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[54] NOVEL PEPTIDES AND COMBINATION OF PEPTIDES FOR USE IN IMMUNOTHERAPY AGAINST HEPATOCELLULAR CARCINOMA (HCC) AND OTHER CANCERS
用於肝細胞癌(HCC)和其他癌症免疫治療的新型肽和肽組合物

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(54) **NOVEL PEPTIDES AND COMBINATION OF PEPTIDES FOR USE IN IMMUNOTHERAPY AGAINST HEPATOCELLULAR CARCINOMA (HCC) AND OTHER CANCERS**

NEUARTIGE PEPTIDE UND KOMBINATION VON PEPTIDEN ZUR VERWENDUNG IN DER IMMUNTHERAPIE GEGEN HEPATOZELLULÄRES KARZINOM (HCC) UND ANDERE KREBSARTEN

NOUVEAUX PEPTIDES ET COMBINAISON DE PEPTIDES À UTILISER DANS L'IMMUNOTHÉRAPIE CONTRE LE CARCINOME HÉPATOCELLULAIRE (HCC) ET D'AUTRES CANCERS

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- **FERNANDES ET AL: "The novel putative bile acid transporter SLC10A5 is highly expressed in liver and kidney", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ELSEVIER, AMSTERDAM, NL, vol. 361, no. 1, 29 July 2007 (2007-07-29) , pages 26-32, XP022176141, ISSN: 0006-291X, DOI: 10.1016/J.BBRC.2007.06.160**

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Description

[0001] The present invention relates to peptides, proteins, nucleic acids and cells for use in immunotherapeutic methods. In particular, the present invention relates to the immunotherapy of cancer. The present invention furthermore relates to tumor-associated T-cell peptide epitopes, alone or in combination with other tumor-associated peptides that can for example serve as active pharmaceutical ingredients of vaccine compositions that stimulate anti-tumor immune responses, or to stimulate T cells *ex vivo* and transfer into patients. Peptides bound to molecules of the major histocompatibility complex (MHC), or peptides as such, can also be targets of antibodies, soluble T-cell receptors, and other binding molecules. In particular, the present invention relates to several novel peptide sequences and their variants derived from HLA class I and class II molecules of human tumor cells that can be used in vaccine compositions for eliciting anti-tumor immune responses or as targets for the development of pharmaceutically / immunologically active compounds and cells.

Background of the invention

[0002] Hepatocellular carcinoma (HCC) is one of the most common tumors in the world and accounts for about 6% of all new cancer cases diagnosed worldwide. In 2012 about 782,000 new cases of HCC occurred in the world, making it the fifth most common cancer in men (554,000 cases) and the ninth in women (228,000 cases) (http://globocan.iarc.fr). HCC is the most common primary liver malignancy accounting for over 80% of all adult primary liver cancers.
[0003] The distribution of HCC varies geographically, and rates of incidence depend on gender. The age-standardized incidence rate (ASR) of HCC in men is highest in Eastern Asia (31.9) and South-Eastern Asia (22.2), intermediate in Southern Europe (9.5) and Northern America (9.3) and lowest in Northern Europe (4.6) and South-Central Asia (3.7). Incident rates of HCC in women are lower than male ASRs. The highest ASR in women occurs in Eastern Asia (10.2) and Western Africa (8.1), the lowest in Northern Europe (1.9) and Micronesia (1.6).
[0004] The overall prognosis for patients with HCC is poor. The 5-year relative survival rate (5Y-RSR) from HCC is about 15%, depending on the stage at the time of diagnosis. For localized HCC, where the cancer is still confined to the liver, the 5Y-RSR is about 28%. For regional and distant HCC, were the cancer has grown into nearby or distant organs, 5Y-RSRs are 7% and 2%, respectively.
[0005] Lately, a limited number of immunotherapy trials for HCC have been conducted. Cytokines have been used to activate subsets of immune cells and/or increase the tumor immunogenicity (Reinisch et al., 2002; Sangro et al., 2004). Other trials have focused on the infusion of Tumor-infiltrating lymphocytes or activated peripheral blood lymphocytes (Shi et al., 2004a; Takayama et al., 1991; Takayama et al., 2000).
[0006] So far, a small number of therapeutic vaccination trials have been executed. Butterfield et al. conducted two trials using peptides derived from alpha-fetoprotein (AFP) as a vaccine or DCs loaded with AFP peptides *ex vivo* (Butterfield et al., 2003; Butterfield et al., 2006). In two different studies, autologous dendritic cells (DCs) were pulsed *ex vivo* with autologous tumor lysate (Lee et al., 2005) or lysate of the hepatoblastoma cell line HepG2 (Palmer et al., 2009). So far, vaccination trials have only shown limited improvements in clinical outcomes.
[0007] Fernandes et al. (2007) discloses that is closes that the full length SLC10A5 protein is highly expressed in liver and kidney, but does not disclose a SLC10A5 peptide comprising SEQ ID NO: 89 for use in therapy, including cancer treatment.

Summary of the invention

[0008] The present invention relates to a peptide consisting of the amino acid sequence of SEQ ID No. 89 as defined in appended claim 1. Further aspects of the invention are defined in the appended claims.
[0009] In a first aspect there is disclosed a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 300 or a variant sequence thereof which is at least 80%, preferably at least 90%, homologous (preferably at least 80% or at least 90% identical) to SEQ ID NO: 1 to SEQ ID NO: 300, wherein said variant binds to MHC and/or induces T cells cross-reacting with said peptide, or a pharmaceutical acceptable salt thereof, wherein said peptide is not the underlying full-length polypeptide.
[0010] Disclosed is also a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 300 or a variant thereof, which is at least 80%, preferably at least 88%, homologous (preferably at least 80% or at least 88% identical) to SEQ ID NO: 1 to SEQ ID NO: 300, wherein said peptide or variant thereof has an overall length of between 8 and 100, preferably between 8 and 30, and most preferred of between 8 and 14 amino acids.
[0011] The following tables show the peptide according to the present disclosure, its respective SEQ ID NO, and the prospective source (underlying) gene for this peptide. The peptide in Table 1 binds to HLA-A*02The peptides in Table 2 are furthermore useful in the diagnosis and/or treatment of various malignancies that involve an over-expression or over-presentation of the respective underlying polypeptide.

Table 1: HLA-A*02 peptide according to the present invention - S* = phosphoserine

SEQ ID No.	Sequence	GeneID(s)	Official Gene Svmbol(s)
89	RLIEEIKNV	347051	SLC10A5

[0012] Disclosed are furthermore generally the peptides as disclosed for use in the treatment of proliferative diseases, such as, for example, pancreatic cancer, colon or rectal cancer, kidney cancer, brain cancer, and/or leukemias.

[0013] Particularly preferred are the peptides - alone or in combination - according to the present disclosure selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 300. More preferred are the peptides - alone or in combination - selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 124 (see Table 1), preferably for A*02 binding, and from the group consisting of SEQ ID NO: 187 to SEQ ID NO: 218 preferably for A*24 binding, and their uses in the immunotherapy of HCC, brain cancer, kidney cancer, pancreatic cancer, colon or rectal cancer or leukemia, and preferably HCC.

[0014] As shown in the following table 2 the peptide according to the present invention can also be used in the immunotherapy of other indications. The table show, for selected peptides on which additional tumor types they were found showing over-presentation (including specific presentation) on more than 5% of the measured tumor samples, or presentation on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3. Over-presentation is defined as higher presentation on the tumor sample as compared to the normal sample with highest presentation. Normal tissues against which over-presentation was tested were: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, cartilage, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, ureter, urinary bladder.

Table 2: Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases - S* = phosphoserine

SEQ ID NO.	Sequence	Additional Entities
89	RLIEEIKNV	SCLC

[0015] Similarly, the peptides as listed in Table 2 as above can form the basis for the - in one preferred embodiment combined - treatment of the diseases as indicated.

[0016] Thus, another aspect of the present disclosure relates to the use of the peptides as disclosed herein for the - preferably combined - treatment of a proliferative disease selected from the group of HCC, brain cancer, kidney cancer, pancreatic cancer, colon or rectal cancer, and leukemia.

[0017] The present disclosure furthermore relates to peptides as disclosed herein that have the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I or - in an elongated form, such as a length-variant - MHC class -II.

[0018] The present disclosure further relates to the peptides as disclosed herein wherein said peptides (each) consist or consist essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 300.

[0019] The present disclosure further relates to the peptides as disclosed herein, wherein said peptide is modified and/or includes non-peptide bonds.

[0020] The present disclosure further relates to the peptides as disclosed herein, wherein said peptide is part of a fusion protein, in particular fused to the N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii), or fused to (or into the sequence of) an antibody, such as, for example, an antibody that is specific for dendritic cells.

[0021] The present disclosure further relates to a nucleic acid, encoding the peptidesas disclosed herein. The present disclosure further relates to the nucleic acid as disclosed herein that is DNA, cDNA, PNA, RNA or combinations thereof.

[0022] The present disclosure further relates to an expression vector capable of expressing and/or expressing a nucleic acid as disclosed herein.

[0023] The present disclosure further relates to a peptide as disclosed herein, a nucleic acid as disclosed herein or an expression vector as disclosed herein for use in the treatment of diseases and in medicine, in particular in the treatment of diseases including cancer and autoimmune / inflammatory / immune pathological diseases.

[0024] The present disclosure further relates to antibodies against the peptides as disclosed herein or complexes of said peptides as disclosed herein with MHC, and methods of making these.

[0025] The present disclosure further relates to T-cell receptors (TCRs), in particular soluble TCR (sTCRs) and cloned TCRs engineered into autologous or allogeneic T cells, and methods of making these, as well as NK cells or other cells bearing said TCR or cross-reacting with said TCRs.

[0026] The antibodies and TCRs are additional embodiments of the immunotherapeutic use of the peptides according to the invention at hand.

[0027] The present disclosure further relates to a host cell comprising a nucleic acid as disclosed herein or an expression vector as described before. The present disclosure further relates to the host cell as disclosed hereinthat is an antigen presenting cell, and preferably is a dendritic cell.

[0028] The present disclosure further relates to a method for producing a peptide as disclosed herein, said method comprising culturing the host cell as disclosed herein, and isolating the peptide from said host cell or its culture medium.

[0029] The present disclosure further relates to said method as disclosed herein, wherein the antigen is loaded onto class I or II MHC molecules expressed on the surface of a suitable antigen-presenting cell or artificial antigen-presenting cell by contacting a sufficient amount of the antigen with an antigen-presenting cell.

[0030] The present disclosure further relates to the method as disclosed herein, wherein the antigen-presenting cell comprises an expression vector capable of expressing or expressing said peptide containing SEQ ID No. 1 to SEQ ID No.: 300, preferably containing SEQ ID No. 1 to SEQ ID No. 124, and SEQ ID No. 187 to SEQ ID No.: 218 or a variant amino acid sequence.

[0031] The present disclosure further relates to activated T cells, produced by the method as disclosed herein, wherein said T cell selectively recognizes a cell which expresses a polypeptide comprising an amino acid sequence as disclosed herein.

[0032] The present disclosure further relates to a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising any amino acid sequence as disclosed herein, the method comprising administering to the patient an effective number of T cells as producedas disclosed herein.

[0033] The present disclosure further relates to the use of any peptide as described, the nucleic acid as disclosed herein, the expression vector as disclosed herein, the cell as disclosed herein, the activated T lymphocyte, the T cell receptor or the antibody or other peptide- and/or peptide-MHC-binding molecules as disclosed herein as a medicament or in the manufacture of a medicament. Preferably, the medicament is active against cancer.

[0034] Preferably, said medicament is for a cellular therapy, a vaccine or a protein based on a soluble TCR or antibody.

[0035] The present disclosure further relates to a use as disclosed herein, wherein said cancer cells are HCC, brain cancer, kidney cancer, pancreatic cancer, colon or rectal cancer or leukemia, and preferably HCC cells.

[0036] The present disclosure further relates to particular marker proteins and biomarkers based on the peptides as disclosed herein, herein called "targets" that can be used in the diagnosis and/or prognosis of HCC. The present disclosure also relates to the use of these novel targets in the context of cancer treatment.

[0037] There are two classes of MHC-molecules, MHC class I and MHC class II. MHC molecules are composed of an alpha heavy chain and beta-2-microglobulin (MHC class I receptors) or an alpha and a beta chain (MHC class II receptors), respectively. Their three-dimensional conformation results in a binding groove, which is used for non-covalent interaction with peptides. MHC class I molecules can be found on most nucleated cells. They present peptides that result from proteolytic cleavage of predominantly endogenous proteins, defective ribosomal products (DRIPs) and larger peptides. MHC class II molecules can be found predominantly on professional antigen presenting cells (APCs), and primarily present peptides of exogenous or transmembrane proteins that are taken up by APCs during endocytosis, and are subsequently processed. Complexes of peptide and MHC class I are recognized by CD8-positive T cells bearing the appropriate TCR (T-cell receptor), whereas complexes of peptide and MHC class II molecules are recognized by CD4-positive-helper-T cells bearing the appropriate TCR. It is well known that the TCR, the peptide and the MHC are thereby present in a stoichiometric amount of 1:1:1.

[0038] CD4-positive helper T cells play an important role in inducing and sustaining effective responses by CD8-positive cytotoxic T cells. The identification of CD4-positive T-cell epitopes derived from tumor associated antigens (TAA) is of great importance for the development of pharmaceutical products for triggering anti-tumor immune responses (Gnjatic et al.,. 2003). At the tumor site, T helper cells, support a cytotoxic T cell- (CTL-) friendly cytokine milieu (Mortara et al2006) and attract effector cells, e.g. CTLs, NK cells, macrophages, granulocytes (Hwang et al., 2007).

[0039] In the absence of inflammation, expression of MHC class II molecules is mainly restricted to cells of the immune system, especially professional antigen-presenting cells (APC), e.g., monocytes, monocyte-derived cells, macrophages, dendritic cells. In cancer patients, cells of the tumor have been found to express MHC class II molecules (Dengjel et al., 2006).

[0040] Elongated (longer) peptides of the disclosure can act as MHC class II active epitopes. T-helper cells, activated by MHC class II epitopes, play an important role in orchestrating the effector function of CTLs in anti-tumor immunity. T-helper cell epitopes that trigger a T-helper cell response of the TH1 type support effector functions of CD8-positive killer T cells, which include cytotoxic functions directed against tumor cells displaying tumor-associated peptide/MHC complexes on their cell surfaces. In this way tumor-associated T-helper cell peptide epitopes, alone or in combination with other tumor-associated peptides, can serve as active pharmaceutical ingredients of vaccine compositions that stimulate anti-tumor immune responses.

[0041] It was shown in mammalian animal models, e.g., mice, that even in the absence of CD8-positive T lymphocytes, CD4-positive T cells are sufficient for inhibiting manifestation of tumors via inhibition of angiogenesis by secretion of interferon-gamma (IFNγ).

[0042] There is evidence for CD4 T cells as direct anti-tumor effectors (Braumuller et al., 2013; Tran et al., 2014).

[0043] Since the constitutive expression of HLA class II molecules is usually limited to immune cells, the possibility of isolating class II peptides directly from primary tumors was not considered possible. However, Dengjel et al. were successful in identifying a number of MHC Class II epitopes directly from tumors (WO 2007/028574, EP 1 760 088 B1).

[0044] The antigens that are recognized by the tumor specific cytotoxic T lymphocytes, that is, the epitopes thereof, can be molecules derived from all protein classes, such as enzymes, receptors, transcription factors, etc. which are expressed and, as compared to unaltered cells of the same origin, usually up-regulated in cells of the respective tumor.

[0045] Since both types of response, CD8 and CD4 dependent, contribute jointly and synergistically to the anti-tumor effect, the identification and characterization of tumor-associated antigens recognized by either CD8+ T cells (ligand: MHC class I molecule + peptide epitope) or by CD4-positive T-helper cells (ligand: MHC class II molecule + peptide epitope) is important in the development of tumor vaccines.

[0046] For an MHC class I peptide to trigger (elicit) a cellular immune response, it also 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 8-12 amino acid residues in length and usually contain two conserved residues ("anchors") in their sequence that interact with the corresponding binding groove of the MHC-molecule. In this way each MHC allele has a "binding motif" determining which peptides can bind specifically to the binding groove.

[0047] In the MHC class I dependent immune reaction, peptides not only have to be able to bind to certain MHC class I molecules expressed by tumor cells, they subsequently also have to be recognized by T cells bearing specific T cell receptors (TCR).

[0048] The current classification of tumor associated antigens comprises the following major groups:

a) Cancer-testis antigens: The first TAAs ever identified that can be recognized by T cells belong to this class, which was originally called cancer-testis (CT) antigens because of the expression of its members in histologically different human tumors and, among normal tissues, only in spermatocytes/spermatogonia of testis and, occasionally, in placenta. Since the cells of testis do not express class I and II HLA molecules, these antigens cannot be recognized by T cells in normal tissues and can therefore be considered as immunologically tumor-specific. Well-known examples for CT antigens are the MAGE family members or NY-ESO-1.

b) Differentiation antigens: These TAAs are shared between tumors and the normal tissue from which the tumor arose; most are found in melanomas and normal melanocytes. Many of these melanocyte lineage-related proteins are involved in the biosynthesis of melanin and are therefore not tumor specific but nevertheless are widely used for cancer immunotherapy. Examples include, but are not limited to, tyrosinase and Melan-A/MART-1 for melanoma or PSA for prostate cancer.

c) Overexpressed TAAs: Genes encoding widely expressed TAAs have been detected in histologically different types of tumors as well as in many normal tissues, generally with lower expression levels. It is possible that many of the epitopes processed and potentially presented by normal tissues are below the threshold level for T-cell recognition, while their overexpression in tumor cells can trigger an anticancer response by breaking previously established tolerance. Prominent examples for this class of TAAs are Her-2/neu, Survivin, Telomerase or WT1.

d) Tumor specific antigens: These unique TAAs arise from mutations of normal genes (such as β-catenin, CDK4, etc.). Some of these molecular changes are associated with neoplastic transformation and/or progression. Tumor specific antigens are generally able to induce strong immune responses without bearing the risk for autoimmune reactions against normal tissues. On the other hand, these TAAs are in most cases only relevant to the exact tumor on which they were identified and are usually not shared between many individual tumors. Tumor-specificity (or -association) of a peptide may also arise if the peptide originates from a tumor- (-associated) exon in case of proteins with tumor-specific (-associated) isoforms.

e) TAAs arising from abnormal post-translational modifications: Such TAAs may arise from proteins which are neither specific nor overexpressed in tumors but nevertheless become tumor associated by posttranslational processes primarily active in tumors. Examples for this class arise from altered glycosylation patterns leading to novel epitopes in tumors as for MUC1 or events like protein splicing during degradation which may or may not be tumor specific.

f) Oncoviral proteins: These TAAs are viral proteins that may play a critical role in the oncogenic process and, because they are foreign (not of human origin), they can evoke a T-cell response. Examples of such proteins are the human papilloma type 16 virus proteins, E6 and E7, which are expressed in cervical carcinoma.

[0049] For proteins to be recognized by cytotoxic T-lymphocytes as tumor-specific or -associated antigens, and to be used in a therapy, particular prerequisites must be fulfilled. The antigen should be expressed mainly by tumor cells and not, or in comparably small amounts, by normal healthy tissues. In a preferred embodiment, the peptide should be over-presented by tumor cells as compared to normal healthy tissues. It is furthermore desirable that the respective antigen is not only present in a type of tumor, but also in high concentrations (i.e. copy numbers of the respective peptide per cell). Tumor-specific and tumor-associated antigens are often derived from proteins directly involved in transformation of a normal cell to a tumor cell due to their function, e.g. in cell cycle control or suppression of apoptosis. Additionally, downstream targets of the proteins directly causative for a transformation may be upregulated und thus may be indirectly tumor-associated. Such indirect tumor-associated antigens may also be targets of a vaccination approach (Singh-Jasuja et al., 2004). It is essential that epitopes are present in the amino acid sequence of the antigen, in order to ensure that such a peptide ("immunogenic peptide"), being derived from a tumor associated antigen, leads to an *in vitro* or *in vivo* T-cell-response.

[0050] Basically, any peptide able to bind an MHC molecule may function as a T-cell epitope. A prerequisite for the induction of an *in vitro* or *in vivo* T-cell-response is the presence of a T cell having a corresponding TCR and the absence of immunological tolerance for this particular epitope.

[0051] Therefore, TAAs are a starting point for the development of a T cell based therapy including but not limited to tumor vaccines. The methods for identifying and characterizing the TAAs are based on the use of T-cells that can be isolated from patients or healthy subjects, or they are based on the generation of differential transcription profiles or differential peptide expression patterns between tumors and normal tissues.

[0052] However, the identification of genes over-expressed in tumor tissues or human tumor cell lines, or selectively expressed in such tissues or cell lines, does not provide precise information as to the use of the antigens being transcribed from these genes in an immune therapy. This is because only an individual subpopulation of epitopes of these antigens are suitable for such an application since a T cell with a corresponding TCR has to be present and the immunological tolerance for this particular epitope needs to be absent or minimal. In a very preferred example it is therefore important to select only those over- or selectively presented peptides against which a functional and/or a proliferating T cell can be found. Such a functional T cell is defined as a T cell, which upon stimulation with a specific antigen can be clonally expanded and is able to execute effector functions ("effector T cell").

[0053] In case of TCRs and antibodies according to the invention the immunogenicity of the underlying peptides is secondary. For TCRs and antibodies disclosed herein the presentation is the determining factor.

[0054] Both therapeutic and diagnostic uses against additional cancerous diseases are disclosed in the following more detailed description of the underlying proteins (polypeptides) of the peptides according to the disclosure.

[0055] A peptide consisting or consisting essentially of the amino acid sequence as indicated herein can have one or two non-anchor amino acids (see below regarding the anchor motif) exchanged without that the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I or -II is substantially changed or is negatively affected, when compared to the non-modified peptide. In another example, in a peptide consisting essentially of the amino acid sequence as indicated herein, one or two amino acids can be exchanged with their conservative exchange partners (see herein below) without that the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I or -II is substantially changed, or is negatively affected, when compared to the non-modified peptide.

[0056] The present disclosure further relates to a peptide as disclosed herein, wherein said peptide is modified and/or includes non-peptide bonds as described herein below.

[0057] The present disclosure further relates to a peptide as disclosed herein, wherein said peptide is part of a fusion protein, in particular fused to the N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii), or fused to (or into the sequence of) an antibody, such as, for example, an antibody that is specific for dendritic cells, i.e. binds to dendritic cells.

[0058] The present disclosure further relates to a nucleic acid, encoding for a peptide as disclosed herein. The present disclosure further relates to the nucleic acid as disclosed herein that is DNA, cDNA, PNA, RNA or combinations thereof.

[0059] The present disclosure further relates to an expression vector capable of expressing, expressing, and/or presenting a nucleic acid as disclosed herein.

[0060] The present disclosure further relates to a peptide as disclosed herein, a nucleic acid as disclosed herein or an expression vector as disclosed herein for use in medicine.

[0061] The present disclosure further relates to antibodies as described further below, and methods of making them. Preferred are antibodies that are specific for the peptides of the present disclosure, and/or for the peptides of the present disclosure when bound to their MHC. Preferred antibodies can be monoclonal.

[0062] The present disclosure further relates to T-cell receptors (TCR), in particular soluble TCR (sTCRs) targeting the peptides as disclosed herein and/or the peptide -MHC complexes thereof, and methods of making them.

[0063] The present disclosure further relates to antibodies or other binding molecules targeting the peptides as disclosed herein and/or the peptide-MHC complexes thereof, and methods of making them.

[0064] The present disclosure further relates to a host cell comprising a nucleic acid as disclosed herein or an expression vector as described before. The present disclosure further relates to the host cell as disclosed herein that is an antigen presenting cell. The present disclosure further relates to the host cell as disclosed herein, wherein the antigen presenting cell is a dendritic cell.

[0065] The present disclosure further relates to a method of producing a peptide as disclosed herein, said method comprising culturing the host cell as disclosed herein, and isolating the peptide from the host cell and/or its culture medium.

[0066] The present disclosure further relates to an *in vitro* method for producing activated T-cells, the method comprising contacting *in vitro* T cells with antigen loaded human class I or II MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate said T cells in an antigen specific manner, wherein said antigen is at least one peptide according to the present invention. The present disclosure further relates to a method, wherein the antigen is loaded onto class I or 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.

[0067] The present disclosure further relates to the method as disclosed herein, wherein the antigen-presenting cell comprises an expression vector capable of expressing said peptide containing SEQ ID NO: 1 to SEQ ID NO: 300, or a variant amino acid sequence thereof.

[0068] The present disclosure further relates to activated T cells, produced by the method as disclosed herein, which selectively recognize a cell which aberrantly expresses a polypeptide comprising an amino acid sequence as disclosed herein.

[0069] The present disclosure further relates to a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising any amino acid sequence as disclosed herein, the method comprising administering to the patient an effective number of T cells as disclosed herein.

[0070] The present disclosure further relates to the use of any peptide described, a nucleic acid as disclosed herein, an expression vector as disclosed herein, a cell as disclosed herein, or an activated T-cell as disclosed herein as a medicament or in the manufacture of a medicament.

[0071] The present disclosure further relates to a use as disclosed herein, wherein said medicament is a vaccine, a cell, a cell population, such as, for example, a cell line, sTCRs and monoclonal antibodies.

[0072] The present disclosure further relates to a use as disclosed herein, wherein the medicament is active against cancer.

[0073] The present disclosure further relates to a use as disclosed herein, wherein said cancer cells are cells of HCC.

[0074] The present disclosure further relates to particular marker proteins and biomarkers based on the peptides according to the present invention that can be used in the diagnosis and/or prognosis of HCC.

[0075] Furthermore, the present disclosure relates to the use of these novel targets for cancer treatment.

[0076] Further, the present disclosure relates to a method for producing a personalized anticancer vaccine for an individual patient using a database (herein designated also as "warehouse") of pre-screened tumor associated peptides.

[0077] Stimulation of an immune response is dependent upon the presence of antigens recognized as foreign by the host immune system. The discovery of the existence of tumor associated antigens has raised the possibility of using a host's immune system to intervene in tumor growth. Various mechanisms of harnessing both the humoral and cellular arms of the immune system are currently being explored for cancer immunotherapy.

[0078] Specific elements of the cellular immune response are capable of specifically recognizing and destroying tumor cells. The isolation of T-cells from tumor-infiltrating cell populations or from peripheral blood suggests that such cells play an important role in natural immune defense against cancer. CD8-positive T-cells in particular, which recognize Class I molecules of the major histocompatibility complex (MHC)-bearing peptides of usually 8 to 10 amino acid residues derived from proteins or defect ribosomal products (DRIPS) located in the cytosol, play an important role in this response. The MHC-molecules of the human are also designated as human leukocyte-antigens (HLA).

[0079] The term "peptide" is used herein to designate a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. The peptides are preferably 9 amino acids in length, but can be as short as 8 amino acids in length, and as long as 10, 11, 12, or 13 and in case of MHC class II peptides (elongated variants of the peptides of the disclosure) they can be as long as 14, 15, 16, 17, 18, 19 or 20 amino acids in length.

[0080] Furthermore, the term "peptide" shall include salts of a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. Preferably, the salts are pharmaceutical acceptable salts of the peptides, such as, for example, the chloride or acetate (trifluoroacetate) salts. It has to be noted that the salts of the peptides according to the present disclosure differ substantially from the peptides in their state(s) *in vivo,* as the peptides are not salts *in vivo.*

[0081] The term "peptide" shall also include "oligopeptide". The term "oligopeptide" is used herein to designate a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. The length of the oligopeptide is not critical to the invention, as long as the correct epitope or epitopes are maintained therein. The oligopeptides are typically less than about 30 amino acid residues in length, and greater than about 15 amino acids in length.

[0082] The term "the peptides of the present invention" shall also include the peptides consisting of or comprising a peptide as defined above according to SEQ ID NO: 1 to SEQ ID NO: 300.

[0083] The term "polypeptide" designates a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. The length of the polypeptide is not critical to the invention as long as the correct epitopes are maintained. In contrast to the terms peptide or oligopeptide, the term polypeptide is meant to refer to molecules containing more than about 30 amino acid residues.

[0084] A peptide, oligopeptide, protein or polynucleotide coding for such a molecule is "immunogenic" (and thus is an "immunogen" within the present invention), if it is capable of inducing an immune response. In the case of the present invention, immunogenicity is more specifically defined as the ability to induce a T-cell response. Thus, an "immunogen" would be a molecule that is capable of inducing an immune response, and in the case of the present invention, a molecule capable of inducing a T-cell response. In another aspect, the immunogen can be the peptide, the complex of the peptide with MHC, oligopeptide, and/or protein that is used to raise specific antibodies or TCRs against it.

[0085] A class I T cell "epitope" requires a short peptide that is bound to a class I MHC receptor, forming a ternary complex (MHC class I alpha chain, beta-2-microglobulin, and peptide) that can be recognized by a T cell bearing a matching T-cell receptor binding to the MHC/peptide complex with appropriate affinity. Peptides binding to MHC class I molecules are typically 8-14 amino acids in length, and most typically 9 amino acids in length.

[0086] In humans there are three different genetic loci that encode MHC class I molecules (the MHC-molecules of the human are also designated human leukocyte antigens (HLA)): HLA-A, HLA-B, and HLA-C. HLA-A*01, HLA-A*02, and HLA-B*07 are examples of different MHC class I alleles that can be expressed from these loci.

Table 3: Expression frequencies F of HLA-A*02 and HLA-A*24 and the most frequent HLA-DR serotypes. Frequencies are deduced from haplotype frequencies Gf within the American population adapted from Mori et al. (Mori M, et al. HLA gene and haplotype frequencies in the North American population: the National Marrow Donor Program Donor Registry. Transplantation. 1997 Oct 15;64(7): 1017-27) employing the Hardy-Weinberg formula $F=1-(1-Gf)^2$. Combinations of A*02 or A*24 with certain HLA-DR alleles might be enriched or less frequent than expected from their single frequencies due to linkage disequilibrium. For details refer to Chanock et al. (S.J. Chanock, et al (2004) HLA-A, -B, -Cw, -DQA1 and DRB1 in an African American population from Bethesda, USA Human Immunology, 65: 1223-1235).

Allele	Population	Calculated phenotype from allele frequency
A*02	Caucasian (North America)	49.1%
A*02	African American (North America)	34.1%
A*02	Asian American (North America)	43.2%
A*02	Latin American (North American)	48.3%
DR1	Caucasian (North America)	19.4%
DR2	Caucasian (North America)	28.2%
DR3	Caucasian (North America)	20.6%
DR4	Caucasian (North America)	30.7%
DR5	Caucasian (North America)	23.3%
DR6	Caucasian (North America)	26.7%
DR7	Caucasian (North America)	24.8%
DR8	Caucasian (North America)	5.7%
DR9	Caucasian (North America)	2.1%
DR1	African (North) American	13.20%
DR2	African (North) American	29.80%
DR3	African (North) American	24.80%
DR4	African (North) American	11.10%
DR5	African (North) American	31.10%
DR6	African (North) American	33.70%
DR7	African (North) American	19.20%
DR8	African (North) American	12.10%

(continued)

Allele	Population	Calculated phenotype from allele frequency
DR9	African (North) American	5.80%
DR1	Asian (North) American	6.80%
DR2	Asian (North) American	33.80%
DR3	Asian North American	9.20%
DR4	Asian (North) American	28.60%
DR5	Asian (North) American	30.00%
DR6	Asian (North) American	25.10%
DR7	Asian (North) American	13.40%
DR8	Asian (North) American	12.70%
DR9	Asian (North) American	18.60%
DR1	Latin (North) American	15.30%
DR2	Latin (North) American	21.20%
DR3	Latin (North) American	15.20%
DR4	Latin (North) American	36.80%
DR5	Latin (North) American	20.00%
DR6	Latin (North) American	31.10%
DR7	Latin (North) American	20.20%
DR8	Latin (North) American	18.60%
DR9	Latin (North) American	2.10%
A*24	Philippines	65%
A*24	Russia Nenets	61%
A*24:02	Japan	59%
A*24	Malaysia	58%
A*24:02	Philippines	54%
A*24	India	47%
A*24	South Korea	40%
A*24	Sri Lanka	37%
A*24	China	32%
A*24:02	India	29%
A*24	Australia West	22%
A*24	USA	22%
A*24	Russia Samara	20%
A*24	South America	20%
A*24	Europe	18%

[0087] The peptides of the disclosure, preferably when included into a vaccine of the disclosure as described herein bind to A*02 or A*24. A vaccine may also include pan-binding MHC class II peptides. Therefore, the vaccine of the disclosure can be used to treat cancer in patients that are either A*02 positive, A*24 positive or positive for A*02 and

A*24, whereas no selection for MHC class II allotypes is necessary due to the pan-binding nature of these peptides.

[0088] Combining for example A*02 and A*24 peptides in one vaccine has the advantage that a higher percentage of any patient population can be treated compared with addressing either MHC class I allele alone. While in most populations less than 50% of patients could be addressed by either allele alone, the vaccine of the disclosure can treat at least 60% of patients in any relevant population. Specifically, the following percentages of patients will be positive for at least one of these alleles in various regions: USA 61%, Western Europe 62%, China 75%, South Korea 77%, Japan 86% (calculated from www.allelefrequencies.net).

[0089] As used herein, reference to a DNA sequence includes both single stranded and double stranded DNA. Thus, the specific sequence, unless the context indicates otherwise, refers to the single strand DNA of such sequence, the duplex of such sequence with its complement (double stranded DNA) and the complement of such sequence. The term "coding region" refers to that portion of a gene which either naturally or normally codes for the expression product of that gene in its natural genomic environment, i.e., the region coding *in vivo* for the native expression product of the gene.

[0090] The coding region can be derived from a non-mutated ("normal"), mutated or altered gene, or can even be derived from a DNA sequence, or gene, wholly synthesized in the laboratory using methods well known to those of skill in the art of DNA synthesis.

[0091] In a preferred embodiment, the term "nucleotide sequence" refers to a heteropolymer of deoxyribonucleotides.

[0092] The nucleotide sequence coding for a particular peptide, oligopeptide, or polypeptide may be naturally occurring or they may be synthetically constructed. Generally, DNA segments encoding the peptides, polypeptides, and proteins of this disclosure are assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene that is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon.

[0093] As used herein the term "a nucleotide coding (or encoding) for a peptide" refers to a nucleotide sequence coding for the peptide including artificial (man-made) start and stop codons compatible for the biological system the sequence is to be expressed by, for example, a dendritic cell or another cell system useful for the production of TCRs.

[0094] The term "expression product" means the polypeptide or protein that is the natural translation product of the gene and any nucleic acid sequence coding equivalents resulting from genetic code degeneracy and thus coding for the same amino acid(s).

[0095] The term "fragment", when referring to a coding sequence, means a portion of DNA comprising less than the complete coding region, whose expression product retains essentially the same biological function or activity as the expression product of the complete coding region.

[0096] The term "DNA segment" refers to a DNA polymer, in the form of a separate fragment or as a component of a larger DNA construct, which has been derived from DNA isolated at least once in substantially pure form, i.e., free of contaminating endogenous materials and in a quantity or concentration enabling identification, manipulation, and recovery of the segment and its component nucleotide sequences by standard biochemical methods, for example, by using a cloning vector. Such segments are provided in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, which are typically present in eukaryotic genes. Sequences of non-translated DNA may be present downstream from the open reading frame, where the same do not interfere with manipulation or expression of the coding regions.

[0097] The term "primer" means a short nucleic acid sequence that can be paired with one strand of DNA and provides a free 3'-OH end at which a DNA polymerase starts synthesis of a deoxyribonucleotide chain.

[0098] The term "promoter" means a region of DNA involved in binding of RNA polymerase to initiate transcription.

[0099] The term "isolated" means that the material is removed from its original environment (e.g., the natural environment, if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment.

[0100] The polynucleotides, and recombinant or immunogenic polypeptides, disclosed in accordance with the present disclosure may also be in "purified" form. The term "purified" does not require absolute purity; rather, it is intended as a relative definition, and can include preparations that are highly purified or preparations that are only partially purified, as those terms are understood by those of skill in the relevant art. For example, individual clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated. Furthermore, a claimed polypeptide which has a purity of preferably 99.999%, or at least 99.99% or 99.9%; and even desirably 99% by weight or greater is expressly contemplated.

[0101] The nucleic acids and polypeptide expression products disclosed according to the presentdisclosure, as well as expression vectors containing such nucleic acids and/or such polypeptides, may be in "enriched form". As used herein, the term "enriched" means that the concentration of the material is at least about 2, 5, 10, 100, or 1000 times its natural concentration (for example), advantageously 0.01 %, by weight, preferably at least about 0.1% by weight. Enriched preparations of about 0.5%, 1%, 5%, 10%, and 20% by weight are also contemplated. The sequences, constructs, vectors, clones, and other materials comprising the present disclosure can advantageously be in enriched or isolated form.

[0102] The term "active fragment" means a fragment, usually of a peptide, polypeptide or nucleic acid sequence, that generates an immune response (i.e., has immunogenic activity) when administered, alone or optionally with a suitable adjuvant or in a vector, to an animal, such as a mammal, for example, a rabbit or a mouse, and also including a human, such immune response taking the form of stimulating a T-cell response within the recipient animal, such as a human. Alternatively, the "active fragment" may also be used to induce a T-cell response *in vitro.*

[0103] As used herein, the terms "portion", "segment" and "fragment," when used in relation to polypeptides, refer to a continuous sequence of residues, such as amino acid residues, which sequence forms a subset of a larger sequence. For example, if a polypeptide were subjected to treatment with any of the common endopeptidases, such as trypsin or chymotrypsin, the oligopeptides resulting from such treatment would represent portions, segments or fragments of the starting polypeptide. When used in relation to polynucleotides, these terms refer to the products produced by treatment of said polynucleotides with any of the endonucleases.

[0104] In accordance with the presentdisclosure, the term "percent homology", "percent identity" or "percent identical", when referring to a sequence, means that a sequence is compared to a claimed or described sequence after alignment of the sequence to be compared (the "Compared Sequence") with the described or claimed sequence (the "Reference Sequence"). The Percent Identity is then determined according to the following formula:

$$\text{Percent Identity} = 100\ [1 - (C/R)]$$

wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference Sequence and the Compared Sequence, wherein

(i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence and
(ii) each gap in the Reference Sequence and
(iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference and
(iiii) the alignment has to start at position 1 of the aligned sequences;

and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

[0105] If an alignment exists between the Compared Sequence and the Reference Sequence for which the Percent Identity as calculated above is about equal to or greater than a specified minimum Percent Identity then the Compared Sequence has the specified minimum Percent Identity to the Reference Sequence even though alignments may exist in which the herein above calculated Percent Identity is less than the specified Percent Identity.

[0106] The original (unmodified) peptides as disclosed herein can be modified by the substitution of one or more residues at different, possibly selective, sites within the peptide chain, if not otherwise stated. Preferably those substitutions are located at the end of the amino acid chain. Such substitutions may be of a conservative nature, for example, where one amino acid is replaced by an amino acid of similar structure and characteristics, such as where a hydrophobic amino acid is replaced by another hydrophobic amino acid. Even more conservative would be replacement of amino acids of the same or similar size and chemical nature, such as where leucine is replaced by isoleucine. In studies of sequence variations in families of naturally occurring homologous proteins, certain amino acid substitutions are more often tolerated than others, and these are often show correlation with similarities in size, charge, polarity, and hydrophobicity between the original amino acid and its replacement, and such is the basis for defining "conservative substitutions."

[0107] Conservative substitutions are herein defined as exchanges within one of the following five groups: Group 1-small aliphatic, nonpolar or slightly polar residues (Ala, Ser, Thr, Pro, Gly); Group 2-polar, negatively charged residues and their amides (Asp, Asn, Glu, Gln); Group 3-polar, positively charged residues (His, Arg, Lys); Group 4-large, aliphatic, nonpolar residues (Met, Leu, Ile, Val, Cys); and Group 5-large, aromatic residues (Phe, Tyr, Trp).

[0108] Less conservative substitutions might involve the replacement of one amino acid by another that has similar characteristics but is somewhat different in size, such as replacement of an alanine by an isoleucine residue. Highly non-conservative replacements might involve substituting an acidic amino acid for one that is polar, or even for one that is basic in character. Such "radical" substitutions cannot, however, be dismissed as potentially ineffective since chemical effects are not totally predictable and radical substitutions might well give rise to serendipitous effects not otherwise predictable from simple chemical principles.

[0109] Of course, such substitutions may involve structures other than the common L-amino acids. Thus, D-amino acids might be substituted for the L-amino acids commonly found in the antigenic peptides of the disclosure and yet still be encompassed by the disclosure herein. In addition, amino acids possessing non-standard R groups (i.e., R groups other than those found in the common 20 amino acids of natural proteins) may also be used for substitution purposes to produce immunogens and immunogenic polypeptides according to the present disclosure.

[0110] If substitutions at more than one position are found to result in a peptide with substantially equivalent or greater antigenic activity as defined below, then combinations of those substitutions will be tested to determine if the combined substitutions result in additive or synergistic effects on the antigenicity of the peptide. At most, no more than 4 positions within the peptide would simultaneously be substituted.

[0111] The peptides of the disclosure can be elongated by up to four amino acids, that is 1, 2, 3 or 4 amino acids can be added to either end in any combination between 4:0 and 0:4.

[0112] Combinations of the elongations according to the disclosure can be depicted from Table 4:

C-terminus	N-terminus
4	0
3	0 or 1
2	0 or 1 or 2
1	0 or 1 or 2 or 3
0	0 or 1 or 2 or 3 or 4
N-terminus	C-terminus
4	0
3	0 or 1
2	0 or 1 or 2
1	0 or 1 or 2 or 3
0	0 or 1 or 2 or 3 or 4

[0113] The amino acids for the elongation/extension can be the peptides of the original sequence of the protein or any other amino acid(s). The elongation can be used to enhance the stability or solubility of the peptides.

[0114] The term "T-cell response" means the specific proliferation and activation of effector functions induced by a peptide *in vitro* or *in vivo.* For MHC class I restricted CTLs, effector functions may be lysis of peptide-pulsed, peptide-precursor pulsed or naturally peptide-presenting target cells, secretion of cytokines, preferably Interferon-gamma, TNF-alpha, or IL-2 induced by peptide, secretion of effector molecules, preferably granzymes or perforins induced by peptide, or degranulation.

[0115] Preferably, when the T cells specific for a peptide as disclosed herein are tested against the substituted peptides, the peptide concentration at which the substituted peptides achieve half the maximal increase in lysis relative to background is no more than about 1 mM, preferably no more than about 1 μM, more preferably no more than about 1 nM, and still more preferably no more than about 100 pM, and most preferably no more than about 10 pM. It is also preferred that the substituted peptide be recognized by T cells from more than one individual, at least two, and more preferably three individuals.

[0116] Thus, the epitopes of the present disclosure may be identical to naturally occurring tumor-associated or tumor-specific epitopes or may include epitopes that differ by no more than four residues from the reference peptide, as long as they have substantially identical antigenic activity.

[0117] MHC class I molecules can be found on most cells having a nucleus which present peptides that result from proteolytic cleavage of mainly endogenous, cytosolic or nuclear proteins, DRIPS, and larger peptides. However, peptides derived from endosomal compartments or exogenous sources are also frequently found on MHC class I molecules. This non-classical way of class I presentation is referred to as cross-presentation in literature.

[0118] Since both types of response, CD8 and CD4 dependent, contribute jointly and synergistically to the anti-tumor effect, the identification and characterization of tumor-associated antigens recognized by either CD8-positive T cells (MHC class I molecule) or by CD4-positive T cells (MHC class II molecule) is important in the development of tumor vaccines. It is therefore an object of the present disclosure, to provide compositions of peptides that contain peptides binding to MHC complexes of either class.

[0119] Considering the severe side-effects and expense associated with treating cancer better prognosis and diagnostic methods are desperately needed. Therefore, there is a need to identify other factors representing biomarkers for cancer in general and HCC in particular. Furthermore, there is a need to identify factors that can be used in the treatment of cancer in general and HCC in particular.

[0120] The present disclosure provides peptides that are useful in treating cancers/tumors, preferably HCC that over- or exclusively present the peptides of the disclosure. These peptides were shown by mass spectrometry to be naturally presented by HLA molecules on primary human HCC samples.

[0121] The source gene/protein (also designated "full-length protein" or "underlying protein") from which the peptides are derived were shown to be highly overexpressed in cancer compared with normal tissues - "normal tissues" in relation to this disclosure shall mean either healthy liver cells or other normal tissue cells, demonstrating a high degree of tumor association of the source genes (see example 2). Moreover, the peptides themselves are strongly over-presented on tumor tissue - "tumor tissue" in relation to this disclosure shall mean a sample from a patient suffering from HCC, but not on normal tissues (see Example 1).

[0122] HLA-bound peptides can be recognized by the immune system, specifically T lymphocytes. T cells can destroy the cells presenting the recognized HLA/peptide complex, e.g. HCC cells presenting the derived peptides.

[0123] The peptides of the present disclosure have been shown to be capable of stimulating T cell responses and / or are over-presented and thus can be used for the production of antibodies and / or TCRs, in particular sTCRs, as disclosed herein (see Example 3). Furthermore, the peptides when complexed with the respective MHC can be used for the production of antibodies and/or TCRs, in particular sTCRs, as disclosed herein, as well. Respective methods are well known to the person of skill, and can be found in the respective literature as well. Thus, the peptides of the present disclosure are useful for generating an immune response in a patient by which tumor cells can be destroyed. An immune response in a patient can be induced by direct administration of the described peptides or suitable precursor substances (e.g. elongated peptides, proteins, or nucleic acids encoding these peptides) to the patient, ideally in combination with an agent enhancing the immunogenicity (i.e. an adjuvant). The immune response originating from such a therapeutic vaccination can be expected to be highly specific against tumor cells because the target peptides of the present disclosure are not presented on normal tissues in comparable copy numbers, preventing the risk of undesired autoimmune reactions against normal cells in the patient.

[0124] A "pharmaceutical composition" preferably is preferably a composition suitable for administration to a human being in a medical setting. Preferably, a pharmaceutical composition is sterile and produced according to GMP guidelines.

[0125] The pharmaceutical compositions comprise the peptides either in the free form or in the form of a pharmaceutically acceptable salt (see also above). As used herein, "a pharmaceutically acceptable salt" refers to a derivative of the disclosed peptides wherein the peptide is modified by making acid or base salts of the agent. For example, acid salts are prepared from the free base (typically wherein the neutral form of the drug has a neutral -NH2 group) involving reaction with a suitable acid. Suitable acids for preparing acid salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methane sulfonic acid, ethane sulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid phosphoric acid and the like. Conversely, preparation of basic salts of acid moieties which may be present on a peptide are prepared using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine or the like.

[0126] In an especially preferred embodiment, the pharmaceutical compositions comprise the peptides as salts of acetic acid (acetates), trifluoro acetates or hydrochloric acid (chlorides).

[0127] Especially preferred is a composition and/or the use of said composition, e.g. in the form of a vaccine.

[0128] The peptides of the present disclosure can be used to generate and develop specific antibodies against MHC/peptide complexes. These can be used for therapy, targeting toxins or radioactive substances to the diseased tissue. Another use of these antibodies can be targeting radionuclides to the diseased tissue for imaging purposes such as PET. This use can help to detect small metastases or to determine the size and precise localization of diseased tissues.

[0129] Therefore, it is a further aspect of the invention to provide a method for producing a recombinant antibody specifically binding to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, the method comprising: immunizing a genetically engineered non-human mammal comprising cells expressing said human major histocompatibility complex (MHC) class I or II with a soluble form of a MHC class I or II molecule being complexed with said HLA-restricted antigen; isolating mRNA molecules from antibody producing cells of said non-human mammal; producing a phage display library displaying protein molecules encoded by said mRNA molecules; and isolating at least one phage from said phage display library, said at least one phage displaying said antibody specifically binding to said human major histocompatibility complex (MHC) class I or II being complexed with said HLA-restricted antigen.

[0130] It is a further aspect of the invention to provide an antibody that specifically binds to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, wherein the antibody preferably is a polyclonal antibody, monoclonal antibody, bi-specific antibody and/or a chimeric antibody.

[0131] Yet another aspect of the present invention then relates to a method of producing said antibody specifically binding to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, the method comprising: immunizing a genetically engineered non-human mammal comprising cells expressing said human major histocompatibility complex (MHC) class I or II with a soluble form of a MHC class I or II molecule being complexed with said HLA-restricted antigen; isolating mRNA molecules from antibody producing cells of said non-human mammal; producing a phage display library displaying protein molecules encoded by said mRNA molecules; and isolating at least one phage from said phage display library, said at least one phage displaying said antibody specifically bindable to said human major histocompatibility complex (MHC) class I or II being complexed with said HLA-restricted antigen. Respective methods for producing such antibodies and single chain class I major histocompatibility complexes, as well as other tools for the production of these antibodies are disclosed in WO 03/068201, WO 2004/084798, WO 01/72768, WO 03/070752, and in publications (Cohen et al., 2003a; Cohen et al., 2003b; Denkberg et al., 2003).

[0132] Preferably, the antibody is binding with a binding affinity of below 20 nanomolar, preferably of below 10 nanomolar, to the complex, which is regarded as "specific" in the context of the present invention.

[0133] It is a further aspect of the invention to provide a method for producing a soluble T-cell receptor (sTCR) recognizing a specific peptide-MHC complex. Such soluble T-cell receptors can be generated from specific T-cell clones, and their affinity can be increased by mutagenesis targeting the complementarity-determining regions. For the purpose of T-cell receptor selection, phage display can be used (US 2010/0113300, Liddy et al., 2012). For the purpose of stabilization of T-cell receptors during phage display and in case of practical use as drug, alpha and beta chain can be linked e.g. by non-native disulfide bonds, other covalent bonds (single-chain T-cell receptor), or by dimerization domains (see Boulter et al., 2003; Card et al., 2004; Willcox et al., 1999). The T-cell receptor can be linked to toxins, drugs, cytokines (see, for example, US 2013/0115191), domains recruiting effector cells such as an anti-CD3 domain, etc., in order to execute particular functions on target cells. Moreover, it could be expressed in T cells used for adoptive transfer. Further information can be found in WO 2004/033685A1 and WO 2004/074322A1. A combination of sTCRs is described in WO 2012/056407A1. Further methods for the production are disclosed in WO 2013/057586A1.

[0134] In addition, the peptides and/or the TCRs or antibodies or other binding molecules of the present disclosure can be used to verify a pathologist's diagnosis of a cancer based on a biopsied sample.

[0135] In order to select over-presented peptides, a presentation profile is calculated showing the median sample presentation as well as replicate variation. The profile juxtaposes samples of the tumor entity of interest to a baseline of normal tissue samples. Each of these profiles can then be consolidated into an over-presentation score by calculating the p-value of a Linear Mixed-Effects Model (Pinheiro et al., 2007) adjusting for multiple testing by False Discovery Rate (Benjamini and Hochberg, 1995).

[0136] For the identification and relative quantitation of HLA ligands by mass spectrometry, HLA molecules from shock-frozen tissue samples were purified and HLA-associated peptides were isolated. The isolated peptides were separated and sequences were identified by online nano-electrospray-ionization (nanoESI) liquid chromatography-mass spectrometry (LC-MS) experiments. The resulting peptide sequences were verified by comparison of the fragmentation pattern of natural TUMAPs recorded from HCC samples (N = 16 A*02-positive samples including thirteen A*02:01-positive samples, N = 15 A*24-positive samples) with the fragmentation patterns of corresponding synthetic reference peptides of identical sequences. Since the peptides were directly identified as ligands of HLA molecules of primary tumors, these results provide direct evidence for the natural processing and presentation of the identified peptides on primary cancer tissue obtained from 31 HCC patients.

[0137] The discovery pipeline XPRESIDENT® v2.1 (see, for example, US 2013-0096016) allows the identification and selection of relevant over-presented peptide vaccine candidates based on direct relative quantitation of HLA-restricted peptide levels on cancer tissues in comparison to several different non-cancerous tissues and organs. This was achieved by the development of label-free differential quantitation using the acquired LC-MS data processed by a proprietary data analysis pipeline, combining algorithms for sequence identification, spectral clustering, ion counting, retention time alignment, charge state deconvolution and normalization.

[0138] Presentation levels including error estimates for each peptide and sample were established. Peptides exclusively presented on tumor tissue and peptides over-presented in tumor versus non-cancerous tissues and organs have been identified.

[0139] HLA-peptide complexes from HCC tissue samples were purified and HLA-associated peptides were isolated and analyzed by LC-MS (see examples). All TUMAPs contained in the present application were identified with this approach on primary HCC samples confirming their presentation on primary HCC.

[0140] TUMAPs identified on multiple HCC tumor and normal tissues were quantified using ion-counting of label-free LC-MS data. The method assumes that LC-MS signal areas of a peptide correlate with its abundance in the sample. All quantitative signals of a peptide in various LC-MS experiments were normalized based on central tendency, averaged per sample and merged into a bar plot, called presentation profile. The presentation profile consolidates different analysis methods like protein database search, spectral clustering, charge state deconvolution (decharging) and retention time alignment and normalization.

[0141] The present disclosure relates to a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 300, or a variant thereof which is at least 90% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 300 or a variant thereof that induces T cells cross-reacting with said peptide, wherein said peptide is not the underlying full-length polypeptide.

[0142] The present disclosure further relates to a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 300 or a variant thereof which is at least 90% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 300, wherein said peptide or variant has an overall length of between 8 and 100, preferably between 8 and 30, and most preferred between 8 and 14 amino acids.

[0143] The present disclosure further relates to the peptides as disclosed herein that have the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I or -II.

[0144] The present disclosure further relates to the peptides as disclosed herein wherein the peptide consists or consists essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 300.

[0145] The present disclosure further relates to the peptides as disclosed herein, wherein the peptide is (chemically) modified and/or includes non-peptide bonds.

[0146] The present disclosure further relates to the peptides as disclosed herein, wherein the peptide is part of a fusion protein, in particular comprising N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii), or wherein the peptide is fused to (or into) an antibody, such as, for example, an antibody that is specific for dendritic cells.

[0147] The present disclosure further relates to a nucleic acid, encoding the peptides as disclosed herein, provided that the peptide is not the complete (full) human protein.

[0148] The present disclosure further relates to the nucleic acid as disclosed herein that is DNA, cDNA, PNA, RNA or combinations thereof.

[0149] The present disclosure further relates to an expression vector capable of expressing a nucleic acid as disclosed herein.

[0150] The present disclosure further relates to a peptide as disclosed herein, a nucleic acid as disclosed herein or an expression vector as disclosed herein for use in medicine, in particular in the treatment of HCC.

[0151] The present disclosure further relates to a host cell comprising a nucleic acid as disclosed herein or an expression vector as disclosed herein.

[0152] The present disclosure further relates to the host cell as disclosed herein that is an antigen presenting cell, and preferably a dendritic cell.

[0153] The present disclosure further relates to the method as disclosed herein, where-in the antigen is loaded onto class I or 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.

[0154] The present disclosure further relates to the method as disclosed herein, wherein the antigen-presenting cell comprises an expression vector capable of expressing said peptide containing SEQ ID NO: 1 to SEQ ID NO: 300 or said variant amino acid sequence.

[0155] The present disclosure further relates to the use of any peptide described, a nucleic acid as disclosed herein, an expression vector as disclosed herein, a cell as disclosed herein, or an activated cytotoxic T lymphocyte as disclosed herein as a medicament or in the manufacture of a medicament. The present disclosure further relates to a use as disclosed herein, wherein the medicament is active against cancer.

[0156] The present disclosure further relates to a use as disclosed herein, wherein the medicament is a vaccine. The present disclosure further relates to a use as disclosed herein, wherein the medicament is active against cancer.

[0157] The present disclosure further relates to a use as disclosed herein, wherein said cancer cells are HCC cells or other solid or haematological tumor cells such as pancreatic cancer, brain cancer, kidney cancer, colon or rectal cancer, or leukemia.

[0158] The present disclosure further relates to particular marker proteins and biomarkers based on the peptides as disclosed herein, herein called "targets" that can be used in the diagnosis and/or prognosis of HCC. The present invention also relates to the use of these novel targets for cancer treatment.

[0159] The term "antibody" or "antibodies" is used herein in a broad sense and includes both polyclonal and monoclonal antibodies. In addition to intact or "full" immunoglobulin molecules, also included in the term "antibodies" are fragments (e.g. CDRs, Fv, Fab and Fc fragments) or polymers of those immunoglobulin molecules and humanized versions of immunoglobulin molecules, as long as they exhibit any of the desired properties (e.g., specific binding of a HCC marker polypeptide, delivery of a toxin to a HCC cell expressing a cancer marker gene at an increased level, and/or inhibiting the activity of a HCC marker polypeptide) as disclosed herein.

[0160] Whenever possible, the antibodies of the disclosure may be purchased from commercial sources. The antibodies of the disclosure may also be generated using well-known methods. The skilled artisan will understand that either full length HCC marker polypeptides or fragments thereof may be used to generate the antibodies of the disclosure. A polypeptide to be used for generating an antibody of the disclosure may be partially or fully purified from a natural source, or may be produced using recombinant DNA techniques.

[0161] For example, a cDNA encoding a peptide as disclosed herein, such as a peptide according to SEQ ID NO: 1 to SEQ ID NO: 300 polypeptide, or a variant or fragment thereof, can be expressed in prokaryotic cells (e.g., bacteria) or eukaryotic cells (e.g., yeast, insect, or mammalian cells), after which the recombinant protein can be purified and used to generate a monoclonal or polyclonal antibody preparation that specifically bind the HCC marker polypeptide used to generate the antibody as disclosed herein.

[0162] One of skill in the art will realize that the generation of two or more different sets of monoclonal or polyclonal antibodies maximizes the likelihood of obtaining an antibody with the specificity and affinity required for its intended use (e.g., ELISA, immunohistochemistry, *in vivo* imaging, immunotoxin therapy). The antibodies are tested for their desired activity by known methods, in accordance with the purpose for which the antibodies are to be used (e.g., ELISA, immunohistochemistry, immunotherapy, etc.; for further guidance on the generation and testing of antibodies, see, e.g., Harlow and Lane, 2013). For example, the antibodies may be tested in ELISA assays or, Western blots, immunohistochemical staining of formalin-fixed cancers or frozen tissue sections. After their initial *in vitro* characterization, antibodies intended for therapeutic or *in vivo* diagnostic use are tested according to known clinical testing methods.

[0163] The term "monoclonal antibody" as used herein refers to an antibody obtained from a substantially homogeneous population of antibodies, i.e.; the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired antagonistic activity (US 4,816,567).

[0164] Monoclonal antibodies of the invention may be prepared using hybridoma methods. In a hybridoma method, a mouse or other appropriate host animal is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro.*

[0165] The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in US 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies).

[0166] *In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art. For instance, digestion can be performed using papain. Examples of papain digestion are described in WO 94/29348 and US 4,342,566. Papain digestion of antibodies typically produces two identical antigen binding fragments, called Fab fragments, each with a single antigen binding site, and a residual Fc fragment. Pepsin treatment yields a F(ab')2 fragment and a pFc' fragment.

[0167] The antibody fragments, whether attached to other sequences or not, can also include insertions, deletions, substitutions, or other selected modifications of particular regions or specific amino acids residues, provided the activity of the fragment is not significantly altered or impaired compared to the non-modified antibody or antibody fragment. These modifications can provide for some additional property, such as to remove/add amino acids capable of disulfide bonding, to increase its bio-longevity, to alter its secretory characteristics, etc. In any case, the antibody fragment must possess a bioactive property, such as binding activity, regulation of binding at the binding domain, etc. Functional or active regions of the antibody may be identified by mutagenesis of a specific region of the protein, followed by expression and testing of the expressed polypeptide. Such methods are readily apparent to a skilled practitioner in the art and can include site-specific mutagenesis of the nucleic acid encoding the antibody fragment.

[0168] The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[0169] Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (US 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[0170] Transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production can be employed. For example, it has been described that the homozygous deletion of the antibody heavy chain joining region gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. Human antibodies can also be produced in phage display libraries.

[0171] Antibodies of the invention are preferably administered to a subject in a pharmaceutically acceptable carrier. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of antibody being administered.

[0172] The antibodies can be administered to the subject, patient, or cell by injection (e.g., intravenous, intraperitoneal, subcutaneous, intramuscular), or by other methods such as infusion that ensure its delivery to the bloodstream in an effective form. The antibodies may also be administered by intratumoral or peritumoral routes, to exert local as well as systemic therapeutic effects. Local or intravenous injection is preferred.

[0173] Effective dosages and schedules for administering the antibodies may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of antibodies that must be administered will vary depending on, for example, the subject that will receive the antibody, the route of administration, the particular type of antibody used and other drugs being administered. A typical daily dosage of the antibody used alone might range from about 1 (μg/kg to up to 100 mg/kg of body weight or more per day, depending on the factors mentioned above. Following administration of an antibody, preferably for treating HCC, the efficacy of the therapeutic antibody can be assessed in various ways well known to the skilled practitioner. For instance, the size, number, and/or distribution of cancer in a subject receiving treatment may be monitored using standard tumor imaging techniques. A therapeutically-administered antibody that arrests tumor growth, results in tumor shrinkage, and/or prevents the development of new tumors, compared to the disease course that would occurs in the absence of antibody administration, is an efficacious antibody for treatment of cancer.

[0174] Because the peptides as mentioned in the Tables above of the disclosure and thus their underlying polypeptides are highly expressed in HCC, and are expressed at rather to extremely low levels in normal cells, the inhibition of a protein selected from the group consisting of protein products of the following genes: Preferred for the inhibition and for antibodies and/or TCRs against are GLUL, GPAM, PLIN2, SLC16A1, SLC9A3R1, PCBD1, SEC16A, AKR1C4, ABCB11, HAL, CYP2E1, C4A, C4B, ALDH1L1, CRP, ACSL4, EEF2, HLTF, FBXO22, GALK1, TMCO1, TMEM33, ZNF318, IPO9, AMACR, C1QTNF3, CYP4F8, CYP4F3, CYP4F11, CYP4F12, CYP4F2, MOCOS, A1CF, COL18A1, HPR, LBP, C19orf80, CFHR5, ITIH4, TMEM110, LARP4, LMF2, SLC10A5, and SLC16A11; still preferred for the inhibition and for antibodies and/or TCRs against are ANKFY1, C12orf44, C16orf58, CPSF1, DCAF8, PEX19, DDX11, DDX12P, DECR2, NME4, DENND5B, DYM, EDC4, ERI3, FAM20A, FNDC3A,GPR107, GYG2, HEATR2, IFT81, KCTD3,SHKBP1, KIAA1324L, KLHL24, MARCH6, MBTPS2, MIR1279, CPSF6, NOC4L, NXF1, PANK2, PCNXL3, PIPSL, PSMD4, PSMD14, SLC35B1, TCP11L2, THNSL2, THOC2, TOMM5, TRAPPC6B, TRIM54, TRIM55, TRIM63, UGGT2, URB1, VPS54, WIZ, ZNF451, RFTN2, SCFD1, SERINC5, CCT7P2, CMAS, ANKS1A, C17orf70, CCT7, CDK5RAP2, CLPTM1, and most preferred for the inhibition and for antibodies and/or TCRs against are APOB, FASN, and/or COPA; and expression or of the activity of these markers may be preferably integrated into a therapeutic strategy, e.g. for treating or preventing HCC.

[0175] The principle of antisense therapy is based on the hypothesis that sequence-specific suppression of gene expression (via transcription or translation) may be achieved by intra-cellular hybridization between genomic DNA or mRNA and a complementary antisense species. The formation of such a hybrid nucleic acid duplex interferes with transcription of the target tumor antigen-encoding genomic DNA, or processing/transport/translation and/or stability of the target tumor antigen mRNA.

[0176] Antisense nucleic acids can be delivered by a variety of approaches. For example, antisense oligonucleotides or anti-sense RNA can be directly administered (e.g., by intravenous injection) to a subject in a form that allows uptake into tumor cells. Alternatively, viral or plasmid vectors that encode antisense RNA (or RNA fragments) can be introduced into cells *in vivo.* Antisense effects can also be induced by sense sequences; however, the extent of phenotypic changes is highly variable. Phenotypic changes induced by effective antisense therapy are assessed according to changes in, e.g., target mRNA levels, target protein levels, and/or target protein activity levels.

[0177] In a specific example, inhibition of HCC target/marker function by antisense gene therapy may be accomplished by direct administration of antisense tumor marker RNA to a subject. The antisense tumor marker RNA may be produced and isolated by any standard technique, but is most readily produced by in vitro transcription using an antisense tumor marker cDNA under the control of a high efficiency promoter (e.g., the T7 promoter). Administration of anti-sense tumor marker RNA to cells can be carried out by any of the methods for direct nucleic acid administration described below.

[0178] An alternative strategy for inhibiting the function of a protein selected from the group consisting of the above-mentioned proteins, and most preferred of APOB, FASN, and/or COPA, involves use of a nucleic acid (e.g. siRNA, or a nucleic acid coding for an anti-protein antibody or a portion thereof, which can be transferred into cancer cells or other cells, leading to intracellular antibody expression and secretion), a protein or small molecule, or any other compound targeting the expression, translation, and/or biological function of this protein.

[0179] In the methods described above, which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), the nucleic acids of the present disclosure can be in the form of naked DNA or the nucleic acids can be in a vector for delivering the nucleic acids to the cells for inhibition of HCC marker protein expression. The vector can be a commercially available preparation, such as an adenovirus vector (Quantum Biotechnologies, Inc. (Laval, Quebec, Canada). Delivery of the nucleic acid or vector to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as Lipofectin, Lipofectamine (GIBCO-25 BRL, Inc., Gaithersburg, Md.), Superfect (Qiagen, Inc. Hilden, Germany) and Transfectam (Promega Biotec, Inc., Madison, Wis., US), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this disclosure can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, US) as well as by means of a Sonoporation machine (ImaRx Pharmaceutical Corp., Tucson, Arizona, US).

[0180] As one example, vector delivery can be via a viral system, such as a retroviral vector system that can package a recombinant retroviral genome. The recombinant retrovirus can then be used to infect and thereby deliver to the infected cells antisense nucleic acid that inhibits expression of a protein selected from the group consisting of the above-mentioned proteins. The exact method of introducing the altered nucleic acid into mammalian cells is, of course, not limited to the use of retroviral vectors. Other techniques are widely available for this procedure including the use of adenoviral vectors, adeno-associated viral (AAV) vectors, lentiviral vectors, pseudotyped retroviral vectors. Physical transduction techniques can also be used, such as liposome delivery and receptor-mediated and other endocytosis mechanisms. This invention can be used in conjunction with any of these or other commonly used gene transfer methods.

[0181] The antibodies may also be used for *in vivo* diagnostic assays. Generally, the antibody is labeled with a radionucleotide (such as ^{111}In, ^{99}Tc, ^{14}C, ^{131}I, ^{3}H, ^{32}P or ^{35}S) so that the tumor can be localized using immunoscintiography. In one embodiment, antibodies or fragments thereof bind to the extracellular domains of two or more targets of a protein selected from the group consisting of the above-mentioned proteins, and the affinity value (Kd) is less than 1 x 10μM.

[0182] Antibodies for diagnostic use may be labeled with probes suitable for detection by various imaging methods. Methods for detection of probes include, but are not limited to, fluorescence, light, confocal and electron microscopy; magnetic resonance imaging and spectroscopy; fluoroscopy, computed tomography and positron emission tomography. Suitable probes include, but are not limited to, fluorescein, rhodamine, eosin and other fluorophores, radioisotopes, gold, gadolinium and other lanthanides, paramagnetic iron, fluorine-18 and other positron-emitting radionuclides. Additionally, probes may be bi- or multi-functional and be detectable by more than one of the methods listed. These antibodies may be directly or indirectly labeled with said probes. Attachment of probes to the antibodies includes covalent attachment of the probe, incorporation of the probe into the antibody, and the covalent attachment of a chelating compound for binding of probe, amongst others well recognized in the art. For immunohistochemistry, the disease tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin. The fixed or embedded section contains the sample are contacted with a labeled primary antibody and secondary antibody, wherein the antibody is used to detect the expression of the proteins in situ.

[0183] As mentioned above, the present disclosure thus provides a peptide comprising a sequence that is selected from the group of consisting of SEQ ID NO: 1 to SEQ ID NO: 300 or a variant thereof which is 90% homologous to SEQ ID NO: 1 to SEQ ID NO: 300, or a variant thereof that will induce T cells cross-reacting with said peptide. The peptides of the disclosure have the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I or elongated versions of said peptides to class II.

[0184] In the present disclosure, the term "homologous" refers to the degree of identity (see Percent Identity above) between sequences of two amino acid sequences, i.e. peptide or polypeptide sequences. The aforementioned "homology" is determined by comparing two sequences aligned under optimal conditions over the sequences to be compared. Such a sequence homology can be calculated by creating an alignment using, for example, the ClustalW algorithm. Commonly available sequence analysis software, more specifically, Vector NTI, GENETYX or other analysis tools are provided by public databases.

[0185] A person skilled in the art will be able to assess, whether T cells induced by a variant of a specific peptide will be able to cross-react with the peptide itself (Fong et al. 2001; Zaremba et al. 1997; Colombetti et al. 2006 ; Appay et al. 2006).

[0186] By a "variant" of the given amino acid sequence the inventors 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 in consisting of SEQ ID NO: 1 to SEQ ID NO: 300. For example, a peptide may be modified so that it at least maintains, if not improves, the ability to interact with and bind to the binding groove of a suitable MHC molecule, such as HLA-A*02 or -DR, and in that way it at least maintains, if not improves, the ability to bind to the TCR of activated T cells.

[0187] These T cells can subsequently cross-react with cells and kill cells that express a polypeptide that contains the natural amino acid sequence of the cognate peptide as defined in the aspects of the disclosure. As can be derived from the scientific literature (Godkin et al. 1997) and databases (Rammensee et al. 1999), certain positions of HLA binding peptides are typically anchor residues forming a core sequence fitting to the binding motif of the HLA receptor, which is defined by polar, electrophysical, hydrophobic and spatial properties of the polypeptide chains constituting the binding groove. Thus, one skilled in the art would be able to modify the amino acid sequences set forth in SEQ ID NO: 1 to SEQ ID NO 300, by maintaining the known anchor residues, and would be able to determine whether such variants maintain the ability to bind MHC class I or II molecules. The variants of the present disclosure retain the ability to bind to the TCR of activated T cells, which can subsequently cross-react with and kill cells that express a polypeptide containing the natural amino acid sequence of the cognate peptide as defined in the aspects of the disclosure.

[0188] The amino acid residues that do not substantially contribute to interactions with the T-cell receptor can be modified by replacement with another amino acid whose incorporation does not substantially affect T-cell reactivity and does not eliminate binding to the relevant MHC. Thus, apart from the proviso given, the peptide of the disclosure may be any peptide (by which term the inventors include oligopeptide or polypeptide), which includes the amino acid sequences or a portion or variant thereof as given.

[0189] Those amino acid residues that do not substantially contribute to interactions with the TCR can be modified by replacement with another amino acid whose incorporation does not substantially affect 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 the inventors include oligopeptide or polypeptide), which includes the amino acid sequences or a portion or variant thereof as given.

[0190] Longer peptides may also be suitable. It is also possible that MHC class I epitopes, although usually between 8 and 11 amino acids long, are generated by peptide processing from longer peptides or proteins that include the actual epitope. It is preferred that the residues that flank the actual epitope are residues that do not substantially affect proteolytic cleavage necessary to expose the actual epitope during processing.

[0191] Accordingly, the present disclosure provides peptides and variants of MHC class I epitopes, wherein the peptide or variant has an overall length of between 8 and 100, preferably between 8 and 30, and most preferred between 8 and 14, namely 8, 9, 10, 11, 12, 13, 14 amino acids, in case of the elongated class II binding peptides the length can also be 15, 16, 17, 18, 19, 20, 21 or 22 amino acids.

[0192] Of course, the peptide or variant according to the present disclosure will have the ability to bind to a molecule of the human major histocompatibility complex (MHC) class I or II. Binding of a peptide or a variant to a MHC complex may be tested by methods known in the art.

[0193] In a particularly preferred example of the disclosure the peptide consists or consists essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 300.

[0194] "Consisting essentially of" shall mean that a peptide according to the present disclosure, in addition to the sequence according to any of SEQ ID NO: 1 to SEQ ID NO 300 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 an epitope for MHC molecules epitope.

[0195] Nevertheless, these stretches can be important to provide an efficient introduction of the peptide according to the present disclosure into the cells. In one embodiment of the present disclosure, the peptide is part of a fusion protein which comprises, for example, 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. In other fusions, the peptides of the present disclosure can be fused to an antibody as described herein, or a functional part thereof, in particular into a sequence of an antibody, so as to be specifically targeted by said antibody, or, for example, to or into an antibody that is specific for dendritic cells as described herein.

[0196] In addition, the peptide or variant may be modified further to improve stability and/or binding to MHC molecules in order to elicit a stronger immune response. Methods for such an optimization of a peptide sequence are well known in the art and include, for example, the introduction of reverse peptide bonds or non-peptide bonds.

[0197] In a reverse peptide bond amino acid residues are not joined by peptide (-CO-NH-) linkages but 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). This approach involves making pseudopeptides containing changes involving the backbone, and not the orientation of side chains. Meziere et al (1997) show that for MHC binding 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.

[0198] A non-peptide bond is, for example, $-CH_2-NH$, $-CH_2S-$, $-CH_2CH_2-$, -CH=CH-, $-COCH_2-$, - $CH(OH)CH_2-$, and $-CH_2SO-$. US 4,897,445 provides a method for the solid phase synthesis of non-peptide bonds ($-CH_2-NH$) in polypeptide chains which involves polypeptides synthesized by standard procedures and the non-peptide bond synthesized by reacting an amino aldehyde and an amino acid in the presence of $NaCNBH_3$.

[0199] Peptides comprising the sequences described above may be synthesized with additional chemical groups present at their amino and/or carboxy termini, to enhance the stability, bioavailability, and/or affinity of the peptides. For example, hydrophobic groups such as carbobenzoxyl, dansyl, ort-butyloxycarbonyl groups may be added to the peptides' amino termini. Likewise, an acetyl group or a 9-fluorenylmethoxy-carbonyl group may be placed at the peptides' amino termini. Additionally, the hydrophobic group, t-butyloxycarbonyl, or an amido group may be added to the peptides' carboxy termini.

[0200] Further, the peptides of the disclosure may be synthesized to alter their steric configuration. For example, the D-isomer of one or more of the amino acid residues of the peptide may be used, rather than the usual L-isomer. Still further, at least one of the amino acid residues of the peptides of the disclosure may be substituted by one of the well-known non-naturally occurring amino acid residues. Alterations such as these may serve to increase the stability, bio-availability and/or binding action of the peptides of the disclosure.

[0201] Similarly, a peptide or variant of the disclosure may be modified chemically by reacting specific amino acids either before or after synthesis of the peptide. Examples for such modifications are well known in the art and are summarized e.g. in R. Lundblad, Chemical Reagents for Protein Modification, 3rd ed. CRC Press, 2005. Chemical modification of amino acids includes but is not limited to, modification by acylation, amidination, pyridoxylation of lysine, reductive alkylation, trinitrobenzylation of amino groups with 2,4,6-trinitrobenzene sulphonic acid (TNBS), amide modification of carboxyl groups and sulphydryl modification by performic acid oxidation of cysteine to cysteic acid, formation of mercurial derivatives, formation of mixed disulphides with other thiol compounds, reaction with maleimide, carboxymethylation with iodoacetic acid or iodoacetamide and carbamoylation with cyanate at alkaline pH, although without limitation thereto. In this regard, the skilled person is referred to Chapter 15 of Current Protocols In Protein Science, Eds. Coligan et al. (John Wiley and Sons NY 1995-2000) for more extensive methodology relating to chemical modification of proteins.

[0202] Briefly, modification of e.g. arginyl residues in proteins is often based on the reaction of vicinal dicarbonyl compounds such as phenylglyoxal, 2,3-butanedione, and 1,2-cyclohexanedione to form an adduct. Another example is the reaction of methylglyoxal with arginine residues. Cysteine can be modified without concomitant modification of other nucleophilic sites such as lysine and histidine. As a result, a large number of reagents are available for the modification of cysteine. The websites of companies such as Sigma-Aldrich (http://www.sigma-aldrich.com) provide information on specific reagents.

[0203] Selective reduction of disulfide bonds in proteins is also common. Disulfide bonds can be formed and oxidized during the heat treatment of biopharmaceuticals. Woodward's Reagent K may be used to modify specific glutamic acid residues. N-(3-(dimethylamino)propyl)-N'-ethylcarbodiimide can be used to form intra-molecular crosslinks between a lysine residue and a glutamic acid residue. For example, diethylpyrocarbonate is a reagent for the modification of histidyl residues in proteins. Histidine can also be modified using 4-hydroxy-2-nonenal. The reaction of lysine residues and other α-amino groups is, for example, useful in binding of peptides to surfaces or the cross-linking of proteins/peptides. Lysine is the site of attachment of poly(ethylene)glycol and the major site of modification in the glycosylation of proteins. Methionine residues in proteins can be modified with e.g. iodoacetamide, bromoethylamine, and chloramine T.

[0204] Tetranitromethane and N-acetylimidazole can be used for the modification of tyrosyl residues. Cross-linking via the formation of dityrosine can be accomplished with hydrogen peroxide/copper ions.

[0205] Recent studies on the modification of tryptophan have used N-bromosuccinimide, 2-hydroxy-5-nitrobenzyl bromide or 3-bromo-3-methyl-2-(2-nitrophenylmercapto)-3H-indole (BPNS-skatole).

[0206] Successful modification of therapeutic proteins and peptides with PEG is often associated with an extension of circulatory half-life while cross-linking of proteins with glutaraldehyde, polyethylene glycol diacrylate and formaldehyde is used for the preparation of hydrogels. Chemical modification of allergens for immunotherapy is often achieved by carbamylation with potassium cyanate.

[0207] A peptide or variant, wherein the peptide is modified or includes non-peptide bonds is a preferred example of the disclosure. Generally, peptides and variants (at least those containing peptide linkages between amino acid residues) may be synthesized by the Fmoc-polyamide mode of solid-phase peptide synthesis as disclosed by Lukas et al. (Solid-phase peptide synthesis under continuous-flow conditions. Proc Natl Acad Sci U S A. May 1981; 78(5): 2791-2795), and references as cited therein. Temporary N-amino group protection is afforded by the 9-fluorenylmethyloxycarbonyl (Fmoc) group. Repetitive cleavage of this highly base-labile protecting group is done 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'-dimethoxy-benzhydryl 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 (functionalizing 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 include ethandithiol, phenol, anisole and water, the exact choice depending on the constituent amino acids of the peptide being synthesized. Also a combination of solid phase and solution phase methodologies for the synthesis of peptides is possible (see, for example, Bruckdorfer et al., 2004, and the references as cited therein).

[0208] 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 lyophilization of the aqueous phase affords the crude peptide free of scavengers. Reagents for peptide synthesis are generally available from e.g. Calbiochem-Novabiochem (Nottingham, UK).

[0209] Purification may be performed by any one, or a combination of, techniques such as recrystallization, size exclusion chromatography, ion-exchange chromatography, hydrophobic interaction chromatography and (usually) re-verse-phase high performance liquid chromatography using e.g. acetonitril/water gradient separation.

[0210] Analysis of peptides may be carried out using thin layer chromatography, electrophoresis, in particular capillary electrophoresis, solid phase extraction (CSPE), 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.

[0211] A further aspect of the disclosure provides a nucleic acid (for example a polynucleotide) encoding a peptide or peptide variant of the disclosure. The polynucleotide may be, for example, DNA, cDNA, PNA, RNA or combinations thereof, either single- and/or double-stranded, or native or stabilized forms of polynucleotides, such as, for example, polynucleotides with a phosphorothioate backbone and it may or may not contain introns so long as it codes for the peptide. Of course, only peptides that contain naturally occurring amino acid residues joined by naturally occurring peptide bonds are encodable by a polynucleotide. A still further aspect of the disclosure provides an expression vector capable of expressing a polypeptide according to the disclosure.

[0212] A variety of methods have been developed to 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.

[0213] Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. 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.

[0214] A desirable method of modifying the DNA encoding the polypeptide of the disclosure employs the polymerase chain reaction as disclosed by Saiki RK, et al. (Saiki et al., 1988). 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. If viral vectors are used, pox- or adenovirus vectors are preferred.

[0215] The DNA (or in the case of retroviral vectors, RNA) may then be expressed in a suitable host to produce a polypeptide comprising the peptide or variant of the disclosure. Thus, the DNA encoding the peptide or variant of the disclosure 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 disclosure. Such techniques include those disclosed, for example, in US 4,440,859, 4,530,901, 4,582,800, 4,677,063, 4,678,751, 4,704,362, 4,710,463, 4,757,006, 4,766,075, and 4,810,648.

[0216] The DNA (or in the case of retroviral vectors, RNA) encoding the polypeptide constituting the compound of the disclosure 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.

[0217] 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 recognized 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.

[0218] Alternatively, the gene for such selectable trait can be on another vector, which is used to co-transform the desired host cell.

[0219] Host cells that have been transformed by the recombinant DNA of the disclosure 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.

[0220] Many expression systems are known, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*), filamentous fungi (for example *Aspergillus spec.*), plant cells, animal cells and insect cells. Preferably, the system can be mammalian cells such as CHO cells available from the ATCC Cell Biology Collection.

[0221] The present disclosure also relates to a host cell transformed with a polynucleotide vector construct of the present disclosure. 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 colon 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. An overview regarding the choice of suitable host cells for expression can be found in, for example, the textbook of Paulina Balbás and Argelia Lorence "Methods in Molecular Biology Recombinant Gene Expression, Reviews and Protocols," Part One, Second Edition, ISBN 978-1-58829-262-9, and other literature known to the person of skill.

[0222] 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) and Sambrook et al (1989) . Transformation of yeast cells is described in Sherman et al (1986). The method of Beggs (1978) 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.

[0223] Successfully transformed cells, i.e. cells that contain a DNA construct of the present invention, can be identified by well-known techniques such as PCR. Alternatively, the presence of the protein in the supernatant can be detected using antibodies.

[0224] It will be appreciated that certain host cells of the disclosure are useful in the preparation of the peptides of the disclosure, 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 disclosure such that they may be loaded into appropriate MHC molecules. Thus, the current invention provides a host cell comprising a nucleic acid or an expression vector according to the invention.

[0225] In a preferred embodiment the host cell is an antigen presenting cell, in particular a dendritic cell or antigen presenting cell. APCs loaded with a recombinant fusion protein containing prostatic acid phosphatase (PAP) were approved by the U.S. Food and Drug Administration (FDA) on April 29, 2010, to treat asymptomatic or minimally symptomatic metastatic HRPC (Sipuleucel-T) (Rini et al., 2006; Small et al., 2006).

[0226] A further aspect of the disclosure provides a method of producing a peptide or its variant, the method comprising culturing a host cell and isolating the peptide from the host cell or its culture medium.

[0227] In another embodiment the peptide, the nucleic acid or the expression vector of the invention are used in medicine. For example, the peptide or its variant may be prepared for intravenous (i.v.) injection, sub-cutaneous (s.c.) injection, intradermal (i.d.) injection, intraperitoneal (i.p.) injection, intramuscular (i.m.) injection. Preferred methods of peptide injection include s.c., i.d., i.p., i.m., and i.v. Preferred methods of DNA injection include i.d., i.m., s.c., i.p. and i.v. Doses of e.g. between 50 μg and 1.5 mg, preferably 125 μg to 500 μg, of peptide or DNA may be given and will depend on the respective peptide or DNA. Dosages of this range were successfully used in previous trials (Walter et al., 2012).

[0228] Another aspect of the present invention includes an *in vitro* method for producing activated T cells, the method comprising contacting *in vitro* T cells with antigen loaded human MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate the T cell in an antigen specific manner, wherein the antigen is a peptide according to the invention. Preferably a sufficient amount of the antigen is used with an antigen-presenting cell.

[0229] Preferably the mammalian cell lacks or has a reduced level or function of the TAP peptide transporter. Suitable cells that lack the TAP peptide transporter include T2, RMA-S and Drosophila cells. TAP is the transporter associated with antigen processing.

[0230] 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 et al. (Ljunggren and Karre. 1985).

[0231] Preferably, before transfection the host cell expresses substantially no MHC class I molecules. It is also preferred that the stimulator cell expresses a molecule important for providing a co-stimulatory signal for T-cells such as any of B7.1, B7.2, ICAM-1 and LFA 3. The nucleic acid sequences of numerous MHC class I molecules and of the co-stimulator molecules are publicly available from the GenBank and EMBL databases.

[0232] In case of a MHC class I epitope being used as an antigen, the T cells are CD8-positive T cells.

[0233] If an antigen-presenting cell is transfected to express such an epitope, preferably the cell comprises an expression vector capable of expressing a peptide containing SEQ ID NO: 1 to SEQ ID NO: 300, or a variant amino acid sequence thereof.

[0234] A number of other methods may be used for generating T cells in vitro. For example, autologous tumor-infiltrating lymphocytes can be used in the generation of CTL. Plebanski et al. (1995) make use of autologous peripheral blood lymphocytes (PLBs) in the preparation of T cells. Furthermore, the production of autologous T cells by pulsing dendritic cells with peptide or polypeptide, or via infection with recombinant virus is possible. Also, B cells can be used in the production of autologous T cells. In addition, macrophages pulsed with peptide or polypeptide, or infected with recombinant virus, may be used in the preparation of autologous T cells. S. Walter et al. (2003) describe the in vitro priming of T cells by using artificial antigen presenting cells (aAPCs), which is also a suitable way for generating T cells against the peptide of choice. In the present disclosure, aAPCs were generated by the coupling of preformed MHC:peptide complexes to the surface of polystyrene particles (microbeads) by biotin:streptavidin biochemistry. This system permits the exact control of the MHC density on aAPCs, which allows to selectively elicit high- or low-avidity antigen-specific T cell responses with high efficiency from blood samples. Apart from MHC:peptide complexes, aAPCs should carry other proteins with co-stimulatory activity like anti-CD28 antibodies coupled to their surface. Furthermore such aAPC-based systems often require the addition of appropriate soluble factors, e. g. cytokines, like interleukin-12.

[0235] Allogeneic cells may also be used in the preparation of T cells and a 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 insect cells, bacteria, yeast, vaccinia-infected target cells. In addition plant viruses may be used (see, for example, Porta et al. (1994)) which describes the development of cowpea mosaic virus as a high-yielding system for the presentation of foreign peptides.

[0236] The activated T cells that are directed against the peptides of the invention are useful in therapy. Thus, a further aspect of the invention provides activated T cells obtainable by the foregoing methods of the invention.

[0237] Activated T cells, which are produced by the above method, will selectively recognize a cell that aberrantly expresses a polypeptide that comprises an amino acid sequence of SEQ ID NO: 1 to SEQ ID NO 300.

[0238] Preferably, the T cell recognizes the cell by interacting through its TCR with the HLA/peptide-complex (for example, binding). The T cells are useful in a method of killing target cells in a patient whose 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 T cells. The T cells that are administered to the patient may be derived from the patient and activated as described above (i.e. they are autologous T cells). Alternatively, the T cells 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" the inventors mean that the individual is generally in good health, preferably has a competent immune system and, more preferably, is not suffering from any disease that can be readily tested for, and detected.

[0239] *In vivo,* the target cells for the CD8-positive T cells according to the present invention can be cells of the tumor (which sometimes express MHC class II) and/or stromal cells surrounding the tumor (tumor cells) (which sometimes also express MHC class II; (Dengjel et al., 2006)).

[0240] The T cells of the present invention may be used as active ingredients of a therapeutic composition. Thus, the disclosure also provides a method of killing target cells in a patient whose target cells aberrantly express a polypeptide comprising an amino acid sequence of the disclosure, the method comprising administering to the patient an effective number of T cells as defined above.

[0241] By "aberrantly expressed" the inventors also mean that the polypeptide is over-expressed compared to normal levels of expression or that the gene is silent in the tissue from which the tumor is derived but in the tumor it is expressed. By "over-expressed" the inventors mean that the polypeptide is present at a level at least 1.2-fold of that present in normal tissue; preferably at least 2-fold, and more preferably at least 5-fold or 10-fold the level present in normal tissue.

[0242] T cells may be obtained by methods known in the art, e.g. those described above.

[0243] Protocols for this so-called adoptive transfer of T cells are well known in the art. Reviews can be found in: Gattinoni et al. (2006) and Morgan, et al. (2006).

[0244] Any molecule of the invention, i.e. the peptide, nucleic acid, antibody, expression vector, cell, activated T cell, T-cell receptor or the nucleic acid encoding it is useful for the treatment of disorders, characterized by cells escaping an immune response. Therefore any molecule of the present invention may be used as medicament or in the manufacture of a medicament. The molecule may be used by itself or combined with other molecule(s) of the invention or (a) known molecule(s).

[0245] Preferably, the medicament of the present invention is a vaccine. It may be administered directly into the patient, into the affected organ or systemically i.d., i.m., s.c., i.p. and i.v., 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 of 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 (see below) 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 for example WO 95/18145). The peptide may also be tagged, may be a fusion protein, or may be a hybrid molecule. The peptides whose sequence is given in the present invention are expected to stimulate CD4 or CD8 T cells. However, stimulation of CD8 T cells is more efficient in the presence of help provided by CD4 T-helper cells. Thus, for MHC Class I epitopes that stimulate CD8 T cells the fusion partner or sections of a hybrid molecule suitably provide epitopes which stimulate CD4-positive T cells. CD4- and CD8-stimulating epitopes are well known in the art and include those identified in the present invention.

[0246] In one aspect, the vaccine comprises at least one peptide having the amino acid sequence set forth SEQ ID No.1 to SEQ ID No. 300, and at least one additional peptide, preferably two to 50, more preferably two to 25, even more preferably two to 20 and most preferably two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen or eighteen peptides. The peptide(s) may be derived from one or more specific TAAs and may bind to MHC class I molecules.

[0247] In another aspect, the vaccine comprises at least one peptide having the amino acid sequence set forth in SEQ ID NO: 1 to SEQ ID NO: 300, and at least one additional peptide, preferably two to 50, more preferably two to 25, even more preferably two to 20 and most preferably two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen or eighteen peptides. The peptide(s) may be derived from one or more specific TAAs and may bind to MHC class I molecules.

[0248] The polynucleotide may be substantially pure, or contained in a suitable vector or delivery system. The nucleic acid may be DNA, cDNA, PNA, RNA or a combination thereof. Methods for designing and introducing such a nucleic acid are well known in the art. An overview is provided by e.g. Pascolo et al., (2005). Polynucleotide vaccines are easy to prepare, but the mode of action of these vectors in inducing an immune response is not fully understood. Suitable vectors and delivery systems include viral DNA and/or RNA, 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 and are well known in the art of DNA delivery. Physical delivery, such as via a "gene-gun" may also be used. The peptide or peptides encoded by the nucleic acid may be a fusion protein, for example with an epitope that stimulates T cells for the respective opposite CDR as noted above.

[0249] Preferred adjuvants are anti-CD40, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, interferon-alpha, CpG oligonucleotides and derivates, poly-(I:C) and derivates, RNA, sildenafil, and particulate formulations with PLG or virosomes.

[0250] In a preferred embodiment, the pharmaceutical composition according to the invention the adjuvant is selected from the group consisting of colony-stimulating factors, such as Granulocyte Macrophage Colony Stimulating Factor (GM-CSF, sargramostim), cyclophosphamide, imiquimod, resiquimod, and interferon-alpha.

[0251] In a preferred embodiment, the pharmaceutical composition according to the invention the adjuvant is selected from the group consisting of colony-stimulating factors, such as Granulocyte Macrophage Colony Stimulating Factor (GM-CSF, sargramostim), cyclophosphamide, imiquimod and resiquimod. In a preferred embodiment of the pharmaceutical composition according to the invention, the adjuvant is cyclophosphamide, imiquimod or resiquimod. Even more preferred adjuvants are Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, poly-ICLC (Hiltonol®) and anti-CD40 mAB, or combinations thereof.

[0252] This composition is used for parenteral administration, such as subcutaneous, intradermal, intramuscular or oral administration. For this, the peptides and optionally other molecules are 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, flavors, 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, 3rd Ed., 2000, American Pharmaceutical Association and pharmaceutical press. The composition can be used for a prevention, prophylaxis and/or therapy of adenomateous or cancerous diseases. Exemplary formulations can be found in, for example, EP2112253.

[0253] The present invention provides a medicament that useful in treating cancer, in particular HCC and other malignancies.

[0254] The present invention is further directed at a kit comprising:

(a) a container containing a pharmaceutical composition as described above, in solution or in lyophilized form;
(b) optionally a second container containing a diluent or reconstituting solution for the lyophilized formulation; and
(c) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.

[0255] The kit may further comprise one or more of (iii) a buffer, (iv) a diluent, (v) a filter, (vi) a needle, or (vii) a syringe. The container is preferably a bottle, a vial, a syringe or test tube; and it may be a multi-use container. The pharmaceutical composition is preferably lyophilized.

[0256] Kits of the present invention preferably comprise a lyophilized formulation of the present invention in a suitable container and instructions for its reconstitution and/or use. Suitable containers include, for example, bottles, vials (e.g. dual chamber vials), syringes (such as dual chamber syringes) and test tubes. The container may be formed from a variety of materials such as glass or plastic. Preferably the kit and/or container contain/s instructions on or associated with the container that indicates directions for reconstitution and/or use. For example, the label may indicate that the lyophilized formulation is to be reconstituted to peptide concentrations as described above. The label may further indicate that the formulation is useful or intended for subcutaneous administration.

[0257] The container holding the formulation may be a multi-use vial, which allows for repeat administrations (e.g., from 2-6 administrations) of the reconstituted formulation. The kit may further comprise a second container comprising a suitable diluent (e.g., sodium bicarbonate solution).

[0258] Upon mixing of the diluent and the lyophilized formulation, the final peptide concentration in the reconstituted formulation is preferably at least 0.15 mg/mL/peptide (=75 μg) and preferably not more than 3 mg/mL/peptide (=1500 μg). The kit may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.

[0259] Kits of the present invention may have a single container that contains the formulation of the pharmaceutical compositions according to the present invention with or without other components (e.g., other compounds or pharmaceutical compositions of these other compounds) or may have distinct container for each component.

[0260] Preferably, kits of the invention include a formulation of the invention packaged for use in combination with the co-administration of a second compound (such as adjuvants (e.g. GM-CSF), a chemotherapeutic agent, a natural product, a hormone or antagonist, an anti-angiogenesis agent or inhibitor, an apoptosis-inducing agent or a chelator) or a pharmaceutical composition thereof. The components of the kit may be pre-complexed or each component may be in a separate distinct container prior to administration to a patient. The components of the kit may be provided in one or more liquid solutions, preferably, an aqueous solution, more preferably, a sterile aqueous solution. The components of the kit may also be provided as solids, which may be converted into liquids by addition of suitable solvents, which are preferably provided in another distinct container.

[0261] The container of a therapeutic kit may be a vial, test tube, flask, bottle, syringe, or any other means of enclosing a solid or liquid. Usually, when there is more than one component, the kit will contain a second vial or other container, which allows for separate dosing. The kit may also contain another container for a pharmaceutically acceptable liquid. Preferably, a therapeutic kit will contain an apparatus (e.g., one or more needles, syringes, eye droppers, pipette, etc.), which enables administration of the agents of the invention that are components of the present kit.

[0262] The present formulation is one that is suitable for administration of the peptides by any acceptable route such as oral (enteral), nasal, ophthal, subcutaneous, intradermal, intramuscular, intravenous or transdermal. Preferably, the administration is s.c., and most preferably i.d. administration may be by infusion pump.

[0263] Since the peptides of the invention were isolated from HCC, the medicament of the invention is preferably used to treat HCC.

[0264] It is important to realize that the immune response triggered by the vaccine according to the invention attacks the cancer in different cell-stages and different stages of development. Furthermore different cancer associated signaling pathways are attacked. This is an advantage over vaccines that address only one or few targets, which may cause the tumor to easily adapt to the attack (tumor escape). Furthermore, not all individual tumors express the same pattern of antigens. Therefore, a combination of several tumor-associated peptides ensures that every single tumor bears at least some of the targets. The composition was specifically designed in such a way that each HLA-A*02 and/or HLA-A*24-positive tumor is expected to express several of the antigens and cover several independent pathways necessary for tumor growth and maintenance. For each of the peptide subsets specific for the two HLA class I alleles (A*02 and A*24) this is independently ensured based on the underlying experimental analyses. Thus, the vaccine can easily be used "off-the-shelf" for a larger patient population. This means that a preselection of patients to be treated with the vaccine can be restricted to HLA typing, does not require any additional biomarker assessments for antigen expression, but it is still ensured that several targets are simultaneously attacked by the induced immune response, which is important for efficacy (Banchereau et al., 2001; Walter et al., 2012).

[0265] In the Figures,

Figure 1 shows the over-presentation of various peptides in normal tissues (dark gray) and HCC (light gray). Figure 1A) APOB, Peptide: ALVDTLKFV (A*02) (SEQ ID NO: 7), tissues from left to right; 1 adipose tissues, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 4 esophagi, 2 gallbladders, 3 GI tracts, 3 hearts, 16 kidneys, 4 leukocyte samples, 45 lungs, 1 lymph node, 1 ovary, 7 pancreas, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 recti, 3 sceletal muscles, 1 serous membrane, 3 skins, 4 spleens, 7 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, and 20 livers; Figure 1B) ALDH1L1, Peptide: KLQAGTVFV (A*02) (SEQ ID NO: 2), tissues from left to right: 1 adipose tissues, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 4 esophagi, 2 gallbladders, 3 GI tracts, 3 hearts, 16 kidneys, 4 leukocyte samples, 45 lungs, 1 lymph node, 1 ovary, 7 pancreas, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 recti, 3 sceletal muscles, 1 serous membrane, 3 skins, 4 spleens, 7 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, and 20 livers; Figure 1C) C8B, Peptide: AYLLQPSQF (A*24) (SEQ ID NO: 200), tissues from left to right: including 2 adrenal glands, 1 artery, 4 brains, 1 breast, 5 colons, 1 hearts, 13 kidneys, 9 lungs, 3 pancreas, 2 recti, 3 skins, 1 spleen, 12 stomachs, 1 thymus, 2 uteri, and 9 livers; Figure 1D) RAD23B Peptide: KIDEKNFVV (SEQ ID NO: 63) 1 serous membrane, 1 adipose tissue, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 2 gallbladders, 3 GI tracts, 3 hearts, 12 kidneys, 4 leukocytes, 19 livers, 43 lungs, 1 lymph node, 1 ovary, 6 pancreases, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 rectums, 3 skeletal muscles, 3 skins, 4 spleens, 5 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, 4 esophagi; Figure 1E) RAD23B Peptide: KIDEKNFVV (SEQ ID NO: 63), shown are only samples on which the peptide was presented: 5 cell-lines, 1 normal tissue (1 adrenal gland), 16 cancer tissues (2 brain cancers, 4 liver cancers, 5 lung cancers, 1 rectum cancer, 1 urinary bladder cancer, 3 uterus cancers) (from left to right); Figure 1F) RFNG RLPPDTLLQQV (SEQ ID NO: 92), shown are only samples on which the peptide was presented: 1 serous membrane, 1 adipose tissue, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 2 gallbladders, 3 GI tracts, 3 hearts, 12 kidneys, 4 leukocytes, 19 livers, 43 lungs, 1 lymph node, 1 ovary, 6 pancreases, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 rectums, 3 skeletal muscles, 3 skins, 4 spleens, 5 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, 4 esophagi; Figure 1G) RFNG Peptide: RLPPDTLLQQV (SEQ ID NO: 92), shown are only samples on which the peptide was presented: 2 cell-lines, 2 normal tissues (2 adrenal glands), 17 cancer tissues (1 brain cancer, 1 breast cancer, 1 esophageal cancer, 5 liver cancers, 4 lung cancers, 1 ovarian cancer, 1 prostate cancer, 2 urinary bladder cancers, 1 uterus cancer) (from left to right); Figure 1H) FLVCR1 Peptide: SVWFGPKEV (SEQ ID NO: 104) 1 serous membrane, 1 adipose tissue, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 2 gallbladders, 3 GI tracts, 3 hearts, 12 kidneys, 4 leukocytes, 19 livers, 43 lungs, 1 lymph node, 1 ovary, 6 pancreases, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 rectums, 3 skeletal muscles, 3 skins, 4 spleens, 5 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, 4 esophagi; Figure 1I) FLVCR1 Peptide: SVWFGPKEV (SEQ ID NO: 104), shown are only samples on which the peptide was presented: 9 cell lines, 1 normal tissue (1 small intestine), 16 cancer tissues (1 brain cancer, 1 breast cancer, 5 liver cancers, 5 lung cancers, 1 skin cancer, 1 stomach cancer, 1 urinary bladder cancer, 1 uterus cancer) (from left to right); Figure 1J) IKBKAP Peptide: LLFPHPVNQV (SEQ ID NO: 156) 1 serous membrane, 1 adipose tissue, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 2 gallbladders, 3 GI tracts, 3 hearts, 12 kidneys, 4 leukocytes, 19 livers, 43 lungs, 1 lymph node, 1 ovary, 6 pancreases, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 rectums, 3 skeletal muscles, 3 skins, 4 spleens, 5 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, 4 esophagi; Figure 1K) IKBKAP Peptide: LLFPHPVNQV (SEQ ID NO: 156), shown are only samples on which the peptide was presented: 7 cell-lines, 2 primary cultures, 1 normal tissue (1 colon), 34 cancer tissues (1 bone marrow cancer, 1 breast cancer, 1 colon cancer, 2 esophageal cancers, 2 leukocytic leukemia cancers, 4 liver cancers, 11 lung cancers, 3 lymph node cancers, 5 ovarian cancers, 4 urinary bladder cancers) (from left to right); Figure 1L) NKD1 Peptide: FLDTPIAKV (SEQ ID NO: 47), 1 serous membrane, 1 adipose tissue, 3 adrenal glands, 2 arteries, 2 bone marrows, 7 brains, 3 breasts, 13 colons, 2 gallbladders, 3 GI tracts, 3 hearts, 12 kidneys, 4 leukocytes, 19 livers, 43 lungs, 1 lymph node, 1 ovary, 6 pancreases, 1 peripheral nerve, 1 pituitary gland, 3 pleuras, 1 prostate, 6 rectums, 3 skeletal muscles, 3 skins, 4 spleens, 5 stomachs, 1 testis, 2 thymi, 3 thyroid glands, 2 uteri, 2 veins, 4 esophagi; Figure 1M) NKD1 Peptide: FLDTPIAKV (SEQ ID NO: 47), shown are only samples on which the peptide was presented: 1 other disease (encephalocele), 2 normal tissues (1 lung, 1 spleen), 35 cancer tissues (5 brain cancers, 6 colon cancers, 1 esophageal cancer, 6 liver cancers, 9 lung cancers, 1 ovarian cancer, 1 prostate cancer, 4 rectum cancers, 2 stomach cancers) (from left to right).

Figure 2 shows exemplary expression profiles (relative expression compared to normal kidney) of source genes of the present invention that are highly over-expressed or exclusively expressed in HCC in a panel of normal tissues (dark gray) and 12 HCC samples (gray). Figure 2A) APOB, tissues from left to right: 1 adrenal gland, 1 artery, 1 bone marrow, 1 brain (whole), 1 breast, 1 colon, 1 esophagus, 1 heart, 3 kidneys, 1 leukocyte sample, 1 liver, 1 lung, 1lymph node, 1 ovary, 1 pancreas, 1 placenta, 1 prostate, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 testis, 1 thymus, 1 thyroid gland, 1 urinary bladder, 1 uterine cervix, 1 uterus, 1 vein; Figure 2B) AMACR, tissues from left to right: 1 adrenal gland, 1 artery, 1 bone marrow, 1 brain (whole), 1 breast, 1 colon, 1 esophagus, 1 heart, 3 kidneys, 1 leukocyte sample, 1 liver, 1 lung, 1lymph node, 1 ovary, 1 pancreas, 1 placenta, 1 prostate, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 testis, 1 thymus, 1 thyroid gland, 1 urinary bladder, 1 uterine cervix, 1 uterus, 1 vein; Figure 2C) ALDH1L1, tissues from left to right: 1 adrenal gland, 1 artery, 1 bone marrow, 1 brain (whole), 1 breast, 1 colon, 1 esophagus, 1 heart, 3 kidneys, 1 leukocyte sample, 1 liver, 1 lung, 1lymph node, 1 ovary, 1 pancreas, 1 placenta, 1 prostate, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 testis, 1 thymus, 1 thyroid gland, 1 urinary bladder, 1 uterine cervix, 1 uterus, 1 vein; Figure 2D) FGG, tissues from left to right: 1 adrenal gland, 1 artery, 1 bone marrow, 1 brain (whole), 1 breast, 1 colon, 1 esophagus, 1 heart, 3 kidneys, 1 leukocyte sample, 1 liver, 1 lung, 1lymph node, 1 ovary, 1 pancreas, 1 placenta, 1 prostate, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 testis, 1 thymus, 1 thyroid gland, 1 urinary bladder, 1 uterine cervix, 1 uterus, 1 vein; Figure 2E) C8B, tissues from left to right: 1 adrenal gland, 1 artery, 1 bone marrow, 1 brain (whole), 1 breast, 1 colon, 1 esophagus, 1 heart, 3 kidneys, 1 leukocyte sample, 1 liver, 1 lung, 1lymph node, 1 ovary, 1 pancreas, 1 placenta, 1 prostate, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 testis, 1 thymus, 1 thyroid gland, 1 urinary bladder, 1 uterine cervix, 1 uterus, 1 vein; and Figure 2F) HSD17B6, tissues from left to right: including 1 adrenal gland, 1 artery, 1 bone marrow, 1 brain (whole), 1 breast, 1 colon, 1 esophagus, 1 heart, 3 kidneys, 1 leukocyte sample, 1 liver, 1 lung, 1lymph node, 1 ovary, 1 pancreas, 1 placenta, 1 prostate, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 testis, 1 thymus, 1 thyroid gland, 1 urinary bladder, 1 uterine cervix, 1 uterus, and 1 vein.

Figure 3 shows exemplary flow cytometry results after peptide-specific multimer staining. Further explanations see example 4.

Figure 4 shows exemplary flow cytometry results after peptide-specific multimer staining. Further explanations see example 4.

EXAMPLES

EXAMPLE 1: Identification and quantitation of tumor associated peptides presented on the cell surface

Tissue samples

[0266] Patients' tumor tissues were obtained from Universitätsklinik für Allgemeine, Viszeral- und Transplantationschirurgie, Tübingen, Germany; Istituto Nazionale Tumori "Pascale". Molecular Biology and Viral Oncology Unit, Via Mariano, Naples, Italy; Bio-Options Inc., Brea, CA, USA; ProteoGenex Inc., Culver City, CA, USA; Asterand Europe, Royston Herts, United Kingdom. Written informed consents of all patients had been given before surgery. Tissues were shock-frozen immediately after surgery and stored until isolation of TUMAPs at -70°C or below.

Isolation of HLA peptides from tissue samples

[0267] HLA peptide pools from shock-frozen tissue samples were obtained by immune precipitation from solid tissues according to a slightly modified protocol (Falk, K., 1991; Seeger, F.H.T., 1999) using the HLA-A*02-specific antibody BB7.2, the HLA-A, -B, -C-specific antibody W6/32, CNBr-activated sepharose, acid treatment, and ultrafiltration.

Mass spectrometry analyses

[0268] The HLA peptide pools as obtained were separated according to their hydrophobicity by reversed-phase chromatography (nanoAcquity UPLC system, Waters) and the eluting peptides were analyzed in LTQ- velos and fusion hybrid mass spectrometers (ThermoElectron) equipped with an ESI source. Peptide pools were loaded directly onto the analytical fused-silica micro-capillary column (75 μm i.d. x 250 mm) packed with 1.7 μm C18 reversed-phase material (Waters) applying a flow rate of 400 nL per minute. Subsequently, the peptides were separated using a two-step 180 minute-binary gradient from 10% to 33% B at a flow rate of 300 nL per minute. The gradient was composed of Solvent A (0.1% formic acid in water) and solvent B (0.1% formic acid in acetonitrile). A gold coated glass capillary (PicoTip, New Objective) was used for introduction into the nanoESI source. The LTQ-Orbitrap mass spectrometers were operated in the data-dependent mode using a TOP5 strategy. In brief, a scan cycle was initiated with a full scan of high mass accuracy in the orbitrap (R = 30 000), which was followed by MS/MS scans also in the orbitrap (R = 7500) on the 5 most abundant precursor ions with dynamic exclusion of previously selected ions. Tandem mass spectra were interpreted by SEQUEST and additional manual control. The identified peptide sequence was assured by comparison of the generated natural peptide fragmentation pattern with the fragmentation pattern of a synthetic sequence-identical reference peptide.

[0269] Label-free relative LC-MS quantitation was performed by ion counting i.e. by extraction and analysis of LC-MS features (Mueller et al. 2007a). The method assumes that the peptide's LC-MS signal area correlates with its abundance in the sample. Extracted features were further processed by charge state deconvolution and retention time alignment (Mueller et al. 2007b; Sturm et al. 2008). Finally, all LC-MS features were cross-referenced with the sequence identification results to combine quantitative data of different samples and tissues to peptide presentation profiles. The quantitative data were normalized in a two-tier fashion according to central tendency to account for variation within technical and biological replicates. Thus each identified peptide can be associated with quantitative data allowing relative quantification between samples and tissues. In addition, all quantitative data acquired for peptide candidates was inspected manually to assure data consistency and to verify the accuracy of the automated analysis. For each peptide a presentation profile was calculated showing the mean sample presentation as well as replicate variations. The profiles juxtapose HCC samples to a baseline of normal tissue samples.

[0270] Presentation profiles of exemplary over-presented peptides are shown in Figure 1. Presentation scores for exemplary peptides are shown in Table 5.

Table 5: Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). S* = phosphoserine

SEQ ID No.	Sequence	Peptide Presentation
89	RLIEEIKNV	+++

EXAMPLE 2

Expression profiling of genes encoding the peptides of the disclosure

[0271] Over-presentation or specific presentation of a peptide on tumor cells compared to normal cells is sufficient for its usefulness in immunotherapy, and some peptides are tumor-specific despite their source protein occurring also in normal tissues. Still, mRNA expression profiling adds an additional level of safety in selection of peptide targets for immunotherapies. Especially for therapeutic options with high safety risks, such as affinity-matured TCRs, the ideal target peptide will be derived from a protein that is unique to the tumor and not found on normal tissues.

RNA sources and preparation

[0272] Surgically removed tissue specimens were provided as indicated above (see Example 1) after written informed consent had been obtained from each patient. Tumor tissue specimens were snap-frozen immediately after surgery and later homogenized with mortar and pestle under liquid nitrogen. Total RNA was prepared from these samples using TRI Reagent (Ambion, Darmstadt, Germany) followed by a cleanup with RNeasy (QIAGEN, Hilden, Germany); both methods were performed according to the manufacturer's protocol.

[0273] Total RNA from healthy human tissues was obtained commercially (Ambion, Huntingdon, UK; Clontech, Heidelberg, Germany; Stratagene, Amsterdam, Netherlands; BioChain, Hayward, CA, USA). The RNA from several individuals (between 2 and 123 individuals) was mixed such that RNA from each individual was equally weighted.

[0274] Quality and quantity of all RNA samples were assessed on an Agilent 2100 Bioanalyzer (Agilent, Waldbronn, Germany) using the RNA 6000 Pico LabChip Kit (Agilent).

Microarray experiments

[0275] Gene expression analysis of all tumor and normal tissue RNA samples was performed by Affymetrix Human Genome (HG) U133A or HG-U133 Plus 2.0 oligonucleotide microarrays (Affymetrix, Santa Clara, CA, USA). All steps were carried out according to the Affymetrix manual. Briefly, double-stranded cDNA was synthesized from 5-8 μg of total RNA, using SuperScript RTII (Invitrogen) and the oligo-dT-T7 primer (MWG Biotech, Ebersberg, Germany) as described in the manual. *In vitro* transcription was performed with the BioArray High Yield RNA Transcript Labelling Kit (ENZO Diagnostics, Inc., Farmingdale, NY, USA) for the U133A arrays or with the GeneChip IVT Labelling Kit (Affymetrix) for the U133 Plus 2.0 arrays, followed by cRNA fragmentation, hybridization, and staining with streptavidin-phycoerythrin and biotinylated anti-streptavidin antibody (Molecular Probes, Leiden, Netherlands). Images were scanned with the Agilent 2500A GeneArray Scanner (U133A) or the Affymetrix Gene-Chip Scanner 3000 (U133 Plus 2.0), and data were analyzed with the GCOS software (Affymetrix), using default settings for all parameters. For normalization, 100 housekeeping genes provided by Affymetrix were used. Relative expression values were calculated from the signal log ratios given by the software and the normal kidney sample was arbitrarily set to 1.0. Exemplary expression profiles of source genes of the present disclosure that are highly over-expressed or exclusively expressed in HCC are shown in Figure 2. Expression scores for further exemplary genes are shown in Table 6.

Table 6: Expression scores. The table lists peptides from genes not related to the invention that are very highly overexpressed in tumors compared to a panel of normal tissues (+++),highly overexpressed in tumors compared to a panel of normal tissues (++) or overexpressed in tumors compared to a panel of normal tissues (+).

SEQ ID No	Sequence	Gene Expression
1	VMAPFTMTI	+++
2	KLQAGTVFV	++
3	ILDDNMQKL	+
4	KLQDFSDQL	+++
5	ALVEQGFTV	+++
7	ALVDTLKFV	+++
10	SLLEEFDFHV	+
13	GLIDTETAMKAV	+++
19	FLEETKATV	+++
20	KLSNVLQQV	+++
21	QLIEVSSPITL	+++
25	SLDGKAALTEL	+++
27	TLPDFRLPEI	+++
28	TLQDHLNSL	+++
29	YIQDEINTI	+++
31	YQMDIQQEL	+++
38	ALADVVHEA	+
39	ALDPKANFST	+
41	ALLELDEPLVL	+++
42	ALLGGNVRMML	+
44	ALQDAIRQL	+
45	ALQDQLVLV	++
46	AMAEMKVVL	++

(continued)

SEQ ID No	Sequence	Gene Expression
48	FLLEQPEIQV	+
49	FLYPEKDEPT	+++
50	FTIPKLYQL	+++
52	GLFNAELLEA	+++
53	GLIHLEGDTV	+++
55	GLYGRTIEL	+++
60	ILSPLSVAL	+
61	KIADFELPTI	+++
62	KIAGTNAEV	+
66	KLHEEIDRV	+++
67	KLKETIQKL	+++
68	KLLAATVLLL	+++
73	KLTLVIISV	+++
74	KLYDLELIV	+++
76	LLADIGGDPFAA	+
81	NLASFIEQVAV	+
82	NVFDGLVRV	+++
83	QLHDFVMSL	+++
84	QLTPVLVSV	++
85	RILPKVLEV	++
87	RLFEENDVNL	+++
90	RLLDVLAPLV	+
93	RLYTMDGITV	+++
94	RMSDVVKGV	+
95	SICNGVPMV	++
97	SLLPQLIEV	+++
100	SLVGDIGNVNM	+++
103	SMGDHLWVA	+
105	SVYDGKLLI	+
106	TLAAIIHGA	++
107	TLGQFYQEV	+++
109	TLYALSHAV	+++
110	TVGGSEILFEV	+++
113	VLMDKLVEL	+++
114	VLSQVYSKV	+++
116	WVIPAISAV	++
117	YAFPKSITV	+
119	YLDKNLTVSV	++

(continued)

SEQ ID No	Sequence	Gene Expression
120	YLGEEYVKA	+++
124	LLIDVVTYL	+++
126	TLLDSPIKV	+++
129	SQADVIPAV	++
130	ALDAGAVYTL	++
132	ALHEEVVGV	++
141	AMGEKSFSV	+
142	AVIGGLIYV	+++
145	FLIAEYFEHV	++
146	FLWTEQAHTV	++
148	GLFAPLVFL	+
149	GLLSGLDIMEV	+++
154	KLTDHLKYV	+++
157	QLLPNLRAV	+
158	RIISGLVKV	++
160	RLLAKIICL	+++
163	RLTESVLYL	++
165	RVIEHVEQV	++
168	SLAVLVPIV	+++
172	SLLNFLQHL	+
173	SLTSEIHFL	+
175	TLFEHLPHI	++
177	VLDEPYEKV	++
182	YLLHFPMAL	+++
183	YLYNNEEQVGL	+++
187	SYPTFFPRF	+
188	RYSAGWDAKF	+++
192	SYITKPEKW	+
193	IYPGAFVDL	+
200	AYLLQPSQF	+++
204	KYRLTYAYF	+++
206	KWPETPLLL	+
215	IYTGNISSF	+++
217	DYIPYVFKL	+++
218	VYQGAIRQI	+++
228	YLITSVELL	+
233	ALLGKLDAI	+
249	LLLGERVAL	+

(continued)

SEQ ID No	Sequence	Gene Expression
255	SLFGQDVKAV +	
259	TLITDGMRSV	+
263	VLYPSLKEI	+
273	AILETAPKEV	+
275	ALIEGAGILL	+
286	KVLDKVFRA	+
296	SLLSGRISTL	+
298	TMAKESSIIGV	+
301	VLADFGARV	++
302	KIQEILTQV	+
315	KVLDGSPIEV	++
318	KLNEINEKI	+++
320	GLADNTVIAKV	+
324	RLFETKITQV	++
327	GLNEEIARV	+
336	YLPTFFLTV	+
341	YLAIGIHEL	++
345	SYNPLWLRI (A*24)	++

EXAMPLE 3: UV-ligand exchange/Peptide binding to HLA-A*02 and HLA-A*24

[0276] Candidate peptides for T cell based therapies according to the present disclosure were further tested for their MHC binding capacity (affinity). The individual peptide-MHC complexes were produced by UV-ligand exchange, where a UV-sensitive peptide is cleaved upon UV-irradiation, and exchanged with the peptide of interest as analyzed. Only peptide candidates that can effectively bind and stabilize the peptide-receptive MHC molecules prevent dissociation of the MHC complexes. To determine the yield of the exchange reaction, an ELISA was performed based on the detection of the light chain (β2m) of stabilized MHC complexes. The assay was performed as generally described in Rodenko et al. (Rodenko et al., 2006).

[0277] 96 well MAXISorp plates (NUNC) were coated over night with 2ug/ml streptavidin in PBS at room temperature, washed 4x and blocked for1h at 37°C in 2% BSA containing blocking buffer. Refolded HLA-A*0201/MLA-001 monomers served as standards, covering the range of 15-500 ng/ml. Peptide-MHC monomers of the UV-exchange reaction were diluted 100 fold in blocking buffer. Samples were incubated for 1h at 37°C, washed four times, incubated with 2ug/ml HRP conjugated anti-β2m for 1h at 37°C, washed again and detected with TMB solution that is stopped with NH_2SO_4. Absorption was measured at 450nm. Candidate peptides that show a high exchange yield (preferably higher than 50%, most preferred higher than 75%) are generally preferred for a generation and production of antibodies or fragments thereof, and/or T cell receptors or fragments thereof, as they show sufficient avidity to the MHC molecules and prevent dissociation of the MHC complexes.

Table 7: MHC class I binding scores

Binding of HLA-class I restricted peptides to HLA-A*02 or HLA-A*24 depending from peptide sequence was classified by peptide exchange yield: ≥10% = +; ≥20% = ++; ≥50 = +++; ≥ 75% = ++++. S* = phosphoserine.		
SEQ ID No	**Sequence**	**Peptide exchange**
89	RLIEEIKNV	"++"

EXAMPLE 4

In vitro immunogenicity for MHC class I presented peptides

[0278] In order to obtain information regarding the immunogenicity of the TUMAPs of the present invention, the inventors performed investigations using an *in vitro* T-cell priming assay based on repeated stimulations of CD8+ T cells with artificial antigen presenting cells (aAPCs) loaded with peptide/MHC complexes and anti-CD28 antibody. This way the inventors could show immunogenicity for 22 HLA-A*0201 restricted TUMAPs of the disclosure so far, demonstrating that these peptides are T-cell epitopes against which CD8+ precursor T cells exist in humans.

In vitro priming of CD8+ T cells

[0279] In order to perform *in vitro* stimulations by artificial antigen presenting cells loaded with peptide-MHC complex (pMHC) and anti-CD28 antibody, the inventors first isolated CD8+ T cells from fresh HLA-A*02 leukapheresis products via positive selection using CD8 microbeads (Miltenyi Biotec, Bergisch-Gladbach, Germany) of healthy donors obtained from the University clinics Mannheim, Germany, after informed consent.

[0280] PBMCs and isolated CD8+ lymphocytes were incubated in T-cell medium (TCM) until use consisting of RPMI-Glutamax (Invitrogen, Karlsruhe, Germany) supplemented with 10% heat inactivated human AB serum (PAN-Biotech, Aidenbach, Germany), 100 U/ml Penicillin/100 μg/ml Streptomycin (Cambrex, Cologne, Germany), 1 mM sodium pyruvate (CC Pro, Oberdorla, Germany), 20 μg/ml Gentamycin (Cambrex). 2.5 ng/ml IL-7 (PromoCell, Heidelberg, Germany) and 10 U/ml IL-2 (Novartis Pharma, Nürnberg, Germany) were also added to the TCM at this step.

[0281] Generation of pMHC/anti-CD28 coated beads, T-cell stimulations and readout was performed in a highly defined *in vitro* system using four different pMHC molecules per stimulation condition and 8 different pMHC molecules per readout condition.

[0282] The purified co-stimulatory mouse IgG2a anti human CD28 Ab 9.3 (Jung et al., 1987) was chemically biotinylated using Sulfo-N-hydroxysuccinimidobiotin as recommended by the manufacturer (Perbio, Bonn, Germany). Beads used were 5.6 μm diameter streptavidin coated polystyrene particles (Bangs Laboratories, Illinois, USA).

[0283] pMHC used for positive and negative control stimulations were A*0201/MLA-001 (peptide ELAGIGILTV from modified Melan-A/MART-1) and A*0201/DDX5-001 (YLLPAIVHI from DDX5), respectively.

[0284] 800.000 beads / 200 μl were coated in 96-well plates in the presence of 4 x 12.5 ng different biotin-pMHC, washed and 600 ng biotin anti-CD28 were added subsequently in a volume of 200 μl. Stimulations were initiated in 96-well plates by co-incubating 1×10^6 CD8+ T cells with 2×10^5 washed coated beads in 200 μl TCM supplemented with 5 ng/ml IL-12 (PromoCell) for 3 days at 37°C. Half of the medium was then exchanged by fresh TCM supplemented with 80 U/ml IL-2 and incubating was continued for 4 days at 37°C. This stimulation cycle was performed for a total of three times. For the pMHC multimer readout using 8 different pMHC molecules per condition, a two-dimensional combinatorial coding approach was used as previously described (Andersen et al., 2012) with minor modifications encompassing coupling to 5 different fluorochromes. Finally, multimeric analyses were performed by staining the cells with Live/dead near IR dye (Invitrogen, Karlsruhe, Germany), CD8-FITC antibody clone SK1 (BD, Heidelberg, Germany) and fluorescent pMHC multimers. For analysis, a BD LSRII SORP cytometer equipped with appropriate lasers and filters was used. Peptide specific cells were calculated as percentage of total CD8+ cells. Evaluation of multimeric analysis was done using the FlowJo software (Tree Star, Oregon, USA). *In vitro* priming of specific multimer+ CD8+ lymphocytes was detected by by comparing to negative control stimulations. Immunogenicity for a given antigen was detected if at least one evaluable *in vitro* stimulated well of one healthy donor was found to contain a specific CD8+ T-cell line after *in vitro* stimulation (i.e. this well contained at least 1% of specific multimer+ among CD8+ T-cells and the percentage of specific multimer+ cells was at least 10x the median of the negative control stimulations).

In vitro immunogenicity for HCC peptides

[0285] For tested HLA class I peptides, *in vitro* immunogenicity could be demonstrated by generation of peptide specific T-cell lines. Exemplary flow cytometry results after TUMAP-specific multimer staining for three peptides of the invention are shown in Figure 3 and Figure 4 together with corresponding negative controls.

a **Exemplary results of peptide-specific *in vitro* CD8+ T cell responses of a healthy HLA-A*02+ donor (Figure 3)**

[0286] CD8+ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*02 in complex with IMA-APOB-002 (Seq ID No 7) peptide (A, right panel) or IMA-APOB-003 (B, right panel, Seq ID No 1), or IMA-ALDH1L1-001 (C, right panel, Seq ID No 2), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*02/ APOB-002 (A) or A*02/ APOB-003 (B), or

A*02/ALDH1L1-001. Left panels (A, B, C) show control staining of cells stimulated with irrelevant A*02/peptide complexes. Viable singlet cells were gated for CD8+ lymphocytes. Boolean gates helped excluding false-positive events detected with multimers specific for different peptides. Frequencies of specific multimer+ cells among CD8+ lymphocytes are indicated.

Exemplary results of peptide-specific *in vitro* CD8+ T cell responses of a healthy HLA-A*24+ donor (Figure 4)

[0287] CD8+ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*24 in complex with IMA-KLHL24-001 (Seq ID No 190) peptide (A, right panel) or IMA-APOB-006 (B, right panel, Seq ID No 218), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*24/ KLHL24-001 (A) or A*24/ APOB-006 (B). Left panels (A and B) show control staining of cells stimulated with irrelevant A*24/peptide complexes. Viable singlet cells were gated for CD8+ lymphocytes. Boolean gates helped excluding false-positive events detected with multimers specific for different peptides. Frequencies of specific multimer+ cells among CD8+ lymphocytes are indicated.

Example 5: Syntheses of peptides

[0288] All peptides were synthesized using standard and well-established solid phase peptide synthesis using the Fmoc-strategy. Identity and purity of each individual peptide have been determined by mass spectrometry and analytical RP-HPLC. The peptides were obtained as white to off-white lyophilizates (trifluoro acetate salt) in purities of >50%. All TUMAPs are preferably administered as trifluoro-acetate salts or acetate salts, other salt-forms are also possible.

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1

Claims

1. A peptide comprising the amino acid sequence of SEQ ID No. 89, or a pharmaceutical acceptable salt thereof, wherein said peptide has an overall length of up to 30 amino acids, and wherein said peptide has the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I.

2. The peptide according to claim 1, wherein said peptide has an overall length of up to 16 amino acids, and preferably wherein the peptide consists of the amino acid sequence according to SEQ ID No. 89.

3. The peptide according to Claim 1 or 2, wherein said peptide includes non-peptide bonds, and/or wherein said peptide

is part of a fusion protein comprising N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii).

4. An antibody, soluble or membrane-bound, that specifically recognizes the peptide according to any one of claims 1 to 3, preferably the peptide according to any one of claims 1 to 3 that is bound to an MHC molecule.

5. A T-cell receptor (TCR), soluble or membrane-bound, that is reactive with an HLA ligand, wherein said ligand has at least 88% identity to, and preferably consists of, the amino acid sequence of SEQ ID No. 89, wherein optionally said TCR is provided as a soluble molecule and further optionally carries a further effector function such as an immune stimulating domain or toxin.

6. A nucleic acid, encoding a peptide according to any one of claims 1 to 3, the antibody according to claim 4, the TCR according to claim 5, or an expression vector expressing said nucleic acid.

7. A host cell comprising the peptide according to any one of claims 1 to 3, or the nucleic acid or the expression vector according to claim 6, wherein said host cell preferably is an antigen presenting cell such as a dendritic cell, or a T cell or NK cell.

8. A method for producing the peptide according to any one of claims 1 to 3, the antibody according to claim 4, or the TCR according to claim 5, the method comprising culturing a host cell according to claim 7 that presents the peptide according to any one of claims 1 to 3, or expresses the nucleic acid or the expression vector according to claim 6, and isolating said peptide, said antibody or said TCR from the host cell and/or its culture medium.

9. An in vitro method for producing activated T lymphocytes, the method comprising contacting in vitro T cells with antigen loaded human class I MHC molecules expressed on the surface of a suitable antigen-presenting cell or an artificial construct mimicking an antigen-presenting cell for a period of time sufficient to activate said T cells in an antigen specific manner, wherein said antigen is a peptide according to claim 1 or 2.

10. An activated T cell, produced by the method according to claim 9, that selectively recognizes a cell which presents a polypeptide comprising an amino acid sequence given in claim 1 or 2

11. A pharmaceutical composition comprising at least one active ingredient selected from the group consisting of the peptide according to any one of claims 1 to 3, the antibody according to claim 4, the TCR according to claim 5, the nucleic acid or the expression vector according to claim 6, the host cell comprising the expression vector according to claim 7, the activated T cell according to claim 10, and a pharmaceutically acceptable carrier, and optionally, pharmaceutically acceptable excipients and/or stabilizers.

12. The peptide according to any one of claims 1 to 3, the antibody according to claim 4, the TCR according to claim 5, the nucleic acid or the expression vector according to claim 6, the host cell comprising the expression vector according to claim 7, the activated T cell according to claim 10, or the pharmaceutical composition according to claim 11 for use in medicine.

13. The peptide according to any one of claims 1 to 3, the antibody according to claim 4, the TCR according to claim 5, the nucleic acid or the expression vector according to claim 6, the host cell comprising the expression vector according to claim 7, the activated T cell according to claim 10, or the pharmaceutical composition according to claim 11 for use in the treatment of cancer.

14. The peptide according to any one of claims 1 to 3, the antibody according to claim 4, the TCR according to claim 5, the nucleic acid or the expression vector according to claim 6, the host cell comprising the expression vector according to claim 7, the activated T cell according to claim 10, or the pharmaceutical composition according to claim 11 for use according to claim 13, wherein said cancer is selected from the group of HCC, brain cancer, kidney cancer, pancreatic cancer, colon or rectal cancer or leukemia and other tumors that show an overexpression of SLC10A5

15. A kit comprising:

(a) a container comprising a pharmaceutical composition according to claim 11, in solution or in lyophilized form;
(b) optionally, a second container containing a diluent or reconstituting solution for the lyophilized formulation;
(c) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation,

and, optionally,
(d) further comprising one or more of (iii) a buffer, (iv) a diluent, (v) a filter, (vi) a needle) or (vii) a syringe

Patentansprüche

1. Peptid, umfassend die Aminosäuresequenz von SEQ ID No. 89, oder ein pharmazeutisch akzeptables Salz davon, wobei das Peptid eine Gesamtlänge von bis zu 30 Aminosäuren aufweist, und wobei das Peptid die Fähigkeit aufweist, an ein Molekül des menschlichen Haupthistokompatibilitätskomplexes (MHC) Klasse-I zu binden.

2. Peptid nach Anspruch 1, wobei das Peptid eine Gesamtlänge von bis zu 16 Aminosäuren aufweist, und wobei bevorzugt das Peptid aus der Aminosäuresequenz gemäß SEQ ID No. 89 besteht.

3. Peptid nach Anspruch 1 oder 2, wobei das Peptid nicht-peptidische Bindungen einschließt, und/oder wobei das Peptid Teil eines Fusionsproteins ist, das die N-terminalen Aminosäuren der HLA-DR Antigen-assoziierten invarianten Kette (Ii) umfasst.

4. Antikörper, löslich oder membrangebunden, der das Peptid nach einem der Ansprüche 1 bis 3 spezifisch erkennt, vorzugsweise das Peptid nach einem der Ansprüche 1 bis 3, das an ein MHC-Molekül gebunden ist.

5. T-Zell-Rezeptor (TCR), löslich oder membrangebunden, der mit einem HLA-Liganden reagiert, wobei der Ligand mindestens 88% Identität mit der Aminosäuresequenz von SEQ ID No. 89 aufweist und vorzugsweise aus dieser besteht, wobei optional der TCR als lösliches Molekül bereitgestellt wird und weiterhin optional eine weitere Effektorfunktion wie eine immunstimulierende Domäne oder Toxin trägt.

6. Nukleinsäure, die ein Peptid nach einem der Ansprüche 1 bis 3, den Antikörper nach Anspruch 4, den TCR nach Anspruch 5 oder einen Expressionsvektor, der die Nukleinsäure exprimiert, kodiert.

7. Wirtszelle, umfassend das Peptid nach einem der Ansprüche 1 bis 3, oder die Nukleinsäure oder den Expressionsvektor nach Anspruch 6, wobei die Wirtszelle vorzugsweise eine antigenpräsentierende Zelle wie eine dendritische Zelle oder eine T-Zelle oder NK-Zelle ist.

8. Verfahren zur Herstellung des Peptids nach einem der Ansprüche 1 bis 3, des Antikörpers nach Anspruch 4 oder des TCR nach Anspruch 5, wobei das Verfahren das Kultivieren einer Wirtszelle nach Anspruch 7, die das Peptid nach einem der Ansprüche 1 bis 3 präsentiert oder die Nukleinsäure oder den Expressionsvektor nach Anspruch 6 exprimiert, und das Isolieren des Peptids, des Antikörpers oder des TCR aus der Wirtszelle und/oder ihrem Kulturmedium umfasst.

9. *In vitro*-Verfahren zur Herstellung von aktivierten T Lymphozyten, wobei das Verfahren ein in Kontakt bringen *in vitro* von T-Zellen mit Antigen-beladenen menschlichen Klasse-I MHC-Molekülen umfasst, die auf der Oberfläche einer geeigneten Antigen-präsentierenden Zelle oder eines künstlichen Konstrukts, das eine Antigen-präsentierende Zelle nachahmt, exprimiert werden, für eine Zeitdauer die ausreichend ist, um die T-Zellen in einer Antigen-spezifischen Weise zu aktivieren, wobei das Antigen ein Peptid nach Anspruch 1 oder 2 ist.

10. Aktivierte T-Zelle, hergestellt nach dem Verfahren nach Anspruch 9, welche selektiv eine Zelle erkennt, die ein Polypeptid umfassend eine Aminosäuresequenz nach Anspruch 1 oder 2 präsentiert.

11. Pharmazeutische Zusammensetzung, umfassend mindestens einen Wirkstoff, ausgewählt aus der Gruppe bestehend aus dem Peptid nach einem der Ansprüche 1 bis 3, dem Antikörper nach Anspruch 4, dem TCR nach Anspruch 5, der Nukleinsäure oder dem Expressionsvektor nach Anspruch 6, wobei die Wirtszelle den Expressionsvektor nach Anspruch 7, die aktivierte T-Zelle nach Anspruch 10 und einen pharmazeutisch akzeptablen Träger umfasst, und gegebenenfalls pharmazeutisch akzeptable Hilfsstoffe und/oder Stabilisatoren.

12. Peptid nach einem der Ansprüche 1 bis 3, der Antikörper nach Anspruch 4, der TCR nach Anspruch 5, die Nukleinsäure oder der Expressionsvektor nach Anspruch 6, wobei die Wirtszelle den Expressionsvektor nach Anspruch 7, die aktivierte T-Zelle nach Anspruch 10 oder die pharmazeutische Zusammensetzung nach Anspruch 11 zur Verwendung in der Medizin umfasst.

13. Peptid nach einem der Ansprüche 1 bis 3, der Antikörper nach Anspruch 4, der TCR nach Anspruch 5, die Nukleinsäure oder der Expressionsvektor nach Anspruch 6, wobei die Wirtszelle den Expressionsvektor nach Anspruch 7, die aktivierte T-Zelle nach Anspruch 10 oder die pharmazeutische Zusammensetzung nach Anspruch 11 zur Verwendung in der Krebsbehandlung umfasst.

14. Peptid nach einem der Ansprüche 1 bis 3, der Antikörper nach Anspruch 4, der TCR nach Anspruch 5, die Nukleinsäure oder der Expressionsvektor nach Anspruch 6, wobei die Wirtszelle den Expressionsvektor nach Anspruch 7, die aktivierte T-Zelle nach Anspruch 10 oder die pharmazeutische Zusammensetzung nach Anspruch 11 zur Verwendung nach Anspruch 13, wobei die Krebsart aus der Gruppe von HCC, Hirnkrebs, Nierenkrebs, Bauchspeicheldrüsenkrebs, Darm- oder Rektumkarzinom oder Leukämie und anderen Tumoren ausgewählt ist, die eine Überexpression von SLC10A5 aufweisen.

15. Kit umfassend:

(a) einen Behälter, welcher die oben beschriebene pharmazeutische Zusammensetzung nach Anspruch 11 in Lösung oder in lyophilisierter Form umfasst;
(b) gegebenenfalls, einen zweiten Behälter enthaltend ein Verdünnungsmittel oder eine Rekonstitutionslösung für die lyophilisierte Formulierung;
(c) gegebenenfalls, Anweisungen zur (i) Verwendung der Lösung oder (ii) der Rekonstitution und/oder der Verwendung der lyophilisierten Formulierung und gegebenenfalls
(d) weiterhin umfassend ein oder mehrere von (iii) ein Puffer, (iv) ein Verdünnungsmittel, (v) einen Filter, (vi) eine Nadel oder (vii) eine Spritze.

Revendications

1. Peptide comprenant la séquence d'acides aminés de SEQ ID n° 89 ou un sel pharmaceutiquement acceptable de ce dernier, où ledit peptide a une longueur globale de jusqu'à 30 acides aminés, et où ledit peptide a la capacité de se lier à une molécule du complexe majeur d'histocompatibilité (CMH) humain de classe I.

2. Peptide conforme à la revendication 1, où ledit peptide a une longueur globale de jusqu'à 16 acides aminés, et de préférence où le peptide consiste en la séquence d'acides aminés conforme à la SEQ ID n° 89.

3. Peptide conforme à la revendication 1 ou 2, où ledit peptide comprend des liaisons non peptidiques et/ou ledit peptide fait partie d'une protéine de fusion comprenant des acides aminés N-terminaux de la chaîne invariante (Ii) associée aux antigènes du système HLA-DR.

4. Anticorps, soluble ou membranaire, qui reconnaît de façon spécifique le peptide conforme à l'une des revendications 1 à 3, de préférence le peptide conforme à l'une des revendications 1 à 3 qui est lié à une molécule du CMH.

5. Récepteur de lymphocytes T (TCR), soluble ou membranaire, qui réagit avec un ligand HLA, où ledit ligand est au moins identique à 88 % à, et consiste de préférence en, la séquence d'acides aminés de SEQ ID n° 89, où facultativement ledit TCR est fourni sous la forme d'une molécule soluble et présente facultativement une fonction effectrice supplémentaire telle qu'un domaine immunostimulant ou une toxine.

6. Acide nucléique, codant pour un peptide conforme à l'une des revendications 1 à 3, anticorps conforme à la revendication 4, TCR conforme à la revendication 5 ou vecteur d'expression exprimant ledit acide nucléique.

7. Cellule hôte comprenant le peptide conforme à l'une des revendications 1 à 3, ou l'acide nucléique ou le vecteur d'expression conforme à la revendication 6, où ladite cellule hôte est de préférence une cellule présentatrice d'antigènes telle qu'une cellule dendritique, un lymphocyte T ou une cellule NK

8. Procédé de production du peptide conforme à l'une des revendications 1 à 3, de l'anticorps conforme à la revendication 4, ou du TCR conforme à la revendication 5, ce procédé comprenant la mise en culture d'une cellule hôte conforme à la revendication 7 qui présente le peptide conforme à l'une des revendications 1 à 3, ou exprime l'acide nucléique ou le vecteur d'expression conforme à la revendication 6, et l'isolement dudit peptide, dudit anticorps ou dudit TCR de la cellule hôte et/ou de son milieu de culture.

9. Procédé *in vitro* de production de lymphocytes T activés, ce procédé comprenant la mise en contact *in vitro* des lymphocytes T avec des molécules du CMH de classe I humain chargées d'antigènes exprimées à la surface d'une cellule présentatrice d'antigènes appropriée ou d'une construction artificielle imitant une cellule présentatrice d'antigènes pendant un temps suffisant pour activer, de manière antigène-spécifique, lesdits lymphocytes T, où ledit antigène est un peptide conforme à la revendication 1 ou 2.

10. Lymphocyte T activé, produit par le procédé conforme à la revendication 9, qui reconnaît de façon sélective une cellule qui présente un polypeptide comprenant une séquence d'acides aminés telle que décrite dans la revendication 1 ou 2.

11. Composition pharmaceutique comprenant au moins un ingrédient actif sélectionné à partir du groupe consistant en le peptide conforme à l'une des revendications 1 à 3, l'anticorps conforme à la revendication 4, le TCR conforme à la revendication 5, l'acide nucléique ou le vecteur d'expression conforme à la revendication 6, la cellule hôte comprenant le vecteur d'expression conforme à la revendication 7, le lymphocyte T activé conforme à la revendication 10, et un transporteur pharmaceutiquement acceptable, et facultativement, des excipients et/ou des stabilisants pharmaceutiquement acceptables.

12. Peptide conforme à l'une des revendications 1 à 3, anticorps conforme à la revendication 4, TCR conforme à la revendication 5, acide nucléique ou vecteur d'expression conforme à la revendication 6, cellule hôte comprenant le vecteur d'expression conforme à la revendication 7, lymphocyte T activé conforme à la revendication 10, ou composition pharmaceutique conforme à la revendication 11 pour usage médical.

13. Peptide conforme à l'une des revendications 1 à 3, anticorps conforme à la revendication 4, TCR conforme à la revendication 5, acide nucléique ou vecteur d'expression conforme à la revendication 6, cellule hôte comprenant le vecteur d'expression conforme à la revendication 7, lymphocyte T activé conforme à la revendication 10, ou composition pharmaceutique conforme à la revendication 11 pour une utilisation dans le traitement du cancer.

14. Peptide conforme à l'une des revendications 1 à 3, anticorps conforme à la revendication 4, TCR conforme à la revendication 5, acide nucléique ou vecteur d'expression conforme à la revendication 6, cellule hôte comprenant le vecteur d'expression conforme à la revendication 7, lymphocyte T activé conforme à la revendication 10, ou composition pharmaceutique conforme à la revendication 11 pour une utilisation conforme à la revendication 13, où ledit cancer est sélectionné parmi le groupe consistant en CHC, cancer du cerveau, cancer rénal, cancer pancréatique, cancer du côlon ou du rectum ou leucémie et autres tumeurs qui présentent une surexpression de SLC10A5.

15. Kit comprenant :

(a) un récipient contenant une composition pharmaceutique conforme à la revendication 11, en solution ou sous forme lyophilisée ;
(b) facultativement, un deuxième récipient contenant un diluant ou une solution de reconstitution pour la formulation lyophilisée ;
(c) facultativement, des instructions sur (i) l'utilisation de la solution ou (ii) la reconstitution et/ou l'utilisation de la formulation lyophilisée, et, facultativement,
(d) comprenant également un ou plusieurs des constituants suivants : (iii) tampon, (iv) diluant, (v) filtre, (vi) aiguille ou (vii) seringue.

Figure 1A

Peptide: ALVDTLKFV (A*02)

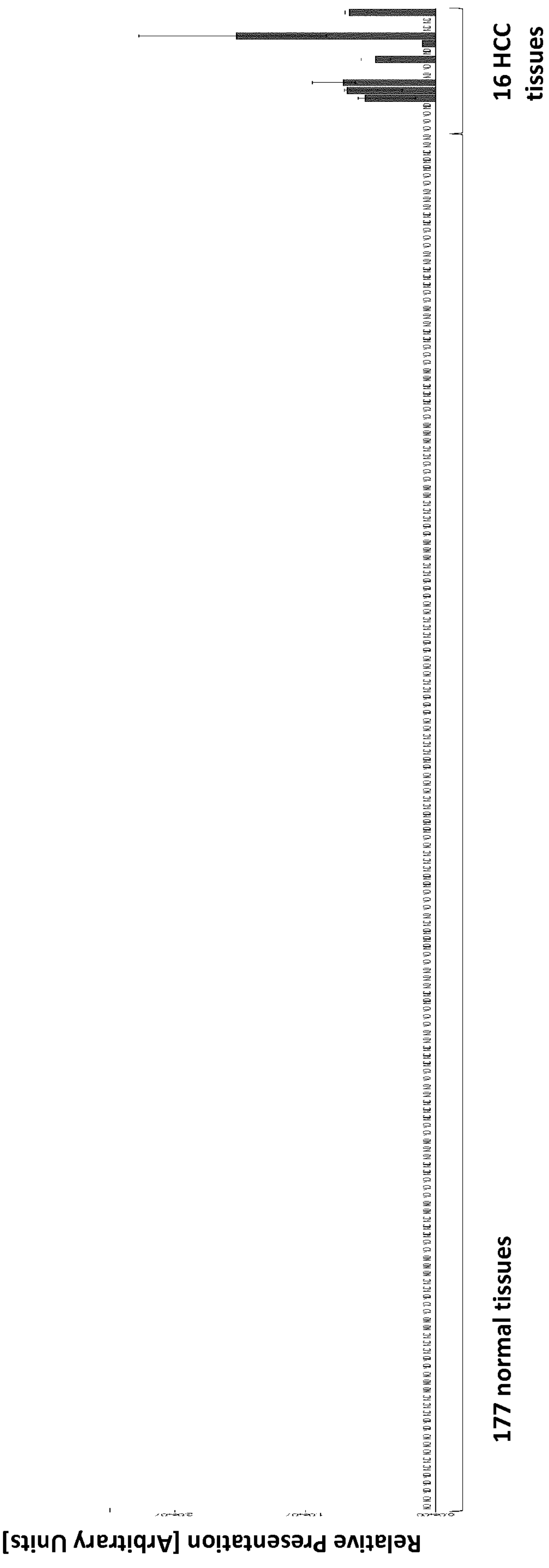


Figure 1B

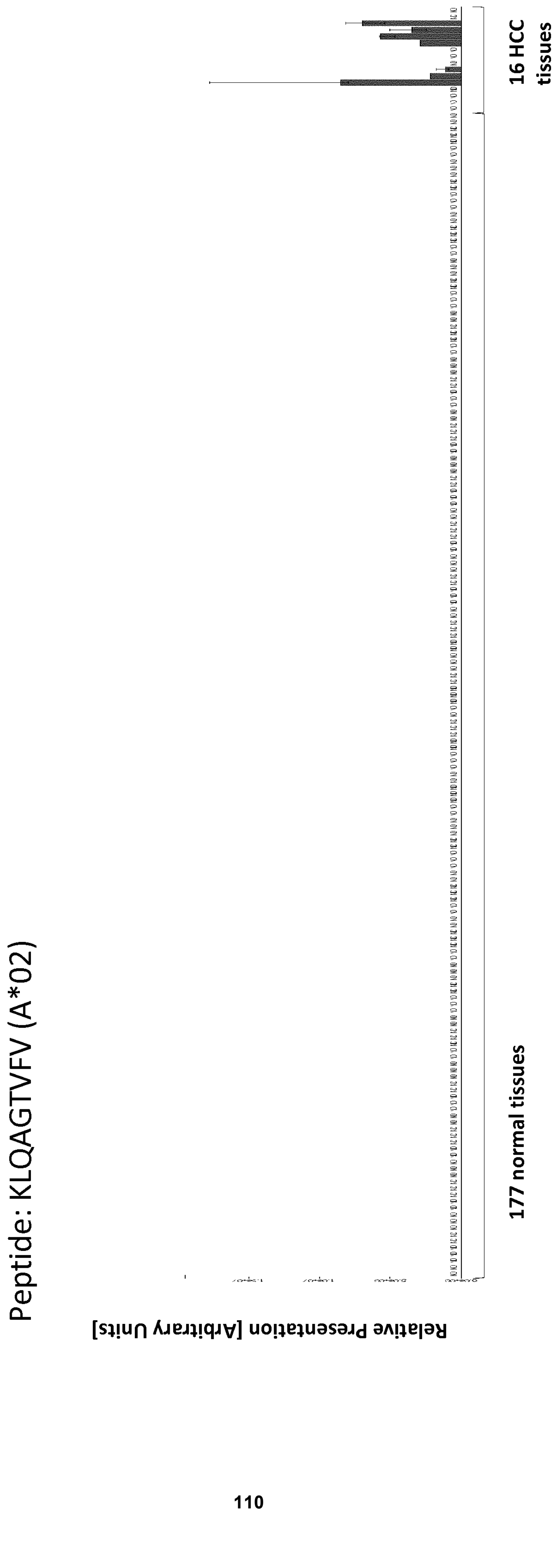

Peptide: KLQAGTVFV (A*02)
Relative Presentation [Arbitrary Units]
177 normal tissues
16 HCC tissues

Figure 1C

Peptide: AYLLQPSQF (A*24)

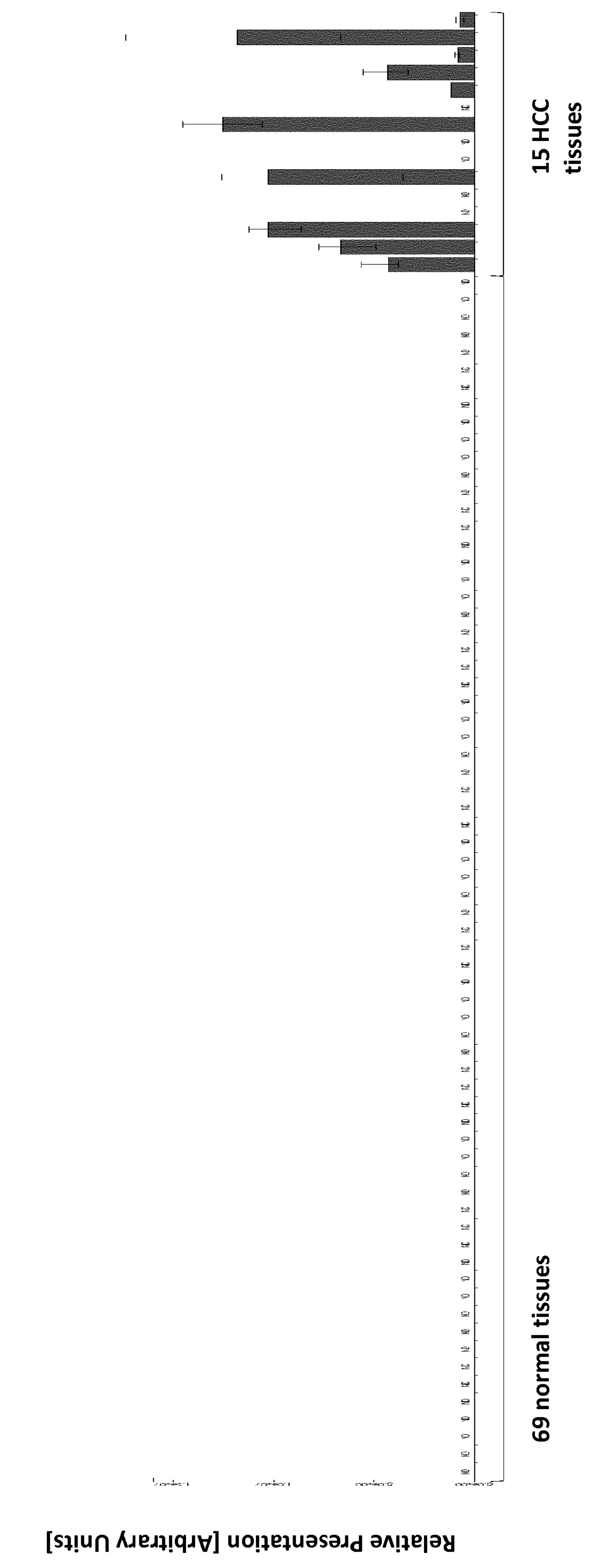


Figure 1D

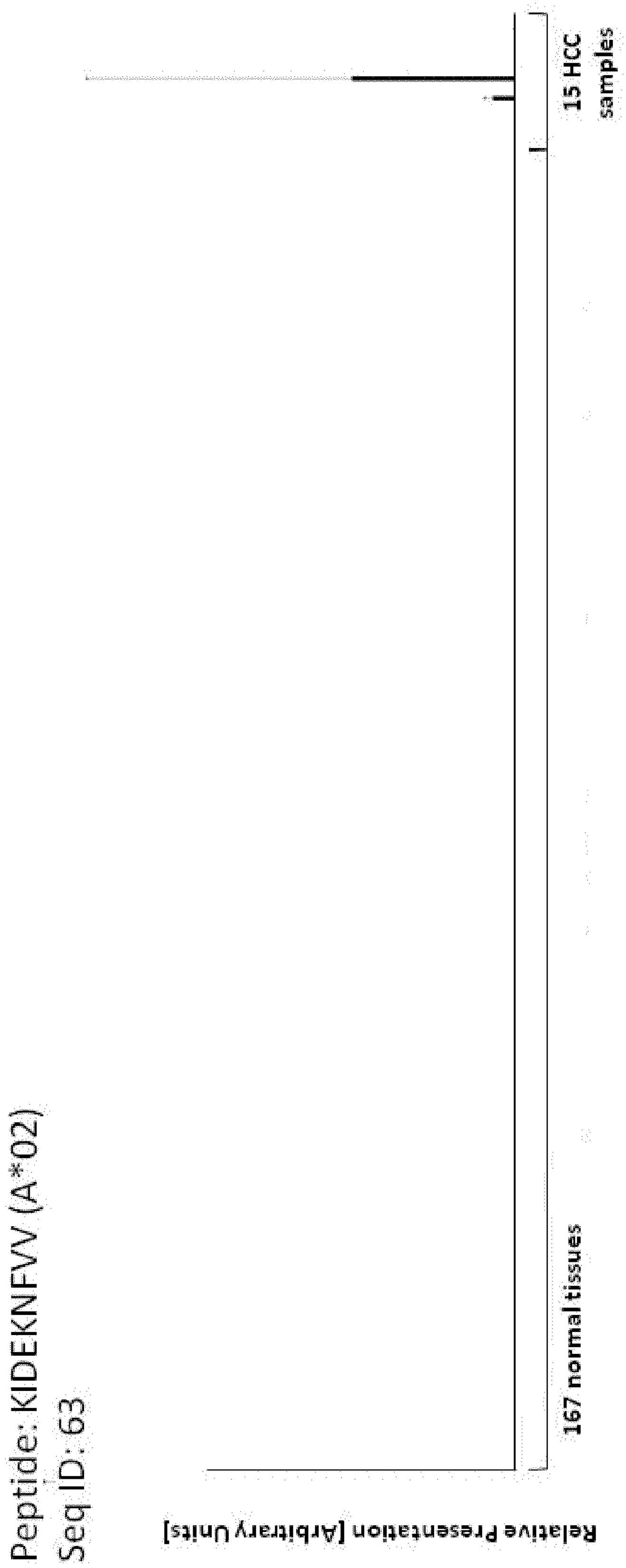

Peptide: KIDEKNFVV (A*02)
Seq ID: 63
Relative Presentation [Arbitrary Units]
167 normal tissues
15 HCC samples

Figure 1E

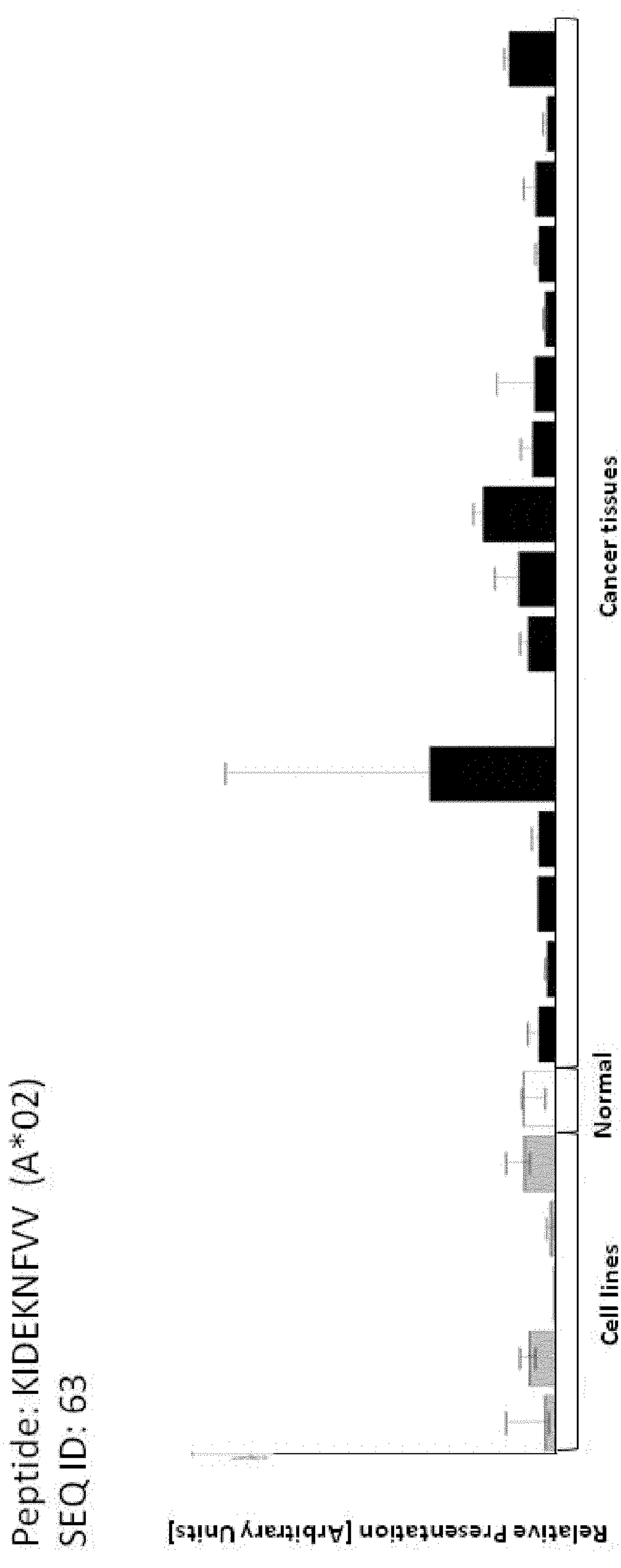

Peptide: KIDEKNFVV (A*02)
SEQ ID: 63
Relative Presentation [Arbitrary Units]
Cell lines
Normal tissue
Cancer tissues

Figure 1F

Peptide: RLPPDTLLQQV (A*02)
Seq ID: 92

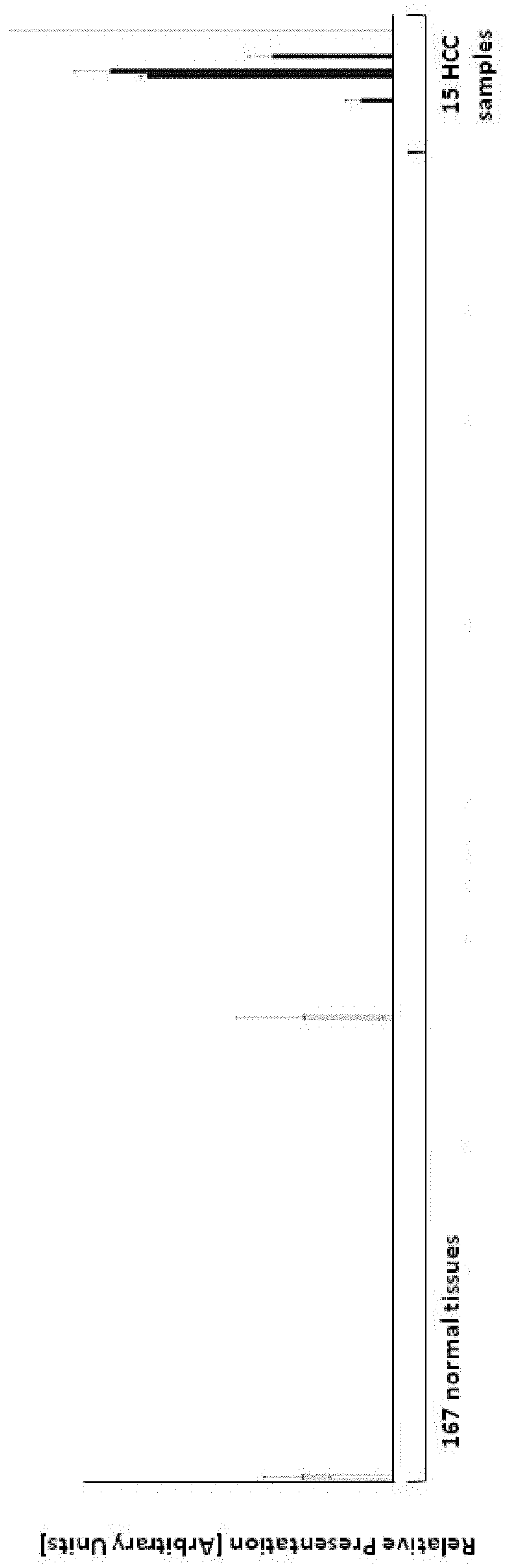


Figure 1G

Peptide: RLPPDTLLQQV (A*02)
SEQ ID: 92

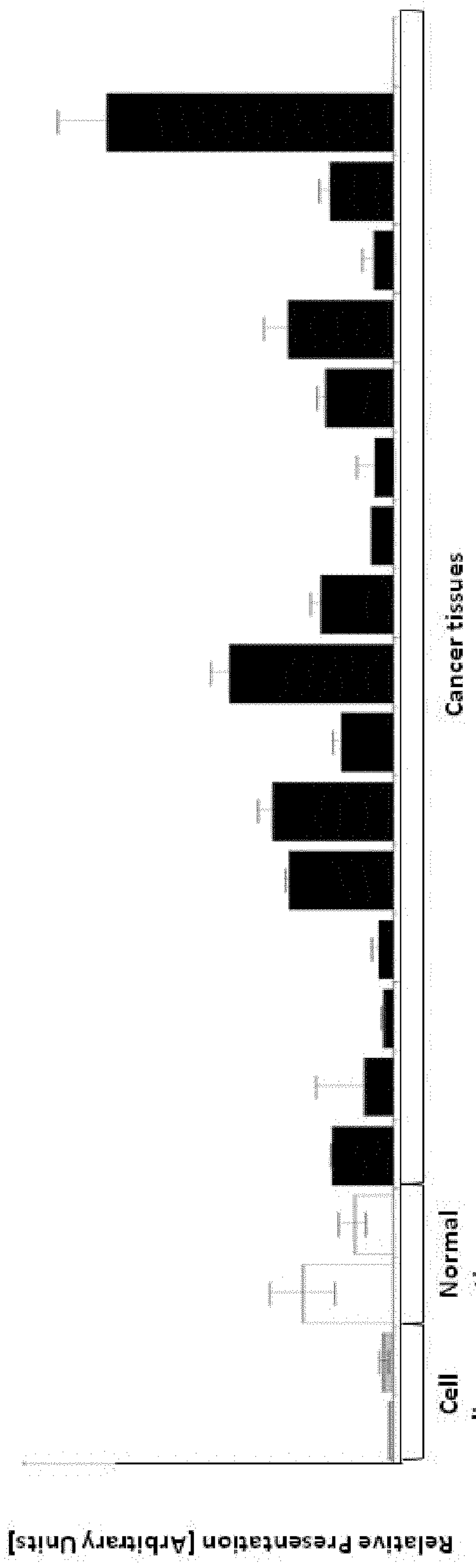


Figure 1H

Peptide: SVWFGPKEV (A*02)
Seq ID: 104

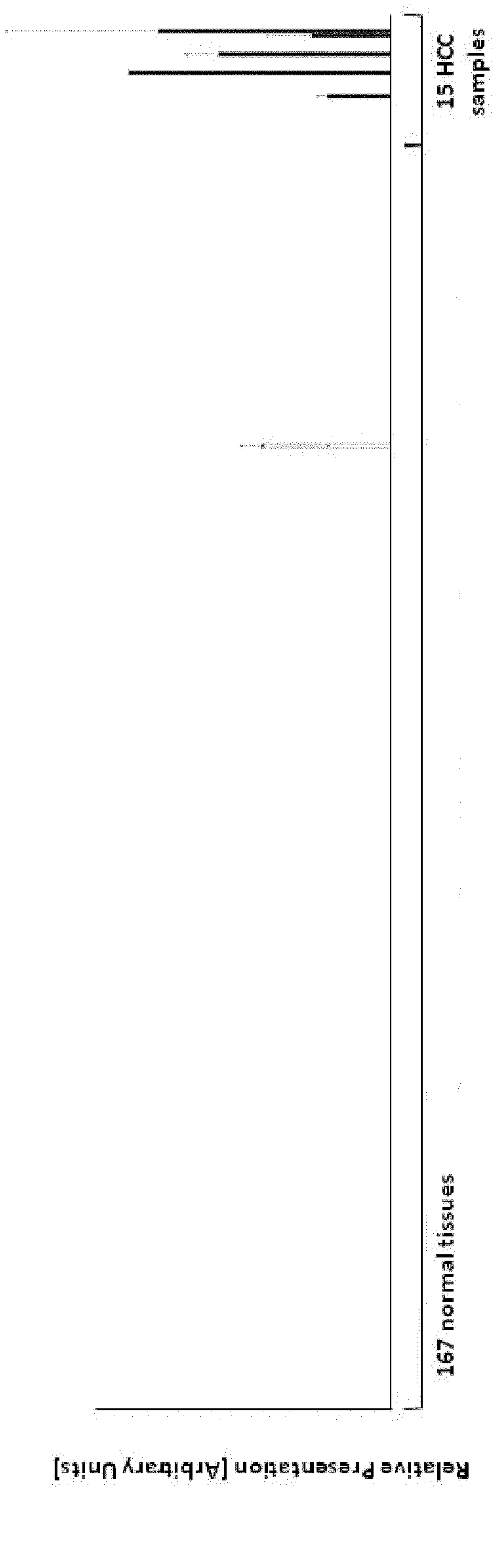


Figure 1I

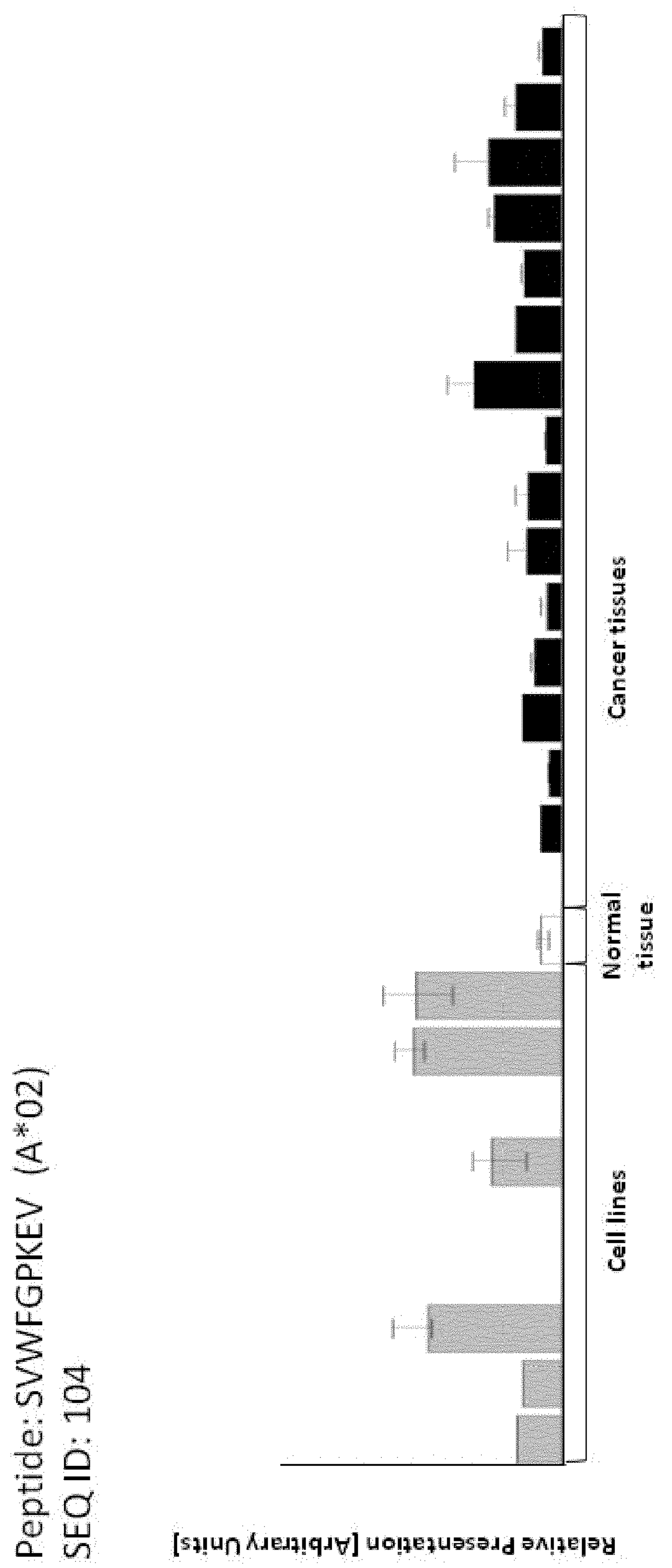

Peptide: SVWFGPKEV (A*02)
SEQ ID: 104
Relative Presentation [Arbitrary Units]
Cell lines
Normal tissue
Cancer tissues

Figure 1J

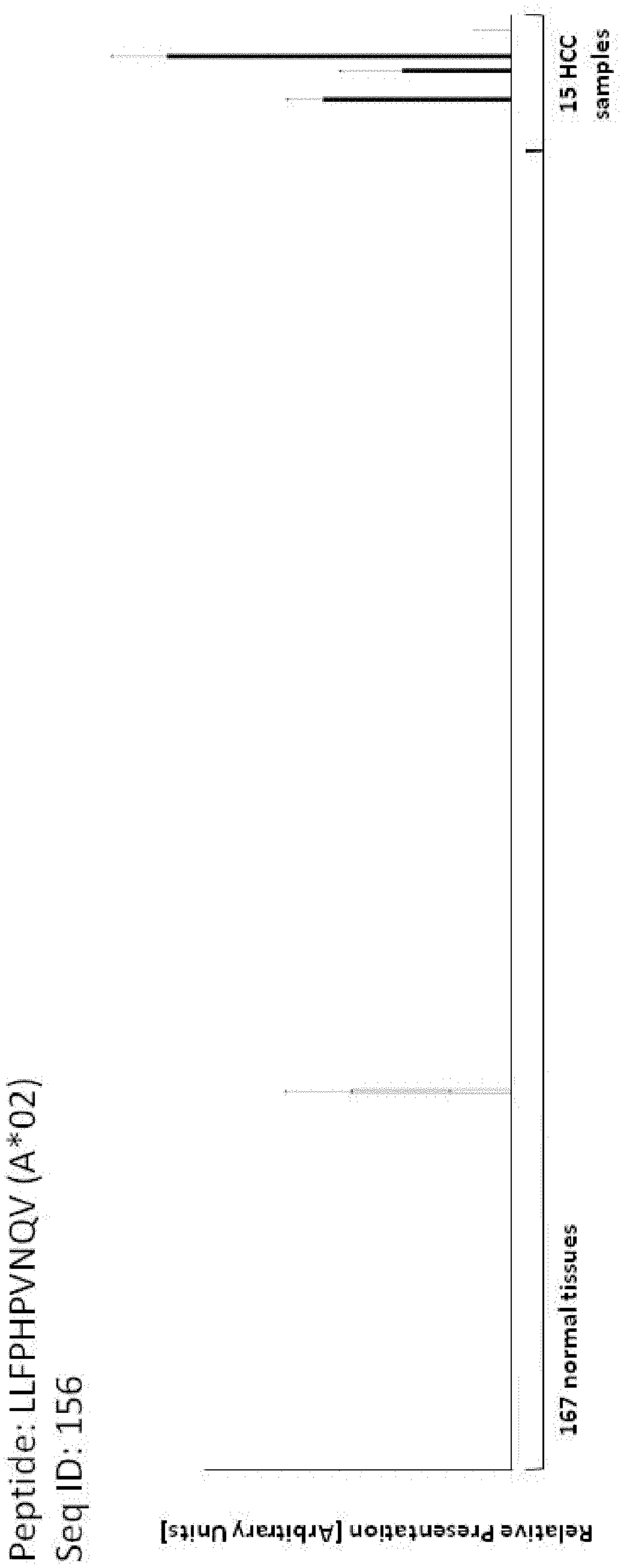

Peptide: LLFPHPVNQV (A*02)
Seq ID: 156
Relative Presentation [Arbitrary Units]
167 normal tissues
15 HCC samples

Figure 1K

Peptide: LLFPHPVNQV (A*02)
SEQ ID: 156

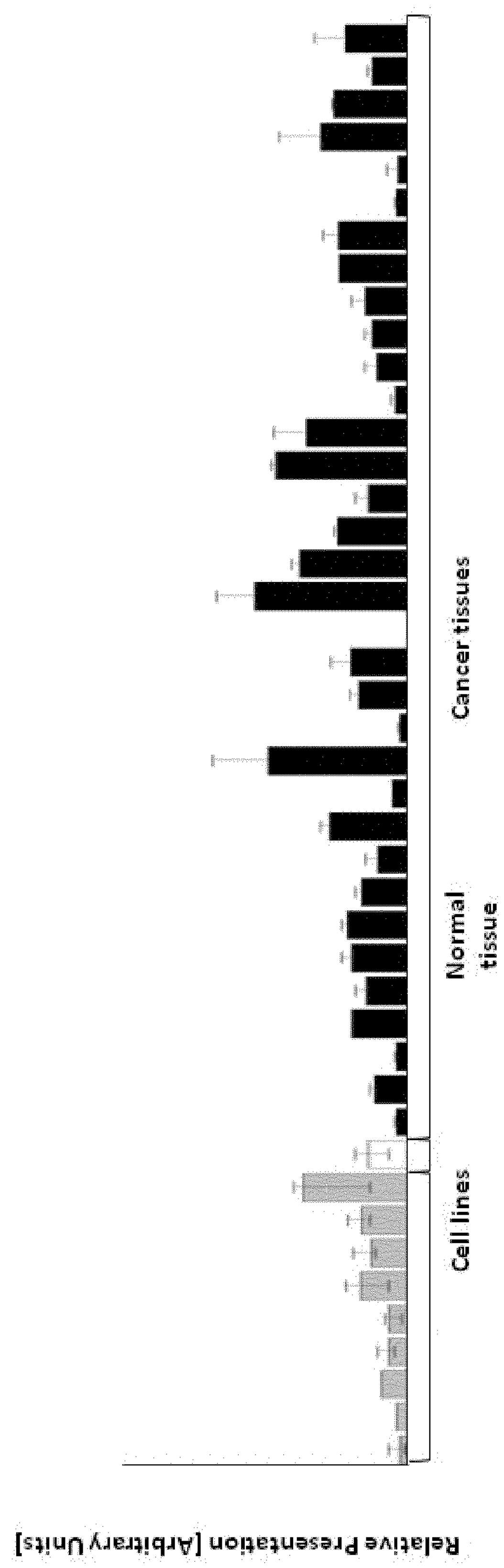


Figure 1L

Peptide: FLDTPIAKV (A*02)
Seq ID: 47

Figure 1M

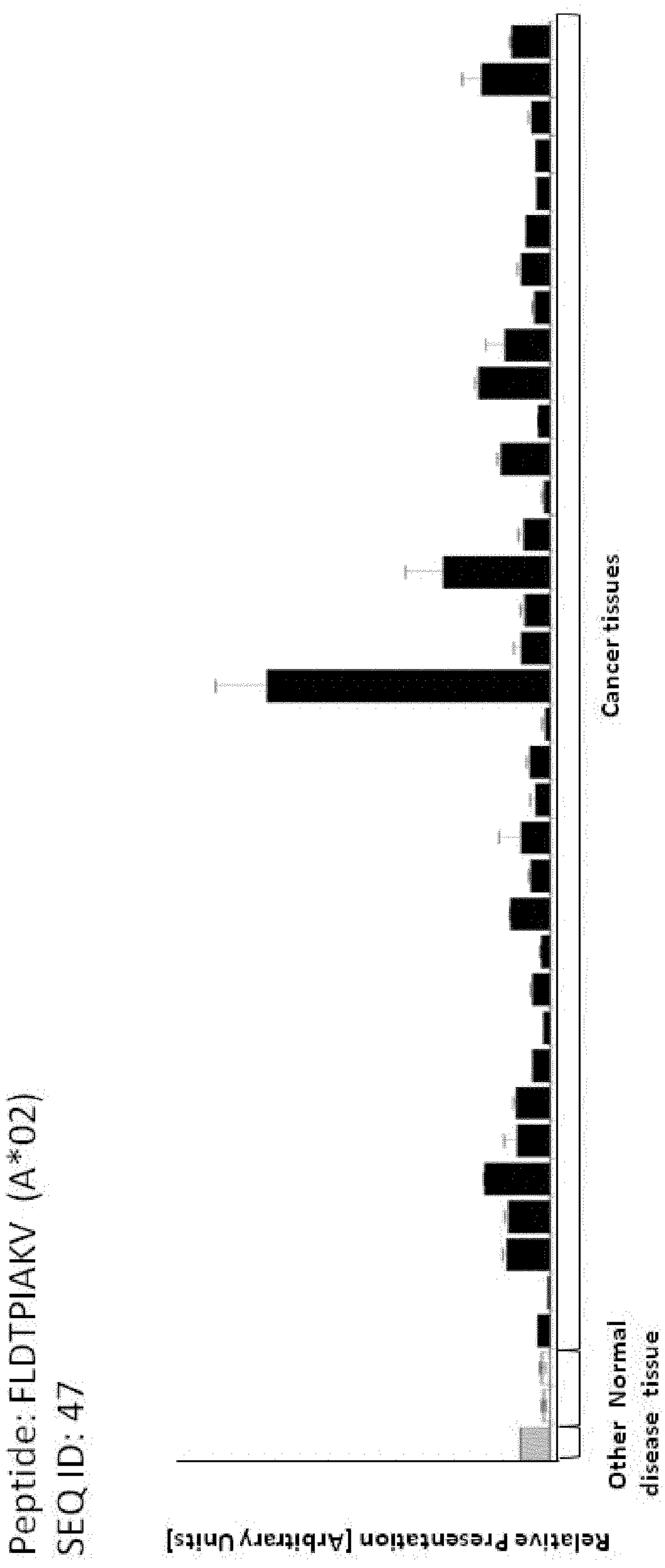

Peptide: FLDTPIAKV (A*02)
SEQ ID: 47
Relative Presentation [Arbitrary Units]
Other disease
Normal tissue
Cancer tissues

Figure 2A

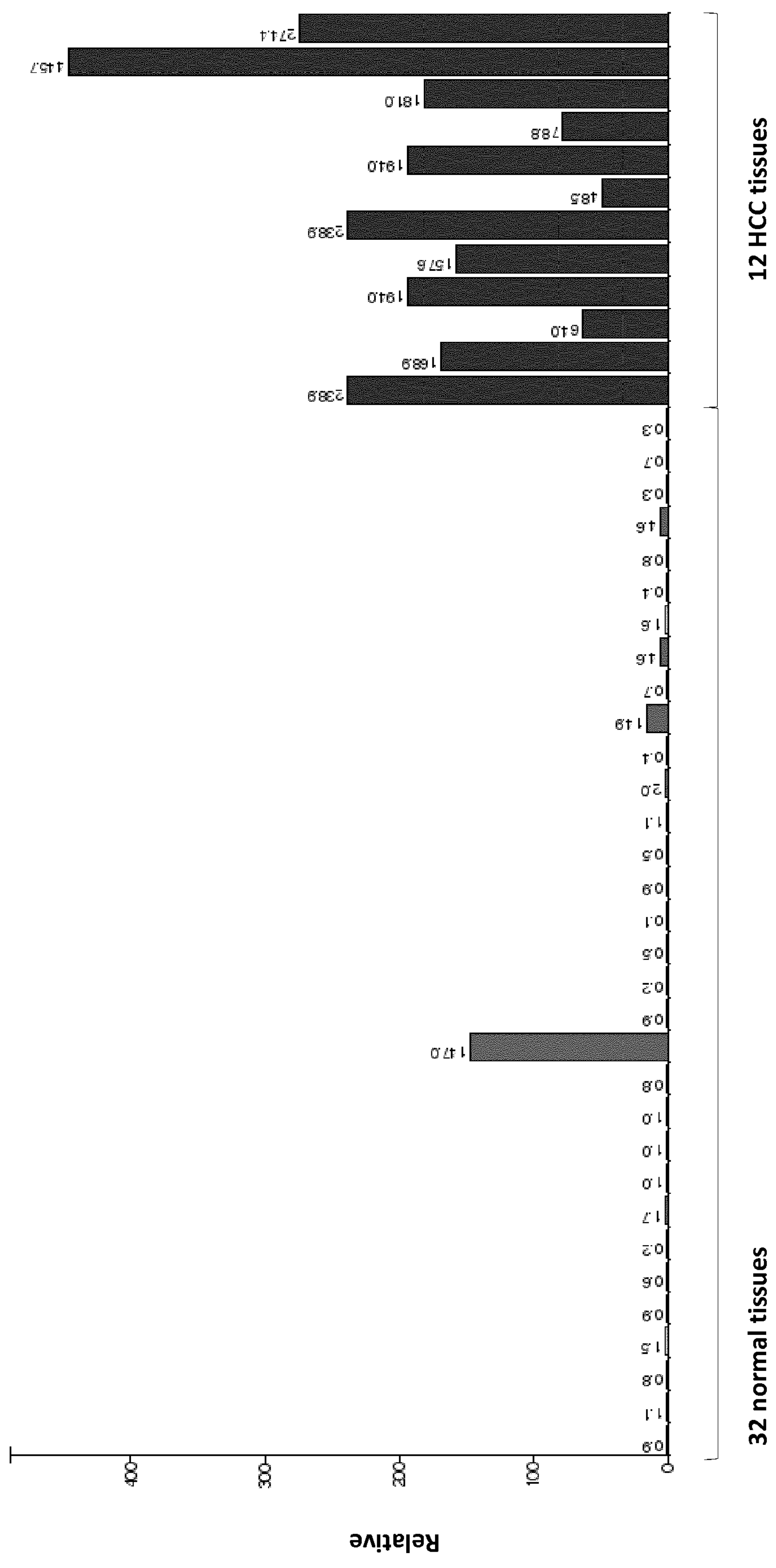


Figure 2B

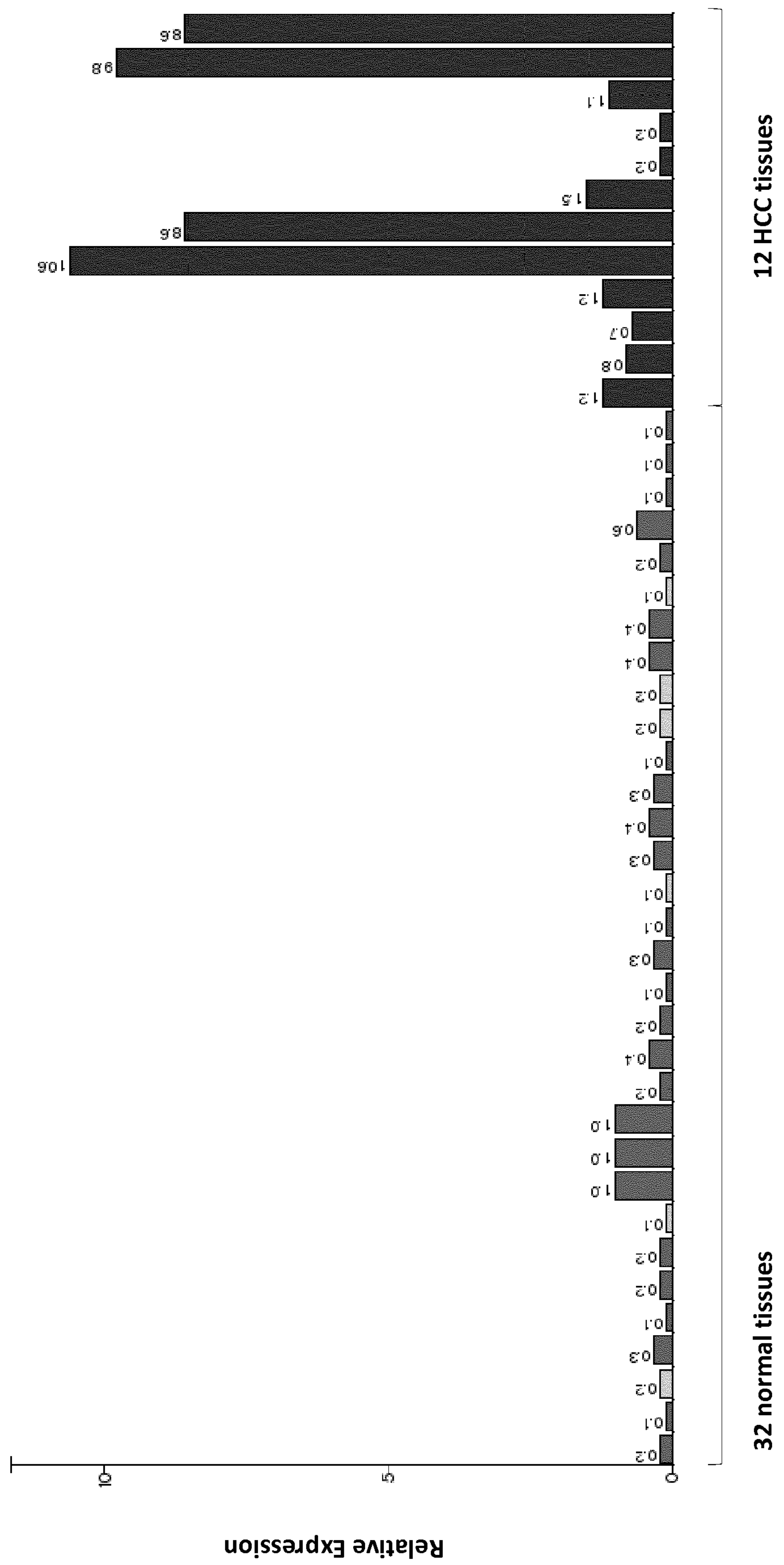

Relative Expression
0
5
10
0.2
0.1
0.2
0.3
0.1
0.2
0.2
0.1
1.0
1.0
1.0
0.2
0.4
0.2
0.1
0.3
0.1
0.1
0.3
0.4
0.3
0.1
0.2
0.2
0.4
0.4
0.1
0.2
0.6
0.1
0.1
0.1
1.2
0.8
0.7
1.2
10.6
8.6
1.5
0.2
0.2
1.1
9.8
8.6
32 normal tissues
12 HCC tissues

Figure 2C

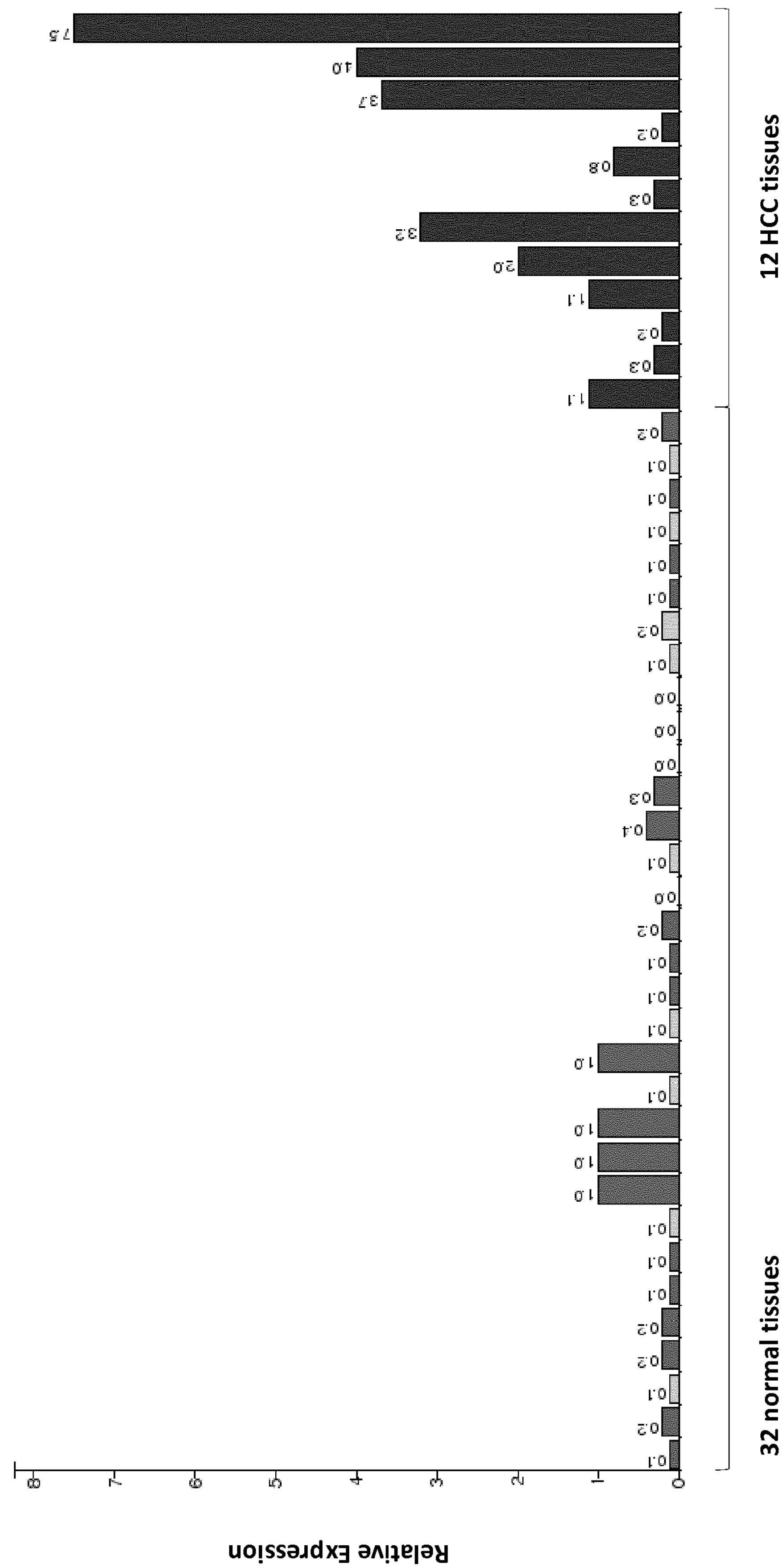


Figure 2D

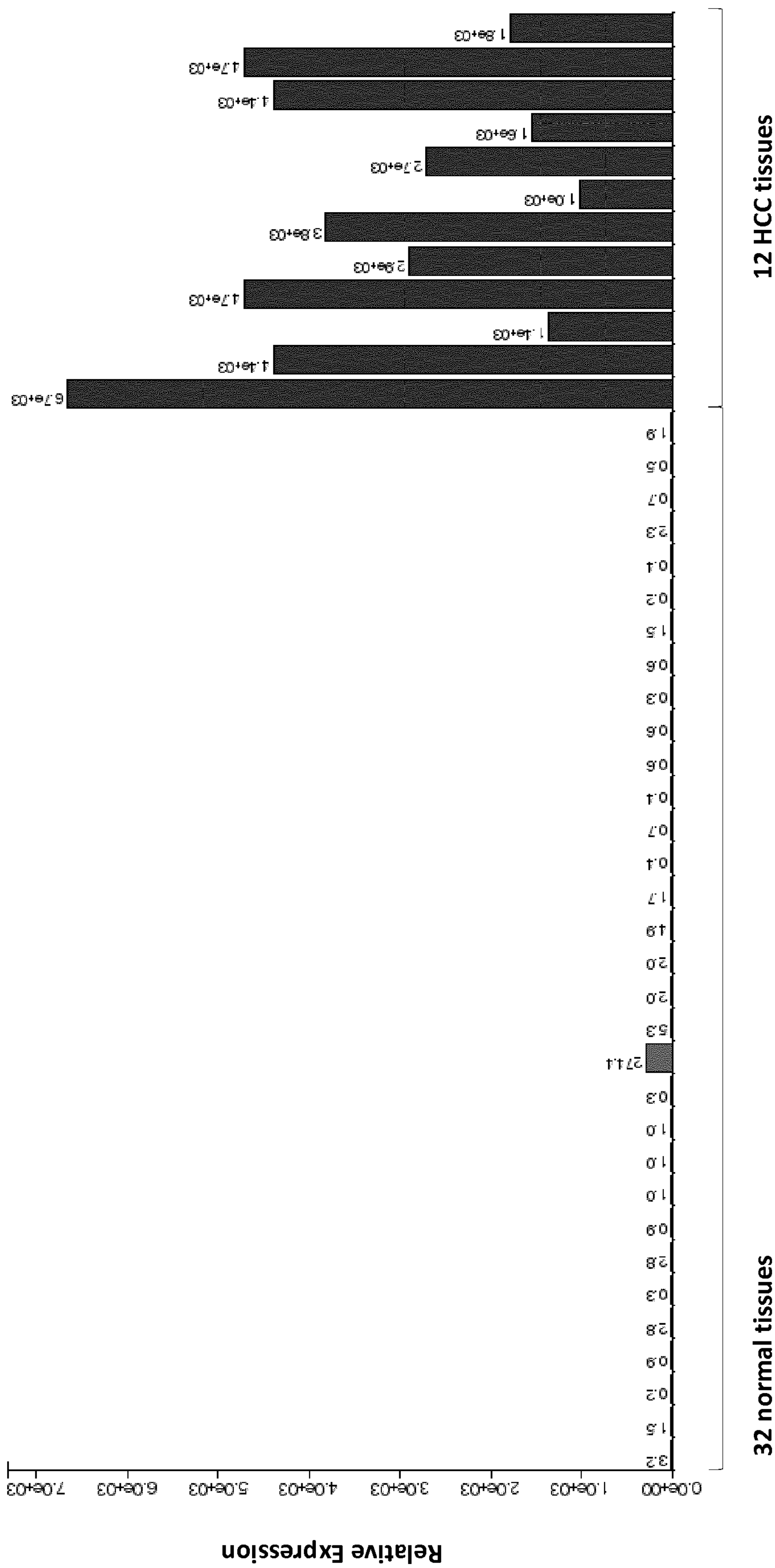

Relative Expression
0.0e+00
1.0e+03
2.0e+03
3.0e+03
4.0e+03
5.0e+03
6.0e+03
7.0e+03
32 normal tissues
12 HCC tissues

Figure 2E

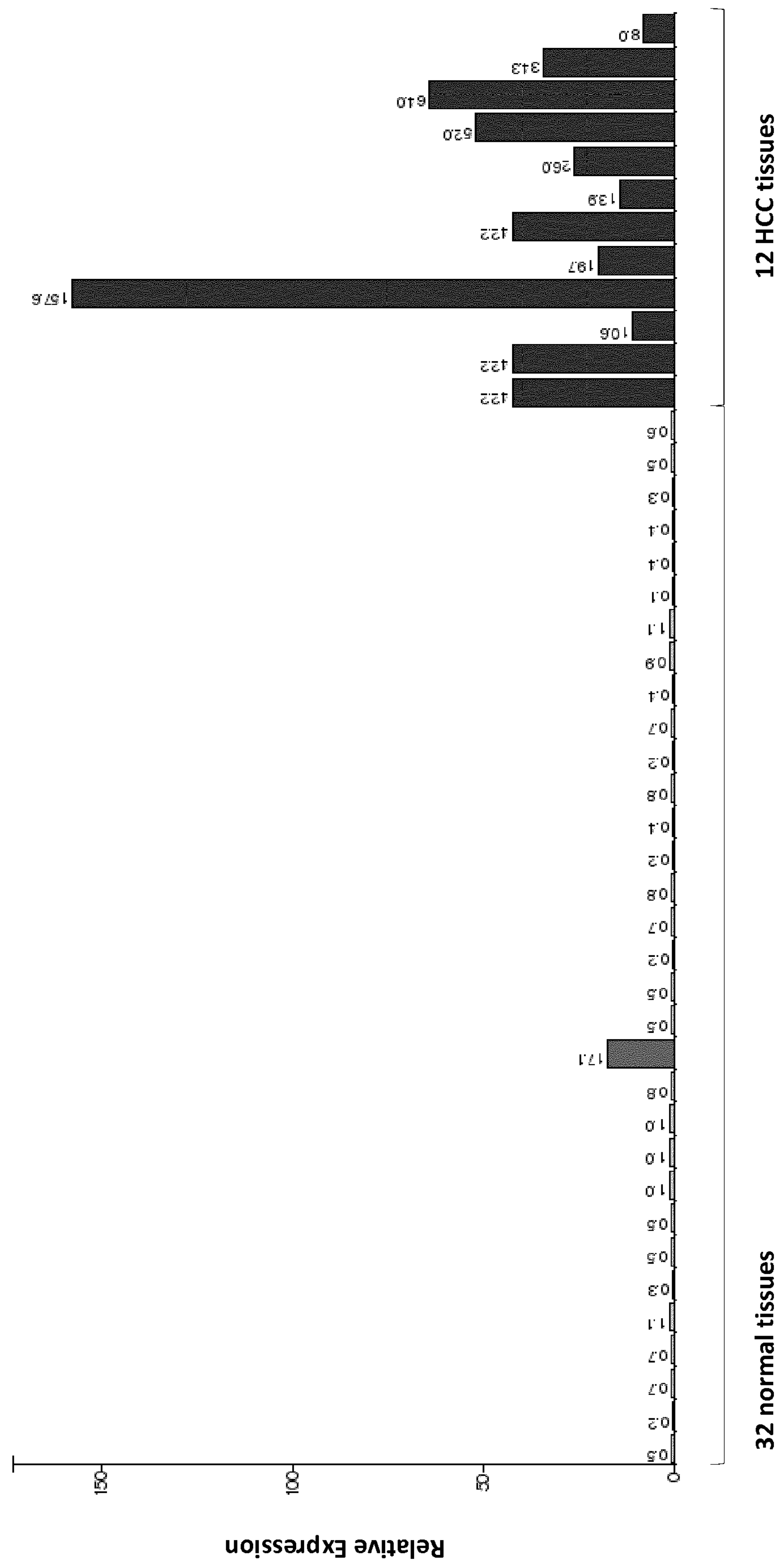

Relative Expression
0
50
100
150
32 normal tissues
12 HCC tissues

Figure 2F

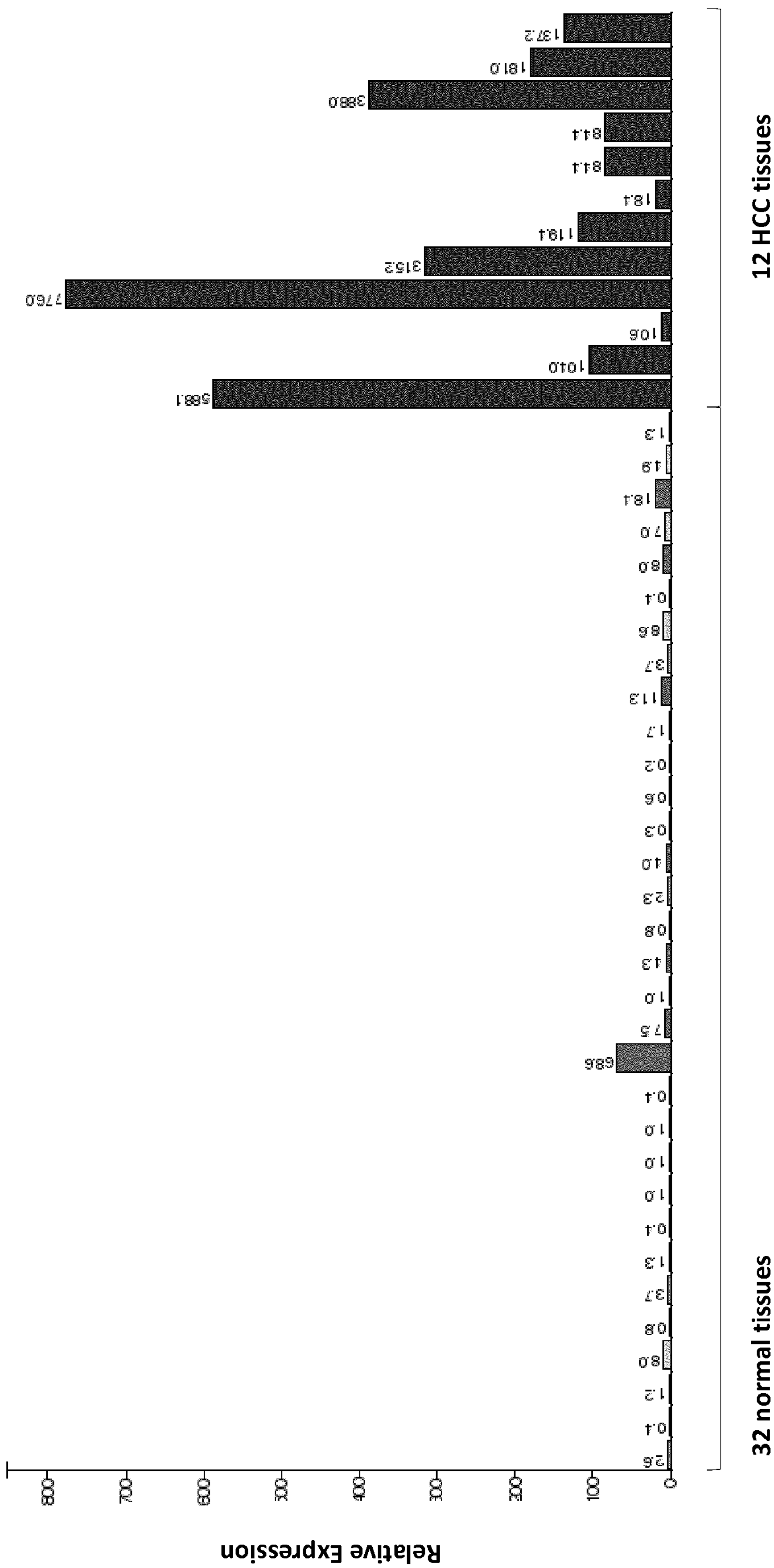

Relative Expression
0
100
200
300
400
500
600
700
800
32 normal tissues
12 HCC tissues

Figure 3

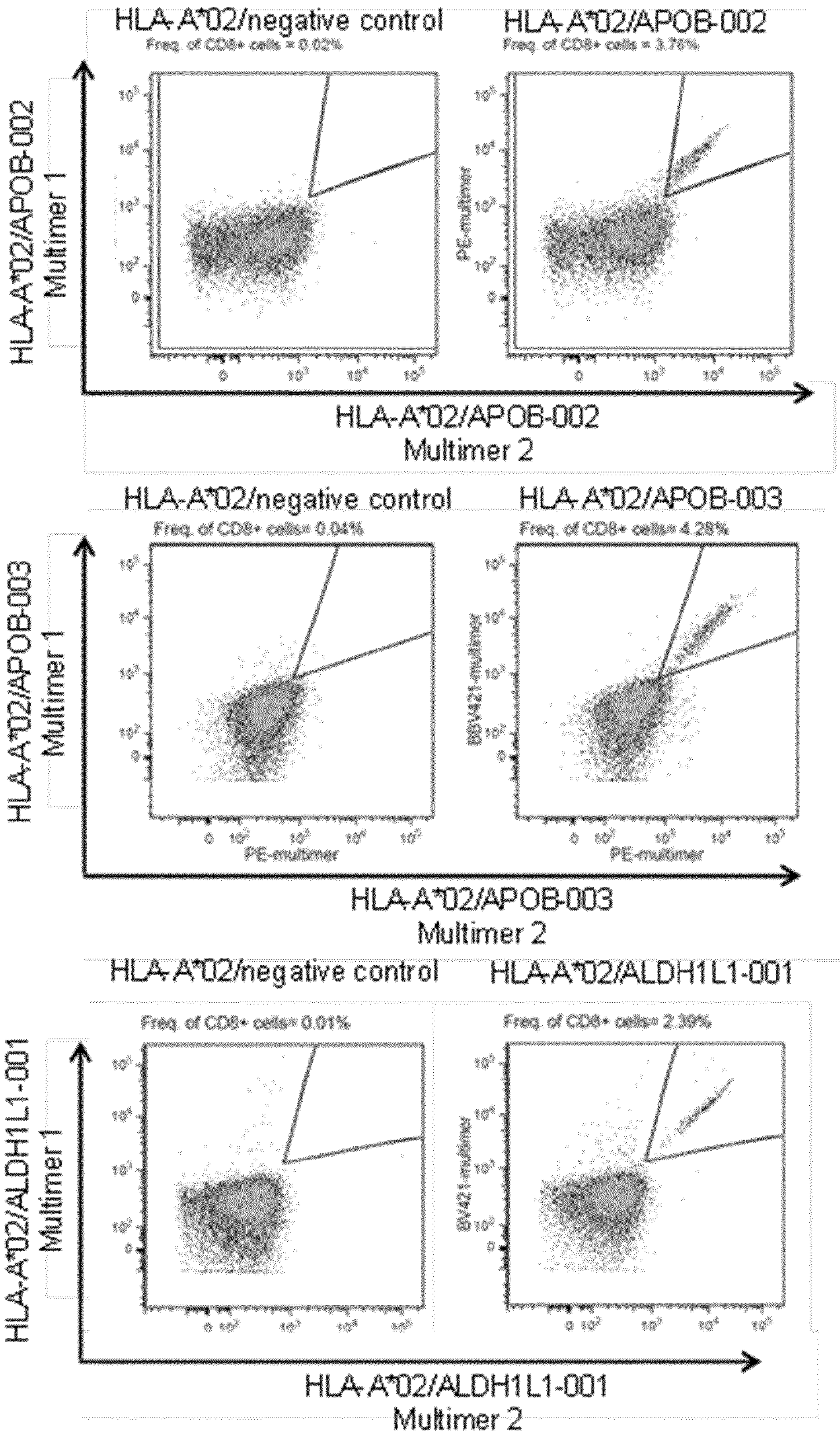
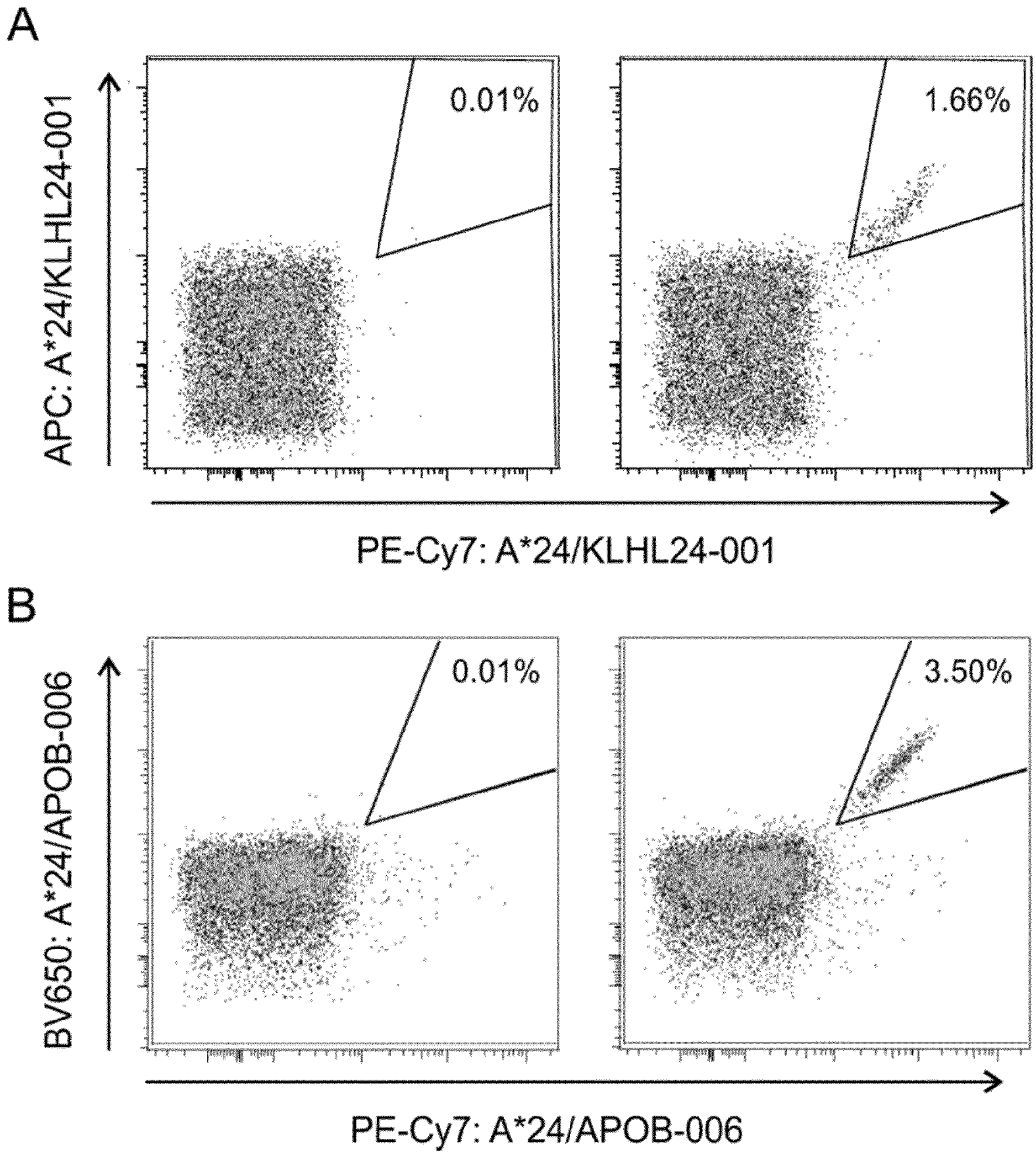

HLA-A*02/negative control
Freq. of CD8+ cells = 0.02%
HLA-A*02/APOB-002
Freq. of CD8+ cells = 3.78%
HLA-A*02/APOB-002 Multimer 1
PE-multimer
HLA-A*02/APOB-002 Multimer 2
HLA-A*02/negative control
Freq. of CD8+ cells= 0.04%
HLA-A*02/APOB-003
Freq. of CD8+ cells= 4.28%
HLA-A*02/APOB-003 Multimer 1
BV421-multimer
PE-multimer
HLA-A*02/APOB-003 Multimer 2
HLA-A*02/negative control
Freq. of CD8+ cells= 0.01%
HLA-A*02/ALDH1L1-001
Freq. of CD8+ cells= 2.39%
HLA-A*02/ALDH1L1-001 Multimer 1
BV421-multimer
HLA-A*02/ALDH1L1-001 Multimer 2

Figure 4


A
0.01%
1.66%
APC: A*24/KLHL24-001
PE-Cy7: A*24/KLHL24-001
B
0.01%
3.50%
BV650: A*24/APOB-006
PE-Cy7: A*24/APOB-006

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This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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