 249, 253, 254 or 255 were suggested to be HLA-A2 restricted epitope peptides that may induce potent and specific immune response against cells expressing MPHOSPH1 and/or DEPDC1, e.g. cancer cells expressing MPHOSPH1 and/or DEPDC1. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor. Thus, the present invention also encompasses a method of inducing anti-tumor immunity using polypeptides having the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 11, 12, 192, 195, 197, 209, 225, 226, 228, 230, 240, 241, 243, 244, 249, 253, 254 or 255 or a variant thereof (i.e., including 1, 2, or several amino acid substitutions, deletions, or additions). In general, anti-tumor immunity includes immune responses such as follows:

- an induction of cytotoxic lymphocytes against tumors containing cells expressing MPHOSPH1 and/or DEPDC1,
- an induction of antibodies that recognize tumors containing cells expressing MPHOSPH1 and/or DEPDC1, and
- an induction of anti-tumor cytokine production.

[0058] Therefore, when a certain peptide induces any one of these immune responses upon inoculation into an animal, the peptide is decided to have anti-tumor immunity inducing effect. The induction of the anti-tumor immunity by a peptide can be detected by observing in vivo or in vitro the response of the immune system in the host against the peptide.

[0059] For example, a method for detecting the induction of cytotoxic T lymphocytes is well known. A foreign substance that enters the living body is presented to T cells and B cells by the action of antigen-presenting cells (APCs). T cells that respond to the antigen presented by APC in antigen specific manner differentiate into cytotoxic T cells (also referred to as cytotoxic T lymphocytes or CTLs) due to stimulation by the antigen, and then proliferate; this process is referred to herein as "activation" of T cells. Therefore, CTL induction by a certain peptide can be evaluated by presenting the peptide to a T cell by APC, and detecting the induction of CTL. Furthermore, APCs have the effect of activating CD4+ T cells, CD8+ T cells, macrophages, eosinophils and NK cells. Since CD4+ T cells are also important in anti-tumor immunity, the anti-tumor immunity inducing action of the peptide can be evaluated using the activation effect of these cells as indicators.

[0060] A method for evaluating the inducing action of CTL using dendritic cells (DCs) as APC is well known in the art. DC is a representative APC having the strongest CTL inducing action among APCs. In this method, the test polypeptide is initially contacted with DC and then this DC is contacted with T cells. Detection of T cells having cytotoxic effects against the cells of interest after the contact with DC shows that the test polypeptide has an activity of inducing the cytotoxic T cells. Activity of CTL against tumors can be detected, for example, using the lysis of ^{51}Cr-labeled tumor cells as the indicator. Alternatively, it is well known to evaluate the degree of tumor cell damage using ^{3}H-thymidine uptake activity or LDH (lactose dehydrogenase)-release as the indicator. Furthermore, it can be also examined by measuring IFN-gamma produced and released by CTL in the presence of antigen-presenting cells that carry immobilized peptides by visualizing using anti-IFN-gamma antibodies, such as an ELISPOT assay.

[0061] Apart from DC, peripheral blood mononuclear cells (PBMCs) may also be used as the APC. The induction of CTL is reported to be enhanced by culturing PBMC in the presence of GM-CSF and IL-4. Similarly, CTL has been shown to be induced by culturing PBMC in the presence of keyhole limpet hemocyanin (KLH) and IL-7.

[0062] The test polypeptides confirmed to possess CTL inducing activity by these methods are polypeptides having DC activation effect and subsequent CTL inducing activity. Therefore, polypeptides that induce CTL against tumor cells are useful as vaccines against diseases associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers. Furthermore, APC that have acquired the ability to induce CTL against a disease associating MPHOSPH1 and/or DEPDC1, e.g. cancers, by contacting with the polypeptides are useful as vaccines against the disease. Furthermore, CTL that have acquired cytotoxicity due to presentation of the polypeptide antigens by APC can be also used as vaccines against a disease associating MPHOSPH1 and/or DEPDC1, e.g.

cancers. Such therapeutic methods for a disease associating MPHOSPH1 and/or DEPDC1, e.g. cancers, using anti-tumor immunity due to APC and CTL, are referred to as cellular immunotherapy. The cancers contemplated include, but are not limited to, bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC, soft tissue tumor.

[0063] Generally, when using a polypeptide for cellular immunotherapy, efficiency of the CTL-induction can be increased by combining a plurality of polypeptides having different structures and contacting them with DC. Therefore, when stimulating DC with protein fragments, it is advantageous to use a mixture of multiple types of fragments.

[0064] The induction of anti-tumor immunity by a polypeptide can be further confirmed by observing the induction of antibody production against tumors. For example, when antibodies against a polypeptide are induced in a laboratory animal immunized with the polypeptide, and when growth, proliferation and/or metastasis of tumor cells is suppressed by those antibodies, the polypeptide is determined to induce anti-tumor immunity.

[0065] Anti-tumor immunity can be induced by administering a vaccine of this invention, and the induction of anti-tumor immunity enables treatment and prevention of a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers. Therapy against or prevention of the onset of a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, may include inhibition of the growth of cells expressing MPHOSPH1 and/or DEPDC1, e.g. cancer cells, involution of these cells and suppression of occurrence of these cells, e.g. cancer cells. Decrease in mortality of individuals having a disease associating MPHOSPH1 and/or DEPDC1, e.g. cancers, decrease of the disease markers in the blood, alleviation of detectable symptoms accompanying the disease and such are also included in the therapy or prevention of the disease, e.g. cancers. Such therapeutic and preventive effects are preferably statistically significant, for example, observed at a significance level of 5% or less, wherein the therapeutic or preventive effect of a vaccine against a disease associating MPHOSPH1 and/or DEPDC1, e.g. cancers, is compared to a control without vaccine administration. For example, Student's t-test, the Mann-Whitney U-test or ANOVA may be used for determining statistical significance.

[0066] In that the present invention provides a method for treating, or preventing a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, the therapeutic compounds or compositions may be administered prophylactically or therapeutically to subjects suffering from or at risk of (or susceptible to) developing the disease. Such subjects may be identified using standard clinical methods. In the context

of the present invention, prophylactic administration occurs prior to the manifestation of overt clinical symptoms of disease, such that a disease or disorder is prevented or alternatively delayed in its progression. In the context of the field of medicine, the term "prevent" encompasses any activity which reduces the burden of mortality or morbidity from disease. Prevention can occur "t primary, secondary and tertiary prevention levels. While primary prevention avoids the development of a disease, secondary and tertiary levels of prevention encompass activities aimed at preventing the progression of a disease and the emergence of symptoms as well as reducing the negative impact of an already established disease by restoring function and reducing disease-related complications.

[0067] In the context of cancer treatment, the term "efficacious" refers to a treatment that leads to a decrease in size, prevalence or metastatic potential of cancer in a subject. When a treatment is applied prophylactically, "efficacious" means that the treatment retards or prevents occurrence of non cancer or alleviates a clinical symptom of cancer. The assessment of cancer can be made using standard clinical protocols. Furthermore, the efficaciousness of a treatment may be determined in association with any known method for diagnosing or treating cancer. For example, cancer can be diagnosed histopathologically or by identifying symptomatic anomalies.

[0068] The above-mentioned peptide, having immunological activity, or a polynucleotide or vector encoding such a peptide, may be combined with an adjuvant. An adjuvant refers to a compound that enhances the immune response against the peptide when administered together (or successively) with the peptide having immunological activity. Examples of suitable adjuvants include cholera toxin, salmonella toxin, alum and such, but are not limited thereto. Furthermore, a vaccine of this invention may be combined appropriately with a pharmaceutically acceptable carrier. Examples of such carriers are sterilized water, physiological saline, phosphate buffer, culture fluid and such. Furthermore, the vaccine may contain as necessary, stabilizers, suspensions, preservatives, surfactants and such. The vaccine is administered systemically or locally. Vaccine administration may be performed by single administration or boosted by multiple administrations.

[0069] When using APC or CTL as the vaccine of this invention, a disease associated with the over-expression of MPHOSPH1 and/or DEPDC1, e.g. cancers, can be treated or prevented, for example, by the ex vivo method. More specifically, PBMCs of the subject receiving treatment or prevention are collected, contacted ex vivo with a peptide of the present invention. Following the induction of APC or CTL, the cells may be administered to the subject. APC can be also induced by introducing a vector encoding the peptide into PBMCs ex vivo. APC or CTL induced in vitro can be cloned prior to administration. By cloning and growing cells having high activity of damaging

target cells, cellular immunotherapy can be performed more effectively. Furthermore, APC and CTL isolated in this manner may be used for cellular immunotherapy not only against individuals from whom the cells are derived, but also against similar types of diseases in other individuals.

[0070] Aspects of the present invention are described in the following examples, which are presented only to illustrate the present invention and to assist one of ordinary skill in making and using the same. The examples are not intended in any way to otherwise limit the scope of the invention.

[0071] Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below.

[0072] EXAMPLES

Hereinafter, the present invention is exemplified, but not restricted, by the following Examples. However, materials, methods and such described herein only illustrate aspects of the invention and in no way are intended to limit the scope of the present invention. As such, materials, methods and such similar or equivalent to those described therein may be used in the practice or testing of the present invention.

[0073] EXAMPLE 1

MATERIALS AND METHODS

Cell lines

A24LCL cells (HLA-A24/24), human B-lymphoblastoid cell lines, T2 cell and COS7 were purchased from ATCC.

[0074] Candidate selection of peptide derived from MPHOSOH1 and DEPDC1

9-mer and 10-mer peptides derived from MPHOSOH1 or DEPDC1 that bind to HLA-A*2402 and HLA-A*0201 molecule were predicted using binding prediction software "BIMAS" (bimas.dcrt.nih.gov/cgi-bin/molbio/ken_parker_comboform) (Parker KC, et al., (1994) J Immunol.;152(1):163-75.; Kuzushima K, et al., (2001) Blood.;98(6):1872-81.). These peptides were synthesized by Sigma (Sapporo, Japan) according to the standard solid phase synthesis method and purified by reversed phase HPLC. The purity (>90%) and the identity of the peptides were determined by analytical HPLC and mass spectrometry analysis, respectively. Peptides were dissolved in dimethylsulfoxide (DMSO) at 20 mg/ml and stored at -80 degrees C.

[0075] In vitro CTL Induction

Monocyte-derived dendritic cells (DCs) were used as antigen-presenting cells (APCs) to induce CTL responses against peptides presented on HLA. DCs were generated in vitro as described elsewhere (Nukaya I et al., (1999) Int. J. Cancer 80, 92-7., Tsai V et al., (1997) J. Immunol 158:1796-802.). Briefly, peripheral blood mononuclear cells (PBMCs) isolated from a normal volunteer (HLA-A*2402 and/or

HLA-A*0201) by Ficoll-Paque (Pharmacia) solution were separated by adherence to a plastic tissue culture flask (Becton Dickinson) so as to enrich them for the monocyte fraction. The monocyte-enriched population was cultured in the presence of 1000 U/ml of GM-CSF (Genzyme) and 1000 U/ml of IL-4 (Genzyme) in AIM-V (Invitrogen) containing 2% heat-inactivated autologous serum (AS). After 7 days in the culture, the cytokine-generated DCs were pulsed with 20 mcg/ml of the synthesized peptides in the presence of 3 mcg/ml of beta 2-microglobulin for 4 hrs at 20 degrees C in AIM-V. These peptide-pulsed DCs were then inactivated by MMC (30 mcg/ml for 30 mins) and mixed at a 1:20 ratio with autologous $CD8^+$ T cells, obtained by positive selection with Dynabeads M-450 CD8 (Dynal) and DETACHa BEAD™ (Dynal). These cultures were set up in 48-well plates (Corning); each well contained $1.5x10^4$ peptide-pulsed DCs, $3x10^5$ $CD8^+$ T cells and 10 ng/ml of IL-7 (Genzyme) in 0.5 ml of AIM-V/2% AS. Three days later, these cultures were supplemented with IL-2 (CHIRON) to a final concentration of 20 IU/ml. On day 7 and 14, the T cells were further restimulated with the autologous peptide-pulsed DCs. The DCs were prepared each time by the same way described above. CTL was tested against peptide-pulsed A24LCL cells or T2 cells after the 3rd round of peptide stimulation on day 21.

[0076] CTL Expansion Procedure

CTLs were expanded in culture using the method similar to that described by Riddell SR, et al., (Walter EA et al., (1995) N Engl J Med 333:1038-44.; Riddel SR, et al., (1996) Nature Med. 2:216-23.). A total $5x10^4$ of CTLs were resuspended in 25 ml of AIM-V/5% AS with 2 kinds of human B-lymphoblastoid cell lines, inactivated by MMC, in the presence of 40 ng/ml of anti-CD3 monoclonal antibody (Pharmingen). One day after initiating the cultures, 120 IU/ml of IL-2 were added to the cultures. The cultures were fed with fresh AIM-V/5% AS containing 30 IU/ml of IL-2 on days 5, 8 and 11.

[0077] Establishment of CTL clones

The dilutions were made to have 0.3, 1, and 3 CTLs/well in 96 round-bottomed micro titer plate (Nalge Nunc International). CTLs were cultured with $7x10^4$ cells/well of 2 kinds of human B-lymphoblastoid cell lines, 30ng/ml of anti-CD3 antibody, and 125 U/ml of IL-2 in total of 150 mcl/well of AIM-V containing 5%AS. 50 mcl /well of IL-2 was added to the medium 10 days later so that IL-2 became 125 U/ml in the final concentration. CTL activity of CTLs was tested on the 14th day, and CTL clones were expanded using the same method above.

[0078] Specific CTL activity

To examine the specific CTL activity, IFN-gamma ELISPOT assay and IFN-gamma ELISA were performed.

Briefly, peptide-pulsed A24-LCL or T2 cell ($1x10^4$/well) was prepared as a

stimulator cell. Cultured Cells in 48 wells or CTL clones after limiting dilution were used as a responder cells. IFN-gamma ELISPOT assay and ELISA were performed under manufacture procedure.

[0079] Cell Culture and Transfection

HLA-A24 B-LCLs (A24LCL), Epstein Bar virus-transformed, was established. Jiyoye, EB-3, COS7, HT1376, RT-4 and J82 were purchased from American Type Culture Collection (Rockville, MD). A24LCL, Jiyoye and EB-3 were maintained in RPMI1640 containing 10% fetal bovine serum (GEMINI Bio-Products) and 1% antibiotic solution (Sigma). COS7, HT1376, RT-4 and J82 were maintained in appropriate medium and antibiotics. Transfection of COS7 and HEK were performed using FUGENE6 (Roche). HEK-A2 cell, HLA-A*0201 molecule expressing stable clone, was established by transfection of pcDNA6.2-HLA-A2 plasmid and isolated by limiting dilution method in the presence of 5 mcg/ml Blastcidin S.

[0080] Immunogenicity of epitope peptides in BALB/c mice

For induction of the peptide-specific CTLs, immunization was given using 100 ml of vaccine mixture, which contains 50 mcl (100 mcg) of HLA-A24 restricted peptide and 50 mcl of IFA per mouse. The vaccine was subcutaneously injected in the right flank for the first immunization on day 0 and in the left flank for the second on the day 7. On day 14, splenocytes of the vaccinated mice, without any in vitro stimulation, were used responder cells, and RLmale1 cells pulsed with or without peptides were used as the stimulator cells for IFN-gamma ELISPOT assay.

[0081] RESULTS

Enhanced MPHOSPH1 and DEPDC1 expression in cancers

The global gene expression profile data obtained from various cancers using cDNA-microarray revealed that MPHOSPH1 (GenBank Accession No. NM_016195; SEQ ID No.1) and DEPDC1 (GenBank Accession No. BM683578) which had two variants; DEPDC1 V1 (SEQ ID Nos.3) and DEPDC1 V2 (SEQ ID No. 5) expression was elevated. MPHOSPH1 expression was validly elevated in 30 out of 31 bladder cancers, 8 out of 36 breast cancers, 18 out of 18 cervical cancers, 5 out of 17 cholangincellular carcinomas, 25 out of 31 CMLs, 6 out of 11 colorectal cancers, 6 out of 14 gastric cancers, 5 out of 5 NSCLCs, 7 out of 7 lymphomas, 6 out of 10 osteosarcomas, 7 out of 22 prostate cancers, 10 out of 18 renal carcinomas and 15 out of 21soft tissue tumors as compared with corresponding normal tissue. DEPDC1 expression was validly elevated in 23 out of 25 bladder cancers, 6 out of 13 breast cancers, 12 out of 12 cervical cancers, 6 out of 6 cholangincellular carcinomas, 3 out of 4 CMLs, 2 out of 4 colorectal cancers, 6 out of 6 NSCLCs, 7 out of 7 lymphomas, 10 out of 14 osteosarcomas, 11 out of 24 prostate cancers, 14 out of 14 SCLCs and 22 out of 31 soft tissue tumors as compared with corresponding normal tissue (Table 1).

[0082] [Table 1]

Ratio of cases observed up-regulation of *MPHOSPH1* or *DEPDC1* in cancerous tissue as compared with normal corresponding tissue

	Bladder cancer	Breast cancer	Cervical cancer	Cholangiocellular Carcinoma	CML	Colorectal cancer	Gastric cancer
MPHOSPH1	30/31	8/36	18/18	5/17	25/31	6/11	6/14
DEPDC1	23/25	6/13	12/12	6/6	3/4	2/4	-

	NSCLC	Lymphoma	Osteosarcoma	Prostate cancer	Renal cancer	SCLC	Soft Tissue Tumor
MPHOSPH1	5/5	7/7	6/10	7/22	10/18	-	15/21
DEPDC1	6/6	7/7	10/14	11/24	-	14/14	22/31

[0083] Prediction of HLA-A24 andHLA-A2 binding peptides derived from MPHOSPH1 or DEPDC1

Table 2 sets forth the HLA-A*2402 binding peptides for MPHOSPH1 in order of binding affinity. Table 2A sets forth 9-mer peptides derived from MPHOSPH1 and Table 2B sets forth 10-mer peptides derived from MPHOSPH1.

Table 3 sets forth the HLA-A*0201 binding peptides for MPHOSPH1 in order of binding affinity. Table 3A sets forth 9-mer peptides derived from MPHOSPH1 and Table 3B sets forth 10-mer peptides derived from MPHOSPH1.

Table 4 sets forth the HLA-A*2402 binding peptides for DEPDC1 V1 and V2 in order of binding affinity. Table 4A sets forth 9-mer peptides derived from DEPDC1 V1 and V2 and Table 4B sets forth 10-mer peptides derived from DEPDC1 V1.

Table 5 sets forth the HLA-A*0201 binding peptides for DEPDC1 V1 and V, Table 5A sets forth 9-mer peptides derived from DEPDC1 V1 and V2 and Table 5B sets forth 10-mer peptides derived from DEPDC1 V1 and V2.

[0084]

[Table 2A]

HLA-A*2402 binding 9-mer peptides derived from *MPHOSPH1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
278	IYNEYIYDL	7	360	179	LFDSLQERL	29	24
1244	DYADLKEKL	13	316.8	268	KFSVWVSFF	30	20
1319	QYERACKDL	14	300	575	KLLDLIEDL	31	17.28
459	CYLAYDETL	15	300	1577	RFPKPELEI	32	16.5
462	AYDETLNVL	16	288	1414	KYNADRKKW	33	16.5
1054	GYKDENNRL	17	288	1230	RTQNLKADL	34	14.4
236	LYGSLTNSL	18	288	1421	KWLEEKMML	35	14.4
1446	KYAEDRERF	19	240	1617	KSNEMEEDL	36	14.4
899	NYDIAIAEL	20	220	1555	KIEDGSVVL	37	14.4
1118	CYKAKIKEL	21	220	1456	KQQNEMEIL	38	12
57	DYLQVCLRI	22	105	389	KTQNEGERL	39	12
676	KFNQIKAEL	23	92.4	1371	KWKEKCNDL	40	11.52
14	SYVFSADPI	24	75	1122	KIKELETIL	41	11.52
326	AYRLLKLGI	25	60	850	FLLTIENEL	42	11.088
255	DYEQANLNM	26	37.5	763	SSLIINNKL	43	11.088
29	NFDGIKLDL	27	28	1400	KLTNLQDEL	44	10.56
286	LFVPVSSKF	28	27.72	133	IMQPVKDLL	45	10.08

Start position indicates the number of amino acid from N-terminal of MPHOSPH1.
Binding score is derived from "BIMAS" described in Materials and Methods.

[0085] [Table 2B]

HLA-A*2402 binding 10-mer peptides derived from *MPHOSPH1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
1414	KYNAdRKKWL	46	600	1274	KLLRiKINEL	56	15.84
278	IYNEyIYDLF	8	252	1332	KIIEdMRMTL	57	14.4
1446	KYAEdRERFF	47	240	1299	RTIQqLKEQL	58	14.4
611	QYWAqREADF	48	100	1134	KVECsHSAKL	59	13.2
1740	LYTSeISSPI	49	70	859	KNEKeEKAEL	60	13.2
293	KFQKrKMLRL	50	60	586	KLINeKKEKL	61	13.2
849	AFLLtIENEL	51	55.44	943	KLMHtKIDEL	62	13.2
1667	TYSLrSQASI	52	50	838	RVLQeNNEGL	63	12
1695	DFLQhSPSIL	53	30	369	RVIRvSELSL	64	12
174	RTLNvLFDSL	54	17.28	1159	RNLKeFQEHL	65	12
870	KQIVhFQQEL	55	15.84	281	EYIYdLFVPV	66	10.8

Start position indicates the number of amino acid from N-terminal of MPHOSPH1.
Binding score is derived from "BIMAS" described in Materials and Methods.

[0086]

[Table 3A]

HLA-A*0201 binding 9-mer peptides derived from *MPHOSPH1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
575	KLLDLIEDL	31	1278.29	1184	KLKEEITQL	93	24.677
282	YIYDLFVPV	9	1096.62	888	TLSKEVQQI	94	23.995
298	KMLRLSQDV	67	650.504	280	NEYIYDLFV	95	23.802
218	ALLRQIKEV	68	591.888	552	LLDEDLDKT	96	23.415
850	FLLTIENEL	42	363.588	461	LAYDETLNV	97	21.546
1108	ALSELTQGV	69	285.163	980	NLPNTQLDL	98	21.362
331	KLGIKHQSV	70	243.432	409	TLGKCINVL	99	20.145
1689	TLQKFGDFL	71	218.772	175	TLNVLFDSL	100	19.888
1251	KLTDAKKQI	72	149.711	923	KLSNEIETA	101	19.596
638	RLAIFKDLV	10	129.506	1389	KEHENNTDV	102	19.407
1467	QLTEKDSDL	73	87.586	987	DLLGNDYLV	103	19.301
1195	NLQDMKHLL	74	87.586	920	KIMKLSNEI	104	18.577
270	SVWVSFFEI	75	83.497	1703	ILQSKAKKI	105	17.736
129	FQGCIMQPV	76	74.608	512	ILNVKRATI	106	17.736
839	VLQENNEGL	77	72.959	1124	KELETILET	107	17.695
1094	TLDVQIQHV	78	63.988	453	IVNISQCYL	108	17.477
1019	AIWEECKEI	79	48.816	771	LICNETVEV	109	16.258
1696	FLQHSPSIL	80	40.289	623	TLLQEREIL	110	15.879
528	DLMEDEDLV	81	38.775	560	TLEENKAFI	111	15.057
406	SLLTLGKCI	82	38.601	1415	YNADRKKWL	112	14.465
1400	KLTNLQDEL	44	36.637	307	KGYSFIKDL	113	13.65
170	GILPRTLNV	83	35.385	133	IMQPVKDLL	45	12.852
171	ILPRTLNVL	84	34.246	1594	KMAVKHPGC	114	12.558
786	KICSERKRV	85	33.472	365	SEMSRVIRV	115	11.509
880	SLSEKKNLT	86	30.553	1191	QLTNNLQDM	116	11.426
944	LMHTKIDEL	87	29.559	871	QIVHFQQEL	117	11.162
1422	WLEEKMMLI	88	28.963	245	NISEFEESI	118	10.951
466	TLNVLKFSA	89	28.814	484	TLNSSQEKL	119	10.468
1539	KLQTEPLST	90	26.082	764	SLIINNKLI	120	10.433
132	CIMQPVKDL	91	24.997	587	LINEKKEKL	121	10.032
1260	KQVQKEVSV	92	24.681				

Start position indicates the number of amino acid from N-terminal of MPHOSPH1.
Binding score is derived from "BIMAS" described in Materials and Methods.

[0087]

[Table 3B]

HLA-A*0201 binding 10-mer peptides derived from *MPHOSPH1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
1274	KLLRiKINEL	56	626.279	1318	QQYErACKDL	140	28.417
551	KLLDeDLDKT	122	445.913	452	MIVNiSQCYL	141	27.464
460	YLAYdETLNV	123	319.939	923	KLSNeIETAT	142	26.082
943	KLMHtKIDEL	62	311.777	1257	KQIKqVQKEV	143	24.681
262	NMANsIKFSV	124	291.346	980	NLPNtQLDLL	144	24.075
178	VLFDsLQERL	125	269.948	985	QLDLIGNDYL	145	23.029
770	KLICnETVEV	126	243.432	1427	MMLItQAKEA	146	22.569
34	KLDLsHEFSL	127	173.463	1523	QIMDiKPKRI	147	21.762
407	LLTLgKCINV	128	118.238	1484	QLVAaLEIQL	148	21.362
1714	TMSSsKLSNV	11	115.534	466	TLNVIKFSAI	149	19.822
1353	QVLEaKLEEV	129	104.046	511	KILNvKRATI	150	18.577
880	SLSEkKNLTL	130	87.586	1340	TLEEqEQTQV	151	18.25
235	TLYGsLTNSL	131	68.36	372	RVSEISLCDL	152	17.627
1019	AIWEeCKEIV	132	65.381	1561	VVLDsCEVST	153	16.816
552	LLDEdLDKTL	133	59.558	309	YSFIkDLQWI	154	14.663
1093	VTLDvQIQHV	134	57.298	353	SIFTvKILQI	155	12.208
559	KTLEeNKAFI	135	42.314	1094	TLDVqIQHVV	156	11.407
1332	KIIEdMRMTL	57	42.151	1688	GTLQkFGDFL	157	11.242
152	GLTNsGKTYT	136	40.986	311	FIKDIQWIQV	158	10.732
830	NIAEiEDIRV	137	39.21	1079	TLIQqLKEEL	159	10.468
586	KLINeKKEKL	61	36.637	1128	TILEtQKVEC	160	10.363
182	SLQErLYTKM	138	30.553	1487	AALEiQLKAL	161	10.352
1043	QQIEkLQAEV	139	28.912	170	GILPrTLNVL	162	10.249
870	KQIVhFQQEL	55	28.807				

Start position indicates the number of amino acid from N-terminal of MPHOSPH1.

Binding score is derived from "BIMAS" described as Materials and Methods.

[0088] [Table 4A]

HLA-A*2402 binding 9-mer peptides derived from *DEPDC1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
295	YYELFVNIL	163	360	505	KQLCRSQSL	167	14.4
294	EYYELFVNI	12	86.4	275	VFRTIADYF	168	14
282	YFLDLPEPL	164	43.2	36	HFKKYGNCF	169	12
118	RYPELRKNN	165	21.6	307	GYITVSDRS	170	10.5
338	SFKSTECLL	166	20	298	LFVNILGLL	171	42

Start position indicates the number of amino acid from N-terminal of DEPDC1.

Binding score is derived from "BIMAS" described in Materials and Methods.

[0089]

[Table 4B]

HLA-A*2402 binding 10-mer peptides derived from *DEPDC1*

Start Position	Amino Acid Sequence	SRQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SRQ ID NO.	Binding Score
294	EYYEIFVNIL	172	288	275	VFRTIADYFL	182	20
281	DYFLdLPEPL	173	240	113	KTLPrRYPEL	183	15.84
118	RYPEIRKNNI	174	216	277	RTIAdYFLDL	184	14.4
770	EYPLiYQKRF	175	150	270	GFERdVFRTI	185	12.6
267	TYVGfERDVF	176	150	146	RTPKrHGLHL	186	12
523	SYINtPVAEI	177	82.5	505	KQLCrSQSLL	187	12
282	YFLDIPEPLL	178	36	340	KSTEcLLLSL	188	11.52
191	RYVIIIYLQT	179	21	295	YYELfVNILV	189	10.5
338	SFKStECLLL	180	20	129	NFSKdKDSIF	190	10
103	LFRFpATSPL	181	20				

Start position indicates the number of amino acid from N-terminal of DEPDC1.

Binding score is derived from "BIMAS" described in Materials and Methods.

[0090] [Table 5A]

HLA-A*0201 binding 9-mer peptides derived from *DEPDC1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
674	FLMDHHQEI	191	728.022	563	RLCKSTIEL	209	21.362
589	LLQPHLERV	192	133.255	506	QLCRSQSLL	210	21.362
575	SLLPASSML	193	79.041	193	VILIYLQTI	211	20.753
246	WVLSAMKCL	194	73.172	297	ELFVNILVV	212	18.201
619	LLMRMISRM	195	71.872	235	ILQNKSDDL	213	17.795
581	SMLTGTQSL	196	57.085	616	KLQLLMRMI	214	16.797
290	LLTFEYYEL	197	54.474	623	MISRMSQNV	215	16.258
220	YIMYNMANT	198	40.111	72	TIQLLRKFL	216	16.155
283	FLDLPEPLL	199	39.307	421	CSLEGIVDV	217	15.841
787	ALFGDKPTI	200	38.601	303	LVVCGYITV	218	15.519
582	MLTGTQSLL	201	36.316	524	YINTPVAEI	219	15.177
773	LIYQKRFPT	202	32.33	194	ILIYLQTIL	220	14.89
114	TLPRRYPEL	203	32.044	239	KSDDLPHWV	221	14.333
505	KQLCRSQSL	167	28.049	576	LLPASSMLT	222	12.668
765	KQFQKEYPL	204	28.049	646	MIHTFSRCV	223	12.356
395	IMGGSCHNL	205	26.228	645	LMIHTFSRC	224	11.589
296	YELFVNILV	206	23.018	653	CVLCCAEEV	225	11.034
278	TIADYFLDL	207	22.882	297	ELFVNILGL	226	13.635
601	ALQLCCLLL	208	21.362				

Start position indicates the number of amino acid from N-terminal of DEPDC1.

Binding score is derived from "BIMAS" described in Materials and Methods.

[0091]

[Table 5B]

HLA-A*0201 binding 10-mer peptides derived from *DEPDC1*

Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score	Start Position	Amino Acid Sequence	SEQ ID NO.	Binding Score
666	LLAGrLVSFL	227	459.398	575	SLLPaSSMLT	241	27.572
674	FLMDhHQEIL	228	299.484	296	YELFvNILVV	242	21.706
588	SLLQpHLERV	229	290.025	506	QLCRsQSLLL	243	21.362
302	ILVVcGYITV	230	177.358	765	KQFQkEYPLI	244	20.547
291	LTFEyYELFV	231	137.017	682	ILQVpSYLQT	245	19.003
201	ILGVpSLEEV	232	133.255	269	VGFErDVFRT	246	16.735
195	LIYLqTILGV	233	119.657	381	QLVNIRNRRV	247	13.91
688	YLQTaVEKHL	234	98.267	283	FLDLpEPLLT	248	13.712
645	LMIHtFSRCV	235	64.9	395	IMGGsCHNLI	249	12.809
581	SMLTgTQSLL	236	57.085	403	LIGLsNMHDL	250	11.485
622	RMISrMSQNV	237	50.232	773	LIYQkRFPTT	251	10.591
618	QLLMrMISRM	238	42.278	488	TLTVqDQEEL	252	10.468
654	VLCCaEEVDL	239	36.316	224	NMANtSKRGV	253	10.046
644	SLMIhTFSRC	240	34.925	296	YELFvNILGL	254	16.26
505	KQLCrSQSLL	187	28.049	301	NILGILQPHL	255	10.868

Start position indicates the number of amino acid from N-terminal of DEPDC1.
Binding score is derived from "BIMAS" described in Materials and Methods.

[0092] Stimulation of the T cells using the predicted peptides from MPHOSPH1 restricted with HLA-A*2402

CTLs for those peptides derived from MPHOSHP1 (SEQ ID No: 2) were generated according to the protocols set forth in "Materials and Methods" section above. Resulting CTLs having detectable specific CTL activity, as assessed by IFN-gamma ELISPOT assay, are shown in Figure 1A and Figure 2A. In Figure 1A, the cells in the well number #4 stimulated with MPHOSPH1-A24-9-278 (SEQ ID NO: 7) demonstrated potent IFN-gamma production as compared with the control. In Figure 2A, the cells in the well number #8 stimulated with MPHOSPH1-A24-10-278 (SEQ ID NO: 8) demonstrated potent IFN-gamma production as compared with the control. Next, these cells in the positive well were expanded and limiting dilution was performed. As shown in Figure 1B (MPHOSPH1-A24-9-278 (SEQ ID NO: 7)) and Figure 2B (MPHOSPH1-A24-10-278 (SEQ ID NO: 8)), CTL clones having higher specific CTL activities against the peptide-pulsed target as compared to the activities against target without peptide pulse were established

[0093] The CTL clones stimulated by the MPHOSPH1-A24-9-278 (IYNEYIYDL (SEQ ID NO: 7)) (Figure 3A) and MPHOSPH1-A24-10-278 (IYNEYIYDLF (SEQ ID NO: 8)) (Figure 3B) demonstrated potent specific CTL activity against the peptide-pulsed target without showing any significant specific CTL activity against targets not pulsed with any peptide. This suggests that the CTL clone has the peptide-specific cytotoxicity.

[0094] Specific CTL activity against the target cells expressing MPHOSPH1

The established CTL clones raised against these peptides were examined for their ability to recognize the target cells endogenously expressing MPHOSPH1 and HLA-A*2402. Specific CTL activity against COS7 transfected with both the full length MPHOSPH1 gene and the HLA-A*2402 molecule, which is a specific model for the target cells endogenously express MPHOSPH1 and HLA-A*2402, was tested using as effector cells the CTL clone raised by MPHOSPH1-A24-9-278 (SEQ ID NO: 7). COS7 transfected with full length MPHOSPH1 but not HLA-A*2402 and COS7 transfected HLA-A*2402 but not full length MPHOSPH1 were prepared as controls. The CTL Clone having the highest specific CTL activity against COS7 was that transfected with both MPHOSPH1 and HLA-A24. However, it did not show significant specific CTL activity against COS7 transfected with neither MPHOSPH1 nor HLA-A24 (Figure 4).

[0095] These results clearly demonstrate that MPHOSPH1-A24-9-278 (SEQ ID NO: 7) was naturally expressed to the target cell surface with HLA-A24 molecule and recognized CTL.

[0096] CTL activity against bladder cancer cell lines endogenously expressing MPHOSPH1

The established CTL clone raised against MPHOSPH1-A24-9-278 (SEQ ID NO: 7) peptide was examined for their ability to recognize the tumor cells endogenously expressing MPHOSPH1. CTL activity against HT1376 cells, which endogenously express MPHOSPH1 and HLA-A24, was tested using the CTL clone raised by MPHOSPH1-A24-9-278 (SEQ ID NO: 7) as effector cells. J82 cells and RT-4 cells were used as the target cells which endogenously express MPHOSPH1 but do not express HLA-A24. The established CTL clone showed high IFN-gamma production against HT1376 cells that express both MPHOSPH1 and HLA-A24. On the other hand, The CTL did not show significant CTL activity against J82 and RT-4 cells which express MPHOSPH1 but not HLA-A24 (Figure 5). It clearly demonstrated that MPHOSPH1-A24-9-278 (SEQ ID NO: 7) peptide was naturally processed to the tumor cell surface with HLA-A24 molecule and recognized by CTL.

[0097] In vivo CTL induction with MPHOSPH1-A24-9-278 peptide in BALB/c mice

It has been known that H-2Kd molecule, one of the mouse MHC class I, has resemble peptide anchor motif for HLA-A24 molecule and partially cross-react HLA-A24 restricted peptide. The present inventors then examined whether MPHOSPH1-A24-9-278 peptide induce the CTL in vivo by vaccination with this peptide using BALB/c mice (H-2Kd). IFA-conjugated peptide was subcutaneously injected into BALB/c mice on the day 0 and 7. On day 14, splenocytes were harvested and used as the responder cells for ELISPOT assay. Splenocytes of all mice injected peptide (Ani1~5) showed potent IFN-gamma production compared with control mice, which were injected IFA alone (nega1~3) (Figure 6). This data indicated that

MPHOSPH1-A24-9-278 peptide could elicit CTL response even in vivo.

[0098] Stimulation of the T cells using the predicted peptides from MPHOSPH1 restricted with HLA-A*0201

Resulting CTLs having detectable specific CTL activity, as assessed by IFN-gamma ELISPOT assay, are shown in Figure 7. As shown in Figure 7A, the cells in the well number #1 and #5, stimulated with MPHOSPH1-A2-9-282 (YIYDLFVPV (SEQ ID NO: 9)) demonstrated potent IFN-gamma production as compared with the control. As shown in Figure 7B, the cells in the well number #8 stimulated with MPHOSPH1-A2-9-638 (RLAIFKDLV (SEQ ID NO: 10)) demonstrated potent IFN-gamma production as compared with the control. As shown in Figure 7C, the cells in the well number #4 stimulated with MPHOSPH1-A2-10-1714 (TMSSsKLSNV (SEQ ID NO: 11)) demonstrated potent IFN-gamma production as compared with the control.

[0099] As shown in figure 8A (MPHOSPH1-A2-9-282 (SEQ ID NO: 9)), figure 8B (MPHOSPH1-A2-9-638 (SEQ ID NO: 10)), and figure 8C (MPHOSPH1-A2-10-1714(SEQ ID NO: 9))., these cells in the positive well were expanded, and CTL lines having higher specific CTL activities against the peptide-pulsed target as compared to the activities against target without peptide pulse were established.

[0100] The CTL clones stimulated by the MPHOSPH1-A2-9-282 (YIYDLFVPV (SEQ ID NO: 9)) (Figure 9A, and 9B) demonstrated potent specific CTL activity against the peptide-pulsed target without any significant specific CTL activity against targets not pulsed with any peptide.

[0101] Stimulation of the T cells using the predicted peptides from DEPDC1 restricted with HLA-A*2402

CTLs for those peptides derived from DEPDC1 were generated according to the protocol described in "Materials and Methods" section above. Resulting CTLs having detectable specific CTL activity, as assessed by IFN-gamma ELISPOT assay, are shown in Figure 10. As shown in Figure 10A, the cells in the well number #10 stimulated with DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)) demonstrated potent IFN-gamma production as compared with the control. Accordingly, these cells in the positive well were expanded and limiting dilution was performed. As shown in Figure 10B (DEPDC1-A24-9-294 (SEQ ID NO: 12)), CTL clones having higher specific CTL activities against the peptide-pulsed target compared to the activities against target without peptide pulse were establishedThe CTL clones stimulated by the DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)) (Figure 11) demonstrated potent specific CTL activity against the peptide-pulsed target without showing any significant specific CTL activity against targets not pulsed with any peptide. The results

suggest that the CTL clone has the peptide-specific cytotoxicity.

[0102] Specific CTL activity against the target cells expressing DEPDC1 and HLA-A*2402

The established CTL clones raised against these peptides were examined for their ability to recognize the target cells endogenously expressing DEPDC1 and HLA-A*2402. Specific CTL activity against COS7 transfected both with the full length DEPDC1 gene and the HLA-A*2402 molecule, which serves as a specific model for the target cells endogenously express DEPDC1 and HLA-A*2402, was tested using as effector cells the CTL clone raised by DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)). COS7 transfected with full length DEPDC1 but not HLA-A*2402 and COS7 transfected with HLA-A*2402 but not full length DEPDC1 were prepared as controls. The CTL Clone demonstrated high specific CTL activity against COS7 transfected both DEPDC1 and HLA-A24. However, it did not demonstrate significant specific CTL activity against COS7 transfected neither DEPDC1 nor HLA-A24 (Figure 12).

[0103] These results clearly demonstrate that DEPDC1-A24-9-294 (EYYELFVNI (SEQ ID NO: 12)) is naturally expressed to the target cell surface with HLA-A24 molecule and recognized CTL.

[0104] CTL activity against bladder cancer cell lines endogenously expressing DEPDC1

The established CTL clone raised against DEPDC1-A24-9-294 peptide was examined for their ability to recognize the tumor cells endogenously expressing DEPDC1. CTL activity against HT1376 cells, which endogenously express DEPDC1 and HLA-A24, was tested using the CTL clone raised by DEPDC1-A24-9-294 as effector cells. J82 cells and RT-4 cells were used as the target cells which endogenously express DEPDC1 but do not express HLA-A24. The established CTL clone showed high IFN-gamma production against HT1376 cells that express both DEPDC1 and HLA-A24. On the other hand, it did not show significant CTL activity against J82 and RT-4 cells which express DEPDC1 but not HLA-A24 (Figure 13). It clearly demonstrated that DEPDC1-A24-9-294 was naturally processed to the tumor cell surface with HLA-A24 molecule and recognized by CTL.

[0105] In vivo CTL induction with DEPDC1-A24-9-294 peptide in BALB/c mice

It has been known that H-2Kd molecule, one of the mouse MHC class I, has resemble peptide anchor motif for HLA-A24 molecule and partially cross-react HLA-A24 restricted peptide. The present inventors then examined whether DEPDC1-A24-9-294 peptide induce the CTL in vivo by vaccination of this peptide using BALB/c mice (H-2Kd). IFA-conjugated peptide was subcutaneously injected into BALB/c mice on the day 0 and 7. On day 14, splenocytes were harvested and used as the responder cells for ELISPOT assay. Splenocytes of all mice injected peptide (Ani1~5) showed potent IFN-gamma production compared with control mice, which were injected IFA alone (nega1, 2) (Figure 14). This data indicated that

DEPDC1-A24-9-294 peptide could elicit CTL response even in vivo.

[0106] Stimulation of the T cells using the predicted peptides from DEPDC1 restricted with HLA-A*0201

Resulting CTLs having detectable specific CTL activity when screened by IFN-gamma ELISPOT assay are shown in Figure 15 and Table 6. The cells in the well number #4 and #7 stimulated with DEPDC1- A02-10-644 ((SLMIHTFSRC SEQ ID NO: 240)) showed potent IFN-gamma production compared with the control. The cells in the well number #2 stimulated with DEPDC1- A02-10-575 (SLLPASSMLT (SEQ ID NO: 241)) showed potent IFN-gamma production compared with the control. The cells in the well number #7 stimulated with DEPDC1- A02-10-506 (QLCRSQSLLL (SEQ ID NO: 243)) showed potent IFN-gamma production compared with the control. The cells in the well number #1 stimulated with DEPDC1- A02-10-765 (KQFQKEYPLI (SEQ ID NO: 244)) showed potent IFN-gamma production compared with the control. The cells in the well number #1 stimulated with DEPDC1-A02-10-395 (IMGGSCHNLI (SEQ ID NO: 249)) showed potent IFN-gamma production compared with the control. The cells in the well number #1 and #2 stimulated with DEPDC1- A02-10-224 (NMANTSKRGV (SEQ ID NO: 253)) showed potent IFN-gamma production compared with the control. The cells in the well number #4 stimulated with DEPDC1- A02-9-297 (ELFVNILGL (SEQ ID NO: 226)) showed potent IFN-gamma production compared with the control. The cells in the well number #3 and #4 stimulated with DEPDC1- A02-10-296 (YELFVNILGL (SEQ ID NO: 254)) showed potent IFN-gamma production compared with the control. The cells in the well number #2, #3, #5 and #7 stimulated with DEPDC1- A02-10-301 (NILGLLQPHL (SEQ ID NO: 255)) showed potent IFN-gamma production compared with the control. The cells in the well number #6 stimulated with DEPDC1-A02-9-598 (LLQPHLERV (SEQ ID NO: 192)) demonstrated potent IFN-gamma production as compared with the control. The cells in the well number #6 stimulated with DEPDC1-A02-9-619 (LLMRMISRM (SEQ ID NO: 195)) demonstrated potent IFN-gamma production as compared with the control. The cells in the well number #2 stimulated with DEPDC1-A02-9-290 (LLTFEYYEL (SEQ ID NO: 197)) demonstrated potent IFN-gamma production as compared with the control. The cells in the well number #5 stimulated with DEPDC1-A02-9-563 (RLCKSTIEL (SEQ ID NO: 209)) demonstrated potent IFN-gamma production as compared with the control. The cells in the well number #1 and #3, stimulated with DEPDC1-A02-9-653 (CVLCCAEEV (SEQ ID NO: 225)), demonstrated potent IFN-gamma production as compared with the control. The cells in the well number #1 stimulated with DEPDC1-A02-10-674 (FLMDhHQEIL (SEQ ID NO: 228)) demonstrated potent IFN-gamma production as compared with the control. Finally, the cells in the well number #2 and #6, stimulated

with DEPDC1-A02-10-302 (ILVVcGYITV (SEQ ID NO: 230)), demonstrated potent IFN-gamma production as compared with the control.

[0107] The CTL lines stimulated by the DEPDC1-A02-10-296 (YELFVNILGL (SEQ ID NO: 254)) and DEPDC1-A02-9-653 (CVLCCAEEV (SEQ ID NO: 225)) (Figure 16) showed potent specific CTL activity against the peptide-pulsed target without showing any significant specific CTL activity against targets not pulsed with any peptide. It demonstrates that the CTL clone has the peptide-specific cytotoxicity.

[0108] [Table 6]

The candidate peptides from DEPDC1 restricted with HLA-A*0201

peptide name	SEQ ID No.	Well No.
DEPDC1-A02-9-589	192	#6
DEPDC1-A02-9-619	195	#6
DEPDC1-A02-9-290	197	#2
DEPDC1-A02-9-563	209	#5
DEPDC1-A02-9-653	225	#1
DEPDC1-A02-9-653	225	#3
DEPDC1-A02-10-674	228	#1
DEPDC1-A02-10-302	230	#2
DEPDC1-A02-10-302	230	#6

[0109] Specific CTL activity against the target cells expressing DEPDC1 and HLA-A*0201

The established CTL lines raised against DEPDC1-A02-10-296 peptide (YELFVNILGL (SEQ ID NO: 254)) and DEPDC1-A02-9-653 (CVLCCAEEV (SEQ ID NO: 225)) were examined for their ability to recognize the target cells endogenously expressing DEPDC1 and HLA-A2. At first, we established HEK293 cell line constitutively expressed HLA-A*0201 (HEK-A2) to efficiently determine specific CTL response. Specific CTL activity against HEK-A2 cells transfected full length of DEPDC1 gene, which is specific model for the target cells expressed DEPDC1 and HLA-A2, was tested using the established CTL lines raised by DEPDC1-A02-10-296 (YELFVNILGL (SEQ ID NO: 254)) or DEPDC1-A02-9-653 (CVLCCAEEV (SEQ ID NO: 225)) as effector cells. HEK-A2 transfected Mock expressed vector and HEK-A2 pulsed with no corresponding peptide derived from DEPDC1 were prepared for the negative control. The established CTL lines showed specific CTL activity against HEK-A2 transfected DEPDC1. On the other hand, the CTL lines did not show significant specific CTL activity against HEK-A2 transfected Mock expressed vector and which pulsed DEPDC1-A02-9-674 peptide or DEPDC1-A02-9-462 peptide (Figure 17). It clearly demonstrated that DEPDC1-A02-10-296 and DEPDC1-A02-9-653

peptide was naturally processed to the target cell surface with HLA-A2 molecule and recognized by CTL.

[0110] Homology analysis of the antigen peptides

The CTLs established against peptides of this invention demonstrated potent specific CTL activity. This suggests that the sequences of MPHOSPH1-A24-9-278 (SEQ ID NO: 7), MPHOSPH1-A24-10-278 (SEQ ID NO: 8), MPHOSPH1-A2-9-282 (SEQ ID NO: 9), MPHOSPH1-A2-9-638 (SEQ ID NO: 10), MPHOSPH1-A2-10-1714 (SEQ ID NO: 11), DEPDC1-A24-9-294 (SEQ ID NO: 12), DEPDC1-A2-9-589 (SEQ ID NO: 192), DEPDC1-A2-9-619 (SEQ ID NO: 195), DEPDC1-A2-9-290 (SEQ ID NO: 197), DEPDC1-A2-9-563 (SEQ ID NO: 209), DEPDC1-A2-9-653 (SEQ ID NO: 225), DEPDC1-A2-10-674 (SEQ ID NO: 228), DEPDC1-A2-10-302 (SEQ ID NO: 230) DEPDC1-A02-10-644 (SEQ ID NO: 240), DEPDC1-A02-10-575 (SEQ ID NO: 241), DEPDC1-A02-10-506 (SEQ ID NO: 243), DEPDC1-A02-10-765 (SEQ ID NO: 244), DEPDC1- A02-10-395 (SEQ ID NO: 249), DEPDC1-A02-10-224 (SEQ ID NO: 253), DEPDC1- A02-9-297 (SEQ ID NO: 226), DEPDC1-A02-10-296 (SEQ ID NO: 254) and DEPDC1-A02-10-301 (SEQ ID NO: 255) are homologous to the peptides derived from other molecules, which are known to sensitize human immune system. To exclude this possibility, homology analysis was performed with the peptide sequences as queries using BLAST algorithm (http://www.ncbi.nlm.nih.gov/blast/blast.cgi) No significant sequence homology was revealed.

[0111] These results suggest that the sequences of MPHOSPH1-A24-9-278 (SEQ ID NO: 7), MPHOSPH1-A24-10-278 (SEQ ID NO: 8), MPHOSPH1-A2-9-282 (SEQ ID NO: 9), MPHOSPH1-A2-9-638 (SEQ ID NO: 10), MPHOSPH1-A2-10-1714 (SEQ ID NO: 11), DEPDC1-A24-9-294 (SEQ ID NO: 12), DEPDC1-A2-9-598 (SEQ ID NO: 192), DEPDC1-A2-9-619 (SEQ ID NO: 195), DEPDC1-A2-9-290 (SEQ ID NO: 197), DEPDC1-A2-9-563 (SEQ ID NO: 209), DEPDC1-A2-9-653 (SEQ ID NO: 225), DEPDC1-A2-10-674 (SEQ ID NO: 228), DEPDC1-A2-10-302 (SEQ ID NO: 230) DEPDC1-A02-10-644 (SEQ ID NO: 240), DEPDC1-A02-10-575 (SEQ ID NO: 241), DEPDC1-A02-10-506 (SEQ ID NO: 243), DEPDC1-A02-10-765 (SEQ ID NO: 244), DEPDC1- A02-10-395 (SEQ ID NO: 249), DEPDC1-A02-10-224 (SEQ ID NO: 253), DEPDC1-A02-9-297 (SEQ ID NO: 226), DEPDC1-A02-10-296 (SEQ ID NO: 254) and DEPDC1-A02-10-301 (SEQ ID NO: 255) are unique and thus possess a low risk of raising unintended immunologic response to any unrelated molecule.

[0112] DISCUSSION

Identification of new TAAs, particularly those that induce potent and specific anti-tumor immune responses, warrants further development of the clinical application of peptide vaccination strategies in various types of cancer (Boon T. et al., (1996) J Exp Med 183: 725-9.; van der Bruggen P et al., (1991) Science 254: 1643-7.; Brichard V et

al., (1993) J Exp Med 178: 489-95.; Kawakami Y et al., (1994) J Exp Med 180: 347-52.; Shichijo S et al., (1998) J Exp Med 187:277-88.; Chen YT et al., (1997) Proc.Natl.Acd. Sci. USA, 94: 1914-8.; Harris CC., (1996) J Natl Cancer Inst 88:1442-5.; Butterfield LH et al., (1999) Cancer Res 59:3134-42.; Vissers JL et al., (1999) Cancer Res 59: 5554-9.; van der Burg SH et al., (1996) J. Immunol 156:3308-14.; Tanaka F et al., (1997) Cancer Res 57:4465-8.; Fujie T et al., (1999) Int J Cancer 80:169-72.; Kikuchi M et al., (1999) Int J Cancer 81 : 459-66.; Oiso M et al., (1999) Int J Cancer 81:387-94.).

[0113] cDNA microarray technologies can disclose comprehensive profiles of gene expression of malignant cells (Lin YM, et al., Oncogene. 2002 Jun 13;21:4120-8.; Kitahara O, et al., Cancer Res. 2001 May 1;61:3544-9.; Suzuki C, et al., Cancer Res. 2003 Nov 1;63:7038-41.; Ashida S, Cancer Res. 2004 Sep 1;64:5963-72.; Ochi K, et al., Int J Oncol. 2004 Mar;24(3):647-55.; Kaneta Y, et al., Int J Oncol. 2003 Sep;23:681-91.; Obama K, Hepatology. 2005 Jun;41:1339-48.; Kato T, et al., Cancer Res. 2005 Jul 1;65:5638-46.; Kitahara O, et al., Neoplasia. 2002 Jul-Aug;4:295-303.; Saito-Hisaminato A et al., DNA Res 2002, 9: 35-45.) and, find utility in the identification of potential TAAs. Among the transcripts that are up-regulated in various cancers, two novel human genes, termed MPHOSPH1 and DEPDC1, respectively, were identified using these technologies.

[0114] As demonstrated above, MPHOSPH1 and DEPDC1, are over-expressed in various cancers but show minimal expression in normal tissues. In addition, these genes have been shown to have a significant function related to cell proliferation (See PCT/JP2006/302684). Thus, peptides derived from MPHOSPH1 and DEPDC1 can serve as TAA epitopes, which, in turn, can be used to induce significant and specific immune responses against cancer cells.

[0115] Thus, as MPHOSPH1 and DEPDC1 are novel TAAs, vaccines using these epitope peptides find utility as immunotherapeutics against various carcinomas or other disease expressing these molecules.

[0116] EXAMPLE 2

MATERIALS AND METHODS

Peptides and adjuvant

The synthesized GMP grade peptides were purchased from Neo Multi Peptide System (MPS) (San Diego, CA). As an adjuvant, incomplete Freund's adjuvant (IFA) (MONTANIDE *ISA51) were used. 1mg of the appropriate peptide was emulsioned with 1mg of IFA.

[0117] Antigen Expression

The present inventors performed immunohistochemical analysis. Tumor cells or tumor tissues from bladder cancers which was obtained from surgery or biopsy was

stained by each MPHOSPH1 and DEPDC1-specific polyclonal antibody. Protocol of staining was established in Human Genome Center, Institute for Medical Science, the University of Tokyo as described previously (Kanehira M et al. Cancer Res.;67(7):3276-3285, 2007., Kanehira M et al. Oncogene. 2007 Apr 23; [Epub ahead of print]). HLA-A*2402 expression was tested to performed at SRL (Tachikawa, Japan)

[0118] Enrolled patients

Enrolled criteria were as follows;

1. Patients with inoperable recurrent bladder cancer with previously treated with standard chemotherapy and turned to be failure.

2. Patients with performance status 0 or 1 in Japanese Criteria.

3. Patients from 20 years old to 80 years old

4. Patients with primary tumor or metastasis which can be recognized by image inspection (CT/MRI) before treatment, regardless of RECIST guideline

5. Patients with more than 4 weeks after prior treatment (surgery, chemotherapy, radiotherapy, thermotherapy, other immunotherapy etc.)

6. Patients expected more than 3 months prognosis

7. Patients with bone marrow function (WBC more than 2000, 15000 less than, plate more than 50000), liver function (GOT less than 150, GPT less than150, T-bil less than 3.0), renal function (Cr less than3.0)

8 Patients with HLA-A*2402

9 Tumor of the patients with expression of MPHOSPH1 and/or DEPDC1

[0119] Exclusion criteria were as follows;

1. Patients with pregnant

2. Patients with breast-feeding

3. Patients willing to be made pregnant

4. Patients with uncontrollable infection

5. Patients with necessity of following medicine in the period of clinical trial

systemic administration of steroid

systemic administration of immunosuppressant

6. Patients who are not thought to be enrolled this trial by doctor or principal investigator

[0120] Protocol

Enrolled bladder cancer patients with HLA-A*2402, whose tumors express M phase phosphoprotein 1 (MPHOSPH1) and/or DEP domain containing 1 (DEPDC1) were immunized with HLA-A*2402-restricted epitope peptides, MPHOSPH1-9-278 (IYNEYIYDL (SEQ ID NO: 7)) and/or DEPDC1-9-294 (EYYELFVNI (SEQ ID NO: 12)). Each peptide was combined with 1mL of incomplete Freund's adjuvant (IFA,

MONTANIDE *ISA51) and was subcutaneously injected into axillary or inguinal lesion once a week. Four times injection is defined as one course, then after 1 course for immunological and clinical evaluation, blood was drawn and CT/MRI was performed.

[0121] Evaluation of Safety

Evaluation of adverse effect was performed along with National Cancer Institute-Common Toxicity Criteria version 3, (NCI-CTC ver.3).

[0122] Immunological evaluation

This is one of secondary endpoint in this study and we confirm whether peptide-specific CTL response occurred or not. Specific CTL response was measure as follows; Peripheral blood mononuclear cells were collected, and re-stimulated by the appropriate peptides. CTL response was tested on the 14th day by IFN-g ELISPOT assay.

[0123] Evaluation of anti-tumor effects

Evaluation of clinical response was performed in accordance with RECIST criteria.

[0124] RESULTS

Table 7 showed the summary of this clinical trial. There were no severe adverse effects, except Grade 2 of exanthema of Case 3. One minor response (Case 3) and one mixed response (Case 4) were obtained. The expression of MPHOSPH1 was 4 of 5 cases, whereas that of DEPDC1 was 5 of 5 cases, respectively.

[0125] [Table 7]

The summary of this clinical trial

Case	Age/ Gender	Vaccination	Adv. Effect	DTH	Eva. Lesion	Eva.	Present Status	Ag expression MPHOSPH1	Ag expression DEPDC1	CTL
1	79/M	1 course	No	No	LNs, Brain	PD	1.8mo, dead	O	O	No
2	72/F	in 3 course	No	No	Local Rec	SD (4.5mo)	5.0mo, alive	O	O	NT
3	49/M	in 4 course	exanthema	No	Lung Mets	Minor Response	3.7mo, alive	×	O	Yes
4	74/M	in 2 course	No	No	Local Rec	Minor Response	1.4mo, alive	O	O	NT
5	78/M	in 2 course	No	No	Local Rec	SD	1.4mo, alive	O	O	NT

NT: not tested

[0126] Case 2

In case 2, 72 years old female with far advanced bladder cancer in standard chemotherapy failure was enrolled this clinical trial. In figure 18, the antigen expression of her tumor revealed both MPHOSPH1 and DEPDC1 were expressed strongly. Therefore, we have vaccinated two kinds of epitope peptides derived from MPHOSPH1 and DEPDC1. Case 2 had local recurrence of the bladder cancer. It was evaluated stable disease (SD) in accordance with RECIST criteria (Figure 19).

[0127] Cace 3

In case 3, 49 years old male with far advanced bladder cancer in standard

chemotherapy failure was enrolled this clinical trial. Only DEPDC1 was expressed strongly (Figure 20). Therefore, we have vaccinated the epitope peptide derived from DEPDC1 alone. Case 3 had multiple lung metastases of the bladder cancer. In right (Figure 21) and left (Figure 22) lobes of lung metastases, the progression rate was decreased after vaccination. Especially, the size of the tumor was decreased after 3rd courses. Figure 23 showed theanti-tumor effect in accordance with RECIST criteria. It was clarified that the progression rate of metastatic tumor was decreased after vaccination. It indicated that minor response was obtained by vaccination using epitope peptide derived from DEPDC1. In terms of immunological evaluation in case 3, specific CTL response was measured before and after vaccination. Specific CTL response was strongly shown after vaccination (Figure 24). It clearly indicated that CTL induced by epitope peptide derived from DEPDC1 may show the anti-tumor effect.

[0128] Cace 4

In case 4, 74 years old male with far advanced bladder cancer in standard chemotherapy failure was enrolled this clinical trial. MPHOSPH1 and DEPDC1 were expressed from his tumor (Figure 25). Therefore, we have vaccinated two kinds of epitope peptides derived from MPHOSPH1 and DEPDC1. Case 4 had local recurrence of the bladder cancer. After 1 course vaccination, the size of the tumor was reduced 20% in accordance with RECIST criteria (Figure 26). However, new metastatic lesions in the lung were appeared. It indicated that mixed response was obtained by vaccination using two kinds of epitope peptides derived from MPHOSPH1 and DEPDC1.

[0129] DISCUSSION

Rationale of this clinical trial is described blow;

1. Since MPHOSPH1 and DEPDC1 are not expressed in normal tissues except testis, both antigens are highly tumor-specific.

2. These peptides are considered to have strong immunogenicity, since potent and specific CTLs were established by these epitope peptides.

3. There is 60% of Japanese population with HLA-A*2402.

4. These peptides are chemically stable enough to apply to the clinical trial.

The purpose of this study is to obtain clinical information of its toxicity, immunological response and anti-tumor activity.

[0130] Previously reported adverse effects of vaccine clinical trial using peptides are fur-like symptom, such as fever, headache and discomfort. In rare cases, radical skin reaction with blisters, considered as transient cross reactivity at injected site, was reported. In this study, there were no severe adverse effects, except Grade 2 of exanthema of Case 3. This patient had clinical history to show exanthema during chemotherapy. It indicated that this adverse effect did not come from this vaccination, and therefore this

protocol may be safe.

[0131] Immunological analysis was performed by specific CTL induction after vaccination. In case 1, specific CTL response was not obtained after vaccination (data not shown). In case 3, specific CTL response against DEPDC1 derived peptide was clearly shown after 1st and 2nd course of vaccination. In case 3, anti-tumor effect was obtained by vaccination. It clearly demonstrated that this DEPDC1 derived peptide showed anti-tumor effect against bladder cancer by induction of the specific CTL.

[0132] In case 4, after only 1st course of vaccination, anti-tumor effect was clearly obtained against the local recurrence of the bladder cancer. This evidence strongly supports that these epitope peptides show anti-tumor effect against bladder cancer.

[0133] In conclusion, it was clarified that this epitope therapy was safe, and furthermore showed strong anti-tumor effect without severe adverse effects.

Industrial Applicability

[0134] The present invention identifies new TAAs, particularly those which induce potent and specific anti-tumor immune responses. Such TAAs warrant further development aspeptide vaccines against diseases associated with MPHOSPH1 and/or DEPDC1, e.g. cancers.

[0135] All patents, patent applications, and publications cited herein are incorporated by reference.

[0136] While the invention has been described in detail and with reference to specific embodiments thereof, it is to be understood that the foregoing description is exemplary and explanatory in nature and is intended to illustrate the invention and its preferred embodiments. Through routine experimentation, one skilled in the art will readily recognize that various changes and modifications can be made therein without departing from the spirit and scope of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

Claims

[1] An isolated peptide having cytotoxic T cell inducibility, wherein said peptide derived from amino acid sequence of SEQ ID NO: 2, 4, or 6.

[2] An isolated peptide of less than about 15 amino acids selected from the group consisting of peptides comprising the amino acid sequences of SEQ ID NO: 7, 8 and 12, or a peptide having cytotoxic T cell inducibility, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 7, 8 and 12, wherein 1, 2, or several amino acids are substituted, deleted, or added.

[3] The peptide having cytotoxic T cell inducibility of claim 2, wherein the second amino acid from the N-terminus is phenylalanine, tyrosine, methionine, or tryptophan.

[4] The peptide having cytotoxic T cell inducibility of claim 2, wherein the C-terminal amino acid is phenylalanine, leucine, isoleucine, tryptophan, or methionine.

[5] An isolated peptide of less than about 15 amino acids selected from the group consisting of peptides comprising the amino acid sequences of SEQ ID NO: 9, 10, 11, 192, 195, 197, 209, 225, 226, 228, 230, 240, 241, 243, 244, 253, 254 and 255, or a peptide having cytotoxic T cell inducibility, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9, 10, 11, 192, 195, 197, 209, 225, 226, 228, 230, 240, 241, 243, 244, 253, 254 and 255, wherein 1, 2, or several amino acids are substituted, deleted, or added.

[6] The peptide having cytotoxic T cell inducibility of claim 5, wherein the second amino acid from the N-terminus is leucine or methionine.

[7] The peptide having cytotoxic T cell inducibility of claim 5, wherein the C-terminal amino acid is valine or leucine.

[8] A vector in which the DNA encodes peptides of any one of claims 1 to 7.

[9] A pharmaceutical composition for treating or preventing a disease associated with over-expression of the genes of SEQ ID NO: 1, 3 and/or 5, said composition comprising one or more peptides of claim 2 or 5.

[10] The pharmaceutical composition of claim 9, wherein the disease is cancer.

[11] The pharmaceutical composition of claim 10, wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC and soft tissue tumor.

[12] An exosome that presents on its surface a complex comprising a peptide of claim

2 or 5 and an HLA antigen.

[13] The exosome of claim 12, wherein the HLA antigen is HLA-A24.

[14] The exosome of claim 13, wherein the HLA antigen is HLA-A2402.

[15] The exosome of claim 12, wherein the HLA antigen is HLA-A2.

[16] The exosome of claim 13, wherein the HLA antigen is HLA-A0201.

[17] A method of inducing antigen-presenting cells having a high cytotoxic T cell inducibility comprising the step of contacting an antigen-presenting cell with a peptide of claim 2 or 5.

[18] A method of inducing cytotoxic T cells by contacting a T cell with a peptide of claim 2 or 5.

[19] A method of inducing antigen-presenting cells having high cytotoxic T cell inducibility, said method comprising the step of transferring a gene comprising a polynucleotide encoding a peptide of claim 2 or 5 to an antigen-presenting cell.

[20] An isolated cytotoxic T cell, which is induced by contacting a T cell with a peptide of any one of claims 1 to 8 or which is transduced with the nucleic acids encoding the TCR subunits polypeptides binding with a peptide of any one claims 1 to 8 in the context of HLA-A24 or HLA-A2.

[21] An antigen-presenting cell, which comprises a complex formed between an HLA antigen and a peptide of claim 2 or 5.

[22] The antigen-presenting cell of claim 21, induced by the method of claim 17.

[23] A vaccine for inhibiting proliferation of cells expressing genes of SEQ ID NO: 1, 3 and/or 5, wherein the vaccine comprises a peptide of claim 2 or 5 as the active ingredient.

[24] The vaccine of claim 23, wherein the cell is a cancer cell.

[25] The vaccine of claim 24, wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma, CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC and soft tissue tumor.

[26] The vaccine of claim 23, formulated for administration to a subject whose HLA antigen is HLA-A24 or HLA-A2.

[27] A method of treating or preventing a disease associated with the over-expression of the genes of SEQ ID NO: 1, 3 and/or 5 in a subject comprising administering to said subject a vaccine comprising one or more peptide of claim 2 or 5, an immunologically active fragment thereof, or a polynucleotide encoding said peptide or immunologically active fragment.

[28] The method of claim 27, wherein the disease is cancer.

[29] The method of claim 28, wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, cervical cancer, cholangincellular carcinoma,

CML, colorectal cancer, gastric cancer, NSCLC, lymphoma, osteosarcoma, prostate cancer, renal carcinoma, SCLC and soft tissue tumor.

SEQUENCE LISTING

<110> ONCOTHERAPY SCIENCE, INC.
THE UNIVERSITY OF TOKYO
FUJIOKA, Tomoaki

<120> PEPTIDE VACCINES FOR CANCERS EXPRESSING MPHOSPH1 OR DEPDC1 POLYPEPTIDES

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Arg Leu Ala Ile Phe Lys Asp Leu Val Gly Lys Cys Asp Thr Arg Glu
        640                 645                 650

gaa gca gcg aaa gac att tgt gcc aca aaa gtt gaa act gaa gaa gct     2079
Glu Ala Ala Lys Asp Ile Cys Ala Thr Lys Val Glu Thr Glu Glu Ala
    655                 660                 665

act gct tgt tta gaa cta aag ttt aat caa att aaa gct gaa tta gct     2127
Thr Ala Cys Leu Glu Leu Lys Phe Asn Gln Ile Lys Ala Glu Leu Ala
670                 675                 680                 685

aaa acc aaa gga gaa tta atc aaa acc aaa gaa gag tta aaa aag aga     2175
Lys Thr Lys Gly Glu Leu Ile Lys Thr Lys Glu Glu Leu Lys Lys Arg
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                690                 695                 700

gaa aat gaa tca gat tca ttg att caa gag ctt gag aca tct aat aag      2223
Glu Asn Glu Ser Asp Ser Leu Ile Gln Glu Leu Glu Thr Ser Asn Lys
            705                 710                 715

aaa ata att aca cag aat caa aga att aaa gaa ttg ata aat ata att      2271
Lys Ile Ile Thr Gln Asn Gln Arg Ile Lys Glu Leu Ile Asn Ile Ile
        720                 725                 730

gat caa aaa gaa gat act atc aac gaa ttt cag aac cta aag tct cat      2319
Asp Gln Lys Glu Asp Thr Ile Asn Glu Phe Gln Asn Leu Lys Ser His
    735                 740                 745

atg gaa aac aca ttt aaa tgc aat gac aag gct gat aca tct tct tta      2367
Met Glu Asn Thr Phe Lys Cys Asn Asp Lys Ala Asp Thr Ser Ser Leu
750                 755                 760                 765

ata ata aac aat aaa ttg att tgt aat gaa aca gtt gaa gta cct aag      2415
Ile Ile Asn Asn Lys Leu Ile Cys Asn Glu Thr Val Glu Val Pro Lys
                770                 775                 780

gac agc aaa tct aaa atc tgt tca gaa aga aaa aga gta aat gaa aat      2463
Asp Ser Lys Ser Lys Ile Cys Ser Glu Arg Lys Arg Val Asn Glu Asn
            785                 790                 795

gaa ctt cag caa gat gaa cca cca gca aag aaa ggg tct atc cat gtt      2511
Glu Leu Gln Gln Asp Glu Pro Pro Ala Lys Lys Gly Ser Ile His Val
        800                 805                 810

agt tca gct atc act gaa gac caa aag aaa agt gaa gaa gtg cga ccg      2559
Ser Ser Ala Ile Thr Glu Asp Gln Lys Lys Ser Glu Glu Val Arg Pro
    815                 820                 825

aac att gca gaa att gaa gac atc aga gtt tta caa gaa aat aat gaa      2607
Asn Ile Ala Glu Ile Glu Asp Ile Arg Val Leu Gln Glu Asn Asn Glu
830                 835                 840                 845

gga ctg aga gca ttt tta ctc act att gag aat gaa ctt aaa aat gaa      2655
Gly Leu Arg Ala Phe Leu Leu Thr Ile Glu Asn Glu Leu Lys Asn Glu
                850                 855                 860

aag gaa gaa aaa gca gaa tta aat aaa cag att gtt cat ttt cag cag      2703
Lys Glu Glu Lys Ala Glu Leu Asn Lys Gln Ile Val His Phe Gln Gln
            865                 870                 875

gaa ctt tct ctt tct gaa aaa aag aat tta act tta agt aaa gag gtc      2751
Glu Leu Ser Leu Ser Glu Lys Lys Asn Leu Thr Leu Ser Lys Glu Val
        880                 885                 890

caa caa att cag tca aat tat gat att gca att gct gaa tta cat gtg      2799
Gln Gln Ile Gln Ser Asn Tyr Asp Ile Ala Ile Ala Glu Leu His Val
    895                 900                 905

cag aaa agt aaa aat caa gaa cag gag gaa aag atc atg aaa ttg tca      2847
Gln Lys Ser Lys Asn Gln Glu Gln Glu Glu Lys Ile Met Lys Leu Ser
910                 915                 920                 925

aat gag ata gaa act gct aca aga agc att aca aat aat gtt tca caa      2895
Asn Glu Ile Glu Thr Ala Thr Arg Ser Ile Thr Asn Asn Val Ser Gln
                930                 935                 940

ata aaa tta atg cac acg aaa ata gac gaa cta cgt act ctt gat tca      2943
Ile Lys Leu Met His Thr Lys Ile Asp Glu Leu Arg Thr Leu Asp Ser
            945                 950                 955

gtt tct cag att tca aac ata gat ttg ctc aat ctc agg gat ctg tca      2991
Val Ser Gln Ile Ser Asn Ile Asp Leu Leu Asn Leu Arg Asp Leu Ser
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960 965 970

aat ggt tct gag gag gat aat ttg cca aat aca cag tta gac ctt tta 3039
Asn Gly Ser Glu Glu Asp Asn Leu Pro Asn Thr Gln Leu Asp Leu Leu
975 980 985

ggt aat gat tat ttg gta agt aag caa gtt aaa gaa tat cga att caa 3087
Gly Asn Asp Tyr Leu Val Ser Lys Gln Val Lys Glu Tyr Arg Ile Gln
990 995 1000 1005

gaa ccc aat agg gaa aat tct ttc cac tct agt att gaa gct att 3132
Glu Pro Asn Arg Glu Asn Ser Phe His Ser Ser Ile Glu Ala Ile
1010 1015 1020

tgg gaa gaa tgt aaa gag att gtg aag gcc tct tcc aaa aaa agt 3177
Trp Glu Glu Cys Lys Glu Ile Val Lys Ala Ser Ser Lys Lys Ser
1025 1030 1035

cat cag att gag gaa ctg gaa caa caa att gaa aaa ttg cag gca 3222
His Gln Ile Glu Glu Leu Glu Gln Gln Ile Glu Lys Leu Gln Ala
1040 1045 1050

gaa gta aaa ggc tat aag gat gaa aac aat aga cta aag gag aag 3267
Glu Val Lys Gly Tyr Lys Asp Glu Asn Asn Arg Leu Lys Glu Lys
1055 1060 1065

gag cat aaa aac caa gat gac cta cta aaa gaa aaa gaa act ctt 3312
Glu His Lys Asn Gln Asp Asp Leu Leu Lys Glu Lys Glu Thr Leu
1070 1075 1080

ata cag cag ctg aaa gaa gaa ttg caa gaa aaa aat gtt act ctt 3357
Ile Gln Gln Leu Lys Glu Glu Leu Gln Glu Lys Asn Val Thr Leu
1085 1090 1095

gat gtt caa ata cag cat gta gtt gaa gga aag aga gcg ctt tca 3402
Asp Val Gln Ile Gln His Val Val Glu Gly Lys Arg Ala Leu Ser
1100 1105 1110

gaa ctt aca caa ggt gtt act tgc tat aag gca aaa ata aag gaa 3447
Glu Leu Thr Gln Gly Val Thr Cys Tyr Lys Ala Lys Ile Lys Glu
1115 1120 1125

ctt gaa aca att tta gag act cag aaa gtt gaa tgt agt cat tca 3492
Leu Glu Thr Ile Leu Glu Thr Gln Lys Val Glu Cys Ser His Ser
1130 1135 1140

gcc aag tta gaa caa gac att ttg gaa aag gaa tct atc atc tta 3537
Ala Lys Leu Glu Gln Asp Ile Leu Glu Lys Glu Ser Ile Ile Leu
1145 1150 1155

aag cta gaa aga aat ttg aag gaa ttt caa gaa cat ctt cag gat 3582
Lys Leu Glu Arg Asn Leu Lys Glu Phe Gln Glu His Leu Gln Asp
1160 1165 1170

tct gtc aaa aac acc aaa gat tta aat gta aag gaa ctc aag ctg 3627
Ser Val Lys Asn Thr Lys Asp Leu Asn Val Lys Glu Leu Lys Leu
1175 1180 1185

aaa gaa gaa atc aca cag tta aca aat aat ttg caa gat atg aaa 3672
Lys Glu Glu Ile Thr Gln Leu Thr Asn Asn Leu Gln Asp Met Lys
1190 1195 1200

cat tta ctt caa tta aaa gaa gaa gaa gaa gaa acc aac agg caa 3717
His Leu Leu Gln Leu Lys Glu Glu Glu Glu Glu Thr Asn Arg Gln
1205 1210 1215

gaa aca gaa aaa ttg aaa gag gaa ctc tct gca agc tct gct cgt 3762
Glu Thr Glu Lys Leu Lys Glu Glu Leu Ser Ala Ser Ser Ala Arg

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                1220                1225                1230

acc cag aat ctg aaa  gca gat ctt cag agg  aag gaa gaa gat tat      3807
Thr Gln Asn Leu Lys  Ala Asp Leu Gln Arg  Lys Glu Glu Asp Tyr
                1235                1240                1245

gct gac ctg aaa gag  aaa ctg act gat gcc  aaa aag cag att aag      3852
Ala Asp Leu Lys Glu  Lys Leu Thr Asp Ala  Lys Lys Gln Ile Lys
                1250                1255                1260

caa gta cag aaa gag  gta tct gta atg cgt  gat gag gat aaa tta      3897
Gln Val Gln Lys Glu  Val Ser Val Met Arg  Asp Glu Asp Lys Leu
                1265                1270                1275

ctg agg att aaa att  aat gaa ctg gag aaa  aag aaa aac cag tgt      3942
Leu Arg Ile Lys Ile  Asn Glu Leu Glu Lys  Lys Lys Asn Gln Cys
                1280                1285                1290

tct cag gaa tta gat  atg aaa cag cga acc  att cag caa ctc aag      3987
Ser Gln Glu Leu Asp  Met Lys Gln Arg Thr  Ile Gln Gln Leu Lys
                1295                1300                1305

gag cag tta aat aat  cag aaa gtg gaa gaa  gct ata caa cag tat      4032
Glu Gln Leu Asn Asn  Gln Lys Val Glu Glu  Ala Ile Gln Gln Tyr
                1310                1315                1320

gag aga gca tgc aaa  gat cta aat gtt aaa  gag aaa ata att gaa      4077
Glu Arg Ala Cys Lys  Asp Leu Asn Val Lys  Glu Lys Ile Ile Glu
                1325                1330                1335

gac atg cga atg aca  cta gaa gaa cag gaa  caa act cag gta gaa      4122
Asp Met Arg Met Thr  Leu Glu Glu Gln Glu  Gln Thr Gln Val Glu
                1340                1345                1350

cag gat caa gtg ctt  gag gct aaa tta gag  gaa gtt gaa agg ctg      4167
Gln Asp Gln Val Leu  Glu Ala Lys Leu Glu  Glu Val Glu Arg Leu
                1355                1360                1365

gcc aca gaa ttg gaa  aaa tgg aag gaa aaa  tgc aat gat ttg gaa      4212
Ala Thr Glu Leu Glu  Lys Trp Lys Glu Lys  Cys Asn Asp Leu Glu
                1370                1375                1380

acc aaa aac aat caa  agg tca aat aaa gaa  cat gag aac aac aca      4257
Thr Lys Asn Asn Gln  Arg Ser Asn Lys Glu  His Glu Asn Asn Thr
                1385                1390                1395

gat gtg ctt gga aag  ctc act aat ctt caa  gat gag tta cag gag      4302
Asp Val Leu Gly Lys  Leu Thr Asn Leu Gln  Asp Glu Leu Gln Glu
                1400                1405                1410

tct gaa cag aaa tat  aat gct gat aga aag  aaa tgg tta gaa gaa      4347
Ser Glu Gln Lys Tyr  Asn Ala Asp Arg Lys  Lys Trp Leu Glu Glu
                1415                1420                1425

aaa atg atg ctt atc  act caa gcg aaa gaa  gca gag aat ata cga      4392
Lys Met Met Leu Ile  Thr Gln Ala Lys Glu  Ala Glu Asn Ile Arg
                1430                1435                1440

aat aaa gag atg aaa  aaa tat gct gag gac  agg gag cgt ttt ttt      4437
Asn Lys Glu Met Lys  Lys Tyr Ala Glu Asp  Arg Glu Arg Phe Phe
                1445                1450                1455

aag caa cag aat gaa  atg gaa ata ctg aca  gcc cag ctg aca gag      4482
Lys Gln Gln Asn Glu  Met Glu Ile Leu Thr  Ala Gln Leu Thr Glu
                1460                1465                1470

aaa gat agt gac ctt  caa aag tgg cga gaa  gaa cga gat caa ctg      4527
Lys Asp Ser Asp Leu  Gln Lys Trp Arg Glu  Glu Arg Asp Gln Leu
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                1475                1480                1485

gtt gca gct tta gaa  ata cag cta aaa gca  ctg ata tcc agt aat      4572
Val Ala Ala Leu Glu  Ile Gln Leu Lys Ala  Leu Ile Ser Ser Asn
                1490                1495                1500

gta cag aaa gat aat  gaa att gaa caa cta  aaa agg atc ata tca      4617
Val Gln Lys Asp Asn  Glu Ile Glu Gln Leu  Lys Arg Ile Ile Ser
                1505                1510                1515

gag act tct aaa ata  gaa aca caa atc atg  gat atc aag ccc aaa      4662
Glu Thr Ser Lys Ile  Glu Thr Gln Ile Met  Asp Ile Lys Pro Lys
                1520                1525                1530

cgt att agt tca gca  gat cct gac aaa ctt  caa act gaa cct cta      4707
Arg Ile Ser Ser Ala  Asp Pro Asp Lys Leu  Gln Thr Glu Pro Leu
                1535                1540                1545

tcg aca agt ttt gaa  att tcc aga aat aaa  ata gag gat gga tct      4752
Ser Thr Ser Phe Glu  Ile Ser Arg Asn Lys  Ile Glu Asp Gly Ser
                1550                1555                1560

gta gtc ctt gac tct  tgt gaa gtg tca aca  gaa aat gat caa agc      4797
Val Val Leu Asp Ser  Cys Glu Val Ser Thr  Glu Asn Asp Gln Ser
                1565                1570                1575

act cga ttt cca aaa  cct gag tta gag att  caa ttt aca cct tta      4842
Thr Arg Phe Pro Lys  Pro Glu Leu Glu Ile  Gln Phe Thr Pro Leu
                1580                1585                1590

cag cca aac aaa atg  gca gtg aaa cac cct  ggt tgt acc aca cca      4887
Gln Pro Asn Lys Met  Ala Val Lys His Pro  Gly Cys Thr Thr Pro
                1595                1600                1605

gtg aca gtt aag att  ccc aag gct cgg aag  agg aag agt aat gaa      4932
Val Thr Val Lys Ile  Pro Lys Ala Arg Lys  Arg Lys Ser Asn Glu
                1610                1615                1620

atg gag gag gac ttg  gtg aaa tgt gaa aat  aag aag aat gct aca      4977
Met Glu Glu Asp Leu  Val Lys Cys Glu Asn  Lys Lys Asn Ala Thr
                1625                1630                1635

ccc aga act aat ttg  aaa ttt cct att tca  gat gat aga aat tct      5022
Pro Arg Thr Asn Leu  Lys Phe Pro Ile Ser  Asp Asp Arg Asn Ser
                1640                1645                1650

tct gtc aaa aag gaa  caa aag gtt gcc ata  cgt cca tca tct aag      5067
Ser Val Lys Lys Glu  Gln Lys Val Ala Ile  Arg Pro Ser Ser Lys
                1655                1660                1665

aaa aca tat tct tta  cgg agt cag gca tcc  ata att ggt gta aac      5112
Lys Thr Tyr Ser Leu  Arg Ser Gln Ala Ser  Ile Ile Gly Val Asn
                1670                1675                1680

ctg gcc act aag aaa  aaa gaa gga aca cta  cag aaa ttt gga gac      5157
Leu Ala Thr Lys Lys  Lys Glu Gly Thr Leu  Gln Lys Phe Gly Asp
                1685                1690                1695

ttc tta caa cat tct  ccc tca att ctt caa  tca aaa gca aag aag      5202
Phe Leu Gln His Ser  Pro Ser Ile Leu Gln  Ser Lys Ala Lys Lys
                1700                1705                1710

ata att gaa aca atg  agc tct tca aag ctc  tca aat gta gaa gca      5247
Ile Ile Glu Thr Met  Ser Ser Ser Lys Leu  Ser Asn Val Glu Ala
                1715                1720                1725

agt aaa gaa aat gtg  tct caa cca aaa cga  gcc aaa cgg aaa tta      5292
Ser Lys Glu Asn Val  Ser Gln Pro Lys Arg  Ala Lys Arg Lys Leu
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                1730                1735                1740

tac aca agt gaa att  tca tct cct att gat  ata tca ggc caa gtg       5337
Tyr Thr Ser Glu Ile  Ser Ser Pro Ile Asp  Ile Ser Gly Gln Val
                1745                1750                1755

att tta atg gac cag  aaa atg aag gag agt  gat cac cag att atc       5382
Ile Leu Met Asp Gln  Lys Met Lys Glu Ser  Asp His Gln Ile Ile
                1760                1765                1770

aaa cga cga ctt cga  aca aaa aca gcc aaa  taa atcacttatg            5425
Lys Arg Arg Leu Arg  Thr Lys Thr Ala Lys
                1775                1780

gaaatgttta atataaattt tatagtcata gtcattggaa cttgcatcct gtattgtaaa   5485

tataaatgta tatattatgc attaaatcac tctgcatata gattgctgtt ttatacatag   5545

tataatttta attcaataaa tgagtcaaaa tttgtatatt tttataaggc ttttttataa   5605

tagcttcttt caaactgtat ttccctatta tctcagacat tggatcagtg aagatcctag   5665

gaaagaggct gttattctca tttattttgc tatacaggat gtaataggtc aggtatttgg   5725

tttacttata tttaacaatg tcttatgaat tttttttact ttatctgtta tacaactgat   5785

tttacatatc tgtttggatt atagctagga tttggagaat aagtgtgtac agatcacaaa   5845

acatgtatat acattattta gaaaagatct caagtcttta attagaatgt ctcacttatt   5905

ttgtaaacat tttgtgggta catagtacat gtatatattt acggggtatg tgagatgttt   5965

tgacacaggc atgcaatgtg aaatacgtgt atcatggaga atgaggtatc catcccctca   6025

agcatttttc ctttgaatta cagataatcc aattacattc tttagatcat ttaaaaatat   6085

acaagtaagt tattattgat tatagtcact ctattgtgct atcagatagt agatcattct   6145

ttttatctta tttgtttttg tacccattaa ccatccccac ctccccctgc aaccgtcagt   6205

acccttacca gccactggta accattcttc tactctgtat gcccatgagg tcaattgatt   6265

ttatttttag atcccataaa taaatgagaa catgcagtct ttgtcaaaaa aaaa         6319
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<210> 2
<211> 1780
<212> PRT
<213> Homo sapiens

<400> 2

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Met Glu Ser Asn Phe Asn Gln Glu Gly Val Pro Arg Pro Ser Tyr Val
1               5                  10                  15

Phe Ser Ala Asp Pro Ile Ala Arg Pro Ser Glu Ile Asn Phe Asp Gly
            20                  25                  30

Ile Lys Leu Asp Leu Ser His Glu Phe Ser Leu Val Ala Pro Asn Thr
        35                  40                  45

Glu Ala Asn Ser Phe Glu Ser Lys Asp Tyr Leu Gln Val Cys Leu Arg
    50                  55                  60
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Ile Arg Pro Phe Thr Gln Ser Glu Lys Glu Leu Glu Ser Glu Gly Cys
65                  70                  75                  80

Val His Ile Leu Asp Ser Gln Thr Val Val Leu Lys Glu Pro Gln Cys
                85                  90                  95

Ile Leu Gly Arg Leu Ser Glu Lys Ser Ser Gly Gln Met Ala Gln Lys
            100                 105                 110

Phe Ser Phe Ser Lys Val Phe Gly Pro Ala Thr Thr Gln Lys Glu Phe
        115                 120                 125

Phe Gln Gly Cys Ile Met Gln Pro Val Lys Asp Leu Leu Lys Gly Gln
    130                 135                 140

Ser Arg Leu Ile Phe Thr Tyr Gly Leu Thr Asn Ser Gly Lys Thr Tyr
145                 150                 155                 160

Thr Phe Gln Gly Thr Glu Glu Asn Ile Gly Ile Leu Pro Arg Thr Leu
                165                 170                 175

Asn Val Leu Phe Asp Ser Leu Gln Glu Arg Leu Tyr Thr Lys Met Asn
            180                 185                 190

Leu Lys Pro His Arg Ser Arg Glu Tyr Leu Arg Leu Ser Ser Glu Gln
        195                 200                 205

Glu Lys Glu Glu Ile Ala Ser Lys Ser Ala Leu Leu Arg Gln Ile Lys
    210                 215                 220

Glu Val Thr Val His Asn Asp Ser Asp Asp Thr Leu Tyr Gly Ser Leu
225                 230                 235                 240

Thr Asn Ser Leu Asn Ile Ser Glu Phe Glu Glu Ser Ile Lys Asp Tyr
                245                 250                 255

Glu Gln Ala Asn Leu Asn Met Ala Asn Ser Ile Lys Phe Ser Val Trp
            260                 265                 270

Val Ser Phe Phe Glu Ile Tyr Asn Glu Tyr Ile Tyr Asp Leu Phe Val
        275                 280                 285

Pro Val Ser Ser Lys Phe Gln Lys Arg Lys Met Leu Arg Leu Ser Gln
    290                 295                 300

Asp Val Lys Gly Tyr Ser Phe Ile Lys Asp Leu Gln Trp Ile Gln Val
305                 310                 315                 320

Ser Asp Ser Lys Glu Ala Tyr Arg Leu Leu Lys Leu Gly Ile Lys His
                325                 330                 335
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Gln Ser Val Ala Phe Thr Lys Leu Asn Asn Ala Ser Ser Arg Ser His
            340                 345                 350

Ser Ile Phe Thr Val Lys Ile Leu Gln Ile Glu Asp Ser Glu Met Ser
        355                 360                 365

Arg Val Ile Arg Val Ser Glu Leu Ser Leu Cys Asp Leu Ala Gly Ser
    370                 375                 380

Glu Arg Thr Met Lys Thr Gln Asn Glu Gly Glu Arg Leu Arg Glu Thr
385                 390                 395                 400

Gly Asn Ile Asn Thr Ser Leu Leu Thr Leu Gly Lys Cys Ile Asn Val
                405                 410                 415

Leu Lys Asn Ser Glu Lys Ser Lys Phe Gln Gln His Val Pro Phe Arg
            420                 425                 430

Glu Ser Lys Leu Thr His Tyr Phe Gln Ser Phe Phe Asn Gly Lys Gly
        435                 440                 445

Lys Ile Cys Met Ile Val Asn Ile Ser Gln Cys Tyr Leu Ala Tyr Asp
    450                 455                 460

Glu Thr Leu Asn Val Leu Lys Phe Ser Ala Ile Ala Gln Lys Val Cys
465                 470                 475                 480

Val Pro Asp Thr Leu Asn Ser Ser Gln Glu Lys Leu Phe Gly Pro Val
                485                 490                 495

Lys Ser Ser Gln Asp Val Ser Leu Asp Ser Asn Ser Asn Ser Lys Ile
            500                 505                 510

Leu Asn Val Lys Arg Ala Thr Ile Ser Trp Glu Asn Ser Leu Glu Asp
        515                 520                 525

Leu Met Glu Asp Glu Asp Leu Val Glu Glu Leu Glu Asn Ala Glu Glu
    530                 535                 540

Thr Gln Asn Val Glu Thr Lys Leu Leu Asp Glu Asp Leu Asp Lys Thr
545                 550                 555                 560

Leu Glu Glu Asn Lys Ala Phe Ile Ser His Glu Glu Lys Arg Lys Leu
                565                 570                 575

Leu Asp Leu Ile Glu Asp Leu Lys Lys Lys Leu Ile Asn Glu Lys Lys
            580                 585                 590

Glu Lys Leu Thr Leu Glu Phe Lys Ile Arg Glu Glu Val Thr Gln Glu
        595                 600                 605
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Phe Thr Gln Tyr Trp Ala Gln Arg Glu Ala Asp Phe Lys Glu Thr Leu
    610                 615                 620

Leu Gln Glu Arg Glu Ile Leu Glu Glu Asn Ala Glu Arg Arg Leu Ala
625                 630                 635                 640

Ile Phe Lys Asp Leu Val Gly Lys Cys Asp Thr Arg Glu Glu Ala Ala
                645                 650                 655

Lys Asp Ile Cys Ala Thr Lys Val Glu Thr Glu Glu Ala Thr Ala Cys
            660                 665                 670

Leu Glu Leu Lys Phe Asn Gln Ile Lys Ala Glu Leu Ala Lys Thr Lys
        675                 680                 685

Gly Glu Leu Ile Lys Thr Lys Glu Glu Leu Lys Lys Arg Glu Asn Glu
    690                 695                 700

Ser Asp Ser Leu Ile Gln Glu Leu Glu Thr Ser Asn Lys Lys Ile Ile
705                 710                 715                 720

Thr Gln Asn Gln Arg Ile Lys Glu Leu Ile Asn Ile Ile Asp Gln Lys
                725                 730                 735

Glu Asp Thr Ile Asn Glu Phe Gln Asn Leu Lys Ser His Met Glu Asn
            740                 745                 750

Thr Phe Lys Cys Asn Asp Lys Ala Asp Thr Ser Ser Leu Ile Ile Asn
        755                 760                 765

Asn Lys Leu Ile Cys Asn Glu Thr Val Glu Val Pro Lys Asp Ser Lys
    770                 775                 780

Ser Lys Ile Cys Ser Glu Arg Lys Arg Val Asn Glu Asn Glu Leu Gln
785                 790                 795                 800

Gln Asp Glu Pro Pro Ala Lys Lys Gly Ser Ile His Val Ser Ser Ala
                805                 810                 815

Ile Thr Glu Asp Gln Lys Lys Ser Glu Glu Val Arg Pro Asn Ile Ala
            820                 825                 830

Glu Ile Glu Asp Ile Arg Val Leu Gln Glu Asn Asn Glu Gly Leu Arg
        835                 840                 845

Ala Phe Leu Leu Thr Ile Glu Asn Glu Leu Lys Asn Glu Lys Glu Glu
    850                 855                 860

Lys Ala Glu Leu Asn Lys Gln Ile Val His Phe Gln Gln Glu Leu Ser
865                 870                 875                 880
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Leu Ser Glu Lys Lys Asn Leu Thr Leu Ser Lys Glu Val Gln Gln Ile
                885                 890                 895

Gln Ser Asn Tyr Asp Ile Ala Ile Ala Glu Leu His Val Gln Lys Ser
            900                 905                 910

Lys Asn Gln Glu Gln Glu Glu Lys Ile Met Lys Leu Ser Asn Glu Ile
        915                 920                 925

Glu Thr Ala Thr Arg Ser Ile Thr Asn Asn Val Ser Gln Ile Lys Leu
    930                 935                 940

Met His Thr Lys Ile Asp Glu Leu Arg Thr Leu Asp Ser Val Ser Gln
945                 950                 955                 960

Ile Ser Asn Ile Asp Leu Leu Asn Leu Arg Asp Leu Ser Asn Gly Ser
                965                 970                 975

Glu Glu Asp Asn Leu Pro Asn Thr Gln Leu Asp Leu Leu Gly Asn Asp
            980                 985                 990

Tyr Leu Val Ser Lys Gln Val Lys  Glu Tyr Arg Ile Gln  Glu Pro Asn
        995                 1000                1005

Arg Glu  Asn Ser Phe His Ser  Ser Ile Glu Ala Ile  Trp Glu Glu
    1010                1015                1020

Cys Lys  Glu Ile Val Lys Ala  Ser Ser Lys Lys Ser  His Gln Ile
    1025                1030                1035

Glu Glu  Leu Glu Gln Gln Ile  Glu Lys Leu Gln Ala  Glu Val Lys
    1040                1045                1050

Gly Tyr  Lys Asp Glu Asn Asn  Arg Leu Lys Glu Lys  Glu His Lys
    1055                1060                1065

Asn Gln  Asp Asp Leu Leu Lys  Glu Lys Glu Thr Leu  Ile Gln Gln
    1070                1075                1080

Leu Lys  Glu Glu Leu Gln Glu  Lys Asn Val Thr Leu  Asp Val Gln
    1085                1090                1095

Ile Gln  His Val Val Glu Gly  Lys Arg Ala Leu Ser  Glu Leu Thr
    1100                1105                1110

Gln Gly  Val Thr Cys Tyr Lys  Ala Lys Ile Lys Glu  Leu Glu Thr
    1115                1120                1125

Ile Leu  Glu Thr Gln Lys Val  Glu Cys Ser His Ser  Ala Lys Leu
    1130                1135                1140
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Glu Gln  Asp Ile Leu Glu Lys  Glu Ser Ile Ile Leu  Lys Leu Glu
    1145                 1150                 1155

Arg Asn  Leu Lys Glu Phe Gln  Glu His Leu Gln Asp  Ser Val Lys
    1160                 1165                 1170

Asn Thr  Lys Asp Leu Asn Val  Lys Glu Leu Lys Leu  Lys Glu Glu
    1175                 1180                 1185

Ile Thr  Gln Leu Thr Asn Asn  Leu Gln Asp Met Lys  His Leu Leu
    1190                 1195                 1200

Gln Leu  Lys Glu Glu Glu Glu  Glu Thr Asn Arg Gln  Glu Thr Glu
    1205                 1210                 1215

Lys Leu  Lys Glu Glu Leu Ser  Ala Ser Ser Ala Arg  Thr Gln Asn
    1220                 1225                 1230

Leu Lys  Ala Asp Leu Gln Arg  Lys Glu Glu Asp Tyr  Ala Asp Leu
    1235                 1240                 1245

Lys Glu  Lys Leu Thr Asp Ala  Lys Lys Gln Ile Lys  Gln Val Gln
    1250                 1255                 1260

Lys Glu  Val Ser Val Met Arg  Asp Glu Asp Lys Leu  Leu Arg Ile
    1265                 1270                 1275

Lys Ile  Asn Glu Leu Glu Lys  Lys Lys Asn Gln Cys  Ser Gln Glu
    1280                 1285                 1290

Leu Asp  Met Lys Gln Arg Thr  Ile Gln Gln Leu Lys  Glu Gln Leu
    1295                 1300                 1305

Asn Asn  Gln Lys Val Glu Glu  Ala Ile Gln Gln Tyr  Glu Arg Ala
    1310                 1315                 1320

Cys Lys  Asp Leu Asn Val Lys  Glu Lys Ile Ile Glu  Asp Met Arg
    1325                 1330                 1335

Met Thr  Leu Glu Glu Gln Glu  Gln Thr Gln Val Glu  Gln Asp Gln
    1340                 1345                 1350

Val Leu  Glu Ala Lys Leu Glu  Glu Val Glu Arg Leu  Ala Thr Glu
    1355                 1360                 1365

Leu Glu  Lys Trp Lys Glu Lys  Cys Asn Asp Leu Glu  Thr Lys Asn
    1370                 1375                 1380

Asn Gln  Arg Ser Asn Lys Glu  His Glu Asn Asn Thr  Asp Val Leu
    1385                 1390                 1395
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Gly Lys  Leu Thr Asn Leu Gln  Asp Glu Leu Gln Glu  Ser Glu Gln
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Lys Tyr  Asn Ala Asp Arg Lys  Lys Trp Leu Glu Glu  Lys Met Met
    1415                 1420                 1425

Leu Ile  Thr Gln Ala Lys Glu  Ala Glu Asn Ile Arg  Asn Lys Glu
    1430                 1435                 1440

Met Lys  Lys Tyr Ala Glu Asp  Arg Glu Arg Phe Phe  Lys Gln Gln
    1445                 1450                 1455

Asn Glu  Met Glu Ile Leu Thr  Ala Gln Leu Thr Glu  Lys Asp Ser
    1460                 1465                 1470

Asp Leu  Gln Lys Trp Arg Glu  Glu Arg Asp Gln Leu  Val Ala Ala
    1475                 1480                 1485

Leu Glu  Ile Gln Leu Lys Ala  Leu Ile Ser Ser Asn  Val Gln Lys
    1490                 1495                 1500

Asp Asn  Glu Ile Glu Gln Leu  Lys Arg Ile Ile Ser  Glu Thr Ser
    1505                 1510                 1515

Lys Ile  Glu Thr Gln Ile Met  Asp Ile Lys Pro Lys  Arg Ile Ser
    1520                 1525                 1530

Ser Ala  Asp Pro Asp Lys Leu  Gln Thr Glu Pro Leu  Ser Thr Ser
    1535                 1540                 1545

Phe Glu  Ile Ser Arg Asn Lys  Ile Glu Asp Gly Ser  Val Val Leu
    1550                 1555                 1560

Asp Ser  Cys Glu Val Ser Thr  Glu Asn Asp Gln Ser  Thr Arg Phe
    1565                 1570                 1575

Pro Lys  Pro Glu Leu Glu Ile  Gln Phe Thr Pro Leu  Gln Pro Asn
    1580                 1585                 1590

Lys Met  Ala Val Lys His Pro  Gly Cys Thr Thr Pro  Val Thr Val
    1595                 1600                 1605

Lys Ile  Pro Lys Ala Arg Lys  Arg Lys Ser Asn Glu  Met Glu Glu
    1610                 1615                 1620

Asp Leu  Val Lys Cys Glu Asn  Lys Lys Asn Ala Thr  Pro Arg Thr
    1625                 1630                 1635

Asn Leu  Lys Phe Pro Ile Ser  Asp Asp Arg Asn Ser  Ser Val Lys
    1640                 1645                 1650
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Lys Glu  Gln Lys Val Ala Ile  Arg Pro Ser Ser Lys  Lys Thr Tyr
    1655                1660                1665

Ser Leu  Arg Ser Gln Ala Ser  Ile Ile Gly Val Asn  Leu Ala Thr
    1670                1675                1680

Lys Lys  Lys Glu Gly Thr Leu  Gln Lys Phe Gly Asp  Phe Leu Gln
    1685                1690                1695

His Ser  Pro Ser Ile Leu Gln  Ser Lys Ala Lys Lys  Ile Ile Glu
    1700                1705                1710

Thr Met  Ser Ser Ser Lys Leu  Ser Asn Val Glu Ala  Ser Lys Glu
    1715                1720                1725

Asn Val  Ser Gln Pro Lys Arg  Ala Lys Arg Lys Leu  Tyr Thr Ser
    1730                1735                1740

Glu Ile  Ser Ser Pro Ile Asp  Ile Ser Gly Gln Val  Ile Leu Met
    1745                1750                1755

Asp Gln  Lys Met Lys Glu Ser  Asp His Gln Ile Ile  Lys Arg Arg
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Leu Arg  Thr Lys Thr Ala Lys
    1775                1780
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ccgggcgctg acagacct atg gag agt cag ggt gtg cct ccc ggg cct tat      111
                      Met Glu Ser Gln Gly Val Pro Pro Gly Pro Tyr
                      1               5                   10

cgg gcc acc aag ctg tgg aat gaa gtt acc aca tct ttt cga gca gga      159
Arg Ala Thr Lys Leu Trp Asn Glu Val Thr Thr Ser Phe Arg Ala Gly
            15                  20                  25

atg cct cta aga aaa cac aga caa cac ttt aaa aaa tat ggc aat tgt      207
Met Pro Leu Arg Lys His Arg Gln His Phe Lys Lys Tyr Gly Asn Cys
        30                  35                  40

ttc aca gca gga gaa gca gtg gat tgg ctt tat gac cta tta aga aat      255
Phe Thr Ala Gly Glu Ala Val Asp Trp Leu Tyr Asp Leu Leu Arg Asn
    45                  50                  55

aat agc aat ttt ggt cct gaa gtt aca agg caa cag act atc caa ctg      303
Asn Ser Asn Phe Gly Pro Glu Val Thr Arg Gln Gln Thr Ile Gln Leu
60                  65                  70                  75
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ttg agg aaa ttt ctt aag aat cat gta att gaa gat atc aaa ggg agg      351
Leu Arg Lys Phe Leu Lys Asn His Val Ile Glu Asp Ile Lys Gly Arg
                80                  85                  90

tgg gga tca gaa aat gtt gat gat aac aac cag ctc ttc aga ttt cct      399
Trp Gly Ser Glu Asn Val Asp Asp Asn Asn Gln Leu Phe Arg Phe Pro
            95                  100                 105

gca act tcg cca ctt aaa act cta cca cga agg tat cca gaa ttg aga      447
Ala Thr Ser Pro Leu Lys Thr Leu Pro Arg Arg Tyr Pro Glu Leu Arg
        110                 115                 120

aaa aac aac ata gag aac ttt tcc aaa gat aaa gat agc att ttt aaa      495
Lys Asn Asn Ile Glu Asn Phe Ser Lys Asp Lys Asp Ser Ile Phe Lys
    125                 130                 135

tta cga aac tta tct cgt aga act cct aaa agg cat gga tta cat tta      543
Leu Arg Asn Leu Ser Arg Arg Thr Pro Lys Arg His Gly Leu His Leu
140                 145                 150                 155

tct cag gaa aat ggc gag aaa ata aag cat gaa ata atc aat gaa gat      591
Ser Gln Glu Asn Gly Glu Lys Ile Lys His Glu Ile Ile Asn Glu Asp
                160                 165                 170

caa gaa aat gca att gat aat aga gaa cta agc cag gaa gat gtt gaa      639
Gln Glu Asn Ala Ile Asp Asn Arg Glu Leu Ser Gln Glu Asp Val Glu
            175                 180                 185

gaa gtt tgg aga tat gtt att ctg atc tac ctg caa acc att tta ggt      687
Glu Val Trp Arg Tyr Val Ile Leu Ile Tyr Leu Gln Thr Ile Leu Gly
        190                 195                 200

gtg cca tcc cta gaa gaa gtc ata aat cca aaa caa gta att ccc caa      735
Val Pro Ser Leu Glu Glu Val Ile Asn Pro Lys Gln Val Ile Pro Gln
    205                 210                 215

tat ata atg tac aac atg gcc aat aca agt aaa cgt gga gta gtt ata      783
Tyr Ile Met Tyr Asn Met Ala Asn Thr Ser Lys Arg Gly Val Val Ile
220                 225                 230                 235

cta caa aac aaa tca gat gac ctc cct cac tgg gta tta tct gcc atg      831
Leu Gln Asn Lys Ser Asp Asp Leu Pro His Trp Val Leu Ser Ala Met
                240                 245                 250

aag tgc cta gca aat tgg cca aga agc aat gat atg aat aat cca act      879
Lys Cys Leu Ala Asn Trp Pro Arg Ser Asn Asp Met Asn Asn Pro Thr
            255                 260                 265

tat gtt gga ttt gaa cga gat gta ttc aga aca atc gca gat tat ttt      927
Tyr Val Gly Phe Glu Arg Asp Val Phe Arg Thr Ile Ala Asp Tyr Phe
        270                 275                 280

cta gat ctc cct gaa cct cta ctt act ttt gaa tat tac gaa tta ttt      975
Leu Asp Leu Pro Glu Pro Leu Leu Thr Phe Glu Tyr Tyr Glu Leu Phe
    285                 290                 295

gta aac att ttg gtt gtt tgt ggc tac atc aca gtt tca gat aga tcc     1023
Val Asn Ile Leu Val Val Cys Gly Tyr Ile Thr Val Ser Asp Arg Ser
300                 305                 310                 315

agt ggg ata cat aaa att caa gat gat cca cag tct tca aaa ttc ctt     1071
Ser Gly Ile His Lys Ile Gln Asp Asp Pro Gln Ser Ser Lys Phe Leu
                320                 325                 330

cac tta aac aat ttg aat tcc ttc aaa tca act gag tgc ctt ctt ctc     1119
His Leu Asn Asn Leu Asn Ser Phe Lys Ser Thr Glu Cys Leu Leu Leu
            335                 340                 345
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agt ctg ctt cat aga gaa aaa aac aaa gaa gaa tca gat tct act gag     1167
Ser Leu Leu His Arg Glu Lys Asn Lys Glu Glu Ser Asp Ser Thr Glu
        350                 355                 360

aga cta cag ata agc aat cca gga ttt caa gaa aga tgt gct aag aaa     1215
Arg Leu Gln Ile Ser Asn Pro Gly Phe Gln Glu Arg Cys Ala Lys Lys
    365                 370                 375

atg cag cta gtt aat tta aga aac aga aga gtg agt gct aat gac ata     1263
Met Gln Leu Val Asn Leu Arg Asn Arg Arg Val Ser Ala Asn Asp Ile
380                 385                 390                 395

atg gga gga agt tgt cat aat tta ata ggg tta agt aat atg cat gat     1311
Met Gly Gly Ser Cys His Asn Leu Ile Gly Leu Ser Asn Met His Asp
                400                 405                 410

cta tcc tct aac agc aaa cca agg tgc tgt tct ttg gaa gga att gta     1359
Leu Ser Ser Asn Ser Lys Pro Arg Cys Cys Ser Leu Glu Gly Ile Val
            415                 420                 425

gat gtg cca ggg aat tca agt aaa gag gca tcc agt gtc ttt cat caa     1407
Asp Val Pro Gly Asn Ser Ser Lys Glu Ala Ser Ser Val Phe His Gln
        430                 435                 440

tct ttt ccg aac ata gaa gga caa aat aat aaa ctg ttt tta gag tct     1455
Ser Phe Pro Asn Ile Glu Gly Gln Asn Asn Lys Leu Phe Leu Glu Ser
    445                 450                 455

aag ccc aaa cag gaa ttc ctg ttg aat ctt cat tca gag gaa aat att     1503
Lys Pro Lys Gln Glu Phe Leu Leu Asn Leu His Ser Glu Glu Asn Ile
460                 465                 470                 475

caa aag cca ttc agt gct ggt ttt aag aga acc tct act ttg act gtt     1551
Gln Lys Pro Phe Ser Ala Gly Phe Lys Arg Thr Ser Thr Leu Thr Val
                480                 485                 490

caa gac caa gag gag ttg tgt aat ggg aaa tgc aag tca aaa cag ctt     1599
Gln Asp Gln Glu Glu Leu Cys Asn Gly Lys Cys Lys Ser Lys Gln Leu
            495                 500                 505

tgt agg tct cag agt ttg ctt tta aga agt agt aca aga agg aat agt     1647
Cys Arg Ser Gln Ser Leu Leu Leu Arg Ser Ser Thr Arg Arg Asn Ser
        510                 515                 520

tat atc aat aca cca gtg gct gaa att atc atg aaa cca aat gtt gga     1695
Tyr Ile Asn Thr Pro Val Ala Glu Ile Ile Met Lys Pro Asn Val Gly
    525                 530                 535

caa ggc agc aca agt gtg caa aca gct atg gaa agt gaa ctc gga gag     1743
Gln Gly Ser Thr Ser Val Gln Thr Ala Met Glu Ser Glu Leu Gly Glu
540                 545                 550                 555

tct agt gcc aca atc aat aaa aga ctc tgc aaa agt aca ata gaa ctt     1791
Ser Ser Ala Thr Ile Asn Lys Arg Leu Cys Lys Ser Thr Ile Glu Leu
                560                 565                 570

tca gaa aat tct tta ctt cca gct tct tct atg ttg act ggc aca caa     1839
Ser Glu Asn Ser Leu Leu Pro Ala Ser Ser Met Leu Thr Gly Thr Gln
            575                 580                 585

agc ttg ctg caa cct cat tta gag agg gtt gcc atc gat gct cta cag     1887
Ser Leu Leu Gln Pro His Leu Glu Arg Val Ala Ile Asp Ala Leu Gln
        590                 595                 600

tta tgt tgt ttg tta ctt ccc cca cca aat cgt aga aag ctt caa ctt     1935
Leu Cys Cys Leu Leu Leu Pro Pro Pro Asn Arg Arg Lys Leu Gln Leu
    605                 610                 615
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tta atg cgt atg att tcc cga atg agt caa aat gtt gat atg ccc aaa     1983
Leu Met Arg Met Ile Ser Arg Met Ser Gln Asn Val Asp Met Pro Lys
620                 625                 630                 635

ctt cat gat gca atg ggt acg agg tca ctg atg ata cat acc ttt tct     2031
Leu His Asp Ala Met Gly Thr Arg Ser Leu Met Ile His Thr Phe Ser
                640                 645                 650

cga tgt gtg tta tgc tgt gct gaa gaa gtg gat ctt gat gag ctt ctt     2079
Arg Cys Val Leu Cys Cys Ala Glu Glu Val Asp Leu Asp Glu Leu Leu
            655                 660                 665

gct gga aga tta gtt tct ttc tta atg gat cat cat cag gaa att ctt     2127
Ala Gly Arg Leu Val Ser Phe Leu Met Asp His His Gln Glu Ile Leu
        670                 675                 680

caa gta ccc tct tac tta cag act gca gtg gaa aaa cat ctt gac tac     2175
Gln Val Pro Ser Tyr Leu Gln Thr Ala Val Glu Lys His Leu Asp Tyr
    685                 690                 695

tta aaa aag gga cat att gaa aat cct gga gat gga cta ttt gct cct     2223
Leu Lys Lys Gly His Ile Glu Asn Pro Gly Asp Gly Leu Phe Ala Pro
700                 705                 710                 715

ttg cca act tac tca tac tgt aag cag att agt gct cag gag ttt gat     2271
Leu Pro Thr Tyr Ser Tyr Cys Lys Gln Ile Ser Ala Gln Glu Phe Asp
                720                 725                 730

gag caa aaa gtt tct acc tct caa gct gca att gca gaa ctt tta gaa     2319
Glu Gln Lys Val Ser Thr Ser Gln Ala Ala Ile Ala Glu Leu Leu Glu
            735                 740                 745

aat att att aaa aac agg agt tta cct cta aag gag aaa aga aaa aaa     2367
Asn Ile Ile Lys Asn Arg Ser Leu Pro Leu Lys Glu Lys Arg Lys Lys
        750                 755                 760

cta aaa cag ttt cag aag gaa tat cct ttg ata tat cag aaa aga ttt     2415
Leu Lys Gln Phe Gln Lys Glu Tyr Pro Leu Ile Tyr Gln Lys Arg Phe
    765                 770                 775

cca acc acg gag agt gaa gca gca ctt ttt ggt gac aaa cct aca atc     2463
Pro Thr Thr Glu Ser Glu Ala Ala Leu Phe Gly Asp Lys Pro Thr Ile
780                 785                 790                 795

aag caa cca atg ctg att tta aga aaa cca aag ttc cgt agt cta aga     2511
Lys Gln Pro Met Leu Ile Leu Arg Lys Pro Lys Phe Arg Ser Leu Arg
                800                 805                 810

taactaactg aattaaaaat tatgtaatac ttgtggaact ttgataaatg aagccatatc   2571

tgagaatgta gctactcaaa aggaagtctg tcattaataa ggtatttcta aataaacaca   2631

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ccagtaaggc tatcatgatg tgtgctaaaa ttttatttac ttgaattttg aaaactgagc   2811

tgtgttaggg attaaactat aattctgttc ttaaaagaaa atttatctgc aaatgtgcaa   2871

gttctgagat attagctaat gaattagttg tttggggtta cttctttgtt tctaagtata   2931

agaatgtgaa gaatatttga aaactcaatg aaataattct cagctgccaa atgttgcact   2991

cttttatata ttctttttcc acttttgatc tatttatata tatgtatgtg tttttaaaat   3051

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tccataaggt atttatttt taatcaaggg agatacacct atcagatgtt taaaataaca 3351

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His Arg Gln His Phe Lys Lys Tyr Gly Asn Cys Phe Thr Ala Gly Glu
35 40 45

Ala Val Asp Trp Leu Tyr Asp Leu Leu Arg Asn Asn Ser Asn Phe Gly
50 55 60

Pro Glu Val Thr Arg Gln Gln Thr Ile Gln Leu Leu Arg Lys Phe Leu
65 70 75 80

Lys Asn His Val Ile Glu Asp Ile Lys Gly Arg Trp Gly Ser Glu Asn
85 90 95

Val Asp Asp Asn Asn Gln Leu Phe Arg Phe Pro Ala Thr Ser Pro Leu
100 105 110

Lys Thr Leu Pro Arg Arg Tyr Pro Glu Leu Arg Lys Asn Asn Ile Glu
115 120 125

Asn Phe Ser Lys Asp Lys Asp Ser Ile Phe Lys Leu Arg Asn Leu Ser
130 135 140

Arg Arg Thr Pro Lys Arg His Gly Leu His Leu Ser Gln Glu Asn Gly
145 150 155 160

Glu Lys Ile Lys His Glu Ile Ile Asn Glu Asp Gln Glu Asn Ala Ile
165 170 175

Asp Asn Arg Glu Leu Ser Gln Glu Asp Val Glu Glu Val Trp Arg Tyr
180 185 190

Val Ile Leu Ile Tyr Leu Gln Thr Ile Leu Gly Val Pro Ser Leu Glu
195 200 205

Glu Val Ile Asn Pro Lys Gln Val Ile Pro Gln Tyr Ile Met Tyr Asn
210 215 220

Met Ala Asn Thr Ser Lys Arg Gly Val Val Ile Leu Gln Asn Lys Ser
225 230 235 240

Asp Asp Leu Pro His Trp Val Leu Ser Ala Met Lys Cys Leu Ala Asn
245 250 255

Trp Pro Arg Ser Asn Asp Met Asn Asn Pro Thr Tyr Val Gly Phe Glu
260 265 270

Arg Asp Val Phe Arg Thr Ile Ala Asp Tyr Phe Leu Asp Leu Pro Glu
275 280 285

Pro Leu Leu Thr Phe Glu Tyr Tyr Glu Leu Phe Val Asn Ile Leu Val
290 295 300

Val Cys Gly Tyr Ile Thr Val Ser Asp Arg Ser Ser Gly Ile His Lys
305 310 315 320

Ile Gln Asp Asp Pro Gln Ser Ser Lys Phe Leu His Leu Asn Asn Leu
325 330 335

Asn Ser Phe Lys Ser Thr Glu Cys Leu Leu Leu Ser Leu Leu His Arg
340 345 350

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

Asn Pro Gly Phe Gln Glu Arg Cys Ala Lys Lys Met Gln Leu Val Asn
370 375 380

Leu Arg Asn Arg Arg Val Ser Ala Asn Asp Ile Met Gly Gly Ser Cys
385 390 395 400

His Asn Leu Ile Gly Leu Ser Asn Met His Asp Leu Ser Ser Asn Ser
405 410 415

Lys Pro Arg Cys Cys Ser Leu Glu Gly Ile Val Asp Val Pro Gly Asn
420 425 430

Ser Ser Lys Glu Ala Ser Ser Val Phe His Gln Ser Phe Pro Asn Ile
435 440 445

Glu Gly Gln Asn Asn Lys Leu Phe Leu Glu Ser Lys Pro Lys Gln Glu
450 455 460

Phe Leu Leu Asn Leu His Ser Glu Glu Asn Ile Gln Lys Pro Phe Ser
465 470 475 480

Ala Gly Phe Lys Arg Thr Ser Thr Leu Thr Val Gln Asp Gln Glu Glu
485 490 495

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Leu Cys Asn Gly Lys Cys Lys Ser Lys Gln Leu Cys Arg Ser Gln Ser
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Leu Leu Leu Arg Ser Ser Thr Arg Arg Asn Ser Tyr Ile Asn Thr Pro
        515                 520                 525

Val Ala Glu Ile Ile Met Lys Pro Asn Val Gly Gln Gly Ser Thr Ser
    530                 535                 540

Val Gln Thr Ala Met Glu Ser Glu Leu Gly Glu Ser Ser Ala Thr Ile
545                 550                 555                 560

Asn Lys Arg Leu Cys Lys Ser Thr Ile Glu Leu Ser Glu Asn Ser Leu
                565                 570                 575

Leu Pro Ala Ser Ser Met Leu Thr Gly Thr Gln Ser Leu Leu Gln Pro
            580                 585                 590

His Leu Glu Arg Val Ala Ile Asp Ala Leu Gln Leu Cys Cys Leu Leu
        595                 600                 605

Leu Pro Pro Pro Asn Arg Arg Lys Leu Gln Leu Leu Met Arg Met Ile
    610                 615                 620

Ser Arg Met Ser Gln Asn Val Asp Met Pro Lys Leu His Asp Ala Met
625                 630                 635                 640

Gly Thr Arg Ser Leu Met Ile His Thr Phe Ser Arg Cys Val Leu Cys
                645                 650                 655

Cys Ala Glu Glu Val Asp Leu Asp Glu Leu Leu Ala Gly Arg Leu Val
            660                 665                 670

Ser Phe Leu Met Asp His His Gln Glu Ile Leu Gln Val Pro Ser Tyr
        675                 680                 685

Leu Gln Thr Ala Val Glu Lys His Leu Asp Tyr Leu Lys Lys Gly His
    690                 695                 700

Ile Glu Asn Pro Gly Asp Gly Leu Phe Ala Pro Leu Pro Thr Tyr Ser
705                 710                 715                 720

Tyr Cys Lys Gln Ile Ser Ala Gln Glu Phe Asp Glu Gln Lys Val Ser
                725                 730                 735

Thr Ser Gln Ala Ala Ile Ala Glu Leu Leu Glu Asn Ile Ile Lys Asn
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Arg Ser Leu Pro Leu Lys Glu Lys Arg Lys Lys Leu Lys Gln Phe Gln
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                       Met Glu Ser Gln Gly Val Pro Pro Gly Pro Tyr
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Arg Ala Thr Lys Leu Trp Asn Glu Val Thr Thr Ser Phe Arg Ala Gly
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atg cct cta aga aaa cac aga caa cac ttt aaa aaa tat ggc aat tgt      207
Met Pro Leu Arg Lys His Arg Gln His Phe Lys Lys Tyr Gly Asn Cys
        30                  35                  40

ttc aca gca gga gaa gca gtg gat tgg ctt tat gac cta tta aga aat      255
Phe Thr Ala Gly Glu Ala Val Asp Trp Leu Tyr Asp Leu Leu Arg Asn
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aat agc aat ttt ggt cct gaa gtt aca agg caa cag act atc caa ctg      303
Asn Ser Asn Phe Gly Pro Glu Val Thr Arg Gln Gln Thr Ile Gln Leu
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ttg agg aaa ttt ctt aag aat cat gta att gaa gat atc aaa ggg agg      351
Leu Arg Lys Phe Leu Lys Asn His Val Ile Glu Asp Ile Lys Gly Arg
                80                  85                  90

tgg gga tca gaa aat gtt gat gat aac aac cag ctc ttc aga ttt cct      399
Trp Gly Ser Glu Asn Val Asp Asp Asn Asn Gln Leu Phe Arg Phe Pro
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gca act tcg cca ctt aaa act cta cca cga agg tat cca gaa ttg aga      447
Ala Thr Ser Pro Leu Lys Thr Leu Pro Arg Arg Tyr Pro Glu Leu Arg
        110                 115                 120

aaa aac aac ata gag aac ttt tcc aaa gat aaa gat agc att ttt aaa      495
Lys Asn Asn Ile Glu Asn Phe Ser Lys Asp Lys Asp Ser Ile Phe Lys
    125                 130                 135

tta cga aac tta tct cgt aga act cct aaa agg cat gga tta cat tta      543
Leu Arg Asn Leu Ser Arg Arg Thr Pro Lys Arg His Gly Leu His Leu
140                 145                 150                 155

tct cag gaa aat ggc gag aaa ata aag cat gaa ata atc aat gaa gat      591
Ser Gln Glu Asn Gly Glu Lys Ile Lys His Glu Ile Ile Asn Glu Asp
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Gln Glu Asn Ala Ile Asp Asn Arg Glu Leu Ser Gln Glu Asp Val Glu
            175                 180                 185

gaa gtt tgg aga tat gtt att ctg atc tac ctg caa acc att tta ggt      687
Glu Val Trp Arg Tyr Val Ile Leu Ile Tyr Leu Gln Thr Ile Leu Gly
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gtg cca tcc cta gaa gaa gtc ata aat cca aaa caa gta att ccc caa      735
Val Pro Ser Leu Glu Glu Val Ile Asn Pro Lys Gln Val Ile Pro Gln
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tat ata atg tac aac atg gcc aat aca agt aaa cgt gga gta gtt ata      783
Tyr Ile Met Tyr Asn Met Ala Asn Thr Ser Lys Arg Gly Val Val Ile
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cta caa aac aaa tca gat gac ctc cct cac tgg gta tta tct gcc atg      831
Leu Gln Asn Lys Ser Asp Asp Leu Pro His Trp Val Leu Ser Ala Met
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Lys Cys Leu Ala Asn Trp Pro Arg Ser Asn Asp Met Asn Asn Pro Thr
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tat gtt gga ttt gaa cga gat gta ttc aga aca atc gca gat tat ttt      927
Tyr Val Gly Phe Glu Arg Asp Val Phe Arg Thr Ile Ala Asp Tyr Phe
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cta gat ctc cct gaa cct cta ctt act ttt gaa tat tac gaa tta ttt      975
Leu Asp Leu Pro Glu Pro Leu Leu Thr Phe Glu Tyr Tyr Glu Leu Phe
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gta aac att ttg gtt gtt tgt ggc tac atc aca gtt tca gat aga tcc     1023
Val Asn Ile Leu Val Val Cys Gly Tyr Ile Thr Val Ser Asp Arg Ser
300                 305                 310                 315

agt ggg ata cat aaa att caa gat gat cca cag tct tca aaa ttc ctt     1071
Ser Gly Ile His Lys Ile Gln Asp Asp Pro Gln Ser Ser Lys Phe Leu
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cac tta aac aat ttg aat tcc ttc aaa tca act gag tgc ctt ctt ctc     1119
His Leu Asn Asn Leu Asn Ser Phe Lys Ser Thr Glu Cys Leu Leu Leu
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agt ctg ctt cat aga gaa aaa aac aaa gaa gaa tca gat tct act gag     1167
Ser Leu Leu His Arg Glu Lys Asn Lys Glu Glu Ser Asp Ser Thr Glu
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aga cta cag ata agc aat cca gga ttt caa gaa aga tgt gct aag aaa     1215
Arg Leu Gln Ile Ser Asn Pro Gly Phe Gln Glu Arg Cys Ala Lys Lys
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atg cag cta gtt aat tta aga aac aga aga gtg agt gct aat gac ata     1263
Met Gln Leu Val Asn Leu Arg Asn Arg Arg Val Ser Ala Asn Asp Ile
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atg gga gga agt tgt cat aat tta ata ggg tta agt aat atg cat gat     1311
Met Gly Gly Ser Cys His Asn Leu Ile Gly Leu Ser Asn Met His Asp
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cta tcc tct aac agc aaa cca agg tgc tgt tct ttg gaa gga att gta     1359
Leu Ser Ser Asn Ser Lys Pro Arg Cys Cys Ser Leu Glu Gly Ile Val
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Gln Lys Pro Phe Ser Ala Gly Phe Lys Arg Thr Ser Thr Leu Thr Val
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Cys Arg Ser Gln Ser Leu Leu Leu Arg Ser Ser Thr Arg Arg Asn Ser
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Tyr Ile Asn Thr
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Ala Val Asp Trp Leu Tyr Asp Leu Leu Arg Asn Asn Ser Asn Phe Gly
    50                  55                  60

Pro Glu Val Thr Arg Gln Gln Thr Ile Gln Leu Leu Arg Lys Phe Leu
65                  70                  75                  80

Lys Asn His Val Ile Glu Asp Ile Lys Gly Arg Trp Gly Ser Glu Asn
                85                  90                  95

Val Asp Asp Asn Asn Gln Leu Phe Arg Phe Pro Ala Thr Ser Pro Leu
            100                 105                 110

Lys Thr Leu Pro Arg Arg Tyr Pro Glu Leu Arg Lys Asn Asn Ile Glu
        115                 120                 125

Asn Phe Ser Lys Asp Lys Asp Ser Ile Phe Lys Leu Arg Asn Leu Ser
    130                 135                 140

Arg Arg Thr Pro Lys Arg His Gly Leu His Leu Ser Gln Glu Asn Gly
145                 150                 155                 160

Glu Lys Ile Lys His Glu Ile Ile Asn Glu Asp Gln Glu Asn Ala Ile
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Asp Asn Arg Glu Leu Ser Gln Glu Asp Val Glu Glu Val Trp Arg Tyr
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Val Ile Leu Ile Tyr Leu Gln Thr Ile Leu Gly Val Pro Ser Leu Glu
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Glu Val Ile Asn Pro Lys Gln Val Ile Pro Gln Tyr Ile Met Tyr Asn
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Met Ala Asn Thr Ser Lys Arg Gly Val Val Ile Leu Gln Asn Lys Ser
225                 230                 235                 240

Asp Asp Leu Pro His Trp Val Leu Ser Ala Met Lys Cys Leu Ala Asn
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Trp Pro Arg Ser Asn Asp Met Asn Asn Pro Thr Tyr Val Gly Phe Glu
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Arg Asp Val Phe Arg Thr Ile Ala Asp Tyr Phe Leu Asp Leu Pro Glu
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Val Cys Gly Tyr Ile Thr Val Ser Asp Arg Ser Ser Gly Ile His Lys
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Ile Gln Asp Asp Pro Gln Ser Ser Lys Phe Leu His Leu Asn Asn Leu
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Asn Ser Phe Lys Ser Thr Glu Cys Leu Leu Leu Ser Leu Leu His Arg
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Glu Lys Asn Lys Glu Glu Ser Asp Ser Thr Glu Arg Leu Gln Ile Ser
        355                 360                 365

Asn Pro Gly Phe Gln Glu Arg Cys Ala Lys Lys Met Gln Leu Val Asn
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Leu Arg Asn Arg Arg Val Ser Ala Asn Asp Ile Met Gly Gly Ser Cys
385                 390                 395                 400

His Asn Leu Ile Gly Leu Ser Asn Met His Asp Leu Ser Ser Asn Ser
                405                 410                 415

Lys Pro Arg Cys Cys Ser Leu Glu Gly Ile Val Asp Val Pro Gly Asn
            420                 425                 430

Ser Ser Lys Glu Ala Ser Ser Val Phe His Gln Ser Phe Pro Asn Ile
        435                 440                 445

Glu Gly Gln Asn Asn Lys Leu Phe Leu Glu Ser Lys Pro Lys Gln Glu
    450                 455                 460

Phe Leu Leu Asn Leu His Ser Glu Glu Asn Ile Gln Lys Pro Phe Ser
465                 470                 475                 480

Ala Gly Phe Lys Arg Thr Ser Thr Leu Thr Val Gln Asp Gln Glu Glu
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Leu Cys Asn Gly Lys Cys Lys Ser Lys Gln Leu Cys Arg Ser Gln Ser
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Leu Leu Leu Arg Ser Ser Thr Arg Arg Asn Ser Tyr Ile Asn Thr
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