



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION
(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2018/01/26
(87) Date publication PCT/PCT Publication Date: 2018/08/02
(85) Entrée phase nationale/National Entry: 2019/06/21
(86) N° demande PCT/PCT Application No.: EP 2018/051952
(87) N° publication PCT/PCT Publication No.: 2018/138257
(30) Priorités/Priorities: 2017/01/27 (US62/451,255);
2017/01/27 (DE10 2017 101 671.6)

(51) Cl.Int./Int.Cl. *A61K 39/00* (2006.01),
C07K 14/47 (2006.01), *C07K 14/705* (2006.01),
C07K 7/06 (2006.01), *C07K 7/08* (2006.01)
(71) Demandeur/Applicant:
IMMATICS BIOTECHNOLOGIES GMBH, DE
(72) Inventeurs/Inventors:
SCHUSTER, HEIKO, DE;
PEPER, JANET, DE;
ROHLE, KEVIN, DE;
WAGNER, PHILIPP, DE;
RAMMENSEE, HANS-GEORG, DE
(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : NOUVEAUX PEPTIDES ET COMBINAISON DE PEPTIDES A UTILISER EN IMMUNOTHERAPIE CONTRE LE
CANCER DE L'OVAIRE ET D'AUTRES CANCERS
(54) Title: NOVEL PEPTIDES AND COMBINATION OF PEPTIDES FOR USE IN IMMUNOTHERAPY AGAINST
OVARIAN CANCER AND OTHER CANCERS

(57) **Abrégé/Abstract:**

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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2018/138257 A1

(43) International Publication Date
02 August 2018 (02.08.2018)

(51) International Patent Classification:

A61K 39/00 (2006.01) *C07K 7/06* (2006.01)
C07K 14/705 (2006.01) *C07K 7/08* (2006.01)
C07K 14/47 (2006.01)

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/EP2018/051952

(22) International Filing Date:

26 January 2018 (26.01.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10 2017 101 671.6
27 January 2017 (27.01.2017) DE
62/451,255 27 January 2017 (27.01.2017) US

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(71) Applicant: IMMATICS BIOTECHNOLOGIES GMBH
[DE/DE]; Paul-Ehrlich-Strasse 15, 72076 Tübingen (DE).

(72) Inventors: SCHUSTER, Heiko; Dorfackerstrasse 22, 72074 Tübingen (DE). PEPPER, Janet; Friedrich-Schaal-Strasse 6, 72074 Tübingen (DE). RÖHLE, Kevin; Eberhardstrasse 25, 72072 Tübingen (DE). WAGNER, Philipp; Bopserstrasse 2, 70180 Stuttgart (DE). RAMMENSEE, Hans-Georg; Sommerhalde 3, 72070 Unterjesingen (DE).

(74) Agent: BOEHMERT & BOEHMERT; Jan B. KRAUSS, Pettenkofferstrasse 20 - 22, 80336 Munich (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

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(57) Abstract: 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.

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Novel peptides and combination of peptides for use in immunotherapy against ovarian cancer and other cancers

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.

The present invention relates to several novel peptide sequences and their variants derived from HLA class I and HLA 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

Ovarian cancer

With an estimated 239 000 new cases in 2012, ovarian cancer is the seventh most common cancer in women, representing 4% of all cancers in women. The fatality rate of ovarian cancer tends to be rather high relative to other cancers of the female reproductive organs, and case fatality is higher in lower-resource settings. Therefore, ovarian cancer is the eighth most frequent cause of cancer death among women, with 152 000 deaths. In 2012, almost 55% of all new cases occurred in countries with high or very high levels of human development; 37% of the new cases and 39% of the deaths occurred in Europe and North America. Incidence rates are highest in northern and eastern Europe, North America, and Oceania, and tend to be relatively low in Africa and

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much of Asia. Incidence rates have been declining in certain countries with very high levels of human development, notably in Europe and North America.

The most common ovarian cancers are ovarian carcinomas, which are also the most lethal gynecological malignancies. Based on histopathology and molecular genetics, ovarian carcinomas are divided into five main types: high-grade serous (70%), endometrioid (10%), clear cell (10%), mucinous (3%), and low-grade serous carcinomas (< 5%), which together account for more than 95% of cases. Much less common are malignant germ cell tumors (dysgerminomas, yolk sac tumors, and immature teratomas) (3% of ovarian cancers) and potentially malignant sex cord stromal tumors (1–2%), the most common of which are granulosa cell tumors.

Ovarian carcinomas most commonly affect nulliparous women and occur least frequently in women with suppressed ovulation, typically by pregnancy or oral contraceptives. These tumors are generally considered to originate from the cells covering the ovarian surface or the pelvic peritoneum. Malignant transformation of this mesothelium has been explained by the “incessant ovulation” theory (La, 2001).

Family history of ovarian cancer accounts for 10% of cases; the risk is increased 3-fold when two or more first-degree relatives have been affected. Women with germline mutations in BRCA1 or BRCA2 have a 30–70% risk of developing ovarian cancer, mainly high-grade serous carcinomas, by age 70 (Risch et al., 2006).

Surgical resection is the primary therapy in early as well as advanced stage ovarian carcinoma. The ultimate goal is the complete removal of the tumor mass in healthy surrounding tissue. Surgical removal is followed by systemic chemotherapy with platinum analogs, except for very low grade ovarian cancers (stage IA, grade 1), where post-operative chemotherapy is not indicated. In advanced stage, ovarian cancer, the first line chemotherapy comprises a combination of carboplatin with paclitaxel, which can be supplemented with bevacizumab. The standard treatment for platinum-resistant ovarian cancers consists of a monotherapy with one of the following chemotherapeutics:

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pegylated liposomal doxorubicin, topotecane, gemcitabine or paclitaxel (S3-Leitlinie maligne Ovarialtumore, 2013).

Immunotherapy appears to be a promising strategy to ameliorate the treatment of ovarian cancer patients, as the presence of pro-inflammatory tumor infiltrating lymphocytes, especially CD8-positive T cells, correlates with good prognosis and T cells specific for tumor-associated antigens can be isolated from cancer tissue.

Therefore, a lot of scientific effort is put into the investigation of different immunotherapies in ovarian cancer. A considerable number of pre-clinical and clinical studies has already been performed and further studies are currently ongoing. Clinical data are available for cytokine therapy, vaccination, monoclonal antibody treatment, adoptive cell transfer and immunomodulation.

Cytokine therapy with interleukin-2, interferon-alpha, interferon-gamma or granulocyte-macrophage colony stimulating factor aims at boosting the patient's own anti-tumor immune response and these treatments have already shown promising results in small study cohorts.

Phase I and II vaccination studies, using single or multiple peptides, derived from several tumor-associated proteins (Her2/neu, NY-ESO-1, p53, Wilms tumor-1) or whole tumor antigens, derived from autologous tumor cells revealed good safety and tolerability profiles, but only low to moderate clinical effects.

Monoclonal antibodies that specifically recognize tumor-associated proteins are thought to enhance immune cell-mediated killing of tumor cells. The anti-CA-125 antibodies oregovomab and abagovomab as well as the anti-EpCAM antibody catumaxomab achieved promising results in phase II and III studies. In contrast, the anti-MUC1 antibody HMFG1 failed to clearly enhance survival in a phase III study.

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An alternative approach uses monoclonal antibodies to target and block growth factor and survival receptors on tumor cells. While administration of trastuzumab (anti-HER2/neu antibody) and MOv18 and MORAb-003 (anti-folate receptor alpha antibodies) only conferred limited clinical benefit to ovarian cancer patients, addition of bevacizumab (anti-VEGF antibody) to the standard chemotherapy in advanced ovarian cancer appears to be advantageous.

Adoptive transfer of immune cells achieved heterogeneous results in clinical trials. Adoptive transfer of autologous, *in vitro* expanded tumor infiltrating T cells was shown to be a promising approach in a pilot trial. In contrast, transfer of T cells harboring a chimeric antigen receptor specific for folate receptor alpha did not induce a significant clinical response in a phase I trial. Dendritic cells pulsed with tumor cell lysate or tumor-associated proteins *in vitro* were shown to enhance the anti-tumor T cell response upon transfer, but the extent of T cell activation did not correlate with clinical effects. Transfer of natural killer cells caused significant toxicities in a phase II study.

Intrinsic anti-tumor immunity as well as immunotherapy are hampered by an immunosuppressive tumor microenvironment. To overcome this obstacle immunomodulatory drugs, like cyclophosphamide, anti-CD25 antibodies and pegylated liposomal doxorubicin are tested in combination with immunotherapy. Most reliable data are currently available for ipilimumab, an anti-CTLA4 antibody, which enhances T cell activity. Ipilimumab was shown to exert significant anti-tumor effects in ovarian cancer patients (Mantia-Smaldone et al., 2012).

Considering the severe side-effects and expense associated with treating cancer, there is a need to identify factors that can be used in the treatment of cancer in general and ovarian cancer in particular. There is also a need to identify factors representing biomarkers for cancer in general and ovarian cancer in particular, leading to better diagnosis of cancer, assessment of prognosis, and prediction of treatment success.

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Immunotherapy of cancer represents an option of specific targeting of cancer cells while minimizing side effects. Cancer immunotherapy makes use of the existence of tumor associated antigens.

The current classification of tumor associated antigens (TAAs) 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 and NY-ESO-1.
- b) Differentiation antigens: These TAAs are shared between tumors and the normal tissue from which the tumor arose. Most of the known differentiation antigens are found in melanomas and normal melanocytes. Many of these melanocyte lineage-related proteins are involved in 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) Over-expressed 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 over-expression 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

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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.

T-cell based immunotherapy targets peptide epitopes derived from tumor-associated or tumor-specific proteins, which are presented by molecules of the major histocompatibility complex (MHC). The antigens that are recognized by the tumor specific 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.

There are two classes of MHC-molecules, MHC class I and MHC class II. MHC class I molecules are composed of an alpha heavy chain and beta-2-microglobulin, MHC class II molecules of an alpha and a beta chain. 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

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ribosomal products (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 the literature (Brossart and Bevan, 1997; Rock et al., 1990). 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 e.g. during endocytosis, and are subsequently processed.

Complexes of peptide and MHC class I are recognized by CD8-positive T cells bearing the appropriate T-cell receptor (TCR), 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.

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 al., 2006) and attract effector cells, e.g. CTLs, natural killer (NK) cells, macrophages, and granulocytes (Hwang et al., 2007).

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).

Elongated (longer) peptides of the invention can act as MHC class II active epitopes.

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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.

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 (IFN γ) (Beatty and Paterson, 2001; Mumberg et al., 1999). There is evidence for CD4 T cells as direct anti-tumor effectors (Braumuller et al., 2013; Tran et al., 2014).

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 previously 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).

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.

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

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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.

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).

For proteins to be recognized by 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 up-regulated and 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.

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.

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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 usually 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. 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 embodiment of the invention 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").

In case of targeting peptide-MHC by specific TCRs (e.g. soluble TCRs) and antibodies or other binding molecules (scaffolds) according to the invention, the immunogenicity of the underlying peptides is secondary. In these cases, the presentation is the determining factor.

SUMMARY OF THE INVENTION

In a first aspect of the present invention, the present invention relates to a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 772 or a variant sequence thereof which is at least 77%, preferably at least 88%, homologous (preferably at least 77% or at least 88% identical) to SEQ ID NO: 1 to SEQ ID NO: 772, 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.

The present invention further relates to a peptide of the present invention comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 772 or a variant thereof, which is at least 77%, preferably at least 88%, homologous (preferably at least 77% or at least 88% identical) to SEQ ID NO: 1 to SEQ ID NO: 772, 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.

The following tables show the peptides according to the present invention, their respective SEQ ID NOs, and the prospective source (underlying) genes for these peptides. In Table 1, peptides with SEQ ID NO: 1 to SEQ ID NO: 9 bind to HLA-A*02, peptides with SEQ ID NO: 10 to SEQ ID NO: 19 bind to HLA-A*24, peptides with SEQ ID NO: 20 to SEQ ID NO: 30 bind to HLA-A*03, peptide with SEQ ID NO: 31 binds to HLA-A*01, peptides with SEQ ID NO: 32 to SEQ ID NO: 41 bind to HLA-B*07, peptides with SEQ ID NO: 42 to SEQ ID NO: 51 bind to HLA-B*08, peptides with SEQ ID NO: 52 to SEQ ID NO: 59 bind to HLA-B*44. In Table 2, peptides with SEQ ID NO: 60 to SEQ ID NO: 75 bind to HLA-A*02, peptides with SEQ ID NO: 76 to SEQ ID NO: 82 bind to HLA-A*24, peptides with SEQ ID NO: 83 to SEQ ID NO: 111 bind to HLA-A*03, peptides with SEQ ID NO: 112 to SEQ ID NO: 116 bind to HLA-A*01, peptides with SEQ ID NO: 117 to SEQ ID NO: 149 bind to HLA-B*07, peptides with SEQ ID NO: 150 to SEQ ID NO: 172 bind to HLA-B*08, peptides with SEQ ID NO: 173 to SEQ ID NO: 215 bind to HLA-B*44. In Table 3, peptides with SEQ ID NO: 216 to SEQ ID NO: 245 bind to HLA-A*02, peptides with SEQ ID NO: 246 to SEQ ID NO: 255 bind to HLA-A*24, peptides with SEQ ID NO: 256 to SEQ ID NO: 287 bind to HLA-A*03, peptides with SEQ ID NO: 288 to SEQ ID NO: 292 bind to HLA-A*01, peptides with SEQ ID NO: 293 to SEQ ID NO: 392 bind to HLA-B*07, peptides with SEQ ID NO: 393 to SEQ ID NO: 395 bind to HLA-B*08, peptides with SEQ ID NO: 396 to SEQ ID NO: 438 bind to HLA-B*44. In Table 4, peptides with SEQ ID NO: 439 to SEQ ID NO: 551 bind to several HLA class I alleles, peptide with SEQ ID NO: 773 binds to HLA-A*02, peptide with SEQ ID NO: 774 binds to HLA-A*24. In Table 5, peptides with SEQ ID NO: 552 to SEQ ID NO: 772 bind to several HLA class II alleles.

Table 1: Peptides according to the present invention.

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
1	MIPTFTALL	LILRB4	Q8NHJ6	A*02
2	TLLKALLEI	IDO1	P14902	A*02
3	ALIYNLVGI	ATP7A, ATP7B, CTAGE1	P35670	A*02
4	ALFKAWAL	IRF4	Q15306	A*02
5	RLLDFINVL	OVGP1	Q12889	A*02
6	SLGKHTVAL	OVGP1	Q12889	A*02
7	ALQAFEFR V	PCDHB5, PCDHB15, PCDHB11, PCDHB10, PCDHB9, PCDHB8, PCDHB7, PCDHB4, PCDHB3, PCDHB2, PCDHB16	Q9Y5E7	A*02
8	YLVTKVVAV	PCDHGA12, PCDHB5, PCDHB1, PCDHB18, PCDHGB7, PCDHGB6, PCDHGB5, PCDHGB3, PCDHGB2, PCDHGB1, PCDHGA11, PCDHGA10, PCDHGA9, PCDHGA7, PCDHGA6, PCDHGA5, PCDHGA4, PCDHGA3, PCDHGA2, PCDHGA1, PCDHGB8P, PCDHB15, PCDHB14, PCDHB13, PCDHB12, PCDHB11, PCDHB10, PCDHB9, PCDHB8, PCDHB7, PCDHB6, PCDHB4, PCDHB3, PCDHB2, PCDHB16, PCDHGB4, PCDHGA8	O60330, Q96TA0, Q9NRJ7, Q9UN66, Q9UN67, Q9UN71, Q9Y5E1, Q9Y5E2, Q9Y5E3, Q9Y5E4, Q9Y5E5, Q9Y5E6, Q9Y5E7, Q9Y5E8, Q9Y5E9, Q9Y5F0, Q9Y5F1, Q9Y5F2, Q9Y5F3, Q9Y5F8, Q9Y5F9, Q9Y5G0, Q9Y5G1, Q9Y5G2, Q9Y5G3, Q9Y5G4, Q9Y5G5, Q9Y5G6, Q9Y5G7, Q9Y5G8, Q9Y5G9, Q9Y5H0, Q9Y5H1, Q9Y5H2, Q9Y5H3, Q9Y5H4	A*02
9	VLLAGFKPP L	RNF17	Q9BXT8	A*02
10	RYSDSVGR VSF	CAPN13	Q6MZZ7	A*24
11	SYSDLHYG F	CAPN13	Q6MZZ7	A*24
12	KYEKIFEML	CT45A3, CT45A4, CT45A5, CT45A6, CT45A1, CT45A2	Q5DJT8	A*24
13	VYTFLSSTL	ESR1	P03372	A*24

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
14	FYFPTPTVL	FOLR1	P15328	A*24
15	VYHDDKQP TF	GXYLT2	A0PJZ3	A*24
16	IYSPQFSRL	MYO3B	Q8WXR4	A*24
17	RFTTMLSTF	OVGP1	Q12889	A*24
18	KYPVHIYRL	RAD54B	Q9Y620	A*24
19	KYVKVFHQ F	ZNF90, ZNF93, ZNF486	Q96H40	A*24
20	RMASPVNV K	C2orf88	Q9BSF0	A*03
21	AVRKPIVLK	CDCA5	Q96FF9	A*03
22	SLKERNPLK	CDH3	P22223	A*03
23	GMMKGGIR K	ESR1	P03372	A*03
24	SMYYPLQL K	GXYLT2	A0PJZ3	A*03
25	GTSPPSVE K	MUC16	Q8WXI7	A*03
26	RISEYLLEK	MYO3B	Q8WXR4	A*03
27	VLYGPAGL GK	NLRP2	Q9NX02	A*03
28	KTYETNLEI KK	NLRP7	Q8WX94	A*03
29	QQFLTALFY	NLRP7, NLRP2	Q8WX94	A*03
30	ALEVAHRLK	ZBTB12	Q9Y330	A*03
31	LLDEGAMLL Y	NLRP7	Q8WX94	A*01
32	SPNKGTLS V	BCAM	P50895	B*07
33	SPTFHLLTL	BCAM	P50895	B*07
34	LPRGPLASL L	CDH3	P22223	B*07
35	FPDNQRPA L	ETV4	P43268	B*07
36	APAAWLRS A	MMP11	P24347	B*07/B*55
37	RPLFQKSS M	MUC16	Q8WXI7	B*07
38	SPHPVTALL TL	MUC16	Q8WXI7	B*07
39	RPAPFEVV F	NXNL2	Q5VZ03	B*07

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
40	KPGTSYRV TL	SPON1	Q9HCB6	B*07
41	RVRSRISNL	TCEA1P2, TCEA1, TCEA2, TCEA3	Q15560	B*07
42	TLKVTSAL	BCAM	P50895	B*08
43	ALKARTVTF	CCR2, CCR5	P51681	B*08
44	LNKQKVTF	CTAGE4, CTAGE5	O15320	B*08
45	VGREKKLA L	CTAGE4, CTAGE5	O15320	B*08
46	DMKKAKEQ L	FUNDC2P2, FUNDC2P3, FUNDC2	Q9BWH2	B*08
47	MPNLRSVD L	LRRTM1	Q86UE6	B*08
48	DVKKKIKEV	MFN1	Q8IWA4	B*08
49	LPRLKAFMI	ST6GALNAC5	Q9BVH7	B*08
50	DMKYKNRV	TCEA1P2, TCEA1, TCEA2	Q15560	B*08
51	SLRLKNVQL	VTCN1	Q7Z7D3	B*08
52	AEFLLRIFL	CAPN13	Q6MZZ7	B*44
53	MEHPGKLL F	ESR1	P03372	B*44
54	AEITITTQTG Y	MUC16	Q8WXI7	B*44
55	HETETRTT W	MUC16	Q8WXI7	B*44
56	SEPDTTAS W	MUC16	Q8WXI7	B*44
57	QESDLRLFL	NLRP7, NLRP2	Q9NX02	B*44
58	GEMEQKQL	PNOC	Q13519	B*44
59	SENVTMKV V	VTCN1	Q7Z7D3	B*44

Table 2: Additional peptides according to the present invention.

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
60	GLLSLTSTL YL	BCAM	P50895	A*02
61	YMVHIQVTL	CD70	P32970	A*02
62	KVLGVNVM L	CRABP2	P29373	A*02
63	MMEEMIFN L	EYA2	O00167	A*02

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
64	FLDPDRHFL	FAM83H	Q6ZRV2	A*02
65	TMFLRETSL	GUCY1A2	P33402	A*02
66	GLLQELSSI	HTR3A	P46098	A*02
67	SLLLPSIFL	HTR3A	P46098	A*02
68	KLFDTQQFL	IRF4	Q15306	A*02
69	TTYEGSITV	MUC16	Q8WXI7	A*02
70	VLQGLLRSL	MUC16	Q8WXI7	A*02
71	YLEDTDRN L	NFE2L3	Q9Y4A8	A*02
72	YLTDLQVSL	NFE2L3	Q9Y4A8	A*02
73	FLIEELLFA	OVGP1	Q12889	A*02
74	SQSPSVSQ L	PRAME	P78395	A*02
75	KVVSVLYN V	VTCN1	Q7Z7D3	A*02
76	KYVAELSLL	CCNA1	P78396	A*24
77	RYGPVFTV	CYP2W1	Q8TAV3	A*24
78	SFAPRSAV F	HOXD9	P28356	A*24
79	SYNEHWNY L	LTBR	P36941	A*24
80	TAYMVSVA AF	SDK2	Q58EX2	A*24
81	VYNHTTRP L	SPINT1	O43278	A*24
82	SYFRGFTLI	SPON1	Q9HCB6	A*24
83	GTYAHTVN R	ALPI, ALPP, ALPPL2	P05187, P09923	A*03/A*31
84	KLQPAQTA AK	ALPP, ALPPL2	P05187	A*03
85	VLLGSLFSR K	BCL2L1	Q07817	A*03
86	VVLLGSLFS RK	BCL2L1	Q07817	A*03/A*31/ A*66
87	AVAPPTPA SK	CBX2	Q14781	A*03/A*11
88	VVHAVFALK	CCR5	P51681	A*03
89	RVAELLLLH	CDKN2A, CDKN2B	P42771, P42772	A*03
90	KVAGERYV YK	ETV1, ETV4, ETV5	P41161, P43268, P50549	A*03
91	RSLRYYYE K	ETV1, ETV4, ETV5	P43268	A*03

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Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
92	SVFPIENIY	EYA2	O00167	A*03
93	KILEEHTNK	FSBP, RAD54B	O95073	A*03
94	ATFERVLLR	GUCY1A2	P33402	A*03/A*11
95	QSMYYPLQ LK	GXYLT2	A0PJZ3	A*03
96	TAFGGFLK Y	LAMA1	P25391	A*03
97	TMLDVEGL FY	LAMA1	P25391	A*03
98	LLQPPPLLA R	MMP11	P24347	A*03
99	KVVDRWNE K	MRPL51	Q4U2R6	A*03
100	RLFTSPIMT K	MUC16	Q8WXI7	A*03
101	RVFTSSIKT K	MUC16	Q8WXI7	A*03
102	SVLTSSLVK	MUC16	Q8WXI7	A*03
103	TSRSVDEA Y	MUC16	Q8WXI7	A*03
104	VLADSVTTK	MUC16	Q8WXI7	A*03
105	RLFSWLVN R	MYO1B	Q8WXR4	A*03
106	AAFVPLLLK	NCAPD2	Q15021	A*03/A*11
107	RLQEWKAL K	PDCL2	Q8N4E4	A*03
108	VLYPVPLES Y	PRAME	P78395	A*03
109	KTFTIKRFL AK	RPL39L	Q96EH5	A*03
110	SAAPPSYF R	SPON1	Q9HCB6	A*03/A*11/ A*66
111	TLPQFREL GY	WNT7A	O00755	A*03
112	TVTGAEQIQ Y	CAPN13	Q6MZZ7	A*01
113	QLDSNRLT Y	LRRTM1	Q86UE6	A*01
114	VMEQSAGI MY	LYPD1	Q8N2G4	A*01
115	FVDNQYWR Y	MMP12	P39900	A*01
116	VLLDEGAM	NLRP7	Q8WX94	A*01

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Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	LLY			
117	APRLLLLAV L	BCAM	P50895	B*07
118	SPASRSISL	CD70	P32970	B*07
119	APLPRPGA VL	CTAG2	O75638	B*07
120	RPAMNYDK L	ETV1, ETV4, ETV5, SPDEF	P43268	B*07
121	VPNQSSES L	EYA2	O00167	B*07/B*35
122	YPGFPQSQ Y	EYA2	O00167	B*07/B*35
123	KPSESIYSA L	FAM111B	Q6SJ93	B*07
124	LPSDSHFKI TF	FAM111B	Q6SJ93	B*07
125	VPVYILLDE M	FAM83H	Q6ZRV2	B*07/B*35
126	KPGPEDKL	FOLR1, FOLR2	P15328	B*07
127	APRAGSQV V	FUNDC2	Q9BWH2	B*07
128	YPRITITPGM	KLK14	Q9P0G3	B*07
129	APRPASSL	MMP11	P24347	B*07
130	FPRLVGPD F	MMP11	P24347	B*07
131	APTEDLKAL	MSLN	Q13421	B*07
132	IPGPAQSTI	MUC16	Q8WXI7	B*07
133	MPNLPSTT SL	MUC16	Q8WXI7	B*07
134	RPIVPGPLL	MUC16	Q8WXI7	B*07
135	RVRSTISSL	MUC16	Q8WXI7	B*07
136	SPFSAEEA NSL	MUC16	Q8WXI7	B*07
137	SPGATSRG TL	MUC16	Q8WXI7	B*07
138	SPMATTSTL	MUC16	Q8WXI7	B*07
139	SPQSMSNT L	MUC16	Q8WXI7	B*07
140	SPRTEASS AVL	MUC16	Q8WXI7	B*07
141	SPMTSLLTS GL	MUC16	Q8WXI7	B*07

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
142	TPGLRETSI	MUC16	Q8WXI7	B*07
143	SPAMTSTS F	MUC16	Q8WXI7	B*07/B*35
144	SPSPVSSTL	MUC16	Q8WXI7	B*07/B*35
145	SPSSPMST F	MUC16	Q8WXI7	B*07/B*35
146	IPRPEVQAL	PLEKHG4	Q58EX7	B*07
147	APRWFPQP TVV	VTCN1	Q7Z7D3	B*07
148	KPYGGSGP L	ZNF217	O75362	B*07
149	GPREALSR L	ZSCAN30, ZNF263, ZNF500, ZKSCAN4, ZNF323, ZKSCAN1, ZNF165, ZNF187, ZKSCAN3, ZNF397, ZSCAN12	O14978, O43309, O60304, P17029, P49910, Q16670, Q86W11, Q8NF99, Q969J2, Q96LW9, Q9BRR0	B*07
150	MAAVKQAL	BCL2L1	Q07817	B*08
151	HLLKVLAF	CCNA1	P78396	B*08
152	MGSARVAE L	CDKN2A, CDKN2B	P42771	B*08
153	NAMLRKVA V	CRABP1	P29762	B*08
154	MLRKIAVAA	CRABP2	P29373	B*08
155	NKKMMKRL M	DPPA2	Q7Z7J5	B*08
156	HVKEKFLL	FAM83H	Q6ZRV2	B*08
157	EAMKRLSYI	LAMC2	Q13753	B*08
158	LPKLAGLL	LINC00176	Q6ZNR8	B*08/B*07
159	VLKHKLDEL	MSLN	Q13421	B*08
160	YPKARLAF	MSLN	Q13421	B*08
161	ALKTTTTAL	DNAJC22, MUC16	Q8WXI7	B*08
162	QAKTHSTL	MUC16	Q8WXI7	B*08
163	QGLLRPVF	MUC16	Q8WXI7	B*08
164	SIKTKSAEM	MUC16	Q8WXI7	B*08
165	SPRFKTGL	MUC16	Q8WXI7	B*08
166	TPKLRETSI	MUC16	Q8WXI7	B*08
167	TSHERLTTL	MUC16	Q8WXI7	B*08
168	TSHERLTTY	MUC16	Q8WXI7	B*08
169	TSMPRSSA M	MUC16	Q8WXI7	B*08
170	YLLEKSRVI	MYO3B, MYH15, MYH6,	A7E2Y1, B0I1T2,	B*08

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
		MYH7, MYO1D, MYO3A, MYH7B	O94832, P12883, P13533, Q8NEV4, Q8WXR4, Q9Y2K3	
171	FAFRKEAL	OVGP1	Q12889	B*08
172	KLKERNRE L	OVGP1	Q12889	B*08
173	AEAQVGDE RDY	BCAM	P50895	B*44
174	AEATARLN VF	BCAM	P50895	B*44
175	AEIEPKADG	BCAM	P50895	B*44
176	AEIEPKADG SW	BCAM	P50895	B*44
177	TEVGTMNL F	BCAT1	P54687	B*44
178	NELFRDGV NW	BCL2L1	Q07817	B*44
179	REAGDEFEL	BCL2L1	Q07817	B*44
180	REAGDEFEL R	BCL2L1	Q07817	B*44
181	GEGPKTSW	CRABP2	P29373	B*44
182	KEATEAQS L	CTAGE4, CTAGE10P, CTAGE16P, CTAGE5, CTAGE1	Q96RT6	B*44/B*40
183	YKKGIMQK V	ETV1, ETV4, ETV5	P43268	B*44/B*49
184	AELEALTDL W	EYA2	O00167	B*44
185	AERQPGAA SL	FAM83H	Q6ZRV2	B*44
186	REGPEEPGL	FAM83H	Q6ZRV2	B*44
187	GEAQTRIA W	FOLR1	P15328	B*44
188	AEFAKKQP WW	FUNDC2	Q9BWH2	B*44
189	KEFLFNMY	HOXA9, HOXA10, HOXB9, HOXC9, HOXC10, HOXD9, HOXD10	P28356	B*44
190	YEVARILNL	HOXD9	P28356	B*44
191	EEDAALFKA	IRF4	Q15306	B*44

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	W			
192	YEFKFPNRL	LGALS1	P09382	B*44/B*18/ B*40
193	LEAQQEAL	MAGEA1, MRPL40	P43355	B*44
194	KEVDPTSH SY	MAGEA11	P43364	B*44
195	AEDKRHYS V	MFN1	Q8IWA4	B*44
196	REMPGGPV W	MMP12	P39900	B*44
197	AEVLLPRLV	MSLN	Q13421	B*44
198	QEAARAAL	MSLN	Q13421	B*44
199	REIDESLIFY	MSLN	Q13421	B*44
200	AESIPTVSF	MUC16	Q8WXI7	B*44
201	AETILTFHA F	MUC16	Q8WXI7	B*44
202	HESEATAS W	MUC16	Q8WXI7	B*44
203	IEHSTQAQD TL	MUC16	Q8WXI7	B*44
204	RETSTSEET SL	MUC16	Q8WXI7	B*44
205	SEITRIEM	MUC16	Q8WXI7	B*44
206	SESVTSRT SY	MUC16	Q8WXI7	B*44
207	TEARATSD SW	MUC16	Q8WXI7	B*44
208	TEVSRTEAI	MUC16	Q8WXI7	B*44
209	TEVSRTEL	MUC16	Q8WXI7	B*44
210	VEAADIFQN F	NXNL2	Q5VZ03	B*44
211	EEKVFPSPL W	PNOC	Q13519	B*44
212	MEQKQLQK RF	PNOC	Q13519	B*44
213	KESIPRWY Y	SPINT1	O43278	B*44
214	VEQTRAGS LL	TDRD5	Q8NAT2	B*44
215	SEDGLPEGI HL	ZNF217	O75362	B*44

Table 3: Additional peptides according to the present invention.

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
216	IMFDDAIER A	ALPP, ALPPL2	P05187	A*02
217	VSSSLTLKV	BCAM	P50895	A*02
218	TIASQRLTP L	CD70	P32970	A*02
219	PLPRPGAV L	CTAG2	O75638	A*02
220	RMTTQLLLL	FOLR1	P15328	A*02/B*13
221	SLLDLYQL	FTHL17	Q9BXU8	A*02/B*35
222	ALMRLIGCP L	GPC2	Q8N158	A*02
223	FAHHGRSL	IRF4	Q15306	A*02
224	SLPRFQVTL	IRF4	Q15306	A*02
225	SVFAHPRK L	MAGEA2B, MAGEA2, MAGEA6, MAGEA12	P43365	A*02
226	QVDPKKRIS M	MELK	Q14680	A*02
227	YTFRYPLSL	MMP11	P24347	A*02
228	RLWDWVPL A	MRPL51	Q4U2R6	A*02
229	ISVPAKTSL	MUC16	Q8WXI7	A*02
230	SAFREGTS L	MUC16	Q8WXI7	A*02
231	SVTESTHHL	MUC16	Q8WXI7	A*02
232	TISSLTHEL	MUC16	Q8WXI7	A*02
233	GSDTSSKS L	MUC16	Q8WXI7	A*02/B*14
234	GVATRVDAL	MUC16	Q8WXI7	A*02/B*14
235	SAIETSAVL	MUC16	Q8WXI7	A*02/B*35
236	SAIPFSMTL	MUC16	Q8WXI7	A*02/B*35
237	SAMGTISIM	MUC16	Q8WXI7	A*02/B*35
238	PLLVLFTI	MUC16	Q8WXI7	A*02/B*51
239	FAVPTGISM	MUC16	Q8WXI7	A*02/C*03
240	FSTDTSIVL	MUC16	Q8WXI7	A*02/C*03
241	RQPNILVHL	MUC16	Q8WXI7	A*02:05
242	STIPALHEI	MUC16	Q8WXI7	A*02:05
243	YASEGVKQ V	SPON1	Q9HCB6	A*02/B*51
244	DTDSSVHV QV	TENM4	Q6N022	A*02

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
245	LAVEGGQS L	UBXN8	O00124	A*02
246	RYLAVVHA VF	CCR5	P51681	A*24/A*23
247	ARPPWMW VL	KLK5	Q9Y337	A*24/B*27
248	SVIQHLGY	MSLN	Q13421	A*24
249	VYTPTLGTL	DNAJC22, MUC16	Q8WXI7	A*24
250	HFPEKTTH SF	MUC16	Q8WXI7	A*24/C*14
251	KQRQVLIF	PCDHB2	Q9Y5E7	A*24/B*15
252	LYQPRASE M	PNOC	Q13519	A*24/A*25
253	AYPEIEKF	PTTG2, PTTG1	O95997	A*24/C*04
254	IIQHLTEQF	STAG3	Q9UJ98	A*24/C*03
255	VFVSFSSLF	ZNF560	Q96MR9	A*24/B*27
256	RTEEVLLTF K	GPR64	Q8IZP9	A*03
257	VTADHSHV F	ALPI, ALPL, ALPP, ALPPL2	P05187	A*03
258	GAYAHTVN R	ALPPL2	P10696	A*03
259	KTLELRVAY	BCAM	P50895	A*03/A*32
260	GTNTVILEY	C2orf88	Q9BSF0	A*03
261	HTFGLFYQ R	FAM111B	Q6SJ93	A*03
262	RSRLNPLV QR	FAM83H	Q6ZRV2	A*03
263	SSSSATISK	HOXD3	P31249	A*03/A*11
264	AIKVIPTVFK	IDO1	P14902	A*03
265	QIHDHVNP K	IDO1	P14902	A*03/A*11
266	ISYSGQFLV K	IGF2BP1	Q9NZI8	A*03
267	VTDLISPRK	LAMA1	P25391	A*03
268	GLLGLSLRY	LRRTM1	Q86UE6	A*03/A*11/ A*29
269	RLKGDAWV YK	MELK	Q14680	A*03
270	AVFNPRFY RTY	MMP12	P39900	A*03/A*11
271	RMFADDLH	MRPL51	Q4U2R6	A*03

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	NLNK			
272	RQPERTILR PR	MSLN	Q13421	A*03
273	RVNAIPFTY	MSLN	Q13421	A*03/A*26
274	KTFPASTVF	MUC16	Q8WXI7	A*03
275	STTFPTLTK	MUC16	Q8WXI7	A*03
276	VSKTTGME F	MUC16	Q8WXI7	A*03
277	TTALKTTSR	DNAJC22, MUC16	Q8WXI7	A*03/A*66
278	NLSSITHER	MUC16	Q8WXI7	A*03/A*68
279	SVSSETTKI KR	MUC16	Q8WXI7	A*03/A*68
280	SVSGVKTT F	MUC16	Q8WXI7	A*03/B*15
281	RAKELEATF	NLRP7, NLRP2	Q9NX02	A*03
282	CLTRTGLFL RF	NLRP7, NLRP2	Q9NX02	A*03
283	IVQEPTEEK	PAGE2, PAGE2B	Q7Z2X7	A*03/A*11
284	KSLIKSWKK	TCEA1P2, TCEA1, TCEA2	P23193, Q15560	A*03/A*11
285	GTVNPTVG K	TENM4	Q6N022	A*03/A*11
286	TVAPPQGV VK	ZBTB12	Q9Y330	A*03/A*68
287	RRIHTGEKP YK	ZNF271, KLF8, ZNF816, ZFP28, ZSCAN29, ZNF597, ZNF480, ZNF714, ZNF836, ZNF600, ZNF320, ZNF100, ZNF721, ZNF841, ZNF678, ZNF860, ZNF429, ZNF888, ZNF761, ZNF701, ZNF83, ZNF695, ZNF471, ZNF22, ZNF28, ZNF137P, ZNF665, ZNF606, ZNF430, ZNF34, ZNF616, ZNF468, ZNF160, ZNF765, ZNF845	Q8IW36	A*03/A*11
288	SPVTSVHG GTY	LILRB4	Q8NHJ6	A*01/B*35

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
289	RWEKTDLT Y	MMP11	P24347	A*01
290	DMDEEIEAE Y	MYO3B	Q8WXR4	A*01/A*25
291	ETIRSVGY	TENM4	Q6N022	A*01/A*25
292	NVTMKVVS VLY	VTCN1	Q7Z7D3	A*01
293	VPDSGATA TAY	ALPP, ALPPL2	P05187	B*07/B*35
294	YPLRGSSIF	ALPP, ALPPL2	P05187	B*07/B*35
295	YPLRGSSIF GL	ALPP, ALPPL2	P05187	B*07/B*35
296	YPLRGSSI	ALPP, ALPPL2	P05187	B*51/B*07
297	TVREASGLL	BCAM	P50895	B*07
298	YPTEHVQF	BCAM	P50895	B*07/B*35
299	HPGSSALH Y	BCAT1	P54687	B*07/B*35
300	IPMAAVKQA L	BCL2L1	Q07817	B*07
301	SPRRSPRIS F	CDCA5	Q96FF9	B*07
302	RVEEVRALL	CDKN2A	P42771	B*07
303	LPMWKVTA F	CLDN6	P56747	B*07
304	LPRPGAVL	CTAG2	O75638	B*07
305	TPWAESST KF	DPEP3	Q9H4B8	B*07/B*35
306	APVIFSHSA	DPEP2, DPEP3	Q9H4B8	B*55/B*56/ B*07
307	LPYGPGE AAAF	ESR1	P03372	B*07/B*35
308	YPEGAAYE F	ESR1	P03372	B*07/B*35
309	FPQSQYPQ Y	EYA2	O00167	B*07/B*35
310	RPNPITIIL	FBN2	P35556	B*07
311	RPLFYVSL	HTR3A	P46098	B*07
312	LPYFREFS M	HTR3A	P46098	B*07/B*35
313	KVKSDRSV F	HTR3A	P46098	B*15/B*07
314	VPDQPHPEI	IRF4	Q15306	B*07/B*35

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
315	SPRENFPD TL	KLK8	O60259	B*07
316	EPKTATVL	LAMA1	P25391	B*42/B*07
317	FPFQPGSV	LGALS1	P09382	B*51/B*07
318	FPNRLNLEA	LGALS1	P09382	B*54/B*55/ B*07
319	SPAEPSVY ATL	LILRB4	Q8NHJ6	B*07
320	FPMSPVTS V	LILRB4	Q8NHJ6	B*07/B*51
321	SPMDTFLLI	LILRB4	Q8NHJ6	B*51/B*07
322	SPDPSKHLL	LRRK1	Q38SD2	B*07/B*35
323	RPMPNLRS V	LRRTM1	Q86UE6	B*55/B*07
324	VPYRVVGL	MEX3D, MEX3C, MEX3B, MEX3A	A1L020	B*51/B*07
325	GPRNAQRV L	MFN1	Q8IWA4	B*07
326	VPSEIDAAF	MMP11	P24347	B*07/B*35
327	SPLPVTSLI	MUC16	Q8WXI7	B*07
328	EPVTSSLPN F	MUC16	Q8WXI7	B*07/B*35
329	FPAMTESG GMIL	MUC16	Q8WXI7	B*07/B*35
330	FPFVTGSTE M	MUC16	Q8WXI7	B*07/B*35
331	FPHPEMTT SM	MUC16	Q8WXI7	B*07/B*35
332	FPHSEMTT L	MUC16	Q8WXI7	B*07/B*35
333	FPHSEMTT VM	MUC16	Q8WXI7	B*07/B*35
334	FPYSEVTTL	MUC16	Q8WXI7	B*07/B*35
335	HPDPVGPG L	MUC16	Q8WXI7	B*07/B*35
336	HPKTESAT PAAY	MUC16	Q8WXI7	B*07/B*35
337	HPVETSSAL	MUC16	Q8WXI7	B*07/B*35
338	HVTKTQAT F	MUC16	Q8WXI7	B*07/B*35
339	LPAGTTGSL VF	MUC16	Q8WXI7	B*07/B*35
340	LPEISTRM	MUC16	Q8WXI7	B*07/B*35

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
341	LPLDTSTTL	MUC16	Q8WXI7	B*07/B*35
342	LPLGTSMTF	MUC16	Q8WXI7	B*07/B*35
343	LPSVSGVK TTF	MUC16	Q8WXI7	B*07/B*35
344	LPTQTTSSL	MUC16	Q8WXI7	B*07/B*35
345	LPTSESLVS F	MUC16	Q8WXI7	B*07/B*35
346	LPWDTSTT LF	MUC16	Q8WXI7	B*07/B*35
347	MPLTTGSQ GM	MUC16	Q8WXI7	B*07/B*35
348	MPNSAIPFS M	MUC16	Q8WXI7	B*07/B*35
349	MPSLSEAM TSF	MUC16	Q8WXI7	B*07/B*35
350	NPSSTTTEF	MUC16	Q8WXI7	B*07/B*35
351	NVLTSTPAF	MUC16	Q8WXI7	B*07/B*35
352	SPAETSTN M	MUC16	Q8WXI7	B*07/B*35
353	SPAMTTPS L	MUC16	Q8WXI7	B*07/B*35
354	SPLPVTSL	MUC16	Q8WXI7	B*07/B*35
355	SPLVTSHIM	MUC16	Q8WXI7	B*07/B*35
356	SPNEFYFTV	MUC16	Q8WXI7	B*07/B*35
357	SPSPVPTTL	MUC16	Q8WXI7	B*07/B*35
358	SPSPVTSTL	MUC16	Q8WXI7	B*07/B*35
359	SPSTIKLTM	MUC16	Q8WXI7	B*07/B*35
360	SPSVSSNT Y	MUC16	Q8WXI7	B*07/B*35
361	SPTHVTQS L	MUC16	Q8WXI7	B*07/B*35
362	SPVPVTSLF	MUC16	Q8WXI7	B*07/B*35
363	TAKTPDATF	MUC16	Q8WXI7	B*07/B*35
364	TPLATTQRF	MUC16	Q8WXI7	B*07/B*35
365	TPLATTQRF TY	MUC16	Q8WXI7	B*07/B*35
366	TPLTTTGSA EM	MUC16	Q8WXI7	B*07/B*35
367	TPSVVTEG F	MUC16	Q8WXI7	B*07/B*35
368	VPTPVFPT M	MUC16	Q8WXI7	B*07/B*35

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
369	FPHSEMTT V	MUC16	Q8WXI7	B*07/B*35/ B*51
370	PGGTRQSL	MUC16	Q8WXI7	B*14:02/B* 07
371	LYVDGFTH W	MUC16	Q8WXI7	B*35/B*55/ B*07
372	IPRNPPPTL L	MYO3B	Q8WXR4	B*07
373	RPRALRDL RIL	NLRP7, NLRP2	Q9NX02	B*07
374	NPIGDTGVK F	NLRP7	Q8WX94	B*07/B*35
375	AAASPLLLL	NMU	P48645	B*07
376	RPRSPAGQ VA	NMU	P48645	B*07/B*55
377	RPRSPAGQ VAAA	NMU	P48645	B*07/B*55
378	RPRSPAGQ VAA	NMU	P48645	B*07/B*56
379	GPFPLVYVL	OVGP1	Q12889	B*07/B*35
380	IPTYGRTF	OVGP1	Q12889	B*07/B*35
381	LPEQTPLAF	OVGP1	Q12889	B*07/B*35
382	SPMHDRWT F	OVGP1	Q12889	B*07/B*35
383	TPTKETVSL	OVGP1	Q12889	B*07/B*35
384	YPGLRGSP M	OVGP1	Q12889	B*07/B*35
385	SPALHIGSV	PCDHB5, PCDHB18, PCDHB17, PCDHB15, PCDHB14, PCDHB11, PCDHB10, PCDHB9, PCDHB8, PCDHB6, PCDHB4, PCDHB3, PCDHB2, PCDHB16	Q96TA0, Q9NRJ7, Q9UN66, Q9UN67, Q9Y5E1, Q9Y5E3, Q9Y5E4, Q9Y5E5, Q9Y5E6, Q9Y5E7, Q9Y5E8, Q9Y5E9, Q9Y5F2	B*07
386	FPFNPLDF	PTTG1	Q95997	B*07/B*35
387	APLKLSRTP A	SPON1	Q9HCB6	B*07/B*55
388	SPAPLKLSR TPA	SPON1	Q9HCB6	B*07/B*55/ B*56
389	SPGAQRTF FQL	STAG3, STAG3L3, STAG3L2, STAG3L1	P0CL83, Q9UJ98	B*07
390	NPDLRRNV L	TCEA2	Q15560	B*07

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
391	APSTPRITTF	TCEA2	Q15560	B*07
392	KPIESTLVA	TMEM158	Q8WZ71	B*07/B*55
393	ASKPHVEI	CRABP1	P29762	B*08
394	MYKMKKPI	MAGEB3	O15480	B*08
395	VLLPRLVSC	MSLN	Q13421	B*08/A*02
396	REASGLLSL	BCAM	P50895	B*44
397	REGDTVQLL	BCAM	P50895	B*44
398	SFEQVVNELF	BCL2L1	Q07817	B*44
399	RELLHLVTL	CAPN13	Q6MZZ7	B*44/B*37
400	GEIEIHLL	CCDC146	Q8IYE0	B*44/B*40
401	EDLKEELL	CPXCR1	Q8N123	B*44/B*18
402	RELANDELI	CRABP1	P29762	B*44
403	EEAQWVRKY	FAM111B	Q6SJ93	B*44
404	NEAIMHQY	FAM111B	Q6SJ93	B*44/B*18
405	NEIWTHSY	FOLR1	P15328	B*44/B*18
406	EDGRLVIEF	FRAS1	Q86XX4	B*44/B*18
407	AEHEGVSVL	GXYLT2	A0PJZ3	B*44
408	LEKALQVF	IDO1	P14902	B*44
409	REFVLSKGDAGL	IDO1	P14902	B*44
410	SEDPSKLEA	IDO1	P14902	B*44
411	LELPPILVY	IDO1	P14902	B*44/B*18
412	QEILTQVKQ	IGF2BP3	O00425	B*44/B*40
413	IEALSGKIEL	IGF2BP3	O00425	B*44/B*45
414	EDAALFKA W	IRF4	Q15306	B*44
415	REEDAALF KAW	IRF4	Q15306	B*44
416	SEEETRVVF	MELK	Q14680	B*44
417	AEHFSMIRA	MEX3C, MEX3B, MEX3A	A1L020, Q5U5Q3, Q6ZN04	B*44/B*50
418	FEDAQGH W	MMP11	P24347	B*44
419	HEFGHVLG	MMP11	P24347	B*44/B*40

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	L			
420	FESHSTVS A	MUC16	Q8WXI7	B*44
421	GEPATTVSL	MUC16	Q8WXI7	B*44
422	SETTFSLIF	MUC16	Q8WXI7	B*44
423	SEVPTGTT A	MUC16	Q8WXI7	B*44
424	TEFPLFSAA	MUC16	Q8WXI7	B*44
425	SEVPLPMAI	MUC16	Q8WXI7	B*44/B*18
426	PEKTTHSF	MUC16	Q8WXI7	B*44/C*04: 01
427	HESSSHHD L	NFE2L3	Q9Y4A8	B*44
428	LDLGLNHI	NLRP2	Q9NX02	B*44/B*47
429	REKFIASVI	OVGP1	Q12889	B*44
430	DEKILYPEF	OVGP1	Q12889	B*44/B*18
431	AEQDPDEL NKA	POMZP3, ZP3	P21754, Q6PJE2	B*44/B*41
432	EEQYIAQF	PRAME	P78395	B*44/B*18
433	SDSQVRAF	STAG1, STAG3, STAG2	Q8N3U4, Q8WVM7, Q9UJ98	B*44/B*37
434	KEAIREHQ M	TCEA1P2, TCEA1, TCEA2	P23193, Q15560	B*44/B*41
435	REEFVSIDH L	TMPRSS3	P57727	B*44
436	REPGDIFSE L	WISP3	O95389	B*44
437	TEAVVTNEL	XPR1	Q9UBH6	B*44
438	SEVDSPNV L	ZNF217	O75362	B*44

Table 4: HLA Class I peptides according to the present invention.

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
439	EALAKLMSL	ATP7B	P35670	B*51
440	ELFEGLKAF	BCAT1	P54687	A*25
441	HQITEVGT M	BCAT1	P54687	B*15
442	ILSKLTDIQY	BCAT1	P54687	B*15
443	GTFNPVSL W	BCAT1	P54687	B*58

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
444	KLSQKGYSW	BCL2L1	Q07817	A*32
445	LHITPGTAY	BCL2L1	Q07817	B*13
446	GRIVAFFSF	BCL2L1	Q07817	B*27
447	MQVLVSRI	BCL2L1	Q07817	B*52/B*13
448	LSQKGYSW	BCL2L1	Q07817	B*57
449	RAFSDLTS QL	BCL2L1	Q07817	C*15
450	KQTFPFPTI	C2orf88	Q9BSF0	B*13
451	DYLNEWGS RF	CDH3	P22223	A*23
452	LKVLGVNV M	CRABP2	P29373	C*07
453	DVKLEKPK	DPPA2	Q7Z7J5	A*68
454	AQTDPTTG Y	LOXL2, ENTPD4	Q9Y4K0	B*15
455	AAAANAQV Y	ESR1	P03372	B*35
456	IPLERPLGE VY	ESR1	P03372	B*35
457	NAAAAANA QVY	ESR1	P03372	B*35
458	TDTLIHLM	ESR1	P03372	B*37
459	KVAGERYV Y	ETV1, ETV4, ETV5	P41161, P43268, P50549	A*32/A*31
460	RLSSATAN ALY	FAM83H	Q6ZRV2	A*26
461	AQRMTTQL L	FOLR1	P15328	B*15
462	QRMTTQLL L	FOLR1	P15328	B*27/C*07
463	VNQSLLDLY	FTHL17	Q9BXU8	A*26
464	MSALRPLL	GPC2	Q8N158	C*15
465	DLIESGQLR	IDO1	P14902	A*66
466	DLIESGQLR ER	IDO1	P14902	A*66
467	MQMQERD TL	IDO1	P14902	B*15
468	ALAKLLPL	KLK10	O43240	B*35
469	QEQSSVVR A	KLK6	Q92876	B*45
470	QGERLLGA	LAG3	P18627	C*03

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	AV			
471	AQRLDPVY F	LAMC2	Q13753	B*15
472	MRLLVAPL	LRRN2	O75325	B*14
473	MLNNNALS AL	LRRN2	O75325	B*35
474	AADGGLRA SVTL	LY6E	Q16553	C*05
475	GRDPTSYP SL	MAGEA11	P43364	B*39
476	ISYPPLHEW	MAGEA3, MAGEA12	P43357	B*57
477	RIQQQTNT Y	MEX3A	A1L020	B*15
478	VVGPKGATI	MEX3D, MEX3C, MEX3B, MEX3A	A1L020, Q5U5Q3, Q6ZN04, Q86XN8	C*14
479	TEGSHFVE A	MFN1	Q8IWA4	B*45
480	GRADIMIDF	MMP11	P24347	B*27
481	GRWEKTDL TY	MMP11	P24347	B*27
482	GRWEKTDL TYR	MMP11	P24347	B*27
483	VRFPVHAA LVW	MMP11	P24347	B*27
484	AWLRSAAA	MMP11	P24347	B*56
485	VRFPVHAA L	MMP11	P24347	C*07
486	DRFFWLKV	MMP12	P39900	B*14
487	GMADILVVF	MMP12	P39900	B*15
488	RSFSLGVP R	MRPL51	Q4U2R6	A*31
489	EVSGLSTE R	MSLN	Q13421	A*68
490	AEVQKLLG P	MSLN	Q13421	B*50
491	EAYSSTSS W	MUC16	Q8WXI7	A*25
492	EVTPWISLT L	MUC16	Q8WXI7	A*25
493	DTNLEPVT R	MUC16	Q8WXI7	A*68
494	ETTASLVSR	MUC16	Q8WXI7	A*68
495	EVPSGATT	MUC16	Q8WXI7	A*68

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	EVSR			
496	EVPTGTTA EVSR	MUC16	Q8WXI7	A*68
497	EVS RTEVIS SR	MUC16	Q8WXI7	A*68
498	EVYPELGT QGR	MUC16	Q8WXI7	A*68
499	SSETTKIKR	MUC16	Q8WXI7	A*68
500	AHVLHSTL	MUC16	Q8WXI7	B*14
501	IQIEPTSSL	MUC16	Q8WXI7	B*14
502	SGDQGITSL	MUC16	Q8WXI7	B*14
503	TVFDKAFTA A	MUC16	Q8WXI7	B*14
504	TVSSVNQG L	MUC16	Q8WXI7	B*14
505	YVPTGAITQ A	MUC16	Q8WXI7	B*14
506	HQFITSTNT F	MUC16	Q8WXI7	B*15
507	TSIFSGQSL	MUC16	Q8WXI7	B*15
508	TVAKTTTTF	MUC16	Q8WXI7	B*15
509	GRGPGGVS W	MUC16	Q8WXI7	B*27
510	RRIPTEPTF	MUC16	Q8WXI7	B*27
511	SRIPQDVS W	MUC16	Q8WXI7	B*27
512	SRSPENPS W	MUC16	Q8WXI7	B*27
513	SRTEISSSR	MUC16	Q8WXI7	B*27
514	SRTEVASS R	MUC16	Q8WXI7	B*27
515	TRIEMESTF	MUC16	Q8WXI7	B*27
516	TASTPISTF	MUC16	Q8WXI7	B*35
517	TAETILTFH AF	MUC16	Q8WXI7	B*35
518	TSDFTPITV	MUC16	Q8WXI7	B*35
519	VTSL LTPG MV	MUC16	Q8WXI7	B*35
520	THSAMTHG F	MUC16	Q8WXI7	B*38
521	THSTASQG F	MUC16	Q8WXI7	B*38

Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
522	THSTISQGF	MUC16	Q8WXI7	B*38
523	APKGIPVKP TSA	MUC16	Q8WXI7	B*55
524	AVSPTVQGL	MUC16	Q8WXI7	C*07
525	QRFPHSEM	MUC16	Q8WXI7	C*07
526	SVPDILST	MUC16	Q8WXI7	C*07
527	QSTPYVNS V	MUC16	Q8WXI7	C*16
528	TRTGLFLRF	NLRP7, NLRP2	Q9NX02	B*27
529	PFSNPRVL	NLRP2	Q9NX02	C*04
530	MLPRAALL	NLRP7	Q8WX94	B*51
531	QGAQLRGA L	NLRP7, NLRP2	Q8WX94	B*52
532	AISFSYKAW	OVGP1	Q12889	A*25
533	GQHLHLET F	PRAME	P78395	B*15
534	CRPGALQIE L	RAD54B	Q9Y620	C*02
535	IKDVRKIK	RNF17	Q9BXT8	B*13
536	VQDQACVA KF	RNF17	Q9BXT8	B*15
537	IRRLKELKD Q	RPL37A, RPL37AP8	A6NKH3, P61513	n/a
538	QLEKALKEI	SAGE1	Q9NXZ1	C*05
539	IPIPSTGSV EM	SPINT1	O43278	B*35/B*42
540	AGIPAVALW	SPINT1	O43278	B*58
541	RLSPAPLKL	SPON1	Q9HCB6	B*13
542	QIIDEETQ F	SPON1	Q9HCB6	B*15
543	MRLSPAPL K	SPON1	Q9HCB6	B*27
544	LRNPSIQKL	SPON1	Q9HCB6	C*07
545	RVGPPLLI	TMEM158	Q8WZ71	B*15
546	GRAFFAAA F	TMEM158	Q8WZ71	B*27
547	EVNKPGRVY TR	TMPRSS3	P57727	A*68
548	VSEASLVSS I	ZBTB12	Q9Y330	C*05
549	ARSKLQQG	ZNF217	O75362	B*27

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Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
	L			
550	RRFKEPWF L	ZNF217, ZNF516, ZNF536	O15090, O75362, Q92618	B*27
551	RLHTGEKP YK	ZNF816, ZNF813, ZNF578, ZNF599, ZNF600, ZNF320, ZNF525, ZNF485, ZNF860, ZNF429, ZNF808, ZNF888, ZNF761, ZNF701, ZNF83, ZNF167, ZFP62, ZNF28, ZSCAN21, ZNF91, ZNF229, ZNF702P, ZNF528, ZNF468, ZNF765, ZNF845	A2RRD8, A6NHJ4, A6NK21, A6NK53, A6NK75, A6NN14, A6NNF4, A6NP11, A8MTY0, A8MUV8, B4DU55, B4DX44, B4DXR9, O14628, O14709, O15090, O43309, O43345, O43361, O75346, O75373, O75437, O75820, O95600, O95780, P0CB33, P0CJ79, P0DKX0, P10073, P17019, P17026, P17035, P17038, P17040, P17097, P35789, P51522, P51815, P52742, Q02386, Q03923, Q03924, Q03936, Q03938, Q05481, Q08AN1, Q09FC8, Q0VGE8, Q14584, Q14586, Q14590, Q14591, Q14593, Q15928, Q15929, Q15937, Q16587, Q2M3W8, Q2M3X9, Q2VY69, Q3KP31, Q3MIS6, Q3SXZ3, Q4V348, Q53GI3, Q5HY98, Q5JNZ3, Q5SXM1, Q5VIY5, Q5VV52, Q68DY1, Q6AZW8, Q6P280, Q6P9G9, Q6PDB4, Q6ZMV8, Q6ZMW2, Q6ZN06, Q6ZN08, Q6ZN19, Q6ZN57, Q6ZNA1,	A*30

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Seq ID No	Sequence	Gene	Uniprot Accession	HLA allotype
			Q6ZNG1, Q6ZR52, Q76KX8, Q7L2R6, Q7L945, Q7Z3V5, Q7Z7L9, Q86TJ5, Q86UE3, Q86V71, Q86XN6, Q86XU0, Q86Y25, Q8IW36, Q8IWy8, Q8IYN0, Q8IZ26, Q8N4W9, Q8N782, Q8N7Q3, Q8N823, Q8N859, Q8N8C0, Q8N8J6, Q8N972, Q8N988, Q8N9F8, Q8NB50, Q8NCK3, Q8NDQ6, Q8NEM1, Q8NF99, Q8NHY6, Q8TAQ5, Q8TBZ5, Q8TD23, Q8TF20, Q8TF32, Q8TF39, Q8WV37, Q8WXB4, Q96CX3, Q96IR2, Q96JC4, Q96LX8, Q96MR9, Q96N22, Q96N38, Q96N58, Q96NI8, Q96NL3, Q96PE6, Q96RE9, Q96SE7, Q99676, Q9BX82, Q9H5H4, Q9H7R5, Q9H8G1, Q9H963, Q9HBT7, Q9HCG1, Q9HCL3, Q9NQX6, Q9NV72, Q9P0L1, Q9P255, Q9P2F9, Q9P2J8, Q9UEG4, Q9UII5, Q9UJW7, Q9UL36, Q9Y2Q1, Q9Y473, Q9Y5A6	
773	ALYGKLLKL	VPS13B		A*02
774	VYVDDIYVI	CASC5		A*24

Table 5: HLA Class II peptides according to the present invention.

Seq ID No	Sequence	Additional Sequence variants	Gene
552	GVNAMLRLKVAVAAASKPHVE		CRABP 1
553		VNAMLRLKVAVAAASKPHVE	CRABP 1
554		GVNAMLRLKVAVAAASKPH	CRABP 1
555		VNAMLRLKVAVAAASKPH	CRABP 1
556		NAMLRLKVAVAAASKPH	CRABP 1
557		AMLRLKVAVAAASKPH	CRABP 1
558		LRKVAVAAASKPH	CRABP 1
559		RKVAVAAASKPH	CRABP 1
560	PNFSGNWKIIRSENFEELLK		CRABP 2
561		PNFSGNWKIIRSENFEELL	CRABP 2
562		GNWKIIRSENFEELLKVL	CRABP 2
563		PNFSGNWKIIRSENFEEL	CRABP 2
564		GNWKIIRSENFEELLKV	CRABP 2
565		NWKIIRSENFEELLKV	CRABP 2
566		NWKIIRSENFEELLK	CRABP 2
567		NWKIIRSENFEELL	CRABP 2
568		WKIIRSENFEELLK	CRABP 2
569		WKIIRSENFEELL	CRABP 2
570		GNWKIIRSENF	CRABP 2
571		PNFSGNWKIIR	CRABP 2
572	INFKVGEEFEEQTV		CRABP 2
573	RLLSADTKGWVRLQ		DPPA2

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Seq ID No	Sequence	Additional Sequence variants	Gene
574	LPDFYNDWMFIAKHLPDL		IDO1
575	VGDDHLLLLQGGEQLRRT		KLK10
576		VGDDHLLLLQGGEQLRR	KLK10
577		GDDHLLLLQGGEQLRR	KLK10
578		DDHLLLLQGGEQLRR	KLK10
579	SGGPLVCDETLQGILS		KLK10
580		GGPLVCDETLQGILS	KLK10
581		GGPLVCDETLQGIL	KLK10
582	GSQPWQVSLFNGLSFH		KLK10
583	LTVKLPDGYEFKFPNRLNLEAINY		LGALS1
584		TVKLPDGYEFKFPNRLNLEAINY	LGALS1
585		LTVKLPDGYEFKFPNRLNL	LGALS1
586		TVKLPDGYEFKFPNRLNL	LGALS1
587	DQANLTVKLPDGYEFKFPNRLNL		LGALS1
588	VAPDAKSFVLNLGKDSNNL		LGALS1
589		APDAKSFVLNLGKDSNNL	LGALS1
590	RVRGEVAPDAKSFVLNLG		LGALS1
591		VRGEVAPDAKSFVLNL	LGALS1
592		VRGEVAPDAKSFVLNLG	LGALS1
593		GEVAPDAKSFVLNLG	LGALS1
594		VRGEVAPDAKSFVLN	LGALS1
595		VRGEVAPDAKSFVL	LGALS1
596	MAADGDFKIKCVAFD		LGALS1
597	SPDAESLFREALSNKVDEL		MAGEA4
598		AESLFREALSNKVDEL	MAGEA4
599		AESLFREALSNKVDE	MAGEA4
600		FREALSNKVDE	MAGEA4
601	LSNKVDELAHFLLRK		MAGEA4
602	KDPVAWEAGMLMH		MAGEB1
603	KARDETRGLNVPQ		MAGEB2
604	KLITQDLVKLKYLEYRQ		MAGEB3
605	LTVAEVQKLLGPHVEGLKAEERH		MSLN

Seq ID No	Sequence	Additional Sequence variants	Gene
	RP		
606		LTVAEVQKLLGPHVEGLKAEE R	MSLN
607		LTVAEVQKLLGPHVEGLKAEE	MSLN
608		LTVAEVQKLLGPHVEGLKAE	MSLN
609		LTVAEVQKLLGPHVEGLKA	MSLN
610		LTVAEVQKLLGPHVEGLK	MSLN
611		LTVAEVQKLLGPHVEGL	MSLN
612		TVAEVQKLLGPHVEGLK	MSLN
613		LTVAEVQKLLGPHVEG	MSLN
614		TVAEVQKLLGPHVEGL	MSLN
615		VAEVQKLLGPHVEGLK	MSLN
616		TVAEVQKLLGPHVEG	MSLN
617		VAEVQKLLGPHVEGL	MSLN
618		VAEVQKLLGPHVEG	MSLN
619		VAEVQKLLGPHVE	MSLN
620		EVQKLLGPHVEG	MSLN
621		LTVAEVQKLLG	MSLN
622	MDALRGLLPVLGQPIIRSIPQGIVA		MSLN
623		ALRGLLPVLGQPIIRSIPQGIVA	MSLN
624		LRGLLPVLGQPIIRSIPQGIVA	MSLN
625		DALRGLLPVLGQPIIRSIPQG	MSLN
626		RGLLPVLGQPIIRSIPQGIVA	MSLN
627		ALRGLLPVLGQPIIRSIPQG	MSLN
628		DALRGLLPVLGQPIIRSIPQ	MSLN
629		GLLPVLGQPIIRSIPQGIVA	MSLN
630		ALRGLLPVLGQPIIRSIPQ	MSLN
631		DALRGLLPVLGQPIIRSIP	MSLN
632		LLPVLGQPIIRSIPQGIVA	MSLN
633		LRGLLPVLGQPIIRSIPQ	MSLN
634		DALRGLLPVLGQPIIRS	MSLN
635		ALRGLLPVLGQPIIRS	MSLN
636		DALRGLLPVLGQPIIR	MSLN
637		ALRGLLPVLGQPIIR	MSLN
638		LRGLLPVLGQPIIRS	MSLN
639		ALRGLLPVLGQPII	MSLN
640		ALRGLLPVLGQPI	MSLN
641		RGLLPVLGQPIIR	MSLN
642		GLLPVLGQPIIR	MSLN
643		LRGLLPVLGQPI	MSLN

Seq ID No	Sequence	Additional Sequence variants	Gene
644		RGLLPVLGQPI	MSLN
645	RGLLPVLGQPIIRSIPQGIVAAWRQ		MSLN
646		GLLPVLGQPIIRSIPQGIVAAWRQ	MSLN
647		LPVLGQPIIRSIPQGIVAAWRQ	MSLN
648		GLLPVLGQPIIRSIPQGIVAA	MSLN
649		LLPVLGQPIIRSIPQGIVAA	MSLN
650		LPVLGQPIIRSIPQGIVA	MSLN
651		LPVLGQPIIRSIPQGIVAA	MSLN
652		PVLGQPIIRSIPQGIVA	MSLN
653		LPVLGQPIIRSIPQGIVA	MSLN
654		PVLGQPIIRSIPQGIVA	MSLN
655		LGQPIIRSIPQGIVAA	MSLN
656		VLGQPIIRSIPQGIVA	MSLN
657		QPIIRSIPQGIVA	MSLN
658	VSTMDALRGLLPVLGQPIIRSIPQG		MSLN
659		VSTMDALRGLLPVLGQPIIRSI PQ	MSLN
660		VSTMDALRGLLPVLGQPIIR	MSLN
661		LRGLLPVLGQPIIRSIPQG	MSLN
662	LRTDAVLPLTVAEVQKLLGPHVEG		MSLN
663		RTDAVLPLTVAEVQKLLGPHVEG	MSLN
664		AVLPLTVAEVQKLLGPHVEG	MSLN
665		VLPLTVAEVQKLLGPHVEG	MSLN
666		LPLTVAEVQKLLGPHVEG	MSLN
667		TDAVLPLTVAEVQ	MSLN
668		AVLPLTVAEVQK	MSLN
669	VLPLTVAEVQKLLGPHVEGLKAE		MSLN
670		VLPLTVAEVQKLLGPHVEGLK	MSLN
671		LPLTVAEVQKLLGPHVEGLK	MSLN
672	LRGLLPVLGQPIIRSIPQGIVAA		MSLN
673	IPFTYEQLDVLKHKLDELYPQ		MSLN
674		IPFTYEQLDVLKHKLDE	MSLN
675		IPFTYEQLDVLKHKLD	MSLN
676	VPPSSIWAVRPQDLDTCDPR		MSLN
677		IWAVRPQDLDTCDPR	MSLN

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Seq ID No	Sequence	Additional Sequence variants	Gene
678		AVRPQDLDTCDPR	MSLN
679	WGVRGSLLSEADVRLGGLA		MSLN
680		GVRGSLLSEADVRLGGLA	MSLN
681		WGVRGSLLSEADVRLGGL	MSLN
682		GVRGSLLSEADVRLGGL	MSLN
683		VRGSLLSEADVRLGGLA	MSLN
684		WGVRGSLLSEADVRLGG	MSLN
685		GVRGSLLSEADVRLGG	MSLN
686		VRGSLLSEADVRLGGL	MSLN
687		WGVRGSLLSEADVRLG	MSLN
688		GVRGSLLSEADVRLG	MSLN
689		WGVRGSLLSEADVRL	MSLN
690		GSLLEADVRLGGL	MSLN
691		GVRGSLLSEADVRL	MSLN
692		RGSLLEADVRLGG	MSLN
693		WGVRGSLLSEADVRA	MSLN
694		GSLLEADVRLGG	MSLN
695		RGSLLEADVRLG	MSLN
696		WGVRGSLLSEADVRL	MSLN
697		GSLLEADVRLG	MSLN
698		VRGSLLSEADVRA	MSLN
699		LLSEADVRLGG	MSLN
700		SLLSEADVRLG	MSLN
701		GSLLEADVRA	MSLN
702		LLSEADVRLG	MSLN
703		LSEADVRLGG	MSLN
704		SEADVRLGG	MSLN
705		EADVRLGG	MSLN
706	LSTERVRELAVALAQKNVK		MSLN
707		LSTERVRELAVALAQKN	MSLN
708		ERVRELAVALAQKNVK	MSLN
709		LSTERVRELAVALAQK	MSLN
710		LSTERVRELAVALAQ	MSLN
711		STERVRELAVALAQK	MSLN
712		TERVRELAVALAQKN	MSLN
713		VRELAVALAQKNVK	MSLN
714	AIPFTYEQLDVLKHKLDE		MSLN
715	GLSTERVRELAVALAQKN		MSLN
716		GLSTERVRELAVALAQ	MSLN

Seq ID No	Sequence	Additional Sequence variants	Gene
717	IPQGIVAAWRQRSSRDPS		MSLN
718		GIVAAWRQRSSRDPS	MSLN
719		IPQGIVAAWRQRSSR	MSLN
720	ALGGLACDLPGRFVAES		MSLN
721	RELAVALAQKNVKLSTE		MSLN
722	LKALLEVNKGHEMSPQ		MSLN
723	TFMKLRTDAVLPLTVA		MSLN
724		FMKLRTDAVLPLTVA	MSLN
725		FMKLRTDAVLPLT	MSLN
726		FMKLRTDAVLPL	MSLN
727	TLGLGLQGGIPNGYLV		MSLN
728	DLPGRFVAESA EVLL		MSLN
729		DLPGRFVAESA EVL	MSLN
730		LPGRFVAESA EVL	MSLN
731		DLPGRFVAESA	MSLN
732	ERHRPV RDWILRQRQ		MSLN
733	SPRQLLGFP CAEVSG		MSLN
734	SRTLAGE TGQE AAPL		MSLN
735	VTSL ETLKALLEVNK		MSLN
736	LGLQGGIPNGYLV L		MSLN
737		LQGGIPNGYLV L	MSLN
738		GGIPNGYLV L	MSLN
739	LQGGIPNGYLV L DL		MSLN
740	APERQRLL PAALA		MSLN
741	FVKIQSFLGGAPT		MSLN
742		FVKIQSFLGG	MSLN
743		FVKIQSFLG	MSLN
744	FLKMSPEDIRK		MSLN
745	WELSQLTNSVTELGPYTLDRD		MUC16
746	EITITTQTGYSLATSQVTLP		MUC16
747	ATTPSWVETHSIVIQGFPH		MUC16
748	GIKELGPYTLDRNSLYVNG		MUC16
749		GIKELGPYTLDRNSL	MUC16
750		GPYTLDRNSLYVNG	MUC16
751		GIKELGPYTLDRN	MUC16
752		LGPYTLDRNSLYV	MUC16
753		LGPYTLDRNSLY	MUC16
754		LGPYTLDRNSL	MUC16
755	IELGPYLLDRGSLYVNG		MUC16

Seq ID No	Sequence	Additional Sequence variants	Gene
756		LGPYLLDRGSLYVNG	MUC16
757		LGPYLLDRGSLYVN	MUC16
758		LGPYLLDRGSLYV	MUC16
759	EELGPYTLDRNSLYVNG		MUC16
760	LKPLFKSTSVGPLYSG		MUC16
761		LKPLFKSTSVGPLYS	MUC16
762		LKPLFKSTSVGPLY	MUC16
763		LKPLFKSTSVGPL	MUC16
764	FDKAFTAATTEVSRTE		MUC16
765	ELGPYTLDRDSLYVN		MUC16
766	GLLKPLFKSTSVGPL		MUC16
767		LLKPLFKSTSVGPL	MUC16
768	SDPYKATSAVVITST		MUC16
769		SDPYKATSAVVITS	MUC16
770	SRKFNTMESVLQGLL		MUC16
771		SRKFNTMESVLQG	MUC16
772	LGFYVLDRDSLFIN		MUC16

The present invention furthermore generally relates to the peptides according to the present invention for use in the treatment of proliferative diseases, such as, for example, hepatocellular carcinoma, colorectal carcinoma, glioblastoma, gastric cancer, esophageal cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, melanoma, breast cancer, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, acute myeloid leukemia, gallbladder cancer and cholangiocarcinoma, urinary bladder cancer, uterine cancer, head and neck squamous cell carcinoma, mesothelioma.

Particularly preferred are the peptides – alone or in combination - according to the present invention selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 772. More preferred are the peptides – alone or in combination - selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 215 (see Tables 1 and 2), and their uses in the immunotherapy of ovarian cancer, hepatocellular carcinoma, colorectal carcinoma, glioblastoma, gastric cancer, esophageal cancer, non-small cell lung cancer,

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small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, melanoma, breast cancer, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, acute myeloid leukemia, gallbladder cancer and cholangiocarcinoma, urinary bladder cancer, uterine cancer, head and neck squamous cell carcinoma, mesothelioma, and preferably ovarian cancer.

Thus, another aspect of the present invention relates to the use of the peptides according to the present invention for the - preferably combined - treatment of a proliferative disease selected from the group of ovarian cancer, hepatocellular carcinoma, colorectal carcinoma, glioblastoma, gastric cancer, esophageal cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, melanoma, breast cancer, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, acute myeloid leukemia, gallbladder cancer and cholangiocarcinoma, urinary bladder cancer, uterine cancer, head and neck squamous cell carcinoma, mesothelioma.

The present invention furthermore relates to peptides according to the present invention 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.

The present invention further relates to the peptides according to the present invention wherein said peptides (each) consist or consist essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 772.

The present invention further relates to the peptides according to the present invention, wherein said peptide is modified and/or includes non-peptide bonds.

The present invention further relates to the peptides according to the present invention, 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

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the sequence of) an antibody, such as, for example, an antibody that is specific for dendritic cells.

The present invention further relates to a nucleic acid, encoding the peptides according to the present invention. The present invention further relates to the nucleic acid according to the present invention that is DNA, cDNA, PNA, RNA or combinations thereof.

The present invention further relates to an expression vector capable of expressing and/or expressing a nucleic acid according to the present invention.

The present invention further relates to a peptide according to the present invention, a nucleic acid according to the present invention or an expression vector according to the present invention for use in the treatment of diseases and in medicine, in particular in the treatment of cancer.

The present invention further relates to antibodies that are specific against the peptides according to the present invention or complexes of said peptides according to the present invention with MHC, and methods of making these.

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

The antibodies and TCRs are additional embodiments of the immunotherapeutic use of the peptides according to the present invention.

The present invention further relates to a host cell comprising a nucleic acid according to the present invention or an expression vector as described before. The present

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invention further relates to the host cell according to the present invention that is an antigen presenting cell, and preferably is a dendritic cell.

The present invention further relates to a method for producing a peptide according to the present invention, said method comprising culturing the host cell according to the present invention, and isolating the peptide from said host cell or its culture medium.

The present invention further relates to said method according to the present invention, 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.

The present invention further relates to the method according to the present invention, 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.: 772, preferably containing SEQ ID No. 1 to SEQ ID No. 215, or a variant amino acid sequence.

The present invention further relates to activated T cells, produced by the method according to the present invention, wherein said T cell selectively recognizes a cell which expresses a polypeptide comprising an amino acid sequence according to the present invention.

The present invention further relates to a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising any amino acid sequence according to the present invention, the method comprising administering to the patient an effective number of T cells as produced according to the present invention.

The present invention further relates to the use of any peptide as described, the nucleic acid according to the present invention, the expression vector according to the present invention, the cell according to the present invention, the activated T lymphocyte, the T

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cell receptor or the antibody or other peptide- and/or peptide-MHC-binding molecules according to the present invention as a medicament or in the manufacture of a medicament. Preferably, said medicament is active against cancer.

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

The present invention further relates to a use according to the present invention, wherein said cancer cells are ovarian cancer, hepatocellular carcinoma, colorectal carcinoma, glioblastoma, gastric cancer, esophageal cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, melanoma, breast cancer, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, acute myeloid leukemia, gallbladder cancer and cholangiocarcinoma, urinary bladder cancer, uterine cancer, head and neck squamous cell carcinoma, mesothelioma, and preferably ovarian cancer cells.

The present invention further relates to biomarkers based on the peptides according to the present invention, herein called "targets" that can be used in the diagnosis of cancer, preferably ovarian cancer. The marker can be over-presentation of the peptide(s) themselves, or over-expression of the corresponding gene(s). The markers may also be used to predict the probability of success of a treatment, preferably an immunotherapy, and most preferred an immunotherapy targeting the same target that is identified by the biomarker. For example, an antibody or soluble TCR can be used to stain sections of the tumor to detect the presence of a peptide of interest in complex with MHC.

Optionally the antibody carries a further effector function such as an immune stimulating domain or toxin.

The present invention also relates to the use of these novel targets in the context of cancer treatment.

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Both therapeutic and diagnostic uses against additional cancerous diseases are disclosed in the following more detailed description of the underlying expression products (polypeptides) of the peptides according to the invention.

ALPP, also known as ALP, PLAP or PALP, encodes an alkaline phosphatase, a metallo-enzyme that catalyzes the hydrolysis of phosphoric acid monoesters (RefSeq, 2002). ALPP was described to be hyper-expressed in various human tumors and their cell lines, particularly in cancers of the testis and ovary (Millan and Fishman, 1995). ALPP was identified as an independent prognostic factor for the survival of osteosarcoma patients which also correlates with lung metastasis. Furthermore, ALPP was described as an immunohistochemical marker of gastrointestinal smooth muscle neoplasms, germ cell tumor precursors, such as carcinoma in situ and gonadoblastoma, and as a promising ovarian cancer biomarker (Ravenni et al., 2014; Wong et al., 2014b; Faure et al., 2016; Han et al., 2012).

ALPPL2, also known as GCAP, encodes a membrane bound glycosylated enzyme, localized to testis, thymus and certain germ cell tumors, which is closely related to both the placental and intestinal forms of alkaline phosphatase (RefSeq, 2002). ALPPL2 was shown to be ectopically expressed in seminoma as well as in many pancreatic cancer cell lines at both mRNA and protein levels and to be involved in cancer cell growth and invasion. Additionally, ALPPL2 was described as a potential diagnostic marker of pancreatic ductal adenocarcinoma (Hofmann and Millan, 1993; Dua et al., 2013; Fishman, 1995). RT-PCR for ALPPL2 was described to be suitable for the sensitive detection of residual germ cell tumor cells in peripheral blood and progenitor cell harvests (Hildebrandt et al., 1998).

BCAM encodes the basal cell adhesion molecule (Lutheran blood group), a member of the immunoglobulin superfamily and a receptor for the extracellular matrix protein, laminin (RefSeq, 2002). BCAM is a specific receptor for laminin alpha5 (LAMA5), a subunit of laminin-511 (LM-511) that is a major component of basement membranes in

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various tissues; the BCAM/LAMA5 system plays a functional role in the metastatic spreading of KRAS-mutant colorectal cancer as well as in the migration of hepatocellular carcinoma (Kikkawa et al., 2013; Kikkawa et al., 2014; Bartolini et al., 2016). Serum levels of BCAM were found to be significantly increased in breast cancer patients and its over-expression was found to be associated with skin, ovarian and pancreatic cancers as well as with endometrioid endometrial carcinoma, ovarian endometrioid carcinoma and cutaneous squamous cell carcinoma (Kikkawa et al., 2008; Planaguma et al., 2011; Latini et al., 2013; Kim et al., 2015a; Li et al., 2017). Being able to form a fusion protein with AKT2, BCAM was identified as AKT2 kinase activator in high-grade serous ovarian cancer (Kannan et al., 2015).

CBX2 encodes chromobox 2 which is a component of the polycomb multiprotein complex, which is required to maintain the transcriptionally repressive state of many genes throughout development via chromatin remodeling and modification of histones (RefSeq, 2002). CBX2 is involved in cell proliferation and metastasis (Clermont et al., 2016). CBX2 is regulated by SMARCE1 leading to suppressed EGFR transcription. CBX2 is involved in the regulation of three tumor suppressor genes encoded in the INK4A/ARF locus (Papadakis et al., 2015; Agherbi et al., 2009; Miyazaki et al., 2008). CBX2 is over-expressed in cancer including breast cancer, ovarian cancer, lung cancer, metastatic castration-resistant and neuroendocrine prostate cancer and basal-like endometrioid endometrial carcinoma (Parris et al., 2010; Clermont et al., 2016; Clermont et al., 2014; Clermont et al., 2015; Jiang et al., 2015; Xu et al., 2016). CBX2 is associated with lower patient survival and metastatic progression. CBX2 is linked to peritumoral inflammatory infiltration, metastatic spread to the cervical lymph nodes, and tumor size (Parris et al., 2014; Clermont et al., 2014; Xu et al., 2016). CBX2 over-expression results in hematopoietic stem cell differentiation and exhaustion (Klauke et al., 2013).

CCNA1 encodes cyclin A1, which belongs to the highly conserved cyclin family involved in the regulation of CDK kinases (RefSeq, 2002). Elevated levels of CCNA1 were detected in epithelial ovarian cancer, lymphoblastic leukemic cell lines as well as in

childhood acute lymphoblastic leukemia patients. Others have observed over-expression of CCNA1 protein and mRNA in prostate cancer and in tumor tissues of anaplastic thyroid carcinoma patients (Holm et al., 2006; Wegiel et al., 2008; Marlow et al., 2012; Arsenic et al., 2015). Recent studies have shown that silencing of CCNA1 in highly cyclin A1 expressing ML1 leukemic cells slowed S phase entry, decreased proliferation and inhibited colony formation (Ji et al., 2005).

CD70 encodes CD70 molecule which is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. It induces proliferation of co-stimulated T cells, enhances the generation of cytolytic T cells, and contributes to T cell activation. This cytokine is also reported to play a role in regulating B-cell activation, cytotoxic function of natural killer cells, and immunoglobulin synthesis (RefSeq, 2002). Targeting of CD70 may be used to specifically target and kill cancer cells. It may be a potential target in oral cancer (Bundela et al., 2014; Jacobs et al., 2015b; Wang et al., 2016a). CD70 is expressed in head-and-neck squamous cell carcinoma. It is ectopically expressed in lymphomas, renal cell carcinomas, and glioblastomas. CD70 expression levels decrease during melanoma progression. CD70 is highly expressed on CD4⁺ CD25⁺ T-cells from patients with acute-type adult T-cell leukemia/lymphoma (Jacobs et al., 2015b; Curran et al., 2015; De et al., 2016; Jacobs et al., 2015a; Masamoto et al., 2016; Pich et al., 2016b; Ruf et al., 2015a). CD70 is involved in immune response, cancer development, and cancer progression (Petrau et al., 2014; Pich et al., 2016a). CD70 up-regulation in clear cell renal cell carcinoma is associated with worse survival (Ruf et al., 2015b). Cisplatin mediates cytotoxicity through APCs expressing relatively higher levels of CD70 (Beyranvand et al., 2016). CD70 expression is almost not affected by ionizing radiation. It is associated with radio sensitivity in lung cancer. Single-dose external beam radiation up-regulates CD70 in PC3 cells (Bernstein et al., 2014; Kumari and Garnett-Benson, 2016; Pu et al., 2014).

CDH3 (also known as P-cadherin) encodes cadherin 3 which is a classical cadherin of the cadherin superfamily. This calcium-dependent cell-cell adhesion protein is comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail. This gene is located in a gene cluster in a region on the long

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arm of chromosome 16 that is involved in loss of heterozygosity events in breast and prostate cancer. In addition, aberrant expression of this protein is observed in cervical adenocarcinomas (RefSeq, 2002). CDH3 is involved in oncogenic signaling and activates integrins, receptor tyrosine kinases, small molecule GTPases, EMT transcription factors, and other cadherin family members. CDH3 signaling induces invasion and metastasis (Albergaria et al., 2011; Paredes et al., 2012; Bryan, 2015; Vieira and Paredes, 2015). Oncogenic activation of CDH3 is involved in gastric carcinogenesis (Resende et al., 2011). CDH3 over-expression promotes breast cancer, bladder cancer, ovarian cancer, prostate cancer, endometrial cancer, skin cancer, gastric cancer, pancreas cancer, and colon cancer (Albergaria et al., 2011; Paredes et al., 2007; Bryan and Tselepis, 2010; Reyes et al., 2013; Vieira and Paredes, 2015). CDH3 is a basal epithelial marker expressed in basal-like breast cancer. BRCA1 carcinomas are characterized by the expression of basal markers like CDH3 and show a high-grade, highly proliferating, ER-negative, and HER3-negative phenotype (Honrado et al., 2006; Palacios et al., 2008; Rastelli et al., 2010; Dewar et al., 2011). CDH3 is a tumor suppressor in melanoma and oral squamous cell carcinoma (Haass et al., 2005; Vieira and Paredes, 2015). CDH3 may be used as EMT marker. There is a shift from E-cadherin to N-cadherin and CDH3 expression during tumor formation and progression (Piura et al., 2005; Bonitsis et al., 2006; Bryan and Tselepis, 2010; Ribeiro and Paredes, 2014). Competitive interaction between CDH3 and beta-catenin causes impaired intercellular interactions and metastases in gastric cancer (Moskvina and Mal'kov, 2010). CDH3 may be an early marker of cancer formation in colon cancer (Alrawi et al., 2006). Dys-regulation of CDH3 is a marker for poor prognosis and increased malignancy (Knudsen and Wheelock, 2005).

CDKN2A (also known as p16 and p16INK4a) encodes cyclin dependent kinase inhibitor 2A which generates several transcript variants which differ in their first exons. At least three alternatively spliced variants encoding distinct proteins have been reported, two of which encode structurally related isoforms known to function as inhibitors of CDK4 kinase. The remaining transcript includes an alternate first exon located 20 Kb upstream of the remainder of the gene; this transcript contains an alternate open reading frame (ARF) that specifies a protein which is structurally unrelated to the products of the other

variants. This ARF product functions as a stabilizer of the tumor suppressor protein p53 as it can interact with, and sequester, the E3 ubiquitin-protein ligase MDM2, a protein responsible for the degradation of p53 (RefSeq, 2002). CDKN2A is mutated in pancreatic ductal adenocarcinoma, cutaneous malignant melanoma, vulvar squamous cell carcinoma, and biliary tract cancer. Mutations may be inherited and increase the risk for developing pancreatic cancer. CDKN2A is deleted in malignant pleural mesothelioma. CDKN2A is down-regulated in bladder cancer (Clancy et al., 2016; Fabbri et al., 2017; Gan et al., 2016; Kleeff et al., 2016; Nabeshima et al., 2016; Pacholczyk et al., 2016; Petersen, 2016; Sohal et al., 2016; Tatarian and Winter, 2016). CDKN2A is involved in cancer cell proliferation, tumorigenesis, metastasis, Wnt signaling, senescence, apoptosis, and DNA repair mechanism (Gupta et al., 2016; Ko et al., 2016; Low et al., 2016; Sedgwick and D'Souza-Schorey, 2016; Zhao et al., 2016). CDKN2A is a tumor suppressor gene which is down-regulated upon over-expression of the oncogenic protein UHRF1. CDKN2A interacts with p53 to suppress breast cancer (Alhosin et al., 2016; Fry et al., 2017). CDKN2A promotor hyper-methylation is associated with increased risk for low-grade squamous intra-epithelial lesion, high-grade squamous intra-epithelial lesion, and cervical cancer and with smoking habit. CDKN2A is epigenetically dysregulated during the development of hepatocellular carcinoma and esophageal squamous cell carcinoma (Han et al., 2017; Khan et al., 2017; Ma et al., 2016a). CDKN2A may be used in the diagnosis of cervical cancer and oropharyngeal squamous cell carcinoma (Mahajan, 2016; Savone et al., 2016; Tjalma, 2017). CDKN2A expression is caused by HPV infection, a virus which is known to have oncogenic potential (Hoff et al., 2017; Lorincz, 2016).

CDKN2B (also known as p15) encodes cyclin dependent kinase inhibitor 2B which lies adjacent to the tumor suppressor gene CDKN2A in a region that is frequently mutated and deleted in a wide variety of tumors. This gene encodes a cyclin-dependent kinase inhibitor, which forms a complex with CDK4 or CDK6, and prevents the activation of the CDK kinases, thus the encoded protein functions as a cell growth regulator that controls cell cycle G1 progression. The expression of this gene was found to be dramatically induced by TGF beta, which suggested its role in the TGF beta induced growth inhibition (RefSeq, 2002). CDKN2B is involved in the regulation of the cell cycle

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progression and the inhibition of cell proliferation (Hu and Zuckerman, 2014; Roy and Banerjee, 2015). CDKN2B deletion is associated with schistosomal-associated bladder cancer. Mutations in CDKN2B may be involved in inherited susceptibility to glial tumors. CDKN2B is altered in meningiomas and mutated in non-muscle-invasive urothelial carcinoma (Mawrin and Perry, 2010; Melin, 2011; Pollard et al., 2010; Alentorn et al., 2013; Idbaih, 2011; Koonrungsomboon et al., 2015). CDKN2B is hyper-methylated in acute myeloid leukemia and pituitary adenomas. CDKN2B is aberrantly regulated in cutaneous malignant melanoma (Bailey et al., 2010; Jiang et al., 2014; Popov and Gil, 2010; van den Hurk et al., 2012; Wolff and Bies, 2013; Zhou et al., 2014). CDKN2B interacts with the tumor suppressor RB and is regulated by Miz-1 and TGF-beta (Zhou et al., 2014; Geyer, 2010; Moroy et al., 2011). CDKN2B is a tumor suppressor gene which is affected by long non-coding RNAs. CDKN2B itself in association with AS1 is part of a long non-coding RNA (ANRIL) which may be involved in cancer development (Popov and Gil, 2010; Aguilo et al., 2016; Shi et al., 2013; Wanli and Ai, 2015).

CLDN6, also known as claudin 6, encodes a member of the claudin family which is a component of tight junction strands and an integral membrane protein (RefSeq, 2002). CLDN6 expression was shown to be associated with lymph node metastasis and TNM stage in non-small cell lung cancer (Wang et al., 2015b). Furthermore, low expression of CLDN6 was shown to be associated with significantly lower survival rates in patients with non-small cell lung cancer (Wang et al., 2015b). Thus, low CLDN6 expression is an independent prognostic biomarker that indicates worse prognosis in patients with non-small cell lung cancer (Wang et al., 2015b). CLDN6 was shown to be down-regulated in cervical carcinoma and gastric cancer (Zhang et al., 2015e; Lin et al., 2013b). CLDN6 was shown to be up-regulated in BRCA1-related breast cancer and ovarian papillary serous carcinoma (Wang et al., 2013; Heerma van Voss et al., 2014). CLDN6 was described as a tumor suppressor for breast cancer (Zhang et al., 2015e). Gain of CLDN6 expression in the cervical carcinoma cell lines HeLa and C33A was shown to suppress cell proliferation, colony formation in vitro, and tumor growth in vivo, suggesting that CLDN6 may function as a tumor suppressor in cervical carcinoma cells (Zhang et al., 2015e). CLDN6 may play a positive role in the invasion and metastasis of ovarian cancer (Wang et al., 2013). CLDN6 was shown to be consistently expressed in

germ cell tumors and thus is a novel diagnostic marker for primitive germ cell tumors (Ushiku et al., 2012). CLDN6 expression was shown to be positive in most tumors of an assessed set of atypical teratoid/rhabdoid tumors of the central nervous system, with strong CLDN6 positivity being a potential independent prognostic factor for outcome of the disease (Dufour et al., 2012).

CT45A1, also known as CT45, encodes the cancer/testis antigen family 45 member A1 protein and is located on chromosome Xq26.3 (RefSeq, 2002). CT45 genes were shown to be potential prognostic biomarkers and therapeutic targets in epithelial ovarian cancer (Zhang et al., 2015d). The CT45A1 protein which is usually only expressed in testicular germ cells was shown to be also expressed in lung cancer, breast cancer and ovarian cancer (Chen et al., 2009). CT45A1 was also shown to be associated with poor prognosis and poor outcomes in multiple myeloma (Andrade et al., 2009). CT45A1 was described as gene up-regulating epithelial-mesenchymal transition (EMT) and metastatic genes, promoting EMT and tumor dissemination. Furthermore, CT45A1 was described as being implicated in the initiation or maintenance of cancer stem-like cells, promoting tumorigenesis and malignant progression (Yang et al., 2015b). CT45A1 over-expression in a breast cancer model was shown to result in the up-regulation of various oncogenic and metastatic genes, constitutively activated ERK and CREB signaling pathways and increased tumorigenesis, invasion and metastasis. Silencing of CT45A1 was shown to reduce cancer cell migration and invasion. Thus, CT45A1 may function as a novel proto-oncogene and may be a target for anticancer drug discovery and therapy (Shang et al., 2014).

CT45A2 encodes one of a cluster of several similar genes, which is a member of the cancer/testis family of antigens and is located on chromosome Xq26.3 (RefSeq, 2002). CT45A2 was shown to be a novel spliced MLL fusion partner in a pediatric patient with de novo bi-phenotypic acute leukemia and thus might be relevant for leukemogenesis (Cerveira et al., 2010). The cancer/testis antigen family 45 was shown to be frequently expressed in both cancer cell lines and lung cancer specimens (Chen et al., 2005). CT45 genes were shown to be potential prognostic biomarkers and therapeutic targets in epithelial ovarian cancer (Zhang et al., 2015d).

CT45A3 encodes the cancer/testis antigen family 45 member A3 protein and is located on chromosome Xq26.3 (RefSeq, 2002). The cancer/testis antigen family 45 was shown to be frequently expressed in both cancer cell lines and lung cancer specimens (Chen et al., 2005). CT45 genes were shown to be potential prognostic biomarkers and therapeutic targets in epithelial ovarian cancer (Zhang et al., 2015d).

CT45A4 encodes the cancer/testis antigen family 45 member A4 protein and is located on chromosome Xq26.3 (RefSeq, 2002). The cancer/testis antigen family 45 was shown to be frequently expressed in both cancer cell lines and lung cancer specimens (Chen et al., 2005). CT45 genes were shown to be potential prognostic biomarkers and therapeutic targets in epithelial ovarian cancer (Zhang et al., 2015d).

CT45A5 encodes the cancer/testis antigen family 45 member A5 and is located on chromosome Xq26.3 (RefSeq, 2002). The cancer/testis antigen family 45 was shown to be frequently expressed in both cancer cell lines and lung cancer specimens (Chen et al., 2005). CT45 genes were shown to be potential prognostic biomarkers and therapeutic targets in epithelial ovarian cancer (Zhang et al., 2015d).

CT45A6 encodes the cancer/testis antigen family 45 member A6 protein and is located on chromosome Xq26.3 (RefSeq, 2002). The cancer/testis antigen family 45 was shown to be frequently expressed in both cancer cell lines and lung cancer specimens (Chen et al., 2005). CT45 genes were shown to be potential prognostic biomarkers and therapeutic targets in epithelial ovarian cancer (Zhang et al., 2015d).

CTAG2 encodes cancer/testis antigen 2 which is an auto immunogenic tumor antigen that belongs to the ESO/LAGE family of cancer-testis antigens. This protein is expressed in a wide array of cancers including melanoma, breast cancer, bladder cancer and prostate cancer. This protein is also expressed in normal testis tissue (RefSeq, 2002). CTAG2 is involved in cancer cell migration and invasiveness (Maine et al., 2016). CTAG2 expression is up-regulated by LSAMP resulting in reduced cell proliferation (Baroy et al., 2014). CTAG2 is expressed in liposarcoma, lung cancer, urothelial cancer, and colorectal cancer. CTAG2 is over-expressed in several entities including esophageal squamous cell carcinoma (Kim et al., 2012; Dyrskjot et al., 2012;

Hemminger et al., 2014; Forghanifard et al., 2011; McCormack et al., 2013; Shantha Kumara et al., 2012). Engineered T cells against CTAG2 may be used in multiple myeloma treatment. Autoantibodies against CTAG2 may be used in cancer diagnosis. CTAG2 may be a target in immunotherapy. CTAG2 expression is associated with shorter progression-free survival (van et al., 2011; Dyrskjot et al., 2012; Hudolin et al., 2013; Pollack et al., 2012; Rapoport et al., 2015; Wang et al., 2015a).

CYP2W1 encodes a member of the cytochrome P450 superfamily of enzymes which are monooxygenases catalyzing many reactions involved in drug metabolism and in the synthesis of cholesterol, steroids and other lipids (RefSeq, 2002). CYP2W1 is over-expressed in a variety of human cancers including hepatocellular, colorectal and gastric cancer. CYP2W1 over-expression is associated with tumor progression and poor survival (Aung et al., 2006; Gomez et al., 2010; Zhang et al., 2014a). Due to tumor-specific expression, CYP2W1 is an interesting drug target or enzymatic activator of pro-drugs during cancer therapy (Karlgrén and Ingelman-Sundberg, 2007; Nishida et al., 2010).

DPPA2 encodes developmental pluripotency associated 2 and is located on chromosome 3q13.13 (RefSeq, 2002). DPPA2 is over-expressed in gastric cancer, non-small cell lung cancer, epithelial ovarian cancer, and colorectal cancer. DPPA2 is an oncogene up-regulated in several entities. DPPA2 is reciprocally repressed in teratoma (Tung et al., 2013; Ghodsi et al., 2015; John et al., 2008; Raeisossadati et al., 2014; Shabestarian et al., 2015; Tchabo et al., 2009; Western et al., 2011). DPPA2 expression correlates with tumor invasion depth, stage, lymph node metastasis, and aggressiveness (Ghodsi et al., 2015; Raeisossadati et al., 2014; Shabestarian et al., 2015). DPPA2 is involved in the pathogenesis of non-small cell lung cancer (Watabe, 2012). DPPA2 is differentially methylated in thyroid cancer (Rodriguez-Rodero et al., 2013).

ENTPD4 (UDPase) encodes ectonucleoside triphosphate diphosphohydrolase 4, a member of the apyrase protein family and may play a role in salvaging nucleotides from lysosomes (RefSeq, 2002). UDPase activity is increased in patients with ovarian cancer

or testicular cancer and decreased after chemotherapy (Papadopoulou-Boutis et al., 1985).

ESR1 encodes an estrogen receptor, a ligand-activated transcription factor important for hormone binding, DNA binding and activation of transcription, that is essential for sexual development and reproductive function (RefSeq, 2002). Mutations and single nucleotide polymorphisms of ESR1 are associated with risk for different cancer types including liver, prostate, gallbladder and breast cancer. The up-regulation of ESR1 expression is connected with cell proliferation and tumor growth but the overall survival of patients with ESR1 positive tumors is better due to the successfully therapy with selective estrogen receptor modulators (Sun et al., 2015; Hayashi et al., 2003; Bogush et al., 2009; Miyoshi et al., 2010; Xu et al., 2011; Yakimchuk et al., 2013; Fuqua et al., 2014). ESR1 signaling interferes with different pathways responsible for cell transformation, growth and survival like the EGFR/IGFR, PI3K/Akt/mTOR, p53, HER2, NFkappaB and TGF-beta pathways (Frasor et al., 2015; Band and Laiho, 2011; Berger et al., 2013; Skandalis et al., 2014; Mehta and Tripathy, 2014; Ciruelos Gil, 2014).

ETV1 encodes ETS variant 1 which is a member of the ETS (E twenty-six) family of transcription factors. The ETS proteins regulate many target genes that modulate biological processes like cell growth, angiogenesis, migration, proliferation and differentiation (RefSeq, 2002). ETV1 is involved in epithelial-to-mesenchymal transition, DNA damage response, AR and PTEN signaling, cancer cell invasion, and metastasis. ETV1 interacts with JMJD2A to promote prostate carcinoma formation and to increase YAP1 expression affecting the Hippo signaling pathway (Mesquita et al., 2015; Baty et al., 2015; Heeg et al., 2016; Higgins et al., 2015; Kim et al., 2016; Lunardi et al., 2015). ETV1 expression is decreased in prostate cancer. ETV1 is over-expressed in pancreatic cancer, gastrointestinal stromal tumors, oligodendroglial tumors, and renal cell carcinoma. ETV1 may be an oncogene in non-small cell lung cancer (Heeg et al., 2016; Gleize et al., 2015; Ta et al., 2016; Al et al., 2015; Hashimoto et al., 2017; Jang et al., 2015). Increased mRNA levels of ETV1 in microvesicles of prostate cancer cell lines are correlated with prostate cancer progression (Lazaro-Ibanez et al., 2017). ETV1 is an oncogene which interacts with the Ewing's sarcoma breakpoint protein EWS. ETV1

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interacts with Sparc and Has2 which mediate in part cancer cell metastasis and desmoplastic stromal expansion (Heeg et al., 2016; Kedage et al., 2016). ETV1 gene fusion products as well as ETV1 promotor methylation status are diagnostically useful (Angulo et al., 2016; 2015; Kumar-Sinha et al., 2015; Linn et al., 2015).

ETV4 (also called E1AF or PEA3) encodes a member of the Ets oncogene family of transcription factors and is involved in the regulation of metastasis gene expression and in the induction of differentiation-associated genes in embryonic stem cell (Akagi et al., 2015; Coutte et al., 1999; Ishida et al., 2006). ETV4 is over-expressed in different cancer entities including breast, lung, colorectal and gastric cancer and is associated with migration, invasion, metastasis and poor prognosis (Benz et al., 1997; Horiuchi et al., 2003; Yamamoto et al., 2004; Keld et al., 2011; Hiroumi et al., 2001). ETV4 is up-regulated by different pathways like ERK/MAPK, HER2, PI3K and Ras following an induction of several targets including MMPs and IL-8 (Maruta et al., 2009; Keld et al., 2010; Chen et al., 2011b; Aytes et al., 2013).

ETV5 encodes the ETS variant 5 protein and is located on chromosome 3q28 (RefSeq, 2002). Pathways including ETV5 were described as being deeply related to the epithelial to mesenchymal process in endometrial cancer (Colas et al., 2012). ETV5 was shown to interact with several signaling pathways such as cell-cycle progression and the TGF-beta signaling pathway in the OV90 ovarian cancer cell line, and ETV5 expression was shown to be associated with the expression of the oncogenic transcription factor FOXM1 in ovarian cancer (Llaurado et al., 2012b). Furthermore, ETV5 was shown to be up-regulated in ovarian cancer. In the spheroid model, the inhibition and up-regulation of ETV5 effected cell proliferation, cell migration, cell adhesion to extracellular matrix components, cell-cell adhesion and cell survival. Thus, ETV5 may play a role in ovarian cancer progression, cell dissemination and metastasis (Llaurado et al., 2012a). Chromosomal rearrangements of ETV5 among other members of the oncogenic PEA3 subfamily, were described to occur in prostate tumors and are thought to be one of the major driving forces in the genesis of prostate cancer. Furthermore, ETV5 was also described as an oncoprotein which is implicated in melanomas, breast and some other types of cancer (Oh et al., 2012). ETV5 was

suggested to have a significant role in regulating matrix metalloproteinase 2 expression and therefore resorption in human chondrosarcoma, and thus may be a targetable upstream effector of the metastatic cascade in this cancer (Power et al., 2013).

EYA2 encodes EYA transcriptional coactivator and phosphatase 2, a member of the eyes absent (EYA) family of proteins involved in eye development (RefSeq, 2002). EYA2 over-expression has been observed in several tumor types such as epithelial ovarian tumor, prostate, breast cancer, urinary tract cancers, glioblastoma, lung adenocarcinoma, cervical cancer, colon and hematopoietic cancers (Bierkens et al., 2013; Zhang et al., 2005; Guo et al., 2009; Patrick et al., 2013; Kohrt et al., 2014). Studies have revealed that EYA2 influences transcription of TGF beta pathway members as well as phosphorylation of TGFBR2, implying a dual role of EYA2 in the pancreas (Vincent et al., 2014).

FAM111B encodes the family with sequence similarity 111 member B, a protein with a trypsin-like cysteine/serine peptidase domain in the C-terminus which leads, in case of a mutation, to mottled pigmentation, telangiectasia, epidermal atrophy, tendon contractures, and progressive pulmonary fibrosis (RefSeq, 2002). FAM111B was found to be down-regulated during metformin and aspirin induced inhibition of pancreatic cancer development (Yue et al., 2015).

FAM83H encodes family with sequence similarity 83 member H which plays an important role in the structural development and calcification of tooth enamel. Defects in this gene are a cause of amelogenesis imperfecta type 3 (AI3) (RefSeq, 2002). The long non-coding RNA FAM83H-AS1 is involved in cell proliferation, migration, and invasion and regulates MET/EGFR signaling (Zhang et al., 2017). The long non-coding RNA FAM83H-AS1 is over-expressed in lung cancer and colorectal cancer. FAM83H is an oncogene over-expressed in several entities including breast cancer and colorectal cancer (Zhang et al., 2017; Kuga et al., 2013; Snijders et al., 2017; Yang et al., 2016c; Yang et al., 2016b). Increased expression of long non-coding RNA FAM83H-AS1 is associated with shorter overall survival. FAM83H-AS1 is associated with poor prognosis (Yang et al., 2016c; Yang et al., 2016b). FAM83H may be involved in androgen

independent prostate cancer (Nalla et al., 2016). FAM83H interacts with CK1alpha to form keratin filaments and desmosomes (Kuga et al., 2016).

FBN2, also known as fibrillin 2, encodes a protein which is a component of the connective tissue and may be involved in elastic fiber assembly (RefSeq, 2002). FBN2 was described as an extracellular matrix regulatory protein of TGF-beta signaling activity (Lilja-Maula et al., 2014). Hyper-methylation of FBN2 was described as an epigenetic biomarker for clear cell renal cell carcinoma and early detection of colorectal cancer and as being associated with poor prognosis by colorectal cancer patients (Ricketts et al., 2014; Rasmussen et al., 2016; Yi et al., 2012). FBN2 was shown to be a candidate cell surface target enriched in medulloblastoma which could be used for the development of tumor-specific probes for guided resection in medulloblastoma (Haeberle et al., 2012).

FOLR1 encodes the folate receptor 1, which binds folic acid and its reduced derivatives, and transports 5-methyltetrahydrofolate into cells; FOLR1 is a secreted protein that either anchors to membranes via a glycosyl-phosphatidylinositol linkage or exists in a soluble form (RefSeq, 2002). Being a major part of the FOLR1/cSrc/ERK1/2/NFkB/p53 pathway, which is required for the up-take of folic acid, FOLR1 is able to regulate the proliferation of cancer cells such as breast, lung and colon cancer (Kuo and Lee, 2016; Cheung et al., 2016). FOLR1 was found to be widely expressed in epithelial ovarian cancer, where its expression increases with tumor stage and might represent a potential therapeutic target (Leung et al., 2016; Ponte et al., 2016; Moore et al., 2016; Hou et al., 2017; Notaro et al., 2016; Bergamini et al., 2016). Reducing FOLR1 expression during colorectal cancer therapy was shown to increase the effectiveness of 5-fluorouracil treatment (Tsukihara et al., 2016). FOLR1 represents an ideal tumor-associated marker for immunotherapy for triple-negative breast cancer as well as colon cancer (Liang et al., 2016; Song et al., 2016).

GPR64 encodes adhesion G protein-coupled receptor G2, a member of the G protein-coupled receptor family described as an epididymis-specific transmembrane protein

(RefSeq, 2002). In breast cancer cell lines, knockdown of GPR64 resulted in a strong reduction in cell adhesion as well as in cell migration (Peeters et al., 2015).

HOXA10 encodes homebox A10. This gene is part of the A cluster on chromosome 7 and encodes a DNA-binding transcription factor that may regulate gene expression, morphogenesis, and differentiation. More specifically, it may function in fertility, embryo viability, and regulation of hematopoietic lineage commitment. Read-through transcription exists between this gene and the downstream homeobox A9 (HOXA9) gene (RefSeq, 2002). HOXA10 is a stem cell factor whose expression correlates with CD133 expression in glioma and may be involved in cancer progression. HOXA10 is involved in cancer cell proliferation, migration, invasion, and metastasis. HOXA10 is involved in multidrug resistance by inducing P-gp and MRP1 expression. HOXA10 promotes epithelial-to-mesenchymal transition. HOXA10 may be a downstream target of miR-218/PTEN/AKT/PI3K signaling. HOXA10 promotes expression of the AML-associated transcription factor Prdm16. HOXA10 may mediate G1 cell cycle arrest in a p21-dependent manner. HOXA10 is involved in TGF-beta2/p38 MAPK signaling promoting cancer cell invasion in a MMP-3-dependent manner (Carrera et al., 2015; Cui et al., 2014; Emmrich et al., 2014; Han et al., 2015; Li et al., 2014a; Li et al., 2016a; Sun et al., 2016; Xiao et al., 2014; Yang et al., 2016a; Yi et al., 2016; Yu et al., 2014; Zhang et al., 2014b; Zhang et al., 2015b). HOXA10 is up-regulated in gastric cancer and acute myeloid leukemia. HOXA10 is differentially expressed in oral squamous cell carcinoma. HOXA10 is differentially methylated in non-serous ovarian carcinoma and glioblastoma (Carrera et al., 2015; Han et al., 2015; Kurscheid et al., 2015; Niskakoski et al., 2014; Oue et al., 2015; Shima et al., 2014). HOXA10 methylation status may be used in breast cancer diagnosis. HOXA10 and CD44 co-expression is correlated with tumor size and patient survival in gastric cancer. HOXA10 and miR-196b co-expression is correlated with poor prognosis in gastric cancer (Han et al., 2015; Lim et al., 2013; Uehiro et al., 2016). SGI-110 treatment hypo-methylate HOXA10 which sensitizes ovarian cancer cells for chemotherapy (Fang et al., 2014a).

HOXA9 encodes homebox protein A9. This gene is part of the A cluster on chromosome 7 and encodes a DNA-binding transcription factor which may regulate

gene expression, morphogenesis, and differentiation. A specific translocation event which causes a fusion between this gene and the NUP98 gene has been associated with myeloid leukemogenesis (RefSeq, 2002). HOXA9 is expressed in acute myeloid leukemia and high expression is associated with adverse prognosis. HOXA9 and MEIS1 co-expression induces AML. HOXA9 is down-regulated in cervical cancer. HOXA9 is frequently methylated in endometrial cancer (Alvarado-Ruiz et al., 2016; Chen et al., 2015; Li et al., 2016b; Li et al., 2016e; Sykes et al., 2016). The gene fusion product NUP98-HOXA9 acts as oncogene (Abe et al., 2016; Sontakke et al., 2016). Response to cisplatin-based chemotherapy is linked to HOXA9 promotor methylation status. HOXA9, MEIS1, and MN1 co-expression in leukemia make the cells sensitive to pharmacologic inhibition of DOT1L (Li et al., 2016c; Riedel et al., 2016; Xylinas et al., 2016). HOXA9 is a tumor suppressor whose expression may be used to diagnose cancer (Ma et al., 2016b). HOXA9 mediates leukemic stem cell self-renewal and HIF-2alpha deletion accelerates this process (Vukovic et al., 2015; Zhu et al., 2016).

HOXB9 encodes homeobox B9 which is a member of the Abd-B homeobox family and encodes a protein with a homeobox DNA-binding domain. It is included in a cluster of homeobox B genes located on chromosome 17. The encoded nuclear protein functions as a sequence-specific transcription factor that is involved in cell proliferation and differentiation. Increased expression of this gene is associated with some cases of leukemia, prostate cancer and lung cancer (RefSeq, 2002). HOXB9 is involved in angiogenic pathways which are regulated by miR-192. HOXB9 is a downstream target of Wnt/beta-catenin signaling induced by N-acetylgalactosaminyltransferase resulting in metastasis. HOXB9 may regulate mesenchymal-to-epithelial transition in gastric carcinoma and colon adenocarcinoma and epithelial-to-mesenchymal transition in breast cancer and hepatocellular carcinoma in a TGF-beta1-dependent manner. HOXB9 is involved in cell proliferation, migration, and invasion. TGF-beta1 down-regulates HOXB9 in a Kindlin-2/PDAC-dependent manner (Chang et al., 2015b; Darda et al., 2015; Hoshino et al., 2014; Huang et al., 2014; Kwon et al., 2015; Seki et al., 2012; Sha et al., 2015; Wu et al., 2016; Zhan et al., 2014; Zhan et al., 2015; Zhussupova et al., 2014). HOXB9 is differentially expressed in PBRM1 mutated clear cell renal cell carcinoma. HOXB9 is over-expressed in platinum-resistant high-grade

serous ovarian cancer, breast cancer, glioma, colon adenocarcinoma, hepatocellular carcinoma, and head and neck squamous cell carcinoma. HOXB9 expression is decreased in gastric carcinoma. HOXB9 is mutated in leukemia (Menezes et al., 2014; Chang et al., 2015b; Darda et al., 2015; Zhan et al., 2014; Zhussupova et al., 2014; Fang et al., 2014b; Hayashida et al., 2010; Kelly et al., 2016; Sha et al., 2013; Shrestha et al., 2012; Wang et al., 2016b; Yuan et al., 2014). HOXB9 expression is regulated by E2F1 and FAT10 (Zhussupova et al., 2014; Yuan et al., 2014). HOXB9 expression is correlated with tumor size in oral cancer. HOXB9 expression is associated with advanced clinical stage in glioma. HOXB9 down-regulation is associated with decreased patient survival in gastric carcinoma (Fang et al., 2014b; Sha et al., 2013; Oliveira-Costa et al., 2015; Tomioka et al., 2010). HOXB9 regulates bladder cancer progression (Zhang et al., 2016b). Long non-coding RNA nc-HOXB9-205 is down-regulated in urothelial carcinoma of the bladder (Luo et al., 2014). BCAS3-HOXB9 gene fusion product is expressed in breast cancer (Schulte et al., 2012).

HOXC10 encodes homeobox C10 which belongs to the homeobox family of genes. The homeobox genes encode a highly conserved family of transcription factors that play an important role in morphogenesis in all multicellular organisms. This gene is one of several homeobox HOXC genes located in a cluster on chromosome 12. The protein level is controlled during cell differentiation and proliferation, which may indicate this protein has a role in origin activation (RefSeq, 2002). HOXC10 is involved in chemo resistance by suppressing apoptosis and up-regulating NF-kappaB and DNA damage repair. HOXC10 induces apoptosis and inhibits cell growth. HOXC10 may be involved in cervical cancer progression and invasion (Pathiraja et al., 2014; Sadik et al., 2016; Zhai et al., 2007). HOXC10 is up-regulated in thyroid cancer, cervical squamous cell carcinoma, and breast cancer (Abba et al., 2007; Zhai et al., 2007; Ansari et al., 2012; Feng et al., 2015). HOXC10 expression correlates with shorter recurrence-free and overall survival in ER-negative breast cancer. HOXC10 expression is associated with advanced stage, poor pathologic stage, poor prognosis, cytokine-cytokine receptor interaction, and chemokine signaling pathways in thyroid cancer (Sadik et al., 2016; Feng et al., 2015). HOXC10 is differentially methylated in oral squamous cell carcinoma

and small B cell lymphoma (Marcinkiewicz and Gudas, 2014a; Marcinkiewicz and Gudas, 2014b; Rahmatpanah et al., 2006).

HOXC9 encodes homeobox C9 which belongs to the homeobox family of genes. The homeobox genes encode a highly conserved family of transcription factors that play an important role in morphogenesis in all multicellular organisms. This gene is one of several homeobox HOXC genes located in a cluster on chromosome 12 (RefSeq, 2002). HOXC9 is involved in cancer cell invasion and proliferation. HOXC9 knock-down results in reduced cell viability, migration, invasion, tumorigenicity, and increased autophagy. HOXC9 is involved in chemo resistance in bladder cancer in a miR-193a-3p-dependent manner. HOXC9 is involved in retinoic acid signaling and is involved in cell growth and differentiation (Hur et al., 2016; Kocak et al., 2013; Lv et al., 2015a; Mao et al., 2011; Simeone et al., 1991; Stornaiuolo et al., 1990; Xuan et al., 2016; Zha et al., 2012). HOXC9 is differentially expressed in breast cancer, lung cancer, and neuroblastoma. HOXC9 is methylated in stage I non-small cell lung cancer. HOXC9 is up-regulated in astrocytoma. HOXC9 is expressed in esophageal cancer and cervical cancer (Hur et al., 2016; Xuan et al., 2016; Gu et al., 2007; Lin et al., 2009; Lopez et al., 2006; Okamoto et al., 2007). HOXC9 may be transcriptionally repressed by Smad4 (Zhou et al., 2008). HOXC9 expression is inversely associated with disease-free survival and distant metastasis-free survival in breast cancer. HOXC9 expression is associated with poor prognosis in glioblastoma (Hur et al., 2016; Xuan et al., 2016). HOXC9 inhibits DAPK1 resulting in disturbed autophagy induced by Beclin-1 (Xuan et al., 2016).

HOXD10 encodes homeobox D10 protein, which functions as a sequence-specific transcription factor that is expressed in the developing limb buds and is involved in differentiation and limb development (RefSeq, 2002). HOXD10 was identified as target gene of miR-10b, which is up-regulated in gastric cancer (GC) and may have a key role in GC pathogenesis and development (Ma et al., 2015; Wang et al., 2015c). HOXD10 was found to be up-regulated in neck squamous cell carcinoma and urothelial cancer promoting cell proliferation and invasion and may represent a new biomarker for ductal invasive breast carcinoma (Sharpe et al., 2014; Vardhini et al., 2014; Heubach et al.,

2015). However, HOXD10 also showed tumor-suppressive functions in cholangiocellular carcinoma by inactivating the RHOC/AKT/MAPK pathway and inducing G1 phase cell cycle arrest (Yang et al., 2015a). As part of the miR-224/HOXD10/p-PAK4/MMP-9 signaling pathway, HOXD10 is contributed to the regulation of cell migration and invasion and provides a new bio target for hepatocellular carcinoma treatment (Li et al., 2014b).

HOXD9 encodes homeobox D9 which belongs to the homeobox family of genes. The homeobox genes encode a highly conserved family of transcription factors that play an important role in morphogenesis in all multicellular organisms. This gene is one of several homeobox HOXD genes located at 2q31-2q37 chromosome regions. Deletions that removed the entire HOXD gene cluster or 5' end of this cluster have been associated with severe limb and genital abnormalities. The exact role of this gene has not been determined (RefSeq, 2002). HOXD9 is involved in epithelial-to-mesenchymal transition, cancer cell migration, invasion, and metastasis in a ZEB1-dependent manner. Over-expressed HOXD9 increases anchorage-independent growth and reduces contact inhibition. HOXD9 is involved in growth arrest and neuronal differentiation. Depletion of HOXD9 results in decreased cell proliferation, cell cycle arrest, and induction of apoptosis (Zha et al., 2012; Lawrenson et al., 2015b; Lv et al., 2015b; Tabuse et al., 2011). HOXD9 is up-regulated in lung squamous carcinoma and invasive hepatocellular carcinoma. HOXD9 is expressed in esophageal carcinoma, astrocytomas and glioblastomas. HOXD9 is differentially expressed in cervical cancer (Bao et al., 2016; Gu et al., 2007; Lv et al., 2015b; Tabuse et al., 2011; Li et al., 2002; Liu et al., 2005). HOXD9 expression is induced by retinoic acid and Wnt signaling (Ishikawa and Ito, 2009). HOXD9 may be involved in cervical carcinogenesis (Lopez-Romero et al., 2015). HOXD9 hyper-methylation is associated with poorer disease-free and overall survival in lymph node metastasis (Marzese et al., 2014). HOXD9 is hyper-methylated in cholangiocarcinoma and melanoma brain metastasis (Marzese et al., 2014; Sriraksa et al., 2013). HOXD9 may be involved in mucinous ovarian carcinoma susceptibility (Kelemen et al., 2015). HOXD9 may be an oncogene (Wu et al., 2013).

HTR3A encodes a 5-hydroxytryptamine (serotonin) receptor belonging to the ligand-gated ion channel receptor superfamily that causes fast, depolarizing responses in neurons after activation (RefSeq, 2002). HTR3A (also called 5-HT3) is de-regulated in several cancer types for example a down-regulation in mantle cell lymphomas, a differential expression in diverse B cell tumors and a decreased expression in breast cancer cell lines (Pai et al., 2009; Rinaldi et al., 2010; Ek et al., 2002).

IGF2BP1, also known as CRD-BP, encodes a member of the insulin-like growth factor 2 mRNA-binding protein family which functions by binding to the mRNAs of certain genes and regulating their translation (RefSeq, 2002). Two members of the IGF2 mRNA binding protein family, including IGF2BP1 were described as bona fide oncofetal proteins which are de novo synthesized in various human cancers and which may be powerful post-transcriptional oncogenes enhancing tumor growth, drug-resistance and metastasis (Lederer et al., 2014). Expression of IGF2BP1 was reported to correlate with an overall poor prognosis and metastasis in various human cancers (Lederer et al., 2014). Thus, IGF2BP1 was suggested to be a powerful biomarker and candidate target for cancer therapy (Lederer et al., 2014). IGF2BP family members were described to be highly associated with cancer metastasis and expression of oncogenic factors such as KRAS, MYC and MDR1 (Bell et al., 2013). IGF2BP1 was shown to interact with C-MYC and was found to be expressed in the vast majority of colon and breast tumors and sarcomas as well as in benign tumors such as breast fibroadenomas and meningiomas (Ioannidis et al., 2003). IGF2BP1 was shown to be up-regulated in hepatocellular carcinoma and basal cell carcinoma (Noubissi et al., 2014; Zhang et al., 2015c). Up-regulation of IGF2BP1 and other genes was shown to be significantly associated with poor post-surgery prognosis in hepatocellular carcinoma (Zhang et al., 2015c). IGF2BP1 was shown to be a target of the tumor suppressor miR-9 and miR-372 in hepatocellular carcinoma and in renal cell carcinoma, respectively (Huang et al., 2015; Zhang et al., 2015c). Loss of stromal IGF2BP1 was shown to promote a tumorigenic microenvironment in the colon, indicating that IGF2BP1 plays a tumor-suppressive role in colon stromal cells (Hamilton et al., 2015). IGF2BP1 was shown to be associated with stage 4 tumors, decreased patient survival and MYCN gene amplification in neuroblastoma and may therefore be a potential oncogene and an independent

negative prognostic factor in neuroblastoma (Bell et al., 2015). IGF2BP1 was described as a direct target of WNT/ β -catenin signaling which regulates GLI1 expression and activities in the development of basal cell carcinoma (Noubissi et al., 2014).

IGF2BP3 encodes insulin-like growth factor II mRNA binding protein 3, an oncofetal protein, which represses translation of insulin-like growth factor II (RefSeq, 2002). Several studies have shown that IGF2BP3 acts in various important aspects of cell function, such as cell polarization, migration, morphology, metabolism, proliferation and differentiation. In vitro studies have shown that IGF2BP3 promotes tumor cell proliferation, adhesion, and invasion. Furthermore, IGF2BP3 has been shown to be associated with aggressive and advanced cancers (Bell et al., 2013; Gong et al., 2014). IGF2BP3 over-expression has been described in numerous tumor types and correlated with poor prognosis, advanced tumor stage and metastasis, as for example in neuroblastoma, colorectal carcinoma, intrahepatic cholangiocarcinoma, hepatocellular carcinoma, prostate cancer, and renal cell carcinoma (Bell et al., 2013; Findeis-Hosey and Xu, 2012; Hu et al., 2014; Szarvas et al., 2014; Jeng et al., 2009; Chen et al., 2011a; Chen et al., 2013; Hoffmann et al., 2008; Lin et al., 2013a; Yuan et al., 2009).

IRF4 encodes the interferon regulatory factor 4, a transcription factor that negatively regulates Toll-like-receptor (TLR) signaling in lymphocytes, what is central to the activation of innate and adaptive immune system (RefSeq, 2002). IRF4 is considered to be a key regulator of several steps in lymphoid, myeloid, and dendritic cell differentiation and maturation and is characterized by varying within the hematopoietic system in a lineage and stage-specific way (Shaffer et al., 2009; Gualco et al., 2010). IRF4 plays a pivotal role in adaptive immunity, cell growth, differentiation and tumorigenesis of chronic myeloid leukemia, primary central nervous system lymphoma, T-cell lymphoma, HTLV-I-induced adult T cell leukemia and intravascular large B-cell lymphoma (Mamane et al., 2002; Orwat and Batalis, 2012; Bisig et al., 2012; Ponzoni et al., 2014; Manzella et al., 2016). IRF4 is a well-known oncogene that is regulated by enhancer of zeste homolog 2 (EZH2) in multiple myeloma (Alzrigat et al., 2016).

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KLK14 encodes kallikrein related peptidase 14 which is a member of the kallikrein subfamily of serine proteases that have diverse physiological functions such as regulation of blood pressure and desquamation. The altered expression of this gene is implicated in the progression of different cancers including breast and prostate tumors. The encoded protein is a precursor that is proteolytically processed to generate the functional enzyme. This gene is one of the fifteen kallikrein subfamily members located in a cluster on chromosome 19 (RefSeq, 2002). KLK14 is involved in cell proliferation via phosphorylation of ERK1/2/MAP kinase and tumorigenesis. KLK14 induces PAR-2 signaling. KLK14 may be involved in tumor progression, growth, invasion, and angiogenesis (Walker et al., 2014; Borgono et al., 2007; Chung et al., 2012a; Devetzi et al., 2013; Gratio et al., 2011; Sanchez et al., 2012; Zhang et al., 2012a). KLK14 is down-regulated by miR-378/422a and androgen receptor signaling. Androgen receptor signaling up-regulates KLK14 expression in breast cancer (Paliouras and Diamandis, 2008b; Lose et al., 2012; Paliouras and Diamandis, 2007; Paliouras and Diamandis, 2008a; Samaan et al., 2014). KLK14 is over-expressed in chronic lymphocytic leukemia, non-small cell lung cancer, salivary gland tumors, and ovarian cancer. KLK14 is differentially expressed in breast cancer (Planque et al., 2008b; Fritzsche et al., 2006; Hashem et al., 2010; Kontos et al., 2016; Papachristopoulou et al., 2013; Planque et al., 2008a). KLK14 expression is inversely associated with overall survival. KLK14 expression may be used as biomarker and to predict risk of disease recurrence. KLK14 expression correlates with clinical tumor stage and positive nodal status (Devetzi et al., 2013; Lose et al., 2012; Fritzsche et al., 2006; Kontos et al., 2016; Borgono et al., 2003; Obiezu and Diamandis, 2005; Rabien et al., 2008; Rajapakse and Takahashi, 2007; Talieri et al., 2009).

KLK8 encodes the kallikrein related peptidase 8, a serine protease that may be involved in proteolytic cascade in the skin and may serve as a biomarker for ovarian cancer (RefSeq, 2002). KLK8 expression was shown to correlate with the progression of breast cancer colorectal cancer (CRC), endometrial carcinoma and ovarian cancer and might represent a potential independent prognostic indicator for colorectal, breast and ovarian cancer (Liu et al., 2017; Jin et al., 2006; Kountourakis et al., 2009; Darling et al., 2008; Michaelidou et al., 2015; Borgono et al., 2006). KLK8 is able to undergo alternative

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splicing that generates an mRNA transcript missing exon 4; this alternative variant is, in contrast to KLK8, significantly down-regulated in cancer cells (Angelopoulou and Karagiannis, 2010). Nevertheless, the KLK8-T4 alternative splice variant, alone or in combination, may be a new independent marker of unfavorable prognosis in lung cancer (Planque et al., 2010). KLK8 expression confers a favorable clinical outcome in non-small cell lung cancer by suppressing tumor cell invasiveness (Sher et al., 2006).

LAMA1 encodes an alpha 1 subunit of laminin an extracellular matrix glycoprotein with heterotrimeric structure, which constitute a major component of the basement membrane (RefSeq, 2002). LAMA1 is de-regulated in different cancer types including up-regulation in glioblastomas, hyper-methylation in colorectal cancer, abnormal methylation in breast cancer and frameshift mutations in gastric cancer (Scrideli et al., 2008; Choi et al., 2015; Simonova et al., 2015; Kim et al., 2011). TGFbeta can induce the expression of LAMA1. LAMA1 in turn promotes collagenase IV production, which leads to an invasive phenotype in benign tumor cells, but is not sufficient to confer metastatic potential (Chakrabarty et al., 2001; Royce et al., 1992).

LAMC2 belongs to the family of laminins, a family of extracellular matrix glycoproteins. Laminins are the major non-collagenous constituent of basement membranes. They have been implicated in a wide variety of biological processes including cell adhesion, differentiation, migration, signaling, neurite outgrowth and metastasis. LAMC2 encodes a protein which is expressed in several fetal tissues and is specifically localized to epithelial cells in skin, lung and kidney (RefSeq, 2002). LAMC2 is highly expressed in anaplastic thyroid carcinoma and is associated with tumor progression, migration, and invasion by modulating signaling of EGFR (Garg et al., 2014). LAMC2 expression predicted poorer prognosis in stage II colorectal cancer patients (Kevans et al., 2011). LAMC2 expression together with three other biomarkers was found to be significantly associated with the presence of LN metastasis in oral squamous cell carcinoma patients (Zanaruddin et al., 2013).

LILRB4 (also known as ILT-3) encodes leukocyte immunoglobulin like receptor B4 which is a member of the leukocyte immunoglobulin-like receptor (LIR) family, which is

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found in a gene cluster at chromosomal region 19q13.4. The receptor is expressed on immune cells where it binds to MHC class I molecules on antigen-presenting cells and transduces a negative signal that inhibits stimulation of an immune response. The receptor can also function in antigen capture and presentation. It is thought to control inflammatory responses and cytotoxicity to help focus the immune response and limit autoreactivity (RefSeq, 2002). Over-expression of LILRB4 may be involved in tolerance of dendritic cells during cancer. LILRB4 may be involved in immune suppression. LILRB4 is involved in cancer immune escape (Zhang et al., 2012b; Trojandt et al., 2016; Cortesini, 2007; de Goeje et al., 2015; Suci-Foca et al., 2007). LILRB4 expression is induced by TNF-alpha. Over-expression of LILRB4 inhibits NF-kappaB activation, transcription of inflammatory cytokines, and co-stimulatory molecules. LILRB4 is over-expressed by cyclosporine resulting in decreased tumor cytotoxicity by natural killer cells (Si et al., 2012; Thorne et al., 2015; Vlad and Suci-Foca, 2012). LILRB4 is over-expressed on dendritic cells in cancer. LILRB4 is expressed in monocytic acute myeloid leukemia. LILRB4 is over-expressed in ovarian cancer (Dobrowolska et al., 2013; Khan et al., 2012; Orsini et al., 2014). LILRB4 expression is associated with shorter survival in non-small cell lung cancer. LILRB4 expression may be used in chronic lymphocytic leukemia prognosis (Colovai et al., 2007; de Goeje et al., 2015).

LOXL2 encodes an extracellular copper-dependent amine oxidase, known as lysyl oxidase like 2. The enzyme is essential to the biogenesis of connective tissue and catalyses the first step in the formation of crosslinks between collagens and elastin (RefSeq, 2002). LOXL2 was shown to be involved in regulation of extracellular and intracellular cell signaling pathways. Extracellularly, LOXL2 remodels the extracellular matrix of the tumor microenvironment. Intracellularly, it regulates the epithelial-to-mesenchymal transition (Cano et al., 2012; Moon et al., 2014). In general, LOXL2 has been associated with tumor progression including the promotion of cancer cell invasion, metastasis, angiogenesis, and the malignant transformation of solid tumors in various tumors. A high expression of LOXL2 is associated with a poor prognosis (Wu and Zhu, 2015). LOXL2 was shown to be overexpressed in colon, esophageal squamous cell, breast cell, clear cell renal cell, hepatocellular, cholangio-, lung squamous cell and head and neck squamous cell carcinomas. In various cancer types, the high expression

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of LOXL2 was associated with higher recurrence, progression, or metastasis. In various cancer cell lines, the high expression of LOXL2 was associated with increased cell mobility and invasion and its silencing showed the opposite effects (Xu et al., 2014a; Kim et al., 2014; Wong et al., 2014a; Hase et al., 2014; Lv et al., 2014; Torres et al., 2015). In gastric cancer, fibroblast-derived LOXL2 was shown potentially to stimulate the motility of gastric cancer cells. The expression of LOXL2 in stromal cells could serve as a prognostic marker (Kasashima et al., 2014). A number of micro RNAs family is significantly reduced in cancer tissues. LOXL2 was shown to be a direct regulator of those tumor-suppressive micro-RNAs (Fukumoto et al., 2016; Mizuno et al., 2016).

EGF induces LRRK1 translocation as it is an EGF receptor specific interaction partner (Ishikawa et al., 2012; Hanafusa and Matsumoto, 2011; Reyniers et al., 2014). LRRK1 is a component of the Grb2/Gab2/Shc1 complex and interacts with Arap1. It may be a component of the MAPK signaling in response to cellular stress (Titz et al., 2010). Arsenic trioxide which is used for acute promyelocytic leukemia treatment up-regulates LRRK1 in breast cancer cells (Wang et al., 2011). LRRK1 shows extreme allele-specific expression in familial pancreatic cancer (Tan et al., 2008). LRRK1 encodes leucine rich repeat kinase 1 and is located on chromosome 15q26.3. It belongs to the ROCO proteins, a novel subgroup of Ras-like GTPases (RefSeq, 2002; Korr et al., 2006).

LYPD1 encodes LY6/PLAUR domain containing 1 and is located on chromosome 2q21.2 (RefSeq, 2002). LYPD1 is over-expressed in brain metastases derived from breast cancer. LYPD1 is over-expressed in metastasis. LYPD1 is differentially expressed in ovarian cancer. LYPD1 is a tumor suppressor which is down-regulated in CD133+ cancer stem cell-like cells derived from uterine carcinosarcoma (Burnett et al., 2015; Chojamts et al., 2011; Dat et al., 2012; Ge et al., 2015b; Lawrenson et al., 2015a). LYPD1 is a negative regulator of cell proliferation (Salazar et al., 2011).

MAGEA11 encodes MAGE family member A11 which is a member of the MAGEA gene family. The members of this family encode proteins with 50 to 80% sequence identity to each other. The promoters and first exons of the MAGEA genes show considerable variability, suggesting that the existence of this gene family enables the same function

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to be expressed under different transcriptional controls. The MAGEA genes are clustered at chromosomal location Xq28 (RefSeq, 2002). MAGEA11 is a cancer germline antigen which is involved in tumor progression and correlates with poor prognosis and survival in silico. MAGEA11 is involved in PR-B signaling and acts as co-regulator for the androgen receptor. MAGEA11 directly interacts with TIF2. MAGEA11 is involved in hypoxic signaling and knock-down leads to decreased HIF-1alpha expression (Aprelikova et al., 2009; Askew et al., 2009; James et al., 2013; Liu et al., 2011; Su et al., 2012; Wilson, 2010; Wilson, 2011). MAGEA11 is up-regulated in oral squamous cell carcinoma, paclitaxel-resistant ovarian cancer, and during prostate cancer progression (Duan et al., 2003; Wilson, 2010; Ge et al., 2015a; Karpf et al., 2009). MAGEA11 expression is associated with hypo-methylation in prostate and epithelial ovarian cancer (James et al., 2013).

MAGEA12 encodes MAGE family member A12 and is closely related to several other genes clustered on chromosome X (RefSeq, 2002). MAGEA12 is expressed in 20.5% of multiple myeloma patients (Andrade et al., 2008). The surfacing of systemic immune reactivity toward a cryptic epitope from the MAGEA12, after temporary regression of a single melanoma metastasis, in response to specific vaccination was reported (Lally et al., 2001). MAGEA12 was expressed at the highest frequencies, relative to the other MAGE antigens, in early stage lesions of malignant melanoma (Gibbs et al., 2000).

MAGEA3 encodes melanoma-associated antigen family member A3. MAGEA3 is widely known as cancer-testis antigen (RefSeq, 2002; Pineda et al., 2015; De et al., 1994). MAGEA3 has been known long time for being used in therapeutic vaccination trials of metastatic melanoma cancer. The currently performed percutaneous peptide immunization with MAGEA3 and 4 other antigens of patients with advanced malignant melanoma was shown to contribute significantly to longer overall survival by complete responders compared to incomplete responders (Coulie et al., 2002; Fujiyama et al., 2014). In NSCLC, MAGEA3 was shown to be frequently expressed. The expression of MAGEA3 correlated with higher number of tumor necrosis in NSCLC tissue samples and was shown to inhibit the proliferation and invasion and promote the apoptosis in lung cancer cell line. By the patients with adenocarcinomas, the expression of MAGEA3

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was associated with better survival. The whole cell anti MAGEA3 vaccine is currently under the investigation in the promising phase III clinical trial for treatment of NSCLC (Perez et al., 2011; Reck, 2012; Hall et al., 2013; Grah et al., 2014; Liu et al., 2015b). MAGEA3 together with 4 other genes was shown to be frequently expressed in HCC. The expression of those genes was correlated with the number of circulating tumor cells, high tumor grade and advanced stage in HCC patients. The frequency of liver metastasis was shown to be significantly higher in cases with tumor samples that expressed MAGE3 than in those that did not express this gene (Bahnassy et al., 2014; Hasegawa et al., 1998). Cancer stem cell-like side populations isolated from a bladder cancer cell line as well as from lung, colon, or breast cancer cell lines showed expression of MAGEA3 among other cancer-testis antigens. In general, cancer stem cells are known for being resistant to current cancer therapy and cause post-therapeutic cancer recurrence and progression. Thus, MAGEA3 may serve as a novel target for immunotherapeutic treatment in particular of bladder cancer (Yamada et al., 2013; Yin et al., 2014). In head and neck squamous cell carcinoma, the expression of MAGEA3 was shown to be associated with better disease-free survival (Zamuner et al., 2015). Furthermore, MAGEA3 can be used as a prognostic marker for ovarian cancer (Szajnik et al., 2013).

MAGEA4, also known as MAGE4, encodes a member of the MAGEA gene family and is located on chromosome Xq28 (RefSeq, 2002). MAGEA4 was described as a cancer testis antigen which was found to be expressed in a small fraction of classic seminomas but not in non-seminomatous testicular germ cell tumors, in breast carcinoma, Epstein-Barr Virus-negative cases of Hodgkin's lymphoma, esophageal carcinoma, lung carcinoma, bladder carcinoma, head and neck carcinoma, and colorectal cancer, oral squamous cell carcinoma, and hepatocellular carcinoma (Ries et al., 2005; Bode et al., 2014; Li et al., 2005; Ottaviani et al., 2006; Hennard et al., 2006; Chen et al., 2003). MAGEA4 was shown to be frequently expressed in primary mucosal melanomas of the head and neck and thus may be a potential target for cancer testis antigen-based immunotherapy (Prasad et al., 2004). MAGEA4 was shown to be preferentially expressed in cancer stem-like cells derived from LHK2 lung adenocarcinoma cells, SW480 colon adenocarcinoma cells and MCF7 breast adenocarcinoma cells (Yamada

et al., 2013). Over-expression of MAGEA4 in spontaneously transformed normal oral keratinocytes was shown to promote growth by preventing cell cycle arrest and by inhibiting apoptosis mediated by the p53 transcriptional targets BAX and CDKN1A (Bhan et al., 2012). MAGEA4 was shown to be more frequently expressed in hepatitis C virus-infected patients with cirrhosis and late-stage hepatocellular carcinoma compared to patients with early stage hepatocellular carcinoma, thus making the detection of MAGEA4 transcripts potentially helpful to predict prognosis (Hussein et al., 2012). MAGEA4 was shown to be one of several cancer/testis antigens that are expressed in lung cancer and which may function as potential candidates in lung cancer patients for polyvalent immunotherapy (Kim et al., 2012). MAGEA4 was described as being up-regulated in esophageal carcinoma and hepatocellular carcinoma (Zhao et al., 2002; Wu et al., 2011). A MAGEA4-derived native peptide analogue called p286-1Y2L9L was described as a novel candidate epitope suitable to develop peptide vaccines against esophageal cancer (Wu et al., 2011).

MAGEA6 encodes melanoma-associated antigen family member A6. MAGEA3 is widely known as cancer-testis antigen (RefSeq, 2002; Pineda et al., 2015; De et al., 1994). MAGEA6 was shown to be frequently expressed in melanoma, advanced myeloma, pediatric rhabdomyosarcoma, sarcoma, lung, bladder, prostate, breast, and colorectal cancers, head and neck squamous cell, esophageal squamous cell, and oral squamous cell carcinomas (Ries et al., 2005; Hasegawa et al., 1998; Gibbs et al., 2000; Dalerba et al., 2001; Otte et al., 2001; van der Bruggen et al., 2002; Lin et al., 2004; Tanaka et al., 1997). MAGEA6 expression has been associated with shorter progression-free survival in multiple myeloma patients. In contrast in head and neck squamous cell carcinoma, the expression of MAGEA6 was shown to be associated with better disease-free survival (van et al., 2011; Zamuner et al., 2015). MAGEA6 was among a set of genes overexpressed in a paclitaxel-resistant ovarian cancer cell line. Moreover, transfection of MAGEA6 also conferred increased drug resistance to paclitaxel-sensitive cells (Duan et al., 2003). MAGEA6 can be used as a prognostic marker for ovarian cancer (Szajnik et al., 2013). Cancer stem cell-like side populations isolated from lung, colon, or breast cancer cell lines showed expression of MAGEA6 among other cancer-testis antigens (Yamada et al., 2013).

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MAGEB2 is classified as cancer testis antigen, since it is expressed in testis and placenta, and in a significant fraction of tumors of various histological types, amongst others multiple myeloma and head and neck squamous cell carcinoma (Pattani et al., 2012; van et al., 2011).

MELK encodes maternal embryonic leucine zipper kinase and is located on chromosome 9p13.2 (RefSeq, 2002). MELK is a member of the SNF1/AMPK family of serine-threonine kinases and is a cell cycle dependent protein kinase. It plays a key role in multiple cellular processes such as the proliferation, cell cycle progression, mitosis and spliceosome assembly and has recently emerged as an oncogene and a biomarker over-expressed in multiple cancer stem cells (Du et al., 2014). MELK is over-expressed in various cancers, including colon, gastric, breast, ovaries, pancreas, prostate and brain cancer and over-expression correlates with poor prognosis (Pickard et al., 2009; Kuner et al., 2013; Gu et al., 2013; Liu et al., 2015a). Inhibition of MELK is under investigation as a therapeutic strategy for a variety of cancers, including breast cancer, lung cancer and prostate cancer. MELK-T1 inhibits catalytic activity and MELK protein stability and might sensitize tumors to DNA-damaging agents or radiation therapy by lowering the DNA-damage threshold. MELK inhibitor OTSSP167 is undergoing phase I clinical trials (Chung et al., 2012b; Ganguly et al., 2014; Beke et al., 2015).

MEX3A encodes a member of the mex-3 RNA binding family which consists of evolutionarily conserved RNA-binding proteins recruited to P bodies and potentially involved in post-transcriptional regulatory mechanisms (Buchet-Poyau et al., 2007). MEX3A is over-expressed and the gene is amplified in Wilms tumors associated with a late relapse (Krepischi et al., 2016). MEX3A regulates CDX2 via a post-transcriptional mechanism with impact in intestinal differentiation, polarity and stemness, contributing to intestinal homeostasis and carcinogeneses (Pereira et al., 2013).

MMP-11, also named stromelysin-3, is a member of the stromelysin subgroup belonging to MMPs superfamily, which has been detected in cancer cells, stromal cells and adjacent microenvironment. Differently, MMP-11 exerts a dual effect on tumors. On the one hand MMP-11 promotes cancer development by inhibiting apoptosis as well as

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enhancing migration and invasion of cancer cells, on the other hand MMP-11 plays a negative role against cancer development via suppressing metastasis in animal models. Overexpression of MMP-11 was discovered in sera of cancer patients compared with normal control group as well as in multiple tumor tissue specimens, such as gastric cancer, breast cancer, and pancreatic cancer (Zhang et al., 2016c). MMP-11 was demonstrated to be over-expressed at mRNA level and protein level in CRC tissue than paired normal mucosa. Further MMP-11 expression was correlated with CRC lymph node metastasis, distant metastasis and TNM stage (Tian et al., 2015). MMP-11 overexpression is associated with aggressive tumor phenotype and unfavorable clinical outcome in upper urinary tract urothelial carcinomas (UTUC) and urinary bladder urothelial carcinomas (UBUC), suggesting it may serve as a novel prognostic and therapeutic target (Li et al., 2016d).

MMP12 (also called MME) encodes a member of the matrix metalloproteinase family which is involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction and tissue remodeling as well as in disease processes, such as arthritis and metastasis (RefSeq, 2002). De-regulation of MMP12 is shown for different cancer entities. MMP12 is up-regulated in lung, skin, pancreatic and gastric cancer and related to tumor invasion and metastasis. In contrast, over-expression of MMP12 mRNA was found in gastric and colorectal cancer and correlated with a better prognosis (Zhang et al., 2007; Yang et al., 2001; Balaz et al., 2002; Zheng et al., 2013; Wen and Cai, 2014; Zhang et al., 2015f). MMP12 is up-regulated by TNF-alpha or EGF via the NF-kappaB/MAPK and JNK/AP-1 pathways (Yu et al., 2010; Yang et al., 2012).

MYO3B encodes the myosin IIIB, a member of a myosin-class that is characterized by an amino-terminal kinase domain and shown to be present in photoreceptors (RefSeq, 2002). MYO3B was identified as an antagonist to trastuzumab treatment among HER2+ cell lines (Lapin et al., 2014). Nucleotide polymorphisms in the MYOB3 gene were found to be associated with changes in the AUA Symptom Score after radiotherapy for prostate cancer (Kerns et al., 2013).

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NFE2L3 encodes nuclear factor, erythroid 2 like 3, a member of the cap 'n' collar basic-region leucine zipper family of transcription factors (RefSeq, 2002). Recent work has revealed that loss of NFE2L3 predisposes mice to lymphoma development. Others have observed high levels of NFE2L3 in colorectal cancer cells, whereas aberrant expression of NFE2L3 was found in Hodgkin lymphoma. Furthermore, NFE2L3 exhibited hypermethylation in ER positive tumors (Kuppers et al., 2003; Chevillard et al., 2011; Palma et al., 2012; Rauscher et al., 2015).

NLRP2 (also known as NALP2) encodes the NLR family, pyrin domain containing 2 protein and is involved in the activation of caspase-1 and may also form protein complexes activating proinflammatory caspases. NLRP7 is a paralog of NLRP2 (RefSeq, 2002; Wu et al., 2010; Slim et al., 2012). The PYRIN domain of NLRP2 inhibits cell proliferation and tumor growth of glioblastoma (Wu et al., 2010). An ATM/NLRP2/MDC1-dependent pathway may shut down ribosomal gene transcription in response to chromosome breaks (Kruhlak et al., 2007). Mutations in NLRP2 can cause rare human imprinting disorders such as familial hydatidiform mole, Beckwith-Wiedemann syndrome and familial transient neonatal diabetes mellitus (Aghajanova et al., 2015; Dias and Maher, 2013; Ulker et al., 2013). NLRP2 inhibits NF-kappaB activation (Kinoshita et al., 2005; Kinoshita et al., 2006; Fontalba et al., 2007; Bruey et al., 2004).

NLRP7 encodes the NLR family pyrin domain containing 7, a member of the NACHT, leucine rich repeat, and PYD containing (NLRP) protein family that may act as a feedback regulator of caspase-1-dependent interleukin 1-beta secretion (RefSeq, 2002). NLRP7 expression correlates significantly with the depth of tumor invasion and poor prognosis in endometrial cancer and was identified as one of the genes highly expressed in embryonal carcinomas (Ohno et al., 2008; Skotheim et al., 2005). NLRP7 might play a crucial role in cell proliferation in testicular tumorigenesis and represents a promising therapeutic target for testicular germ cell tumors (Okada et al., 2004).

OVGP1 or oviduct-specific glycoprotein, encodes a large, carbohydrate-rich, epithelial glycoprotein which is secreted from non-ciliated oviductal epithelial cells and associates

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with ovulated oocytes, blastomeres and spermatozoan acrosomal regions (RefSeq, 2002). Gain of OVGP1 was shown to be associated with the development of endometrial hyperplasia and endometrial cancer (Woo et al., 2004). OVGP1 was described as a molecular marker for invasion in endometrial tumorigenesis and a differentiation-based marker of different ovarian cancers (Maines-Bandiera et al., 2010; Wang et al., 2009).

PAGE2 encodes a member of the PAGE protein family, which is predominantly expressed in testis (Brinkmann et al., 1998). The cancer-testis gene PAGE2 is up-regulated by de-methylation during spontaneous differentiation of colorectal cancer cells resulting in mesenchymal-to-epithelial transition (MET). Accordingly, down-regulation of PAGE2 has been shown in EMT (Yilmaz-Ozcan et al., 2014). A genome-wide screening identifies PAGE2 as a possible regulator of telomere signaling in human cells (Lee et al., 2011).

PNOC encodes prepronociceptin which is a preproprotein that is proteolytically processed to generate multiple protein products. These products include nociceptin, nocistatin, and orphanin FQ2 (OFQ2). Nociceptin, also known as orphanin FQ, is a 17-amino acid neuropeptide that binds to the nociceptin receptor to induce increased pain sensitivity, and may additionally regulate body temperature, learning and memory, and hunger. Another product of the encoded preproprotein, nocistatin, may inhibit the effects of nociception (RefSeq, 2002). Inhibition of cancer pain also inhibits tumor growth and lung metastasis. PNOC is involved in morphine tolerance development. PNOC is involved in neuronal growth. PNOC is involved in cell damage, viability, inflammation and impaired immune function (Caputi et al., 2013; Chan et al., 2012; Kirkova et al., 2009; Kuraishi, 2014; Stamer et al., 2011). PNOC is up-regulated in ganglioglioma. PNOC expression is down-regulated in end-stage cancer. PNOC is highly expressed in the plasma of hepatocellular carcinoma patients (Chan et al., 2012; Stamer et al., 2011; Horvath et al., 2004; Spadaro et al., 2006; Szalay et al., 2004). Cebranopadol is an analgesic PNOC peptide may be used in bone cancer treatment and buprenorphine in lung cancer treatment (Davis, 2012; Linz et al., 2014). PNOC is involved in c-Fos expression (Gottlieb et al., 2007; Kazi et al., 2007).

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PRAME encodes an antigen that is preferentially expressed in human melanomas and acts as a repressor of retinoic acid receptor, likely conferring a growth advantage to cancer cell via this function (RefSeq, 2002). PRAME was shown to be up-regulated in multiple myeloma, clear cell renal cell carcinoma, breast cancer, acute myeloid leukemia, melanoma, chronic myeloid leukemia, head and neck squamous cell carcinoma and osteosarcoma cell lines (Dannenmann et al., 2013; Yao et al., 2014; Zou et al., 2012; Szczepanski and Whiteside, 2013; Zhang et al., 2013; Beard et al., 2013; Abdelmalak et al., 2014; Qin et al., 2014). PRAME is associated with myxoid and round-cell liposarcoma (Hemminger et al., 2014). PRAME is associated with shorter progression-free survival and chemotherapeutic response in diffuse large B-cell lymphoma treated with R-CHOP, markers of poor prognosis in head and neck squamous cell carcinoma, poor response to chemotherapy in urothelial carcinoma and poor prognosis and lung metastasis in osteosarcoma (Tan et al., 2012; Dyrskjot et al., 2012; Szczepanski et al., 2013; Mitsuhashi et al., 2014). PRAME is associated with lower relapse, lower mortality and overall survival in acute lymphoblastic leukemia (Abdelmalak et al., 2014). PRAME may be a prognostic marker for diffuse large B-cell lymphoma treated with R-CHOP therapy (Mitsuhashi et al., 2014).

RAD54 encodes a protein belonging to the DEAD-like helicase superfamily. It shares similarity with *Saccharomyces cerevisiae* RAD54 and RDH54, both of which are involved in homologous recombination and repair of DNA. This protein binds to double-stranded DNA, and displays ATPase activity in the presence of DNA. This gene is highly expressed in testis and spleen, which suggests active roles in meiotic and mitotic recombination (RefSeq, 2002). Homozygous mutations of RAD54B were observed in primary lymphoma and colon cancer (Hiramoto et al., 1999). RAD54B counteracts genome-destabilizing effects of direct binding of RAD51 to dsDNA in human tumor cells (Mason et al., 2015).

RNF17 encodes ring finger protein 17 which is similar to a mouse gene that encodes a testis-specific protein containing a RING finger domain. Alternatively spliced transcript variants encoding different isoforms have been found (RefSeq, 2002). RNF17 is involved in cytokine production and apoptosis. RNF17 enhances c-Myc function

(Jnawali et al., 2014; Lee et al., 2013; Yin et al., 1999; Yin et al., 2001). RNF17 is up-regulated upon RHOXF1 knock-down (Seifi-Alan et al., 2014). RNF17 is expressed in liver cancer (Yoon et al., 2011). RNF17 is a cancer-associated marker (de Matos et al., 2015).

SDK2 encodes the sidekick cell adhesion molecule 2, a member of the immunoglobulin superfamily that contains two immunoglobulin domains and thirteen fibronectin type III domains which represent binding sites for DNA, heparin and the cell surface (RefSeq, 2002). It was shown that SDK2 guides axonal terminals to specific synapses in developing neurons and promotes lamina-specific targeting of retinal dendrites in the inner plexiform layer (Kaufman et al., 2004; Yamagata and Sanes, 2012).

SPDEF (also called PDEF) encodes SAM pointed domain containing ETS transcription factor, a member of the E26 transformation-specific (ETS) family of transcription factors. It is highly expressed in prostate epithelial cells where it functions as an androgen-independent transactivator of prostate specific antigen (PSA) promoter (RefSeq, 2002). SPDEF expression is often lost or down-regulated in late-stage of tumor progression which means that it plays a role in tumor cell invasion and metastasis. In earlier stages of tumor progression SPDEF is sometimes up-regulated. De-regulation of SPDEF is described for several cancer entities including breast, prostate and colorectal cancer (Moussa et al., 2009; Schaefer et al., 2010; Steffan and Koul, 2011). SPDEF induces the transcription of E-cadherin and suppresses thereby cell invasion and migration (Pal et al., 2013). SPDEF interacts with beta-catenin and blocks the transcriptional activity resulting in lower protein levels of the oncogenes cyclin D1 and c-Myc (Noah et al., 2013).

SPON1 encodes spondin 1 and is located on chromosome 11p15.2 (RefSeq, 2002). SPON1 is involved in cancer cell proliferation, migration, invasion, and metastasis. SPON1 is involved in Fak and Src signaling. SPON1 is involved in IL-6 maintenance via MEKK/p38 MAPK/NF-kappaB signaling and this may support murine neuroblastoma survival (Chang et al., 2015a; Cheng et al., 2009; Dai et al., 2015). SPON1 is down-regulated by miR-506 (Dai et al., 2015). SPON1 is over-expressed in ovarian cancer

(Davidson et al., 2011; Jiao et al., 2013; Pyle-Chenault et al., 2005). SPON1 may have diagnostic potential in cancer prognosis (Pagnotta et al., 2013).

STAG3 encodes stromal antigen 3, which is expressed in the nucleus and is a subunit of the cohesin complex which regulates the cohesion of sister chromatids during cell division (RefSeq, 2002). Researchers have reported the involvement of a common allele of STAG3 in the development of epithelial ovarian cancer. Another group has identified STAG3 to be capable of effectively discriminating lung cancer, chronic obstructive lung disease and fibrotic interstitial lung diseases. Others have detected expression of the STAG3 gene in p53 mutated lymphoma cells (Notaridou et al., 2011; Wielscher et al., 2015; Kalejs et al., 2006).

TDRD5 encodes tudor domain containing 5 and is located on chromosome 1q25.2 (RefSeq, 2002). TDRD5 may be over-expressed in breast cancer (Jiang et al., 2016). TDRD5 methylation is altered upon resveratrol treatment in triple negative breast cancer (Medina-Aguilar et al., 2017). TDRD5 is part of a run of homozygosity associated with thyroid cancer (Thomsen et al., 2016).

TENM4 encodes teneurin transmembrane protein 4 which is expressed in the nervous systems and mesenchymal tissues and is a regulator of chondrogenesis (Suzuki et al., 2014). Among the four most frequently mutated genes was TENM4 showing protein-changing mutations in primary CNS lymphomas (Vater et al., 2015). MDA-MB-175 cell line contains a chromosomal translocation that leads to the fusion of TENM4 and receptors of the ErbB family. Chimeric genes were also found in neuroblastomas (Wang et al., 1999; Boeva et al., 2013).

TMPRSS3 encodes transmembrane protease, serine 3 which is a protein that belongs to the serine protease family. The encoded protein contains a serine protease domain, a transmembrane domain, an LDL receptor-like domain, and a scavenger receptor cysteine-rich domain. Serine proteases are known to be involved in a variety of biological processes, whose malfunction often leads to human diseases and disorders. This gene was identified by its association with both congenital and childhood onset autosomal recessive deafness. This gene is expressed in fetal cochlea and many other

tissues, and is thought to be involved in the development and maintenance of the inner ear or the contents of the perilymph and endolymph. This gene was also identified as a tumor-associated gene that is overexpressed in ovarian tumors (RefSeq, 2002). TMPRSS3 is involved in cell proliferation, invasion, and migration. TMPRSS3 induces ERK1/2 signaling (Zhang et al., 2016a). TMPRSS3 affects E-cadherin, vimentin, and Twist expression. TMPRSS3 is down-regulated by hexamethylene bisacetamide (Zhang et al., 2016a; Zhang et al., 2004). TMPRSS3 is up-regulated in breast cancer, pancreatic cancer, and ovarian cancer. TMPRSS3 is de-regulated in gastric cancer and pancreatic ductal adenocarcinoma (Rui et al., 2015; Zhang et al., 2016a; Zhang et al., 2004; Amsterdam et al., 2014; Iacobuzio-Donahue et al., 2003; Luo et al., 2017; Underwood et al., 2000; Wallrapp et al., 2000). TMPRSS3 is associated with TNM stage, lymph node metastasis, distant organ metastasis, shorter survival, shorter disease-free survival, and poor prognosis. TMPRSS3 may be used as biomarker in cancer. TMPRSS3 mutations are associated with cancer risk. TMPRSS3 may be used for early pancreatic ductal adenocarcinoma detection (Rui et al., 2015; Amsterdam et al., 2014; Luo et al., 2017; Dorn et al., 2014; Luostari et al., 2014; Pelkonen et al., 2015; Sawasaki et al., 2004). TMPRSS3 is hypo-methylated in cancer (Guerrero et al., 2012).

VTCN1, also known as B7-H4, encodes a member of the B7 costimulatory protein family which is present on the surface of antigen-presenting cells and interacts with ligands bound to receptors on the surface of T cells (RefSeq, 2002). VTCN1 was shown to be up-regulated in lung cancer, colorectal cancer, hepatocellular carcinoma, osteosarcoma, breast cancer, cervical cancer, urothelial cell carcinoma, gastric cancer, endometrial cancer, thyroid cancer and laryngeal carcinoma (Klatka et al., 2013; Zhu et al., 2013; Vanderstraeten et al., 2014; Shi et al., 2014; Fan et al., 2014; Wang et al., 2014; Leong et al., 2015; Dong and Ma, 2015; Zhang et al., 2015a; Peng et al., 2015; Xu et al., 2015a). VTCN1 is associated with poor overall survival and higher recurrence probability in hepatocellular carcinoma and poor overall survival in osteosarcoma, urothelial cell carcinoma, pancreatic cancer, gastric cancer, cervical cancer, melanoma and thyroid cancer (Zhu et al., 2013; Seliger, 2014; Liu et al., 2014b; Chen et al., 2014; Fan et al., 2014; Dong and Ma, 2015; Zhang et al., 2015a). VTCN1 is associated with clear cell renal cell carcinoma (Xu et al., 2014b). VTCN1 expression levels were shown

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to be inversely correlated with patient survival in ovarian cancer (Smith et al., 2014). VTCN1 may be a potential prognostic indicator of urothelial cell carcinoma and gastric cancer (Shi et al., 2014; Fan et al., 2014).

WNT7A encodes Wnt family member 7A which is a member of the WNT gene family. These proteins have been implicated in oncogenesis and in several developmental processes, including regulation of cell fate and patterning during embryogenesis. This gene is involved in the development of the anterior-posterior axis in the female reproductive tract, and also plays a critical role in uterine smooth muscle patterning and maintenance of adult uterine function. Mutations in this gene are associated with Fuhrmann and Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndromes (RefSeq, 2002). WNT7A is induced by STAT4 resulting in the activation of cancer-associated fibroblasts. WNT7A potentiates TGF-beta receptor signaling. WNT7A is involved in cell proliferation and migration. WNT7A is an upstream inducer of senescence. PG545 interacts with WNT7A resulting in inhibited cell proliferation. WNT7A suppresses tumor growth. WNT7A is involved in Wnt/beta-catenin signaling and regulates hsa-miR29b (Avasarala et al., 2013; Avgustinova et al., 2016; Bikkavilli et al., 2015; Borowicz et al., 2014; Jung et al., 2015; King et al., 2015; Ramos-Solano et al., 2015; Zhao et al., 2017). WNT7A is regulated by miR-15b and down-regulated by DNMT1. Endosulfan disrupts WNT7A. WNT7A is a target gene of miR-199a-5p and miR-195/497. WNT7A is down-regulated by chronic ethanol exposure and rescued by PPAR-delta agonist treatment. Dkk-1 affects WNT7A. Bilobalide enhances WNT7A expression (Kim et al., 2015a; Chandra et al., 2014; Ingaramo et al., 2016; Itesako et al., 2014; Liu et al., 2014a; MacLean et al., 2016; Mercer et al., 2014; Mercer et al., 2015; Xu et al., 2015b). WNT7A is down-regulated and hyper-methylated in cervical cancer. WNT7A is lost in lung cancer. WNT7A is over-expressed in endometrial cancer (Ramos-Solano et al., 2015; Kim et al., 2015b; Liu et al., 2013). WNT7A expression correlates with poor prognosis and poor patient outcome. WNT7A promotor methylation correlates with advanced tumor stage, distant metastasis, and loss of E-cadherin. Decreased WNT7A expression correlates with decreased overall survival in malignant pleural mesothelioma and may be used for chemosensitivity prediction (Avgustinova et al., 2016; King et al.,

2015; Kim et al., 2015b; Hirata et al., 2015). WNT7A may be a tumor suppressor gene in nasopharyngeal cancer (Nawaz et al., 2015).

DETAILED DESCRIPTION OF THE INVENTION

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.

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).

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 cytotoxic T cells, 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.

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

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in length, but can be as short as 8 amino acids in length, and as long as 10, 11, or 12 or longer, and in case of MHC class II peptides (elongated variants of the peptides of the invention) they can be as long as 13, 14, 15, 16, 17, 18, 19 or 20 or more amino acids in length.

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 invention differ substantially from the peptides in their state(s) *in vivo*, as the peptides are not salts *in vivo*.

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.

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.

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

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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.

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.

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 6: Expression frequencies F of HLA-A*02, HLA-A*01, HLA-A*03, HLA-A*24, HLA-B*07, HLA-B*08 and HLA-B*44 serotypes. Haplotype frequencies Gf are derived from a study which used HLA-typing data from a registry of more than 6.5 million volunteer donors in the U.S. (Gragert et al., 2013). The haplotype frequency is the frequency of a distinct allele on an individual chromosome. Due to the diploid set of chromosomes within mammalian cells, the frequency of genotypic occurrence of this allele is higher and can be calculated employing the Hardy-Weinberg principle ($F = 1 - (1-Gf)^2$).

Allele	Population	Calculated phenotype from allele frequency (F)
A*02	African (N=28557)	32.3%
	European Caucasian	49.3%

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Allele	Population	Calculated phenotype from allele frequency (F)
	(N=1242890)	
	Japanese (N=24582)	42.7%
	Hispanic, S + Cent Amer. (N=146714)	46.1%
	Southeast Asian (N=27978)	30.4%
A*01	African (N=28557)	10.2%
	European Caucasian (N=1242890)	30.2%
	Japanese (N=24582)	1.8%
	Hispanic, S + Cent Amer. (N=146714)	14.0%
	Southeast Asian (N=27978)	21.0%
A*03	African (N=28557)	14.8%
	European Caucasian (N=1242890)	26.4%
	Japanese (N=24582)	1.8%
	Hispanic, S + Cent Amer. (N=146714)	14.4%
	Southeast Asian (N=27978)	10.6%
A*24	African (N=28557)	2.0%
	European Caucasian (N=1242890)	8.6%
	Japanese (N=24582)	35.5%
	Hispanic, S + Cent Amer. (N=146714)	13.6%
	Southeast Asian (N=27978)	16.9%
B*07	African (N=28557)	14.7%
	European Caucasian (N=1242890)	25.0%
	Japanese (N=24582)	11.4%
	Hispanic, S + Cent Amer. (N=146714)	12.2%
	Southeast Asian (N=27978)	10.4%
B*08	African (N=28557)	6.0%
	European Caucasian (N=1242890)	21.6%
	Japanese (N=24582)	1.0%
	Hispanic, S + Cent Amer. (N=146714)	7.6%
	Southeast Asian (N=27978)	6.2%

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Allele	Population	Calculated phenotype from allele frequency (F)
B*44	African (N=28557)	10.6%
	European Caucasian (N=1242890)	26.9%
	Japanese (N=24582)	13.0%
	Hispanic, S + Cent Amer. (N=146714)	18.2%
	Southeast Asian (N=27978)	13.1%

The peptides of the invention, preferably when included into a vaccine of the invention as described herein bind to A*02, A*01, A*03, A*24, B*07, B*08 or B*44. A vaccine may also include pan-binding MHC class II peptides. Therefore, the vaccine of the invention can be used to treat cancer in patients that are A*02-, A*01-, A*03-, A*24-, B*07-, B*08- or B*44-positive, whereas no selection for MHC class II allotypes is necessary due to the pan-binding nature of these peptides.

If A*02 peptides of the invention are combined with peptides binding to another allele, for example A*24, 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, a vaccine comprising HLA-A*24 and HLA-A*02 epitopes 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.allelefreqencies.net).

Table 7: HLA alleles coverage in European Caucasian population (calculated from (Gragert et al., 2013)).

	coverage (at least one A- allele)	combined with B*07	combined with B*44	combined with B*07 and B*44
A*02 / A*01	70%	78%	78%	84%
A*02 / A*03	68%	76%	76%	83%
A*02 / A*24	61%	71%	71%	80%

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A*01 / A*03	52%	64%	65%	75%
A*01 / A*24	44%	58%	59%	71%
A*03 / A*24	40%	55%	56%	69%
A*02 / A*01 / A*03	84%	88%	88%	91%
A*02 / A*01 / A*24	79%	84%	84%	89%
A*02 / A*03 / A*24	77%	82%	83%	88%
A*01 / A*03 / A*24	63%	72%	73%	81%
A*02 / A*01 / A*03 / A*24	90%	92%	93%	95%

In a preferred embodiment, the term “nucleotide sequence” refers to a heteropolymer of deoxyribonucleotides.

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 invention 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.

As used herein the term “a nucleotide coding for (or encoding) 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.

As used herein, reference to a nucleic acid sequence includes both single stranded and double stranded nucleic acid. Thus, for example for DNA, 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

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environment, i.e., the region coding *in vivo* for the native expression product of the gene.

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.

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).

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.

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.

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.

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The term “promoter” means a region of DNA involved in binding of RNA polymerase to initiate transcription.

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.

The polynucleotides, and recombinant or immunogenic polypeptides, disclosed in accordance with the present invention 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 encompassed.

The nucleic acids and polypeptide expression products disclosed according to the present invention, 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 invention can advantageously be in

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enriched or isolated form. 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*.

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.

In accordance with the present invention, the term “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

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(iii) 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.

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.

As mentioned above, the present invention thus provides a peptide comprising a sequence that is selected from the group of consisting of SEQ ID NO: 1 to SEQ ID NO: 772 or a variant thereof which is 88% homologous to SEQ ID NO: 1 to SEQ ID NO: 772, or a variant thereof that will induce T cells cross-reacting with said peptide. The peptides of the invention 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.

In the present invention, 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 tools are provided by public databases.

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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 (Appay et al., 2006; Colombetti et al., 2006; Fong et al., 2001; Zaremba et al., 1997).

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: 772. 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.

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 invention. As can be derived from the scientific literature and databases (Rammensee et al., 1999; Godkin et al., 1997), 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 772, 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 invention 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 invention.

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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."

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).

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.

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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 invention and yet still be encompassed by the disclosure herein. In addition, non-standard amino acids (i.e., other than the common naturally occurring proteinogenic amino acids) may also be used for substitution purposes to produce immunogens and immunogenic polypeptides according to the present invention.

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 be simultaneously substituted.

A peptide 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 embodiment, 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.

The amino acid residues that do not substantially contribute to interactions with the T-cell receptor can be modified by replacement with other 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.

		V								Y	
		V								R	
		V								F	
		T									
		T								Y	
		T								R	
		T								F	
Position	1	2	3	4	5	6	7	8	9	10	
SEQ ID No 108	V	L	Y	P	V	P	L	E	S	Y	
Variant										K	
										R	
										F	
		I								K	
		I									
		I								R	
		I								F	
		M								K	
		M									
		M								R	
		M								F	
		V								K	
		V									
		V								R	
		V								F	
		T								K	
		T									
		T								R	
		T								F	
Position	1	2	3	4	5	6	7	8	9		
SEQ ID No 113	Q	L	D	S	N	R	L	T	Y		
Variant		S									
		S							A		
		S	E								
		S	E						A		
		T									
		T							A		
		T	E								
		T	E						A		
Position	1	2	3	4	5	6	7	8	9	10	
SEQ ID No 114	V	M	E	Q	S	A	G	I	M	Y	
Variant		S	D								

[illegible]

					R				F		
					R						
					R				V		
					R				I		
					R				M		
					R				F		
					H						
					H				V		
					H				I		
					H				M		
					H				F		
			L								
			L						V		
			L						I		
			L						M		
			L						F		
			L		R						
			L		R				V		
			L		R				I		
			L		R				M		
			L		R				F		
			L		H						
			L		H				V		
			L		H				I		
			L		H				M		
			L		H				F		
Position	1	2	3	4	5	6	7	8	9		
SEQ ID No 172	K	L	K	E	R	N	R	E	L		
Variant					K						
					K				V		
					K				I		
					K				M		
					K				F		
									V		
									I		
									M		
									F		
					H						
					H				V		
					H				I		
					H				M		

					H				F		
			R		K						
			R		K				V		
			R		K				I		
			R		K				M		
			R		K				F		
			R								
			R						V		
			R						I		
			R						M		
			R						F		
			R		H						
			R		H				V		
			R		H				I		
			R		H				M		
			R		H				F		
			L		K						
			L		K				V		
			L		K				I		
			L		K				M		
			L		K				F		
			L								
			L						V		
			L						I		
			L						M		
			L						F		
			L		H						
			L		H				V		
			L		H				I		
			L		H				M		
			L		H				F		
Position	1	2	3	4	5	6	7	8	9	10	11
SEQ ID No 54	A	E	I	T	I	T	T	Q	T	G	Y
Variant											F
											W
											L
		D									F
		D									W
		D									
		D									L
Position	1	2	3	4	5	6	7	8	9		

SEQ ID No 57	Q	E	S	D	L	R	L	F	L		
Variant									F		
									W		
									Y		
		D							F		
		D							W		
		D							Y		
		D									

Longer (elongated) peptides may also be suitable. It is 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.

The peptides of the invention 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. Combinations of the elongations according to the invention can be found in Table 9.

Table 9: Combinations of the elongations of peptides of the invention

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

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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.

Thus, the epitopes of the present invention 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.

In an alternative embodiment, the peptide is elongated on either or both sides by more than 4 amino acids, preferably to a total length of up to 30 amino acids. This may lead to MHC class II binding peptides. Binding to MHC class II can be tested by methods known in the art.

Accordingly, the present invention 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, 22, 23, 24 or 25 amino acids.

Of course, the peptide or variant according to the present invention 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.

Preferably, when the T cells specific for a peptide according to the present invention 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 μ M, 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

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recognized by T cells from more than one individual, at least two, and more preferably three individuals.

In a particularly preferred embodiment of the invention the peptide consists or consists essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 772.

“Consisting essentially of” shall mean that a peptide according to the present invention, in addition to the sequence according to any of SEQ ID NO: 1 to SEQ ID NO 772 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.

Nevertheless, these stretches can be important to provide an efficient introduction of the peptide according to the present invention into the cells. In one embodiment of the present invention, 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 invention 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.

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.

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) (Meziere et al., 1997), incorporated herein by reference. This approach

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involves making pseudopeptides containing changes involving the backbone, and not the orientation of side chains. Meziere et al. (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.

A non-peptide bond is, for example, -CH₂-NH, -CH₂S-, -CH₂CH₂-, -CH=CH-, -COCH₂-, -CH(OH)CH₂-, and -CH₂SO-. US 4,897,445 provides a method for the solid phase synthesis of non-peptide bonds (-CH₂-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 NaCNBH₃.

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 carbobenzoxy, dansyl, or t-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.

Further, the peptides of the invention 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 invention 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, bioavailability and/or binding action of the peptides of the invention.

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Similarly, a peptide or variant of the invention 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, 2004 (Lundblad, 2004), which is incorporated herein by reference. 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) (Coligan et al., 1995) for more extensive methodology relating to chemical modification of proteins.

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.

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.

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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.

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.

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).

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.

A peptide or variant, wherein the peptide is modified or includes non-peptide bonds is a preferred embodiment of the invention.

Another embodiment of the present invention relates to a non-naturally occurring peptide wherein said peptide consists or consists essentially of an amino acid sequence according to SEQ ID No: 1 to SEQ ID No: 772 and has been synthetically produced (e.g. synthesized) as a pharmaceutically acceptable salt. Methods to synthetically produce peptides are well known in the art. The salts of the peptides according to the present invention differ substantially from the peptides in their state(s) *in vivo*, as the peptides as generated *in vivo* are no salts. The non-natural salt form of the peptide

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mediates the solubility of the peptide, in particular in the context of pharmaceutical compositions comprising the peptides, e.g. the peptide vaccines as disclosed herein. A sufficient and at least substantial solubility of the peptide(s) is required in order to efficiently provide the peptides to the subject to be treated. Preferably, the salts are pharmaceutically acceptable salts of the peptides. These salts according to the invention include alkaline and earth alkaline salts such as salts of the Hofmeister series comprising as anions PO_4^{3-} , SO_4^{2-} , CH_3COO^- , Cl^- , Br^- , NO_3^- , ClO_4^- , I^- , SCN^- and as cations NH_4^+ , Rb^+ , K^+ , Na^+ , Cs^+ , Li^+ , Zn^{2+} , Mg^{2+} , Ca^{2+} , Mn^{2+} , Cu^{2+} and Ba^{2+} . Particularly salts are selected from $(\text{NH}_4)_3\text{PO}_4$, $(\text{NH}_4)_2\text{HPO}_4$, $(\text{NH}_4)\text{H}_2\text{PO}_4$, $(\text{NH}_4)_2\text{SO}_4$, $\text{NH}_4\text{CH}_3\text{COO}$, NH_4Cl , NH_4Br , NH_4NO_3 , NH_4ClO_4 , NH_4I , NH_4SCN , Rb_3PO_4 , Rb_2HPO_4 , RbH_2PO_4 , Rb_2SO_4 , $\text{Rb}_4\text{CH}_3\text{COO}$, Rb_4Cl , Rb_4Br , Rb_4NO_3 , Rb_4ClO_4 , Rb_4I , Rb_4SCN , K_3PO_4 , K_2HPO_4 , KH_2PO_4 , K_2SO_4 , KCH_3COO , KCl , KBr , KNO_3 , KClO_4 , KI , KSCN , Na_3PO_4 , Na_2HPO_4 , NaH_2PO_4 , Na_2SO_4 , NaCH_3COO , NaCl , NaBr , NaNO_3 , NaClO_4 , NaI , NaSCN , ZnCl_2 , Cs_3PO_4 , Cs_2HPO_4 , CsH_2PO_4 , Cs_2SO_4 , CsCH_3COO , CsCl , CsBr , CsNO_3 , CsClO_4 , CsI , CsSCN , Li_3PO_4 , Li_2HPO_4 , LiH_2PO_4 , Li_2SO_4 , LiCH_3COO , LiCl , LiBr , LiNO_3 , LiClO_4 , LiI , LiSCN , Cu_2SO_4 , $\text{Mg}_3(\text{PO}_4)_2$, Mg_2HPO_4 , $\text{Mg}(\text{H}_2\text{PO}_4)_2$, Mg_2SO_4 , $\text{Mg}(\text{CH}_3\text{COO})_2$, MgCl_2 , MgBr_2 , $\text{Mg}(\text{NO}_3)_2$, $\text{Mg}(\text{ClO}_4)_2$, MgI_2 , $\text{Mg}(\text{SCN})_2$, MnCl_2 , $\text{Ca}_3(\text{PO}_4)_2$, Ca_2HPO_4 , $\text{Ca}(\text{H}_2\text{PO}_4)_2$, CaSO_4 , $\text{Ca}(\text{CH}_3\text{COO})_2$, CaCl_2 , CaBr_2 , $\text{Ca}(\text{NO}_3)_2$, $\text{Ca}(\text{ClO}_4)_2$, CaI_2 , $\text{Ca}(\text{SCN})_2$, $\text{Ba}_3(\text{PO}_4)_2$, Ba_2HPO_4 , $\text{Ba}(\text{H}_2\text{PO}_4)_2$, BaSO_4 , $\text{Ba}(\text{CH}_3\text{COO})_2$, BaCl_2 , BaBr_2 , $\text{Ba}(\text{NO}_3)_2$, $\text{Ba}(\text{ClO}_4)_2$, BaI_2 , and $\text{Ba}(\text{SCN})_2$. Particularly preferred are NH acetate, MgCl_2 , KH_2PO_4 , Na_2SO_4 , KCl , NaCl , and CaCl_2 , such as, for example, the chloride or acetate (trifluoroacetate) salts.

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. (Lukas et al., 1981) and by 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),

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butyloxycarbonyl derivative (in the case of lysine and histidine), trityl derivative (in the case of cysteine) and 4-methoxy-2,3,6-trimethylbenzenesulphonyl derivative (in the case of arginine). Where glutamine or asparagine are C-terminal residues, use is made of the 4,4'-dimethoxybenzhydryl group for protection of the side chain amido functionalities. The solid-phase support is based on a polydimethyl-acrylamide polymer constituted from the three monomers dimethylacrylamide (backbone-monomer), bisacryloylethylene diamine (cross linker) and acryloylsarcosine methyl ester (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-dicyclohexylcarbodiimide/1hydroxybenzotriazole 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 ethanedithiol, 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).

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).

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

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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.

For the identification 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 tumor-associated peptides (TUMAPs) recorded from ovarian cancer samples ($N \geq 80$ 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 ≥ 80 ovarian cancer patients (cf. Example 1).

The discovery pipeline XPRESIDENT® v2.1 (see, for example, US 2013-0096016, which is hereby incorporated by reference in its entirety) 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.

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HLA-peptide complexes from ovarian cancer tissue samples were purified and HLA-associated peptides were isolated and analyzed by LC-MS (see example 1). All TUMAPs contained in the present application were identified with this approach on primary ovarian cancer samples confirming their presentation on primary ovarian cancer.

Besides presentation of the peptide, mRNA expression of the underlying gene was tested. mRNA data were obtained via RNASeq analyses of normal tissues and cancer tissues (cf. Example 2, Figure 1). Peptides which are derived from proteins whose coding mRNA is highly expressed in cancer tissue, but very low or absent in vital normal tissues, were preferably included in the present invention.

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

Many of the source gene/proteins (also designated “full-length proteins” or “underlying proteins”) from which the peptides are derived were shown to be highly over-expressed in cancer compared with normal tissues – “normal tissues” in relation to this invention shall mean either healthy ovarian 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 presented on tumor tissue – “tumor tissue” in relation to this invention shall mean a sample from a patient suffering from ovarian cancer.

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. ovarian cancer cells presenting the derived peptides.

The peptides of the present invention 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

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antibodies and/or TCRs, such as soluble TCRs, according to the present invention (see Example 3, Example 4). Furthermore, the peptides when complexed with the respective MHC can be used for the production of antibodies and/or TCRs, in particular sTCRs, according to the present invention, as well. Respective methods are well known to the person of skill, and can be found in the respective literature as well (see also below). Thus, the peptides of the present invention 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 invention are not presented on normal tissues in comparable copy numbers, preventing the risk of undesired autoimmune reactions against normal cells in the patient.

The present description further relates to T-cell receptors (TCRs) comprising an alpha chain and a beta chain ("alpha/beta TCRs"). Also provided are peptides according to the invention capable of binding to TCRs and antibodies when presented by an MHC molecule.

The present description also relates to fragments of the TCRs according to the invention that are capable of binding to a peptide antigen according to the present invention when presented by an HLA molecule. The term particularly relates to soluble TCR fragments, for example TCRs missing the transmembrane parts and/or constant regions, single chain TCRs, and fusions thereof to, for example, with Ig.

The present description also relates to nucleic acids, vectors and host cells for expressing TCRs and peptides of the present description; and methods of using the same.

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The term "T-cell receptor" (abbreviated TCR) refers to a heterodimeric molecule comprising an alpha polypeptide chain (alpha chain) and a beta polypeptide chain (beta chain), wherein the heterodimeric receptor is capable of binding to a peptide antigen presented by an HLA molecule. The term also includes so-called gamma/delta TCRs.

In one embodiment the description provides a method of producing a TCR as described herein, the method comprising culturing a host cell capable of expressing the TCR under conditions suitable to promote expression of the TCR.

The description in another aspect relates to methods according to the description, 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 or the antigen is loaded onto class I or II MHC tetramers by tetramerizing the antigen/class I or II MHC complex monomers.

The alpha and beta chains of alpha/beta TCR's, and the gamma and delta chains of gamma/delta TCRs, are generally regarded as each having two "domains", namely variable and constant domains. The variable domain consists of a concatenation of variable region (V), and joining region (J). The variable domain may also include a leader region (L). Beta and delta chains may also include a diversity region (D). The alpha and beta constant domains may also include C-terminal transmembrane (TM) domains that anchor the alpha and beta chains to the cell membrane.

With respect to gamma/delta TCRs, the term "TCR gamma variable domain" as used herein refers to the concatenation of the TCR gamma V (TRGV) region without leader region (L), and the TCR gamma J (TRGJ) region, and the term TCR gamma constant domain refers to the extracellular TRGC region, or to a C-terminal truncated TRGC sequence. Likewise the term "TCR delta variable domain" refers to the concatenation of the TCR delta V (TRDV) region without leader region (L) and the TCR delta D/J

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(TRDD/TRDJ) region, and the term “TCR delta constant domain” refers to the extracellular TRDC region, or to a C-terminal truncated TRDC sequence.

TCRs of the present description preferably bind to an peptide-HLA molecule complex with a binding affinity (KD) of about 100 μ M or less, about 50 μ M or less, about 25 μ M or less, or about 10 μ M or less. More preferred are high affinity TCRs having binding affinities of about 1 μ M or less, about 100 nM or less, about 50 nM or less, about 25 nM or less. Non-limiting examples of preferred binding affinity ranges for TCRs of the present invention include about 1 nM to about 10 nM; about 10 nM to about 20 nM; about 20 nM to about 30 nM; about 30 nM to about 40 nM; about 40 nM to about 50 nM; about 50 nM to about 60 nM; about 60 nM to about 70 nM; about 70 nM to about 80 nM; about 80 nM to about 90 nM; and about 90 nM to about 100 nM.

As used herein in connect with TCRs of the present description, “specific binding” and grammatical variants thereof are used to mean a TCR having a binding affinity (KD) for a peptide-HLA molecule complex of 100 μ M or less.

Alpha/beta heterodimeric TCRs of the present description may have an introduced disulfide bond between their constant domains. Preferred TCRs of this type include those which have a TRAC constant domain sequence and a TRBC1 or TRBC2 constant domain sequence except that Thr 48 of TRAC and Ser 57 of TRBC1 or TRBC2 are replaced by cysteine residues, the said cysteines forming a disulfide bond between the TRAC constant domain sequence and the TRBC1 or TRBC2 constant domain sequence of the TCR.

With or without the introduced inter-chain bond mentioned above, alpha/beta heterodimeric TCRs of the present description may have a TRAC constant domain sequence and a TRBC1 or TRBC2 constant domain sequence, and the TRAC constant domain sequence and the TRBC1 or TRBC2 constant domain sequence of the TCR may be linked by the native disulfide bond between Cys4 of exon 2 of TRAC and Cys2 of exon 2 of TRBC1 or TRBC2.

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TCRs of the present description may comprise a detectable label selected from the group consisting of a radionuclide, a fluorophore and biotin. TCRs of the present description may be conjugated to a therapeutically active agent, such as a radionuclide, a chemotherapeutic agent, or a toxin.

In an embodiment, a TCR of the present description having at least one mutation in the alpha chain and/or having at least one mutation in the beta chain has modified glycosylation compared to the unmutated TCR.

In an embodiment, a TCR comprising at least one mutation in the TCR alpha chain and/or TCR beta chain has a binding affinity for, and/or a binding half-life for, a peptide-HLA molecule complex, which is at least double that of a TCR comprising the unmutated TCR alpha chain and/or unmutated TCR beta chain. Affinity-enhancement of tumor-specific TCRs, and its exploitation, relies on the existence of a window for optimal TCR affinities. The existence of such a window is based on observations that TCRs specific for HLA-A2-restricted pathogens have KD values that are generally about 10-fold lower when compared to TCRs specific for HLA-A2-restricted tumor-associated self-antigens. It is now known, although tumor antigens have the potential to be immunogenic, because tumors arise from the individual's own cells only mutated proteins or proteins with altered translational processing will be seen as foreign by the immune system. Antigens that are upregulated or overexpressed (so called self-antigens) will not necessarily induce a functional immune response against the tumor: T-cells expressing TCRs that are highly reactive to these antigens will have been negatively selected within the thymus in a process known as central tolerance, meaning that only T-cells with low-affinity TCRs for self-antigens remain. Therefore, affinity of TCRs or variants of the present description to peptides can be enhanced by methods well known in the art.

The present description further relates to a method of identifying and isolating a TCR according to the present description, said method comprising incubating PBMCs from

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HLA-A*02-negative healthy donors with, for example, A2/peptide monomers, incubating the PBMCs with tetramer-phycoerythrin (PE) and isolating the high avidity T-cells by fluo-rescence activated cell sorting (FACS)—Calibur analysis.

The present description further relates to a method of identifying and isolating a TCR according to the present description, said method comprising obtaining a transgenic mouse with the entire human TCR $\alpha\beta$ gene loci (1.1 and 0.7 Mb), whose T-cells express a diverse human TCR repertoire that compensates for mouse TCR deficiency, immunizing the mouse with a peptide, incubating PBMCs obtained from the transgenic mice with tetramer-phycoerythrin (PE), and isolating the high avidity T-cells by fluorescence activated cell sorting (FACS)—Calibur analysis.

In one aspect, to obtain T-cells expressing TCRs of the present description, nucleic acids encoding TCR-alpha and/or TCR-beta chains of the present description are cloned into expression vectors, such as gamma retrovirus or lentivirus. The recombinant viruses are generated and then tested for functionality, such as antigen specificity and functional avidity. An aliquot of the final product is then used to transduce the target T-cell population (generally purified from patient PBMCs), which is expanded before infusion into the patient.

In another aspect, to obtain T-cells expressing TCRs of the present description, TCR RNAs are synthesized by techniques known in the art, e.g., in vitro transcription systems. The in vitro-synthesized TCR RNAs are then introduced into primary CD8⁺ T-cells obtained from healthy donors by electroporation to re-express tumor specific TCR-alpha and/or TCR-beta chains.

To increase the expression, nucleic acids encoding TCRs of the present description may be operably linked to strong promoters, such as retroviral long terminal repeats (LTRs), cytomegalovirus (CMV), murine stem cell virus (MSCV) U3, phosphoglycerate kinase (PGK), β -actin, ubiquitin, and a simian virus 40 (SV40)/CD43 composite promoter, elongation factor (EF)-1a and the spleen focus-forming virus (SFFV)

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promoter. In a preferred embodiment, the promoter is heterologous to the nucleic acid being expressed.

In addition to strong promoters, TCR expression cassettes of the present description may contain additional elements that can enhance transgene expression, including a central polypurine tract (cPPT), which promotes the nuclear translocation of lentiviral constructs (Follenzi et al., 2000), and the woodchuck hepatitis virus posttranscriptional regulatory element (wPRE), which increases the level of transgene expression by increasing RNA stability (Zufferey et al., 1999).

The alpha and beta chains of a TCR of the present invention may be encoded by nucleic acids located in separate vectors, or may be encoded by polynucleotides located in the same vector.

Achieving high-level TCR surface expression requires that both the TCR-alpha and TCR-beta chains of the introduced TCR be transcribed at high levels. To do so, the TCR-alpha and TCR-beta chains of the present description may be cloned into bicistronic constructs in a single vector, which has been shown to be capable of overcoming this obstacle. The use of a viral intraribosomal entry site (IRES) between the TCR-alpha and TCR-beta chains results in the coordinated expression of both chains, because the TCR-alpha and TCR-beta chains are generated from a single transcript that is broken into two proteins during translation, ensuring that an equal molar ratio of TCR-alpha and TCR-beta chains are produced (Schmitt et al., 2009).

Nucleic acids encoding TCRs of the present description may be codon optimized to increase expression from a host cell. Redundancy in the genetic code allows some amino acids to be encoded by more than one codon, but certain codons are less “optimal” than others because of the relative availability of matching tRNAs as well as other factors (Gustafsson et al., 2004). Modifying the TCR-alpha and TCR-beta gene sequences such that each amino acid is encoded by the optimal codon for mammalian gene expression, as well as eliminating mRNA instability motifs or cryptic splice sites,

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has been shown to significantly enhance TCR-alpha and TCR-beta gene expression (Scholten et al., 2006).

Furthermore, mispairing between the introduced and endogenous TCR chains may result in the acquisition of specificities that pose a significant risk for autoimmunity. For example, the formation of mixed TCR dimers may reduce the number of CD3 molecules available to form properly paired TCR complexes, and therefore can significantly decrease the functional avidity of the cells expressing the introduced TCR (Kuball et al., 2007).

To reduce mispairing, the C-terminus domain of the introduced TCR chains of the present description may be modified in order to promote interchain affinity, while decreasing the ability of the introduced chains to pair with the endogenous TCR. These strategies may include replacing the human TCR-alpha and TCR-beta C-terminus domains with their murine counterparts (murinized C-terminus domain); generating a second interchain disulfide bond in the C-terminus domain by introducing a second cysteine residue into both the TCR-alpha and TCR-beta chains of the introduced TCR (cysteine modification); swapping interacting residues in the TCR-alpha and TCR-beta chain C-terminus domains ("knob-in-hole"); and fusing the variable domains of the TCR-alpha and TCR-beta chains directly to CD3 ζ (CD3 ζ fusion) (Schmitt et al., 2009).

In an embodiment, a host cell is engineered to express a TCR of the present description. In preferred embodiments, the host cell is a human T-cell or T-cell progenitor. In some embodiments the T-cell or T-cell progenitor is obtained from a cancer patient. In other embodiments the T-cell or T-cell progenitor is obtained from a healthy donor. Host cells of the present description can be allogeneic or autologous with respect to a patient to be treated. In one embodiment, the host is a gamma/delta T-cell transformed to express an alpha/beta TCR.

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A "pharmaceutical composition" is 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.

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 $-NH_2$ 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.

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

Preferably, the medicament of the present invention is an immunotherapeutic such as 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

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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 WO 95/18145 and (Longenecker et al., 1993)). 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.

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. 772, 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.

A further aspect of the invention provides a nucleic acid (for example a polynucleotide) encoding a peptide or peptide variant of the invention. 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 invention provides an expression vector capable of expressing a polypeptide according to the invention.

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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.

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.

A desirable method of modifying the DNA encoding the polypeptide of the invention 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.

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 invention. Thus, the DNA encoding the peptide or variant of the invention may be used in accordance with known techniques, appropriately modified in view of the teachings contained herein, to construct an expression vector, which is then used to transform an appropriate host cell for the expression and production of the polypeptide of the invention. Such techniques include those disclosed, 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.

The DNA (or in the case of retroviral vectors, RNA) encoding the polypeptide constituting the compound of the invention may be joined to a wide variety of other DNA sequences for introduction into an appropriate host. The companion DNA will depend

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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.

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.

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

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

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.

A typical mammalian cell vector plasmid for constitutive expression comprises the CMV or SV40 promoter with a suitable poly A tail and a resistance marker, such as neomycin. One example is pSVL available from Pharmacia, Piscataway, NJ, USA. An example of

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an inducible mammalian expression vector is pMSG, also available from Pharmacia. Useful yeast plasmid vectors are pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers HIS3, TRP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps). CMV promoter-based vectors (for example from Sigma-Aldrich) provide transient or stable expression, cytoplasmic expression or secretion, and N-terminal or C-terminal tagging in various combinations of FLAG, 3xFLAG, c-myc or MAT. These fusion proteins allow for detection, purification and analysis of recombinant protein. Dual-tagged fusions provide flexibility in detection.

The strong human cytomegalovirus (CMV) promoter regulatory region drives constitutive protein expression levels as high as 1 mg/L in COS cells. For less potent cell lines, protein levels are typically ~0.1 mg/L. The presence of the SV40 replication origin will result in high levels of DNA replication in SV40 replication permissive COS cells. CMV vectors, for example, can contain the pMB1 (derivative of pBR322) origin for replication in bacterial cells, the b-lactamase gene for ampicillin resistance selection in bacteria, hGH polyA, and the f1 origin. Vectors containing the pre-pro-trypsin leader (PPT) sequence can direct the secretion of FLAG fusion proteins into the culture medium for purification using ANTI-FLAG antibodies, resins, and plates. Other vectors and expression systems are well known in the art for use with a variety of host cells.

In another embodiment two or more peptides or peptide variants of the invention are encoded and thus expressed in a successive order (similar to "beads on a string" constructs). In doing so, the peptides or peptide variants may be linked or fused together by stretches of linker amino acids, such as for example LLLLLL, or may be linked without any additional peptide(s) between them. These constructs can also be used for cancer therapy, and may induce immune responses both involving MHC I and MHC II.

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The present invention also relates to a host cell transformed with a polynucleotide vector construct of the present invention. The host cell can be either prokaryotic or eukaryotic. Bacterial cells may be preferred prokaryotic host cells in some circumstances and typically are a strain of *E. coli* such as, for example, the *E. coli* strains DH5 available from Bethesda Research Laboratories Inc., Bethesda, MD, USA, and RR1 available from the American Type Culture Collection (ATCC) of Rockville, MD, USA (No ATCC 31343). Preferred eukaryotic host cells include yeast, insect and mammalian cells, preferably vertebrate cells such as those from a mouse, rat, monkey or human fibroblastic and 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.

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. (Cohen et al., 1972) and (Green and Sambrook, 2012) . Transformation of yeast cells is described in Sherman et al. (Sherman et al., 1986) . The method of Beggs (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

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and is well known in the art for transforming yeast cell, bacterial cells, insect cells and vertebrate cells.

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.

It will be appreciated that certain host cells of the invention are useful in the preparation of the peptides of the invention, for example bacterial, yeast and insect cells. However, other host cells may be useful in certain therapeutic methods. For example, antigen-presenting cells, such as dendritic cells, may usefully be used to express the peptides of the invention such that they may be loaded into appropriate MHC molecules. Thus, the current invention provides a host cell comprising a nucleic acid or an expression vector according to the invention.

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).

A further aspect of the invention 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.

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

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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).

The polynucleotide used for active vaccination 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. Teufel et al. (Teufel 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.

The medicament of the invention may also include one or more **adjuvants**. Adjuvants are substances that non-specifically enhance or potentiate the immune response (e.g., immune responses mediated by CD8-positive T cells and helper-T (TH) cells to an antigen, and would thus be considered useful in the medicament of the present invention. Suitable adjuvants include, but are not limited to, 1018 ISS, aluminum salts, AMPLIVAX®, AS15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, flagellin or TLR5 ligands derived from flagellin, FLT3 ligand, GM-CSF, IC30, IC31, Imiquimod (ALDARA®), resiquimod, ImuFact IMP321, Interleukins as IL-2, IL-13, IL-21, Interferon-alpha or -beta, or pegylated derivatives thereof, IS Patch, ISS, ISCOMATRIX, ISCOMs, JuvImmune®, LipoVac, MALP2, MF59, monophosphoryl lipid A, Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, water-in-oil and oil-in-water emulsions, OK-432, OM-174, OM-197-MP-EC, ONTAK, OspA, PepTel® vector system, poly(lactid co-glycolid) [PLG]-based and dextran microparticles, talactoferrin SRL172,

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Virosomes and other Virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, Aquila's QS21 stimulon, which is derived from saponin, mycobacterial extracts and synthetic bacterial cell wall mimics, and other proprietary adjuvants such as Ribi's Detox, Quil, or Superfos. Adjuvants such as Freund's or GM-CSF are preferred. Several immunological adjuvants (e.g., MF59) specific for dendritic cells and their preparation have been described previously (Allison and Krummel, 1995). Also cytokines may be used. Several cytokines have been directly linked to influencing dendritic cell migration to lymphoid tissues (e.g., TNF-), accelerating the maturation of dendritic cells into efficient antigen-presenting cells for T-lymphocytes (e.g., GM-CSF, IL-1 and IL-4) (U.S. Pat. No. 5,849,589, specifically incorporated herein by reference in its entirety) and acting as immunoadjuvants (e.g., IL-12, IL-15, IL-23, IL-7, IFN-alpha. IFN-beta) (Gabrilovich et al., 1996).

CpG immunostimulatory oligonucleotides have also been reported to enhance the effects of adjuvants in a vaccine setting. Without being bound by theory, CpG oligonucleotides act by activating the innate (non-adaptive) immune system via Toll-like receptors (TLR), mainly TLR9. CpG triggered TLR9 activation enhances antigen-specific humoral and cellular responses to a wide variety of antigens, including peptide or protein antigens, live or killed viruses, dendritic cell vaccines, autologous cellular vaccines and polysaccharide conjugates in both prophylactic and therapeutic vaccines. More importantly it enhances dendritic cell maturation and differentiation, resulting in enhanced activation of TH1 cells and strong cytotoxic T-lymphocyte (CTL) generation, even in the absence of CD4 T cell help. The TH1 bias induced by TLR9 stimulation is maintained even in the presence of vaccine adjuvants such as alum or incomplete Freund's adjuvant (IFA) that normally promote a TH2 bias. CpG oligonucleotides show even greater adjuvant activity when formulated or co-administered with other adjuvants or in formulations such as microparticles, nanoparticles, lipid emulsions or similar formulations, which are especially necessary for inducing a strong response when the antigen is relatively weak. They also accelerate the immune response and enable the antigen doses to be reduced by approximately two orders of magnitude, with comparable antibody responses to the full-dose vaccine without CpG in some

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experiments (Krieg, 2006). US 6,406,705 B1 describes the combined use of CpG oligonucleotides, non-nucleic acid adjuvants and an antigen to induce an antigen-specific immune response. A CpG TLR9 antagonist is dSLIM (double Stem Loop Immunomodulator) by Mologen (Berlin, Germany) which is a preferred component of the pharmaceutical composition of the present invention. Other TLR binding molecules such as RNA binding TLR 7, TLR 8 and/or TLR 9 may also be used.

Other examples for useful adjuvants include, but are not limited to chemically modified CpGs (e.g. CpR, Idera), dsRNA analogues such as Poly(I:C) and derivatives thereof (e.g. AmpliGen®, Hiltonol®, poly-(ICLC), poly(IC-R), poly(I:C12U), non-CpG bacterial DNA or RNA as well as immunoactive small molecules and antibodies such as cyclophosphamide, sunitinib, Bevacizumab®, celebrex, NCX-4016, sildenafil, tadalafil, vardenafil, sorafenib, temozolomide, temsirolimus, XL-999, CP-547632, pazopanib, VEGF Trap, ZD2171, AZD2171, anti-CTLA4, other antibodies targeting key structures of the immune system (e.g. anti-CD40, anti-TGFbeta, anti-TNFalpha receptor) and SC58175, which may act therapeutically and/or as an adjuvant. The amounts and concentrations of adjuvants and additives useful in the context of the present invention can readily be determined by the skilled artisan without undue experimentation.

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

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.

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

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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.

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 (Kibbe, 2000). The composition can be used for a prevention, prophylaxis and/or therapy of adenomatous or cancerous diseases. Exemplary formulations can be found in, for example, EP2112253.

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 is designed in such a way that each tumor is expected to express several of the antigens and cover several independent pathways necessary for tumor growth and maintenance. Thus, the vaccine can easily be used "off-the-shelf" for a larger patient population. This means that a pre-selection of patients to be treated with the vaccine can be restricted to HLA typing, does not require any additional

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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).

As used herein, the term "scaffold" refers to a molecule that specifically binds to an (e.g. antigenic) determinant. In one embodiment, a scaffold is able to direct the entity to which it is attached (e.g. a (second) antigen binding moiety) to a target site, for example to a specific type of tumor cell or tumor stroma bearing the antigenic determinant (e.g. the complex of a peptide with MHC, according to the application at hand). In another embodiment a scaffold is able to activate signaling through its target antigen, for example a T cell receptor complex antigen. Scaffolds include but are not limited to antibodies and fragments thereof, antigen binding domains of an antibody, comprising an antibody heavy chain variable region and an antibody light chain variable region, binding proteins comprising at least one ankyrin repeat motif and single domain antigen binding (SDAB) molecules, aptamers, (soluble) TCRs and (modified) cells such as allogenic or autologous T cells. To assess whether a molecule is a scaffold binding to a target, binding assays can be performed.

"Specific" binding means that the scaffold binds the peptide-MHC-complex of interest better than other naturally occurring peptide-MHC-complexes, to an extent that a scaffold armed with an active molecule that is able to kill a cell bearing the specific target is not able to kill another cell without the specific target but presenting other peptide-MHC complex(es). Binding to other peptide-MHC complexes is irrelevant if the peptide of the cross-reactive peptide-MHC is not naturally occurring, i.e. not derived from the human HLA-peptidome. Tests to assess target cell killing are well known in the art. They should be performed using target cells (primary cells or cell lines) with unaltered peptide-MHC presentation, or cells loaded with peptides such that naturally occurring peptide-MHC levels are reached.

Each scaffold can comprise a labelling which provides that the bound scaffold can be detected by determining the presence or absence of a signal provided by the label. For

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example, the scaffold can be labelled with a fluorescent dye or any other applicable cellular marker molecule. Such marker molecules are well known in the art. For example a fluorescence-labelling, for example provided by a fluorescence dye, can provide a visualization of the bound aptamer by fluorescence or laser scanning microscopy or flow cytometry.

Each scaffold can be conjugated with a second active molecule such as for example IL-21, anti-CD3, and anti-CD28. For further information on polypeptide scaffolds see for example the background section of WO 2014/071978A1 and the references cited therein.

The present invention further relates to aptamers. Aptamers (see for example WO 2014/191359 and the literature as cited therein) are short single-stranded nucleic acid molecules, which can fold into defined three-dimensional structures and recognize specific target structures. They have appeared to be suitable alternatives for developing targeted therapies. Aptamers have been shown to selectively bind to a variety of complex targets with high affinity and specificity.

Aptamers recognizing cell surface located molecules have been identified within the past decade and provide means for developing diagnostic and therapeutic approaches. Since aptamers have been shown to possess almost no toxicity and immunogenicity they are promising candidates for biomedical applications. Indeed aptamers, for example prostate-specific membrane-antigen recognizing aptamers, have been successfully employed for targeted therapies and shown to be functional in xenograft *in vivo* models. Furthermore, aptamers recognizing specific tumor cell lines have been identified.

DNA aptamers can be selected to reveal broad-spectrum recognition properties for various cancer cells, and particularly those derived from solid tumors, while non-tumorigenic and primary healthy cells are not recognized. If the identified aptamers recognize not only a specific tumor sub-type but rather interact with a series of tumors,

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this renders the aptamers applicable as so-called broad-spectrum diagnostics and therapeutics.

Further, investigation of cell-binding behavior with flow cytometry showed that the aptamers revealed very good apparent affinities that are within the nanomolar range.

Aptamers are useful for diagnostic and therapeutic purposes. Further, it could be shown that some of the aptamers are taken up by tumor cells and thus can function as molecular vehicles for the targeted delivery of anti-cancer agents such as siRNA into tumor cells.

Aptamers can be selected against complex targets such as cells and tissues and complexes of the peptides comprising, preferably consisting of, a sequence according to any of SEQ ID NO 1 to SEQ ID NO 772, according to the invention at hand with the MHC molecule, using the cell-SELEX (Systematic Evolution of Ligands by Exponential enrichment) technique.

The peptides of the present invention 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.

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 (preferably a peptide according to the present invention), 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

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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.

It is thus 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.

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), which for the purposes of the present invention are all explicitly incorporated by reference in their entireties.

Preferably, the antibody is binding with a binding affinity of below 20 nanomolar, preferably of below 10 nanomolar, to the complex, which is also regarded as “specific” in the context of the present invention.

The present invention relates to a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 772, or a variant thereof which is at least 88% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 772 or a variant thereof that induces T cells cross-reacting with said peptide, wherein said peptide is not the underlying full-length polypeptide.

The present invention further relates to a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 772 or a variant thereof which is at least 88% homologous (preferably identical) to SEQ ID NO: 1 to SEQ

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ID NO: 772, 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.

The present invention further relates to the peptides according to the invention that have the ability to bind to a molecule of the human major histocompatibility complex (MHC) class-I or -II.

The present invention further relates to the peptides according to the invention wherein the peptide consists or consists essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 772.

The present invention further relates to the peptides according to the invention, wherein the peptide is (chemically) modified and/or includes non-peptide bonds.

The present invention further relates to the peptides according to the invention, 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.

The present invention further relates to a nucleic acid, encoding the peptides according to the invention, provided that the peptide is not the complete (full) human protein.

The present invention further relates to the nucleic acid according to the invention that is DNA, cDNA, PNA, RNA or combinations thereof.

The present invention further relates to an expression vector capable of expressing a nucleic acid according to the present invention.

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The present invention further relates to a peptide according to the present invention, a nucleic acid according to the present invention or an expression vector according to the present invention for use in medicine, in particular in the treatment of ovarian cancer.

The present invention further relates to a host cell comprising a nucleic acid according to the invention or an expression vector according to the invention.

The present invention further relates to the host cell according to the present invention that is an antigen presenting cell, and preferably a dendritic cell.

The present invention further relates to a method of producing a peptide according to the present invention, said method comprising culturing the host cell according to the present invention, and isolating the peptide from said host cell or its culture medium.

The present invention further relates to the method according to the present invention, 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.

The present invention further relates to the method according to the invention, wherein the antigen-presenting cell comprises an expression vector capable of expressing said peptide containing SEQ ID NO: 1 to SEQ ID NO: 772 or said variant amino acid sequence.

The present invention further relates to activated T cells, produced by the method according to the present invention, wherein said T cells selectively recognizes a cell which aberrantly expresses a polypeptide comprising an amino acid sequence according to the present invention.

The present invention further relates to a method of killing target cells in a patient which target cells aberrantly express a polypeptide comprising any amino acid sequence

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according to the present invention, the method comprising administering to the patient an effective number of T cells as according to the present invention.

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

The present invention further relates to a use according to the invention, wherein the medicament is a vaccine. The present invention further relates to a use according to the invention, wherein the medicament is active against cancer.

The present invention further relates to a use according to the invention, wherein said cancer cells are ovarian cancer cells or other solid or hematological tumor cells such as hepatocellular carcinoma, colorectal carcinoma, glioblastoma, gastric cancer, esophageal cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, melanoma, breast cancer, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, acute myeloid leukemia, gallbladder cancer and cholangiocarcinoma, urinary bladder cancer, uterine cancer, head and neck squamous cell carcinoma, mesothelioma.

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

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

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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 ovarian cancer marker (poly)peptide, delivery of a toxin to a ovarian cancer cell expressing a cancer marker gene at an increased level, and/or inhibiting the activity of a ovarian cancer marker polypeptide) according to the invention.

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

For example, a cDNA encoding a peptide according to the present invention, such as a peptide according to SEQ ID NO: 1 to SEQ ID NO: 772 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 ovarian cancer marker polypeptide used to generate the antibody according to the invention.

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., Greenfield, 2014 (Greenfield, 2014)). For example, the antibodies may be tested in ELISA assays or, Western blots, immunohistochemical staining of formalin-

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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.

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, which is hereby incorporated in its entirety).

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*.

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).

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

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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.

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.

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

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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.

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.

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.

Antibodies of the invention are preferably administered to a subject in a pharmaceutically acceptable carrier. Typically, an appropriate amount of a

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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.

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.

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 ($\mu\text{g}/\text{kg}$) 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 ovarian cancer, 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 occur in the absence of antibody administration, is an efficacious antibody for treatment of cancer.

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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 (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), and 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.

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

The antibodies or TCRs 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 , ^3H , ^{32}P or ^{35}S) so that the tumor can be localized using immunoscintigraphy. 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 (K_d) is less than $1 \times 10\mu\text{M}$.

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

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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.

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.

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.

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

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ATCC under Catalogue No CRL 19863; the mouse RMA-S cell line is described in Ljunggren et al. (Ljunggren and Karre, 1985).

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.

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

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: 772, or a variant amino acid sequence thereof.

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. (Plebanski et al., 1995) made 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. (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 invention, 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 eliciting high- or low-avidity antigen-specific T cell responses with high efficiency from blood samples. Apart

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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.

Allogeneic cells may also be used in the preparation of T cells and a method is described in detail in WO 97/26328, incorporated herein by reference. 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, and vaccinia-infected target cells. In addition plant viruses may be used (see, for example, Porta et al. (Porta et al., 1994) which describes the development of cowpea mosaic virus as a high-yielding system for the presentation of foreign peptides.

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.

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 772.

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,

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preferably has a competent immune system and, more preferably, is not suffering from any disease that can be readily tested for, and detected.

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)).

The T cells of the present invention may be used as active ingredients of a therapeutic composition. Thus, the invention 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 invention, the method comprising administering to the patient an effective number of T cells as defined above.

By "aberrantly expressed" the inventors also mean that the polypeptide is over-expressed compared to levels of expression in normal tissues 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.

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

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

Another aspect of the present invention includes the use of the peptides complexed with MHC to generate a T-cell receptor whose nucleic acid is cloned and is introduced into a host cell, preferably a T cell. This engineered T cell can then be transferred to a patient for therapy of cancer.

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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).

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.

The kit may further comprise one or more of (iii) a buffer, (iv) a diluent, (v) a filter, (vi) a needle, or (v) 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.

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.

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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).

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.

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.

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.

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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.

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.

Since the peptides of the invention were isolated from ovarian cancer, the medicament of the invention is preferably used to treat ovarian cancer.

The present invention further relates to a method for producing a **personalized pharmaceutical** for an individual patient comprising manufacturing a pharmaceutical composition comprising at least one peptide selected from a warehouse of pre-screened TUMAPs, wherein the at least one peptide used in the pharmaceutical composition is selected for suitability in the individual patient. In one embodiment, the pharmaceutical composition is a vaccine. The method could also be adapted to produce T cell clones for down-stream applications, such as TCR isolations, or soluble antibodies, and other treatment options.

A “personalized pharmaceutical” shall mean specifically tailored therapies for one individual patient that will only be used for therapy in such individual patient, including actively personalized cancer vaccines and adoptive cellular therapies using autologous patient tissue.

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As used herein, the term “warehouse” shall refer to a group or set of peptides that have been pre-screened for immunogenicity and/or over-presentation in a particular tumor type. The term “warehouse” is not intended to imply that the particular peptides included in the vaccine have been pre-manufactured and stored in a physical facility, although that possibility is contemplated. It is expressly contemplated that the peptides may be manufactured *de novo* for each individualized vaccine produced, or may be pre-manufactured and stored. The warehouse (e.g. in the form of a database) is composed of tumor-associated peptides which were highly overexpressed in the tumor tissue of ovarian cancer patients with various HLA-A HLA-B and HLA-C alleles. It may contain MHC class I and MHC class II peptides or elongated MHC class I peptides. In addition to the tumor associated peptides collected from several ovarian cancer tissues, the warehouse may contain HLA-A*02, HLA-A*01, HLA-A*03, HLA-A*24, HLA-B*07, HLA-B*08 and HLA-B*44 marker peptides. These peptides allow comparison of the magnitude of T-cell immunity induced by TUMAPS in a quantitative manner and hence allow important conclusion to be drawn on the capacity of the vaccine to elicit anti-tumor responses. Secondly, they function as important positive control peptides derived from a “non-self” antigen in the case that any vaccine-induced T-cell responses to TUMAPs derived from “self” antigens in a patient are not observed. And thirdly, it may allow conclusions to be drawn, regarding the status of immunocompetence of the patient.

TUMAPs for the warehouse are identified by using an integrated functional genomics approach combining gene expression analysis, mass spectrometry, and T-cell immunology (XPresident®). The approach assures that only TUMAPs truly present on a high percentage of tumors but not or only minimally expressed on normal tissue, are chosen for further analysis. For initial peptide selection, ovarian cancer samples from patients and blood from healthy donors were analyzed in a stepwise approach:

1. HLA ligands from the malignant material were identified by mass spectrometry
2. Genome-wide messenger ribonucleic acid (mRNA) expression analysis was used to identify genes over-expressed in the malignant tissue (ovarian cancer) compared with a range of normal organs and tissues

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3. Identified HLA ligands were compared to gene expression data. Peptides presented on tumor tissue, preferably encoded by selectively expressed or over-expressed genes as detected in step 2 were considered suitable TUMAP candidates for a multi-peptide vaccine.
4. Literature research was performed in order to identify additional evidence supporting the relevance of the identified peptides as TUMAPs
5. The relevance of over-expression at the mRNA level was confirmed by redetection of selected TUMAPs from step 3 on tumor tissue and lack of (or infrequent) detection on healthy tissues.
6. In order to assess, whether an induction of *in vivo* T-cell responses by the selected peptides may be feasible, *in vitro* immunogenicity assays were performed using human T cells from healthy donors as well as from ovarian cancer patients.

In an aspect, the peptides are pre-screened for immunogenicity before being included in the warehouse. By way of example, and not limitation, the immunogenicity of the peptides included in the warehouse is determined by a method comprising *in vitro* T-cell priming through repeated stimulations of CD8⁺ T cells from healthy donors with artificial antigen presenting cells loaded with peptide/MHC complexes and anti-CD28 antibody.

This method is preferred for rare cancers and patients with a rare expression profile. In contrast to multi-peptide cocktails with a fixed composition as currently developed, the warehouse allows a significantly higher matching of the actual expression of antigens in the tumor with the vaccine. Selected single or combinations of several “off-the-shelf” peptides will be used for each patient in a multitarget approach. In theory, an approach based on selection of e.g. 5 different antigenic peptides from a library of 50 would already lead to approximately 17 million possible drug product (DP) compositions.

In an aspect, the peptides are selected for inclusion in the vaccine based on their suitability for the individual patient based on the method according to the present invention as described herein, or as below.

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The HLA phenotype, transcriptomic and peptidomic data is gathered from the patient's tumor material, and blood samples to identify the most suitable peptides for each patient containing "warehouse" and patient-unique (i.e. mutated) TUMAPs. Those peptides will be chosen, which are selectively or over-expressed in the patients' tumor and, where possible, show strong *in vitro* immunogenicity if tested with the patients' individual PBMCs.

Preferably, the peptides included in the vaccine are identified by a method comprising: (a) identifying tumor-associated peptides (TUMAPs) presented by a tumor sample from the individual patient; (b) comparing the peptides identified in (a) with a warehouse (database) of peptides as described above; and (c) selecting at least one peptide from the warehouse (database) that correlates with a tumor-associated peptide identified in the patient. For example, the TUMAPs presented by the tumor sample are identified by: (a1) comparing expression data from the tumor sample to expression data from a sample of normal tissue corresponding to the tissue type of the tumor sample to identify proteins that are over-expressed or aberrantly expressed in the tumor sample; and (a2) correlating the expression data with sequences of MHC ligands bound to MHC class I and/or class II molecules in the tumor sample to identify MHC ligands derived from proteins over-expressed or aberrantly expressed by the tumor. Preferably, the sequences of MHC ligands are identified by eluting bound peptides from MHC molecules isolated from the tumor sample, and sequencing the eluted ligands. Preferably, the tumor sample and the normal tissue are obtained from the same patient.

In addition to, or as an alternative to, selecting peptides using a warehousing (database) model, TUMAPs may be identified in the patient *de novo*, and then included in the vaccine. As one example, candidate TUMAPs may be identified in the patient by (a1) comparing expression data from the tumor sample to expression data from a sample of normal tissue corresponding to the tissue type of the tumor sample to identify proteins that are over-expressed or aberrantly expressed in the tumor sample; and (a2) correlating the expression data with sequences of MHC ligands bound to MHC class I and/or class II molecules in the tumor sample to identify MHC ligands derived from

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proteins over-expressed or aberrantly expressed by the tumor. As another example, proteins may be identified containing mutations that are unique to the tumor sample relative to normal corresponding tissue from the individual patient, and TUMAPs can be identified that specifically target the mutation. For example, the genome of the tumor and of corresponding normal tissue can be sequenced by whole genome sequencing: For discovery of non-synonymous mutations in the protein-coding regions of genes, genomic DNA and RNA are extracted from tumor tissues and normal non-mutated genomic germline DNA is extracted from peripheral blood mononuclear cells (PBMCs). The applied NGS approach is confined to the re-sequencing of protein coding regions (exome re-sequencing). For this purpose, exonic DNA from human samples is captured using vendor-supplied target enrichment kits, followed by sequencing with e.g. a HiSeq2000 (Illumina). Additionally, tumor mRNA is sequenced for direct quantification of gene expression and validation that mutated genes are expressed in the patients' tumors. The resultant millions of sequence reads are processed through software algorithms. The output list contains mutations and gene expression. Tumor-specific somatic mutations are determined by comparison with the PBMC-derived germline variations and prioritized. The *de novo* identified peptides can then be tested for immunogenicity as described above for the warehouse, and candidate TUMAPs possessing suitable immunogenicity are selected for inclusion in the vaccine.

In one exemplary embodiment, the peptides included in the vaccine are identified by: (a) identifying tumor-associated peptides (TUMAPs) presented by a tumor sample from the individual patient by the method as described above; (b) comparing the peptides identified in a) with a warehouse of peptides that have been prescreened for immunogenicity and overpresentation in tumors as compared to corresponding normal tissue; (c) selecting at least one peptide from the warehouse that correlates with a tumor-associated peptide identified in the patient; and (d) optionally, selecting at least one peptide identified *de novo* in (a) confirming its immunogenicity.

In one exemplary embodiment, the peptides included in the vaccine are identified by: (a) identifying tumor-associated peptides (TUMAPs) presented by a tumor sample from the

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individual patient; and (b) selecting at least one peptide identified de novo in (a) and confirming its immunogenicity.

Once the peptides for a personalized peptide based vaccine are selected, the vaccine is produced. The vaccine preferably is a liquid formulation consisting of the individual peptides dissolved in between 20-40% DMSO, preferably about 30-35% DMSO, such as about 33% DMSO.

Each peptide to be included into a product is dissolved in DMSO. The concentration of the single peptide solutions has to be chosen depending on the number of peptides to be included into the product. The single peptide-DMSO solutions are mixed in equal parts to achieve a solution containing all peptides to be included in the product with a concentration of ~2.5 mg/ml per peptide. The mixed solution is then diluted 1:3 with water for injection to achieve a concentration of 0.826 mg/ml per peptide in 33% DMSO. The diluted solution is filtered through a 0.22 µm sterile filter. The final bulk solution is obtained.

Final bulk solution is filled into vials and stored at -20°C until use. One vial contains 700 µL solution, containing 0.578 mg of each peptide. Of this, 500 µL (approx. 400 µg per peptide) will be applied for intradermal injection.

In addition to being useful for treating cancer, the peptides of the present invention are also useful as **diagnostics**. Since the peptides were generated from ovarian cancer cells and since it was determined that these peptides are not or at lower levels present in normal tissues, these peptides can be used to diagnose the presence of a cancer.

The presence of claimed peptides on tissue biopsies in blood samples can assist a pathologist in diagnosis of cancer. Detection of certain peptides by means of antibodies, mass spectrometry or other methods known in the art can tell the pathologist that the tissue sample is malignant or inflamed or generally diseased, or can be used as a

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biomarker for ovarian cancer. Presence of groups of peptides can enable classification or sub-classification of diseased tissues.

The detection of peptides on diseased tissue specimen can enable the decision about the benefit of therapies involving the immune system, especially if T-lymphocytes are known or expected to be involved in the mechanism of action. Loss of MHC expression is a well described mechanism by which infected or malignant cells escape immunosurveillance. Thus, presence of peptides shows that this mechanism is not exploited by the analyzed cells.

The peptides of the present invention might be used to analyze lymphocyte responses against those peptides such as T cell responses or antibody responses against the peptide or the peptide complexed to MHC molecules. These lymphocyte responses can be used as prognostic markers for decision on further therapy steps. These responses can also be used as surrogate response markers in immunotherapy approaches aiming to induce lymphocyte responses by different means, e.g. vaccination of protein, nucleic acids, autologous materials, adoptive transfer of lymphocytes. In gene therapy settings, lymphocyte responses against peptides can be considered in the assessment of side effects. Monitoring of lymphocyte responses might also be a valuable tool for follow-up examinations of transplantation therapies, e.g. for the detection of graft versus host and host versus graft diseases.

The present invention will now be described in the following examples which describe preferred embodiments thereof, and with reference to the accompanying figures, nevertheless, without being limited thereto. For the purposes of the present invention, all references as cited herein are incorporated by reference in their entireties.

FIGURES

Figure 1A through Figure 1S show exemplary expression profile of source genes of the present invention that are over-expressed in different cancer samples. Tumor (black dots) and normal (grey dots) samples are grouped according to organ of origin, and

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box-and-whisker plots represent median, 25th and 75th percentile (box), and minimum and maximum (whiskers) RPKM values. Normal organs are ordered according to risk categories. RPKM = reads per kilobase per million mapped reads. Normal samples: blood cells; blood vessel; brain; heart; liver; lung; adipose: adipose tissue; adren.gl.: adrenal gland; bile duct; bladder; BM: bone marrow; cartilage; esoph: esophagus; eye; gallb: gallbladder; head and neck; kidney; large_int: large intestine; LN: lymph node; nerve; pancreas; parathyr: parathyroid; pituit: pituitary; skel.mus: skeletal muscle; skin; small_int: small intestine; spleen; stomach; thyroid; trachea; bladder; breast; ovary; placenta; prostate; testis; thymus; uterus. Tumor samples: AML: acute myeloid leukemia; BRCA: breast cancer; CLL: chronic lymphocytic leukemia; CRC: colorectal cancer; GALB: gallbladder cancer; GB: glioblastoma; GC: gastric cancer; HCC: hepatocellular carcinoma; HNSCC: head-and-neck cancer; MEL: melanoma; NHL: non-hodgkin lymphoma; NSCLC: non-small cell lung cancer; OC: ovarian cancer; OSC_GC: esophageal / gastric cancer; OSCAR: esophageal cancer; PC: pancreatic cancer; PCA: prostate cancer; RCC: renal cell carcinoma; SCLC: small cell lung cancer; UBC: urinary bladder carcinoma; UEC: uterine and endometrial cancer. Figure 1A) Gene symbol: CT45A2, Peptide: KYEKIFEML (SEQ ID No.: 12), Figure 1B) Gene symbol: NLRP2, Peptide: VLYGPAGLGK (SEQ ID No.: 27), Figure 1C) Gene symbol: NLRP7, Peptide: LLDEGAMLLY (SEQ ID No.: 31), Figure 1D) Gene symbol: HTR3A, Peptide: GLLQELSSI (SEQ ID No.: 66), Figure 1E) Gene symbol: VTCN1, Peptide: KVVSVLYNV (SEQ ID No.: 75), Figure 1F) Gene symbol: CYP2W1, Peptide: RYGPVFTV (SEQ ID No.: 98), Figure 1G) Gene symbol: MMP11, Peptide: LLQPPPLLAR (SEQ ID No.: 98), Figure 1H) Gene symbol: MMP12, Peptide: FVDNQYWRY (SEQ ID No.: 115), Figure 1I) Gene symbol: CTAG2, Peptide: APLPRPGAVL (SEQ ID No.: 119), Figure 1J) Gene symbol: FAM111B, Peptide: KPSESIYSAL (SEQ ID No.: 123), Figure 1K) Gene symbol: CCNA1, Peptide: HLLLKVLAFL (SEQ ID No.: 151), Figure 1L) Gene symbol: FAM83H, Peptide: HVKEKFLL (SEQ ID No.: 156), Figure 1M) Gene symbol: MAGEA11, Peptide: KEVDPTSHSY (SEQ ID No.: 194), Figure 1N) Gene symbol: MMP11, Peptide: YTFRYPLSL (SEQ ID No.: 227), Figure 1O) Gene symbol: ZNF560, Peptide: VFVSFSSLF (SEQ ID No.: 255), Figure 1P) Gene symbol: IGF2BP1, Peptide:

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ISYSGQFLVK (SEQ ID No.: 266), Figure 1Q) Gene symbol: CLDN6, Peptide: LPMWKVTAF (SEQ ID No.: 303), Figure 1R) Gene symbol: IGF2BP3, Peptide: IEALSGKIEL (SEQ ID No.: 413), Figure 1S) Gene symbol: PRAME, Peptide: EEQYIAQF (SEQ ID No.: 432).

Figures 1T through 1V show exemplary expression profiles of source genes of the present invention, that are over-expressed in different cancer samples. Tumor (black dots) and normal (grey dots) samples are grouped according to organ of origin. Box-and-whisker plots represent median FPKM value, 25th and 75th percentile (box) plus whiskers that extend to the lowest data point still within 1.5 interquartile range (IQR) of the lower quartile and the highest data point still within 1.5 IQR of the upper quartile. Normal organs are ordered according to risk categories. FPKM: fragments per kilobase per million mapped reads. Normal samples: *blood cells*; *bloodvess* (blood vessels); *brain*; *heart*; *liver*; *lung*; *adipose* (adipose tissue); *adrenal gl* (adrenal gland); *bile duct*; *bladder*; *bone marrow*; *cartilage*; *esoph* (esophagus); *eye*; *gall bl* (gallbladder); *head&neck*; *intest. la* (large intestine); *intest. sm* (small intestine); *kidney*; *lymph node*; *nerve perith* (peripheral nerve); *pancreas*; *parathyr* (parathyroid gland); *perit* (peritoneum); *pituit* (pituitary); *pleura*; *skel. mus* (skeletal muscle); *skin*; *spleen*; *stomach*; *thyroid*; *trachea*; *ureter*; *breast*; *ovary*; *placenta*; *prostate*; *testis*; *thymus*; *uterus*. Tumor samples: *AML* (acute myeloid leukemia); *BRCA* (breast cancer); *CCC* (cholangiocellular carcinoma); *CLL* (chronic lymphocytic leukemia); *CRC* (colorectal cancer); *GBC* (gallbladder cancer); *GBM* (glioblastoma); *GC* (gastric cancer); *HCC* (hepatocellular carcinoma); *HNSCC* (head and neck squamous cell carcinoma); *MEL* (melanoma); *NHL* (non-hodgkin lymphoma); *NSCLCaden* (non-small cell lung cancer adenocarcinoma); *NSCLCother* (NSCLC samples that could not unambiguously be assigned to NSCLCaden or NSCLCsquam); *NSCLCsquam* (squamous cell non-small cell lung cancer); *OC* (ovarian cancer); *OSCAR* (esophageal cancer); *PACA* (pancreatic cancer); *PRCA* (prostate cancer); *RCC* (renal cell carcinoma); *SCLC* (small cell lung cancer); *UBC* (urinary bladder carcinoma); *UEC* (uterine and endometrial cancer). Figure 1T) Gene symbol: MAGEA4, Peptide: SPDAESLFREALSNKVDEL (SEQ ID No.: 597), Figure 1U) Gene symbol: MAGEA4, Peptide: LSNKVDELAHFLLRK (SEQ ID No.:

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601), Figure 1V) Gene symbol: MAGEB3, Peptide: KLITQDLVKLKYLEYRQ (SEQ ID No.: 604).

Figure 2 shows exemplary results of peptide-specific in vitro CD8⁺ T cell responses of a healthy HLA-A*02⁺ donor. CD8⁺ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*02 in complex with SeqID No 773 peptide (ALYGKLLKL, Seq ID NO: 773) (A, left panel. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*02/SeqID No 773 (A). Right panel (A) 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.

Figure 3 shows exemplary results of peptide-specific in vitro CD8⁺ T cell responses of a healthy HLA-A*24⁺ donor. CD8⁺ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*24 in complex with SeqID No 774 peptide (A, left panel). After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*24/SeqID No 774 (VYVDDIYVI, Seq ID NO: 774) (A). Right panel (A) shows 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.

Figure 4 shows exemplary results of peptide-specific in vitro CD8⁺ T cell responses of a healthy HLA-A*02⁺ donor. CD8⁺ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*02 in complex with SeqID No 67 peptide SLLLPSIFL (A, left panel) and SeqID No 75 peptide KVVSVLYNV (B, left panel), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*02/SeqID No 67 (A) or A*02/SeqID No 75 (B). Right panels (A

and B) 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.

Figure 5 shows exemplary results of peptide-specific in vitro CD8+ T cell responses of a healthy HLA-A*24+ donor. CD8+ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*24 in complex with SeqID No 11 peptide SYSDLHYGF (A, left panel) and SeqID No 79 peptide SYNEHWNYL (B, left panel), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*24/SeqID No 11 (A) or A*24/SeqID No 79 (B). Right 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.

Figure 6 shows exemplary results of peptide-specific in vitro CD8+ T cell responses of a healthy HLA-B*07+ donor. CD8+ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-B*07 in complex with SeqID No 33 peptide SPTFHLTL (A, left panel) and SeqID No 40 peptide KPGTSYRVTL (B, left panel), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with B*07/SeqID No 33 (A) or B*07/SeqID No 40 (B). Right panels (A and B) show control staining of cells stimulated with irrelevant B*07/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.

Figure 7 shows exemplary results of peptide-specific in vitro CD8+ T cell responses of a healthy HLA-A*01+ donor. CD8+ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*01 in complex with SeqID No 113 peptide QLDSNRLTY (A, left panel) and SeqID No 115 peptide FVDNQYWRY (B, left panel), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D

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multimer staining with A*01/SeqID No 113 (A) or A*01/SeqID No 115 (B). Right panels (A and B) show control staining of cells stimulated with irrelevant A*01/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.

Figure 8 shows exemplary results of peptide-specific in vitro CD8⁺ T cell responses of a healthy HLA-A*03⁺ donor. CD8⁺ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*03 in complex with SeqID No 23 peptide GMMKGGIRK (A, left panel) and SeqID No 90 peptide KVAGERYVYK (B, left panel), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with A*03/SeqID No 23 (A) or A*03/SeqID No 90 (B). Right panels (A and B) show control staining of cells stimulated with irrelevant A*03/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.

Figure 9 shows exemplary results of peptide-specific in vitro CD8⁺ T cell responses of a healthy HLA-B*44⁺ donor. CD8⁺ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-B*44 in complex with SeqID No 200 peptide AESIPTVSF (A, left panel) and SeqID No 211 peptide EEKVFPSPWL (B, left panel), respectively. After three cycles of stimulation, the detection of peptide-reactive cells was performed by 2D multimer staining with B*44/SeqID No 200 (A) or B*44/SeqID No 211 (B). Right panels (A and B) show control staining of cells stimulated with irrelevant B*44/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.

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EXAMPLES

EXAMPLE 1

Identification of tumor associated peptides presented on the cell surfaceTissue samples

Patients' tumor tissues and normal tissues were obtained from the University Hospital Tübingen (Tübingen, Germany). Written informed consents of all patients had been given before surgery or autopsy. Tissues were shock-frozen immediately after excision and stored until isolation of TUMAPs at -70°C or below.

Isolation of HLA peptides from tissue samples

HLA peptide pools from shock-frozen tissue samples were obtained by immune precipitation from solid tissues according to a slightly modified protocol (Falk et al., 1991; Seeger et al., 1999) using the HLA-A*02-specific antibody BB7.2, the HLA-A, -B, -C-specific antibody W6/32, the HLA-DR specific antibody L243 and the pan-HLA class II specific antibody Tü39, CNBr-activated sepharose, acid treatment, and ultrafiltration.

Mass spectrometry analyses

The HLA peptide pools as obtained were separated according to their hydrophobicity by reversed-phase chromatography (Ultimate 3000 RSLC Nano UHPLC System, Dionex)) and the eluting peptides were analyzed in LTQ-Orbitrap and Fusion Lumos hybrid mass spectrometers (ThermoElectron) equipped with an ESI source. Peptide samples were loaded with 3% of solvent B (20% H₂O, 80% acetonitrile and 0.04% formic acid) on a 2 cm PepMap 100 C18 Nanotrap column (Dionex) at a flowrate of 4 µl/min for 10 min. Separation was performed on either 25 cm or 50 cm PepMap C18 columns with a particle size of 2 µm (Dionex) mounted in a column oven running at 50°C. The applied gradient ranged from 3 to 32% solvent B within 90 min at a flow rate of 300 nl/min (for 25 cm columns) or 140 min at a flow rate of 175 nl/min (for 50 cm columns). (Solvent A: 99% H₂O, 1% ACN and 0.1% formic acid; Solvent B: 20% H₂O, 80% ACN and 0.1% formic acid).

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Mass spectrometry analysis was performed in data dependent acquisition mode employing a top five method (i.e. during each survey scan the five most abundant precursor ions were selected for fragmentation). Alternatively, a TopSpeed method was employed for analysis on Fusion Lumos instruments,

Survey scans were recorded in the Orbitrap at a resolution of 60,000 (for Orbitrap XL) or 120,000 (for Orbitrap Fusion Lumos). MS/MS analysis was performed by collision induced dissociation (CID, normalized collision energy 35%, activation time 30 ms, isolation width 1.3 m/z) with subsequent analysis in the linear trap quadrupole (LTQ). Mass range for HLA class I ligands was limited to 400-650 m/z with possible charge states 2+ and 3+ selected for fragmentation. For HLA class II mass range was set to 300-1500 m/z allowing for fragmentation with all positive charge states ≥ 2 .

Tandem mass spectra were interpreted by MASCOT or SEQUEST at a fixed false discovery rate ($q \leq 0.05$) and additional manual control. In cases where the identified peptide sequence was uncertain it was additionally validated by comparison of the generated natural peptide fragmentation pattern with the fragmentation pattern of a synthetic sequence-identical reference peptide.

Table 19 shows the presentation on various cancer entities for selected peptides, and thus the particular relevance of the peptides as mentioned for the diagnosis and/or treatment of the cancers as indicated (e.g. peptide SEQ ID No. 1 for colorectal cancer, gallbladder cancer, non-hodgkin lymphoma, non-small cell lung cancer, and uterine and endometrial cancer, peptide SEQ ID No. 2 for breast cancer, cholangiocellular carcinoma, colorectal cancer, gallbladder cancer, gastric cancer, head and neck squamous cell carcinoma, melanoma, non-hodgkin lymphoma, non-small cell lung cancer, esophageal cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, small cell lung cancer, and uterine and endometrial cancer).

Table 19: Overview of presentation of selected tumor-associated peptides of the present invention across tumor types.

AML: acute myeloid leukemia; BRCA: breast cancer; CCC: cholangiocellular carcinoma; CLL: chronic lymphocytic leukemia; CRC: colorectal cancer; GBC: gallbladder cancer; GBM: glioblastoma; GC: gastric cancer; GEJC: gastro-esophageal junction cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; MEL: melanoma; NHL: non-hodgkin lymphoma; NSCLC: non-small cell lung cancer; OC: ovarian cancer; OSCAR: esophageal cancer; PACA: pancreatic cancer; PRCA: prostate cancer; RCC: renal cell carcinoma; SCLC: small cell lung cancer; UBC: urinary bladder carcinoma; UEC: uterine and endometrial cancer

Seq ID No	Sequence	Peptide Presentation on tumor types
1	MIPTFTALL	CRC, GBC, NHL, NSCLC, UEC
2	TLLKALLEI	BRCA, CCC, CRC, GBC, GC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UEC
3	ALIYNLVGI	HCC
4	ALFKAWAL	AML, BRCA, CLL, CRC, GBC, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, RCC, SCLC, UBC, UEC
5	RLLDFINVL	UEC
7	ALQAFEFRV	GC, GEJC, HNSCC, NSCLC, PACA, SCLC, UBC
8	YLVTKVVAV	AML, BRCA, CCC, CLL, CRC, GBC, GBM, GC, GEJC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
10	RYSDSVGRVSF	BRCA, CRC, GBC, GC, NSCLC, SCLC, UBC, UEC
11	SYSDLHYGF	GC, NSCLC, UEC
12	KYEKIFEML	AML, NSCLC
13	VYTFLSSTL	NSCLC
14	FYFPTPTVL	GBC, NSCLC
15	VYHDDKQPTF	GBM, GC, NSCLC, OSCAR, UEC
16	IYSPQFSRL	BRCA, NHL, NSCLC, OSCAR, UBC, UEC
18	KYPVHIYRL	AML, BRCA, GBC, GC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, RCC, UBC, UEC

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Seq ID No	Sequence	Peptide Presentation on tumor types
19	KYVKVFHQF	AML, BRCA, CLL, CRC, GBC, GBM, GC, HCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
20	RMASPVNVK	CLL
21	AVRKPIVLK	AML, BRCA, CCC, CRC, GBC, GBM, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, RCC, SCLC, UBC, UEC
22	SLKERNPLK	NSCLC
24	SMYYPLQLK	BRCA, CRC, GBM, HCC, NHL, RCC
25	GTSPPSVEK	UEC
27	VLYGPAGLGK	HCC, HNSCC, NSCLC, OSCAR, PACA, SCLC, UBC, UEC
28	KTYETNLEIKK	NSCLC, UBC
29	QQFLTALFY	PACA, PRCA
31	LLDEGAMLLY	GBC, HNSCC, NSCLC, SCLC, UBC
32	SPNKGTLNV	NSCLC
33	SPTFHLLT	NSCLC, PRCA, SCLC, UBC, UEC
34	LPRGPLASLL	HNSCC, NSCLC, OSCAR, PACA, SCLC
35	FPDNQRPAL	BRCA, CRC, GBC, MEL, NSCLC, PACA, UBC, UEC
36	APAAWLRSA	BRCA, CCC, CRC, GBC, GC, HCC, HNSCC, NSCLC, OSCAR, PACA, SCLC, UBC, UEC
38	SPHPVTALLT	PACA, UEC
40	KPGTSYRVTL	GBM
43	ALKARTVTF	BRCA, CCC, GBM, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PRCA, SCLC, UBC, UEC
48	DVKKKIKEV	NSCLC, RCC, SCLC
53	MEHPGKLLF	UEC
56	SEPDTTASW	NSCLC, UEC
57	QESDLRLFL	BRCA, CLL, CRC, GC, GEJC, HNSCC, NHL, NSCLC, PACA, UBC, UEC
59	SENVTMKVV	UEC
60	GLLSLTSTLYL	BRCA
62	KVLGVNVML	BRCA, HNSCC, MEL, NSCLC, SCLC
63	MMEEMIFNL	UBC
64	FLDPDRHFL	BRCA, CCC, CRC, GBC, GC, GEJC, HCC, HNSCC, MEL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
65	TMFLRETSL	MEL, NHL, NSCLC, PRCA, SCLC
68	KLFDTQQFL	AML, BRCA, CRC, HCC, HNSCC, MEL,

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Seq ID No	Sequence	Peptide Presentation on tumor types
		NHL, NSCLC, OSCAR, RCC
69	TTYEGSITV	NSCLC, UEC
71	YLEDTDRNL	AML, BRCA, CCC, CRC, GBC, GC, GEJC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
72	YLTDLQVSL	AML, BRCA, CCC, CLL, CRC, GBC, GBM, GC, GEJC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
74	SQSPSVSQL	UEC
75	KVVSVLNV	BRCA, UEC
77	RYGPVFTV	CCC, GC
78	SFAPRSAVF	SCLC
79	SYNEHWNYL	BRCA, CCC, CRC, GBC, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
81	VYNHTTRPL	OSCAR
85	VLLGSLFSRK	AML, CRC, HCC, MEL, NHL, NSCLC, RCC, UEC
86	VVLLGSLFSRK	AML, CRC, GC, HCC, PACA, RCC
87	AVAPPTPASK	AML, CRC, GBC, MEL, NSCLC, OSCAR, RCC, SCLC, UEC
90	KVAGERYVYK	CCC, UEC
92	SVFPIENIY	UEC
94	ATFERVLLR	BRCA, NSCLC
96	TAFGGFLKY	OSCAR, RCC
97	TMLDVEGLFY	GC
99	KVVDRWNEK	CRC, NHL, RCC
101	RVFTSSIKTK	NSCLC, PACA, UEC
106	AAFVPLLLK	AML, BRCA, NHL, NSCLC, SCLC
108	VLYPVPLESY	AML, MEL, NHL, NSCLC, RCC, SCLC, UEC
109	KTFTIKRFLAK	BRCA, CCC, MEL, NHL, NSCLC, OSCAR, SCLC, UEC
110	SAAPPSYFR	RCC, UEC
113	QLDSNRLTY	HCC
115	FVDNQYWRY	BRCA, GBC, GC, GEJC, NSCLC, OSCAR, PACA, SCLC
116	VLLDEGAMLLY	NSCLC, PACA
117	APRLLLLAVL	BRCA, CRC, HNSCC, MEL, NSCLC, OSCAR, PRCA, RCC, SCLC, UBC, UEC

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Seq ID No	Sequence	Peptide Presentation on tumor types
118	SPASRSISL	NHL, OSCAR, RCC
119	APLPRPGAVL	MEL, OSCAR
120	RPAMNYDKL	CRC
123	KPSESIYSAL	BRCA, CRC, HNSCC, MEL, NHL, NSCLC, OSCAR, SCLC, UBC
124	LPSDSHFKITF	CRC, HNSCC, NHL, OSCAR, SCLC
125	VPVYILLDEM	CCC, GC, HNSCC, UEC
127	APRAGSQVV	AML, BRCA, CRC, GBM, HCC, HNSCC, MEL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
129	APRPASSL	BRCA, CRC, NSCLC, OSCAR, SCLC, UEC
133	MPNLPSTTSL	UEC
141	SPMTSLLTSGL	UEC
146	IPRPEVQAL	AML, CRC, GC, HNSCC, MEL
147	APRWFPQPTVV	BRCA
148	KPYGGSGPL	AML, BRCA, NHL, RCC
149	GPREALSRL	AML, BRCA, CCC, CRC, HCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UEC
150	MAAVKQAL	CCC, NSCLC, PACA
151	HLLLKVLAF	HNSCC
152	MGSARVAEL	HNSCC
156	HVKEKFLL	CCC, HNSCC
157	EAMKRLSYI	CCC, HNSCC, PACA
174	AEATARLNVF	NSCLC
176	AEIEPKADGSW	CCC, NSCLC, PRCA
178	NELFRDGVNW	AML, BRCA, CCC, CLL, CRC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, SCLC, UBC, UEC
179	REAGDEFEL	CCC, NSCLC, SCLC
180	REAGDEFELRY	CRC, HCC, MEL, NSCLC, OSCAR, PACA, RCC, UEC
181	GEGPKTSW	NSCLC
182	KEATEAQSL	NSCLC
184	AELEALTDLW	NHL, NSCLC, NSCLC
186	REGPEEPGL	GC
188	AEFAKKQPWW	CCC, CLL, CRC, MEL, NHL, NSCLC
191	EEDAALFKAW	AML, BRCA, CCC, CLL, CRC, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC

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Seq ID No	Sequence	Peptide Presentation on tumor types
192	YEFKFPNRL	BRCA, HCC, NSCLC, OSCAR, UEC
196	REMPGGPVW	BRCA, CCC, CRC, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, SCLC, UBC, UEC
197	AEVLLPRLV	NSCLC, PACA, UEC
199	REIDESLIFY	NSCLC
200	AESIPTVSF	NSCLC
208	TEVSRTEAI	NSCLC, UEC
211	EEKVFPSPLW	NHL
215	SEDGLPEGIHL	CLL, GC, GEJC, HNSCC, NHL, NSCLC, PACA
216	IMFDDAIERA	UEC
217	VSSSLTLKV	BRCA, RCC
224	SLPRFQVTL	BRCA, HCC, NHL, NSCLC, OSCAR, UBC, UEC
225	SVFAHPRKL	BRCA, OSCAR
226	QVDPKKRISM	BRCA, NHL, NSCLC, SCLC
227	YTFRYPLSL	CCC, CRC, GBC, GC, HCC, HNSCC, NSCLC, OSCAR, PACA, SCLC, UBC, UEC
228	RLWDWVPLA	AML, NHL
235	SAIETSAVL	NSCLC, UEC
237	SAMGTISIM	UEC
240	FSTDTSIVL	PACA
241	RQPNILVHL	UEC
243	YASEGVKQV	UEC
245	LAVEGGQSL	AML, BRCA, CCC, CRC, GBC, GBM, GC, GEJC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
246	RYLAVVHAVF	HCC, NHL, NSCLC, PACA, SCLC
247	ARPPWMWVL	BRCA, GBC, HNSCC, OSCAR
251	KQRQVLIF	GBM, NSCLC, OSCAR, PACA, RCC
252	LYQPRASEM	NHL
256	RTEEVLLTFK	RCC, SCLC, UEC
257	VTADHSHVF	UEC
259	KTLELRVAY	GBC, HNSCC
260	GTNTVILEY	MEL, PACA, UEC
262	RSRLNPLVQR	HNSCC, NSCLC
264	AIKVIPTVFK	HNSCC, MEL, NSCLC, RCC, UEC
268	GLLGLSLRY	PRCA

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Seq ID No	Sequence	Peptide Presentation on tumor types
269	RLKGDAWVYK	MEL, NHL, OSCAR, UEC
271	RMFADDLHNLNK	NSCLC
273	RVNAIPFTY	GBC
275	STTFPTLTK	UEC
277	TTALKTTSR	NSCLC
279	SVSSETTKIKR	UEC
280	SVSGVKTTF	HCC, UEC
281	RAKELEATF	CLL, GC, NSCLC
283	IVQEPTEEK	HCC, NHL, NSCLC
286	TVAPPQGVVK	HCC
288	SPVTSVHGGTY	NHL
289	RWEKTDLTY	CRC, UEC
291	ETIRSVGY	GBM, NSCLC, UBC
295	YPLRGSSIFGL	UEC
296	YPLRGSSI	UEC
299	HPGSSALHY	AML, CCC, CRC, GC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, UEC
300	IPMAAVKQAL	AML, BRCA, CLL, CRC, GC, HCC, HNSCC, MEL, NSCLC, OSCAR, PACA, RCC, UEC
302	RVEEVRALL	BRCA, CRC, GBM, UBC
306	APVIFSHSA	AML, CCC, HCC, MEL, NSCLC, UBC
307	LPYGPGEAAAF	BRCA, UEC
308	YPEGAAYEF	PRCA, UEC
314	VPDQPHPEI	PACA
315	SPRENFPDTL	HNSCC
317	FPFQPGSV	AML, BRCA, CLL, CRC, GBC, GBM, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
318	FPNRLNLEA	CCC, CLL, GC, HNSCC, MEL, NSCLC, PRCA, RCC, SCLC, UBC
319	SPAEPSVYATL	BRCA, GC, NSCLC, OSCAR
320	FPMSPVTSV	AML, BRCA, CCC, CRC, GBC, GBM, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC, UBC, UEC
321	SPMDTFLLI	AML, BRCA, CLL, CRC, GBC, GBM, GC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, SCLC,

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Seq ID No	Sequence	Peptide Presentation on tumor types
		UBC, UEC
322	SPDPSKHLL	NHL, NSCLC, PRCA, RCC
324	VPYRVVGL	CLL, CRC, GC, MEL, NHL, NSCLC, PRCA, SCLC
325	GPRNAQRVL	CRC, GBC, NHL, NSCLC
326	VPSEIDAAF	BRCA, CCC, CRC, GBC, GC, NSCLC, OSCAR, PACA, RCC, SCLC, UEC
330	FPFVTGSTEM	UEC
331	FPHPEMTTSM	UEC
332	FPHSEM TTL	NSCLC, PACA
333	FPHSEM TTVM	NSCLC, SCLC, UEC
334	FPYSEV TTL	NSCLC, SCLC, UEC
335	HPDPVGPGL	NSCLC, UEC
337	HPVETSSAL	UEC
355	SPLVTSHIM	UEC
363	TAKTPDATF	CCC
369	FPHSEM TTV	PACA, UEC
371	LYVDGFTHW	NSCLC, UEC
376	RPRSPAGQVA	PACA
378	RPRSPAGQVAA	NHL, PACA, SCLC
385	SPALHIGSV	BRCA, GBM, HCC, NSCLC, PRCA, SCLC, UBC, UEC
386	FPFNPLDF	GC, NHL
388	SPAPLKLSRTPA	MEL
389	SPGAQRTFFQL	AML, MEL
391	APSTPRITTF	HCC, NHL
392	KPIESTLVA	GBM, MEL, NSCLC, UEC
393	ASKPHVEI	CRC
395	VLLPRLVSC	NSCLC
399	RELLHLVTL	NSCLC, SCLC, UEC
403	EEAQWVRKY	BRCA, CLL, NHL
404	NEAIMHQY	BRCA, CCC, CLL, CRC, GBC, GC, HCC, MEL, NHL, NSCLC, OSCAR, SCLC, UBC, UEC
405	NEIWTHSY	NSCLC, UEC
407	AEHEGVSVL	NSCLC, UEC
408	LEKALQVF	CRC, GC, HNSCC, OSCAR, UEC
409	REFVLSKGDAGL	GBC, GC, GEJC, HNSCC, NSCLC
410	SEDPSKLEA	BRCA, HNSCC, NSCLC, OSCAR, SCLC, UEC

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Seq ID No	Sequence	Peptide Presentation on tumor types
411	LELPPILVY	BRCA, CRC, GBC, GBM, GC, NHL, NSCLC, OSCAR, PRCA, SCLC, UBC, UEC
414	EDAALFKAW	CLL, CRC, MEL, NHL
415	REEDAALFKAW	BRCA, CLL, CRC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PRCA, UBC, UEC
416	SEEETRVVF	AML, CRC, HNSCC, NSCLC, UEC
417	AEHFISMIRA	AML, BRCA, CRC, GBM, GC, HNSCC, NHL, NSCLC, OSCAR, PACA, PRCA, RCC, UEC
418	FEDAQGHIW	BRCA, CCC, CRC, HCC, NSCLC, OSCAR, PACA, UBC, UEC
419	HEFGHVLGL	BRCA, CCC, CRC, GC, HNSCC, MEL, NSCLC, OSCAR, PACA, UEC
420	FESHSTVSA	UEC
423	SEVPTGTTA	GBC, GBM
425	SEVPLPMAl	NSCLC, UEC
429	REKFIASVI	UEC
430	DEKILYPEF	UEC
431	AEQDPDELNKA	CRC, OSCAR, SCLC, UEC
432	EEQYIAQF	OSCAR, SCLC
433	SDSQVRAF	GBM, GC, HCC, HNSCC, NSCLC, OSCAR, RCC, SCLC, UEC
436	REPGDIFSEL	CRC
437	TEAVVTNEL	CRC, GC, NSCLC, SCLC, UEC
438	SEVDSPNVL	CCC, CLL, CRC, GC, HNSCC, MEL, NHL, NSCLC, SCLC, UBC
442	ILSKLTDIQY	BRCA, GBM, NHL, NSCLC
443	GTFNPVSLW	BRCA, GBC, GBM, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, SCLC
444	KLSQKGYSW	BRCA, CCC, CRC, GBM, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, SCLC, UBC
445	LHITPGTAY	HCC, PRCA
446	GRIVAFFSF	AML, BRCA, CRC, HCC, HNSCC, MEL, NHL, NSCLC, OSCAR, PACA, PRCA, SCLC, UBC, UEC
447	MQVLVSRI	GC, NSCLC, PACA, PRCA, RCC, SCLC
448	LSQKGYSW	NHL, NSCLC, UBC
451	DYLNEWGSRF	NSCLC, OSCAR, UEC
454	AQTDPTTGY	GBM, GC, NSCLC

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Seq ID No	Sequence	Peptide Presentation on tumor types
455	AAAANAQVY	BRCA, UEC
456	IPLERPLGEVY	BRCA, UEC
457	NAAAAANAQVY	BRCA, NSCLC, UEC
458	TDTLIHLM	UEC
459	KVAGERYVY	BRCA, CCC, CRC, GBM, HNSCC, MEL, NSCLC, OSCAR, PACA, PRCA, SCLC, UBC
460	RLSSATANALY	GBC
461	AQRMTTQLL	CRC, MEL, NSCLC, RCC
462	QRMTTQLLL	NSCLC, RCC, UEC
466	DLIESGQLRER	UEC
467	MQMQERDTL	GEJC, HNSCC, NHL, NSCLC, OSCAR
471	AQRLDPVYF	CCC, CRC, GBC, GEJC, NSCLC, OSCAR, PACA, SCLC, UBC
472	MRLLVAPL	SCLC, UEC
474	AADGGLRASVTL	BRCA, NSCLC, OSCAR
477	RIQQQTNTY	GBM, SCLC
479	TEGSHFVEA	BRCA, SCLC, UEC
480	GRADIMIDF	BRCA, CRC, HNSCC, MEL, NSCLC, OSCAR, SCLC, UEC
481	GRWEKTDLT	BRCA, GBC, HNSCC, MEL, NSCLC, OSCAR, PACA, SCLC, UBC, UEC
482	GRWEKTDLT	HNSCC, NSCLC, OSCAR, PACA, SCLC, UEC
484	AWLRSAAA	CCC
485	VRFPVHAAL	MEL, NSCLC, OSCAR
486	DRFFWLKV	NSCLC, SCLC
487	GMADILVVF	NSCLC
488	RSFSLGVPR	AML, CLL, GC, HCC, HNSCC, NHL, NSCLC, PRCA, SCLC, UEC
490	AEVQKLLGP	HNSCC, NSCLC, OSCAR, UEC
491	EAYSSTSSW	GBC, UEC
493	DTNLEPVTR	UEC
495	EVPSGATTEVSR	UEC
496	EVPTGTAEVSR	UEC
498	EVYPELGTQGR	UEC
503	TVFDKAFTAA	NSCLC
507	TSIFSGQSL	UEC
508	TVAKTTTTF	UEC
509	GRGPGGVSW	NSCLC
518	TSDFPTITV	PACA

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Seq ID No	Sequence	Peptide Presentation on tumor types
520	THSAMTHGF	NHL
527	QSTPYVNSV	UEC
528	TRTGLFLRF	HNSCC, NSCLC, UEC
533	GQHLHLETf	AML, CCC, GBC, GC, HCC, MEL, NHL, NSCLC, OSCAR, RCC, SCLC, UBC, UEC
537	IRRLKELKDQ	NSCLC
539	IPIPSTGSVEM	CCC, GC, HNSCC, NSCLC, OSCAR, PRCA, SCLC, UBC, UEC
540	AGIPAVALW	HCC, NSCLC, OSCAR
541	RLSPAPLKL	GBM, NSCLC
544	LRNPSIQKL	GBM
545	RVGPPLLI	BRCA, CRC, NSCLC, OSCAR, UEC
546	GRAFFAAAF	CRC, GBM, HNSCC, MEL, NSCLC, OSCAR, PACA, SCLC, UBC, UEC
547	EVNKPGVYTR	HCC, UEC
549	ARSKLQQGL	MEL
550	RRFKEPWFL	BRCA, HCC, MEL, NSCLC, PRCA, SCLC, UBC, UEC
563	PNFSGNWKIIRSENFEE	NSCLC
589	APDAKSFVLNLGKDSNNL	NSCLC
590	RVRGEVAPDAKSFVLNLG	NSCLC
591	VRGEVAPDAKSFVLNL	NSCLC, RCC
592	VRGEVAPDAKSFVLNLG	NSCLC, RCC
593	GEVAPDAKSFVLNLG	NSCLC, RCC
594	VRGEVAPDAKSFVLN	NSCLC, RCC
598	AESLFREALSNKVDEL	NSCLC
599	AESLFREALSNKVDE	NSCLC
607	LTVAEVQKLLGPHVEGLKAEE	NSCLC
608	LTVAEVQKLLGPHVEGLKAE	NSCLC
609	LTVAEVQKLLGPHVEGLKA	NSCLC
610	LTVAEVQKLLGPHVEGLK	NSCLC
611	LTVAEVQKLLGPHVEGL	NSCLC
612	TVAEVQKLLGPHVEGLK	NSCLC
613	LTVAEVQKLLGPHVEG	NSCLC
614	TVAEVQKLLGPHVEGL	NSCLC
615	VAEVQKLLGPHVEGLK	NSCLC
616	TVAEVQKLLGPHVEG	NSCLC
617	VAEVQKLLGPHVEGL	NSCLC
618	VAEVQKLLGPHVEG	NSCLC

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Seq ID No	Sequence	Peptide Presentation on tumor types
619	VAEVQKLLGPHVE	NSCLC
620	EVQKLLGPHVEG	NSCLC
625	DALRGLLPVLGQPIIRSIPQG	NSCLC
628	DALRGLLPVLGQPIIRSIPQ	NSCLC
629	GLLPVLGQPIIRSIPQGIVA	NSCLC
630	ALRGLLPVLGQPIIRSIPQ	NSCLC
633	LRGLLPVLGQPIIRSIPQ	NSCLC
634	DALRGLLPVLGQPIIRS	NSCLC
635	ALRGLLPVLGQPIIRS	NSCLC
637	ALRGLLPVLGQPIIR	NSCLC
638	LRGLLPVLGQPIIRS	NSCLC
639	ALRGLLPVLGQPII	NSCLC
646	GLLPVLGQPIIRSIPQGIVAAGRQ	NSCLC
648	GLLPVLGQPIIRSIPQGIVAA	NSCLC
651	LPVLGQPIIRSIPQGIVAA	NSCLC
653	LPVLGQPIIRSIPQGIVA	NSCLC
654	PVLGQPIIRSIPQGIVA	GC, NSCLC
656	VLGQPIIRSIPQGIVA	NSCLC
661	LRGLLPVLGQPIIRSIPQG	NSCLC
666	LPLTVAEVQKLLGPHVEG	NSCLC
668	AVLPLTVAEVQK	BRCA, CRC, GBC, GC, NSCLC, PACA, UEC
677	IWAVRPQDLDTCDPR	NSCLC
680	GVRGSLLSEADVRLGGLA	NSCLC
682	GVRGSLLSEADVRLGGL	NSCLC
686	VRGSLLSEADVRLGGL	NSCLC
694	GSLLSEADVRLGG	NSCLC
695	RGSLLEADVRLG	NSCLC
697	GSLLSEADVRLG	NSCLC
717	IPQGIVAAWRQRSSRDPS	GC
730	LPGRFVAESAEVL	NSCLC

EXAMPLE 2

Expression profiling of genes encoding the peptides of the invention

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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

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.

Total RNA from healthy human tissues for RNASeq experiments was obtained from: Asterand (Detroit, MI, USA & Royston, Herts, UK); Bio-Options Inc. (Brea, CA, USA); Geneticist Inc. (Glendale, CA, USA); ProteoGenex Inc. (Culver City, CA, USA); Tissue Solutions Ltd (Glasgow, UK).

Total RNA from tumor tissues for RNASeq experiments was obtained from: Asterand (Detroit, MI, USA & Royston, Herts, UK); BioCat GmbH (Heidelberg, Germany); BioServe (Beltsville, MD, USA); Geneticist Inc. (Glendale, CA, USA); Istituto Nazionale Tumori "Pascale" (Naples, Italy); ProteoGenex Inc. (Culver City, CA, USA); University Hospital Heidelberg (Heidelberg, Germany).

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).

RNAseq experiments

Gene expression analysis of - tumor and normal tissue RNA samples was performed by next generation sequencing (RNAseq) by CeGaT (Tübingen, Germany). Briefly, sequencing libraries are prepared using the Illumina HiSeq v4 reagent kit according to the provider's protocol (Illumina Inc., San Diego, CA, USA), which includes RNA fragmentation, cDNA conversion and addition of sequencing adaptors. Libraries derived from multiple samples are mixed equimolar and sequenced on the Illumina HiSeq 2500 sequencer according to the manufacturer's instructions, generating 50 bp single end reads. Processed reads are mapped to the human genome (GRCh38) using the STAR software. Expression data are provided on transcript level as RPKM (Reads Per Kilobase per Million mapped reads, generated by the software Cufflinks) and on exon level (total reads, generated by the software Bedtools), based on annotations of the ensembl sequence database (Ensembl77). Exon reads are normalized for exon length and alignment size to obtain RPKM values.

Exemplary expression profiles of source genes of the present invention that are highly over-expressed or exclusively expressed in ovarian cancer are shown in Figure 1. Expression scores for further exemplary genes are shown in Table 10.

Table 10: Expression scores. The table lists peptides from genes that are very highly over-expressed in OC tumors compared to a panel of normal tissues (+++), highly over-expressed in OC tumors compared to a panel of normal tissues (++) or over-expressed in OC tumors compared to a panel of normal tissues (+). The baseline for this score was calculated from measurements of the following relevant normal tissues: adipose tissue, adrenal gland, bile duct, blood cells, blood vessels, bone marrow, brain, cartilage, esophagus, eye, gallbladder, heart, head&neck, kidney, large intestine, liver, lung, lymph node, nerve, parathyroid, pancreas, pituitary, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, urinary bladder. In case expression data for several samples of the same tissue type were available, the arithmetic mean of all respective samples was used for the calculation.

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Seq ID No	Sequence	Gene Expression
1	MIPTFTALL	++
5	RLLDFINVL	+++
6	SLGKHTVAL	+++
10	RYSDSVGRVSF	+
11	SYSDLHYGF	++
12	KYEKIFEML	+++
13	VYTFLSSTL	+++
14	FYFPTPTVL	++
16	IYSPQFSRL	+++
17	RFTTMLSTF	+++
18	KYPVHIYRL	+
20	RMASPVNVK	++
21	AVRKPIVLK	+
22	SLKERNPLK	++
23	GMMKGGIRK	+++
25	GTSPPSVEK	++
26	RISEYLLEK	+++
27	VLYGPAGLGK	+++
28	KTYETNLEIKK	+++
29	QQFLTALFY	+++
30	ALEVAHRLK	+
31	LLDEGAMLLY	+++
32	SPNKGTLNV	+
33	SPTFHLLT	+
34	LPRGPLASLL	++
35	FPDNQRPAL	++
36	APAAWLRSA	+++
37	RPLFQKSSM	+++
38	SPHPVTALLT	++
39	RPAPFEVVF	++
40	KPGTSYRVTL	+++
42	TLKVTSAL	+
43	ALKARTVTF	+
47	MPNLRSVDL	+++
51	SLRLKNVQL	+++
52	AEFLLRIFL	+
53	MEHPGKLLF	+++
54	AEITITTQGY	++
55	HETETRRTW	++

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Seq ID No	Sequence	Gene Expression
56	SEPDTTASW	++
57	QESDLRLFL	+++
58	GEMEQKQL	+++
59	SENVTMKVV	+++
60	GLLSLTSTLYL	+
61	YMVHIQVTL	++
62	KVLGVNVML	++
63	MMEEMIFNL	++
64	FLDPDRHFL	++
66	GLLQELSSI	+++
67	SLLLPSIFL	+++
69	TTYEGSITV	++
70	VLQGLLRSL	+++
71	YLEDTDRNL	+
72	YLTDLQVSL	+
73	FLIEELLFA	+++
74	SQSPSVSQL	+++
75	KVVSVLNV	+++
76	KYVAELSLL	+++
77	RYGPVFTV	+++
78	SFAPRSAVF	++
82	SYFRGFTLI	+++
83	GTYAHTVNR	+++
84	KLQPAQTAAK	+++
87	AVAPPTPASK	++
88	VVHAVFALK	+
89	RVAELLLLH	+++
90	KVAGERYVYK	++
91	RSLRYYYEK	++
92	SVFPIENIY	++
96	TAFGGFLKY	+++
97	TMLDVEGLFY	++
98	LLQPPPLLAR	+++
100	RLFTSPIMTK	++
101	RVFTSSIKTK	++
102	SVLTSSLVK	++
103	TSRSVDEAY	++
104	VLADSVTTK	++
107	RLQEWKALK	+++

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Seq ID No	Sequence	Gene Expression
108	VLYPVPLESY	+++
110	SAAPPSYFR	+++
111	TLPQFRELGY	++
112	TVTGAEQIQY	++
113	QLDSNRPTY	++
114	VMEQSAGIMY	+++
115	FVDNQYWRY	+++
116	VLLDEGAMLLY	+++
117	APRLLLLAVL	++
118	SPASRSISL	++
119	APLPRPGAVL	+++
120	RPAMNYDKL	++
121	VPNQSSESL	+++
122	YPGFPQSQY	+++
123	KPSESIYSAL	+++
124	LPSDSHFKITF	+++
125	VPVYILLDEM	++
126	KPGPEDKL	++
128	YPRITITPGM	+
129	APRPASSL	++
130	FPRLVGPDPF	+
131	APTEDLKAL	++
132	IPGPAQSTI	++
133	MPNLPSTTSL	++
135	RVRSTISSL	++
136	SPFSAEEANSL	++
137	SPGATSRGTL	++
138	SPMATTSTL	++
139	SPQSMSNTL	++
140	SPRTEASSAVL	++
141	SPMTSLLTSGL	++
142	TPGLRETSI	++
143	SPAMTSTSF	++
144	SPSPVSSTL	++
145	SPSSPMSTF	++
147	APRWFPQPTVV	+++
151	HLLKVLAF	+++
152	MGSARVAEL	+++
154	MLRKIAVAA	++

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Seq ID No	Sequence	Gene Expression
155	NKKMMKRLM	+++
156	HVKEKFL	++
157	EAMKRLSYI	+
159	VLKHKLDEL	++
160	YPKARLAF	++
161	ALKTTTTAL	++
162	QAKTHSTL	++
163	QGLLRPVF	+++
164	SIKTKSAEM	++
165	SPRFKTGL	++
166	TPKLRETSI	++
167	TSHERLTTL	++
168	TSHERLTTY	++
169	TSMPRSSAM	++
170	YLLEKSRVI	+++
171	FAFRKEAL	+++
172	KLKERNREL	+++
173	AEAQVGDERDY	+
174	AEATARLNVF	+
175	AEIEPKADG	+
176	AEIEPKADGSW	+
177	TEVGTMNLF	++
181	GEGPKTSW	+
183	YEKGIMQKV	++
184	AELEALTDLW	++
185	AERQPGAASL	++
186	REGPEEPGL	++
187	GEAQTRIAW	++
189	KEFLFNMY	++
190	YEVARILNL	++
193	LEAQQEAL	++
194	KEVDPTSHSY	+++
195	AEDKRHYSV	+
196	REMPGGPVW	+++
197	AEVLLPRLV	++
198	QEAARAAL	++
199	REIDESLIFY	++
200	AESIPTVSF	++
201	AETILTFHAF	++

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Seq ID No	Sequence	Gene Expression
202	HESEATASW	++
203	IEHSTQAQDTL	++
204	RETSTSEETSL	++
205	SEITRIEM	++
206	SESVTSRTSY	+++
207	TEARATSDSW	++
208	TEVSRTEAI	++
209	TEVSRTEL	++
210	VEAADIFQNF	++
211	EEKVFPSPLW	+++
212	MEQKQLQKRF	+++
214	VEQTRAGSLL	++
216	IMFDDAIERA	+++
217	VSSSLTLKV	+
218	TIASQRLTPL	++
219	PLPRPGAVL	+++
220	RMTTQLLLL	++
225	SVFAHPRKL	++
226	QVDPKKRISM	++
227	YTFRYPLSL	++
229	ISVPAKTSL	++
230	SAFREGTSL	++
231	SVTESTHHL	++
232	TISSLTHEL	++
233	GSDTSSKSL	++
234	GVATRVDAL	+++
235	SAIETSAVL	++
236	SAIPFSMTL	++
237	SAMGTISIM	++
238	PLLVLFTI	+++
239	FAVPTGISM	++
240	FSTDTSIVL	++
241	RQPNILVHL	++
242	STIPALHEI	++
243	YASEGVKQV	++
244	DTDSSVHVQV	++
246	RYLAVVHAVF	+
247	ARPPWMWVL	+++
248	SVIQHLGY	++

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Seq ID No	Sequence	Gene Expression
249	VYTPTLGTL	++
250	HFPEKTTHSF	++
252	LYQPRASEM	+++
254	IIQHLTEQF	+++
255	VFVSFSSLF	+++
256	RTEEVLLTFK	++
257	VTADHSHVF	+++
258	GAYAHTVNR	+++
259	KTLELRVAY	+
260	GTNTVILEY	++
261	HTFGLFYQR	++
262	RSRLNPLVQR	++
263	SSSSATISK	++
266	ISYSGQFLVK	+++
267	VTDLISPRK	+++
268	GLLGLSLRY	+++
269	RLKGDAWVYK	++
270	AVFNPRFYRTY	+++
272	RQPERTILRPR	++
273	RVNAIPFTY	++
274	KTFPASTVF	++
275	STTFPTLTK	++
276	VSKTTGMEF	++
277	TTALKTTSR	++
278	NLSSITHER	++
279	SVSSETTKIKR	++
280	SVSGVKTTF	++
281	RAKELEATF	+++
282	CLTRTGLFLRF	+++
285	GTVNPTVGK	++
286	TVAPPQGVVK	+
287	RRIHTGEKPYK	++
288	SPVTSVHGGTY	+
289	RWEKTDLTY	++
290	DMDEEIEAEY	+++
291	ETIRSVGY	++
292	NVTMKVSVLY	+++
293	VPDSGATATAY	+++
294	YPLRGSSIF	+++

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Seq ID No	Sequence	Gene Expression
295	YPLRGSSIFGL	+++
296	YPLRGSSI	+++
297	TVREASGLL	+
298	YPTEHVQF	+
299	HPGSSALHY	++
301	SPRRSPRISF	+
302	RVEEVRALL	+++
303	LPMWKVTAF	+++
304	LPRPGAVL	+++
305	TPWAESSTKF	++
306	APVIFSHSA	++
307	LPYGPGSEAAAF	+++
308	YPEGAAYEF	+++
309	FPQSQYPQY	+++
310	RPNPITIIL	+++
311	RPLFYVVSL	+++
312	LPYFREFSM	+++
313	KVKSDRSVF	+++
315	SPRENFPDTL	+++
316	EPKTATVL	++
320	FPMSPVTSV	+
321	SPMDTFLLI	+
322	SPDPSKHLL	+
323	RPMPNLRSV	+++
324	VPYRVVGL	+++
326	VPSEIDAAF	++
327	SPLPVTSLI	++
328	EPVTSSLPNF	++
329	FPAMTESGGMIL	++
330	FPFVTGSTEM	++
331	FHPPEMTTSM	++
332	FPHSEM TTL	++
333	FPHSEM TTVM	++
334	FPYSEV TTL	++
335	HPDPVGPGL	+++
336	HPKTESATPAAY	++
337	HPVETSSAL	++
338	HVTKTQATF	++
339	LPAGTTGSLVF	++

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Seq ID No	Sequence	Gene Expression
340	LPEISTRM	++
341	LPLDTSTTL	++
342	LPLGTSMTF	++
343	LPSVSGVKTF	++
344	LPTQTTSSL	++
345	LPTSESLVSF	++
346	LPWDTSTTLF	++
347	MPLTTGSQGM	++
348	MPNSAIPFSM	++
349	MPSLSEAMTSF	++
350	NPSSTTTEF	++
351	NVLTSTPAF	++
352	SPAETSTNM	++
353	SPAMTTPSL	++
354	SPLPVTSL	++
355	SPLVTSHIM	++
356	SPNEFYFTV	++
357	SPSPVPTTL	++
358	SPSPVTSTL	++
359	SPSTIKLTM	++
360	SPSVSSNTY	++
361	SPTHVTQSL	++
362	SPVPVTSLF	++
363	TAKTPDATF	++
364	TPLATTQRF	++
365	TPLATTQRFTY	++
366	TPLTTTGSAEM	++
367	TPSVVTEGF	++
368	VPTPVFPTM	++
369	FPHSEMTTV	++
370	PGGTRQSL	++
372	IPRNPPPTLL	+++
373	RPRALRDLRIL	+++
374	NPIGDTGVKF	+++
375	AAASPLLLL	+++
376	RPRSPAGQVA	+++
377	RPRSPAGQVAAA	+++
378	RPRSPAGQVAA	+++
379	GPFPLVYVL	+++

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Seq ID No	Sequence	Gene Expression
380	IPTYGRTF	+++
381	LPEQTPLAF	+++
382	SPMHDRWTF	+++
383	TPTKETVSL	+++
384	YPGLRGSPM	+++
387	APLKLSRTPA	+++
388	SPAPLKLSRTPA	+++
389	SPGAQRTFFQL	++
395	VLLPRLVSC	++
396	REASGLLSL	+
397	REGDTVQLL	+
399	RELLHLVTL	+
400	GEIEIHLL	+
403	EEAQWVRKY	++
404	NEAIMHQY	++
405	NEIWTHSY	++
411	LELPILVY	+
412	QEILTQVKQ	+++
413	IEALSGKIEL	+++
416	SEEETRVVF	++
417	AEHFSMIRA	+++
418	FEDAQGHIW	++
419	HEFGHVLGL	++
420	FESHSTVSA	++
421	GEPATTVSL	++
422	SETTFSLIF	++
423	SEVPTGTTA	++
424	TEFPLFSAA	++
425	SEVPLPMAl	++
426	PEKTTHSF	++
427	HESSSHHDL	+
428	LDLGLNHI	++
429	REKFIASVI	+++
430	DEKILYPEF	+++
432	EEQYIAQF	+++
433	SDSQVRAF	+++
435	REEFVSIDHL	+++
436	REPGDIFSEL	+++
437	TEAVVTNEL	+

EXAMPLE 3

In vitro immunogenicity for MHC class I presented peptides

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 HLA-A*02:01, HLA-A*24:02, HLA-A*01:01, HLA-A*03:01, HLA-B*07:02 and HLA-B*44:02 restricted TUMAPs of the invention, demonstrating that these peptides are T-cell epitopes against which CD8⁺ precursor T cells exist in humans (Table 11).

In vitro priming of CD8⁺ T cells

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, HLA-A*24, HLA-A*01, HLA-A*03, HLA-B*07 or HLA-B*44 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.

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.

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.

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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).

pMHC used for positive and negative control stimulations were A*0201/MLA-001 (peptide ELAGIGILTV (SEQ ID NO. 775) from modified Melan-A/MART-1) and A*0201/DDX5-001 (YLLPAIVHI from DDX5, SEQ ID NO. 776), respectively.

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 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 ovarian cancer peptides

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 14 peptides of the invention are shown in Figures 2 through 9 together with corresponding negative controls. Results for 118 peptides from the invention are summarized in Table 11a and Table 11b.

Table 11a: *in vitro* immunogenicity of HLA class I peptides of the invention. Exemplary results of *in vitro* immunogenicity experiments conducted by the applicant for the peptides of the invention. <20 % = +; 20 % - 49 % = ++; 50 % - 69 % = +++; ≥ 70 % = ++++

Seq ID	Sequence	Wells positive [%]
773	ALYGKLLKL	+++
774	VYVDDIYVI	+++

Table 11b: *in vitro* immunogenicity of HLA class I peptides of the invention. Exemplary results of *in vitro* immunogenicity experiments conducted by the applicant for the peptides of the invention. <20 % = +; 20 % - 49 % = ++; 50 % - 69 % = +++; ≥ 70 % = ++++

Seq ID No	Sequence	Wells positive [%]	HLA
2	TLLKALLEI	++	A*02
3	ALIYNLVGI	++	A*02
4	ALFKAWAL	++++	A*02
5	RLLDFINVL	++	A*02
7	ALQAFEFRV	++++	A*02
60	GLLSLTSTLYL	+	A*02
62	KVLGVNVMML	++	A*02
64	FLDPDRHFL	+++	A*02
66	GLLQELSSI	+	A*02
67	SLLLPSIFL	+++	A*02
71	YLEDTDRNL	+	A*02

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Seq ID No	Sequence	Wells positive [%]	HLA
73	FLIEELLFA	+++	A*02
75	KVVSVLNV	+++	A*02
11	SYSDLHYGF	+++	A*24
12	KYEKIFEML	+	A*24
13	VYTFLSSTL	+	A*24
16	IYSPQFSRL	+	A*24
18	KYPVHIYRL	+	A*24
79	SYNEHWNYL	+	A*24
80	TAYMVSVAAF	+	A*24
82	SYFRGFTLI	+	A*24
113	QLDSNRLTY	+	A*01
115	FVDNQYWRY	+	A*01
20	RMASPVNVK	+	A*03
21	AVRKPIVLK	+	A*03
22	SLKERNPLK	+	A*03
23	GMMKGGIRK	++	A*03
24	SMYYPLQLK	+	A*03
25	GTSPPSVEK	+++	A*03
26	RISEYLLEK	+	A*03
27	VLYGPAGLGK	+	A*03
28	KTYETNLEIKK	+	A*03
30	ALEVAHRLK	++	A*03
83	GTYAHTVNR	+	A*03
84	KLQPAQTAAK	+	A*03
85	VLLGSLFSRK	+	A*03
86	VVLLGSLFSRK	+	A*03
87	AVAPPTPASK	+	A*03
90	KVAGERYVYK	+++	A*03
91	RSLRYYYEK	++	A*03
94	ATFERVLLR	+	A*03
95	QSMYYPLQLK	+	A*03
99	KVVDRWNEK	++	A*03
100	RLFTSPIMTK	+	A*03
102	SVLTSSLVK	+	A*03
106	AAFVPLLLK	+++	A*03
109	KTFTIKRFLAK	+	A*03
110	SAAPPSYFR	++	A*03
32	SPNKGTLNV	+	B*07
33	SPTFHLTL	++++	B*07

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Seq ID No	Sequence	Wells positive [%]	HLA
34	LPRGPLASLL	+	B*07
35	FPDNQRPAL	+	B*07
36	APAAWLRSA	+++	B*07
37	RPLFQKSSM	+	B*07
38	SPHPVTALLTL	+	B*07
39	RPAPFEVVF	+++	B*07
40	KPGTSYRVTL	++++	B*07
41	RVRSRISNL	+	B*07
118	SPASRSISL	+	B*07
119	APLPRPGAVL	++	B*07
120	RPAMNYDKL	+	B*07
121	VPNQSSESL	+	B*07
123	KPSESIYSAL	++	B*07
124	LPSDSHFKITF	++	B*07
128	YPRTITPGM	+	B*07
129	APRPASSL	+	B*07
130	FPRLVGPDF	+++	B*07
131	APTEDLKAL	++	B*07
133	MPNLPSTTSL	++++	B*07
134	RPIVPGPLL	++	B*07
139	SPQSMSNTL	+	B*07
140	SPRTEASSAVL	+	B*07
141	SPMTSLLTSGL	++	B*07
146	IPRPEVQAL	+++	B*07
147	APRWFPQPTVV	++	B*07
148	KPYGGSGPL	+	B*07
149	GPREALSRL	++	B*07
52	AEFLLRIFL	+	B*44
53	MEHPGKLLF	+	B*44
55	HETETRRTTW	+++	B*44
57	QESDLRLFL	+	B*44
58	GEMEQKQL	++++	B*44
59	SENVTMKVV	++	B*44
174	AEATARLNVF	+	B*44
175	AEIEPKADG	++++	B*44
177	TEVGTMNLF	++	B*44
178	NELFRDGVNW	+	B*44
179	REAGDEFEL	+	B*44
180	REAGDEFELRY	++++	B*44

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Seq ID No	Sequence	Wells positive [%]	HLA
181	GEGPKTSW	+	B*44
182	KEATEAQSL	+	B*44
183	YEKGIMQKV	+++++	B*44
184	AELEALTDLW	+	B*44
186	REGPEEPGL	+	B*44
187	GEAQTRIAW	++	B*44
188	AEFAKKQPWW	++	B*44
189	KEFLFNMY	+++++	B*44
190	YEVARILNL	+++++	B*44
191	EEDAALFKAW	+++	B*44
192	YEFKFPNRL	+	B*44
195	AEDKRHYSV	+++	B*44
197	AEVLLPRLV	++	B*44
198	QEAARAAL	++	B*44
199	REIDESLIFY	+	B*44
200	AESIPTVSF	+++	B*44
201	AETILTFHAF	+++	B*44
202	HESEATASW	++	B*44
203	IEHSTQAQDTL	+++++	B*44
205	SEITRIEM	+++++	B*44
207	TEARATSDSW	+	B*44
208	TEVSRTEAI	+	B*44
209	TEVSRTEL	+++++	B*44
210	VEAADIFQNF	+	B*44
211	EEKVFPSPLW	+++	B*44
212	MEQKQLQKRF	++	B*44
213	KESIPRWYY	+	B*44

EXAMPLE 4

Synthesis of peptides

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 lyophilizes (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.

EXAMPLE 5

MHC Binding Assays

Candidate peptides for T cell based therapies according to the present invention 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 ($\beta 2m$) of stabilized MHC complexes. The assay was performed as generally described in Rodenko et al. (Rodenko et al., 2006).

96 well MAXISorp plates (NUNC) were coated over night with 2ug/ml streptavidin in PBS at room temperature, washed 4x and blocked for 1h at 37°C in 2% BSA containing blocking buffer. Refolded HLA-A*02:01/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- $\beta 2m$ 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 12: MHC class I binding scores. Binding of HLA-class I restricted peptides to HLA-A*02:01 was ranged by peptide exchange yield: >10% = +; >20% = ++; >50 = +++; > 75% = ++++

Seq ID No	Sequence	Peptide exchange
1	MIPTFTALL	+++

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Seq ID No	Sequence	Peptide exchange
2	TLLKALLEI	++++
3	ALIYNLVGI	++++
4	ALFKAWAL	++++
5	RLLDFINVL	++++
6	SLGKHTVAL	+++
7	ALQAFEFRV	++++
8	YLVTKVVAV	++++
9	VLLAGFKPPL	+
60	GLLSLTSTLYL	++++
61	YMVHIQVTL	++++
62	KVLGVNVML	++++
63	MMEEMIFNL	++++
64	FLDPDRHFL	++++
66	GLLQELSSI	++++
67	SLLLPSIFL	++++
68	KLFDTQQFL	++++
69	TTYEGSITV	++++
70	VLQGLLRSL	++++
71	YLEDTDRNL	++++
72	YLTDLQVSL	++++
73	FLIEELLFA	++++
75	KVVSVLYNV	++++
216	IMFDDAIERA	++++
217	VSSSLTLKV	+
219	PLPRPGAVL	+
220	RMTTQLLLL	+++
221	SLLDLYQL	++
222	ALMRLIGCPL	++++
223	FAHHGRSL	+
224	SLPRFQVTL	++++
225	SVFAHPRKL	+++
227	YTFRYPLSL	+++
228	RLWDWVPLA	++++
229	ISVPAKTSL	+
231	SVTESTHHL	+++
232	TISSLTHEL	++++
234	GVATRVDAL	++
236	SAIPFSMTL	+++
241	RQPNILVHL	++

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Seq ID No	Sequence	Peptide exchange
242	STIPALHEI	+++
243	YASEGVKQV	+++
244	DTDSSVHVQV	+

Table 13: MHC class I binding scores. Binding of HLA-class I restricted peptides to HLA-A*24:02 was ranged by peptide exchange yield: >10% = +; >20% = ++; >50 = +++; > 75% = ++++

Seq ID No	Sequence	Peptide exchange
10	RYSDSVGRVSF	++++
11	SYSDLHYGF	++++
12	KYEKIFEML	++++
13	VYTFLSSTL	++++
14	FYFPTPTVL	++++
15	VYHDDKQPTF	++++
16	IYSPQFSRL	++++
17	RFTTMLSTF	++++
18	KYPVHIYRL	++++
19	KYVKVFHQF	++++
76	KYVAELSLL	++++
77	RYGPVFTV	++++
78	SFAPRSAVF	++++
79	SYNEHWNYL	++++
80	TAYMVSVAAF	+++
81	VYNHTTRPL	++++
82	SYFRGFTLI	++++
246	RYLAVVHAVF	++++
249	VYTPTLGTL	++++
252	LYQPRASEM	+++
255	VFVSFSSLF	+++

Table 14: MHC class I binding scores. Binding of HLA-class I restricted peptides to HLA-A*01:01 was ranged by peptide exchange yield: >10% = +; >20% = ++; >50 = +++; > 75% = ++++

Seq ID No	Sequence	Peptide exchange
31	LLDEGAMLLY	++++

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Seq ID No	Sequence	Peptide exchange
112	TVTGAEQIQY	++
113	QLDSNRLTY	+++
114	VMEQSAGIMY	++
115	FVDNQYWRY	+++
116	VLLDEGAMLLY	++
288	SPVTSVHGGTY	++
289	RWEKTDLT	++
290	DMDEEIEAEY	++
291	ETIRSVGY	+++
292	NVTMKVSVLY	+++

Table 15: MHC class I binding scores. Binding of HLA-class I restricted peptides to HLA-A*03:01 was ranged by peptide exchange yield: >10% = +; >20% = ++; >50 = +++; > 75% = ++++

Seq ID No	Sequence	Peptide exchange
20	RMASPVNVK	++++
21	AVRKPIVLK	+++
22	SLKERNPLK	++
23	GMMKGGIRK	+++
24	SMYYPLQLK	+++
25	GTSPPSVEK	++
26	RISEYLLEK	++
27	VLYGPAGLGK	+++
28	KTYETNLEIKK	+++
30	ALEVAHRLK	++
83	GTYAHTVNR	+++
84	KLQPAQTAAK	++
85	VLLGSLFSRK	++
86	VLLGSLFSRK	++
87	AVAPPTPASK	++
88	VVHAVFALK	+++
89	RVAELLLH	++
90	KVAGERYVYK	+++
91	RSLRYYYEK	++
93	KILEEHTNK	++
94	ATFERVLLR	+++
95	QSMYYPLQLK	++

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Seq ID No	Sequence	Peptide exchange
98	LLQPPPLLAR	++
99	KVVDRWNEK	++
100	RLFTSPIMTK	+++
101	RVFTSSIKTK	++
102	SVLTSSLVK	++
104	VLADSVTTK	++
105	RLFSWLVNR	+++
106	AAFVPLLLK	++
107	RLQEWKALK	+++
109	KTFTIKRFLAK	++
110	SAAPPSYFR	++
256	RTEEVLLTFK	++
257	VTADHSHVF	+
258	GAYAHTVNR	+++
259	KTLELRVAY	++
260	GTNTVILEY	+++
261	HTFGLFYQR	++
262	RSRLNPLVQR	++
263	SSSSATISK	++
264	AIKVIPTVFK	++
265	QIHDHVNPK	++
266	ISYSGQFLVK	+++
267	VTDLISPRK	++
269	RLKGDAWVYK	+++
270	AVFNPRFYRTY	++
271	RMFADDLHNLNK	+++
272	RQPERTILRPR	++
273	RVNAIPFTY	+++
274	KTFPASTVF	+
275	STTFPTLTK	++
276	VSKTTGMEF	+
277	TTALKTTSR	+
278	NLSSITHER	++
279	SVSSETTKIKR	++
280	SVSGVKTTF	++
281	RAKELEATF	+
283	IVQEPTEEK	++
284	KSLIKSWKK	++
285	GTVNPTVGK	++

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Seq ID No	Sequence	Peptide exchange
286	TVAPPQGVVK	++
287	RRIHTGEKPYK	++

Table 16: MHC class I binding scores. Binding of HLA-class I restricted peptides to HLA-B*07:02 was ranged by peptide exchange yield: >10% = +; >20% = ++; >50 = +++; > 75% = ++++

Seq ID No	Sequence	Peptide exchange
32	SPNKGTL SV	"++++"
33	SPTFHLTL	"++++"
34	LPRGPLASLL	"++++"
35	FPDNQRPAL	"++++"
36	APAAWL RSA	"++"
37	RPLFQKSSM	"++++"
38	SPHPVTALLTL	"++++"
39	RPAPFEVVF	"++++"
40	KPGTSYRVTL	"++++"
41	RVRSRISNL	"++++"
118	SPASRSISL	"++++"
119	APLPRPGAVL	"++++"
120	RPAMNYDKL	"++"
121	VPNQSSESL	"++++"
122	YPGFPQSQY	"++"
123	KPSESIYSAL	"++++"
124	LPSDSHFKITF	"++++"
125	VPVYILLDEM	"++"
126	KPGPEDKL	"++"
127	APRAGSQVV	"++++"
128	YPR TITPGM	"++++"
129	APRPASSL	"++++"
130	FPRLVGPDF	"++++"
131	APTEDLKAL	"++++"
132	IPGPAQSTI	"++"
133	MPNLPSTTSL	"++++"
134	RPIVPGPLL	"++++"
135	RVRSTISSL	"++++"
136	SPFSAEEANSL	"++++"
137	SPGATSRGTL	"++++"

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Seq ID No	Sequence	Peptide exchange
138	SPMATTSTL	"+++"
139	SPQSMSNTL	"+++"
140	SPRTEASSAVL	"+++"
141	SPMTSLLTSGL	"+++"
142	TPGLRETSI	"++"
143	SPAMTSTSF	"++"
144	SPSPVSSTL	"+++"
145	SPSSPMSTF	"++"
146	IPRPEVQAL	"+++"
147	APRWFPQPTVV	"+++"
148	KPYGGSGPL	"+++"
149	GPREALSRL	"+++"
293	VPDSGATATAY	"++"
294	YPLRGSSIF	"+++"
295	YPLRGSSIFGL	"+++"
296	YPLRGSSI	"++"
297	TVREASGLL	"+++"
298	YPTEHVQF	"++"
299	HPGSSALHY	"++"
300	IPMAAVKQAL	"+++"
301	SPRRSPRISF	"++"
302	RVEEVRALL	"+++"
303	LPMWKVTAF	"+++"
304	LPRPGAVL	"+++"
305	TPWAESSTKF	"++"
306	APVIFSHSA	"++"
307	LPYGPGSEAAAF	"+++"
308	YPEGAAYEF	"++"
309	FPQSQYPQY	"++++"
311	RPLFYVVS	"++"
312	LPYFREFSM	"+++"
313	KVKSDRSVF	"+"
314	VPDQPHPEI	"+++"
315	SPRENFPDTL	"+++"
316	EPKTATVL	"++"
317	FPFQPGSV	"+++"
318	FPNRLNLEA	"+++"
319	SPAEPSVYATL	"++++"
320	FPMSPVTSV	"+++"

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Seq ID No	Sequence	Peptide exchange
321	SPMDTFLLI	"++"
322	SPDPSKHLL	"++"
323	RPMPNLRSV	"+++"
324	VPYRVVGL	"++"
325	GPRNAQRVL	"+++"
326	VPSEIDAAF	"++"
327	SPLPVTSLI	"+++"
328	EPVTSSLPNF	"++"
329	FPAMTESGGMIL	"+++"
330	FPFVTGSTEM	"++"
331	FPHPEMTTSM	"+++"
332	FPHSEM TTL	"+++"
333	FPHSEM TTVM	"+++"
334	FPYSEV TTL	"+++"
335	HPDPVGPGL	"++"
336	HPKTESATPAAY	"++"
337	HPVETSSAL	"+++"
338	HVTKTQATF	"++"
339	LPAGTTGSLVF	"+++"
340	LPEISTRM	"++"
341	LPLDTSTTL	"+++"
342	LPLGTSM TF	"+++"
343	LPSVSGVK TTF	"++"
344	LPTQTTSSL	"+++"
345	LPTSESLVSF	"++"
346	LPWDTSTTLF	"+++"
347	MPLTTGSQGM	"++"
348	MPNSAIPFSM	"+++"
349	MPSLSEAMTSF	"+++"
350	NPSSTTTEF	"+++"
351	NVLTSTPAF	"++"
352	SPAETSTNM	"+++"
353	SPAMTTPSL	"+++"
354	SPLPVTSL L	"+++"
355	SPLVTSHIM	"+++"
356	SPNEFYFTV	"+++"
357	SPSPVPTTL	"+++"
358	SPSPVTSTL	"+++"
359	SPSTIKLTM	"+++"

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Seq ID No	Sequence	Peptide exchange
360	SPSVSSNTY	"++"
361	SPTHVTQSL	"+++"
362	SPVPVTSLF	"+++"
363	TAKTPDATF	"++"
364	TPLATTQRF	"++"
365	TPLATTQRFTY	"++"
367	TPSVVTEGF	"++"
368	VPTPVFPTM	"++"
369	FPHSEMTTV	"+++"
370	PGGTRQSL	"+"
371	LYVDGFTHW	"++"
372	IPRNPPPTLL	"+++"
373	RPRALRDLRIL	"+++"
374	NPIGDTGVKF	"+++"
375	AAASPLLLL	"++"
376	RPRSPAGQVA	"+++"
377	RPRSPAGQVAAA	"+++"
378	RPRSPAGQVAA	"+++"
379	GPFPLVYVL	"+++"
380	IPTYGRTF	"+++"
381	LPEQTPLAF	"++"
382	SPMHDRWTF	"+++"
383	TPTKETVSL	"+++"
384	YPGLRGSPM	"++++"
385	SPALHIGSV	"+++"
386	FPFNPLDF	"++"
387	APLKLSRTPA	"+++"
388	SPAPLKLSRTPA	"++"
389	SPGAQRTFFQL	"+++"
390	NPDLRRNVL	"+++"
391	APSTPRITTF	"+++"
392	KPIESTLVA	"+++"

Table 17: MHC class I binding scores. Binding of HLA-class I restricted peptides to HLA-B*44:02 was measured by peptide exchange yield: >10% = +; >20% = ++; >50 = +++; > 75% = ++++

Seq ID No	Sequence	Peptide exchange
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Seq ID No	Sequence	Peptide exchange
52	AEFLLRIFL	"++"
53	MEHPGKLLF	"++++"
54	AEITITTQTGY	"+++"
55	HETETRRTTW	"+++"
56	SEPDTTASW	"+++"
57	QESDLRLFL	"+++"
58	GEMEQKQL	"++"
59	SENVTMKVV	"+++"
173	AEAQVGDERDY	"+++"
174	AEATARLNVF	"++++"
175	AEIEPKADG	"++"
176	AEIEPKADGSW	"+++"
177	TEVGTMNLF	"+++"
178	NELFRDGVNW	"+++"
179	REAGDEFEL	"++"
180	REAGDEFELRY	"++"
181	GEGPKTSW	"++"
182	KEATEAQSL	"+++"
183	YKGMIMQKV	"++"
184	AELEALTDLW	"+++"
185	AERQPGAASL	"++"
186	REGPEEPGL	"++"
187	GEAQTRIAW	"+++"
188	AEFAKKQPWW	"+++"
189	KEFLFNMY	"++"
190	YEVARILNL	"++"
191	EEDAALFKAW	"+++"
192	YEFKFPNRL	"+++"
193	LEAQQEAL	"++"
194	KEVDPTSHSY	"++"
195	AEDKRHYSV	"++"
196	REMPGGPVW	"+++"
197	AEVLLPRLV	"+++"
198	QEAARAAL	"++"
199	REIDESLIFY	"+++"
200	AESIPTVSF	"+++"
201	AETILTFHAF	"+++"
202	HESEATASW	"+++"
203	IEHSTQAQDTL	"++"

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Seq ID No	Sequence	Peptide exchange
204	RETSTSEETSL	"+++"
205	SEITRIEM	"++"
206	SESVTSRTSY	"+++"
207	TEARATSDSW	"+++"
208	TEVSRTEAI	"++"
209	TEVSRTEL	"++"
210	VEAADIFQNF	"+++"
211	EEKVFPSPLW	"+++"
212	MEQKQLQKRF	"+++"
213	KESIPRWYY	"++"
214	VEQTRAGSLL	"++"
215	SEDGLPEGIHL	"++"
396	REASGLLSL	"+++"
397	REGDTVQLL	"++"
398	SFEQVVNELF	"++"
399	RELLHLVTL	"+++"
400	GEIEIHLL	"+"
402	RELANDELIL	"++"
403	EEAQWVRKY	"++"
404	NEAIMHQY	"++"
405	NEIWTHSY	"+"
406	EDGRLVIEF	"+"
407	AEHEGVSVL	"++"
408	LEKALQVF	"++"
409	REFVLSKGDAGL	"+++"
410	SEDPSKLEA	"+"
411	LELPPILVY	"+"
412	QEILTQVKQ	"++"
413	IEALSGKIEL	"++"
414	EDAALFKAW	"++"
415	REEDAALFKAW	"+++"
416	SEEETRVVF	"+++"
417	AEHFISMIRA	"++"
418	FEDAQGHIW	"+++"
419	HEFGHVLGL	"++"
420	FESHSTVSA	"+"
421	GEPATTVSL	"++"
422	SETTFSLIF	"+++"
423	SEVPTGTTA	"++"

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Seq ID No	Sequence	Peptide exchange
424	TEFPLFSAA	"+"
425	SEVPLPMAl	"+++"
426	PEKTTHSF	"+"
427	HESSSHHDL	"++"
429	REKFIASVI	"++"
431	AEQDPDELNKA	"++"
432	EEQYIAQF	"+"
433	SDSQVRAF	"+"
434	KEAIREHQM	"++"
435	REEFVSIDHL	"++"
436	REPGDIFSEL	"++"
437	TEAVVTNEL	"++"
438	SEVDSPNVL	"+++"

EXAMPLE 6

Stability of peptide-MHC class I complexes

Peptide-MHC stability assays for HLA-B*08:01 peptides were performed. The data were obtained using a proximity based, homogenous, real-time assay in order to measure the dissociation of peptides from HLA class I molecules. First, human recombinant HLA-B*08:01 and b2m were expressed in *E. coli* and purified in a series of liquid chromatography based steps (Ferre et al., 2003; Ostergaard et al., 2001). Then, the stability of a peptide-MHC complex (pMHC) was determined by measuring the amount of b2m associated with the MHC heavy chain over time at 37°C (Harndahl et al., 2012). The stability of each pMHC, expressed as the half life of b2m associated with the respective heavy chain, was calculated by fitting the data to a one-phase dissociation equation.

The pMHC stabilities were measured in three independent experiments with the peptides in question, and for HLA-B*08:01 were found to span the range from weak-binders (+) to very stable binders (+++). The mean half-life (T_{1/2}) is shown in Table 18.

Table 18: Mean half-life (T1/2) based on three individual measurements. T1/2 > 2 h = +; T1/2 > 4 h = ++; T1/2 > 6 h = +++; T1/2 > 10 h = ++++

Seq ID No	Sequence	Mean Half-life (T1/2)
43	ALKARTVTF	+++
44	LNKQKVTF	++++
45	VGREKKLAL	++
46	DMKKAKEQL	+
47	MPNLRSDVL	++
48	DVKKKIKEV	+
49	LPRLKAFMI	++
50	DMKYKNRV	+
51	SLRLKNVQL	+
150	MAAVKQAL	++
151	HLLLKVLAF	++
152	MGSARVAEL	++
153	NAMLRKVAV	+
154	MLRKIAVAA	+
156	HVKEKFLL	++
157	EAMKRLSYI	+
158	LPKLAGLL	+
159	VLKHKLDEL	+
160	YPKARLAF	+++
161	ALKTTTTAL	+
162	QAKTHSTL	+
163	QGLLRPVF	++
164	SIKTKSAEM	+++
166	TPKLRETSI	++
167	TSHERLTTL	++
169	TSMPRSSAM	+++
170	YLLEKSRVI	++
171	FAFRKEAL	++
172	KLKERNREL	+++
394	MYKMKKPI	+
395	VLLPRLVSC	+

EXAMPLE 7

Binding scores of selected peptides for HLA Class II allotypes

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Major histocompatibility complex class II (MHC-II) molecules are predominantly expressed on the surface of professional antigen presenting cells, where they display peptides to T helper cells, which orchestrate the onset and outcome of many host immune responses. Understanding which peptides will be presented by the MHC-II molecule is therefore important for understanding the activation of T helper cells and can be used to identify T-cell epitopes. Peptides presented by the MHC class II molecule bind to a binding groove formed by residues of the MHC α - and β -chain. The peptide-MHC binding affinity is primarily determined by the amino acid sequence of the peptide-binding core. HLA class II binding prediction algorithms are only available for the most important class II alleles and have been tested using the SYFPEITHI algorithm (Rammensee et al., 1999). The algorithm has already been successfully used to identify class I and class II epitopes from a wide range of antigens, e.g. from the human tumor-associated antigens TRP2 (class I) (Sun et al., 2000) and SSX2 (class II) (Neumann et al., 2004). Table 20 shows the HLA class II allotypes which are likely to bind the selected peptides. The peptide was considered as binding to an HLA molecule if the SYFPEITHI score was equal to or higher than 18.

Table 20: Binding of the class II peptides to various HLA class II allotypes. Based on the prediction by the SYFPEITHI algorithm, the selected peptides are likely to bind to at least 4 of the HLA class II allotypes with known binding motif. Listed are all HLA class II alleles for which a SYFPEITHI prediction matrix is available.

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
552	GVNAMLRKVAVAASKPH VE	DRB1*11:04	DQA1*05:01/DQB1*02:01 (DQ2), QA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*13:02, DRB1*15:01	15
560	PNFSGNWKIIRSENFEELL K	DRB1*07:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*11:01, DRB1*13:02, DRB1*15:01, DRB1*15:02	14
574	LPDFYNDWMFIAKHLPLD	DRB1*11:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*11:01, DRB1*11:04, DRB1*13:02, DRB1*15:01, DRB1*15:02	15
575	VGDDHLLLLQGEQLRRT	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*09:01, DRB1*15:01, DRB1*15:02	8
579	SGGPLVCDETLQGILS	DQA1*0501/DQB1*02 01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7),	8

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*15:01	
582	GSQPWQVSLFNGLSFH	DRB1*15:01	DQA1*05:01/DQB1*02:01 (DQ2), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*07:01, DRB1*09:01, DRB1*15:01, DRB1*15:02	10
583	LTVKLPGYEFKFPNRLNL EAINY	DQA1*05:01/DQB1*02:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*11:01, DRB1*13:02, DRB1*15:01, DRB1*15:02	14
587	DQANLTVKLPGYEFKFPN RLNL	DQA1*05:01/DQB1*02:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*11:01, DRB1*13:02, DRB1*15:01, DRB1*15:02	13
588	VAPDAKSFVLNLGKDSNNL	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*11:01, DRB1*13:01, DRB1*13:02	16
590	RVRGEVAPDAKSFVLNLG	DRB1*03:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*07:01, DRB1*09:01, DRB1*15:01	10
596	MAADGDFKIKCVAFD	DQA1*05:01/DQB1*02:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2),	10

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
		2:01 (DQ2); DRB1*03:01; DRB1*07:01	DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:03, DRB1*09:01, DRB1*15:01	
597	SPDAESLFREALSNKVDL	DRB1*07:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01	8
601	LSNKVDELAHFLRK	DQA1*05:01/DQB1*02:01 (DQ2) 2:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*11:01, DRB1*11:04, DRB1*15:01, DRB1*15:02	14
604	KLITQDLVKLKYLEYRQ	DQA1*05:01/DQB1*02:01 (DQ2) 2:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*08:02, DRB1*13:01, DRB1*13:02, DRB1*15:01	9
605	LTVAEVQKLLGPHVEGLKA EERHRP	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01, DRB1*15:02	15
622	MDALRGLLPVLGQPIIRSIP QGIVA	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*15:01,	15

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*15:02	
645	RGLLPVLGQPIIRSIPQGIV AAWRQ	DRB1*01:01; DRB1*09:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*15:01, DRB1*15:02	14
658	VSTMDALRGLLPVLGQPIIR SIPQG	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*15:01, DRB1*15:02	14
662	LRTDAVLPLTVAEVQKLLG PHVEG	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01, DRB1*15:02	15
669	VLPLTVAEVQKLLGPHVEG LKAEE	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01, DRB1*15:02	15
672	LRGLLPVLGQPIIRSIPQGIV AA	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01,	14

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*04:01, DRB1*04:02, DRB1*04:04, , DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*15:01, DRB1*15:02	
673	IPFTYEQLDVLKHKLDLYP Q	DRB1*08:03	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:02, DRB1*15:01, DRB1*15:02	15
676	VPPSSIWAVRPQDLDTCD PR	DQA1*05:01/DQB1*02:01 (DQ2), 2:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:03, DRB1*09:01, DRB1*15:01	10
679	WGVRGSLLEADVRALGG LA	DRB1*09:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*15:01	12
706	LSTERVRELAVALAQKNVK	DQA1*05:01/DQB1*03:01 (DQ7)	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01, DRB1*15:02	15
714	AIPFTYEQLDVLKHKLDE	DRB1*08:03	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01,	15

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*11:01, DRB1*11:04, DRB1*13:02, DRB1*15:01, DRB1*15:02	
715	GLSTERVRELAVALAQKN	DQA1*05:01/DQB1*03:01 (DQ7)	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01, DRB1*15:02	15
717	IPQGIVAAWRQRSSRDPS	DRB1*11:04	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01	13
720	ALGGLACDLPGRFVAES	DQA1*05:01/DQB1*02:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:05, DRB1*11:01, DRB1*11:04	8
721	RELAVALAQKNVKLSTE	DQA1*05:01/DQB1*03:01 (DQ7)	DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*09:01, DRB1*11:04, DRB1*13:01, DRB1*15:01	11
722	LKALLEVNKGHEMSPQ	DQA1*05:01/DQB1*02:01 (DQ2); DRB1*01:01; DRB1*04:05; DRB1*08:03; DRB1*11:04	DQA1*05:01/DQB1*02:01 (DQ2), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*08:03, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01	13

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
723	TFMKLRTDVLP LTVA	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*13:02, DRB1*15:01, DRB1*15:02	13
727	TLGLGLQGGIN GYL V	DQA1*05:01/DQB1*02:01(DQ2); DRB1*01:01; DRB1*15:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*07:01, DRB1*09:01, DRB1*15:01	9
728	DLPGRFVAESA EVLL	DQA1*05:01/DQB1*02:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*15:01, DRB1*15:02	12
732	ERHRPVRDWILRQRQ	DRB1*15:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*04:01, DRB1*04:04, DRB1*15:01	4
733	SPRQLLGFP CAEVS G	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*04:01, DRB1*04:04, DRB1*15:01, DRB1*15:02	8
734	SRTLGETGQE AAPL	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*15:01	6
735	VTSLETLKALLEV NK	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:03, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*15:01,	15

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*15:02	
745	WELSQLTNSVTELGPYTLDRD	DQA1*05:01/DQB1*02:01 (DQ2), 2:01 (DQ2); DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*13:01, DRB1*15:01, DRB1*15:02	13
746	EITITTQTGYSLATSQVTLP	DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*15:01	10
747	ATTPSWVETHSIVIQGFPH	DRB1*07:01	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DRB1*01:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*15:01, DRB1*15:02	9
748	GIKELGPYTLDRNSLYVNG	DQA1*05:01/DQB1*02:01 (DQ2), 2:01 (DQ2); DRB1*01:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*09:01, DRB1*13:02, DRB1*15:01, DRB1*15:02	13
755	IELGPYLLDRGSLYVNG	DQA1*05:01/DQB1*02:01 (DQ2), 2:01 (DQ2)	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*09:01, DRB1*11:04, DRB1*13:02, DRB1*15:01, DRB1*15:02	14
759	EELGPYTLDRNSLYVNG	DRB1*03:01	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*03:01, DRB1*04:01, DRB1*04:02,	12

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*09:01, DRB1*13:02, DRB1*15:01, DRB1*15:02	
760	LKPLFKSTSVGPLYSG	DRB1*11:04	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*13:02, DRB1*15:01	16
764	FDKAFTAAATTEVSRTE	DQA1*05:01/DQB1*03:01 (DQ7), 3:01 (DQ7)	DRB1*01:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*11:01, DRB1*15:01	9
765	ELGPYTLDRDSL YVN	DQA1*05:01/DQB1*02:01 (DQ2), 2:01 (DQ2)	DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*13:02, DRB1*15:01, DRB1*15:02	11
766	GLLKPLFKSTSVGPL	DRB1*11:04	DQA1*05:01/DQB1*02:01 (DQ2), DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:02, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*08:02, DRB1*08:03, DRB1*09:01, DRB1*11:01, DRB1*11:04, DRB1*13:01, DRB1*13:02, DRB1*15:01	16
768	SDPYKATSAAVITST	DQA1*05:01/DQB1*03:01 (DQ7), 3:01 (DQ7)	DQA1*05:01/DQB1*02:01 (DQ2), DQA1*05:01/DQB1*03:01 (DQ7), DQB1*06:02, DRB1*01:01, DRB1*04:01, DRB1*04:04, DRB1*07:01, DRB1*09:01, DRB1*15:01, DRB1*15:02	10
770	SRKFNTMESVLQGLL	DRB1*09:01	DQA1*05:01/DQB1*03:01 (DQ7),	10

Seq ID No	Sequence	Best HLA class II binders	HLA Class II binders	No of HLA Class II binder
			DRB1*01:01, DRB1*03:01, DRB1*04:01, DRB1*04:04, DRB1*04:05, DRB1*07:01, DRB1*09:01, DRB1*13:02, DRB1*15:01	

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CLAIMS

1. A peptide comprising an amino acid sequence selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 772, and variant sequences thereof which are at least 88% homologous to SEQ ID No. 1 to SEQ ID No. 772, and wherein said variant binds to molecule(s) of the major histocompatibility complex (MHC) and/or induces T cells cross-reacting with said variant peptide; and a pharmaceutical acceptable salt thereof, wherein said peptide is not a full-length polypeptide.
2. The peptide according to claim 1, wherein said peptide has the ability to bind to an MHC class-I or -II molecule, and wherein said peptide, when bound to said MHC, is capable of being recognized by CD4 and/or CD8 T cells.
3. The peptide or variant thereof according to claim 1 or 2, wherein the amino acid sequence thereof comprises a continuous stretch of amino acids according to any one of SEQ ID No. 1 to SEQ ID No. 772.
4. The peptide or variant thereof according to any of claims 1 to 3, wherein said peptide or variant thereof has an overall length of from 8 to 100, preferably from 8 to 30, and more preferred from 8 to 16 amino acids, and most preferred wherein the peptide consists or consists essentially of an amino acid sequence according to any of SEQ ID No. 1 to SEQ ID No. 772.
5. The peptide or variant thereof according to any of Claims 1 to 4, wherein said peptide is modified and/or includes non-peptide bonds.
6. The peptide or variant thereof according to any of Claims 1 to 5, wherein said peptide is part of a fusion protein, in particular comprising N-terminal amino acids of the HLA-DR antigen-associated invariant chain (Ii).

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7. An antibody, in particular a soluble or membrane-bound antibody, preferably a monoclonal antibody or fragment thereof, that specifically recognizes the peptide or variant thereof according to any of claims 1 to 5, preferably the peptide or variant thereof according to any of claims 1 to 5 when bound to an MHC molecule.
8. A T-cell receptor, preferably soluble or membrane-bound, or a fragment thereof, that is reactive with an HLA ligand, wherein said ligand is the peptide or variant thereof according to any of claims 1 to 5, preferably the peptide or variant thereof according to any of claims 1 to 5 when bound to an MHC molecule.
9. The T-cell receptor according to claim 8, wherein said ligand amino acid sequence is at least 88% identical to any one of SEQ ID No. 1 to SEQ ID No. 772, or wherein said ligand amino acid sequence consists of any one of SEQ ID No. 1 to SEQ ID No. 772.
10. The T-cell receptor according to claim 8 or 9, wherein said T-cell receptor is provided as a soluble molecule and optionally carries a further effector function such as an immune stimulating domain or toxin.
11. An aptamer that specifically recognizes the peptide or variant thereof according to any of claims 1 to 5, preferably the peptide or variant thereof according to any of claims 1 to 5 that is bound to an MHC molecule.
12. A nucleic acid, encoding for a peptide or variant thereof according to any one of claims 1 to 5, an antibody or fragment thereof according to claim 7, a T-cell receptor or fragment thereof according to claim 8 or 9, optionally linked to a heterologous promoter sequence, or an expression vector expressing said nucleic acid.
13. A recombinant host cell comprising the peptide according to any one of claims 1 to 6, the antibody or fragment thereof according to claim 7, the T-cell receptor or fragment thereof according to claim 8 or 9 or the nucleic acid or the expression vector according

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to claim 12, wherein said host cell preferably is selected from an antigen presenting cell, such as a dendritic cell, a T cell or an NK cell.

14. An *in vitro* method for producing activated T lymphocytes, 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 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 any one of claims 1 to 4.

15. An activated T lymphocyte, produced by the method according to claim 14, that selectively recognizes a cell which presents a polypeptide comprising an amino acid sequence given in any one of claims 1 to 4.

16. 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 6, the antibody or fragment thereof according to claim 7, the T-cell receptor or fragment thereof according to claim 8 or 9, the aptamer according to claim 11, the nucleic acid or the expression vector according to claim 12, the host cell according to claim 13, or the activated T lymphocyte according to claim 15, or a conjugated or labelled active ingredient, and a pharmaceutically acceptable carrier, and optionally, pharmaceutically acceptable excipients and/or stabilizers.

17. A method for producing the peptide or variant thereof according to any of claims 1 to 6, the antibody or fragment thereof according to claim 7, or the T-cell receptor or fragment thereof according to claim 8 or 9, the method comprising culturing the host cell according to claim 13, and isolating the peptide or variant thereof, the antibody or fragment thereof or the T cell receptor or fragment thereof from said host cell and/or its culture medium.

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18. The the peptide according to any one of claims 1 to 6, the antibody or fragment thereof according to claim 7, the T-cell receptor or fragment thereof according to claim 8 or 9, the aptamer according to claim 11, the nucleic acid or the expression vector according to claim 12, the host cell according to claim 13, or the activated T lymphocyte according to claim 15 for use in medicine.

19. A method for killing target cells in a patient which target cells present a polypeptide comprising an amino acid sequence given in any one of claims 1 to 4, the method comprising administering to the patient an effective number of activated T cells as defined in claim 15.

20. The peptide according to any one of claims 1 to 6, the antibody or fragment thereof according to claim 7, the T-cell receptor or fragment thereof according to claim 8 or 9, the aptamer according to claim 11, the nucleic acid or the expression vector according to claim 12, the host cell according to claim 13, or the activated T lymphocyte according to claim 15 for use in diagnosis and/or treatment of cancer, or for use in the manufacture of a medicament against cancer.

21. The use according to claim 20, wherein said cancer is selected from the group of ovarian cancer, hepatocellular carcinoma, colorectal carcinoma, glioblastoma, gastric cancer, esophageal cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, melanoma, breast cancer, chronic lymphocytic leukemia, Non-Hodgkin lymphoma, acute myeloid leukemia, gallbladder cancer and cholangiocarcinoma, urinary bladder cancer, uterine cancer, head and neck squamous cell carcinoma, mesothelioma and other tumors that show an overexpression of a protein from which a peptide SEQ ID No. 1 to SEQ ID No. 772 is derived from.

22. A kit comprising:

a) a container comprising a pharmaceutical composition containing the peptide(s) or the variant according to any one of claims 1 to 6, the antibody or fragment thereof according

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to claim 7, the T-cell receptor or fragment thereof according to claim 8 or 9, the aptamer according to claim 11, the nucleic acid or the expression vector according to claim 12, the host cell according to claim 13, or the activated T lymphocyte according to claim 15, in solution or in lyophilized form;

b) optionally, a second container containing a diluent or reconstituting solution for the lyophilized formulation;

c) optionally, at least one more peptide selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 774, and

d) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.

23. The kit according to claim 22, further comprising one or more of (iii) a buffer, (iv) a diluent, (v) a filter, (vi) a needle, or (v) a syringe.

24. A method for producing a personalized anti-cancer vaccine or a compound-based and/or cellular therapy for an individual patient, said method comprising:

a) identifying tumor-associated peptides (TUMAPs) presented by a tumor sample from said individual patient;

b) comparing the peptides as identified in a) with a warehouse of peptides that have been pre-screened for immunogenicity and/or over-presentation in tumors as compared to normal tissues;

c) selecting at least one peptide from the warehouse that matches a TUMAP identified in the patient; and

d) manufacturing and/or formulating the personalized vaccine or compound-based or cellular therapy based on step c).

25. The method according to claim 24, wherein said TUMAPs are identified by:

a1) comparing expression data from the tumor sample to expression data from a sample of normal tissue corresponding to the tissue type of the tumor sample to identify proteins that are over-expressed or aberrantly expressed in the tumor sample; and

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a2) correlating the expression data with sequences of MHC ligands bound to MHC class I and/or class II molecules in the tumor sample to identify MHC ligands derived from proteins over-expressed or aberrantly expressed by the tumor.

26. The method according to claim 24 or 25, wherein the sequences of MHC ligands are identified by eluting bound peptides from MHC molecules isolated from the tumor sample, and sequencing the eluted ligands.

27. The method according to any of claims 24 to 26, wherein the normal tissue corresponding to the tissue type of the tumor sample is obtained from the same patient.

28. The method according to any of claims 24 to 27, wherein the peptides included in the warehouse are identified based on the following steps:

aa. Performing genome-wide messenger ribonucleic acid (mRNA) expression analysis by highly parallel methods, such as microarrays or sequencing-based expression profiling, comprising identify genes that over-expressed in a malignant tissue, compared with a normal tissue or tissues;

ab. Selecting peptides encoded by selectively expressed or over-expressed genes as detected in step aa, and

ac. Determining an induction of *in vivo* T-cell responses by the peptides as selected comprising *in vitro* immunogenicity assays using human T cells from healthy donors or said patient; or

ba. Identifying HLA ligands from said tumor sample using mass spectrometry;

bb. Performing genome-wide messenger ribonucleic acid (mRNA) expression analysis by highly parallel methods, such as microarrays or sequencing-based expression profiling, comprising identify genes that over-expressed in a malignant tissue, compared with a normal tissue or tissues;

bc. Comparing the identified HLA ligands to said gene expression data;

bd. Selecting peptides encoded by selectively expressed or over-expressed genes as detected in step bc;

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be. Re-detecting of selected TUMAPs from step bd on tumor tissue and lack of or infrequent detection on healthy tissues and confirming the relevance of over-expression at the mRNA level; and

bf. Determining an induction of in vivo T-cell responses by the peptides as selected comprising *in vitro* immunogenicity assays using human T cells from healthy donors or said patient.

29. The method according to any of claims 24 to 28, wherein the immunogenicity of the peptides included in the warehouse is determined by a method comprising in vitro immunogenicity assays, patient immunomonitoring for individual HLA binding, MHC multimer staining, ELISPOT assays and/or intracellular cytokine staining.

30. The method according to any of claims 24 to 29, wherein said warehouse comprises a plurality of peptides selected from the group consisting of SEQ ID No. 1 to SEQ ID No. 774.

31. The method according to any of claims 24 to 30, further comprising identifying at least one mutation that is unique to the tumor sample relative to normal corresponding tissue from the individual patient, and selecting a peptide that correlates with the mutation for inclusion in the vaccine or for the generation of cellular therapies.

32. The method according to claim 31, wherein said at least one mutation is identified by whole genome sequencing.

Figure 1A

Gene: CT45A2; Peptide: KYEKIFEML; SEQ ID No: 12

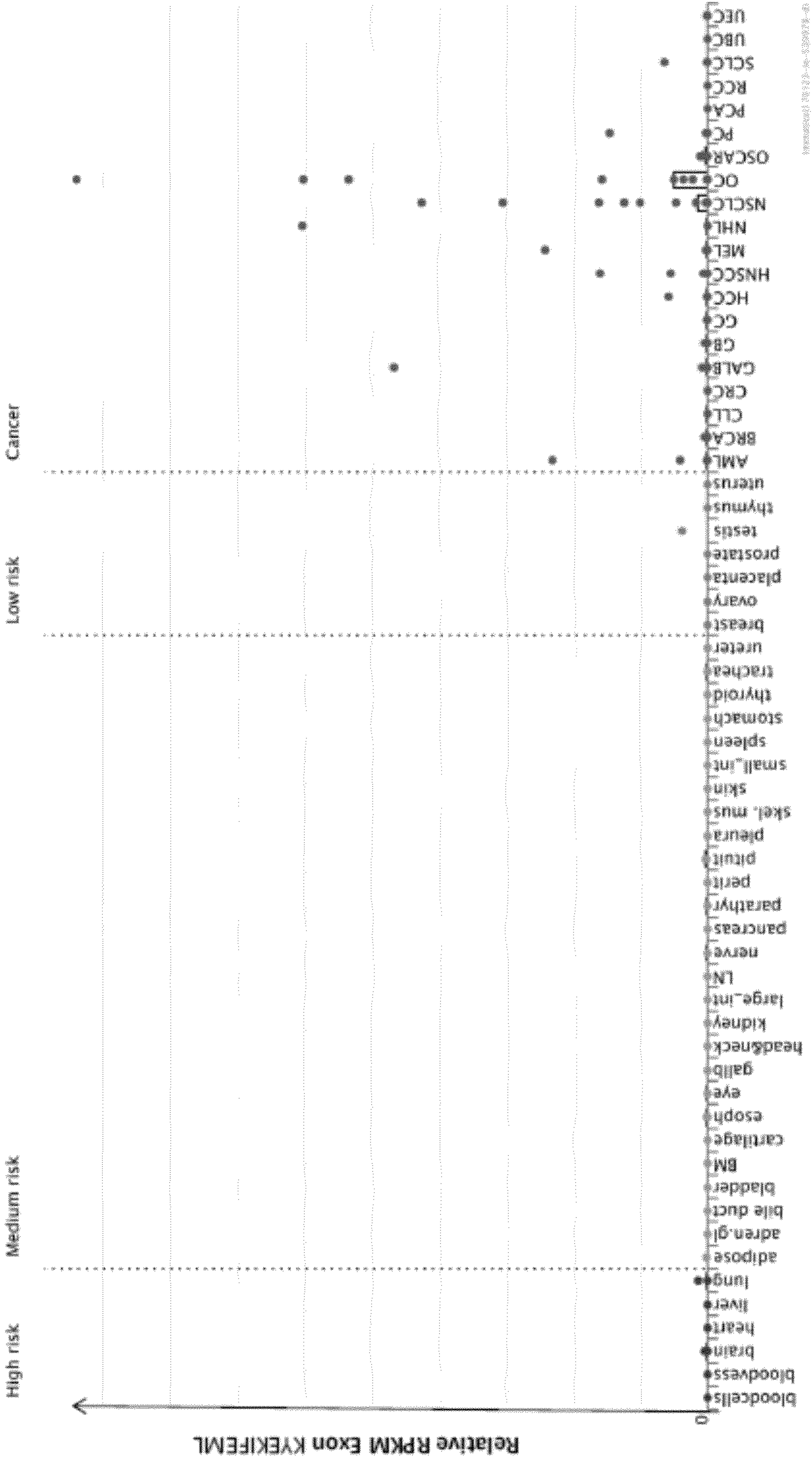


Figure 1B

Gene: NLRP2; Peptide: VLYGPAGLGK; SEQ ID No: 27

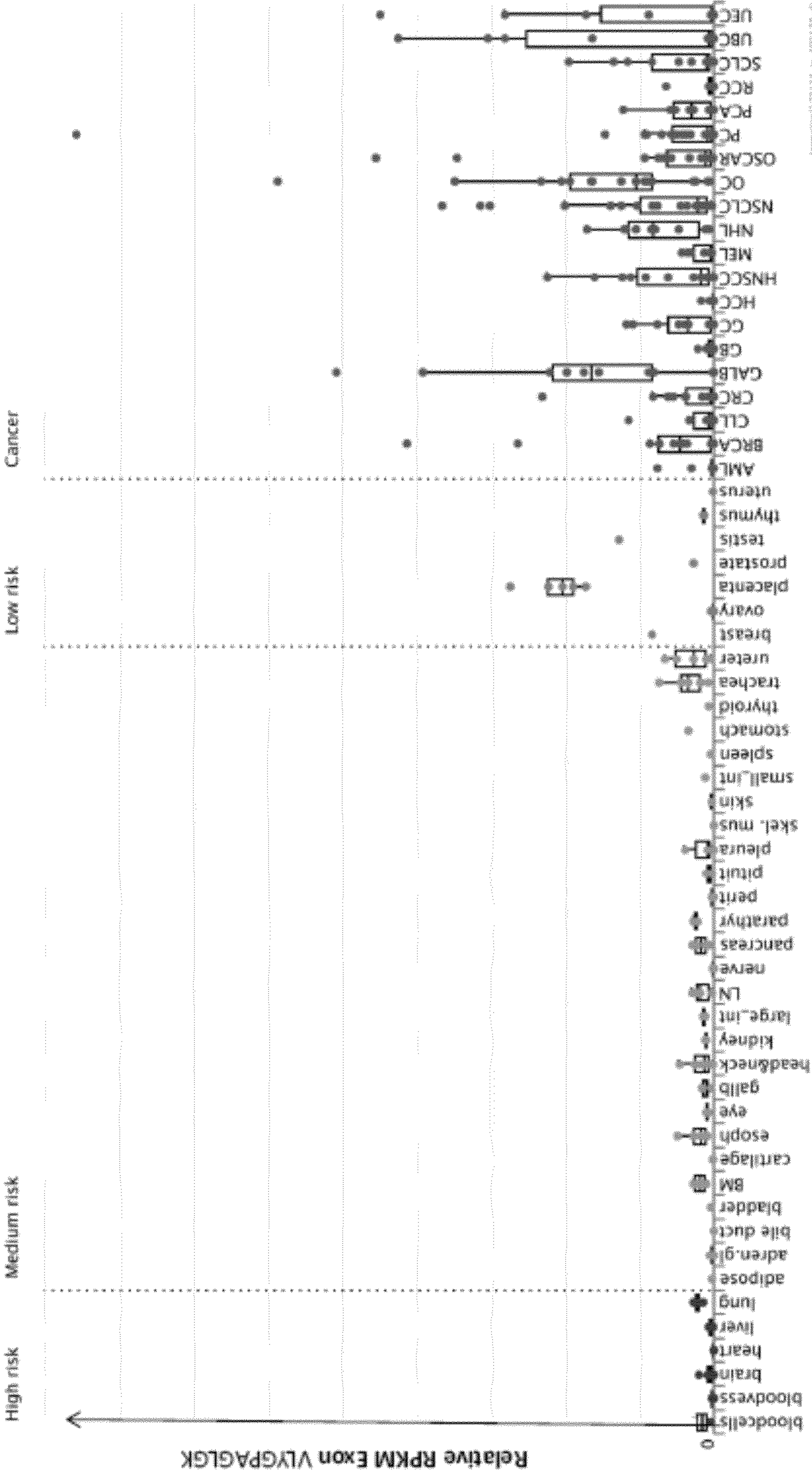


Figure 1C

Gene: NLRP7; Peptide: LLDEGAMLLY; SEQ ID No: 31

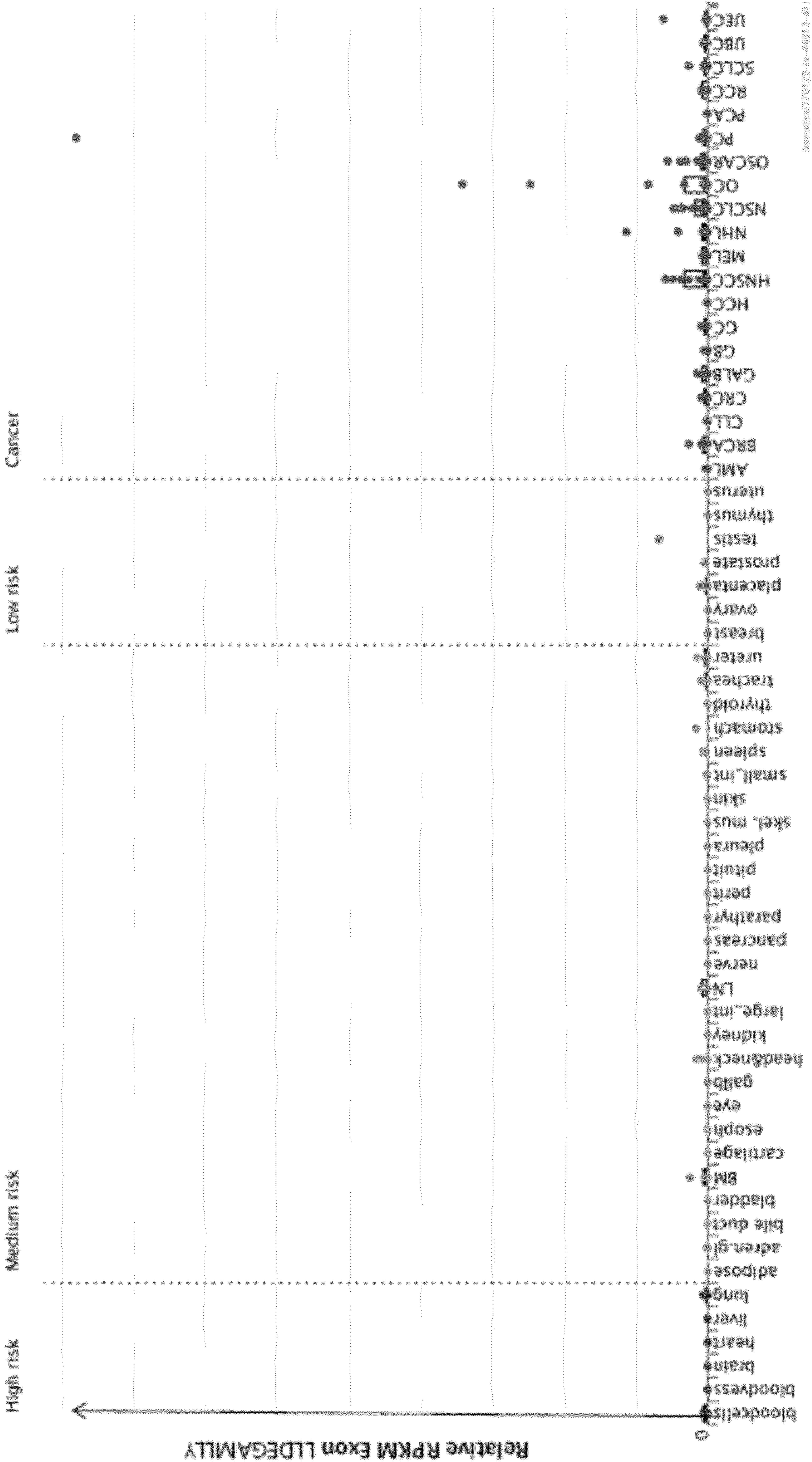


Figure 1D

Gene: HTR3A; Peptide: GLLQLSSI; SEQ ID No: 66

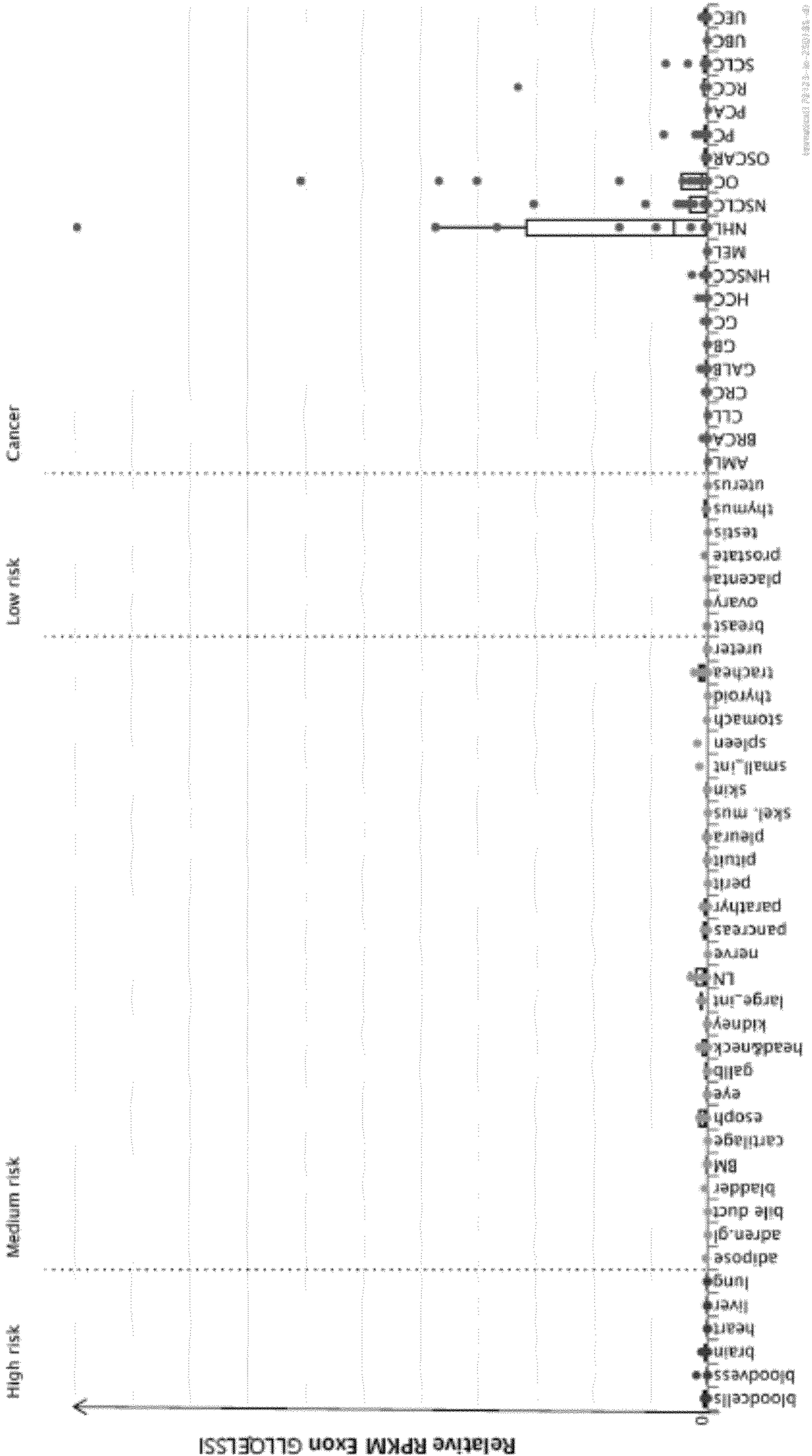


Figure 1E

Gene: VTCN1; Peptide: KVVSVLYNV; SEQ ID No: 75

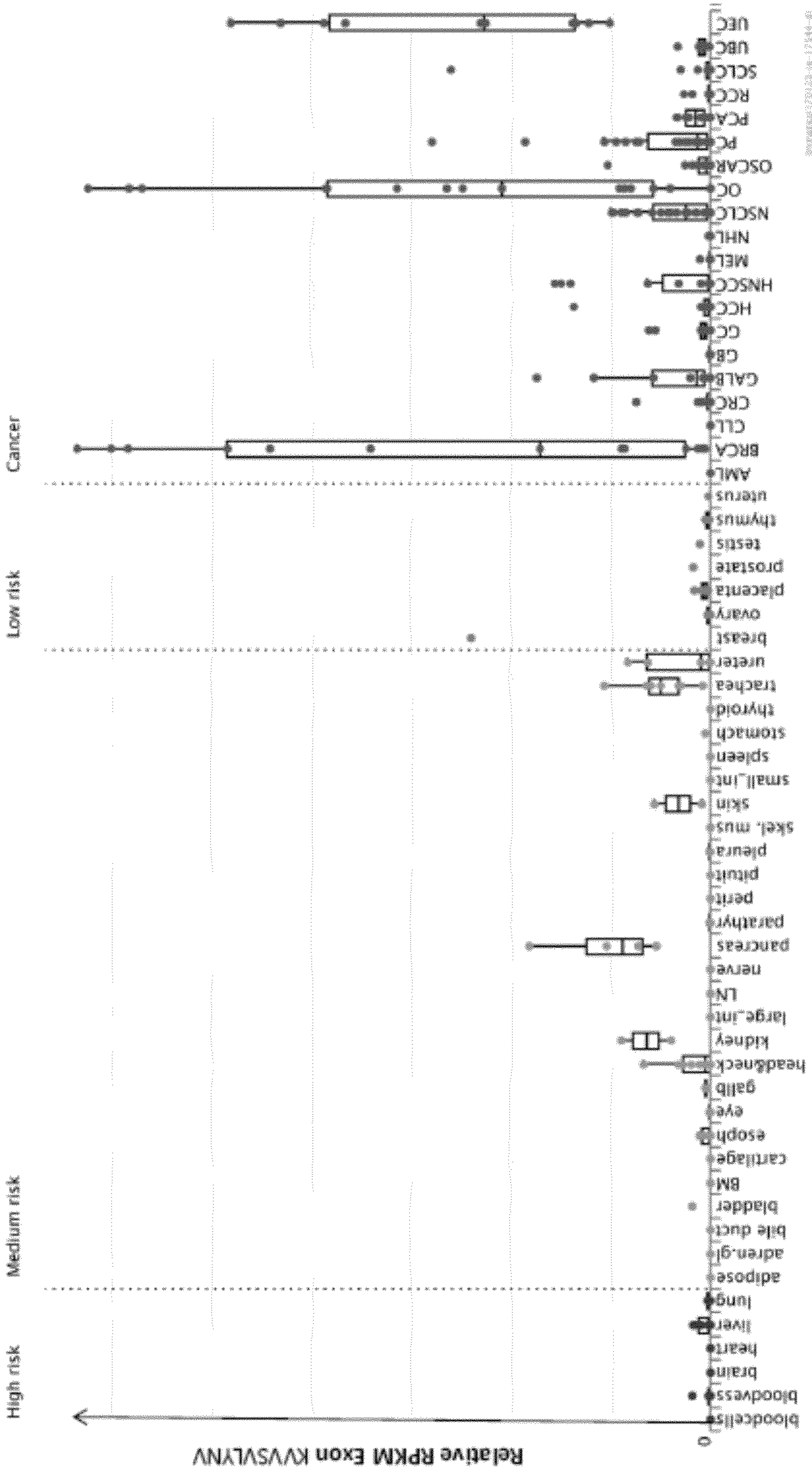


Figure 1F

Gene: CYP2W1

Peptide: RYGPVFTV

SEQ ID No: 77

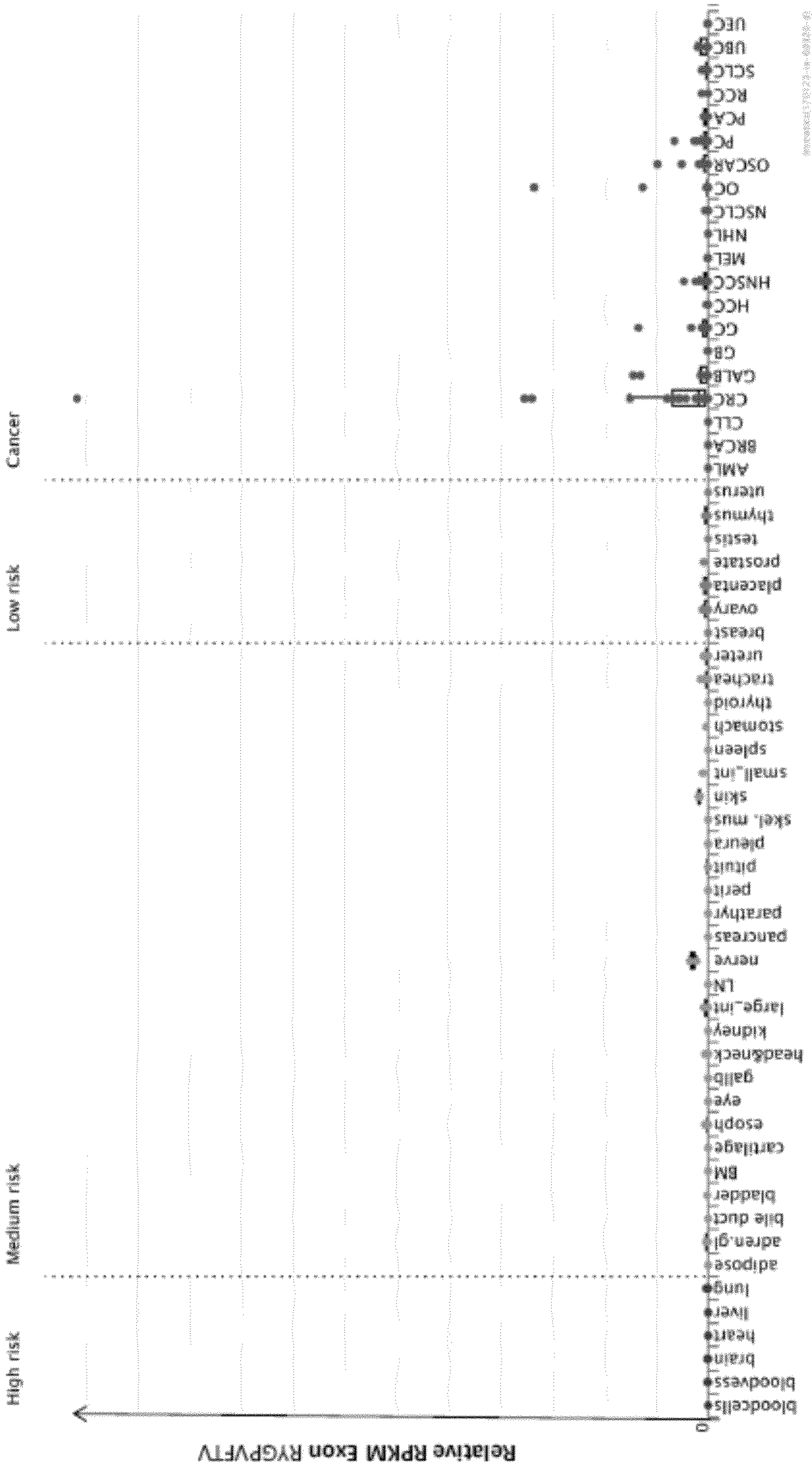


Figure 1G

Gene: MMP11; Peptide: LLQPPPLLAR; SEQ ID No: 98

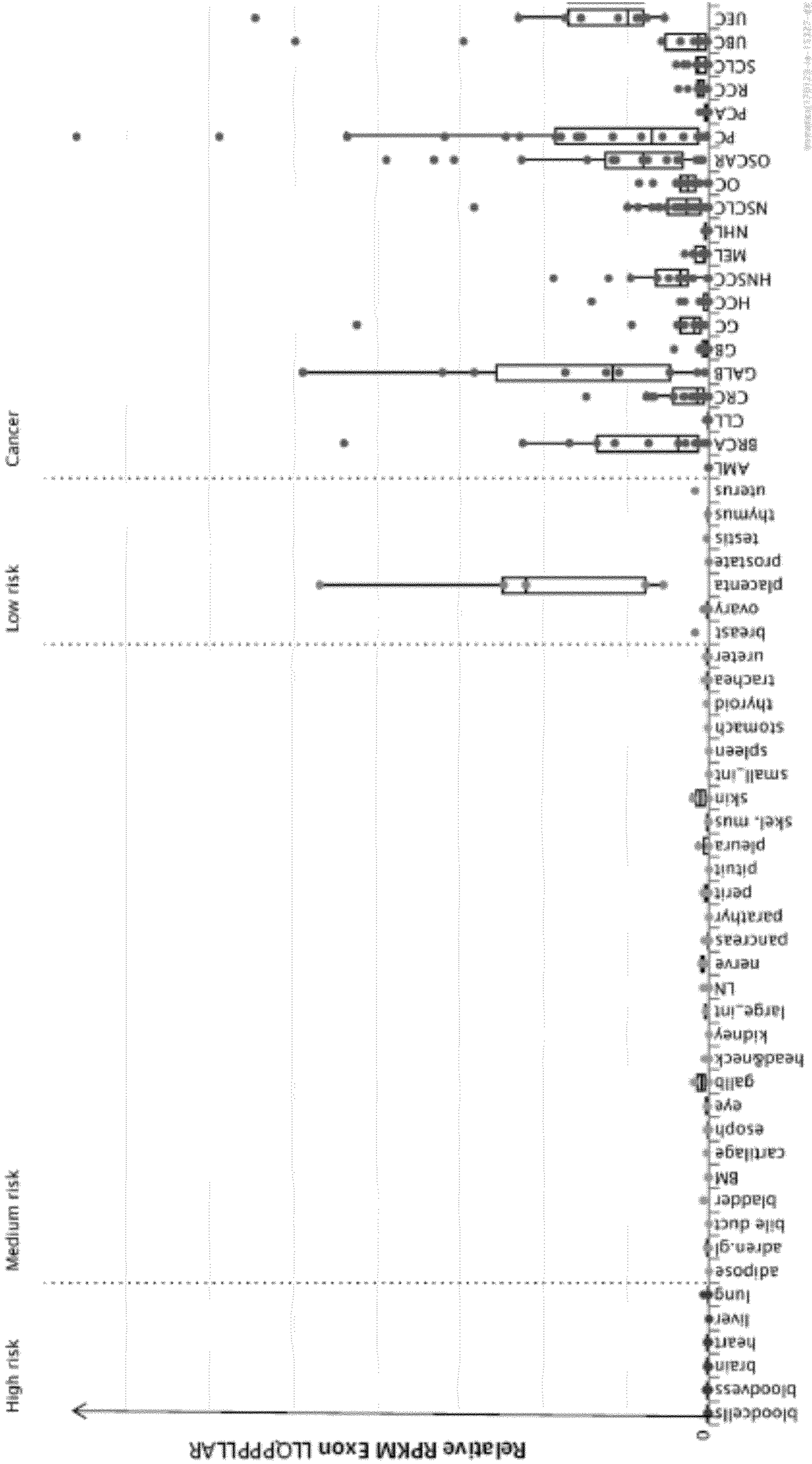


Figure 1H

Gene: MMP12; Peptide: FVDNQWRY; SEQ ID No: 115

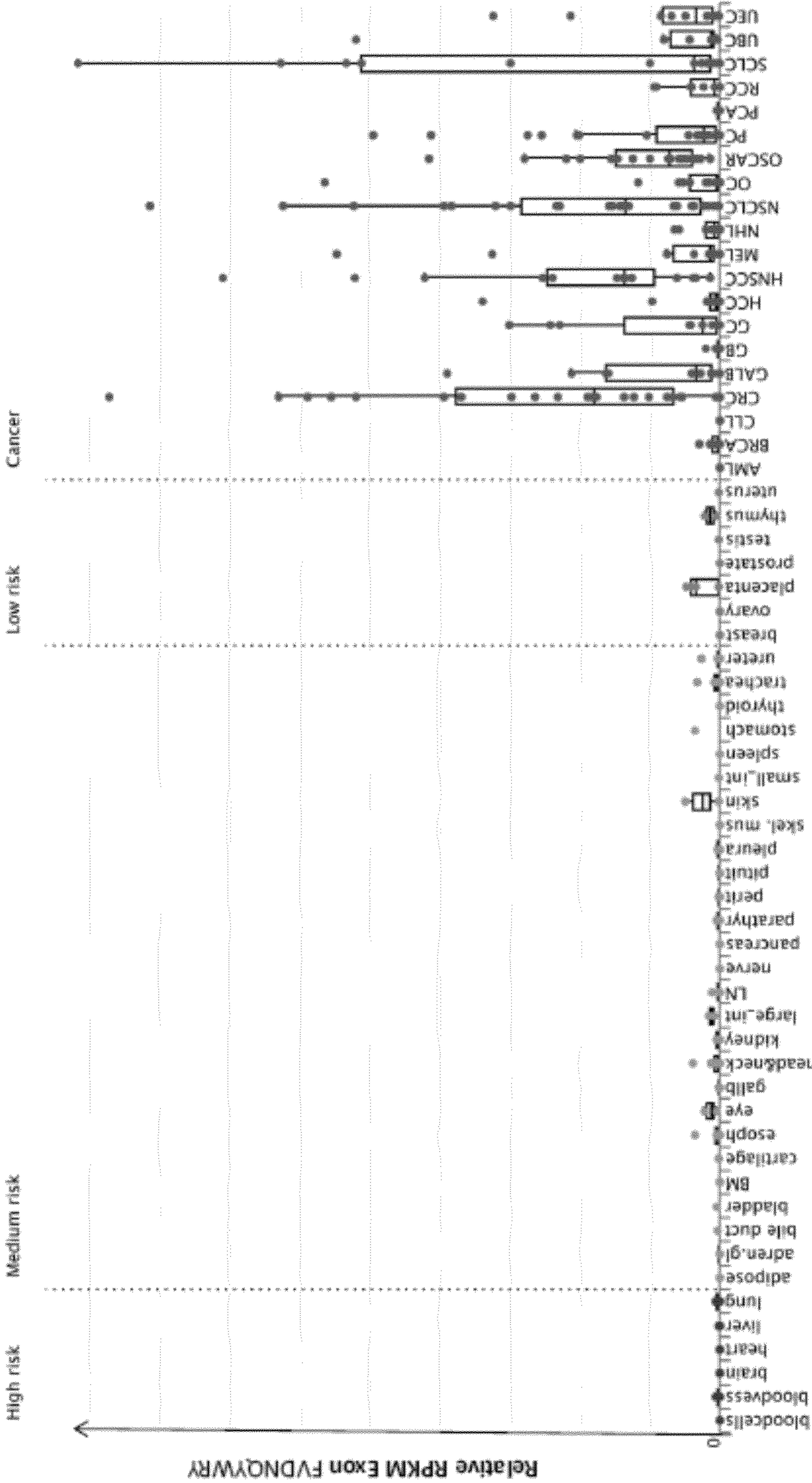


Figure 1I

Gene: CTAG2; Peptide: APLPRPGAVL; SEQ ID No: 119

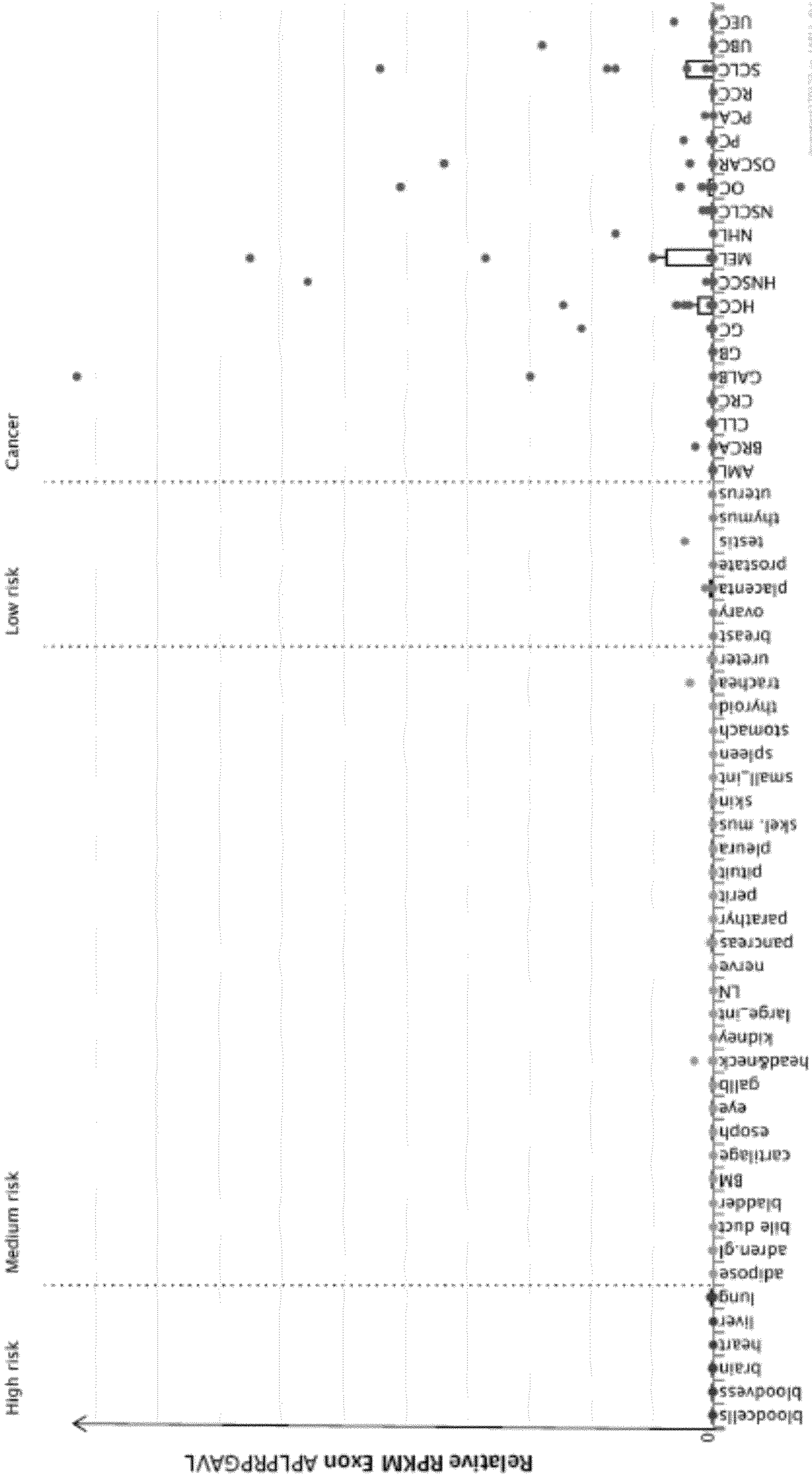


Figure 1J

Gene: FAM1111B; Peptide: KPSESIYSAL; SEQ ID No: 123

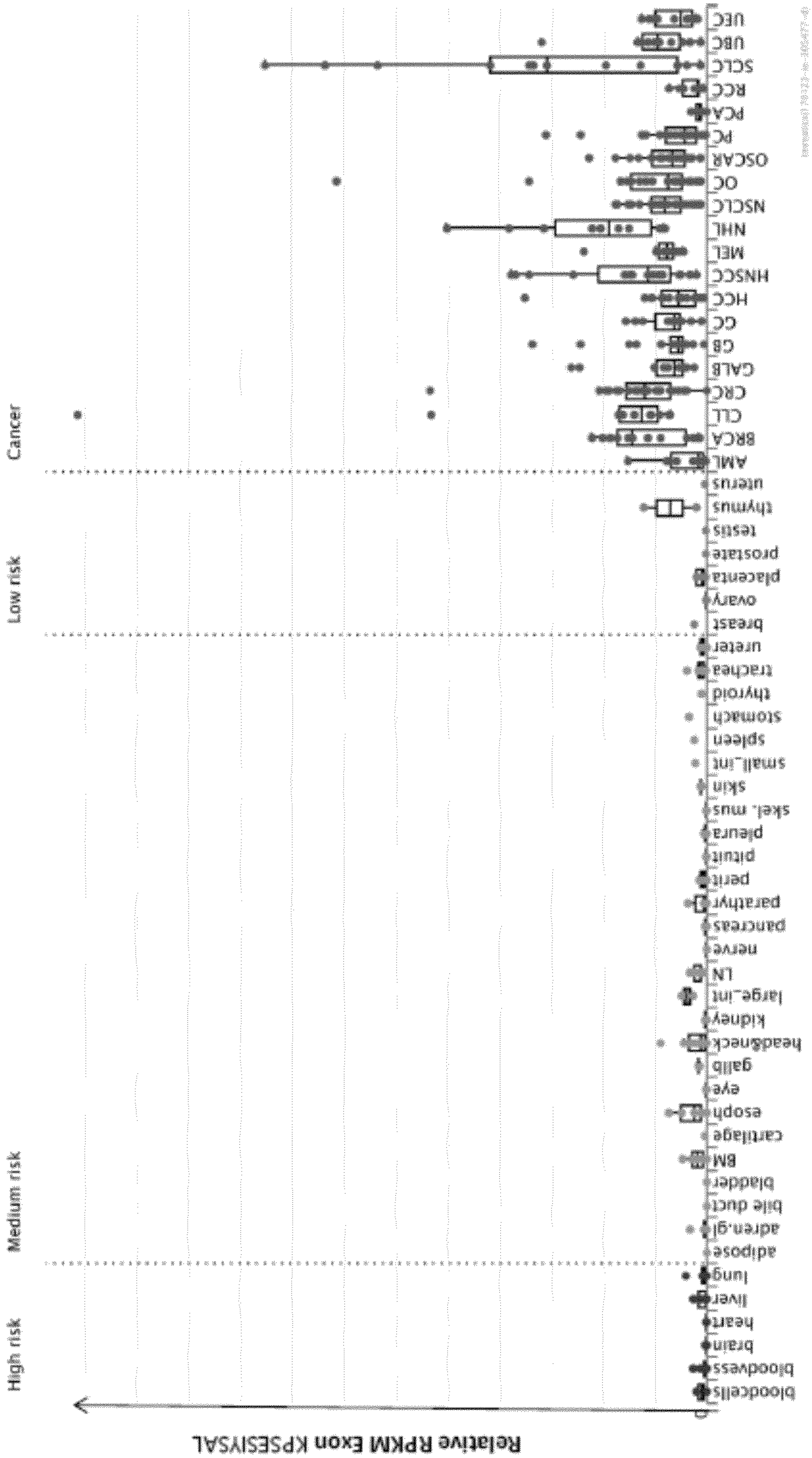


Figure 1K

Gene: CCNA1; Peptide: HLLKVLAF; SEQ ID No: 151

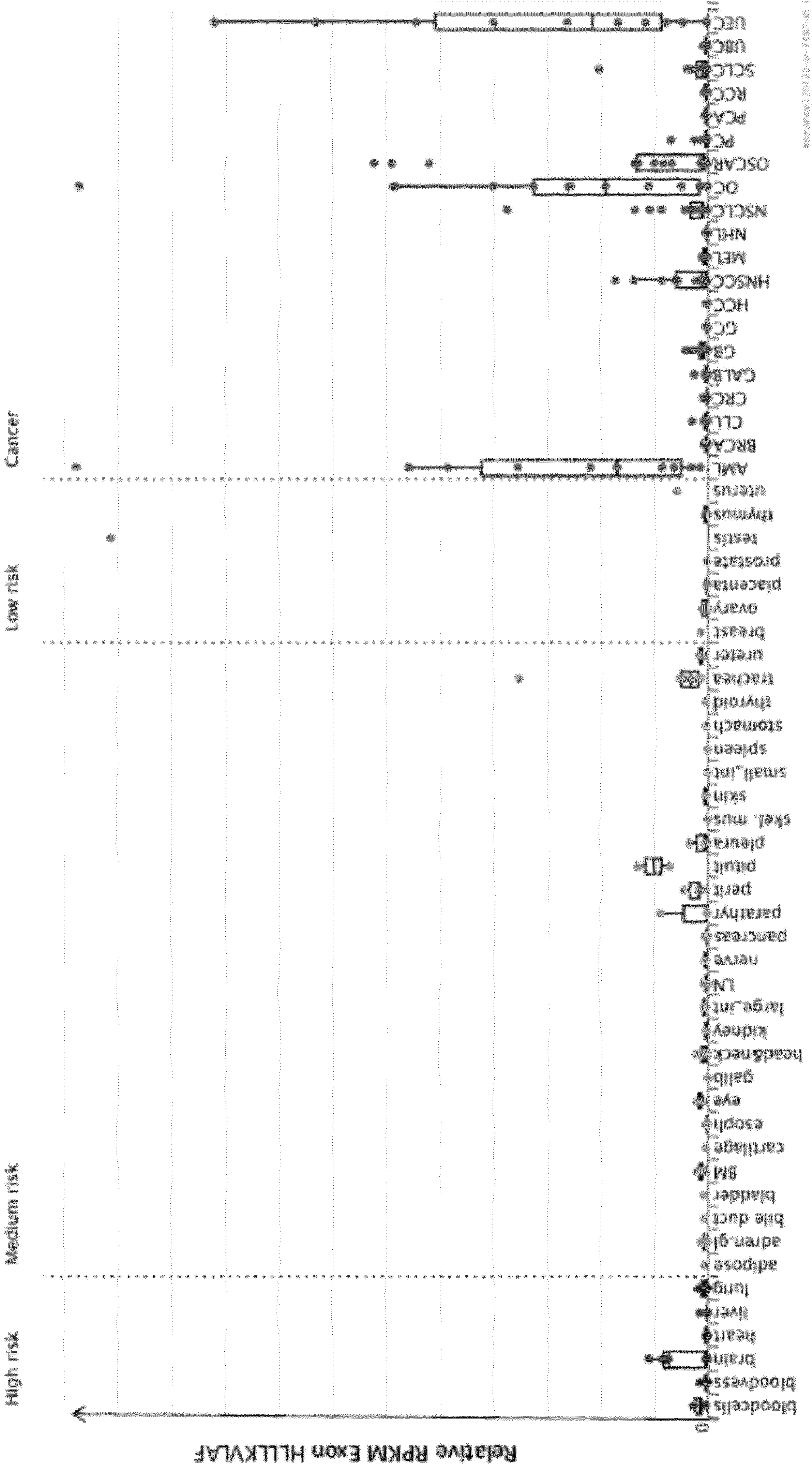


Figure 1L

Gene: FAM83H; Peptide: HVKEKFLL; SEQ ID No: 156

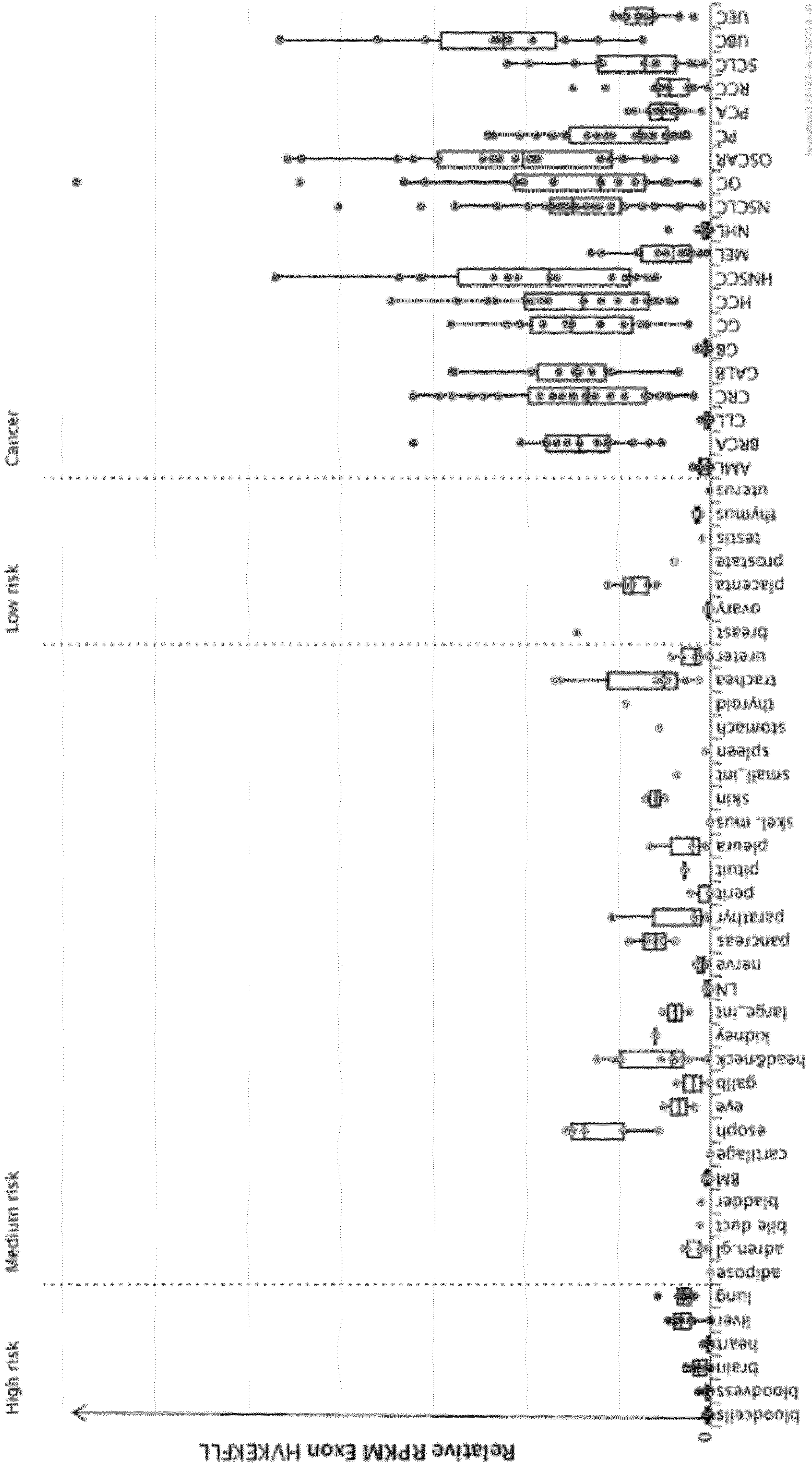


Figure 1M

Gene: MAGEA11; Peptide: KEVDPTSHSY; SEQ ID No: 194

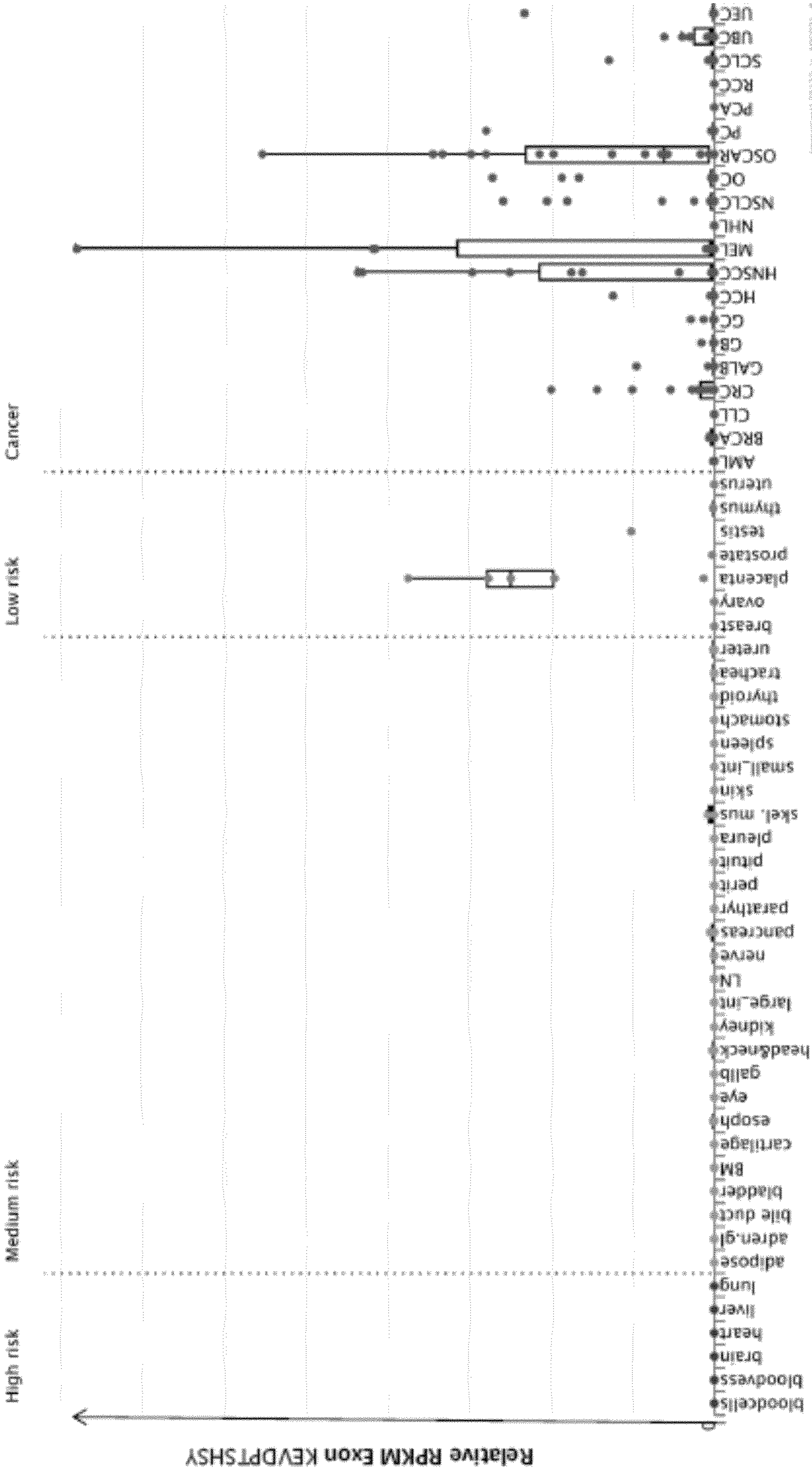


Figure 1N

Gene: MMP11; Peptide: YTFRYPLSL; SEQ ID No: 227

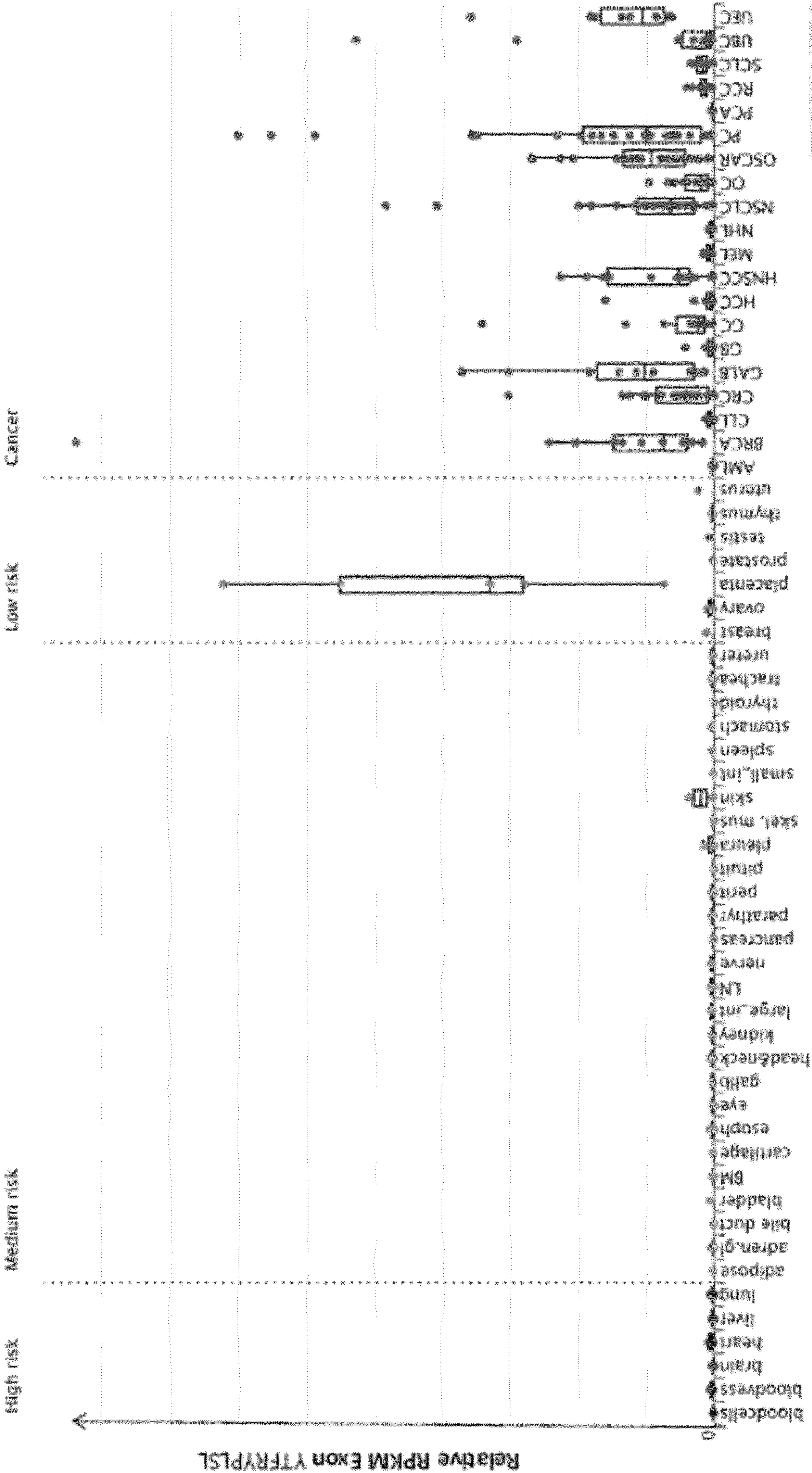


Figure 10

Gene: ZNF560
Peptide: VFVSFSSLF
SEQ ID No: 255

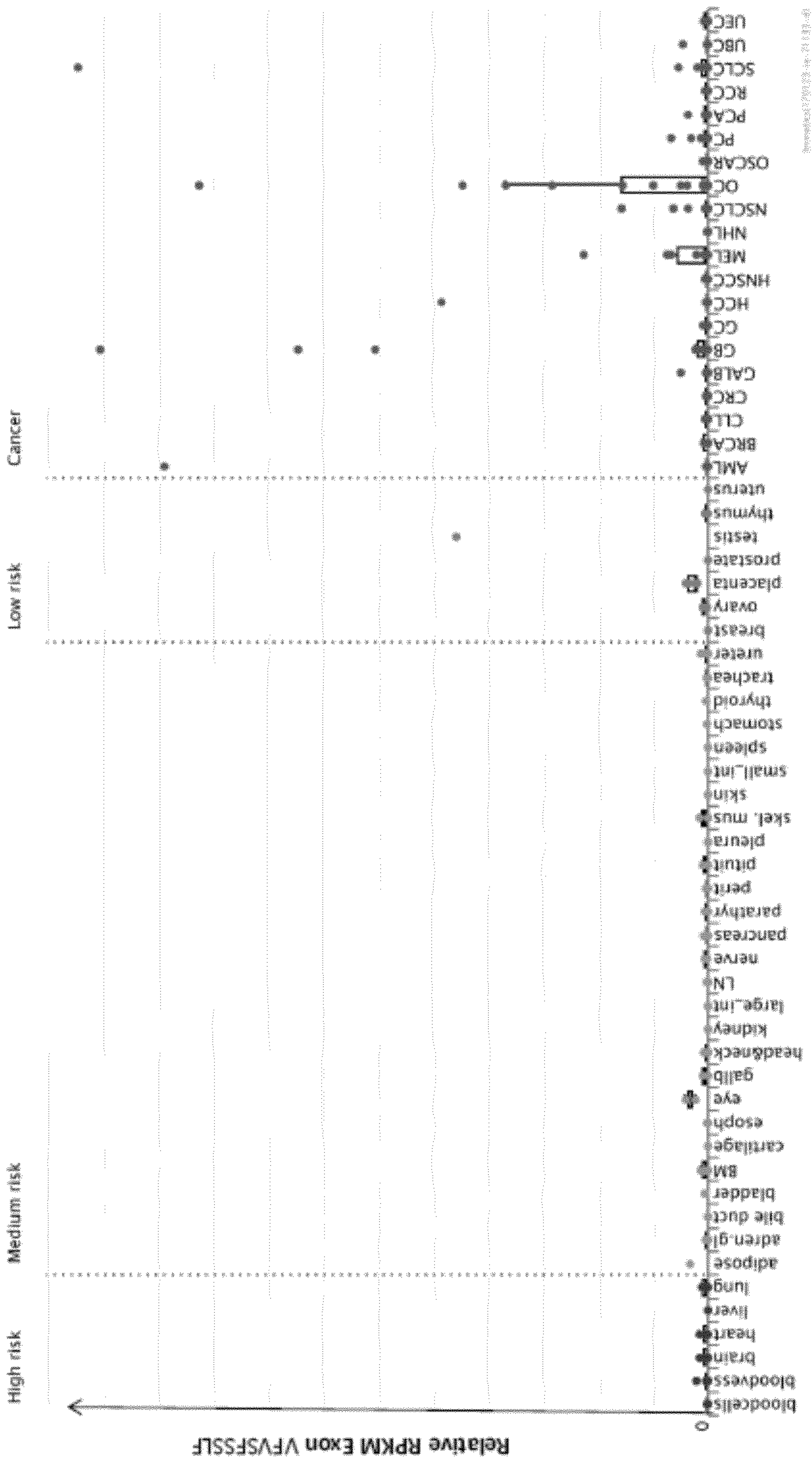


Figure 1P

Gene: IGF2BP1; Peptide: ISYSGQFLVK; SEQ ID No: 266

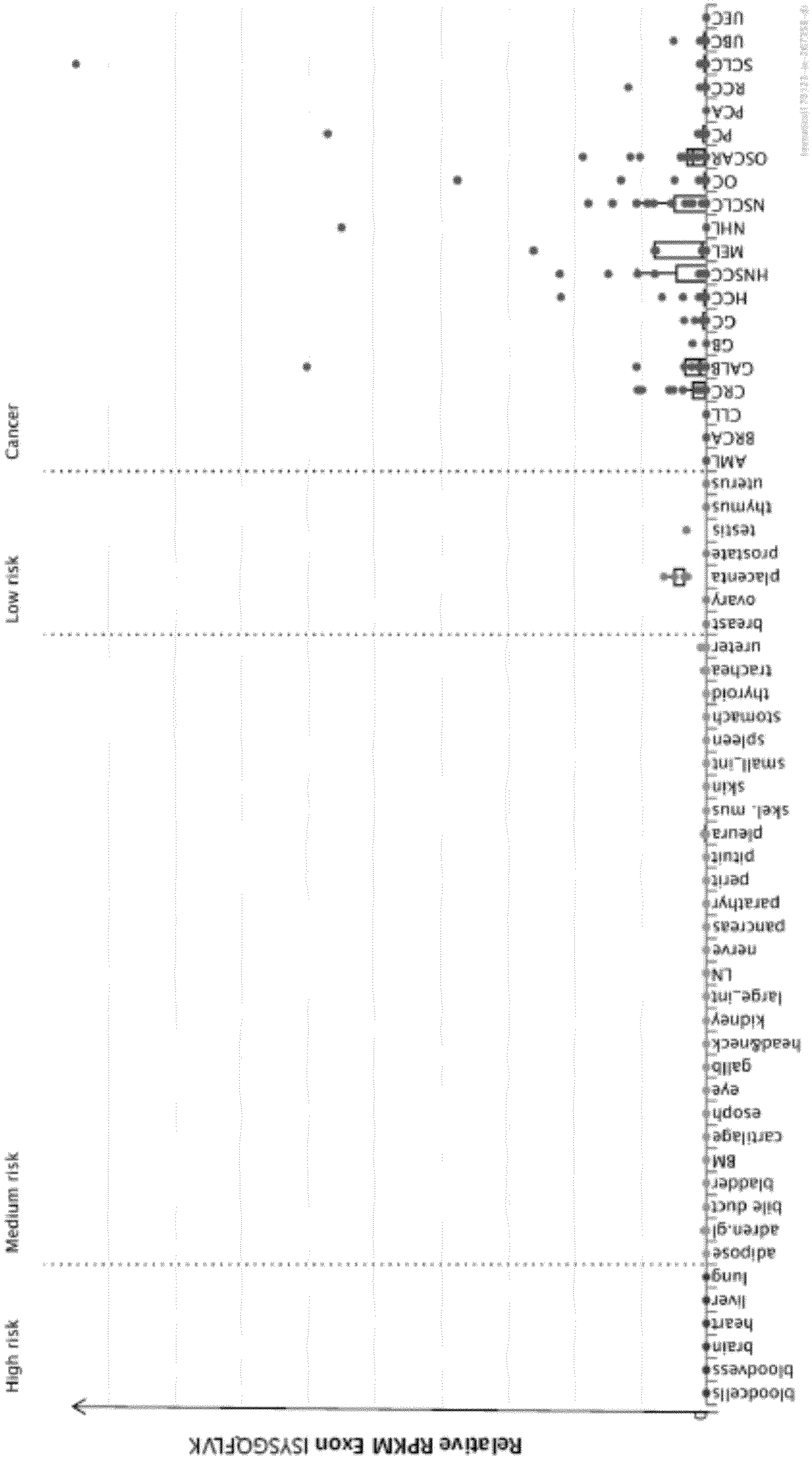


Figure 1Q

Gene: CLDN6; Peptide: LPMWKVTAF; SEQ ID No: 303

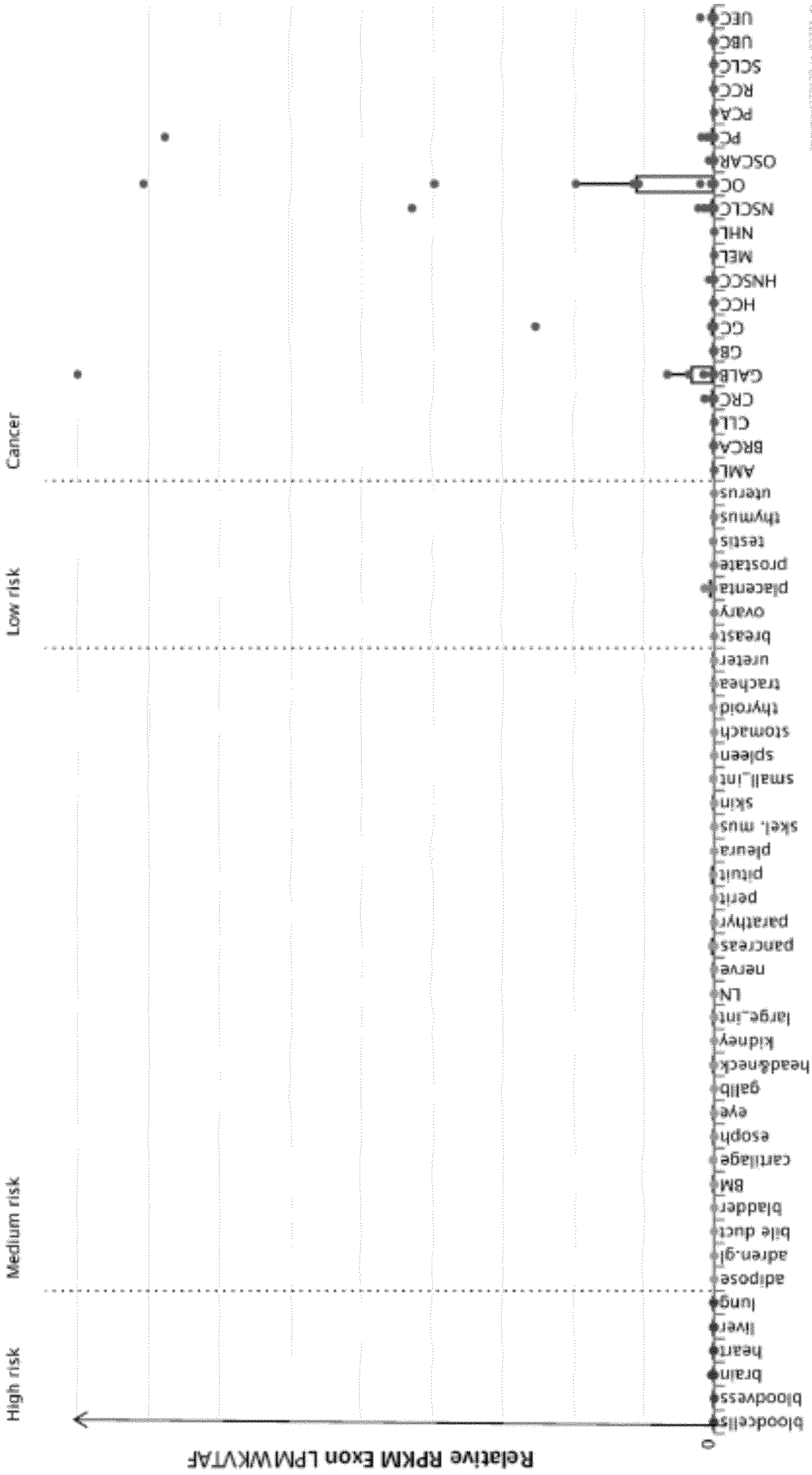


Figure 1R

Gene: IGF2BP3; Peptide: IEALSGKIEL; SEQ ID No: 413

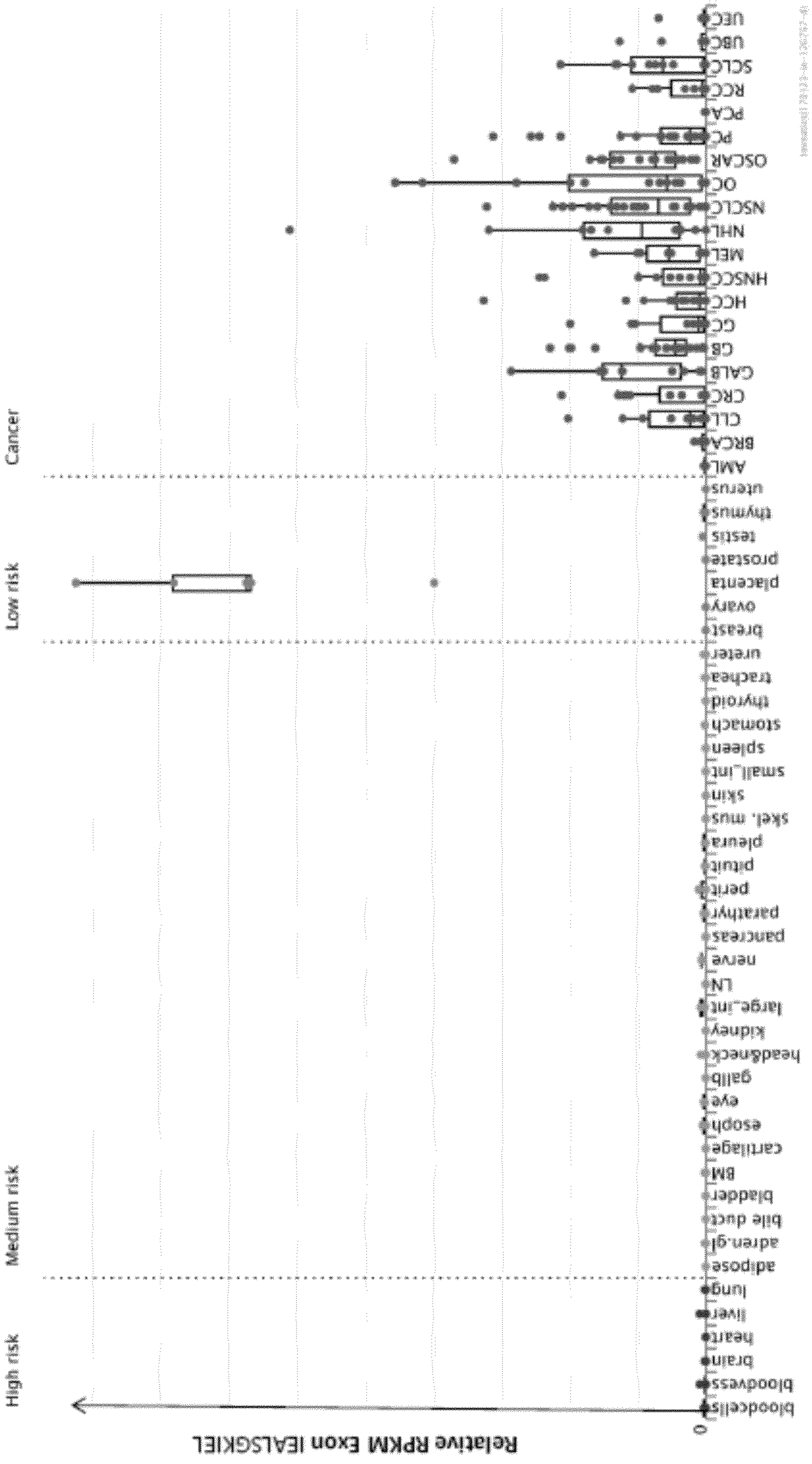


Figure 1S

Gene: PRAME; Peptide: EEQYIAQF; SEQ ID No: 432

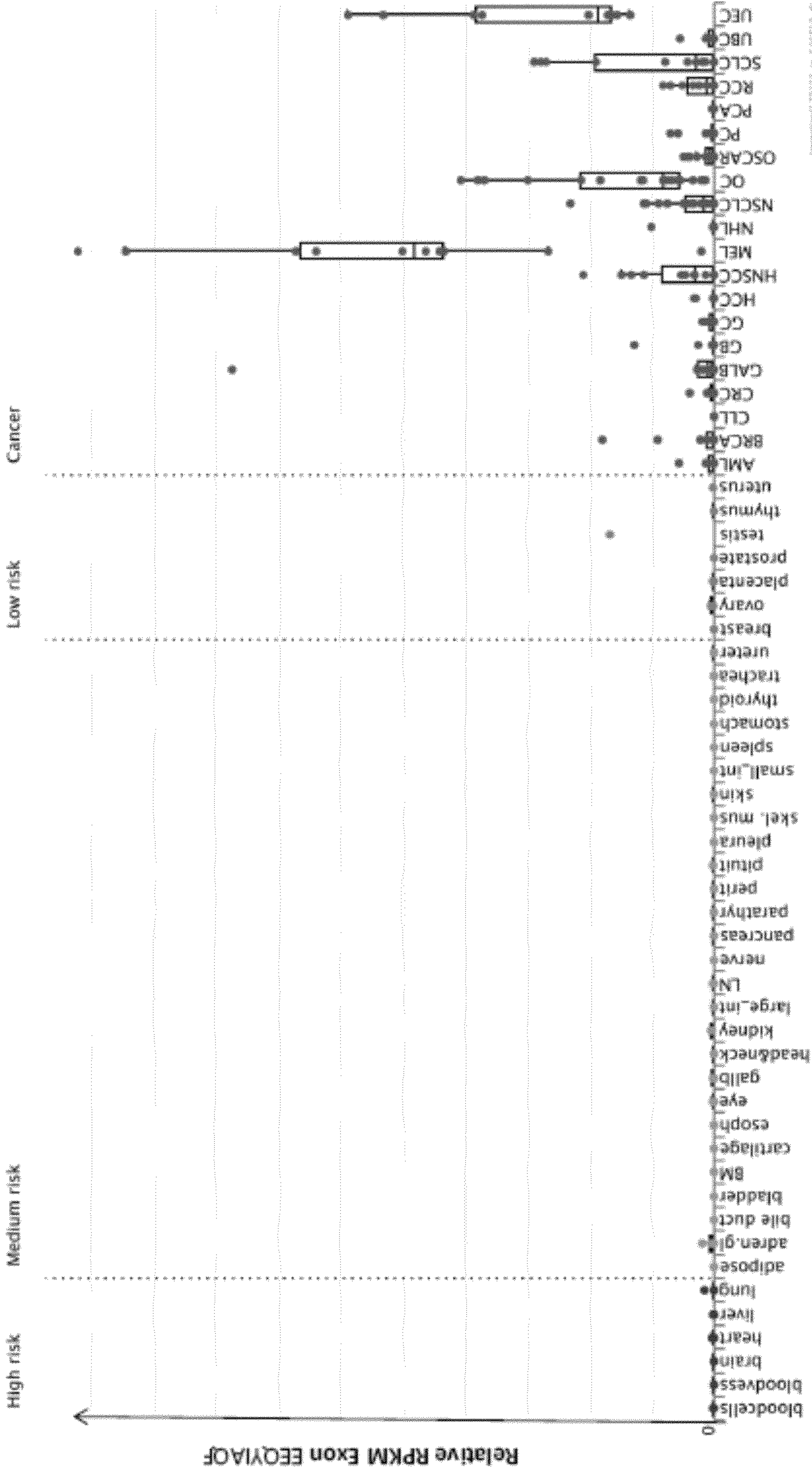


Figure 1T

Gene: MAGEA4
Peptide: SPDAESLFREALSNKVDL
SEQ ID: 597

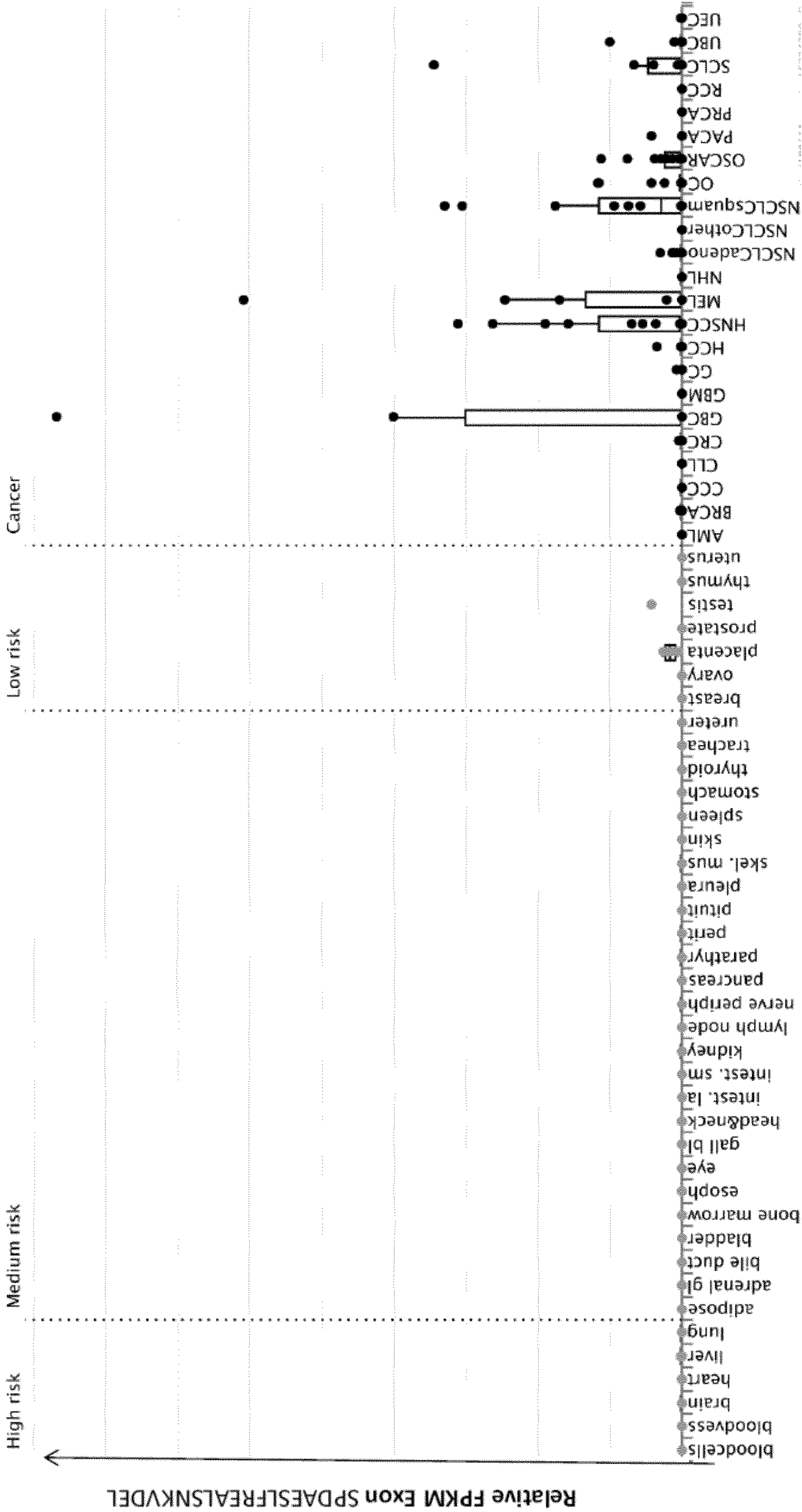


Figure 1U

Gene: MAGEA4

Peptide: LSNKVDELAHFLLRK

SEQ ID: 601

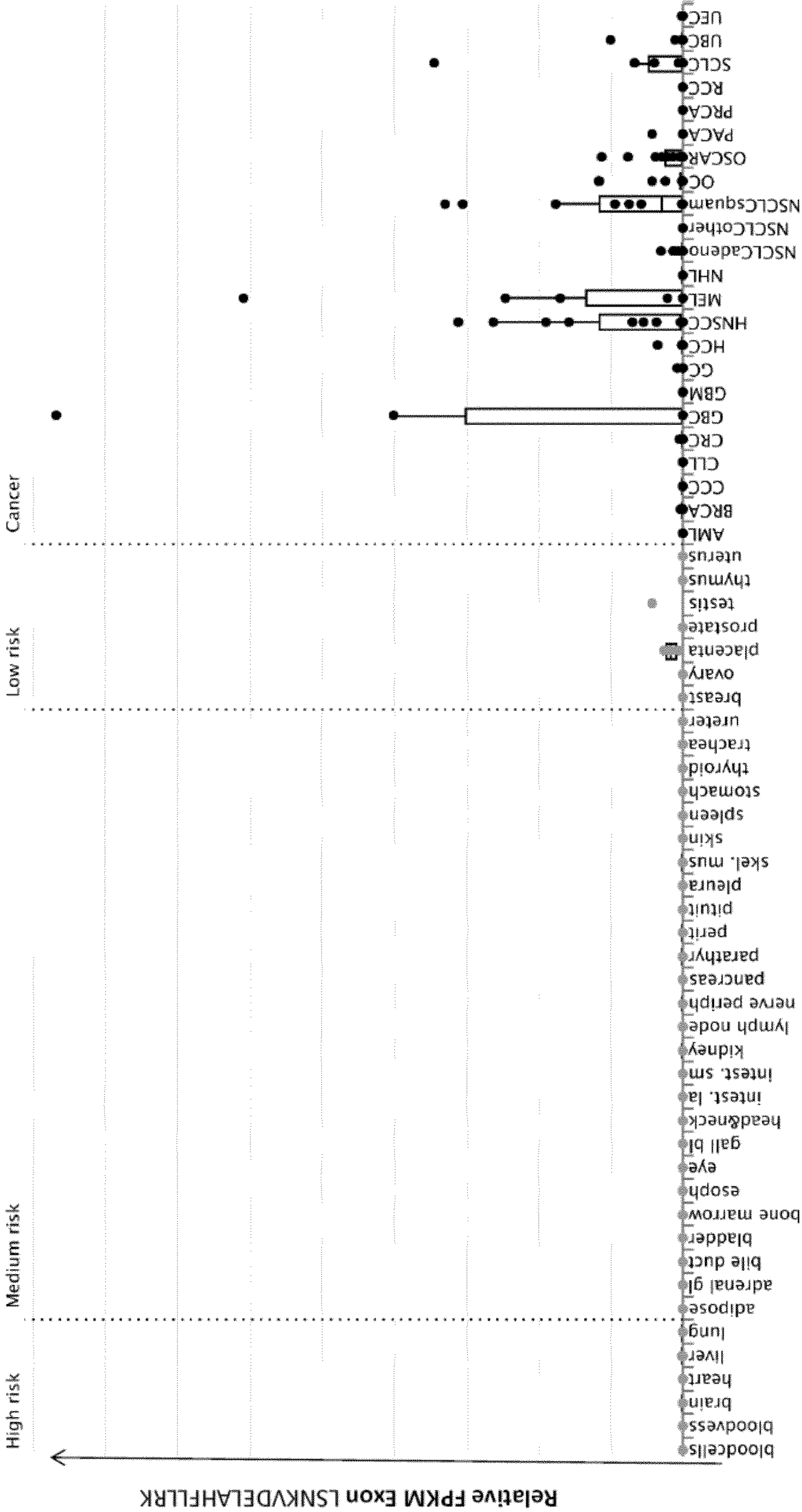


Figure 1V

Gene: MAGEB3

Peptide: KLITQDLVKKLYEYRQ

SEQ ID: 604

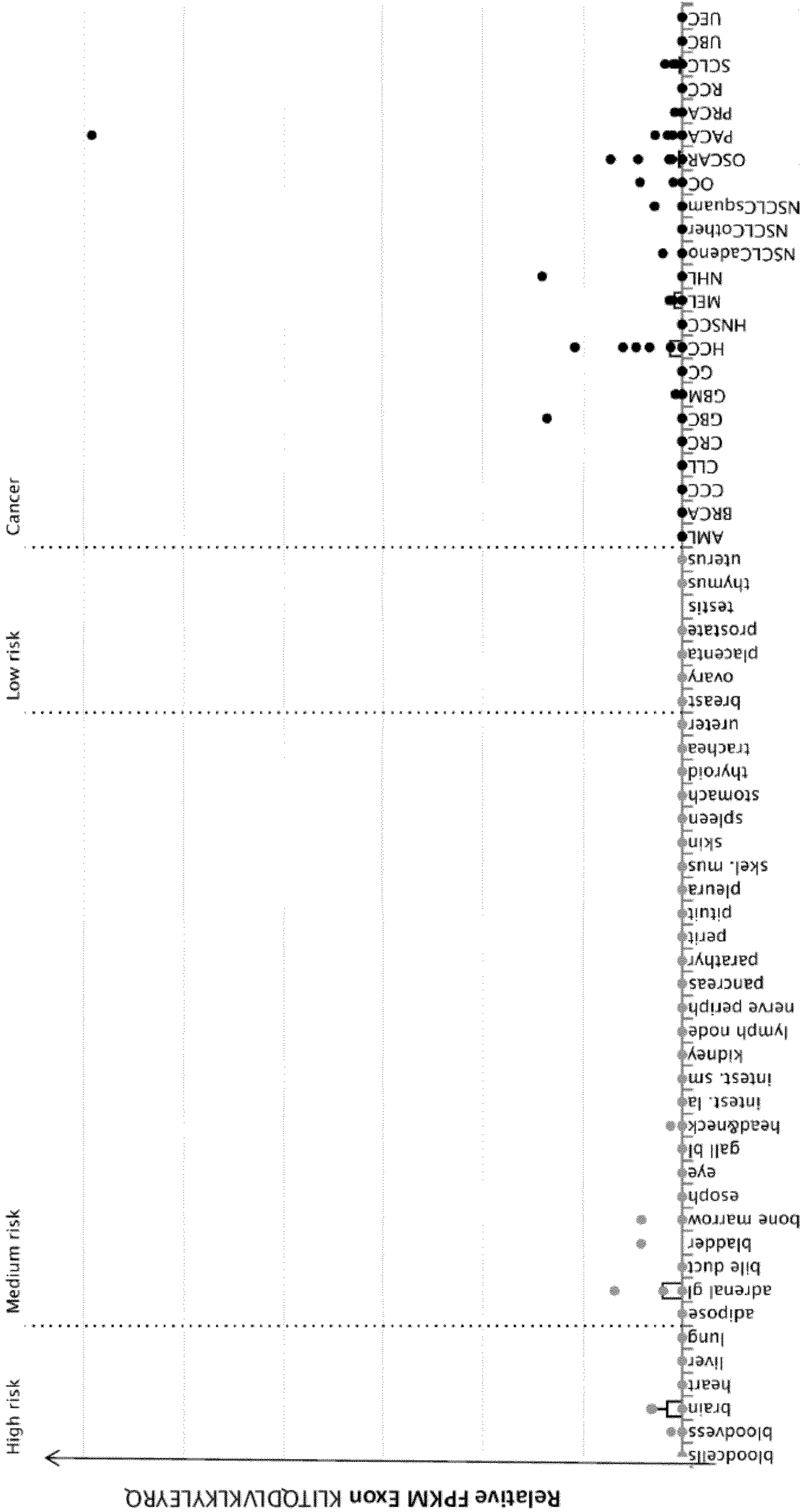


Figure 2

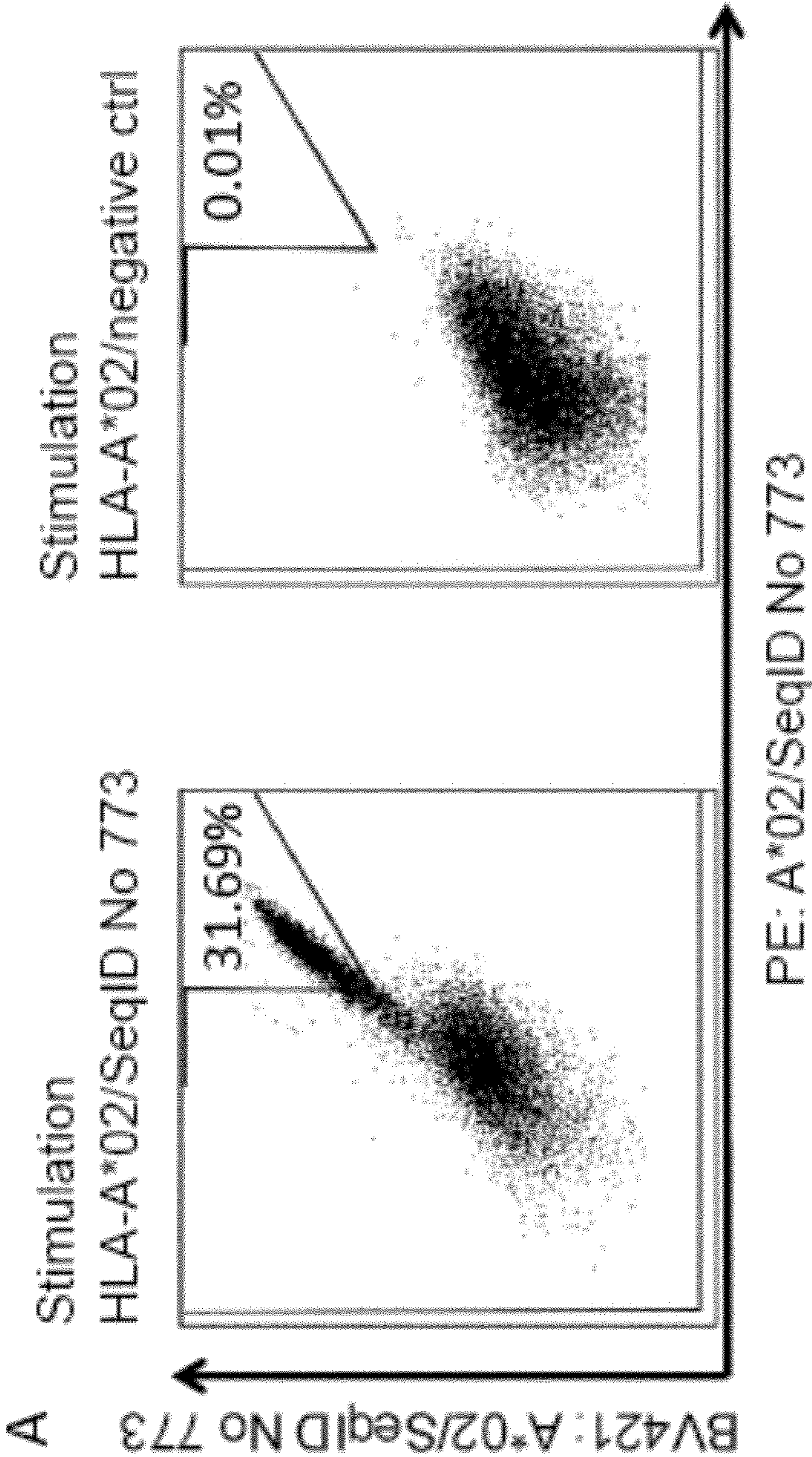


Figure 3

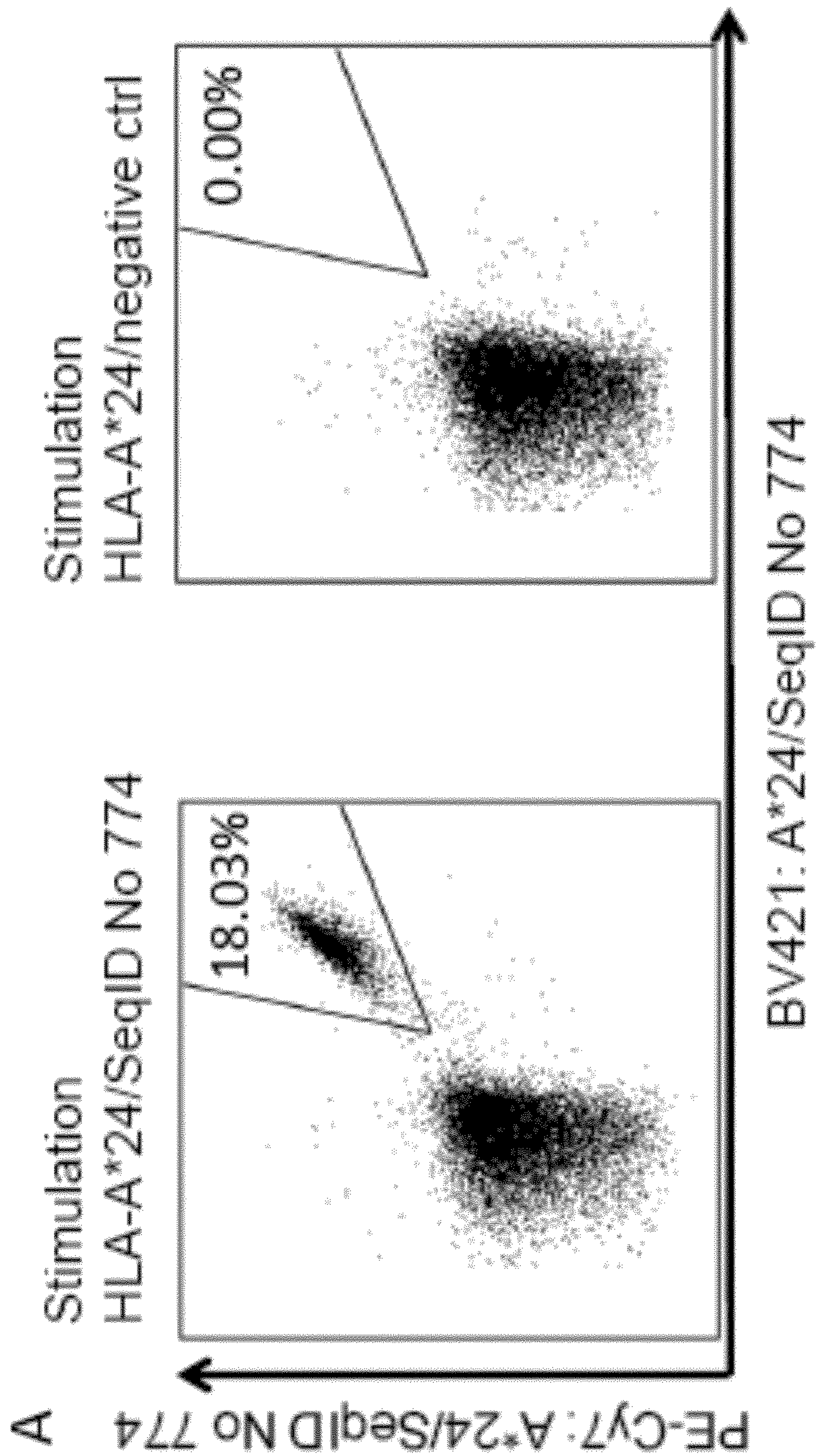


Figure 4

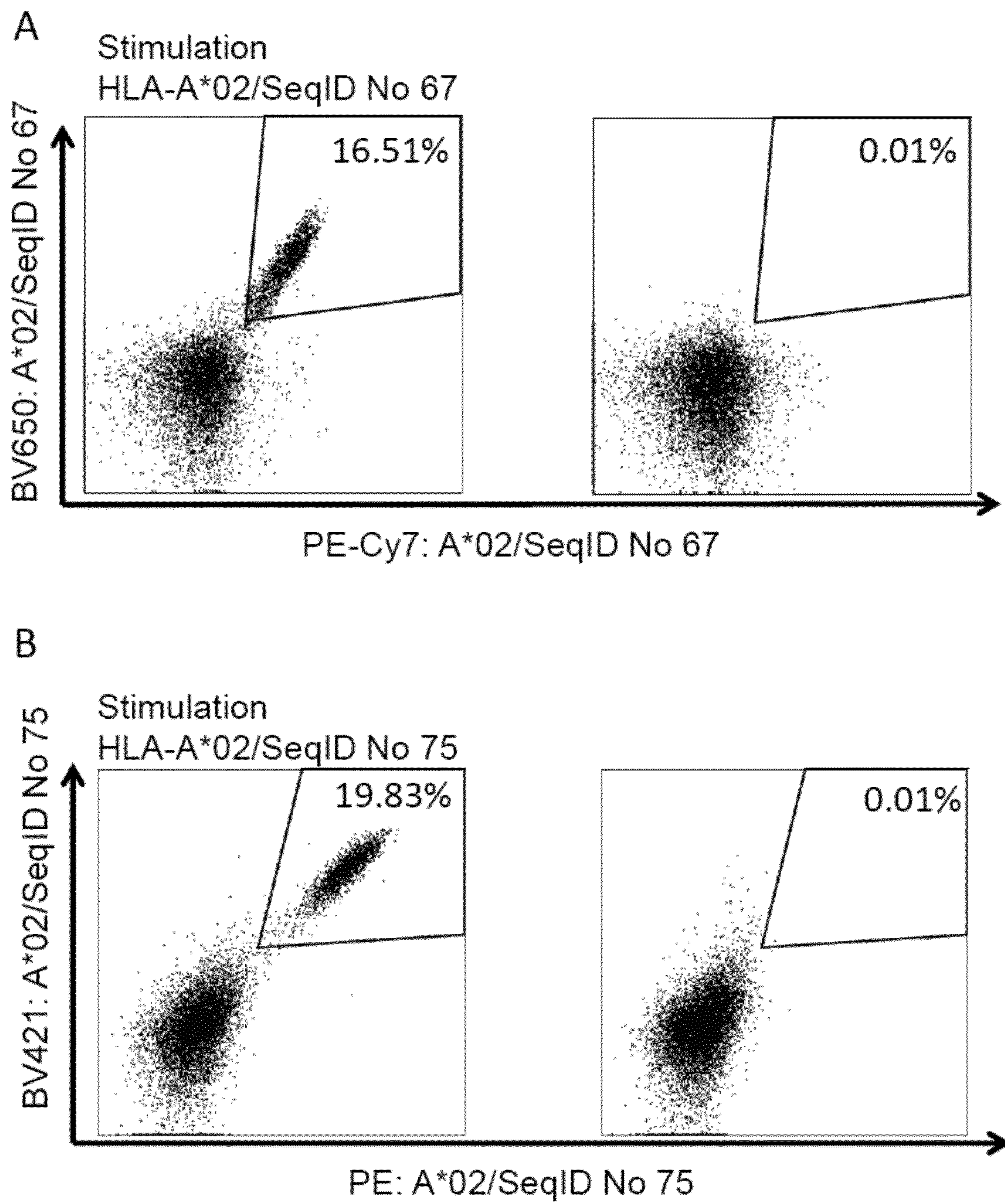


Figure 5

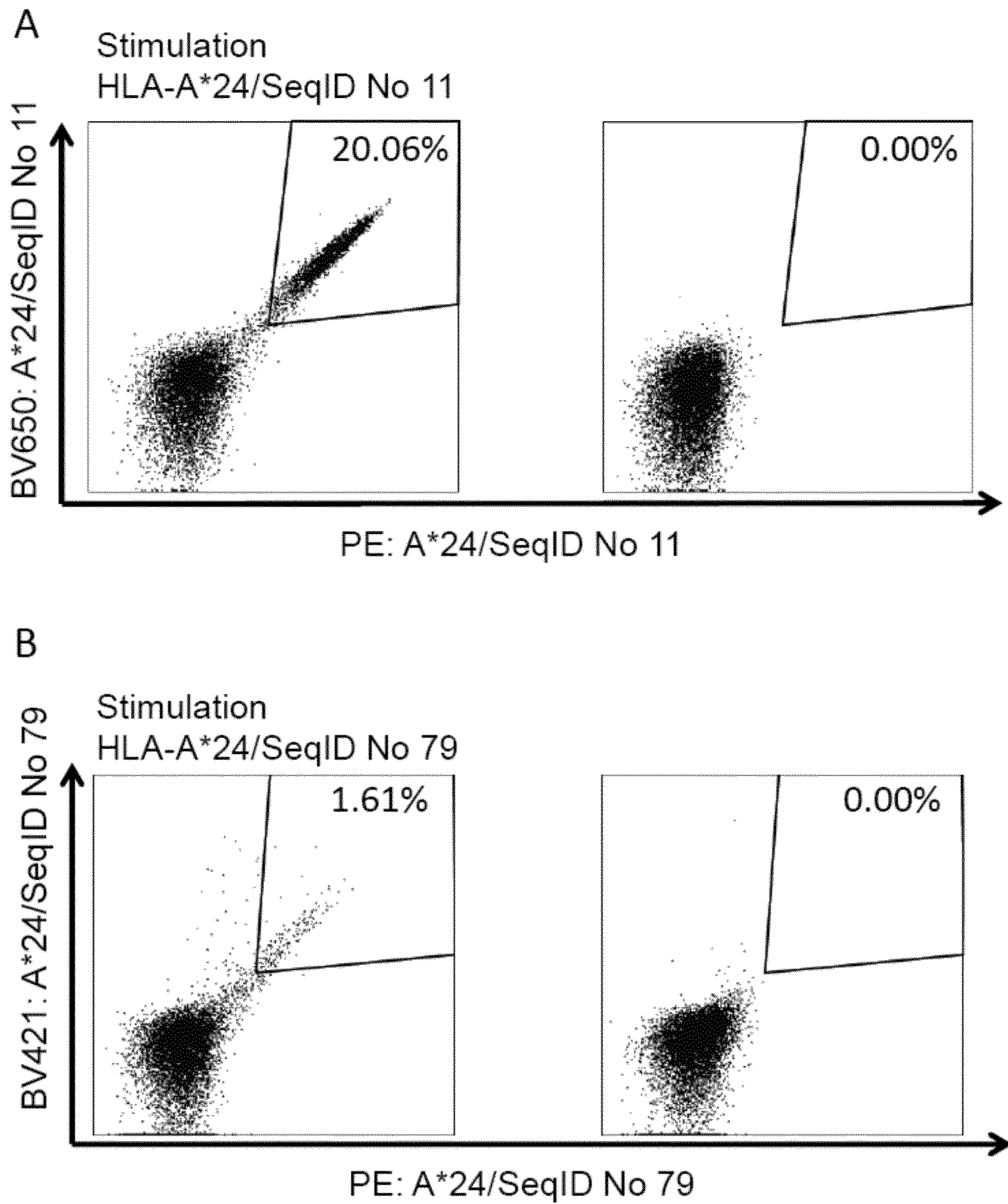


Figure 6

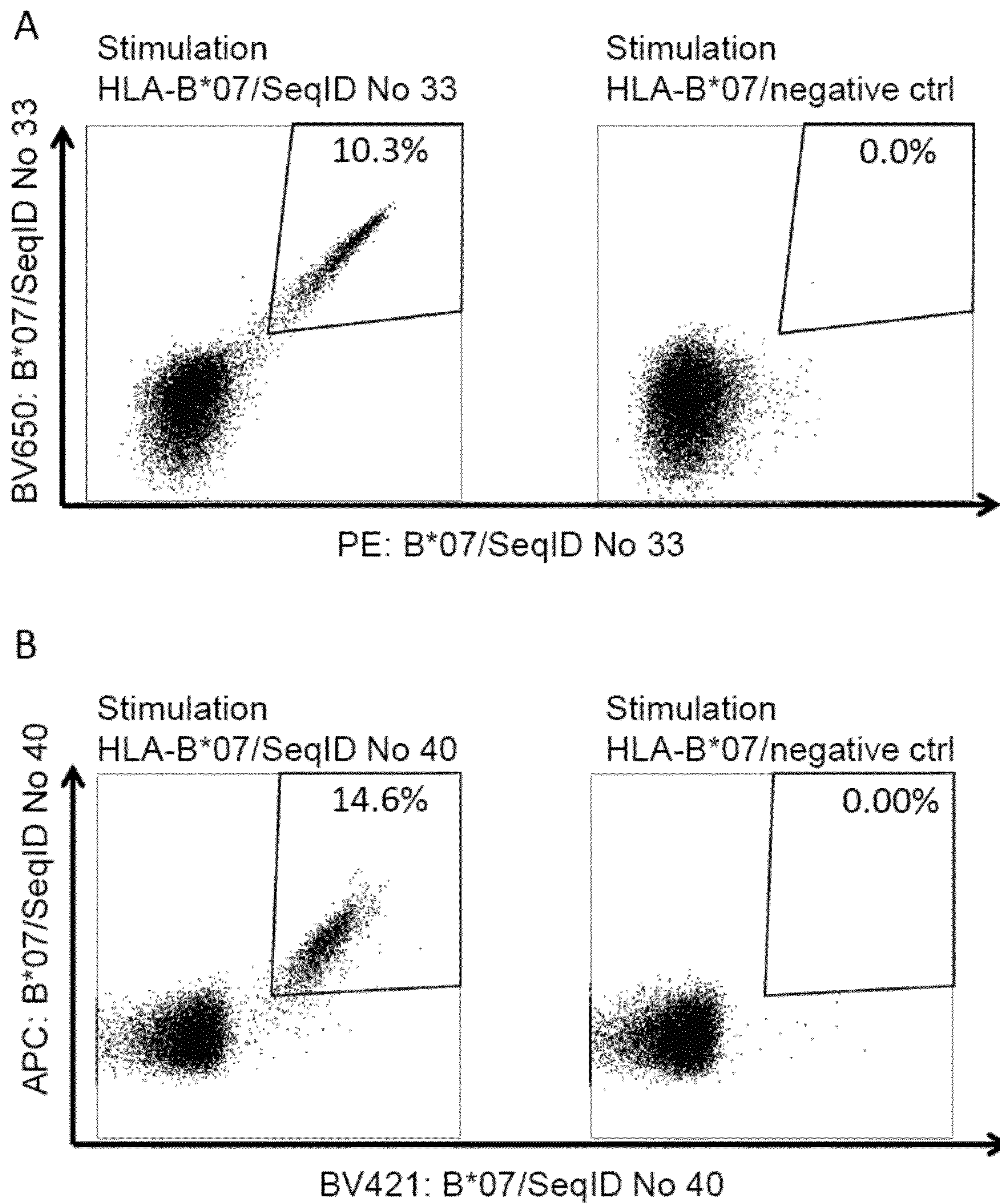


Figure 7

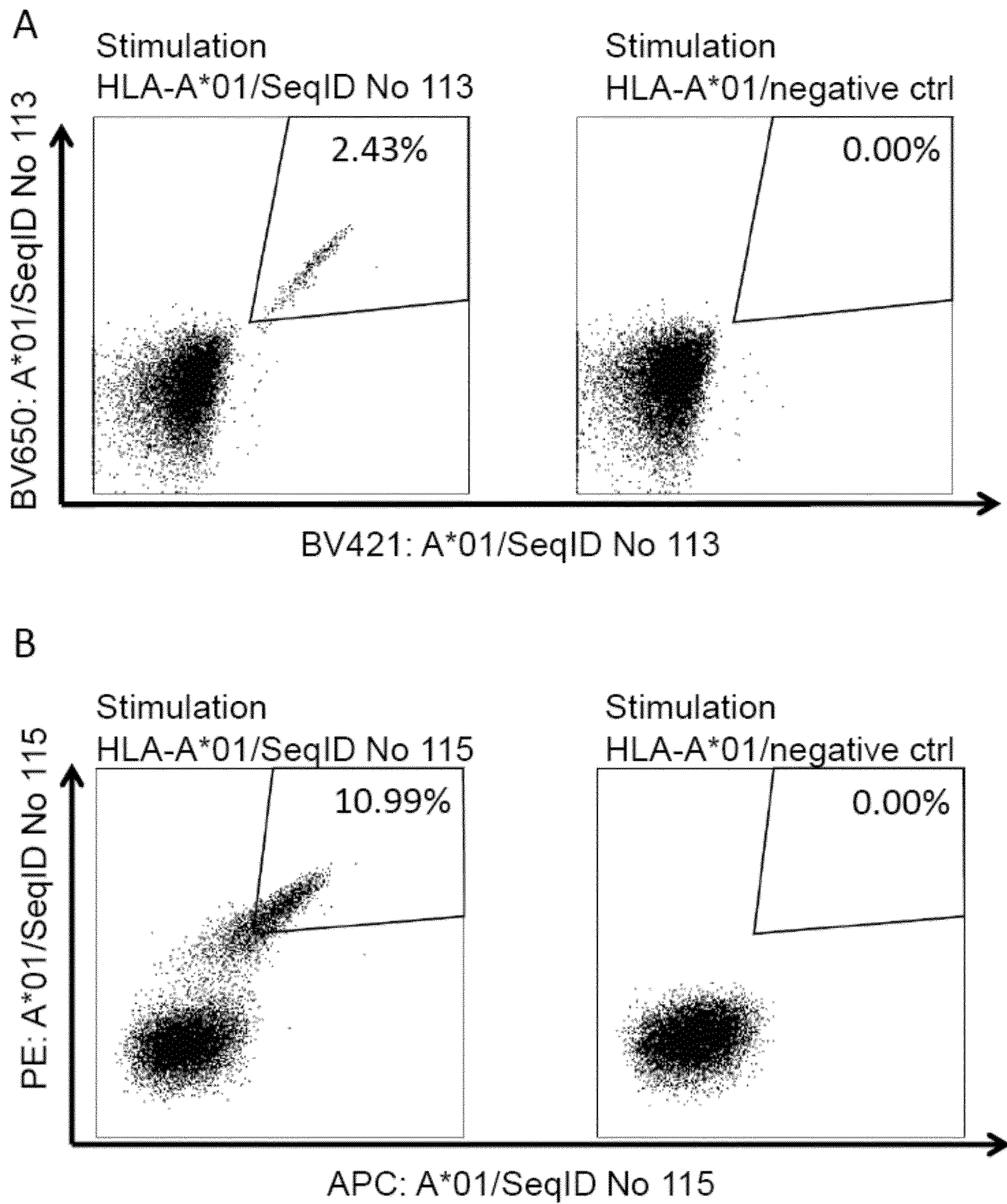


Figure 8

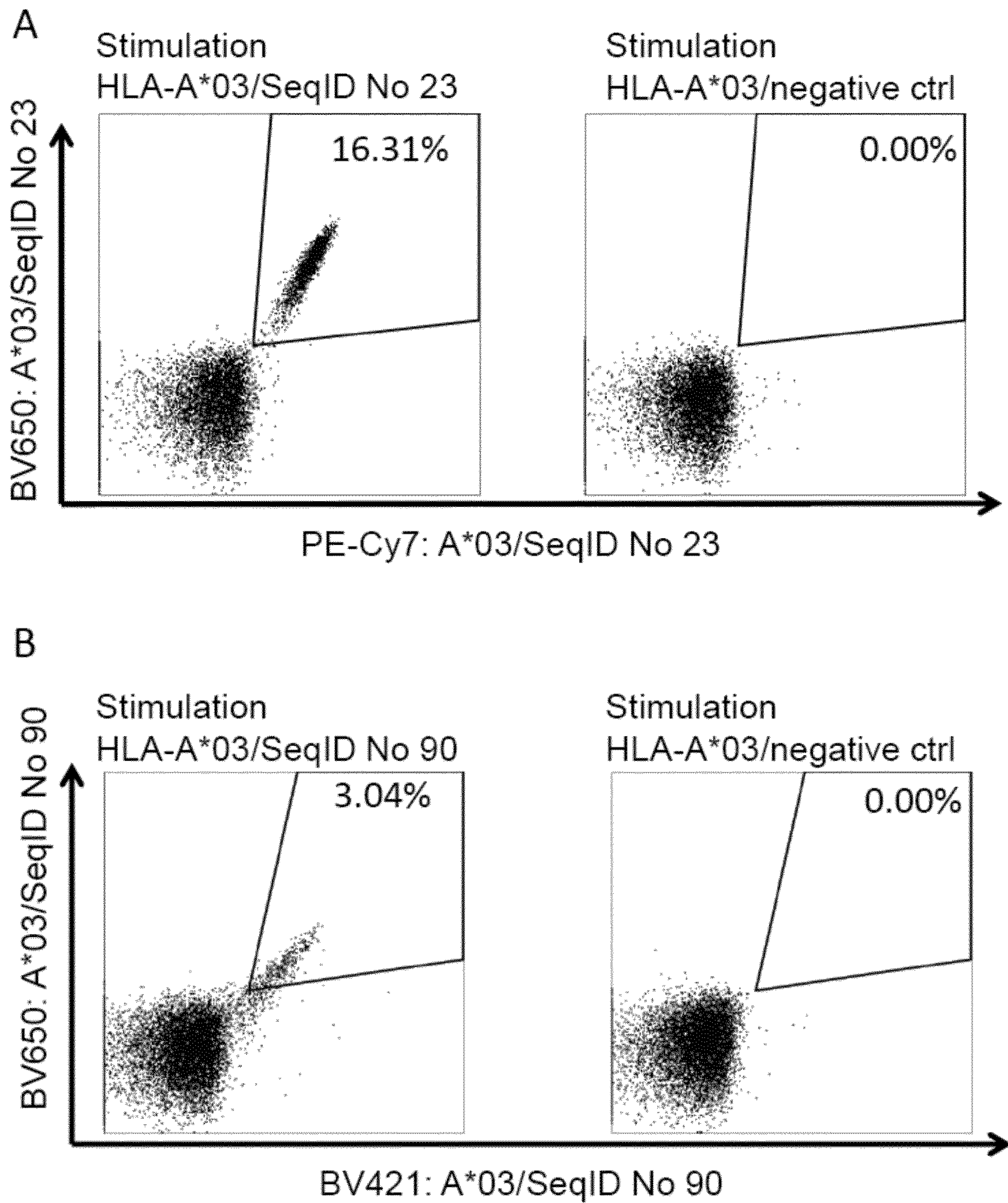


Figure 9

