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(54) **IMMUNOGENIC T-HELPER EPITOPES FROM HUMAN TUMOUR ANTIGENS AND IMMUNOTHERAPEUTIC METHODS USING SAID EPITOPES**

IMMUNOGENE T-HELPER EPITOPE VON MENSCHLICHEN TUMORANTIGENEN UND DEREN VERWENDUNG IN IMMUNOTHERAPEUTISCHEN METHODEN

EPITOPES DE LYMPHOCYTES T AUXILIAIRES IMMUNOGENES PROVENANT D'ANTIGENES TUMORAUX HUMAINS ET PROCEDES IMMUNOTHERAPEUTIQUES UTILISANT CES EPITOPES

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Description

[0001] The present invention relates to immunotherapeutic methods, and molecules and cells for use in immunotherapeutic methods. In particular, the present invention relates to the immunotherapy of cancer, in particular renal cancer. The present invention furthermore relates to tumour-associated T-helper cell peptide epitopes, alone or in combination with other tumour-associated peptides, that serve as active pharmaceutical ingredients of vaccine compositions which stimulate anti-tumour immune responses. In particular, the present invention relates to 338 novel peptide sequences derived from HLA class II molecules of human tumour cell lines which can be used in vaccine compositions for eliciting anti-tumour immune responses.

BACKGROUND OF THE INVENTION

[0002] Stimulation of an immune response is dependent upon the presence of antigens recognised as foreign by the host immune system. The discovery of the existence of tumour associated antigens has now raised the possibility of using a host's immune system to intervene in tumour growth. Various mechanisms of harnessing both the humoral and cellular arms of the immune system are currently being explored for cancer immunotherapy.

[0003] Specific elements of the cellular immune response are capable of specifically recognising and destroying tumour cells. The isolation of cytotoxic T cells (CTL) from tumour-infiltrating cell populations or from peripheral blood suggests that such cells play an important role in natural immune defences against cancer (Cheever et al., *Annals N.Y. Acad. Sci.* 1993 690:101-112). CD8⁺ T-cells (TCD8⁺) in particular, which recognise Class I molecules of the major histocompatibility complex (MHC)-bearing peptides of usually 8 to 10 residues derived from proteins located in the cytosols, play an important role in this response. The MHC-molecules of the human are also designated as human leukocyte-antigens (HLA).

[0004] There are two classes of MHC-molecules: MHC-I- molecules, that can be found on most cells having a nucleus that present peptides that result from proteolytic cleavage of endogenous proteins and larger peptides. MHC-II-molecules can be found only on professional antigen presenting cells (APC), and present peptides of exogenous proteins that are taken up by APCs during the course of endocytosis, and are subsequently processed. Complexes of peptide and MHC-I are recognised by CD8-positive cytotoxic T-lymphocytes, complexes of peptide and MHC-II are recognised by CD4⁺-helper-T-cells.

[0005] In order for a peptide to trigger (elicit) a cellular immune response, it must bind to an MHC-molecule. This process is dependent on the allele of the MHC-molecule and specific polymorphisms of the amino acid sequence of the peptide. MHC-class-I-binding peptides are usually 8-10 residues in length and contain two conserved residues ("anchor") in their sequence that interact with the corresponding binding groove of the MHC-molecule.

[0006] There are now numerous examples of both mouse and human TCD8⁺ that specifically recognise tumour cells and have therapeutic activity after adoptive transfer, in some cases inducing complete remission. However, despite the potential for T cells to eradicate tumours, it is obvious from the progressive growth of most cancers that many tumours escape recognition by TCD8⁺ in vivo. Though a variety of tumours have been found to be immunogenic, stimulation of an effective antitumour immune response has been difficult to demonstrate.

[0007] The antigens that are recognised by the tumour specific cytotoxic T- lymphocytes, that is, their epitopes, can be molecules derived from all protein classes, such as enzymes, receptors, transcription factors, etc. Furthermore, tumour associated antigens, for example, can also be present in tumour cells only, for example as products of mutated genes. Another important class of tumour associated antigens are tissue-specific structures, such as CT("cancer testis")-antigens that are expressed in different kinds of tumours and in healthy tissue of the testis.

[0008] Various tumour associated antigens have been identified. Further, much research effort is being expended to identify additional tumour associated antigens. Some groups of tumour associated antigens, also referred to in the art as tumour specific antigens, are tissue specific. Examples include, but are not limited to, tyrosinase for melanoma, PSA and PSMA for prostate cancer and chromosomal cross-overs such as bcr/abl in lymphoma. However, many tumour associated antigens identified occur in multiple tumour types, and some, such as oncogenic proteins and/or tumour suppressor genes (tumour suppressor genes are, for example reviewed for renal cancer in Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol.* 2003 Dec;170(6 Pt 1):2163-72) which actually cause the transformation event, occur in nearly all tumour types. For example, normal cellular proteins that control cell growth and differentiation, such as p53 (which is an example for a tumour suppressor gene), ras, c-met, myc, pRB, VHL, and HER-2/neu, can accumulate mutations resulting in upregulation of expression of these gene products thereby making them oncogenic (McCartey et al. *Cancer Research* 1998 15:58 2601-5; Disis et al. *Ciba Found. Symp.* 1994 187:198-211). These mutant proteins can be the target of a tumour specific immune response in multiple types of cancer.

[0009] A tumour suppressor gene is a gene that reduces the probability that a cell in a multicellular organism will turn into a tumour cell. A mutation or deletion of such a gene will increase the probability of a tumour. In that way, a tumour suppressor gene is similar to an oncogene. Tumour suppressor genes, or more precisely, the proteins they code for,

have a dampening or repressive effect on the regulation of the cell cycle. This is basically done by the tumour suppression genes/proteins in three ways : 1.Repression of genes that are essential for the continuing of the cell cycle. If these genes are not expressed, the cell cycle will not continue, effectively inhibiting cell division. 2.Coupling the cell cycle to DNA damage. As long as there is damaged DNA in the cell, it should not divide. If the damage can be repaired, the cell cycle can continue. 3.If the damage can not be repaired, the cell should initiate apoptosis, the programmed cell death, to remove the threat it poses for the greater good of the organism. The first tumour suppressor protein discovered was the pRb protein in human retinoblastoma. An important tumour suppressor is the p53 gene (see above).

[0010] Transforming proteins from oncogenic viruses such as E6 and E7 from HPV or EBNA1 from Epstein Barr virus (EBV) also occur in many tumour types and can be the target of a tumour specific immune response in multiple types of cancer (McKaig et al. Head Neck 1998 20(3):250-65; Punwaney et al. Head Neck 1999 21(1):21-9; Serth et al. Cancer Res. 1999 15:59(4):823-5; Pagano, J. S. Proc. Assoc. Am. Physicians 1999 111(6):573-80). Non-oncogenic host proteins such as MAGE and MUC family are also ubiquitous. Specifically, the MAGE family of antigens have been found in many different cancers including breast cancer, lung cancer, esophageal cancer, hepatic cancer, thyroid cancer, neuroblastoma, gastric cancer, multiple myeloma and melanoma (Gillespie, A. M. and Coleman, R. E. Cancer Treat. Rev. 1999 25(4):219-27). The MUC family of antigens has been associated with ovarian and endometrial cancer, breast cancer, multiple myeloma, pancreatic cancer, and colon and rectal cancer (Segal-Eiras, A. and Croce, M. V. Allergol. Immunopathol. 1997 25(4):176-81).

[0011] Further, most cancers are associated with more than one antigen. Examples of tumours that express more than one tumour antigen include, but are not limited to, breast cancer which has been shown to be associated with MUC-1, HER-2/neu, MAGE, p53, T/Tn and CEA, colon cancer which has been shown to be associated with MUC-2 and MUC-4, CEA, p53 and the MAGE family, melanoma which has been shown to be associated with members of the MAGE family, MART-1 and gp100, and prostate cancer which has been associated with GM2, Tn, sTn, Thompson-Friedenreich antigen (TF), MUC1, MUC2, the beta chain of human chorionic gonadotropin (hCG beta), HER2/neu, PSMA and PSA. In fact, panels of antigens have been suggested for use in immunotherapy against cancer to compensate for the fact that antigen-loss variants of the tumours can grow out under immune system pressure (Zhang et al. Clin. Cancer Res. 1998 4:2669; Kawashima et al. Hum. Immunol. 1998 59: 1).

[0012] In order for the proteins to be recognised by the cytotoxic T-lymphocytes as tumour-specific antigen, and in order to be used in a therapy, particular prerequisites must be fulfilled. The antigen should be expressed mainly by tumour cells and not by normal healthy tissues or in rather small amounts. It is furthermore desirable, that the respective antigen is not only present in one type of tumour, but also in high concentrations (e.g. copy numbers per cell). Essential is the presence of epitopes in the amino acid sequence of the antigen, since such peptide ("immunogenic peptide") that is derived from a tumour associated antigen should lead to an in vitro or in vivo T-cell-response.

[0013] Until now, numerous strategies to target antigens into the class II processing pathway have been described. It is possible to incubate antigen presenting cells (APCs) with the antigen of interest in order to be taken up and processed (Chaux, P., Vantomme, V., Stroobant, V., Thielemans, K., Corthals, J., Luiten, R., Eggermont, A. M., Boon, T. & van der, B. P. (1999) J. Exp. Med. 189, 767-778). Other strategies use fusion proteins which contain lysosomal target sequences. Expressed in APCs, such fusion proteins direct the antigens into the class II processing compartment (Marks, M. S., Roche, P. A., van Donselaar, E., Woodruff, L., Peters, P. J. & Bonifacio, J. S. (1995) J. Cell Biol. 131, 351-369, Rodriguez, F., Harkins, S., Redwine, J. M., de Pereda, J. M. & Whitton, J. L. (2001) J. Virol. 75,10421-10430).

[0014] T-helper cells play an important role in orchestrating the effector function of CTLs in anti-tumour immunity. T-helper cell epitopes that trigger a T-helper cell response of the Th1 type support effector functions of CD8⁺ Killer T-cells, which include cytotoxic functions directed against tumour cells displaying tumour-associated peptide/MHC complexes on their cell surfaces. In this way tumour-associated T-helper cell peptide epitopes, alone or in combination with other tumour-associated peptides, can serve as active pharmaceutical ingredients of vaccine compositions which stimulate anti-tumour immune responses.

[0015] The major task in the development of a tumour vaccine is therefore the identification and characterisation of novel tumour associated antigens and immunogenic T-helper epitopes derived therefrom, that can be recognised by CD4⁺ CTLs. It is therefore an object of the present invention, to provide novel amino acid sequences for such peptide that has the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-II.

[0016] According to the present invention, this object is solved by providing a tumour associated peptide consisting of a major histocompatibility complex (MHC) class-II core amino acid sequence, optionally with N- and/or C-terminal extensions of between 1 to 10 amino acids in length, comprising a sequence according to SEQ ID No. 273 of the attached sequence listing, and having the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-II.

[0017] The present invention relates to 338 peptide sequences derived from HLA class II molecules of human tumour cell lines, in particular renal cancer cell lines, which can be used in vaccine compositions for eliciting anti-tumour immune responses. The peptide sequences have been identified by a new and generally applicable combined approach for the identification of unknown naturally processed HLA class II ligands of defined - e.g. tumour associated - antigens. Thus, promising candidates for peptide-based immunotherapy have been identified in a manner that includes selection of

tumour antigens of outstanding interest and careful determination of peptide sequences derived thereof.

[0018] Described are peptides, comprising an amino acid sequence according to any of SEQ ID No. 1 to SEQ ID No. 338 or a variant thereof provided that the peptide is not the intact human polypeptide from which the amino acid sequence is derived (i.e. one of the full-length sequences as listed in the locus link IDs (Accession numbers, see the attached table, below).

[0019] As described herein below, the peptides that are described have all been identified as being presented by MHC class II bearing cells (Awells cells). Thus, these particular peptides as well as other peptides containing the sequence (i.e. derived peptides) will most likely all elicit a specific T-cell response, although the extent to which such response will be induced might vary from individual peptide to peptide. Differences, for example, could be caused due to mutations in said peptides (see below). The person of skill in the present art is well aware of methods that can be applied in order to determine the extent to which a response is induced by an individual peptide, in particular with reference to the examples herein and the respective literature.

[0020] Preferably, the peptide according to the present invention consists of an amino acid sequence according to SEQ ID No. 273.

[0021] "Consisting essentially of" shall mean that a peptide in addition to the sequence according to any of SEQ ID No. 1 to SEQ ID No. 338 or a variant thereof, contains additional N- and/or C-terminally located stretches of amino acids that are not necessarily forming part of the peptide that functions as core sequence of the peptide comprising the binding motif and as an immunogenic T-helper epitope.

[0022] Nevertheless, these stretches can be important in order to provide for an efficient introduction of the peptide according to the present invention into the cells. In one embodiment of the present invention, the peptide of the present invention is a fusion protein comprising the 80 N-terminal amino acids of the HLA-DR antigen-associated invariant chain (p33, in the following "Ii") as derived from the NCBI, GenBank Accession-number X00497 (Strubin, M., Mach, B. and Long, E.O. The complete sequence of the mRNA for the HLA-DR-associated invariant chain reveals a polypeptide with an unusual transmembrane polarity EMBO J. 3 (4), 869-872 (1984)).

[0023] By a "variant" of the given amino acid sequence we mean that the side chains of, for example, one or two of the amino acid residues are altered (for example by replacing them with the side chain of another naturally occurring amino acid residue or some other side chain) such that the peptide is still able to bind to an HLA molecule in substantially the same way as a peptide consisting of the given amino acid sequence. For example, a peptide may be modified so that it at least maintains, if not improves, the ability to interact with and bind a suitable MHC molecule, such as HLA-DR, and so that it at least maintains, if not improves, the ability to generate activated CTL which can recognise and kill cells which aberrantly express a polypeptide which contains an amino acid sequence as defined in the aspects of the invention. As can be derived from the database as described in the following, certain positions of HLA-DR binding peptides are typically anchor residues forming a core sequence fitting to the binding motif of the HLA binding groove. Modifications of these and other residues involved in binding HLA-DR may enhance binding without altering CTL recognition.

[0024] Those amino acid residues that are not essential to interact with the T cell receptor can be modified by replacement with another amino acid whose incorporation does not substantially effect T cell reactivity and does not eliminate binding to the relevant MHC. Thus, apart from the proviso given, the peptide of the invention may be any peptide (by which term we include oligopeptide or polypeptide) which includes the amino acid sequences or a portion or variant thereof as given.

[0025] It is furthermore known for MHC-class II presented peptides that these peptides are composed of a "core sequence" having a certain HLA-specific amino acid motif and, optionally, N-and/or C-terminal extensions which do not interfere with the function of the core sequence (i.e. are deemed as irrelevant for the interaction of the peptide and the T-cell). The N- and/or C-terminal extensions can be between 1 to 10 amino acids in length, respectively. Thus, a preferred peptide of the present invention can be used either directly in order to load MHC class II molecules or the sequence can be cloned into the vectors according to the description hereinbelow.

[0026] If a peptide which is greater than around 12 amino acid residues is used directly to bind to a MHC molecule, it is preferred that the residues that flank the core HLA binding region are ones that do not substantially affect the ability of the peptide to bind specifically to the binding groove of the MHC molecule or to present the peptide to the CTL. However, as already indicated above, it will be appreciated that larger peptides may be used, especially when encoded by a polynucleotide, since these larger peptides may be fragmented by suitable antigen-presenting cells.

[0027] Examples for peptides of MHC ligands, motifs, variants, as well as certain examples for N-and/or C-terminal extensions can be, for example, derived from the database SYFPEITHI (Rammensee H, Bachmann J, Emmerich NP, Bachor OA, Stevanovic S. SYFPEITHI: database for MHC ligands and peptide motifs. Immunogenetics. 1999 Nov;50 (3-4):213-9. Review.) at <http://syfpeithi.bmi-heidelberg.com/> and the references as cited therein.

[0028] As non-limiting examples, certain peptides for HLA-DR in the database are **K H K V Y A C E V T H Q G L S** derived from Ig kappa chain 188-203 (Kovats et al. Eur J Immunol. 1997 Apr;27(4):1014-21); **K V Q W K V D N A L Q S G N S** derived from Ig kappa chain 145-159 (Kovats et al. Eur J Immunol. 1997 Apr;27(4):1014-21), **L P R L I A F T S E H S H F** derived from GAD65 270-283 (Endl et al, J Clin Invest. 1997 May 15;99(10):2405-15) or **F F R M V I S**

N P A A T H Q D I D F L I derived from GAD65 556-575 (Endl et al. J Clin Invest. 1997 May 15;99(10):2405-15). In addition, peptides can also be derived from mutated sequences of antigens, such as in the case of A T G F K Q S S K A L Q R P V A S derived from bcr-abl 210 kD fusion protein (ten Bosch et al. Blood. 1996 Nov 1;88(9):3522-7), G Y K V L V L N P S V A A T derived from HCV-1 NS3 28-41 Diepolder et al. J Virol. 1997 Aug;71(8):6011-9), or F R K Q N P D I V IQYMDDLTVG derived from HIV-1 (HXB2) RT 326-345 (van der Burg et al. J Immunol. 1999 Jan 1;162(1):152-60). All "anchor" amino acids (see Friede et al., Biochim Biophys Acta. 1996 Jun 7;1316(2):85-101; Sette et al. J Immunol. 1993 Sep 15;151(6):3163-70.; Hammer et al. Cell. 1993 Jul 16;74(1):197-203., and Hammer et al. J Exp Med. 1995 May 1;181(5):1847-55. As examples for HLA-DR4) have been indicated in bold, the putative core sequences have been underlined.

[0029] All the above described peptides are encompassed by the term "variants" of the given amino acid sequence.

[0030] By "peptide" we include not only molecules in which amino acid residues are joined by peptide (-CO-NH-) linkages but also molecules in which the peptide bond is reversed. Such retro-inverso peptidomimetics may be made using methods known in the art, for example such as those described in Meziere et al (1997) J. Immunol. 159,3230-3237, incorporated herein by reference. This approach involves making pseudopeptides containing changes involving the backbone, and not the orientation of side chains. Meziere et al (1997) show that, at least for MHC class II and T helper cell responses, these pseudopeptides are useful. Retro-inverse peptides, which contain NH-CO bonds instead of CO-NH peptide bonds, are much more resistant to proteolysis.

[0031] Typically, the peptide of the invention is one which, if expressed in an antigen presenting cell, may be processed so that a fragment is produced which is able to bind to an appropriate MHC molecule and may be presented by a suitable cell and elicit a suitable T cell response. It will be appreciated that a fragment produced from the peptide may also be a peptide of the invention. Conveniently, the peptide of the invention contains a portion which includes the given amino acid sequence or a portion or variant thereof and a further portion which confers some desirable property. For example, the further portion may include a further T cell epitope (whether or not derived from the same polypeptide as the first T cell epitope-containing portion) or it may include a carrier protein or peptide. Thus, in one embodiment the peptide of the invention is a truncated human protein or a fusion protein of a protein fragment and another polypeptide portion provided that the human portion includes one or more inventive amino acid sequences.

[0032] In a particularly preferred embodiment, the peptide of the invention includes the amino acid sequence of the invention and at least one further T cell epitope wherein the further T cell epitope is able to facilitate the production of a T cell response directed at the type of tumour that aberrantly expresses a tumour-associated antigen. Thus, the peptides of the invention include so-called "beads on a string" polypeptides which can also be used as vaccines.

[0033] It will be appreciated from the following that in some applications the peptides of the invention may be used directly (i.e. they are not produced by expression of a polynucleotide in a patient's cell or in a cell given to a patient); in such applications it is preferred that the peptide has fewer than 100 residues.

[0034] It is preferred if the peptides of the invention are able to bind to HLA-DR. It is particularly preferred if the peptides bind selectively to HLA-DR4.

[0035] The peptides of the invention are particularly useful in immunotherapeutic methods to target and kill cells which aberrantly express polypeptides that form the basis for the present peptides of the invention. Since these specific peptides consisting of the given amino acid sequences bind to HLA-DR it is preferred that the peptides of the invention are ones which bind HLA-DR and when so bound the HLA-DR-peptide complex, when present on the surface of a suitable antigen-presenting cell, is capable of eliciting the production of a CTL which recognises a cell which aberrantly expresses a polypeptide comprising the given amino acid sequence.

[0036] In one embodiment of the present invention, the peptide of the present invention comprises the 80 N-terminal amino acids of the HLA-DR antigen-associated invariant chain (p33, in the following "Ii") as derived from the NCBI, GenBank Accession-number X00497 (see also below).

[0037] By "aberrantly expressed" we include the meaning that the polypeptide is overexpressed compared to normal levels of expression or that the gene is silent in the tissue from which the tumour is derived but in the tumour it is expressed. By "overexpressed" we mean that the polypeptide is present at a level at least 1.2 x that present in normal tissue; preferably at least 2 x and more preferably at least 5 x or 10 x the level present in normal tissue.

[0038] Peptides (at least those containing peptide linkages between amino acid residues) may be synthesised by the Fmoc-polyamide mode of solid-phase peptide synthesis as disclosed by Lu et al (1981) J. Org. Chem. 46,3433 and references therein. Temporary N-amino group protection is afforded by the 9-fluorenylmethyloxycarbonyl (Fmoc) group. Repetitive cleavage of this highly base-labile protecting group is effected using 20 % piperidine in N, N-dimethylformamide. Side-chain functionalities may be protected as their butyl ethers (in the case of serine threonine and tyrosine), butyl esters (in the case of glutamic acid and aspartic acid), butyloxycarbonyl derivative (in the case of lysine and histidine), trityl derivative (in the case of cysteine) and 4-methoxy-2,3,6-trimethylbenzenesulphonyl derivative (in the case of arginine). Where glutamine or asparagine are C-terminal residues, use is made of the 4,4'-dimethoxybenzhydryl group for protection of the side chain amido functionalities. The solid-phase support is based on a polydimethyl-acrylamide polymer constituted from the three monomers dimethylacrylamide (backbone-monomer), bisacryloylethylene diamine

(cross linker) and acryloylsarcosine methyl ester (functionalising agent). The peptide-to-resin cleavable linked agent used is the acid-labile 4-hydroxymethyl-phenoxyacetic acid derivative. All amino acid derivatives are added as their preformed symmetrical anhydride derivatives with the exception of asparagine and glutamine, which are added using a reversed N, N-dicyclohexyl-carbodiimide/lhydroxybenzotriazole mediated coupling procedure. All coupling and deprotection reactions are monitored using ninhydrin, trinitrobenzene sulphonic acid or isotin test procedures. Upon completion of synthesis, peptides are cleaved from the resin support with concomitant removal of side-chain protecting groups by treatment with 95% trifluoroacetic acid containing a 50 % scavenger mix. Scavengers commonly used are ethanedithiol, phenol, anisole and water, the exact choice depending on the constituent amino acids of the peptide being synthesised.

[0039] Trifluoroacetic acid is removed by evaporation in vacuo, with subsequent trituration with diethyl ether affording the crude peptide. Any scavengers present are removed by a simple extraction procedure which on lyophilisation of the aqueous phase affords the crude peptide free of scavengers. Reagents for peptide synthesis are generally available from Calbiochem-Novabiochem (UK) Ltd, Nottingham NG7 2QJ, UK.

[0040] Purification may be effected by any one, or a combination of, techniques such as size exclusion chromatography, ion-exchange chromatography and (usually) reverse-phase high performance liquid chromatography.

[0041] Analysis of peptides may be carried out using thin layer chromatography, reverse-phase high performance liquid chromatography, amino-acid analysis after acid hydrolysis and by fast atom bombardment (FAB) mass spectrometric analysis, as well as MALDI and ESI-Q-TOF mass spectrometric analysis.

[0042] A further aspect of the invention provides a nucleic acid (e.g. polynucleotide) encoding a peptide of the invention. The polynucleotide may be DNA, cDNA, PNA, CNA, RNA or combinations thereof and it may or may not contain introns so long as it codes for the peptide. Of course, it is only peptides which contain naturally occurring amino acid residues joined by naturally occurring peptide bonds which are encodable by a polynucleotide. A still further aspect of the invention provides an expression vector capable of expressing a polypeptide according to the invention.

[0043] A variety of methods have been developed to operably link polynucleotides, especially DNA, to vectors for example via complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted to the vector DNA. The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

[0044] Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. The DNA segment, generated by endonuclease restriction digestion as described earlier, is treated with bacteriophage T4 DNA polymerase or E. coli DNA polymerase I, enzymes that remove protruding, 3'-single-stranded termini with their 3'-5'-exonucleolytic activities, and fill in recessed 3'-ends with their polymerising activities.

[0045] The combination of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyse the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

[0046] Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc, New Haven, CN, USA.

[0047] A desirable way to modify the DNA encoding the polypeptide of the invention is to use the polymerase chain reaction as disclosed by Saiki et al (1988) Science 239,487-491. This method may be used for introducing the DNA into a suitable vector, for example by engineering in suitable restriction sites, or it may be used to modify the DNA in other useful ways as is known in the art. In this method the DNA to be enzymatically amplified is flanked by two specific primers which themselves become incorporated into the amplified DNA. The said specific primers may contain restriction endonuclease recognition sites which can be used for cloning into expression vectors using methods known in the art.

[0048] The DNA (or in the case of retroviral vectors, RNA) is then expressed in a suitable host to produce a polypeptide comprising the compound of the invention. Thus, the DNA encoding the polypeptide constituting the compound of the invention may be used in accordance with known techniques, appropriately modified in view of the teachings contained herein, to construct an expression vector, which is then used to transform an appropriate host cell for the expression and production of the polypeptide of the invention. Such techniques include those disclosed in US Patent Nos. 4,440,859 issued 3 April 1984 to Rutter et al, 4,530,901 issued 23 July 1985 to Weissman, 4,582,800 issued 15 April 1986 to Cowl, 4,677,063 issued 30 June 1987 to Mark et al, 4,678,751 issued 7 July 1987 to Goeddel, 4,704,362 issued 3 November 1987 to Itakura et al, 4,710,463 issued 1 December 1987 to Murray, 4,757,006 issued 12 July 1988 to Toole, Jr. et al, 4,766,075 issued 23 August 1988 to Goeddel et al and 4,810,648 issued 7 March 1989 to Stalker.

[0049] The DNA (or in the case of retroviral vectors, RNA) encoding the polypeptide constituting the compound of the invention may be joined to a wide variety of other DNA sequences for introduction into an appropriate host. The companion DNA will depend upon the nature of the host, the manner of the introduction of the DNA into the host, and whether episomal maintenance or integration is desired.

[0050] Generally, the DNA is inserted into an expression vector, such as a plasmid, in proper orientation and correct

reading frame for expression. If necessary, the DNA may be linked to the appropriate transcriptional and translational regulatory control nucleotide sequences recognised by the desired host, although such controls are generally available in the expression vector. The vector is then introduced into the host through standard techniques. Generally, not all of the hosts will be transformed by the vector. Therefore, it will be necessary to select for transformed host cells. One selection technique involves incorporating into the expression vector a DNA sequence, with any necessary control elements, that codes for a selectable trait in the transformed cell, such as antibiotic resistance.

[0051] Alternatively, the gene for such selectable trait can be on another vector, which is used to co-transform the desired host cell.

[0052] Host cells that have been transformed by the recombinant DNA of the invention are then cultured for a sufficient time and under appropriate conditions known to those skilled in the art in view of the teachings disclosed herein to permit the expression of the polypeptide, which can then be recovered.

[0053] Many expression systems are known, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*), filamentous fungi (for example *Aspergillus*), plant cells, animal cells and insect cells. Preferably, the system can be Awells cells.

[0054] A promoter is an expression control element formed by a DNA sequence that permits binding of RNA polymerase and transcription to occur. Promoter sequences compatible with exemplary bacterial hosts are typically provided in plasmid vectors containing convenient restriction sites for insertion of a DNA segment of the present invention. Typical prokaryotic vector plasmids are pUC18, pUC19, pBR322 and pBR329 available from Biorad Laboratories, (Richmond, CA, USA) and pTrc99A and pKK223-3 available from Pharmacia, Piscataway, NJ, USA.

[0055] A typical mammalian cell vector plasmid is pSVL available from Pharmacia, Piscataway, NJ, USA. This vector uses the SV40 late promoter to drive expression of cloned genes, the highest level of expression being found in T antigen-producing cells, such as COS-1 cells. An example of an inducible mammalian expression vector is pMSG, also available from Pharmacia. This vector uses the glucocorticoid-inducible promoter of the mouse mammary tumour virus long terminal repeat to drive expression of the cloned gene. Useful yeast plasmid vectors are pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (Ylps) and incorporate the yeast selectable markers HIS3, TRP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps). Other vectors and expression systems are well known in the art for use with a variety of host cells.

[0056] The present invention also relates to a host cell transformed with a polynucleotide vector construct of the present invention. The host cell can be either prokaryotic or eukaryotic. Bacterial cells may be preferred prokaryotic host cells in some circumstances and typically are a strain of *E. coli* such as, for example, the *E. coli* strains DH5 available from Bethesda Research Laboratories Inc., Bethesda, MD, USA, and RR1 available from the American Type Culture Collection (ATCC) of Rockville, MD, USA (No ATCC 31343). Preferred eukaryotic host cells include yeast, insect and mammalian cells, preferably vertebrate cells such as those from a mouse, rat, monkey or human fibroblastic and kidney cell lines. Yeast host cells include YPH499, YPH500 and YPH501 which are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Preferred mammalian host cells include Chinese hamster ovary (CHO) cells available from the ATCC as CCL61, NIH Swiss mouse embryo cells NIH/3T3 available from the ATCC as CRL 1658, monkey kidney-derived COS-1 cells available from the ATCC as CRL 1650 and 293 cells which are human embryonic kidney cells. Preferred insect cells are Sf9 cells which can be transfected with baculovirus expression vectors.

[0057] Transformation of appropriate cell hosts with a DNA construct of the present invention is accomplished by well known methods that typically depend on the type of vector used. With regard to transformation of prokaryotic host cells, see, for example, Cohen et al (1972) Proc. Natl. Acad. Sci. USA 69,2110 and Sambrook et al (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. Transformation of yeast cells is described in Sherman et al (1986) Methods In Yeast Genetics, A Laboratory Manual, Cold Spring Harbor, NY. The method of Beggs (1978) Nature 275,104-109 is also useful. With regard to vertebrate cells, reagents useful in transfecting such cells, for example calcium phosphate and DEAE-dextran or liposome formulations, are available from Stratagene Cloning Systems, or Life Technologies Inc., Gaithersburg, MD 20877, USA. Electroporation is also useful for transforming and/or transfecting cells and is well known in the art for transforming yeast cell, bacterial cells, insect cells and vertebrate cells.

[0058] Successfully transformed cells, i.e. cells that contain a DNA construct of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an expression construct of the present invention can be grown to produce the polypeptide of the invention. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using a method such as that described by Southern (1975) J. Mol. Biol. 98,503 or Berent et al (1985) Biotech. 3,208. Alternatively, the presence of the protein in the supernatant can be detected using antibodies as described below.

[0059] In addition to directly assaying for the presence of recombinant DNA, successful transformation can be confirmed by well known immunological methods when the recombinant DNA is capable of directing the expression of the protein. For example, cells successfully transformed with an expression vector produce proteins displaying appropriate antigenicity. Samples of cells suspected of being transformed are harvested and assayed for the protein using suitable

antibodies. Thus, in addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium.

[0060] It will be appreciated that certain host cells of the invention are useful in the preparation of the peptides of the invention, for example bacterial, yeast and insect cells. However, other host cells may be useful in certain therapeutic methods. For example, antigen-presenting cells, such as dendritic cells, may usefully be used to express the peptides of the invention such that they may be loaded into appropriate MHC molecules.

[0061] A further aspect of the invention provides a method of producing a peptide for intravenous (i. v.) injection, subcutaneous (s. c.) injection, intradermal (i. d.) injection, intraperitoneal (i. p.) injection, intramuscular (i. m.) injection. Preferred ways of peptide injection are s. c., i. d., i. p., i. m., and i. v. Preferred ways of DNA injection are i. d., i. m., s. c., i. p. and i. v. Doses of between 1 and 500 mg of peptide or DNA may be given.

[0062] The peptide or peptide-encoding nucleic acid constitutes a tumour or cancer vaccine. It may be administered directly into the patient, into the affected organ or systemically, or applied ex vivo to cells derived from the patient or a human cell line which are subsequently administered to the patient, or used in vitro to select a subpopulation from immune cells derived from the patient, which are then re-administered to the patient. If the nucleic acid is administered to cells in vitro, it may be useful for the cells to be transfected so as to co-express immune-stimulating cytokines, such as interleukin-2. The peptide may be substantially pure, or combined with an immune-stimulating adjuvant such as Detox, or used in combination with immune-stimulatory cytokines, or be administered with a suitable delivery system, for example liposomes. The peptide may also be conjugated to a suitable carrier such as keyhole limpet haemocyanin (KLH) or mannan (see WO 95/18145 and Longenecker et al (1993) Ann. NY Acad. Sci. 690,276-291). The peptide may also be tagged, or be a fusion protein, or be a hybrid molecule. The peptides whose sequence is given in the present invention are expected to stimulate CD4 CTL. However, stimulation is more efficient in the presence of help provided by CD4⁺ T cells. Thus, the fusion partner or sections of a hybrid molecule suitably provide epitopes which stimulate CD4⁺ T cells. CD4⁺ stimulating epitopes are well known in the art and include those identified in tetanus toxoid. The polynucleotide may be substantially pure, or contained in a suitable vector or delivery system.

[0063] Suitable vectors and delivery systems include viral, such as systems based on adenovirus, vaccinia virus, retroviruses, herpes virus, adeno-associated virus or hybrids containing elements of more than one virus. Non-viral delivery systems include cationic lipids and cationic polymers as are well known in the art of DNA delivery. Physical delivery, such as via a "gene-gun" may also be used. The peptide or peptide encoded by the nucleic acid may be a fusion protein, for example with an epitope from tetanus toxoid which stimulates CD4⁺ T cells.

[0064] The peptide for use in a cancer vaccine may be any suitable peptide.

[0065] Suitably, any nucleic acid administered to the patient is sterile and pyrogen free. Naked DNA may be given intramuscularly or intradermally or subcutaneously. The peptides may be given intramuscularly, intradermally or subcutaneously.

[0066] Vaccination results in CTL responses stimulated by professional antigen presenting cells; once CTL are primed, there may be an advantage in enhancing MHC expression in tumour cells.

[0067] It may also be useful to target the vaccine to specific cell populations, for example antigen presenting cells, either by the site of injection, use of targeting vectors and delivery systems, or selective purification of such a cell population from the patient and ex vivo administration of the peptide or nucleic acid (for example dendritic cells may be sorted as described in Zhou et al (1995) Blood 86,3295-3301; Roth et al (1996) Scand. J. Immunology 43,646-651). For example, targeting vectors may comprise a tissue- or tumour-specific promoter which directs expression of the antigen at a suitable place.

[0068] A further aspect of the invention therefore provides a vaccine effective against cancer, or cancer or tumour cells, comprising an effective amount of the peptide according to the invention, or comprising a nucleic acid encoding such a peptide.

[0069] A further aspect of the invention therefore provides a vaccine effective against cancer, further comprising at least one additional tumour associated peptide of between 9 and 30 amino acids comprising at least one sequence according to SEQ ID No. 1 to SEQ ID No. 272 and SEQ ID No. 274 to SEQ ID No. 338.

[0070] It is particularly preferred if the vaccine is a nucleic acid vaccine. It is known that inoculation with a nucleic acid vaccine, such as a DNA vaccine, encoding a polypeptide leads to a T cell response.

[0071] Conveniently, the nucleic acid vaccine may comprise any suitable nucleic acid delivery means. The nucleic acid, preferably DNA, may be naked (i.e. with substantially no other components to be administered) or it may be delivered in a liposome or as part of a viral vector delivery system.

[0072] It is believed that uptake of the nucleic acid and expression of the encoded polypeptide by dendritic cells may be the mechanism of priming of the immune response; however, dendritic cells may not be transfected but are still important since they may pick up expressed peptide from transfected cells in the tissue.

[0073] It is preferred if the vaccine, such as DNA vaccine, is administered into the muscle. It is also preferred if the vaccine is administered into the skin. The nucleic acid vaccine may be administered without adjuvant. The nucleic acid

vaccine may also be administered with an adjuvant such as BCG or alum. Other suitable adjuvants include Aquila's QS21 stimulon (Aquila Biotech, Worcester, MA, USA) which is derived from saponin, mycobacterial extracts and synthetic bacterial cell wall mimics, and proprietary adjuvants such as Ribi's Detox. Quil A, another saponin derived adjuvant, may also be used (Superfos, Denmark). It is preferred if the nucleic acid vaccine is administered without adjuvant. Other adjuvants such as Freund's may also be useful. It may also be useful to give the peptide conjugated to keyhole limpet haemocyanin, preferably also with an adjuvant.

[0074] Polynucleotide-mediated immunisation therapy of cancer is described in Conry et al (1996) *Seminars in Oncology* 23,135-147; Condon et al (1996) *Nature Medicine* 2,1122-1127; Gong et al (1997) *Nature Medicine* 3,558-561; Zhai et al (1996) *J. Immunol.* 156,700-710; Graham et al (1996) *Int J. Cancer* 65,664-670; and Burchell et al (1996) pp 309-313 In: *Breast Cancer, Advances in biology and therapeutics*, Calvo et al (eds), John Libbey Eurotext.

[0075] A still further aspect of the present invention provides the use of the peptide according to the invention, or of a polynucleotide or expression vector encoding such a peptide, in the manufacture of a medicament for killing target cells in a patient which target cells aberrantly express a polypeptide comprising an amino acid sequence of the invention.

[0076] A further aspect of the invention provides a method for producing activated cytotoxic T lymphocytes (CTL) in vitro, the method comprising contacting in vitro CTL with antigen-loaded human class II MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate, in an antigen specific manner, said CTL wherein the antigen is the peptide according to the invention.

[0077] Suitably, the CTL are CD4⁺ helper cells, preferably of TH1-type. The MHC class II molecules may be expressed on the surface of any suitable cell and it is preferred if the cell is one which does not naturally express MHC class II molecules (in which case the cell is transfected to express such a molecule) or, if it does, it is defective in the antigen-processing or antigen-presenting pathways. In this way, it is possible for the cell expressing the MHC class II molecule to be primed substantially completely with a chosen peptide antigen before activating the CTL.

[0078] The antigen-presenting cell (or simulator cell) typically has an MHC class II molecule on its surface and preferably is substantially incapable of itself loading said MHC class II molecule with the selected antigen. As is described in more detail below, the MHC class II molecule may readily be loaded with the selected antigen in vitro.

[0079] Preferably the mammalian cell lacks or has a reduced level or has reduced function of the TAP peptide transporter. Suitable cells which lack the TAP peptide transporter include T2, RMA-S and Drosophila cells. TAP is the Transporter Associated with antigen Processing.

[0080] The human peptide loading deficient cell line T2 is available from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, USA under Catalogue No CRL 1992; the Drosophila cell line Schneider line 2 is available from the ATCC under Catalogue No CRL 19863; the mouse RMA-S cell line is described in Karre and Ljunggren (1985) *J. Exp. Med.* 162, 1745.

[0081] Conveniently said host cell before transfection expresses substantially no MHC class I molecules. It is also preferred if the stimulator cell expresses a molecule important for T cell costimulation such as any of B7.1, 87.2, ICAM-1 and LFA 3.

[0082] The nucleic acid sequences of numerous MHC class II molecules, and of the costimulator molecules, are publicly available from the GenBank and EMBL databases.

[0083] In a further embodiment, combinations of HLA molecules may also be used.

[0084] The use of recombinant polyepitope vaccines for the delivery of multiple CD8⁺ CTL epitopes is described in Thomson et al (1996) *J. Immunol.* 157, 822-826 and WO 96/03144. In relation to the present invention, it may be desirable to include in a single vaccine, a peptide (or a nucleic acid encoding a peptide) wherein the peptide includes, in any order, an amino acid sequence of the present invention and a CD4⁺ T cell-stimulating epitope (such as from tetanus toxoid). Such a vaccine would be particularly useful for treating cancers. Such "bead-on-a-string" vaccines are typically DNA vaccines.

[0085] A number of other methods may be used for generating CTL in vitro. For example, the methods described in Peoples et al (1995) *Proc. Natl. Acad. Sci. USA* 92,432-436 and Kawakami et al (1992) *J. Immunol.* 148,6386-43 use autologous tumour-infiltrating lymphocytes in the generation of CTL. Plebanski et al (1995) *Eur. J. Immunol.* 25,1783-1787 makes use of autologous peripheral blood lymphocytes (PLBs) in the preparation of CTL. Jochmus et al (1997) *J. Gen. Virol.* 78, 1689-1695 describes the production of autologous CTL by employing pulsing dendritic cells with peptide or polypeptide, or via infection with recombinant virus. Hill et al (1995) *J. Exp. Med.* 181,2221-2228 and Jerome et al (1993) *J. Immunol.* 151,1654-1662 make use of B cells in the production of autologous CTL. In addition, macrophages pulsed with peptide or polypeptide, or infected with recombinant virus, may be used in the preparation of autologous CTL.

[0086] Allogeneic cells may also be used in the preparation of CTL and this method is described in detail in WO 97/26328. For example, in addition to Drosophila cells and T2 cells, other cells may be used to present antigens such as CHO cells, baculovirus-infected insects cells, bacteria, yeast, vaccinia-infected target cells. In addition plant viruses may be used (see, for example, Porta et al (1994) *Virology* 202,449-955 which describes the development of cowpea mosaic virus as a high-yielding system for the presentation of foreign peptides.

[0087] The activated CTL which are directed against the peptides of the invention are useful in therapy.

[0088] Preferably, the CTL recognises the said cell by interacting with the HLA/peptide-complex (for example, binding). The CTL are useful in a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising an amino acid sequence of the invention wherein the patient is administered an effective number of the activated CTL. The CTL which are administered to the patient may be derived from the patient and activated as described above (i.e. they are autologous CTL). Alternatively, the CTL are not from the patient but are from another individual. Of course, it is preferred if the individual is a healthy individual. By "healthy individual" we mean that the individual is generally in good health, preferably has a competent immune system and, more preferably, is not suffering from any disease which can be readily tested for, and detected.

[0089] The activated CTL express a T cell receptor (TCR) which is involved in recognising cells which express the aberrant polypeptide. It is useful if the cDNA encoding the TCR is cloned from the activated CTL and transferred into a further CTL for expression.

[0090] In vivo, the target cells for the CD4⁺ CTL can be cells of the tumour (which sometimes express MHC class II) and/or stromal cells surrounding the tumour (tumour cells) (which sometimes also express MHC class II).

[0091] The TCRs of CTL clones specific for the peptides of the invention are cloned. The TCR usage in the CTL clones is determined using (i) TCR variable region-specific monoclonal antibodies and (ii) RT PCR with primers specific for Va and Vp gene families. A cDNA library is prepared from poly-A mRNA extracted from the CTL clones. Primers specific for the C-terminal portion of the TCR α and β chains and for the N-terminal portion of the identified Va and P segments are used. The complete cDNA for the TCR α and β chain is amplified with a high fidelity DNA polymerase and the amplified products cloned into a suitable cloning vector. The cloned α and β chain genes may be assembled into a single chain TCR by the method as described by Chung et al (1994) Proc. Natl. Acad. Sci. USA 91,12654-12658. In this single chain construct the VaJ segment is followed by the VDJ segment, followed by the Cp segment followed by the transmembrane and cytoplasmic segment of the CD3 chain. This single chain TCR is then inserted into a retroviral expression vector (a panel of vectors may be used based on their ability to infect mature human CD8⁺ T lymphocytes and to mediate gene expression: the retroviral vector system Kat is one preferred possibility (see Finer et al (1994) Blood 83,43). High titre amphotrophic retrovirus are used to infect purified CD8⁺ or CD4⁺ T lymphocytes isolated from the peripheral blood of tumour patients (following a protocol published by Roberts et al (1994) Blood 84, 2878-2889). Anti-CD3 antibodies are used to trigger proliferation of purified CD8⁺ T cells, which facilitates retroviral integration and stable expression of single chain TCRs. The efficiency of retroviral transduction is determined by staining of infected CD8⁺ T cells with antibodies specific for the single chain TCR. In vitro analysis of transduced CD8⁺ T cells establishes that they display the same tumour-specific killing as seen with the allo-restricted CTL clone from which the TCR chains were originally cloned. Populations of transduced CD8⁺ T cells with the expected specificity may be used for adoptive immunotherapy of the tumour patients. Patients may be treated with in between 10⁸ to 10¹¹ autologous, transduced CTL. Analogously to CD8⁺, transduced CD4⁺ T helper cells carrying related constructs can be generated.

[0092] Other suitable systems for introducing genes into CTL are described in Moritz et al (1994) Proc. Natl. Acad. Sci. USA 91, 4318-4322, incorporated herein by reference. Eshhar et al (1993) Proc. Natl. Acad. Sci. USA 90,720-724 and Hwu et al (1993) J. Exp. Med. 178, 361-366 also describe the transfection of CTL.

[0093] As well as the TCR, functionally equivalent molecules to the TCR are described in the invention. These include any molecule which is functionally equivalent to a TCR which can perform the same function as a TCR. In particular, such molecules include genetically engineered three-domain single-chain TCRs as made by the method described by Chung et al (1994) Proc. Natl. Acad. Sci. USA 91, 12654-12658, and referred to above.

[0094] It is, however, preferred that the expression vectors are ones which are able to express the TCR in a CTL following transfection.

[0095] The invention describes a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising an amino acid sequence of the invention, the method comprising the steps of (1) obtaining CTL from the patient; (2) introducing into said cells a polynucleotide encoding a TCR, or a functionally equivalent molecule, as defined above; and (3) introducing the cells produced in step (2) into the patient.

[0096] The invention describes a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising an amino acid sequence as defined in the first or second or third aspects of the invention, the method comprising the steps of (1) obtaining antigen presenting cells, such as dendritic cells, from said patient; (2) contacting said antigen presenting cells with a peptide as defined in the first or second or third aspects of the invention, or with a polynucleotide encoding such a peptide, ex vivo; and (3) reintroducing the so treated antigen presenting cells into the patient.

[0097] Preferably, the antigen presenting cells are dendritic cells. Suitably, the dendritic cells are autologous dendritic cells which are pulsed with an antigenic peptide. The antigenic peptide may be any suitable antigenic peptide which gives rise to an appropriate T cell response. T-cell therapy using autologous dendritic cells pulsed with peptides from a tumour associated antigen is disclosed in Murphy et al (1996) The Prostate 29,371-380 and Tjua et al (1997) The Prostate 32,272-278.

[0098] In a further embodiment the antigen presenting cells, such as dendritic cells, are contacted with a polynucleotide

which encodes a peptide of the invention. The polynucleotide may be any suitable polynucleotide and it is preferred that it is capable of transducing the dendritic cell thus resulting in the presentation of a peptide and induction of immunity.

[0099] Conveniently, the polynucleotide may be comprised in a viral polynucleotide or virus. For example, adenovirus-transduced dendritic cells have been shown to induce antigen-specific antitumour immunity in relation to MUC1 (see Gong et al (1997) *Gene Ther.* 4,1023-1028). Similarly, adenovirus-based systems may be used (see, for example, Wan et al (1997) *Hum. Gene Ther.* 8,1355-1363); retroviral systems may be used (Specht et al (1997) *J. Exp. Med.* 186, 1213-1221 and Szabo et al (1997) *Blood* particle-mediated transfer to dendritic cells may also be used (Tuting et al (1997) *Eur. J. Immunol.* 27,2702-2707); and RNA may also be used (Ashley et al (1997) *J. Exp. Med.* 186, 1177-1182).

[0100] It will be appreciated that, with respect to the methods of killing target cells in a patient, it is particularly preferred that the target cells are cancer cells, more preferably renal cancer cells.

[0101] It is particularly preferred if the patients who are treated by the methods as described have the HLA-DR haplotype. Thus, in a preferred embodiment the HLA haplotype of the patient is determined prior to treatment. HLA haplotyping may be carried out using any suitable method; such methods are well known in the art.

[0102] The invention includes in particular the use of the peptides of the invention (or polynucleotides encoding them) for active in vivo vaccination; for manipulation of autologous dendritic cells in vitro followed by introduction of the so-manipulated dendritic cells in vivo to activate CTL responses; to activate autologous CTL in vitro followed by adoptive therapy (i.e. the so-manipulated CTL are introduced into the patient); and to activate CTL from healthy donors (MHC matched or mismatched) in vitro followed by adoptive therapy.

[0103] In a preferred embodiment, the vaccines of the present invention are administered to a host either alone or in combination with another cancer therapy to inhibit or suppress the formation of tumours.

[0104] The peptide vaccine may be administered without adjuvant. The peptide vaccine may also be administered with an adjuvant such as BCG or alum. Other suitable adjuvants include Aquila's QS21 stimulon (Aquila Biotech, Worcester, MA, USA) which is derived from saponin, mycobacterial extracts and synthetic bacterial cell wall mimics, and proprietary adjuvants such as Ribi's Detox. Quil A, another saponin derived adjuvant, may also be used (Superfos, Denmark). Other adjuvants such as Freund's or GMCSF may also be useful. It may also be useful to give the peptide conjugated to keyhole limpet haemocyanin, preferably also with an adjuvant.

[0105] The peptides as described can also be used as diagnostic reagents. Using the peptides it can be analysed, whether in a CTL-population CTLs are present that are specifically directed against a peptide or are induced by a therapy. Furthermore, the increase of precursor T-cells can be tested with those peptides that have a reactivity against the defined peptide. Furthermore, the peptide can be used as marker in order to monitor the progression of the disease of a tumour that expresses said antigen of which the peptide is derived from.

[0106] In the attached table 1 the peptides as identified are listed. In addition, in the table the proteins are designated, from which the peptide is derived, and the respective position of the peptide in the respective protein. Furthermore the respective Ace-Numbers are given that relate to the Genbank of the "National Centre for Biotechnology Information" of the National Institute of Health (see <http://www.ncbi.nlm.nih.gov>).

[0107] In another preferred described embodiment the peptides are used for staining of leukocytes, in particular of T-lymphocytes. This use is of particular advantage if it should be proven, whether in a CTL-population specific CTLs are present that are directed against a peptide. Furthermore the peptide can be used as marker for determining the progression of a therapy in a tumorous disease or disorder.

[0108] In another preferred described embodiment the peptides are used for the production of an antibody. Polyclonal antibodies can be obtained in a standard fashion by Immunisation of Animals via injection of the peptide and subsequent purification of the immune globulin.

[0109] Monoclonal antibodies can be produced according to standard protocols such as described, for example, in *Methods Enzymol.* (1986), 121, Hybridoma technology and monoclonal antibodies.

[0110] The invention in a further aspect relates to a pharmaceutical composition, that contains the peptides according to the invention. This composition is used for parenteral administration, such as subcutaneous, intradermal, intramuscular or oral administration. For this, the peptides is dissolved or suspended in a pharmaceutically acceptable, preferably aqueous carrier. In addition, the composition can contain excipients, such as buffers, binding agents, blasting agents, diluents, flavours, lubricants, etc.. The peptides can also be administered together with immune stimulating substances, such as cytokines. An extensive listing of excipients that can be used in such a composition, can be, for example, taken from A. Kibbe, *Handbook of Pharmaceutical Excipients*, 3, Ed., 2000, American Pharmaceutical Association and pharmaceutical press. The composition can be used for a prevention, prophylaxis and/or therapy of tumorous diseases.

[0111] The pharmaceutical preparation, containing the peptide of the present invention comprising SEQ ID No. 273 is administered to a patient that suffers from a tumorous disease that is associated with the respective peptide or antigen. By this, a CTL-specific immune response can be triggered.

[0112] In another aspect of the present invention, a combination of two or several peptides according to the present invention can be used as vaccine, either in direct combination or within the same treatment regimen. Furthermore, combinations with other peptides, for example MHC class I specific peptides can be used. The person of skill will be

able to select preferred combinations of immunogenic peptides by testing, for example, the generation of T-cells *in vitro* as well as their efficiency and overall presence, the proliferation, affinity and expansion of certain T-cells for certain peptides, and the functionality of the T-cells, e.g. by analysing the IFN- γ production (see also examples below). Usually, the most efficient peptides are then combined as a vaccine for the purposes as described above.

[0113] A suitable vaccine will contain 2, 3, 4, 5, 6, 7, 8, 9 or 10 different peptides, preferably 4, 5, 6 or 7 different peptides, and most preferably 6 different peptides.

[0114] Finally, the vaccine can be dependent from the specific type of cancer that the patient to be treated is suffering from as well as the status of the disease, earlier treatment regimens, the immune status of the patient, and, of course, the HLA-haplotype of the patient.

[0115] It has been shown that the 80 N-terminal amino acids of Ii are sufficient to direct proteins into the class II processing pathway (Sanderson, S., Frauwirth, K. & Shastri, N. (1995) *Proc. Natl. Acad. Sci. U. S. A.* 92, 7217-7221, Wang, R. F., Wan, X., Atwood, A. C., Topalian, S. L. & Rosenberg, S. A. (1999) *Science* 284, 1351-1354). To deliver an exemplary proof of concept for the present invention, the inventors generated fusion proteins consisting of the 80 N-terminal amino acids of Ii and an exemplary antigen associated with various malignancies, cyclin D1 (CCND1).

[0116] Cyclin D1 is a cell cycle regulator involved in the G1-S transition through interactions with cyclin-dependent kinases. Moreover, cyclin D1 is a proto-oncogene and has been shown to be overexpressed in several tumour types (Hedberg, Y., Davoodi, E., Roos, G., Ljungberg, B. & Landberg, G. (1999) *Int. J. Cancer* 84, 268-272, Vasef, M. A., Brynes, R. K., Sturm, M., Bromley, C. & Robinson, R. A. (1999) *Mod. Pathol.* 12, 412-416, - Troussard, X., Avet-Loiseau, H., Macro, M., Mellerin, M. P., Malet, M., Roussel, M. & Sola, B. (2000) *Hematol. J.* 1, 181-185) whereas it is expressed at low level in a large panel of healthy organs and tissues without any particular distribution with the exception of liver and high aortic smooth muscle cells (Weinschenk, T., Gouttefangeas, C., Schirle, M., Obermayr, F., Walter, S., Schoor, O., Kurek, R., Loeser, W., Bichler, K. H., Wernet, D. et al. (2002) *Cancer Res.* 62, 5818-5827). In a differential mass spectrometric approach the inventors compared mass spectra of purified HLA peptides from transfected and non transfected cells and used the resulting peptides of interest in *in vitro* CD4+ T-helper cell priming experiments in order to prove the immunogenic character of these HLA class II ligands.

[0117] The identification of T-helper cell epitopes of tumour associated antigens remains an important task in anti-tumour immunotherapy. Here we report a new and generally applicable method and peptides that have been derived from differential peptide analysis by MS to identify naturally processed and presented MHC class II ligands of tumour associated antigens. This approach combines for the first time a transfection step of APC with a vector encoding for a fusion protein between the Ii chain and the Ag of interest, elution of the HLA-bound peptides and MS identification of the Ag-derived peptides presented by the transfectant by comparison to the non-transfected cells. Moreover, we could validate the method by showing that T cells induced against the identified peptide specifically recognise transfectants overexpressing the cognate Ag. Although the identified peptides still have to be tested for their immunogenicity *in vivo*, our approach leads to the exact characterisation of naturally processed MHC class II ligands. Thus, the inventors avoid testing either synthetic overlapping peptides of tumour associated antigens, or a broad range of peptides selected by epitope prediction, which is less accurate as compared to class I epitope prediction. In contrast to laborious T-cell assays, which might lead to the identification of cryptic T-cell epitopes unable to induce T-cell activation *in vivo* (Anderton, S. M., Viner, N. J., Matharu, P., Lowrey, P. A. & Wraith, D. C. (2002) *Nat. Immunol.* 3, 175-181), the work can be focused on the few peptides which are found to be presented. Moreover, using this method it is not necessary to produce the recombinant Ag or to possess Ag-expressing tumour cell lines in order to prove that the peptides are naturally processed.

[0118] The inventors used the N-terminus of Ii to direct tumour associated antigens into the class II processing compartment of EBV-transformed B cells. In order to achieve this we constructed a versatile vector with which we can express any antigen as a fusion protein with Ii and which helps us to determine the expression level of the protein in transfected cells by Western blot analysis. It has already been shown that the N-terminus of Ii is sufficient to target proteins into the class II processing compartment. But until now this has only been described in a model using ovalbumin (Sanderson, S., Frauwirth, K. & Shastri, N. (1995) *Proc. Natl. Acad. Sci. U. S. A.* 92, 7217-7221), in order to identify unknown Ag using fusion protein-encoding cDNA libraries (Wang, R. F., Wang, X., Atwood, A. C., Topalian, S. L. & Rosenberg, S. A. (1999) *Science* 284, 1351-1354) or to confirm the specificity of known T-cell clones (Chaux, P., Vantomme, V., Stroobant, V., Thielemans, K., Corthals, J., Luiten, R., Eggermont, A. M., Boon, T. & van der, B. P. (1999) *J Exp. Med.* 189, 767-778). To our knowledge this method has never been used before to identify naturally presented MHC class II bound peptides of known tumour associated antigens. The differential analysis of class II ligands of transfected and non transfected cells by MALDI-MS and the further characterisation of the differentially expressed peptides by ESI-MS results in a straightforward method for identifying class II ligands of antigens of interest. Transfection of cells with keratin 18 fusion proteins proved that our method is generally applicable for antigens of interest, again, we were also able to describe an HLA-DR-presented peptide from a model transgene, keratin 18.

[0119] The inventors identified an immunogenic HLA-DR4-presented cyclin D1 peptide antigen having the sequence NPPSMVAAGSVVAHV (SEQ ID No. 1), as well as 337 other HLA class II-associated peptides eluted from a transfected human tumour cell line. The Cyclin D1 peptide and other peptides identified from the human tumour cell line are possible

candidates for clinical development of therapeutic vaccines for the treatment of human cancers (Weinschenk, T., Gouttefangeas, C., Schirle, M., Obermayr, F., Walter, S., Schoor, O., Kurek, R., Loeser, W., Bichler, K. H., Wernet, D. et al. (2002) Cancer Res. 62, 5818-5827).

[0120] The invention will now be described in more detail by reference to the following Figures, the Sequence listing, and the Examples. The following examples are provided for illustrative purposes only and are not intended to limit the invention.

[0121] SEQ ID No 1 to SEQ ID No 338 show peptide sequences of T-cell epitope containing peptides that are presented by MHC class II.

[0122] SEQ ID No 339 to SEQ ID No 350 show primer sequences as used in the examples.

Figure 1 shows a first Western blot analysis of fusion proteins that have been produced in the course of the experiments.

Figure 2 shows a second Western blot analysis of fusion proteins that have been produced in the course of the experiments.

Figure 3 shows the HPLC-chromatograms of the untransfected cell line and the A wells-li-cyclin D1 clone.

Figures 4 and 5 show the mass spectrometric analyses of a preferred fraction having a striking individual signal.

Figure 6 shows the identification of the peptides NPPSMVAAGSVVAAV (SEQ ID No. 1) (cyclin D 1₁₉₈₋₂₁₂).

Figure 7 shows the specific stimulation of T cells by the cyclin D1 peptide, (upper panel) and cytokine production of the T cells in response to the peptide (lower panel).

Figure 8 shows a negative control for eventual unspecific activation of CD4+ T-helper cells with T-cell receptors specific for HLA-DR4/cyclin D1₁₉₈₋₂₁₂.

EXAMPLES

[0123] As will be obvious to those of skill in the art upon this disclosure and the present examples, the invention is also related to other epitopes of tumour associated antigens as specifically used in the following examples that are related to an immunogenic HLA-DR4-presented cyclin D1 peptide antigen having the sequence NPPSMVAAGSVVAAV (SEQ ID No. 1), and keratin 18. The examples are to be seen as general examples and outlines, which can be easily applied by those of skill in the art to the epitopes of the tumour associated antigens of the present invention (i.e. comprising the sequences of SEQ ID No. 273) in order to fully enable the present invention.

[0124] Abbreviations used throughout the present application:

Ab:	Antibody
Ag:	Antigen
APC:	antigen presenting cell
CD:	Cluster of Differentiation
cpm:	counts per minute
DC:	Dendritic Cell
EBV:	Epstein-Barr Virus
ESI:	electrospray ionisation
HLA:	Human Leukocyte Antigen
HPLC:	High Performance Liquid Chromatography
IFN:	Interferon
Ii:	invariant chain (CD74)
IL:	Interleukin
MALDI:	matrix assisted laser desorption/ionisation
MHC:	Major Histocompatibility Complex
MS:	mass spectrometry
OD ₄₅₀ :	Optical Density at a wavelength of 450 nm
PBMC:	Peripheral Blood Mononuclear Cells
PCR:	Polymerase Chain Reaction
PHA:	Phytohaemagglutinin

SDS-PAGE: Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
 S.I.: stimulation index
 TOF: time of flight

5 Cells and antibodies

[0125] The human B-lymphoblastoid cell line Awells (IHW-No. 9090; HLA-DRB1*0401, HLA-DRB4*0101) was maintained in RPMI 1640 (C.C.Pro, Neustadt, Germany) medium containing 10 % FCS (Pan, Aidenbach, Germany) and supplemented with 2 mM L-glutamine (BioWhittaker, Verviers, Belgium), 100 U/ml penicillin and 100 µg/ml streptomycin (BioWhittaker). In the case of the transfected cell clones 0.8 mg/ml G418 (PAA Laboratories, Linz, Austria) was added. Stable transfectants were generated by electroporation of Awells (280 V, 975 µF; Gene Pulser II, Biorad, München, Germany) cells, followed by cloning using the limiting dilution method. The antibodies L243 (anti-HLA-DR) (Lampson, L. A. & Levy, R. (1980) J. Immunol. 125, 293-299) and W6/32 (anti HLA class I) (Brodsky, F. M. & Parham, P. (1982) J. Immunol. 128, 129-135) were purified from hybridoma culture supernatants using protein A-Sepharose beads (Pharmacia, Uppsala, Sweden). The Th-cell line was induced and cultured in IMDM (BioWhittaker) containing 10 % human AB serum (Pel-Freez Clinical Systems, LLC, Milwaukee, WI, USA) and supplemented with 100 U/ml penicillin and 100 µg/ml streptomycin, 2 mM L-glutamine and 50 µM β-mercaptoethanol. Antibodies used in flow cytometry analysis were from PharMingen (San Diego, CA, USA).

20 Plasmid DNA constructs

[0126] The cDNA encoding the 80 N-terminal amino acids of li (NCBI, GenBank Accession Number X00497) was amplified in a PCR reaction out of the vector pBluescript II KS(+) 41-1 (Stratagene, Heidelberg, Germany) obtained from A. Melms (Malcherek, G., Wirblich, C., Willcox, N., Rammensee, H. G., Trowsdale, J. & Melms, A. (1998) Eur. J. Immunol. 28, 1524-1533) and subcloned into the Hind III and Bam HI sites of pcDNA3 (pcDNA3-li; Invitrogen, Karlsruhe, Germany) using the 5' primer ATCGAAGCTTCCAAGATGCACAGGAGGAGAAGC (SEQ ID NO. 339) and the 3' primer ATCGGGATCCTTTGTCCAGCCGGCCCTGCTG (SEQ ID NO. 340). The genes of interest were amplified in a PCR reaction from cDNA from malignant renal tissue using the 5' primer ATCGGAATTCTGAGCTTCACCACTCGCTCC (SEQ ID NO. 341) and the 3' primer ATCGGCGGCCGCTTAATGCCTCAGAACTTTGGT (SEQ ID NO. 342) for Keratin 18 (NCBI, GenBank Accession Number X12881) and the 5' primer ATCGGAATTCTGGAACACCAGCTCCTGTGC (SEQ ID NO. 343) and the 3' primer ATCGGCGGCCGCTCAGATGTCCACGTCCCGCAC (SEQ ID NO. 344) for Cyclin D1 (NCBI, GenBank X59798), respectively. The obtained cDNA was subcloned using TOPO TA cloning (Invitrogen, Karlsruhe, Germany) and finally inserted into the EcoR I and Not I sites of pcDNA3-li, in frame with the li sequence.

35 Real-time quantitative PCR

[0127] RNA from cells was isolated using TRIzol reagent (Invitrogen, Karlsruhe, Germany) according to the manufacturer's recommendations. cDNA was synthesized from 1 µg of total RNA. Real-time quantitative PCR (qPCR) was performed using the ABI PRISM 7000 Sequence Detection System (Applied Biosystems, Darmstadt, Germany). SYBR Green PCR Master Mix (Applied Biosystems) was used for PCR amplification and real-time detection of PCR products. Primer sequences are as follows: 18S rRNA, 5' primer CGGCTACCACATCCAAGGAA (SEQ ID NO. 345) and 3' primer GCTGGAATTACCGCGGCT (SEQ ID NO. 346); Keratin 18, 5' primer GAGCCTGGAGACCGAGAAC (SEQ ID NO. 347) and 3' primer TTGCGAAGATCTGAGCCC (SEQ ID NO. 348); Cyclin D1, 5' primer CACGATTTCATTGAACACTTCC (SEQ ID NO. 349) and 3' primer TGAATTTCACATCTGTGGCAC (SEQ ID NO. 350). PCR reactions were carried out in 20 µl with 300 nM of each primer (18S reverse primer: only 50 nM). All samples were amplified in duplicate. Expression differences between transfected and wildtype cells for different genes were calculated from PCR amplification curves by relative quantification using the comparative threshold cycle (C_T) method (retrievable at <http://docs.appliedbiosystems.com/pebiidocs/04303859.pdf>). 18S ribosomal RNA was chosen as reference gene for normalisations.

50 Detection of fusion proteins

[0128] Fusion proteins were detected by Western blot analysis using the mAb PIN.1 (Stressgen, Biomol, Hamburg, Germany) which binds to amino acid residues 12-28 of li. Briefly, cells were lysed as described (Hsieh, C. S., deRoos, P., Honey, K., Beers, C. & Rudensky, A. Y. (2002) J. Immunol. 168, 2618-2625), lysates were boiled in Laemmli loading buffer, separated on a 12 % SDS-PAGE and transferred onto nitrocellulose membranes. After a saturation step with BSA, membranes were incubated for 1 h at room temperature with the mAb PIN.1 (1 µg/ml). Proteins were visualised using a peroxidase-coupled sheep anti-mouse IgG (Amersham Pharmacia, Freiburg, Germany). In some cases, transfected cells were cultured in the presence of 10-100 µM chloroquin (Sigma, Steinheim, Germany) in order to investigate

the endosomal/lysosomal targeting of the fusion proteins. Cells were then lysed and proteins were detected by Western blot as described above.

[0129] Ii-keratin 18 was also detected by immunoprecipitation and subsequent *in situ* digestion with trypsin followed by mass spectrometric analysis. Briefly, cells were lysed as described (Hsieh, C. S., deRoos, P., Honey, K., Beers, C. & Rudensky, A. Y. (2002) J. Immunol. 168, 2618-2625) and incubated with the mAb PIN.1 and protein A-sepharose beads (Pharmacia, Uppsala, Sweden). Sepharose pellets were washed, boiled in Laemmli loading buffer and run on a 12 % SDS-PAGE. Protein spots were excised from the gel and digested *in situ* with trypsin, essentially as described (Shevchenko, A., Wilm, M., Vorm, O. & Mann, M. (1996) Anal. Chem. 68, 850-858). The subsequent analysis was performed on a MALDI-TOF mass spectrometer (Reflex III, Bruker Daltonik, Bremen, Germany). The protein identity was verified by tandem MS spectra recorded on a hybrid quadrupole orthogonal acceleration time-of-flight tandem mass spectrometer (QStar Pulsar i Qqoa ToF; Applied Biosystems-MDS Sciex, Weiterstadt, Germany)

Elution of MHC Class II bound Peptides

[0130] Frozen cell pellets (3.5 to 5×10^{10} cells) were processed as previously described (Schirle, M., Keilholz, W., Weber, B., Gouttefangeas, C., Dumrese, T., Becker, H. D., Stevanovic, S. & Rammensee, H. G. (2000) Eur. J. Immunol. 30, 2216-2225) and peptides were isolated according to standard protocols (Seeger, F. H., Schirle, M., Keilholz, W., Rammensee, H. G. & Stevanovic, S. (1999) Immunogenetics 49, 996-999) using the HLA-DR specific mAb L243 (Lampson, L. A. & Levy, R. (1980) J. Immunol. 125, 293-299).

Molecular analysis of DR-eluted peptides

[0131] Peptides were separated by reversed-phase high performance liquid chromatography (HPLC, SMART system, μ RPC C2/C18 SC 2.1/10; Amersham Pharmacia Biotech, Freiburg, Germany), and fractions were analysed by MALDI-TOF mass spectrometry (MS) using a Bruker Reflex III mass spectrometer (Bruker Daltonik). Differentially presented peptides were further analysed by nano-ESI (electrospray ionisation) tandem MS on a hybrid quadrupole orthogonal acceleration time-of-flight tandem mass spectrometer (Q-TOF; Micromass, Manchester, United Kingdom) as described (Schirle, M., Keilholz, W., Weber, B., Gouttefangeas, C., Dumrese, T., Becker, H. D., Stevanovic, S. & Rammensee, H. G. (2000) Eur. J. Immunol. 30, 2216-2225).

Peptide synthesis and analysis

[0132] Peptides were synthesised in an automated peptide synthesiser EPS221 (Abimed, Langenfeld, Germany) following the Fmoc/tBu strategy. After removal from the resin by treatment with TFA/phenol/ethanedithiol/thioanisole/water (90/3.75/1.25/2.5/2.5 by vol.) for 1 h or 3 h (arginine-containing peptides) peptides were precipitated from methyl-tert. butyl ether, washed once with methyl-tert. butyl ether and twice with diethyl ether and resuspended in water prior to lyophilization. Synthesis products were analysed by HPLC (Varian star, Zinsser analytics, München, Germany) and MALDI-TOF mass spectrometry (future, GSG, Bruchsal, Germany). Peptides of less than 80 % purity were purified by preparative HPLC.

Monocyte-derived dendritic cells

[0133] Peripheral blood mononuclear cells (PBMC) were prepared according to classical procedures from an HLA-DRB1*0408-, HLA-DRB1*1101-, HLA-DRB3*0202-, HLA-DRB4*01-positive donor. Dendritic cells (DC) were obtained from plastic-adherent PBMC cultured in the presence of GM-CSF and IL-4 for 6 days as described previously (Bender, A., Sapp, M., Schuler, G., Steinman, R. M. & Bhardwaj, N. (1996) J. Immunol. Methods 196, 121-135), except that the medium used was X-VIVO 15 (BioWhittaker) without serum. At day 6, immature DC were analysed by flow cytometry for CD1a, CD11c, CD14, CD40, CD83, CD86 as well as HLA-DR cell surface expression on a FACScalibur apparatus with CELLQuest software (Becton Dickinson, Mountain View, CA). DC were then matured in the presence of 50 μ g/ml polyinosinic-polycytidylic acid (Poly I/C, Amersham Pharmacia, Uppsala, Sweden) and 10 ng/ml TNF- α (PharMingen) for two additional days and analysed again by flow cytometry for CD14, CD80, CD83 and CD86 cell surface expression. Mature DC showed a clear up-regulation of CD80, CD83 and CD86 molecules.

Generation of peptide-specific T-helper cells

[0134] 3×10^5 matured DC were loaded for two hours with 10 μ M of peptide NPPSMVAAGSVVAHV in a 24-well plate and extensively washed. Then 4×10^6 fresh autologous PBMC were added onto DC in the presence of 10 ng/ml IL-12p70 in order to favour Th-1 development. PBMC were weekly restimulated with peptide-loaded irradiated autologous PBMC

in the presence of 10 U/ml IL-2 and 5 ng/ml IL-7. After 3 and 5 restimulations, T cells were pooled and tested against autologous PBMC in the presence of peptide. The T-helper cell line was then amplified every 1-2 weeks with irradiated allogenic PBMC in the presence of 1 μ g/ml PHA, 25-50 U/ml IL-2 and 5 ng/ml IL-7 and then tested for the recognition of the transfected cell lines. Every three to four weeks, the T-helper cell line was restimulated with irradiated autologous PBMC in the presence of 10 μ M peptide, 10 U/ml IL-2 and 5 ng/ml IL-7.

Functional assays and characterisation of the T-helper cell line

[0135] T-helper cell activation was tested by cell proliferation as estimated by thymidine incorporation as well as cytokine secretion. Briefly, 2×10^5 cells were incubated in triplicates in a 96-well plate with 2×10^5 irradiated autologous PBMC in the presence or absence of 10 μ M peptide or 3 μ g/ml PHA. After 24 hours, two portions of 50 μ l supernatant were harvested and frozen and 50 μ l fresh medium was added to the cells. After 54 hours, 50 μ l of tritiated thymidine-containing medium (0.074 MBq/well, Hartmann Analytic, Braunschweig, Germany) was added and thymidine incorporation measured at 72 hours using a scintillation counter (Microbeta, Wallac, Freiburg, Germany). Cell proliferation is expressed as a stimulation index (S.I.), which corresponds to the ratio: (mean cpm of stimulated T cells)/(mean cpm of unstimulated T cells). IL-2 secretion was measured using the IL-2 dependent CTLL-2 cell line. Briefly, 10^4 cells were incubated in the presence of supernatants for 20-24 hours. Then, thymidine-containing-medium (0.055 MBq/well) was added for 7-8 additional hours and thymidine incorporation was measured as described above. Results are also expressed as a S.I.

[0136] IFN- γ , IL-4 and IL-6 secretion was measured by sandwich ELISA using antibody pairs and peroxidase-conjugated streptavidin from PharMingen and according to Manufacturer's recommendations. We used the Supersensitive TMB (Sigma, Deisenhofen, Germany) as a substrate and the reaction was stopped using a 2 M H_2SO_4 solution. OD_{450} was then measured and results expressed in pg/ml according to the standards.

Recognition of cyclin D1-transfected cells by the peptide-specific T-helper cell line

[0137] Absence of detectable alloreaction of T cells against the transfectants was demonstrated by co-culturing fresh PBMC from the donor used to generate the T-helper line in the presence of different cell numbers of irradiated transfectants. Cell proliferation as well as IL-2, IL-4, IL-6 and IFN- γ secretion was measured as described above and the Effector/Target ratio to be used in further experiments was thus determined.

[0138] Recognition of the naturally processed peptide derived from cyclin D1 was tested by co-culturing the peptide-specific T-helper cell line (2×10^5 cells) in the presence of irradiated Awells (4×10^4 cells) transfected with a plasmid coding for either cyclin D1 or keratin 18 as a negative control and according to the cell ratio determined above. Irradiated autologous PBMC in the presence of 10 μ M peptide or 3 μ g/ml PHA served as positive controls. Cell proliferation as well as IL-2 and IFN- γ secretion was measured as described above. In some experiments, cells were cultured in the presence of 20 μ g/ml of purified L243 antibody.

Results

Generation of fusion protein-expressing cell clones

[0139] We cloned the cDNA encoding the 80 N-terminal amino acids of Ii in the vector pcDNA3 in such a way that the 3' end of the insert was followed by a general cloning site (GCS). This gave us a versatile vector to express fusion proteins of Ii and the genes of interest. In frame with Ii we cloned the cDNA of cyclin D1, as well as keratin 18 as a control.

[0140] The Awells cell line was stably transfected with vectors encoding the two fusion proteins using electroporation. Subsequently, single-cell-clones were generated and tested on their antigen expression on mRNA and protein level. Compared to the wildtype (untransfected cell line), the best Ii-keratin 18 clone expressed 5,700 times more keratin 18 and the best Ii-cyclin D1 clone expressed 1,200 times more cyclin D1, as determined by real-time quantitative PCR analysis. The data were normalised on 18S ribosomal RNA.

[0141] In Western blot analysis, the PIN.1 antibody was used to detect the I1-fusion proteins. Compared to the wildtype, where only two bands corresponding to two isoforms of Ii (Warmerdam, P. A., Long, E. O. & Roche, P. A. (1996) J. Cell Biol. 133, 281-291) were detected, one additional band could be observed in each clone, representing the Ii-keratin 18 or Ii-cyclin D1 fusion proteins with the expected molecular weights (**Figure 1**). In the case of the clone Awells-Ii-keratin 18 the fusion protein was also identified via immunoprecipitation followed by an *in situ* digestion with trypsin and subsequent MS/MS analysis.

[0142] The clones were also tested for their HLA class I and class II cell surface expression levels by flow cytometry, in order to determine whether the transfection and cloning procedure interfered with it. Both clones showed normal expression levels of HLA class I and class II molecules, as compared to the untransfected cell line.

Endosomal/lysosomal targeting of the fusion proteins

[0143] It has already been described that the N-terminus of Ii is sufficient to target proteins into the MHC class II pathway (Sanderson, S., Frauwirth, K. & Shastri, N. (1995) Proc. Natl. Acad. Sci. U. S. A 92, 7217-7221, Wang, R. F., Wang, X., Atwood, A. C., Topalian, S. L. & Rosenberg, S. A. (1999) Science 284, 1351-1354, Malcherek, G., Wirblich, C., Willcox, N., Rammensee, H. G., Trowsdale, J. & Melms, A. (1998) Eur. J. Immunol. 28, 1524-1533). To test whether our constructs really followed that route of Ag processing, we incubated the transfectants for 4 h with increasing amounts of chloroquin, a cytotoxic drug which inhibits lysosomal degradation of proteins by raising the lysosomal pH (Kaplan, J. & Keogh, E. A. (1981) Cell 24, 925-932, Tietze, C., Schlesinger, P. & Stahl, P. (1982) J. Cell Biol. 92, 417-424, Seglen, P. O. (1983) Methods Enzymol. 96:737-64., 737-764). Cells were then lysed and fusion proteins were detected by Western blot. **Figure 2** shows that the protein bands get more and more intense with increasing amounts of chloroquin, indicating that fusion protein amounts increase with chloroquin concentrations and thus proving that the fusion proteins follow the MHC class II pathway of protein degradation.

Differential mass spectrometric analysis of HLA-DR-bound peptides

[0144] 3.5 to 5×10^{10} cells from each clone and from the untransfected cell line were grown and the HLA-DR-bound peptides isolated and separated via HPLC as described previously (Seeger, F. H., Schirle, M., Keilholz, W., Rammensee, H. G. & Stevanovic, S. (1999) Immunogenetics 49, 996-999). The HPLC-chromatograms of the untransfected cell line and the Awells-Ii-cyclin D1 clone were compared (**Figure 3**). Minor, mostly quantitative differences in the HLA-DR-presented peptide repertoire summed up to slightly different UV traces as shown in **Figure 3**. As expected from our experience, no distinct UV signals could be assigned to peptides exclusively presented by the transfectants. The only subtle differences in HLA-DR-restricted peptide presentation between Awells and the transfected lines became also visible by MALDI-TOF analysis where most of the HPLC fractions contained identical patterns. **Figure 4** shows the mass spectrometric analysis of the only fraction with a striking individual signal (m/z : 1732.96) which occurred only in the peptide mixture eluted from the keratin 18-transfected line and represented a keratin-18-derived peptide. In **Figure 5**, the m/z signal at 1370.1 indicates an exclusively presented peptide from the cyclin D1-transfectant. Both peptides were analysed in greater detail by nanoflow ESI MS/MS (tandem MS). The inventors were able to identify the peptides NPPSMVAAGSVVAHV (SEQ ID No. 1) (cyclin D1₁₉₈₋₂₁₂) (**Figure 6**) and SHYFKIIEDLRAQI (SEQ ID No. 2) (keratin 18₁₂₆₋₁₃₉) derived from the two transfected fusion proteins, respectively. The sequences were verified by mass spectra of the corresponding synthetic peptides.

Generation and characterisation of a peptide-specific T-helper cell line

[0145] To establish a proof of concept for the identification of novel, HLA-class II-derived, tumour-associated and putatively immunogenic peptides, T cells specific for the identified cyclin D1 peptide were induced by *in vitro* stimulation with the corresponding synthetic peptide loaded onto HLA-DR4⁺ dendritic cells. After the third and the fifth round of *in vitro* (re-)stimulation, respectively, the specificity of the T-helper cell line was tested. T cells were specifically stimulated by the cyclin D1 peptide, as shown in **Figure 7** (upper panel). T cells proliferated in response to autologous PBMC loaded with the cyclin D1 peptide (S.I. = 5.4). As a positive control, PHA induced a strong T-cell proliferation (S.I. = 330). The inventors next analysed which type of T-helper cells (Th1 versus Th2) was stimulated in response to the peptide by examining the cytokine profile. As also shown in **Figure 7** (lower panel), the T cells produced IL-2 in response to the peptide, although to a low extent, whereas they were still sensitive to PHA stimulation. On the contrary, peptide-induced T-cell stimulation resulted in a strong IFN- γ secretion (3250 pg/ml, Fig. 7C) but no IL-4 or IL-6 secretion, although T-cells were still highly and moderately sensitive to PHA-induced cytokine secretion, respectively. Stimulation with an unrelated peptide as a negative control for eventual unspecific activation of CD4⁺ T-helper cells with T-cell receptors specific for HLA-DR4/cyclin D1₁₉₈₋₂₁₂ is presented in **Figure 8**. In conclusion, the established CD4⁺ T-helper cell line is specific for the cyclin D1₁₉₈₋₂₁₂ peptide and is of the Th1 type. This type is particularly important in helping specific CD8⁺ killer T cells in the elimination of tumour cells.

The peptide-specific T-helper cell line also recognises cyclin D1-transfected cells

[0146] Because Awells cells and the T-cell line are not perfectly HLA-matched, we first tested whether any alloreaction could arise by co-culturing both. Briefly, different cell numbers of irradiated Awells-Ii-keratin 18 or Awells-Ii-cyclin D1 transfectants were co-cultured in the presence of a fixed number of PBMC from the T cell donor, and cell proliferation as well as IL-2, IL-4, IL-6 and IFN- γ secretion were measured. A moderate T-cell proliferation was induced by both transfectants at high cell numbers but no cytokine secretion was observed (data not shown). We thus decided to use an (effector T cells)/(target cells) ratio of 5/1, at which only a slight T-cell proliferation was observed in the absence of

cytokine secretion. As a consequence, T-cell activation resulting in cytokine secretion could only be induced specifically by the cognate antigen presented by the transfectant.

[0147] The T-helper cell line specific for the cyclin D1 peptide was able to recognise the transfected cells over-expressing the cyclin D1 protein and naturally processing and presenting the cyclin D1 peptide in association with HLA-DR molecules. As shown in Figure 8, irradiated Awells-li-cyclin D1 transfectants were able to specifically activate the T-helper cell line as observed by IL-2 secretion (S.I. = 4.0). On the contrary, Awells-li-keratin 18 transfectants (used as negative control for T-cell stimulation and known to present the unrelated keratin 18 peptide₁₂₆₋₁₃₉ in association with HLA-DR) did not induce T-cell activation, indicating that the peptide-specific T-helper cell line specifically recognises the cognate antigen. Moreover, these results prove that the cyclin D1 peptide used in the present invention is a naturally processed peptide containing a T-cell epitope. This activation could be inhibited (by 71.2%) by the presence of the HLA-DR-specific blocking L243 Ab.

Production of activated cytotoxic lymphocytes (CTL) using Class II molecules and the peptides antigen cyclin D1₁₉₈₋₂₁₂ and their administration

[0148] Activated cytotoxic T lymphocytes (CTLs) are produced using HLA-DR Class II molecules and the peptide from cyclin D1₁₉₈₋₂₁₂ (SEQ ID No. 1).

[0149] In general, the method described in PCT patent application WO 93/17095 is used to produce the CTLs. Awells cells are used to present the peptide antigen to CTL. The HLA-DR molecule is expressed in the Awells cells. The peptide to be tested is synthesised on an Applied Biosystems synthesiser, ABI 431A (Foster City, CA, USA) and subsequently purified by HPLC. As is described in detail in WO 93/17095, in order to optimise the in vitro conditions for the generation of specific cytotoxic T cells, the culture of stimulator cells is maintained in an appropriate medium. The stimulator cells are Awells cells, which are preferably maintained in serum-free medium (e.g. Excell 400).

[0150] Prior to incubation of the stimulator cells with the cells to be activated, e.g. precursor CD4⁺ cells, an amount of antigenic peptide is added to the stimulator cell culture, of sufficient quantity to become loaded onto the human Class II molecules to be expressed on the surface of the stimulator cells. A sufficient amount of peptide is an amount that will allow about 200, and preferably 200 or more, human Class II MHC molecules loaded with peptide to be expressed on the surface of each stimulator cell. The stimulator cells are typically incubated with > 20 pg/ml peptide.

[0151] Resting or precursor CD4⁺ cells are then incubated in culture with the appropriate stimulator cells for a time period sufficient to activate the CD4⁺ cells. The CD4⁺ cells shall thus be activated in an antigen-specific manner. The ratio of resting or precursor CD4⁺ (effector) cells to stimulator cells may vary from individual to individual and may further depend upon variables such as the amenability of an individual's lymphocytes to culturing conditions. The lymphocyte: stimulator cell (Awells cell) ratio is typically in the range of about 30: 1 to 300: 1. For example, 3 x 10¹ human PBL and 1 x 10⁶ live Awells cells are admixed and maintained in 20 ml of RPMI 1640 culture medium.

[0152] The effector/stimulator culture are maintained for as long a time as is necessary to stimulate a therapeutically usable or effective number of CD4⁺ cells. The optimum time is typically between about one and five days, with a "plateau", i.e. a "maximum" specific CD4⁺ activation level, generally being observed after five days of culture. In vitro activation of CD4⁺ cells is typically detected within a brief period of time after transfection of a cell line. Transient expression in a transfected cell line capable of activating CD4⁺ cells is detectable within 48 hours of transfection. This clearly indicates that either stable or transient cultures of transformed cells expressing human Class II MHC molecules are effective in activating CD4⁺ cells.

[0153] Activated CD4⁺ cells may be effectively separated from the stimulator (Awells) cells using monoclonal antibodies specific for the stimulator cells, for the peptides loaded onto the stimulator cells, or for the CD4⁺ cells (or a segment thereof) to bind their appropriate complementary ligand. Antibody-tagged molecules are then extracted from the stimulator effector cell admixture via immunoprecipitation or immunoassay methods.

[0154] Effective, cytotoxic amounts of the activated CD4⁺ cells can vary between in vitro and in vivo uses, as well as with the amount and type of cells that are the ultimate target of these killer cells between about 1x10⁶ and 1X10¹² activated CTL are used for adult humans.

[0155] The activated CD4⁺ cells are harvested from the Awells cell culture prior to administration of the CD4⁺ cells to the individual being treated.

[0156] Methods of re-introducing cellular components are used such as those exemplified in US Patent No 4,844,893 to Honsik et al and US Patent No 4,690,915 to Rosenberg. For example, administration of activated CD8 cells via intravenous infusion is appropriate.

Table 1: Tumour-associated T-helper cell peptide epitopes as identified in the present invention

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
1.	NPPSMVAAGSVVAHV	198-212	P24385	SEQ ID-No. 1

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
		CCND 1		
5	2. SHWKIIEDLRAQI	126-139 KART18	P05783	SEQ ID-No. 2
	3. SGTQFVCETVIRSL	644-657 M17S2	Q14596	SEQ ID-No. 3
10	4. SGTQFVCETVIRSLT	644-658 M17S2	Q14596	SEQ ID-No. 4
	5. LKPAFKKDGSTTAGN	260-274 ACAA 1	P09110	SEQ ID-No. 5
15	6. RDLTDYLMKILTERGYS	183-199 ACTG1	P02571	SEQ ID-No. 6
	7. TDYLMKILTERGYS	186-199 ACTG1	P02571	SEQ ID-No. 7
20	8. TDYLMKILTERGYSFT	186-201 ACTG1	P02571	SEQ ID-No. 8
	9. WISKQEYDESGPSIVHRKCF	356-375 ACTG 1	P02571	SEQ ID-No. 9
25	10. YPEEAYIADLDAKSGAS	247-263 ACLY	P53396	SEQ ID-No. 10
	11. EGRSFLAFPTLRAYHTL	1378-1394 AGRN	XP_ 372195	SEQ ID-No. 11
30	12. GRSFLAFPTLRAYHT	1379-1393 AGRN	XP_ 372195	SEQ ID-No. 12
	13. GRSFLAFPTLRAYHTL	1379-1394 AGRN	XP_ 372195	SEQ ID-No. 13
35	14. ISRAQFVPLPVSVSVE	185-200 AHSG	P12763	SEQ ID-No. 14
	15. SPDLPKLPDPNTLCDEF	133-150 ALB	P02769	SEQ ID-No. 15
40	16. APGKGILAADESTGSIA	24-40 ALDOA	P04075	SEQ ID-No. 16
	17. DVPKWISIMTERSVPHLQ	208-225 ANXA2	P07355	SEQ ID-No. 17
45	18. VPKWISIMTERSVPH	209-223 ANXA2	P07355	SEQ ID-No. 18
	19. SASYKADTVAKVQG	1848-1861 APOB	P04114	SEQ ID-No. 19
50	20. IVVYTGDRVTMGRIA	257-271 ATP1A1	P05023	SEQ ID-No. 20
	21. IWYTGDRVTMGRIAT	257-272 ATP1A1	P05023	SEQ ID-No. 21
55	22. FYLLYYTEFTPTEKDEY	82-98 B2M	P61769	SEQ ID-No. 22

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	23. FYLLYYTEFTPTEKDEYA	82-99 B2M	P61769	SEQ ID-No. 23
	24. LLYYTEFTPTEK	84-95 B2M	P61769	SEQ ID-No. 24
10	25. LLYYTEFTPTEKD	84-96 B2M	P61769	SEQ ID-No. 25
	26. LLYYTEFTPTEKDE	84-97 B2M	P61769	SEQ ID-No. 26
15	27. LLYYTEFTPTEKDEYA	84-99 B2M	P61769	SEQ ID-No. 27
	28. YLLYYTEFTPTEK	83-95 B2M	P61769	SEQ ID-No. 28
20	29. YLLYYTEFTPTEKDE	83-97 B2M	P61769	SEQ ID-No. 29
	30. YLLYYTEFTPTEKDEY	83-98 B2M	P61769	SEQ ID-No. 30
25	31. YLLYYTEFTPTEKDEYA	83-99 B2M	P61769	SEQ ID-No. 31
	32. YTEFTPTEKDEY	87-98 B2M	P61769	SEQ ID-No. 32
30	33. YYTEFTPTEKDEY	86-98 B2M	P61769	SEQ ID-No. 33
35	34. TGKTPGAEIDFKYALIGTAV GVA	74-96 C10orf1 28	XP_ 378226	SEQ ID-No. 34
	35. TEEFEVTKTAVAHKPG	138-153 C19orf10	NP_ 061980	SEQ ID-No. 35
40	36. RGYMEIEQSVKSFK	173-186 C5orf15	NP_ 064584	SEQ ID-No. 36
	37. IPWFVSDTTIHDFN	285-298 C6orf211	NP_ 078849	SEQ ID-No. 37
45	38. IAYDVTYSLACVR	306-318 CCR7	P32248	SEQ ID-No. 38
	39. NIAYDVTYSLACVR	305-318 CCR7	P32248	SEQ ID-No. 39
50	40. SLMVTNDGATILKN	60-73 CCT2	P78371	SEQ ID-No. 40
	41. ATQYFADRDMFCAGRVP	299-315 CCT7	Q99832	SEQ ID-No. 41
55	42. VATQYFADRDMFCAGRVP	298-315 CCT7	Q99832	SEQ ID-No. 42
	43. GPKPLFRMSSLVGP	26-40	P11836	SEQ ID-No. 43

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
		MS4A1		
5	44. GPKPLFRRMSSLVGPT	26-41 MS4A1	P11836	SEQ ID-No. 44
	45. GPKPLFRRMSSLVGPTQS	26-43 MS4A1	P11836	SEQ ID-No. 45
10	46. SGPKPLFRRMSSLVGPTQS	25-43 MS4A1	P11836	SEQ ID-No. 46
	47. SGPKPLFRRMSSLVGPTQSF	25-44 MS4A 1	P11836	SEQ ID-No. 47
15	48. RDMFTLEDTL	140-149 CD38	P28907	SEQ ID-No. 48
	49. RDMFTLEDTLLG	140-151 CD38	P28907	SEQ ID-No. 49
20	50. RDMFTLEDTLLGYLAD	140-155 CD3 8	P28907	SEQ ID-No. 50
	51. VQRDMFTLEDTL	138-149 CD38	P28907	SEQ ID-No. 51
25	52. SPGEPQIIFCRSEAAHQG	389-406 PTPRC	P08575	SEQ ID-No. 52
	53. SPGEPQIIFCRSEAAHQGVI	389-408 PTPRC	P08575	SEQ ID-No. 53
30	54. ATPLLMQALPMGALPQGP	110-127 CD74	P04233	SEQ ID-No. 54
	55. GHLKIMHDAIGFR	160-172 CLN5	075503	SEQ ID-No. 55
35	56. LGHLKIMHDAIGFR	159-172 CLN5	075503	SEQ ID-No. 56
	57. NPPLFALDKDAPLRY	47-61 CLSTN3	Q9BQT9	SEQ ID-No. 57
40	58. LEKIVLDNSVFSEHRN	1008-1023 CLTCLI	P53675	SEQ ID-No. 58
	59. GQRRFNLQKNFVGKVA	177-192 COCH	043405	SEQ ID-No. 59
45	60. IGQRRFNLQKNFVGKVAL	176-193 COCH	043405	SEQ ID-No. 60
	61. RRFNLQKNFVGKVA	179-192 COCH	043405	SEQ ID-No. 61
50	62. VPGTYKITASARGYN	836-850 CPD	075976	SEQ ID-No. 62
	63. LAKWVAIQSVSAWPE	22-36 CNDP2	Q96KP4	SEQ ID-No. 63
55	64. VARFAAAATQQQTA	404-417 CPNE3	075131	SEQ ID-No. 64

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	65. WGALATISTLEAVR	68-81 CREW	Nip_ 003842	SEQ ID-No. 65
	66. VGVPRITVTAVSASG	385-400 IL27RA	NP_ 004834	SEQ ID-No. 66
10	67. VPYRITVTAVSASG	387-400 IL27RA	NP_ 004834	SEQ ID-No. 67
	68. DHNFVKAINAIQKSW	171-185 CTSC	P53634	SEQ ID-No. 68
15	69. KKVVVYLQKLDYDDL	62-79 CTSC	P53634	SEQ ID-No. 69
	70. KYDHNFVKAINAIQKSWT	169-186 CTSC	P53634	SEQ ID-No. 70
20	71. SGMDYWIVKNSWGTGWG	418-434 CTSC	P53634	SEQ ID-No. 71
	72. YDHNFVKAINAIQK	170-183 CTSC	P53634	SEQ ID-No. 72
25	73. YDHNFVKAINAIQKSWT	170-186 CTSC	P53634	SEQ ID-No. 73
	74. IFSFYLSRDPDAQPG	228-242 CTSD	P07339	SEQ ID-No. 74
30	75. LSRDPDAQPGGE	233-244 CTSD	P07339	SEQ ID-No. 75
	76. GKEYWLKNSWGHN	290-303 CTSS	P25774	SEQ ID-No. 76
35	77. KNLKFVMLHNLHSM	54-68 CTSS	P25774	SEQ ID-No. 77
	78. TTAFQYIIDNKGID	186-199 CTSS	P25774	SEQ ID-No. 78
40	79. GTEYWIVRNSWGEPW	253-267 CTS	Q9UBR2	SEQ ID-No. 79
	80. GYLPNQLFRTF	730-740 DDX1	Q92499	SEQ ID-No. 80
45	81. IRFVVDGKVKEM	367-379 DHX34	Q14147	SEQ ID-No. 81
	82. MEKYNIEKDIAAYIK	29-43 Dlc2	NP_ 542408	SEQ ID-No. 82
50	83. LPFGAQSTQRGHTE	114-127 DPP7	Q9UHL4	SEQ ID-No. 83
	84. SKYYVTIIDAPGHRD	83-97 EEF1A1	P04720	SEQ ID-No. 84
55	85. IEKFEKEA,AEMGKG	39-52 EEF1A2	Q05639	SEQ ID-No. 85
	86. IEKFEKEAAEMGKGS	39-53	Q05639	SEQ ID-No. 86

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
		EEF1A2		
5	87. IEKFEKEAAEMGKGSF	39-54 EEF1A2	Q05639	SEQ ID-No. 87
	88. TIEKFEKEAAEMGKGSF	38-54 EEF1A2	Q05639	SEQ ID-No. 88
10	89. DIDAIFKDLSIRSVR	57-71 WBSCR1	Q15056	SEQ ID-No. 89
	90. GVPLYRHIADLAGN	126-139 ENO1	P06733	SEQ ID-No. 90
15	91. GVPLYRHIADLAGNSEV	126-142 ENO1	P06733	SEQ ID-No. 91
	92. IKEKYGKDATNVGDEG	195-210 ENO1	P06733	SEQ ID-No. 92
20	93. IKEKYGKDATNVGDEGG	195-211 ENO1	P06733	SEQ ID-No. 93
	94. KEKYGKDATNVGDEGG	196-211 ENO1	P06733	SEQ ID-No. 94
25	95. VIKEKYGKDATNVGDEGG	194-211 ENO1	P06733	SEQ ID-No. 95
	96. VPLYRHIADLAGN	127-139 ENO1	P06733	SEQ ID-No. 96
30	97. VPLYRHIADLAGNSE	127-141 ENO1	P06733	SEQ ID-No. 97
	98. VPLYRHIADLAGNSEV	127-142 ENO1	P06733	SEQ ID-No. 98
35	99. VPLYRHIADLAGNSEVI	127-143 ENO1	P06733	SEQ ID-No. 99
	100. LLQKLILWRVL	305-315 FLJ32752	NP_ 653267	SEQ ID-No. 100
40	101. LQNIIPASTGAAKAVG	202-217 GAPD	P04406	SEQ ID-No. 101
	102. EPIEQKFVSISDLLVPK	374-390 GDI2	P50395	SEQ ID-No. 102
45	103. AIFLFVDKTPQSS	75-88 GABARAPL2	P60520	SEQ ID-No. 103
	104. AIFLFVDKTPQSSSL	75-89 GABARAPL2	P60520	SEQ ID-No. 104
50	105. AIFLFVDKTPQSSSLT	75-90 GABARAPL2	P60520	SEQ ID-No. 105
	106. FVDKTPQSSSL	79-89 GABARAPL2	P60520	SEQ ID-No. 106
55	107. LPSEKAIFLFVDKTPQSSSLT	70-90 GABARAPL2	P60520	SEQ ID-No. 107

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	108. KVNLLKIKTELCKKEV	1035-1050 GLG1	Q92896	SEQ ID-No. 108
	109. LGKWCSEKTETGQE	643-656 GLG1	Q92896	SEQ ID-No. 109
10	110. VNLLKIKTELCKKEV	1036-1050 GLG	Q92896	SEQ ID-No. 110
	111. GNYRIESVLSSSG	166-178 GM2A	P17900	SEQ ID-No. 111
15	112. GNYRIESVLSSSGK	166-179 GM2A	P17900	SEQ ID-No. 112
	113. LGCIKIAASLKGI	181-193 GM2A	P17900	SEQ ID-No. 113
20	114. RLGCIKIAASLKGI	180-193 GM2A	P17900	SEQ ID-No. 114
	115. TGNRYIESVLSSSG	165-178 GM2A	P17900	SEQ ID-No. 115
25	116. TGNRYIESVLSSSGK	165-179 GM2A	P17900	SEQ ID-No. 116
	117. TGNRYIESVLSSSGKR	165-180 GM2A	P17900	SEQ ID-No. 117
30	118. TTGNRYIESVLSSSG	164-178 GM2A	P17900	SEQ ID-No. 118
	119. TTGNRYIESVLSSSGK	164-179 GM2A	P17900	SEQ ID-No. 119
35	120. VTRAFVAARTFAQGL	211-225 GPC4	075487	SEQ ID-No. 120
	121. DIFERIASEASRL	68-80 HIST1H2BL	Q99880	SEQ ID-No. 121
40	122. DIFERIASEASRLA	68-81 HIST1H2BL	Q99880	SEQ ID-No. 122
	123. DIFERIASEASRLAH	68-82 HIST1H2BL	Q99880	SEQ ID-No. 123
45	124. DIFERIASEASRLAHY	68-83 HIST1H2BL	Q99880	SEQ ID-No. 124
	125. VNDIFERIASEASRLAHYN	66-84 HIST1H2BL	Q99880	SEQ ID-No. 125
50	126. DDTQFVRFDSDAASQR	53-68 - HLA-A	CAA73716	SEQ ID-No. 126
	127. DDTQFVRFDSDAASQRME	53-70 HLA-A	CAA73716	SEQ ID-No. 127
55	128. DDTQF VRFDSDAA S QRMEP	53-71 HLA-A	CAA73716	SEQ ID-No. 128

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	129. DDTQFVRFDSDAASQRMEP R	53-72 HLA-A	CAA73716	SEQ ID-No. 129
10	130. DTEFVRFDSDAASQRME	54-70 HLA-A	CAA73716	SEQ ID-No. 130
	131. DTEFVRFDSDAASQRMEP	54-71 HLA-A	CAA73716	SEQ ID-No. 131
15	132. DTQFVRFDSDAASQ	54-67 HLA-A	CAA73716	SEQ ID-No. 132
	133. DTQFVRFDSDAASQR	54-68 HLA-A	CAA73716	SEQ ID-No. 133
20	134. DTQFVRFDSDAASQRM	54-69 HLA-A	CAA73716	SEQ ID-No. 134
	135. DTQFVRFDSDAASQRME	54-70 HLA-A	CAA73716	SEQ ID-No. 135
25	136. DTQFVRFDSDAASQRMEP	54-71 HLA-A	CAA73716	SEQ ID-No. 136
30	137. DTQFVRFDSDAASQRMEPR AP	54-74 HLA-A	CAA73716	SEQ ID-No. 137
	138. FVRFDSDAASQR	57-68 HLA-A	CAA73716	SEQ ID-No. 138
35	139. FVRFDSDAASQRME	57-70 HLA-A	CAA73716	SEQ ID-No. 139
	140. KHKWEAAHVAEQLR	168-181 HLA-A	CAA73716	SEQ ID-No. 140
40	141. QFVRFDSDAASQRME	56-70 HLA-A	CAA73716	SEQ ID-No. 141
	142. TQFVRFDSDAASQ	55-67 HLA-A	CAA73716	EQ ID-No. 142
45	143. TQFVRFDSDAASQR	55-68 HLA-A	CAA73716	SEQ ID-No. 143
	144. TTKHKWEAAHVAEQLR	166-181 HLA-A	CAA73716	SEQ ID-No. 144
50	145. VDDTEFVRFDSDAASQR	52-68 HLA-A	CAA73716	SEQ ID-No. 145
55	146. VDDTQFVRFDSDAASQRME PRAPW	52-75 HLA-A	CAA73716	SEQ ID-No. 146
	147.	52-77	CAA73716	SEQ ID-No. 147

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	VDDTQFVRFDSDAASQRME PRAPWIE	HLA-A		
148.	DLSSWTAADTAAQIT .	153-167 HLA-B	P30481	SEQ ID-No. 148
10	149. DLSSWTAADTAAQITQ	153-168 HLA-B	P30481	SEQ ID-No. 149
150.	DLSSWTAADTAAQITQRKW	153-171 HLA-B	P30481	SEQ ID-No. 150
15	151. DLSSWTAADTAAQITQRKW EAARVA	153-177 HLA-B	P30481	SEQ ID-No. 151
20	152. DTLFVRFDSDATSPRKEPRA P	54-74 HLA-B	P30481	SEQ ID-No. 152
25	153. EDLSSWTAADTAAQIT	152-167 HLA-B	P30481	SEQ ID-No. 153
154.	EDLSSWTAADTAAQITQR	152-169 HLA-B	P30481	SEQ ID-No. 154
30	155. EDLSSWTAADTAAQITQRK W	152-171 HLA-B	P30481	SEQ ID-No. 155
35	156. EDLSSWTAADTAAQITQRK WE	152-172 HLA-B	P30481	SEQ ID-No. 156
40	157. EDLSSWTAADTAAQITQRK WEAARVA	152-177 HLA-B	P30481	SEQ ID-No. 157
158.	GPEYWDRETQISKTN	80-94 HLA-B	P30481	SEQ ID-No. 158
45	159. KDYIALNEDLSSWTA	145-159 HLA-B	P30481	SEQ ID-No. 159
160.	LNEDLSSWTAADTAAQITQR KWE	150-172 HLA-B	P30481	SEQ ID-No. 160
50	161. LRWEPSSQSTVPIVGIVAG	296-314 HLA-B	P30481	SEQ ID-No. 161
162.	LSSWTAADTAAEITERKWE	154-172 HLA-B	P30481	SEQ ID-No. 162
55	163. LSSWTAADTAAQITQR	154-169 HLA-B	P30481	SEQ ID-No. 163

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	164. LSSWTAADTAAQITQRKW	154-171 HLA-B	P30481	SEQ ID-No. 164
	165. LSSWTAADTAAQITQRKWE	154-172 HLA-B	P30481	SEQ ID-No. 165
10	166. NEDLSSWTAADTAAQITQRK W	151-171 HLA-B	P30481	SEQ ID-No. 166
	167. TLFVRFDS DATSP	55-67 HLA-B	P30481	SEQ ID-No. 167
15	168. VDDTLFVRFDS DATSPRKEP RAP	52-74 HLA-B	P30481	SEQ ID-No. 168
20	169. DDTQFVQFSDAASPR	53-68 HLA-C	Q9TNN7	SEQ ID-No. 169
	170. DGKDYIALNEDLRSWT	143-158 HLA-C	Q9TNN7	SEQ ID-No. 170
25	171. DGKDYIALNEDLRSWTA	143-159 HLA-C	Q9TNN7	SEQ ID-No. 171
	172. DGKDYIALNEDLRSWTAA	143-160 HLA-C	Q9TNN7	SEQ ID-No. 172
30	173. DTQFVQFSDAASPR	54-68 HLA-C	Q9TNN7	SEQ ID-No. 173
	174. DTQFVQFSDAASPRG	54-69 HLA-C	Q9TNN7	SEQ ID-No. 174
35	175. DTQFVQFSDAASPRGEPR	54-72 HLA-C	Q9TNN7	SEQ ID-No. 175
40	176. DTQFVQFSDAASPRGEPR P	54-74 HLA-C	Q9TNN7	SEQ ID-No. 176
	177. DYIALNEDLRSWTA	146-159 HLA-C	Q9TNN7	SEQ ID-No. 177
45	178. FVQFSDAASPRGEP	57-71 HLA-C	Q9TNN7	SEQ ID-No. 178
	179. GKDYIALNEDLRSWT	144-158 HLA-C	Q9TNN7	SEQ ID-No. 179
50	180. GRLLRGYNQFAYDGK	131-145 HLA-C	Q9TNN7	SEQ ID-No. 180
	181. KDYIALNEDLRSW	145-157 HLA-C	Q9TNN7	SEQ ID-No. 181
55	182. TQFVQFSDAASPR	55-68 HLA-C	Q9TNN7	SEQ ID-No. 182

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(continued)

	Sequence	Position/ Gene symbol ⁱ	Acc. No. ⁱⁱ	SEQ ID-No.
5	183. TQFVQFSDAASPRGEPR	55-72 HLA-C	Q9TNN7	SEQ ID-No. 183
10	184. VDDTQFVQFSDAASPRGEPR	52-72 HLA-C	Q9TNN7	SEQ ID-No. 184
15	185. VDDTQFVQFSDAASPRGERAP	52-74 HLA-C	Q9TNN7	SEQ ID-No. 185
20	186. YVDDTQFVQFSDAASPRGEPRAP	51-74 HLA-C	Q9TNN7	SEQ ID-No. 186
25	187. FGPTFVSAVDGLSFQ	167-181 HLA-DMA	CAA54170	SEQ ID-No. 187
30	188. NREEFVRFDSDVGEFR	24-39 HLA-DPB 1	AAA36255	SEQ ID-No. 188
35	189. REEFVRFDSDVGEFR	25-39 HLA-DPB 1	AAA36255	SEQ ID-No. 189
40	190. DVEVYRAVTLGPPD	35-49 HLA-DQB 1	CAA71450	SEQ ID-No. 190
45	191. AQGALANIAVDKANLEI	81-97 HLA-DRA	P01903	SEQ ID-No. 191
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ⁱ : According to HUGO gene nomenclature ⁱⁱ : Accession Number according to Entrez Protein Database (NCBI)				

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 Thr Gln Ser Phe
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    Ser Pro Gly Glu Pro Gln Ile Ile Phe Cys Arg Ser Glu Ala Ala His
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    Gln Gly

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    1           5           10           15

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    Gln Gly Val Ile

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 Gly Pro
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Gly Gln Arg Arg Phe Asn Leu Gln Lys Asn Phe Val Gly Lys Val Ala
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Ile Gly Gln Arg Arg Phe Asn Leu Gln Lys Asn Phe Val Gly Lys Val
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Ala Leu

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Arg Arg Phe Asn Leu Gln Lys Asn Phe Val Gly Lys Val Ala
1 5 10

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Val Pro Gly Thr Tyr Lys Ile Thr Ala Ser Ala Arg Gly Tyr Asn
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Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly
1 5 10

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Asp His Asn Phe Val Lys Ala Ile Asn Ala Ile Gln Lys Ser Trp
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Lys Lys Val Val Val Tyr Leu Gln Lys Leu Asp Thr Ala Tyr Asp Asp
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Leu Gly

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<400> 70

Lys Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Ile Gln Lys Ser
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Trp Thr

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<400> 71

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Ser Gly Met Asp Tyr Trp Ile Val Lys Asn Ser Trp Gly Thr Gly Trp
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5 Gly

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Tyr Asp His Asn Phe Val Lys Ala Ile Asn Ala Ile Gln Lys
1 5 10

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Thr

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1 5 10 15

50 <210> 75
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<400> 75

55 Leu Ser Arg Asp Pro Asp Ala Gln Pro Gly Gly Glu
1 5 10

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 Gly Lys Glu Tyr Trp Leu Val Lys Asn Ser Trp Gly His Asn
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 Lys Asn Leu Lys Phe Val Met Leu His Asn Leu Glu His Ser Met
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 Thr Thr Ala Phe Gln Tyr Ile Ile Asp Asn Lys Gly Ile Asp
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 Gly Thr Glu Tyr Trp Ile Val Arg Asn Ser Trp Gly Glu Pro Trp
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Gly Tyr Leu Pro Asn Gln Leu Phe Arg Thr Phe
 1 5 10

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Ile Arg Phe Val Val Asp Ser Gly Lys Val Lys Glu Met
 1 5 10

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Met Glu Lys Tyr Asn Ile Glu Lys Asp Ile Ala Ala Tyr Ile Lys
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 Leu Pro Phe Gly Ala Gln Ser Thr Gln Arg Gly His Thr Glu
 1 5 10

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Ser Lys Tyr Tyr Val Thr Ile Ile Asp Ala Pro Gly His Arg Asp
 1 5 10 15

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Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met Gly Lys Gly

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1

5

10

10

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<212> PRT

<213> Homo sapiens

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<400> 86

Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met Gly Lys Gly Ser

20

1

5

10

15

<210> 87

<211> 16

<212> PRT

<213> Homo sapiens

25

<400> 87

30

Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met Gly Lys Gly Ser Phe

1

5

10

15

35

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<212> PRT

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Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met Gly Lys Gly Ser

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10

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45

Phe

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<213> Homo sapiens

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<400> 89

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Asp Ile Asp Ala Ile Phe Lys Asp Leu Ser Ile Arg Ser Val Arg
1 5 10 15

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Gly Val Pro Leu Tyr Arg His Ile Ala Asp Leu Ala Gly Asn
1 5 10

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Gly Val Pro Leu Tyr Arg His Ile Ala Asp Leu Ala Gly Asn Ser Glu
1 5 10 15

30 Val

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<400> 92

Ile Lys Glu Lys Tyr Gly Lys Asp Ala Thr Asn Val Gly Asp Glu Gly
1 5 10 15

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<212> PRT
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<400> 93

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Ile Lys Glu Lys Tyr Gly Lys Asp Ala Thr Asn Val Gly Asp Glu Gly
1 5 10 15

55

Gly

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	1				5					10					15	

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Gly Gly

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<400> 96

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	Val	Pro	Leu	Tyr	Arg	His	Ile	Ala	Asp	Leu	Ala	Gly	Asn
	1				5					10			

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	Val	Pro	Leu	Tyr	Arg	His	Ile	Ala	Asp	Leu	Ala	Gly	Asn	Ser	Glu
	1				5					10				15	

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<400> 98

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Val Pro Leu Tyr Arg His Ile Ala Asp Leu Ala Gly Asn Ser Glu Val
1 5 10 15

5

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Val Pro Leu Tyr Arg His Ile Ala Asp Leu Ala Gly Asn Ser Glu Val
15 1 5 10 15

Ile

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Leu Leu Gln Lys Leu Ile Leu Trp Arg Val Leu
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35

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Leu Gln Asn Ile Ile Pro Ala Ser Thr Gly Ala Ala Lys Ala Val Gly
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Glu Pro Ile Glu Gln Lys Phe Val Ser Ile Ser Asp Leu Leu Val Pro
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Lys

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10	Ala	Ile	Phe	Leu	Phe	Val	Asp	Lys	Thr	Val	Pro	Gln	Ser	Ser
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<400> 104

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Ala	Ile	Phe	Leu	Phe	Val	Asp	Lys	Thr	Val	Pro	Gln	Ser	Ser	Leu
1				5					10					15

25

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<400> 105

Ala	Ile	Phe	Leu	Phe	Val	Asp	Lys	Thr	Val	Pro	Gln	Ser	Ser	Leu	Thr
1				5					10					15	

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Phe	Val	Asp	Lys	Thr	Val	Pro	Gln	Ser	Ser	Leu
1				5					10	

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Leu Pro Ser Glu Lys Ala Ile Phe Leu Phe Val Asp Lys Thr Val Pro
1 5 10 15

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Gln Ser Ser Leu Thr
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Lys Val Asn Leu Leu Lys Ile Lys Thr Glu Leu Cys Lys Lys Glu Val
1 5 10 15

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<210> 109
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<212> PRT
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<400> 109

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Leu Gly Lys Trp Cys Ser Glu Lys Thr Glu Thr Gly Gln Glu
1 5 10

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Val Asn Leu Leu Lys Ile Lys Thr Glu Leu Cys Lys Lys Glu Val
1 5 10 15

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Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly
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10 Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys
1 5 10

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<400> 113

20 Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly Ile
1 5 10

<210> 114
25 <211> 14
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<400> 114

30 Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly Ile
1 5 10

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<400> 115

45 Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly
1 5 10

<210> 116
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55 Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys
1 5 10 15

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 Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg
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 <210> 118
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 Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly
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 Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys
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 Val Thr Arg Ala Phe Val Ala Ala Arg Thr Phe Ala Gln Gly Leu
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 <210> 121
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 <212> PRT
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    1          5          10

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<212> PRT
10 <213> Homo sapiens

<400> 122

15    Asp Ile Phe Glu Arg Ile Ala Ser Glu Ala Ser Arg Leu Ala
    1          5          10

<210> 123
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<212> PRT
20 <213> Homo sapiens

<400> 123

25    Asp Ile Phe Glu Arg Ile Ala Ser Glu Ala Ser Arg Leu Ala His
    1          5          10          15

30 <210> 124
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35 <400> 124

40    Asp Ile Phe Glu Arg Ile Ala Ser Glu Ala Ser Arg Leu Ala His Tyr
    1          5          10          15

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45 <212> PRT
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50    Val Asn Asp Ile Phe Glu Arg Ile Ala Ser Glu Ala Ser Arg Leu Ala
    1          5          10          15

55    His Tyr Asn

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<400> 127

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Asp	Asp	Thr	Gln	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln	Arg
1				5					10					15	

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Met Glu

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<400> 128

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Asp	Asp	Thr	Gln	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln	Arg
1				5					10					15	

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Met Glu Pro

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<400> 129

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Asp	Asp	Thr	Gln	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln	Arg
1				5					10					15	

55

Met Glu Pro Arg
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10	Asp	Thr	Glu	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln	Arg	Met
	1				5					10				15		

Glu

15

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<400> 131

25	Asp	Thr	Glu	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln	Arg	Met
	1				5					10				15		

Glu Pro

30

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40	Asp	Thr	Gln	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln
	1				5					10				

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 <213> Homo sapiens

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<400> 133

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Asp	Thr	Gln	Phe	Val	Arg	Phe	Asp	Ser	Asp	Ala	Ala	Ser	Gln	Arg
1				5					10				15	

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<400> 134

Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met
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<210> 135

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<213> Homo sapiens

<400> 135

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Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met
1 5 10 15

20 Glu

<210> 136

<211> 18

25 <212> PRT

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<400> 136

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Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met
1 5 10 15

35 Glu Pro

<210> 137

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<212> PRT

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<400> 137

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Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met
1 5 10 15

50 Glu Pro Arg Ala Pro
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55 <210> 138

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1 5 10

<210> 139

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<213> Homo sapiens

<400> 139

15 Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg Met Glu
1 5 10

20 <210> 140

<211> 14

<212> PRT

<213> Homo sapiens

25 <400> 140

30 Lys His Lys Trp Glu Ala Ala His Val Ala Glu Gln Leu Arg
1 5 10

<210> 141

<211> 15

<212> PRT

35 <213> Homo sapiens

<400> 141

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1 5 10 15

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55 Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10

<210> 143

<211> 14

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<400> 143

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Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln Arg
1 5 10

10

<210> 144
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15

<400> 144

20

Thr Thr Lys His Lys Trp Glu Ala Ala His Val Ala Glu Gln Leu Arg
1 5 10 15

25

<210> 145
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<400> 145

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Val Asp Asp Thr Glu Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

35

Arg

40

<210> 146
<211> 24
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<213> Homo sapiens

<400> 146

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Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1 5 10 15

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Arg Met Glu Pro Arg Ala Pro Trp
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55

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<212> PRT
<213> Homo sapiens

<400> 147

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Val Asp Asp Thr Gln Phe Val Arg Phe Asp Ser Asp Ala Ala Ser Gln
1          5          10          15

5
Arg Met Glu Pro Arg Ala Pro Trp Ile Glu
          20          25

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<212> PRT
<213> Homo sapiens

15
<400> 148

Asp Leu Ser Ser Trp Thr Ala Ala Asp Thr Ala Ala Gln Ile Thr
1          5          10          15

20

<210> 149
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Arg Lys Trp

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Arg Lys Trp Glu Ala Ala Arg Val Ala
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 Pro Arg

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Ser Asp Trp Leu
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Leu Pro Ser Tyr Glu Glu Ala Leu Ser Leu Pro Ser Lys Thr Pro
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Gly

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Pro Glu

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25

Claims

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1. A tumour associated peptide consisting of a major histocompatibility complex (MHC) class-II core amino acid sequence of a sequence according to SEQ ID No. 273 optionally with N- and/or C-terminal extensions of between 1 to 10 amino acids in length, and having the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-II.

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2. The tumour associated peptide according to Claim 1, wherein said peptide consists of an amino acid sequence according to SEQ ID No. 273.

3. The tumour associated peptide according to Claim 1 or 2, wherein said molecule of the human major histocompatibility complex (MHC) class-II is HLA-DR4.

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4. The tumour associated peptide according to any of Claims 1 to 3, wherein the peptide includes non-peptide bonds.

5. The tumour associated peptide according to any of Claims 1 to 4, wherein the peptide is a fusion protein, in particular comprising N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii).

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6. A nucleic acid, encoding a peptide according to any one of Claims 1 to 5.

7. The nucleic acid according to Claim 6 which is DNA, cDNA, DNA, CNA, RNA or combinations thereof

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8. An expression vector capable of expressing a nucleic acid according to Claim 6 or 7.

9. A host cell comprising a nucleic acid according to Claim 6 or 7 or an expression vector according to Claim 8.

10. The host cell according to Claim 9 that is a recombinant Awells cell.

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11. A method of producing a tumour associated peptide according to any one of Claims 1 to 5, the method comprising culturing the host cell according to Claim 9 or 10, and isolating the peptide from the host cell or its culture medium.

12. A pharmaceutical composition comprising a tumour associated peptide according to any one of Claims 1 to 5, a

nucleic acid according to Claim 6 or 7 or an expression vector according to Claim 8, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition according to claim 12, further comprising at least one additional tumour associated peptide of between 9 and 30 amino acids comprising at least one sequence according to SEQ ID No. 1 to SEQ ID No. 272 and SEQ 117 No. 274 to SEQ ID No. 338.

14. The pharmaceutical composition according to claim 12 or 13, which is in the form of a cancer vaccine.

15. A tumour associated peptide according to any one of Claims 1 to 5, a nucleic acid according to Claim 6 or 7 or an expression vector according to Claim 8 for use in medicine.

16. Use of a tumour associated peptide according to any one of Claims 1 to 5 or a nucleic acid according to Claim 6 or 7 or an expression vector according to Claim 8 in the manufacture of a medicament for the treatment of tumorous cells in a patient, wherein said tumorous cells aberrantly express a polypeptide comprising an amino acid sequence as given in any of Claims 1 to 3.

17. An *in vitro* method for producing activated cytotoxic T lymphocytes (CTL), the method comprising contacting in vitro CTL with antigen loaded human class II MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate, in an antigen specific manner, said CTL wherein the antigen is a peptide according to any one of Claims 1 to 5.

18. The method according to Claim 17, wherein the antigen is loaded onto class II MHC molecules expressed on the surface of a suitable antigen-presenting cell by contacting a sufficient amount of the antigen with an antigen-presenting cell.

19. The method according to Claim 18, wherein the antigen-presenting cell comprises an expression vector according to Claim 8.

20. The method according to any one of Claims 17 to 19, wherein the class n MHC molecule is HLA-DR4.

21. Activated cytotoxic T lymphocyte (CTL), produced by the method according to any one of Claims 17 to 20, which selectively recognises a cell which aberrantly expresses a polypeptide comprising an amino acid sequence given in any one of Claims 1 to 3.

22. AT-cell receptor (PCR) (which recognises a cell which aberrantly expresses a polypeptide comprising an amino acid sequence given in any one of Claims 1 to 3, the TCR being obtainable from the cytotoxic T lymphocyte (CTL) of Claim 21, or a functionally equivalent molecule to the TCR,

23. Use of cytotoxic T lymphocytes as defined in Claim 21 in the manufacture of a medicament for the treatment of tumorous cells in a patient, wherein said tumorous cells aberrantly express a polypeptide comprising an amino acid sequence given in any one of Claims 1 to 3.

Patentansprüche

1. Tumor-assoziiertes Peptid bestehend aus einer Kemaminosäuresequenz des menschlichen Haupthistokompatibilitätskomplexes (MHC) Klasse-II entsprechend der Sequenz SEQ ID Nr. 273, optional mit N- und/oder C-terminalen Verlängerungen mit einer Länge zwischen 1 und 10 Aminosäuren, und welches die Fähigkeit hat, an einem Molekül des menschlichen Haupthistokompatibilitätskomplexes (MHC) Klasse-II zu binden.

2. Tumorassoziiertes Peptid nach Anspruch 1, wobei das Peptid aus der Aminosäuresequenz gemäß SEQ ID Nr. 273 besteht.

3. Tumorassoziiertes Peptid nach Anspruch 1 oder 2, wobei das Molekül des menschlichen Haupthistokompatibilitätskomplexes (MHC) Klasse-II HLA-DR4 ist.

4. Tumorassoziiertes Peptid nach einem der Ansprüche 1 bis 3, wobei das Peptid nichtpeptidische Bindungen ein-

schließt.

5. Tumorassoziiertes Peptid nach einem der Ansprüche 1 bis 4, wobei das Peptid ein Fusionsprotein ist, insbesondere umfassend N-terminale Aminosäuren der HLA-DR Antigenassoziierten invarianten Kette (Ii).
6. Nukleinsäure, die ein Peptid nach einem der Ansprüche 1 bis 5 kodiert.
7. Nukleinsäure nach Anspruch 6, die DNA, cDNA, PNA, CNA, RNA oder Kombinationen davon ist.
8. Expressionsvektor, der in der Lage ist, eine Nukleinsäure nach Anspruch 6 oder 7 zu exprimieren.
9. Wirtszelle umfassend eine Nukleinsäure nach Anspruch 6 oder 7 oder einen Expressionsvektor nach Anspruch 8.
10. Wirtszelle nach Anspruch 9, die eine rekombinante Awells-Zelle ist.
11. Verfahren zur Herstellung eines tumorassoziierten Peptids nach einem der Ansprüche 1 bis 5, wobei das Verfahren Kultivieren der Wirtszelle nach Anspruch 9 oder 10 und Isolieren des Peptids aus der Wirtszelle oder ihrem Kulturmedium umfasst.
12. Pharmazeutische Zusammensetzung umfassend ein tumorassoziiertes Peptid nach einem der Ansprüche 1 bis 5, eine Nukleinsäure nach Anspruch 6 oder 7 oder einen Expressionsvektor nach Anspruch 8 und einen pharmazeutisch akzeptablen Träger.
13. Pharmazeutische Zusammensetzung nach Anspruch 12, weiter umfassend mindestens ein zusätzliches tumorassoziiertes Peptid von zwischen 9 und 30 Aminosäuren, umfassend mindestens eine Sequenz gemäß SEQ ID Nr. 1 bis SEQ ID Nr. 272 und SEQ ID Nr. 274 bis SEQ ID Nr. 338.
14. Pharmazeutische Zusammensetzung nach Anspruch 12 oder 13, die die Form eines Krebsimpfstoffes hat.
15. Tumorassoziiertes Peptid nach einem der Ansprüche 1 bis 5, eine Nukleinsäure nach Anspruch 6 oder 7 oder ein Expressionsvektor nach Anspruch 8 zur Verwendung in der Medizin.
16. Verwendung eines tumorassoziierten Peptids nach einem der Ansprüche 1 bis 5 oder einer Nukleinsäure nach Anspruch 6 oder 7 oder eines Expressionsvektors nach Anspruch 8 zur Herstellung eines Medikaments zur Behandlung von Tumorzellen in einem Patienten, wobei die Tumorzellen aberrant ein Polypeptid umfassend eine Aminosäuresequenz, wie in einem der Ansprüche 1 bis 3 angegeben, exprimieren.
17. Ein *in vitro* Verfahren zur Produktion aktivierter zytotoxischer T-Lymphozyten (CTL), das Verfahren umfassend das *in vitro* in Kontakt bringen von CTL mit Antigen beladenen humanen MHC-Klasse-II-Molekülen, die an der Oberfläche einer geeigneten Antigen-präsentierenden Zelle für eine ausreichende lange Zeit, um besagte CTL in einer antigenspezifischen Art und Weise zu aktivieren, exprimiert werden, wobei das Antigen ein Peptid nach einem der Ansprüche 1 bis 5 ist.
18. Verfahren gemäß Anspruch 17, wobei das Antigen auf ein MHC-Klasse-II-Molekül beladen ist, welches an der Oberfläche einer geeigneten Antigen-präsentierenden Zelle durch in Kontakt bringen einer ausreichenden Menge des Antigens mit der Antigen-präsentierenden Zelle exprimiert wird.
19. Verfahren nach Anspruch 18, wobei die Antigen-präsentierende Zelle einen Expressionsvektor nach Anspruch 8 umfasst.
20. Verfahren nach einem der Ansprüche 17 bis 19, wobei das MHC-Klasse-II-Molekül HLA-DR4 ist.
21. Aktivierte zytotoxische T-Lymphozyten (CTL), hergestellt nach dem Verfahren nach einem der Ansprüche 17 bis 20, welche selektiv eine Zelle erkennen, die aberrant ein Polypeptid umfassend eine Aminosäuresequenz nach einem der Ansprüche 1 bis 3 exprimiert.
22. T-Zellrezeptor (TCR), der eine Zelle erkennt, die aberrant ein Polypeptid exprimiert, welches eine Aminosäuresequenz nach einem der Ansprüche 1 bis 3 umfasst, wobei der TCR von einer T-Lymphozyte (CTL) nach Anspruch

21 erhalten wurde, oder ein funktionell äquivalentes Molekül zu dem TCR.

23. Verwendung von zytotoxischen T-Lymphozyten, wie in Anspruch 21 definiert, zur Herstellung eines Medikaments zur Behandlung von Tumorzellen in einem Patienten, wobei die genannten Tumorzellen aberrant ein Polypeptid umfassend eine Aminosäuresequenz, wie in einem der Ansprüche 1 bis 3 angegeben, exprimieren.

Revendications

1. Peptide associé à une tumeur consistant en une séquence d'acides aminés essentielle du complexe majeur d'histocompatibilité (CMH) de classe II d'une séquence correspondant à la séquence SEQ ID n°273, facultativement avec des extensions N-et/ou C-terminales d'une longueur comprise entre 1 et 10 acides aminés, capable de se lier à une molécule du complexe majeur d'histocompatibilité (CMH) humain de classe II.
2. Peptide associé à une tumeur conforme à la revendication 1, dans lequel ledit peptide consiste en une séquence d'acides aminés correspondant à la séquence SEQ ID n°273.
3. Peptide associé à une tumeur conforme à la revendication 1 ou 2, dans lequel ladite molécule du complexe majeur d'histocompatibilité (CMH) humain de classe II est HLA-DR4.
4. Peptide associé à une tumeur conforme à l'une des revendications 1 à 3, dans lequel ledit peptide comprend des liaisons non peptidiques.
5. Peptide associé à une tumeur conforme à l'une des revendications 1 à 4, dans lequel ledit peptide est une protéine de fusion, comprenant en particulier des acides aminés N-terminaux de la chaîne invariante (li) associée aux antigènes du système HLA-DR.
6. Acide nucléique, codant pour un peptide tel que décrit dans l'une des revendications 1 à 5.
7. Acide nucléique conforme à la revendication 6, qui est un ou des combinaisons d'ADN, ADNc, PNA, CNA, ARN.
8. Vecteur d'expression capable d'exprimer un acide nucléique conforme à la revendication 6 ou 7.
9. Cellule hôte comprenant un acide nucléique conforme à la revendication 6 ou 7 ou un vecteur d'expression conforme à la revendication 8.
10. Cellule hôte conforme à la revendication 9, qui est une cellule Awells recombinante.
11. Méthode de production d'un peptide associé à une tumeur conforme à l'une des revendications 1 à 5, comprenant la culture de la cellule hôte conforme à la revendication 9 ou 10 et l'isolement du peptide de la cellule hôte ou de son milieu de culture.
12. Composition pharmaceutique comprenant un peptide associé à une tumeur conforme à l'une des revendications 1 à 5, un acide nucléique conforme à la revendication 6 ou 7 ou un vecteur d'expression conforme à la revendication 8, ainsi qu'un transporteur pharmaceutiquement acceptable.
13. Composition pharmaceutique conforme à la revendication 12, comprenant également au moins un peptide associé à une tumeur supplémentaire d'une longueur comprise entre 9 et 30 acides aminés comprenant au moins une séquence correspondant aux séquences SEQ ID n°1 à SEQ ID n°272 et SEQ ID n°274 à SEQ ID n°338.
14. Composition pharmaceutique conforme à la revendication 12 ou 13, qui se présente sous la forme d'un vaccin anticancéreux.
15. Peptide associé à une tumeur conforme à l'une des revendications 1 à 5, acide nucléique conforme à la revendication 6 ou 7 ou vecteur d'expression conforme à la revendication 8, pour usage médical.
16. Utilisation d'un peptide associé à une tumeur conforme à l'une des revendications 1 à 5 ou d'un acide nucléique conforme à la revendication 6 ou 7 ou d'un vecteur d'expression conforme à la revendication 8 dans la fabrication

d'un médicament destiné au traitement des cellules tumorales d'un patient, chez lequel lesdites cellules tumorales expriment anormalement un polypeptide comprenant une séquence d'acides aminés telle que décrite dans l'une des revendications 1 à 3.

- 5 **17.** Méthode *in vitro* de production de lymphocytes T cytotoxiques (CTL) activés, comprenant la mise en contact *in vitro* des CTL avec des molécules du CMH de classe II humain chargées d'antigènes exprimées à la surface d'une cellule présentatrice d'antigènes appropriée pendant un temps suffisant pour activer, de manière antigène-spécifique, lesdits CTL dans lesquels l'antigène est un peptide conforme à l'une des revendications 1 à 5.
- 10 **18.** Méthode conforme à la revendication 17, dans laquelle l'antigène est chargé sur les molécules du CMH de classe II exprimées à la surface d'une cellule présentatrice d'antigènes appropriée, en mettant en contact une quantité suffisante de l'antigène avec une cellule présentatrice d'antigènes.
- 15 **19.** Méthode conforme à la revendication 18, dans laquelle la cellule présentatrice d'antigènes comprend un vecteur d'expression conforme à la revendication 8.
- 20.** Méthode conforme à l'une des revendications 17 à 19, dans laquelle la molécule du CMH de classe II est HLA-DR4.
- 20 **21.** Lymphocyte T cytotoxique (CTL) activé, produit par la méthode conforme à l'une des revendications 17 à 20, qui reconnaît de façon sélective une cellule exprimant anormalement un polypeptide comprenant une séquence d'acides aminés telle que décrite dans l'une des revendications 1 à 3.
- 25 **22.** Récepteur des cellules T (TCR) qui reconnaît une cellule exprimant anormalement un polypeptide comprenant une séquence d'acides aminés telle que décrite dans l'une des revendications 1 à 3, le TCR pouvant être obtenu à partir du lymphocyte T cytotoxique (CTL) de la revendication 21 ou d'une molécule fonctionnellement équivalente au TCR.
- 30 **23.** Utilisation de lymphocytes T cytotoxiques tels que définis dans la revendication 21, dans la fabrication d'un médicament destiné au traitement des cellules tumorales d'un patient, chez lequel lesdites cellules tumorales expriment anormalement un polypeptide comprenant une séquence d'acides aminés telle que décrite dans l'une des revendications 1 à 3.

Figure 1

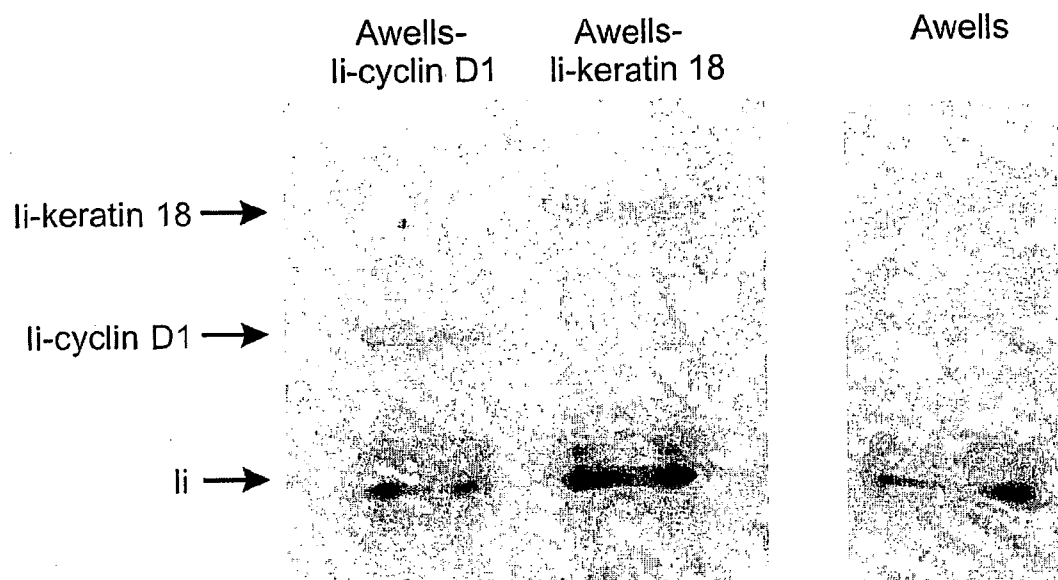


Figure 2

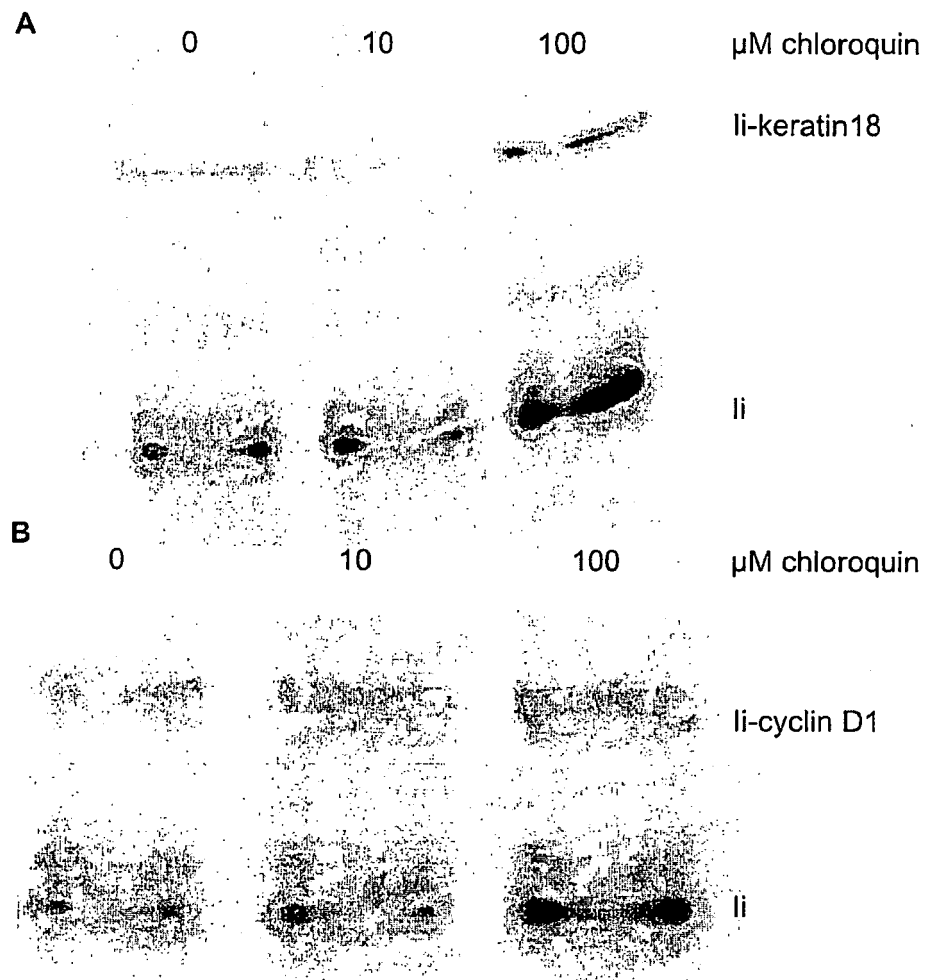


Figure 3

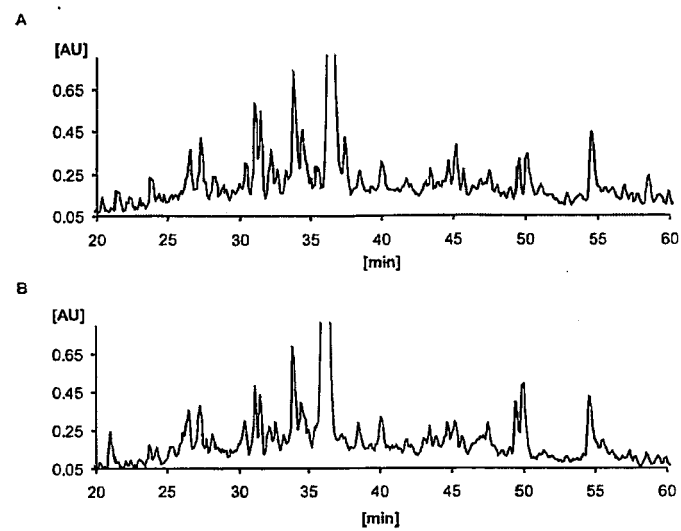


Figure 4

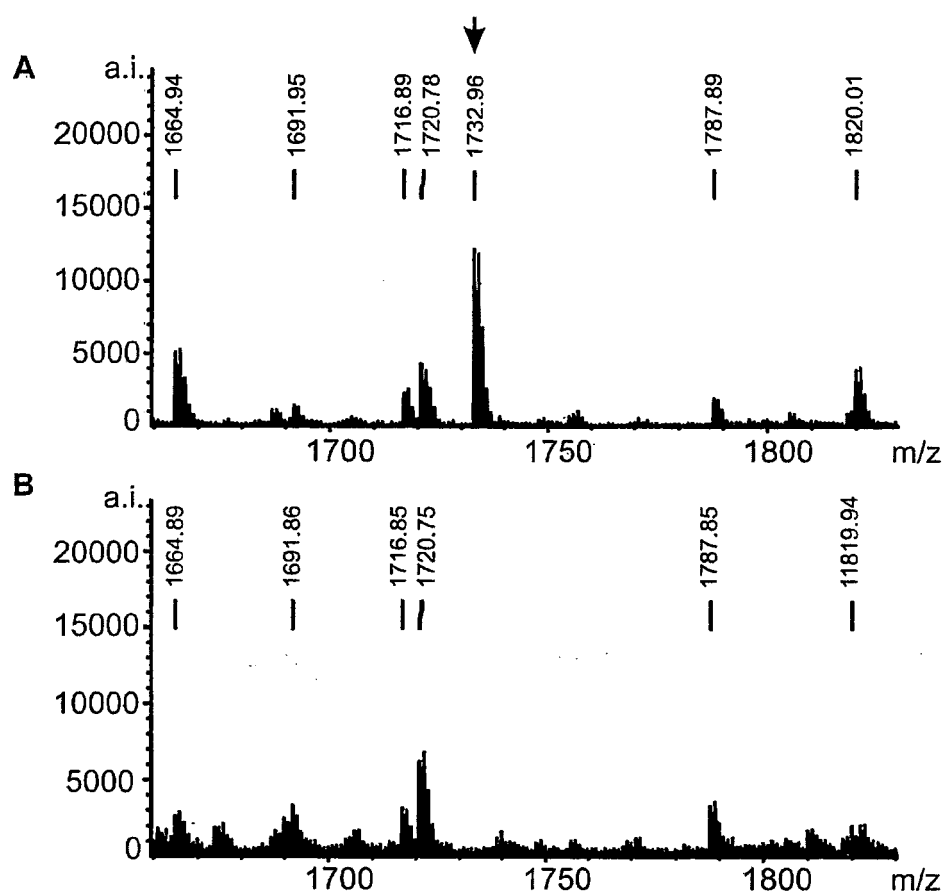


Figure 5

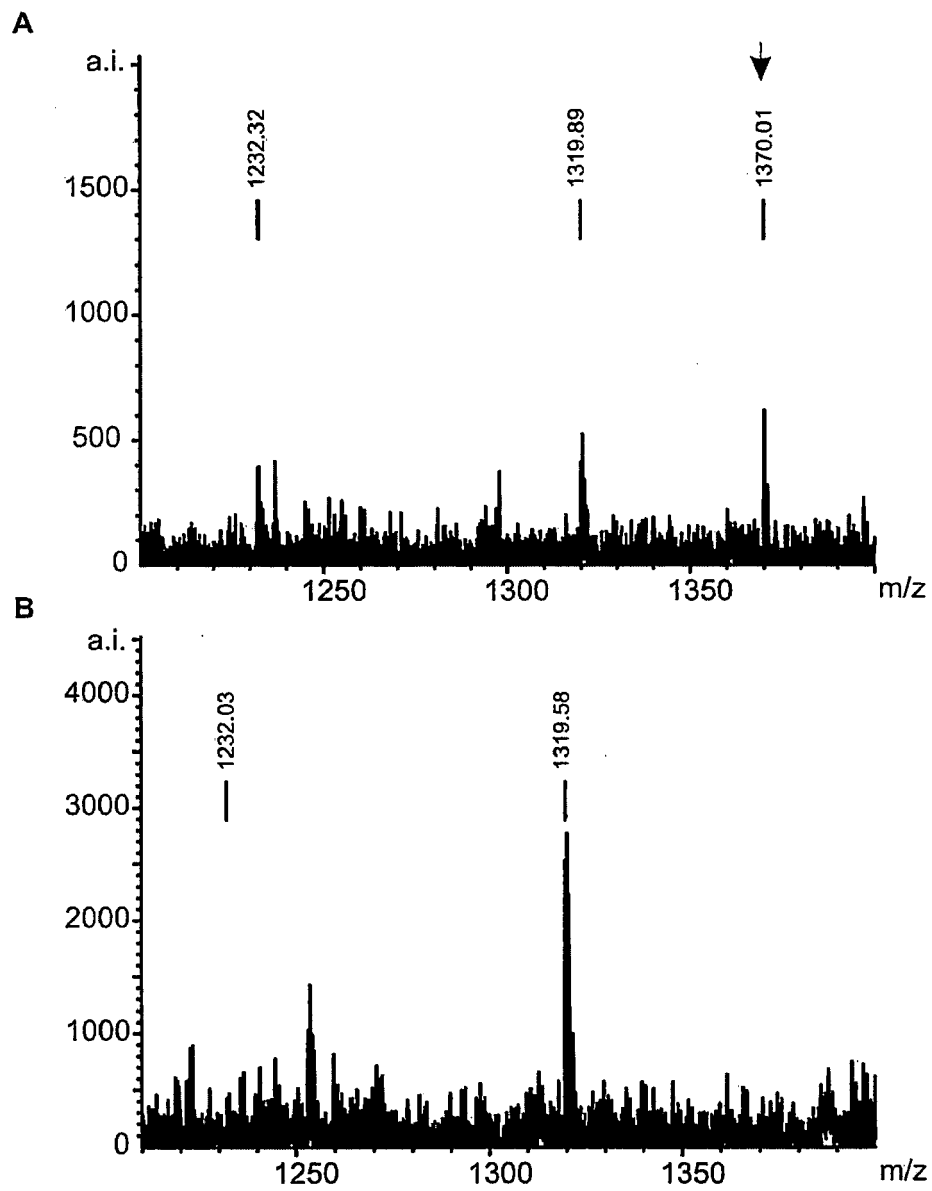


Figure 6

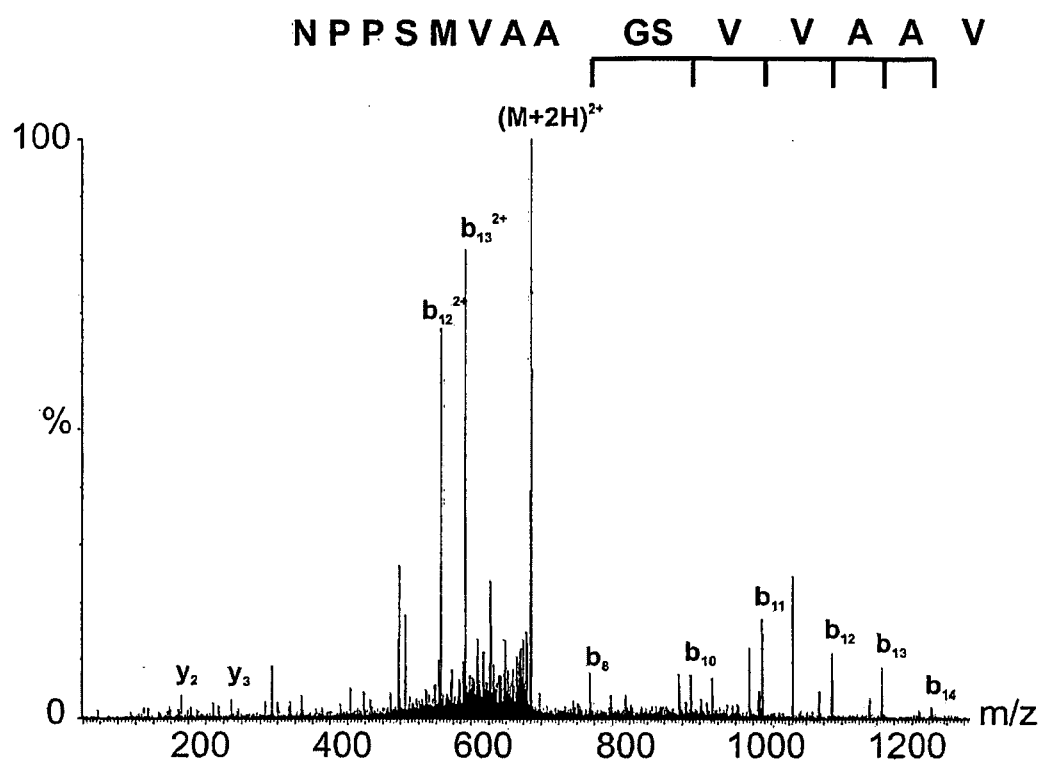


Figure 7

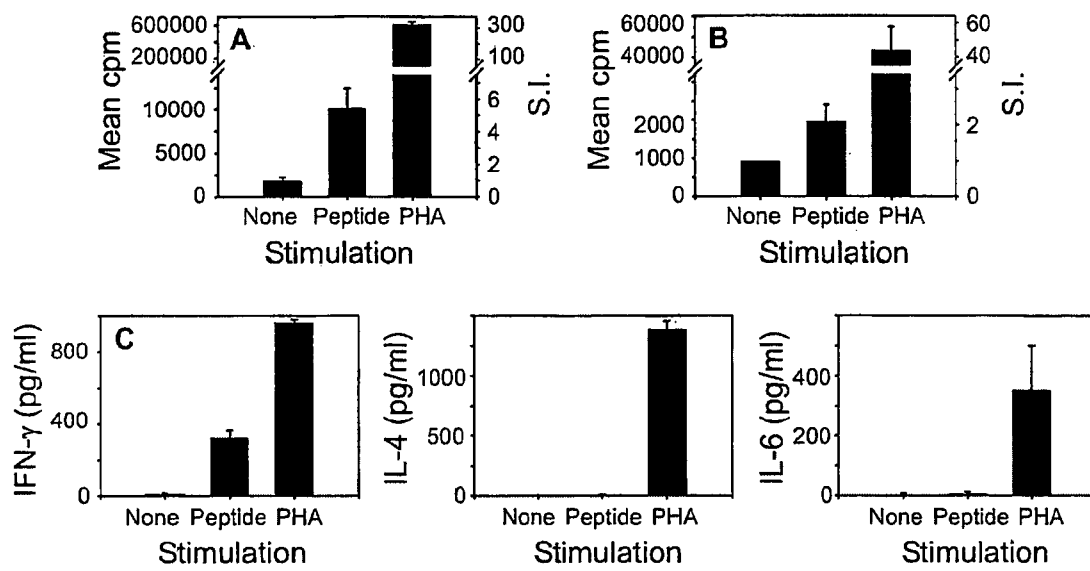
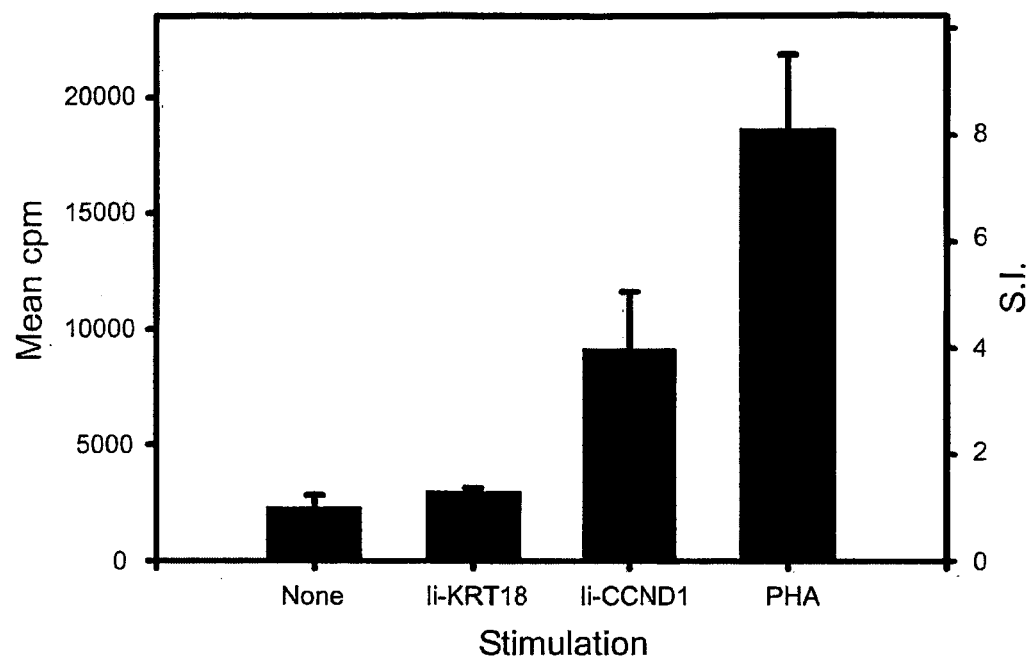


Figure 8



REFERENCES CITED IN THE DESCRIPTION

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