US 20200054727A1

(19) **United States**

(12) **Patent Application Publication**

**MAHR et al.**

(10) **Pub. No.: US 2020/0054727 A1**

(43) **Pub. Date: Feb. 20, 2020**

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

(71) Applicant: **Immatics Biotechnologies GmbH**, Tuebingen (DE)

(72) Inventors: **Andrea MAHR**, Tuebingen (DE); **Toni WEINSCHENK**, Aichwald (DE); **Anita WIEBE**, Ruebgarten (DE); **Oliver SCHOOR**, Tuebingen (DE); **Jens FRITSCHE**, Dusslingen (DE); **Harpreet SINGH**, Muenchen (DE)

(21) Appl. No.: **16/669,622**

(22) Filed: **Oct. 31, 2019**

**Related U.S. Application Data**

(63) Continuation of application No. 16/415,671, filed on May 17, 2019, which is a continuation of application No. 15/375,070, filed on Dec. 9, 2016, now Pat. No. 10,398,766.

(60) Provisional application No. 62/265,615, filed on Dec. 10, 2015.

(30) **Foreign Application Priority Data**

Dec. 10, 2015 (GB) .................................. 1521746.6

**Publication Classification**

(51) **Int. Cl.**

| | |
|---|---|
| ***A61K 39/00*** | (2006.01) |
| ***C07K 16/28*** | (2006.01) |
| ***C07K 14/74*** | (2006.01) |
| ***C12N 15/115*** | (2006.01) |
| ***C12N 5/0783*** | (2006.01) |
| ***C07K 16/30*** | (2006.01) |
| ***C07K 14/725*** | (2006.01) |
| ***C07K 14/47*** | (2006.01) |
| ***C07K 7/08*** | (2006.01) |
| ***C07K 7/06*** | (2006.01) |

(52) **U.S. Cl.**

CPC .......... ***A61K 39/0011*** (2013.01); *A61K 35/17* (2013.01); ***C07K 14/70539*** (2013.01); ***C12N 15/115*** (2013.01); ***C12N 5/0636*** (2013.01); ***C07K 16/30*** (2013.01); ***C07K 14/7051*** (2013.01); ***C07K 14/4748*** (2013.01); ***C07K 7/08*** (2013.01); ***C07K 7/06*** (2013.01); ***C07K 14/47*** (2013.01); *C12N 2310/16* (2013.01); *C07K 2317/34* (2013.01); *A61K 2039/5158* (2013.01); ***C07K 16/2833*** (2013.01)

(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.

**Specification includes a Sequence Listing.**

Figure 1A

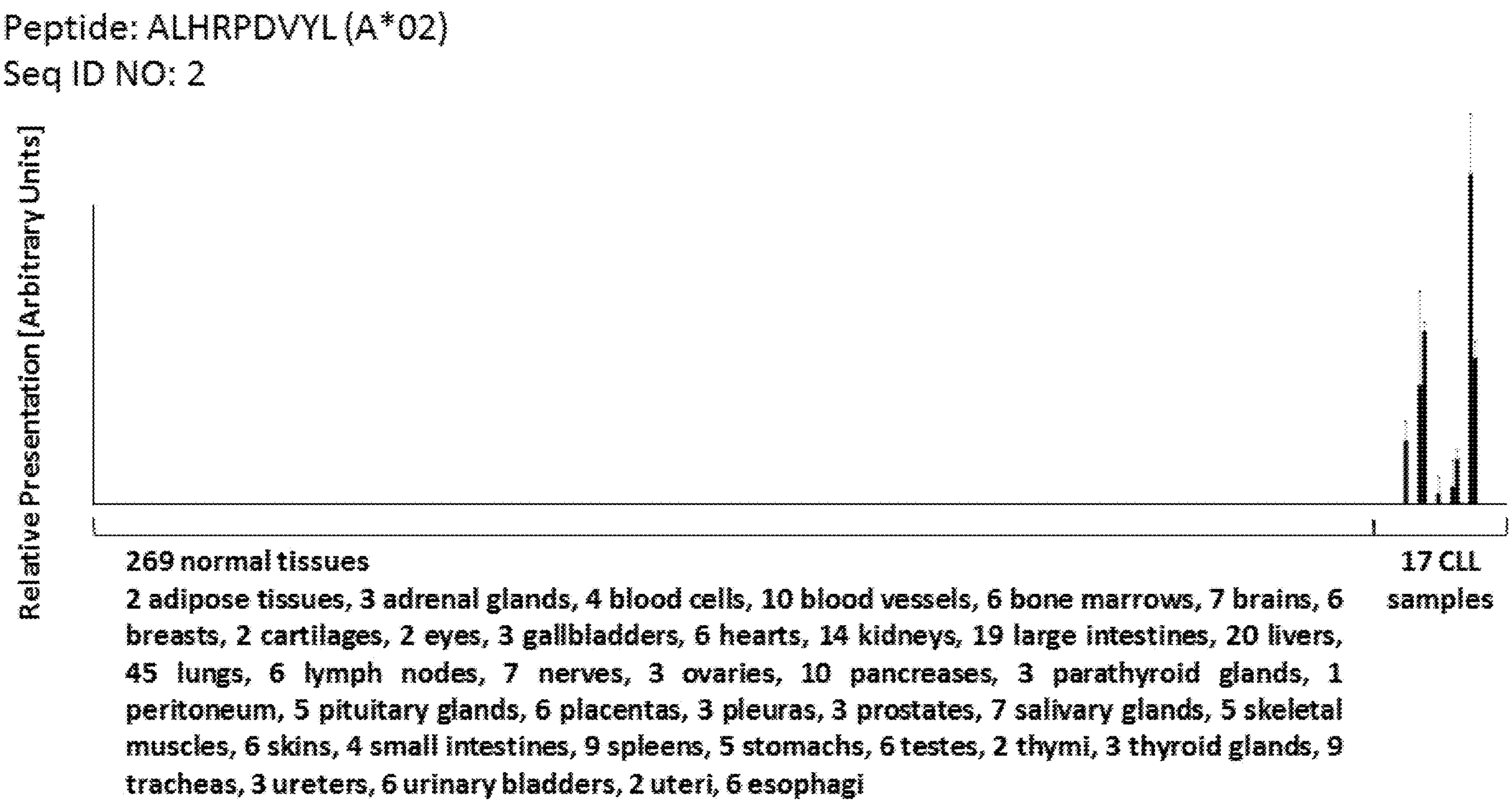

Peptide: ALHRPDVYL (A*02)
Seq ID NO: 2
Relative Presentation [Arbitrary Units]
269 normal tissues
2 adipose tissues, 3 adrenal glands, 4 blood cells, 10 blood vessels, 6 bone marrows, 7 brains, 6 breasts, 2 cartilages, 2 eyes, 3 gallbladders, 6 hearts, 14 kidneys, 19 large intestines, 20 livers, 45 lungs, 6 lymph nodes, 7 nerves, 3 ovaries, 10 pancreases, 3 parathyroid glands, 1 peritoneum, 5 pituitary glands, 6 placentas, 3 pleuras, 3 prostates, 7 salivary glands, 5 skeletal muscles, 6 skins, 4 small intestines, 9 spleens, 5 stomachs, 6 testes, 2 thymi, 3 thyroid glands, 9 tracheas, 3 ureters, 6 urinary bladders, 2 uteri, 6 esophagi
17 CLL samples

Figure 1B

Peptide: VIAELPPKV (A*02)
SEQ ID NO: 3

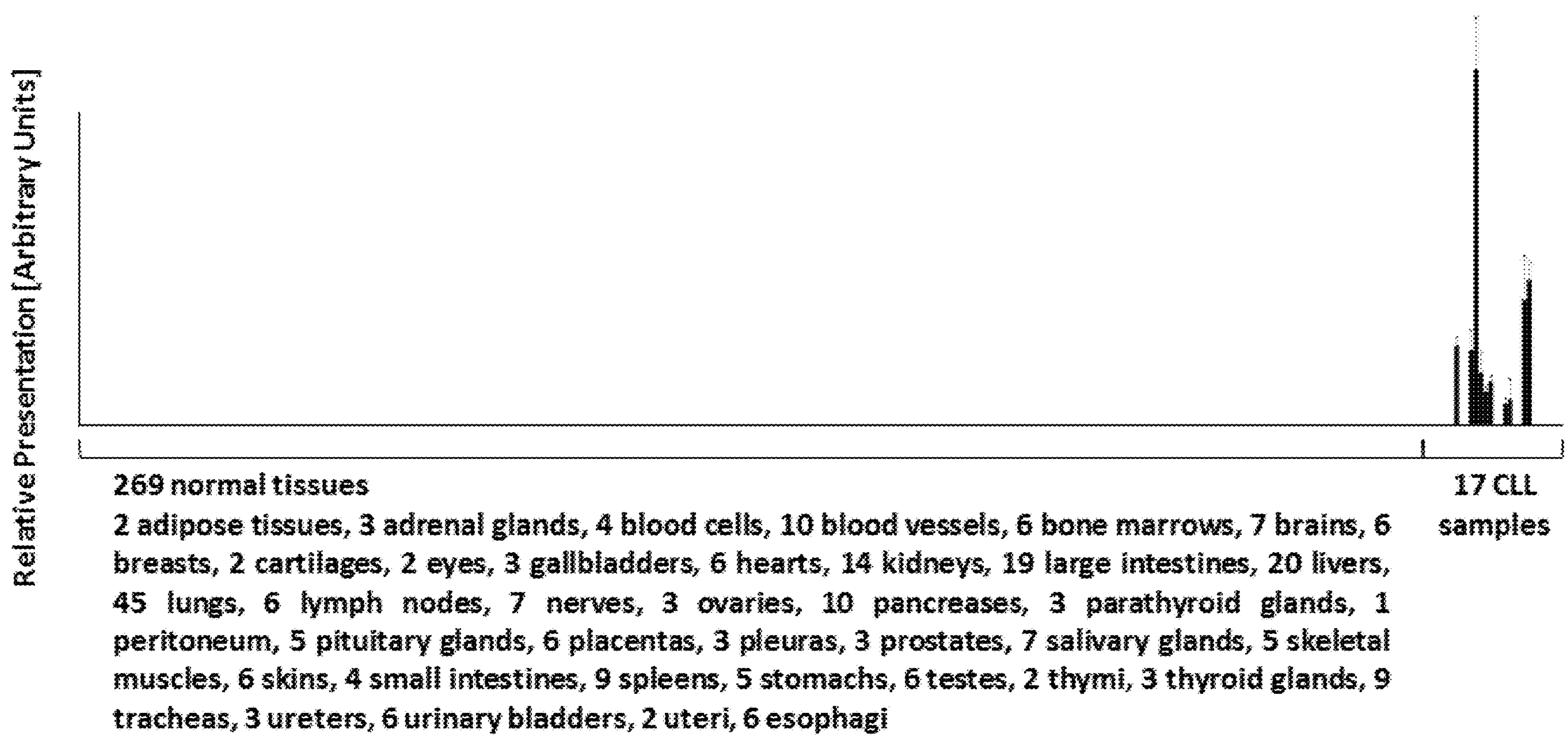


Figure 1C

Peptide: VIAELPPKVSV (A*02)
SEQ ID NO: 4

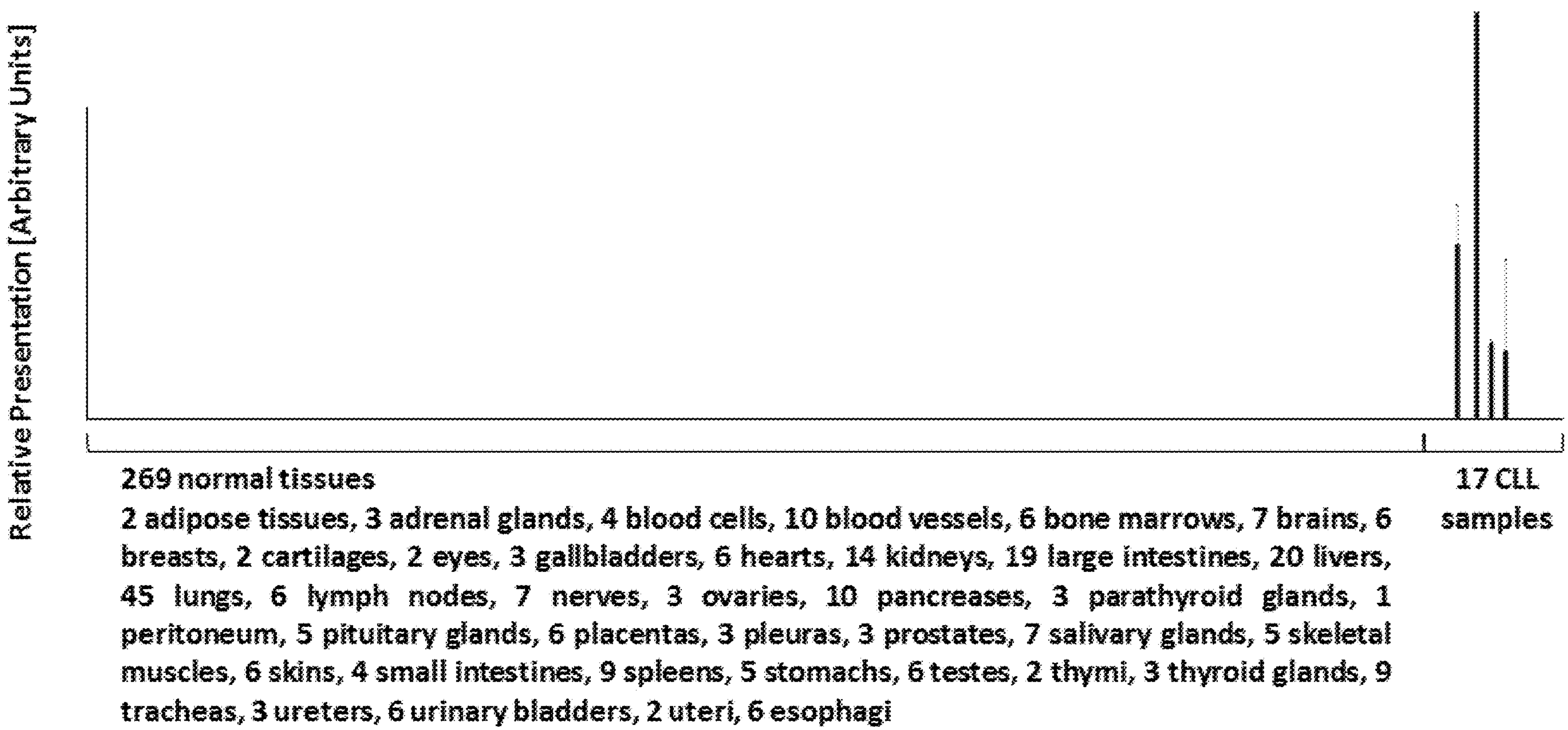
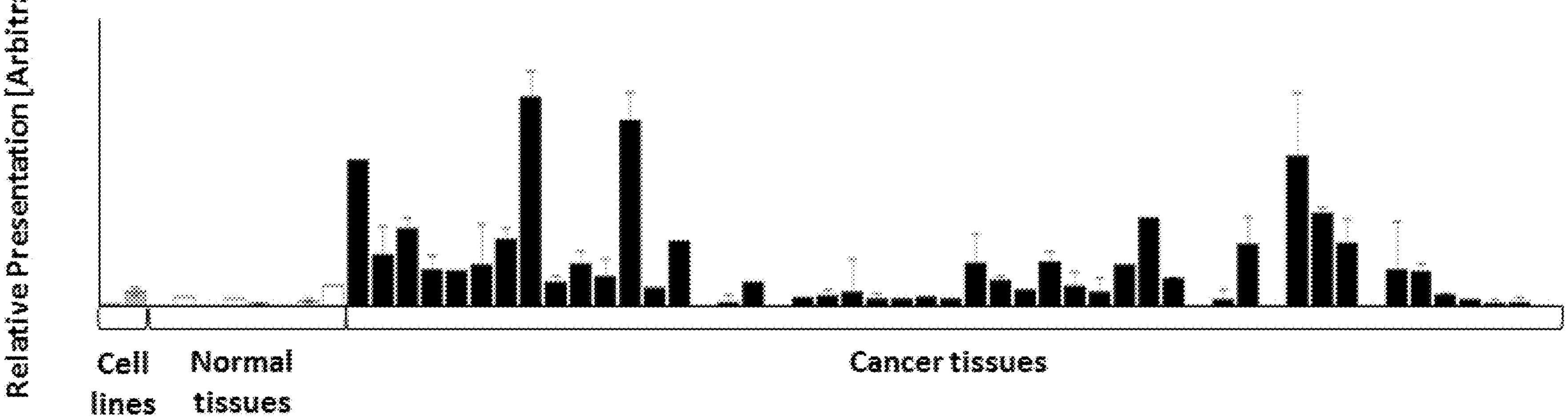


Figure 1D

Peptide: RLYEITIEV (A*02)
SEQ ID NO: 121

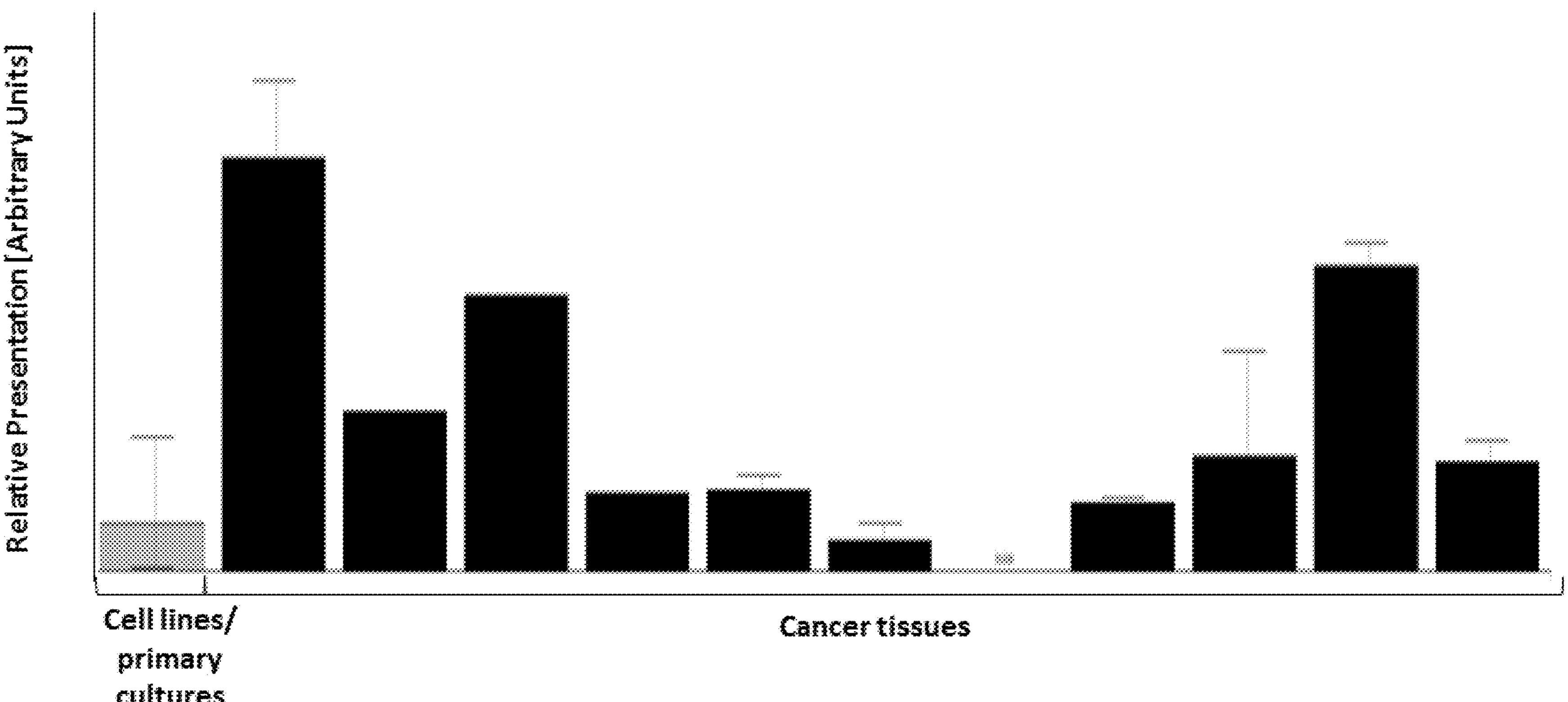



**Peptide detected on**
**1 PBMC culture, 1 benign prostate, 8 normal tissues (3 lungs, 4 spleens, 1 trachea), 49 cancer tissues (2 brain cancers, 2 breast cancers, 1 colon cancer, 13 leukocytic leukemia cancers, 13 lung cancers, 8 lymph node cancers, 1 myeloid cells cancer, 4 ovarian cancers, 2 skin cancers, 1 urinary bladder cancer, 2 uterus cancers) (from left to right)**

Figure 1E

Peptide: ALLRLLPGL (A*02)

SEQ ID NO: 14



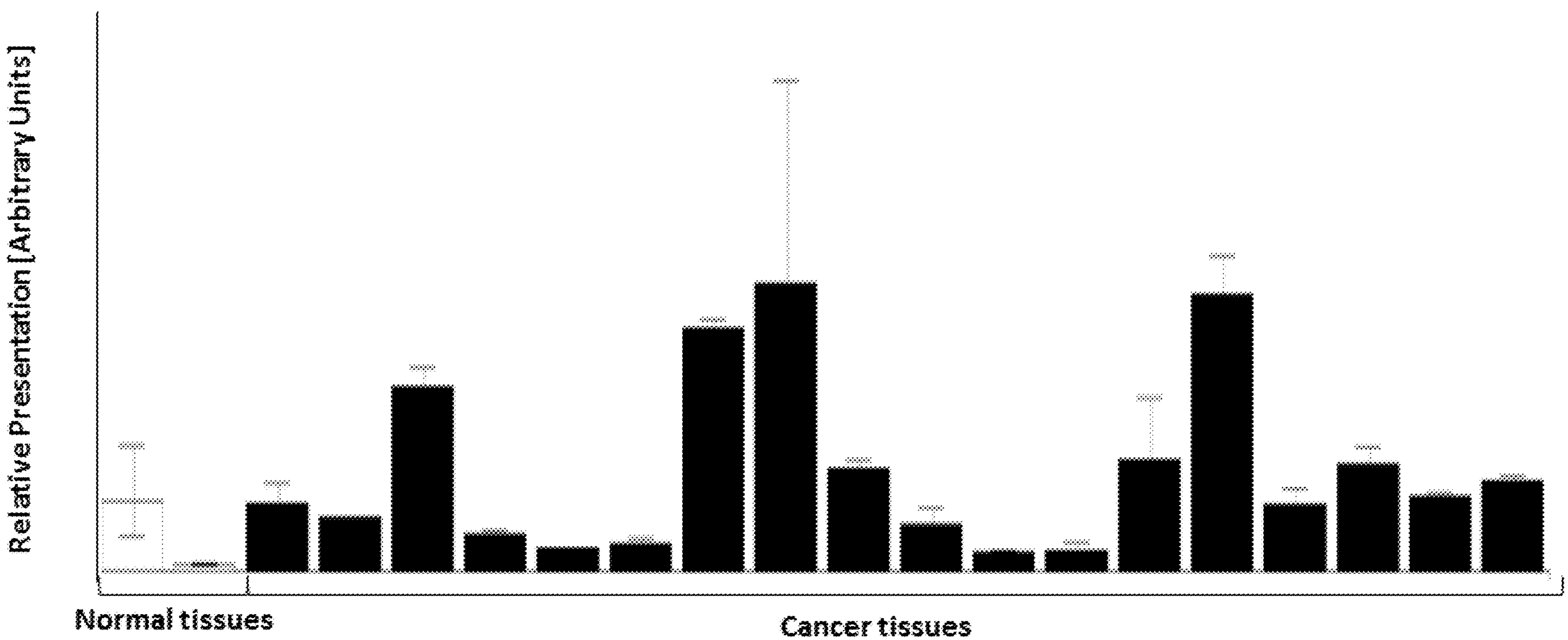

Peptide detected on

1 cell line, 11 cancer tissues (1 breast cancer, 1 colon cancer, 1 head and neck cancer, 2 leukocytic leukemia cancers, 1 liver cancer, 1 lung cancer, 2 lymph node cancers, 1 myeloid cell cancer, 1 skin cancer) (from left to right)

Figure 1F

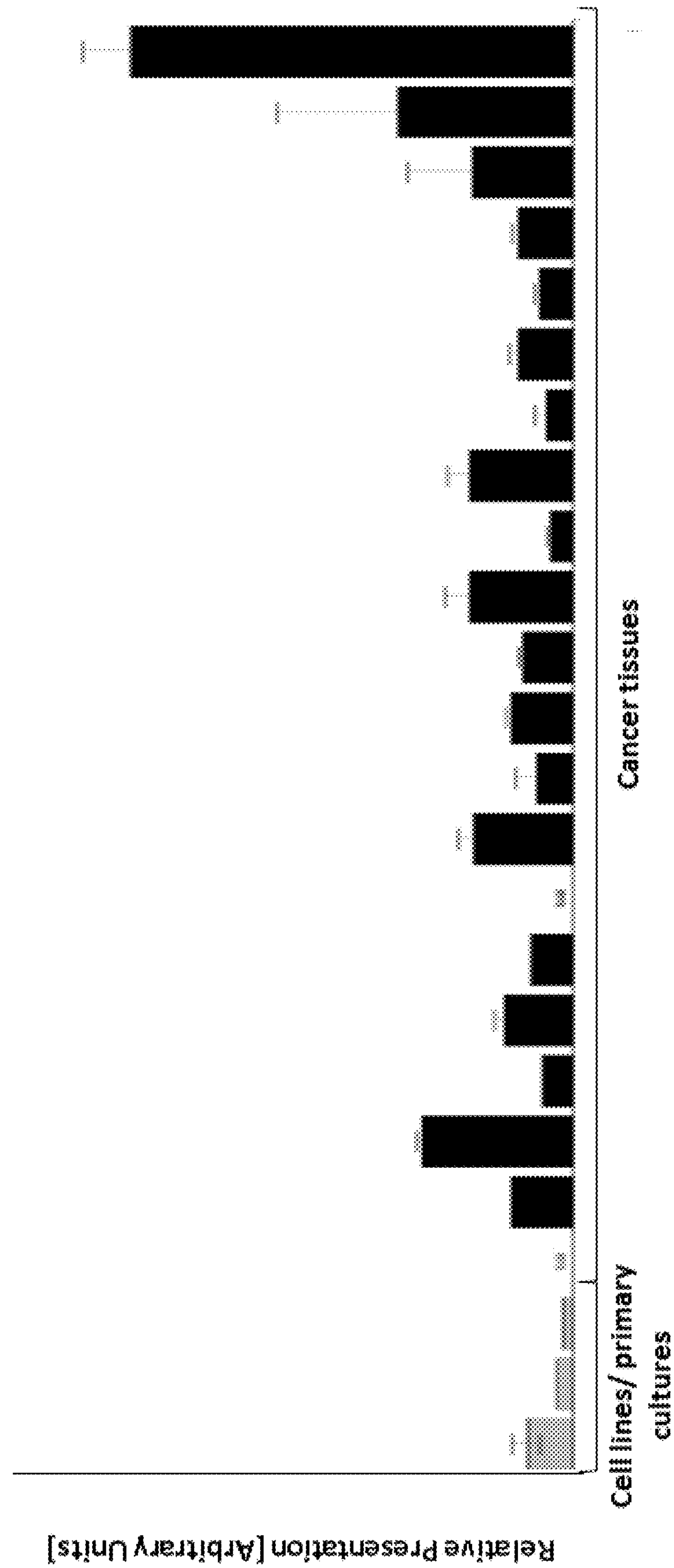
Peptide: GIIDGSPRL (A*02)

SEQ ID NO: 62




Peptide detected on
2 normal tissues (1 lymph node, 1 spleen), 18 cancer tissues (2 colon cancers, 9 leukocytic leukemia cancers, 6 lymph node cancers, 1 rectum cancer) (from left to right)

Figure 1G
Peptide: GLDQQFAGLDL (A*02)
SEQ ID NO: 68

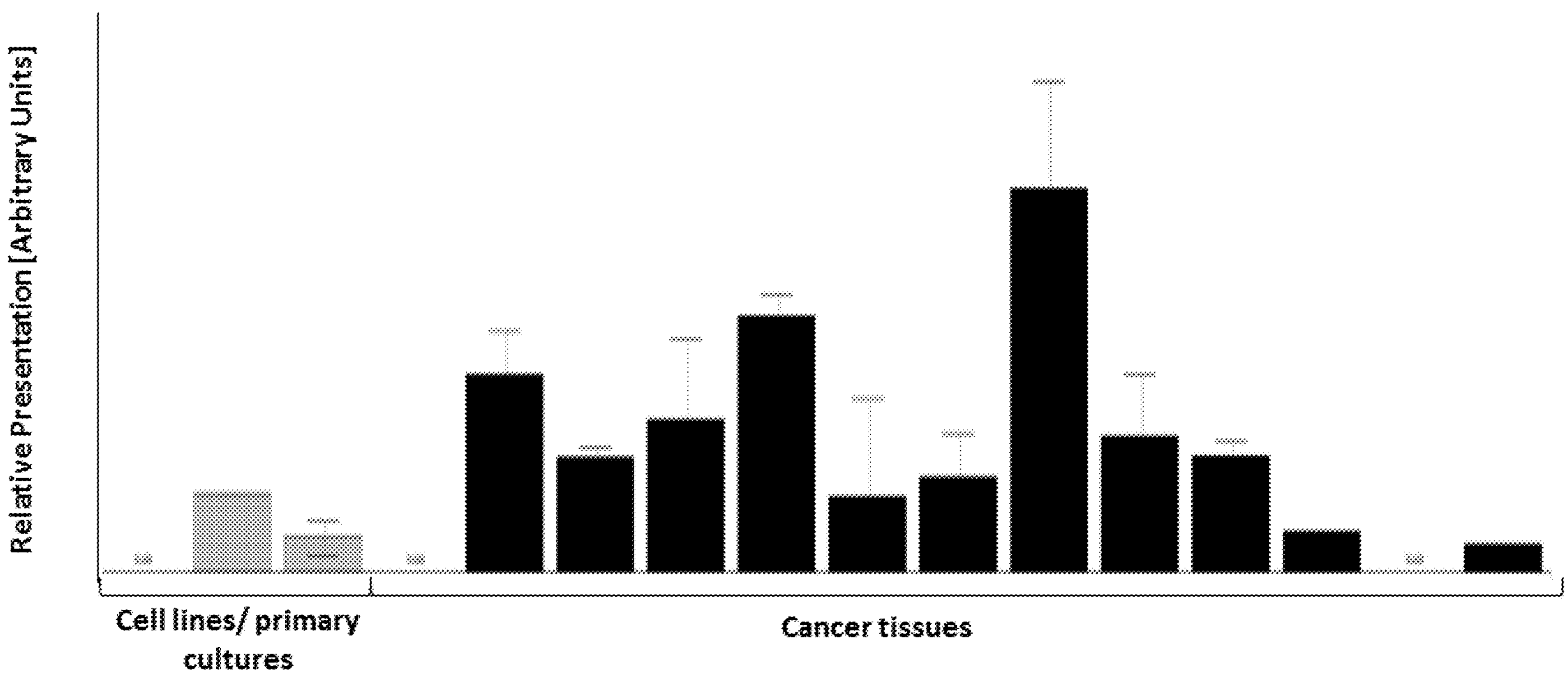



Peptide detected on
1 cell line, 2 primary cultures, 21 cancer tissues (1 bile duct cancer, 1 brain cancer, 1 breast cancer, 1 head and neck cancer, 2 kidney cancers, 3 leukocytic leukemia cancers, 2 liver cancers, 2 lung cancers, 2 lymph node cancers, 3 ovarian cancers, 1 rectum cancer, 1 skin cancer, 1 uterus cancer) (from left to right)

Figure 1H

Peptide: KTLDVDATYEI (A*02)

SEQ ID NO: 112



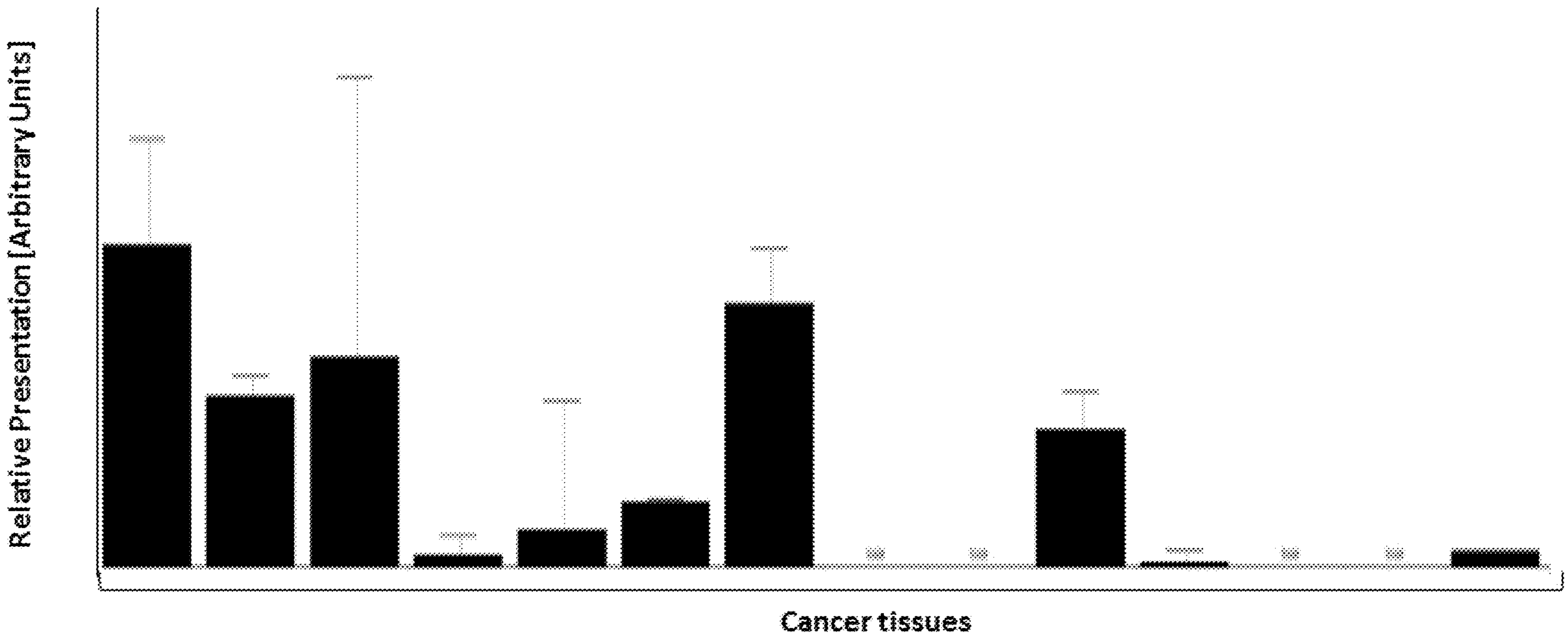

Peptide detected on

2 cell lines, 1 primary culture, 13 cancer tissues (1 esophageal cancer, 2 leukocytic leukemia cancers, 1 liver cancer, 3 lung cancers, 2 lymph node cancers, 2 ovarian cancers, 1 skin cancer, 1 uterus cancer) (from left to right)

Figure 1I

Peptide: SIIEGPIIKL (A*02)

SEQ ID NO: 146

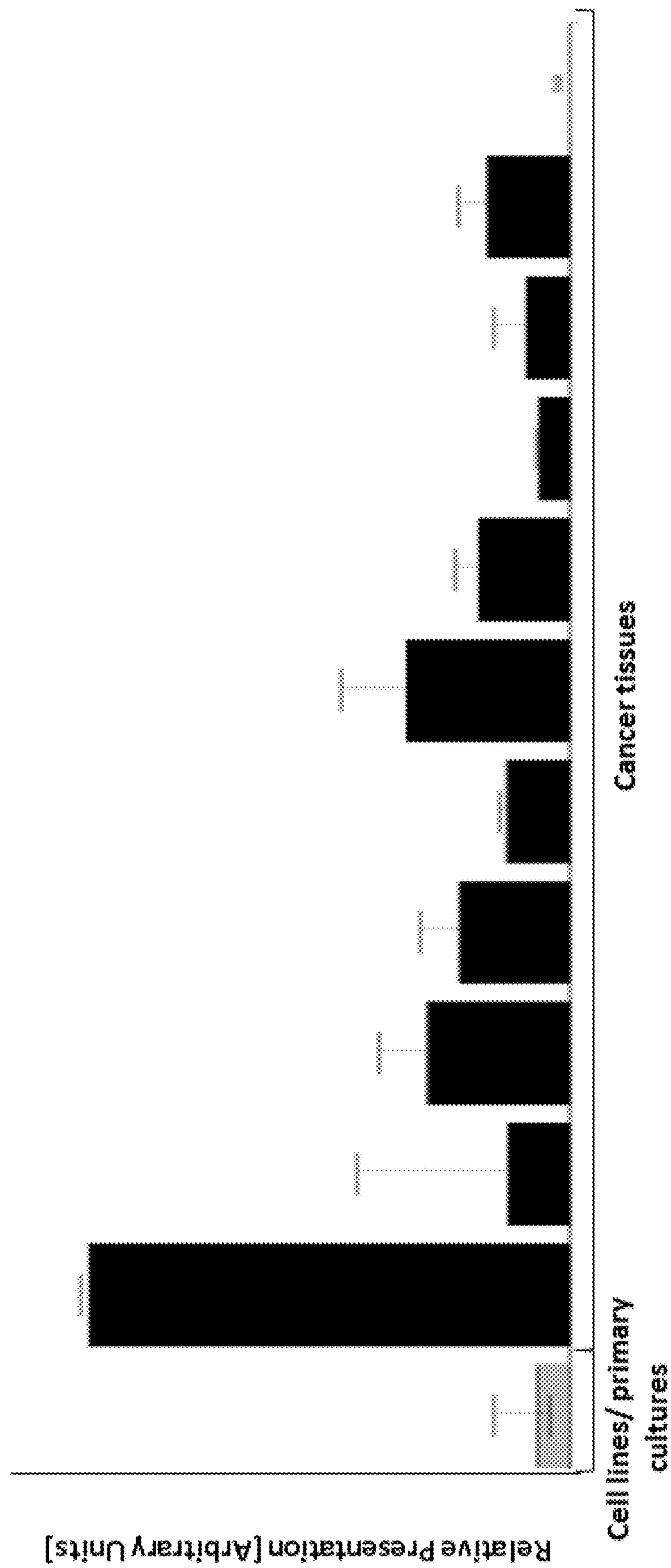



Peptide detected on
14 cancer tissues (1 head and neck cancer, 3 leukocytic leukemia cancers, 6 lung cancers, 1 lymph node cancer, 1 ovarian cancer, 2 urinary bladder cancers) (from left to right)

Figure 1J

Peptide: SILETVATL (A*02)

SEQ ID NO: 147

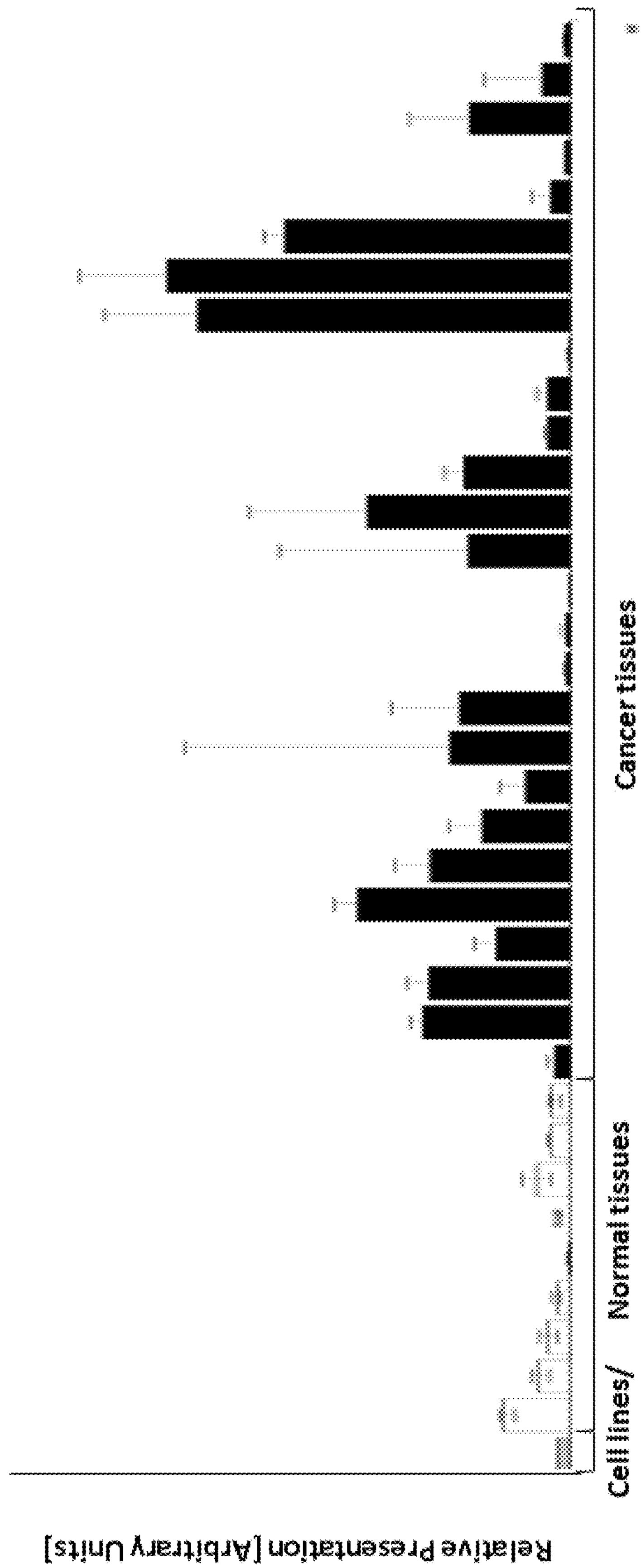



Peptide detected on
1 primary culture, 11 cancer tissues (1 colon cancer, 4 leukocytic leukemia cancers, 1 lung cancer, 3 lymph node cancers, 1 myeloid cell cancer, 1 skin cancer) (from left to right)

Figure 1K

Peptide: SLLAELHVL (A*02)

SEQ ID NO: 153



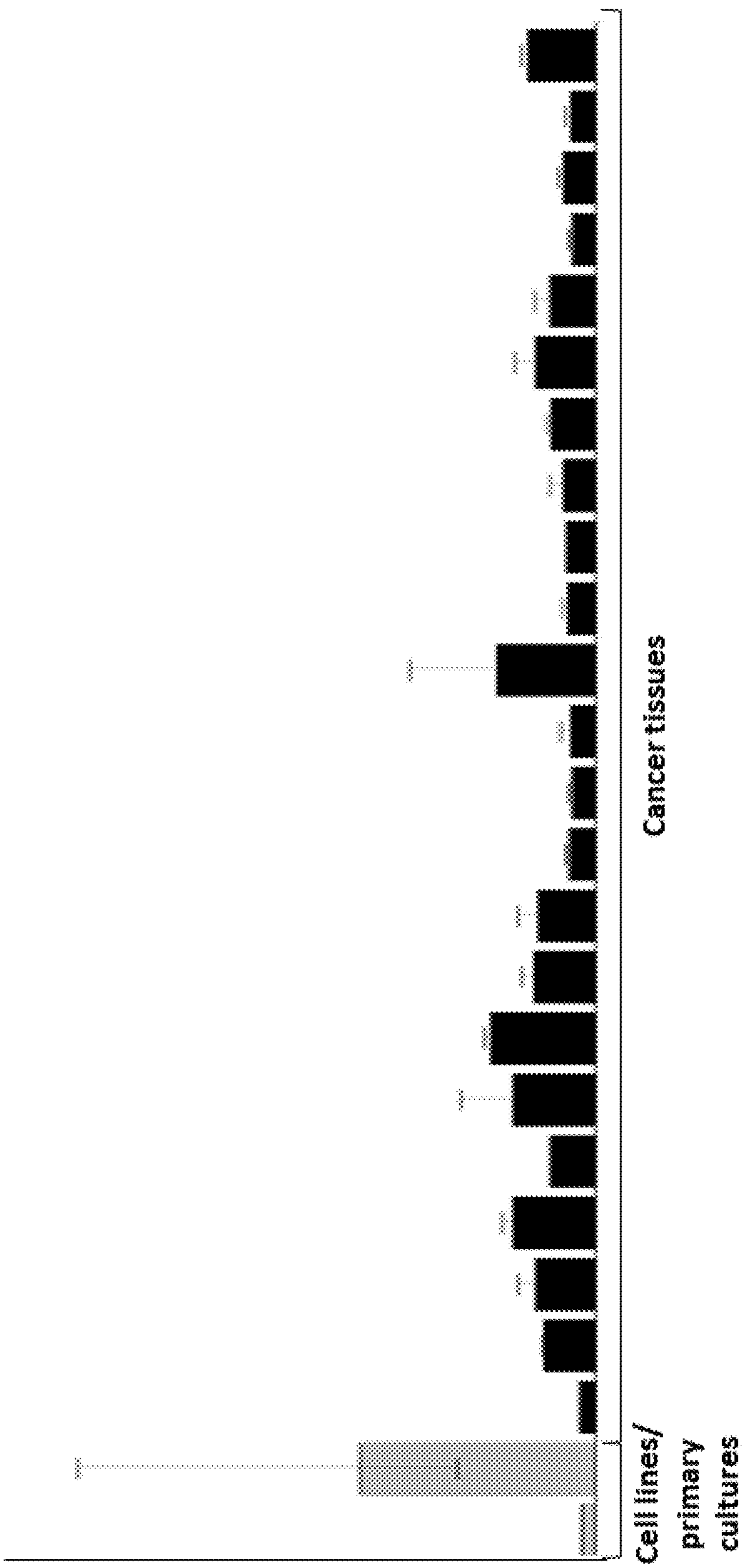

Peptide detected on

1 cell line, 9 normal tissues (1 lymph node, 1 rectum, 7 spleens), 27 cancer tissues (1 breast cancer, 1 kidney cancer, 10 leukocytic leukemia cancers, 14 lymph node cancers, 1 skin cancer) (from left to right)

Figure 1L

Peptide: SLQEEKLIYV (A*02)

SEQ ID NO: 159

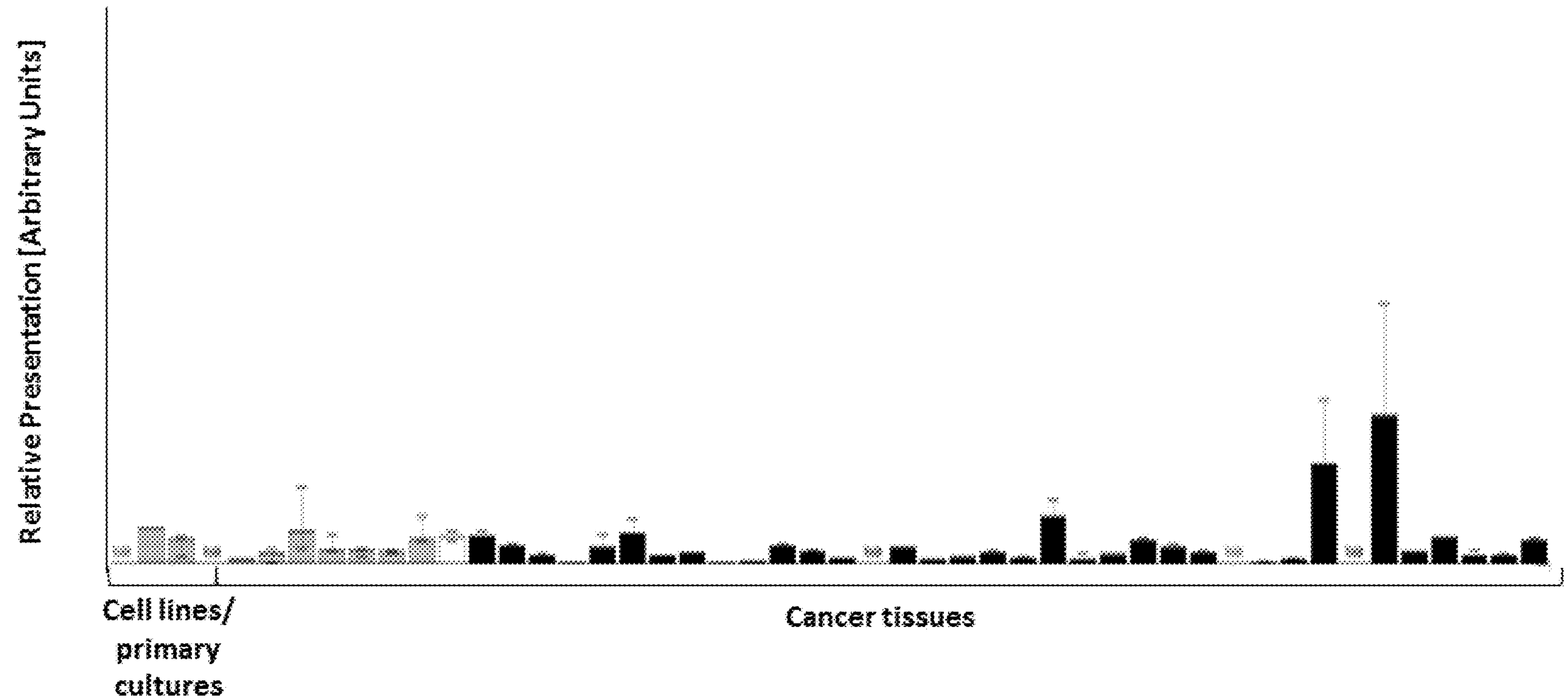



Peptide detected on
2 cell lines, 23 cancer tissues (5 brain cancers, 1 breast cancer, 1 esophageal cancer, 3 head and neck cancers, 2 leukocytic leukemia cancers, 5 lung cancers, 3 lymph node cancers, 1 skin cancer, 2 urinary bladder cancers)
(from left to right)

Figure 1M

Peptide: SVHKGFAFV (A*02)

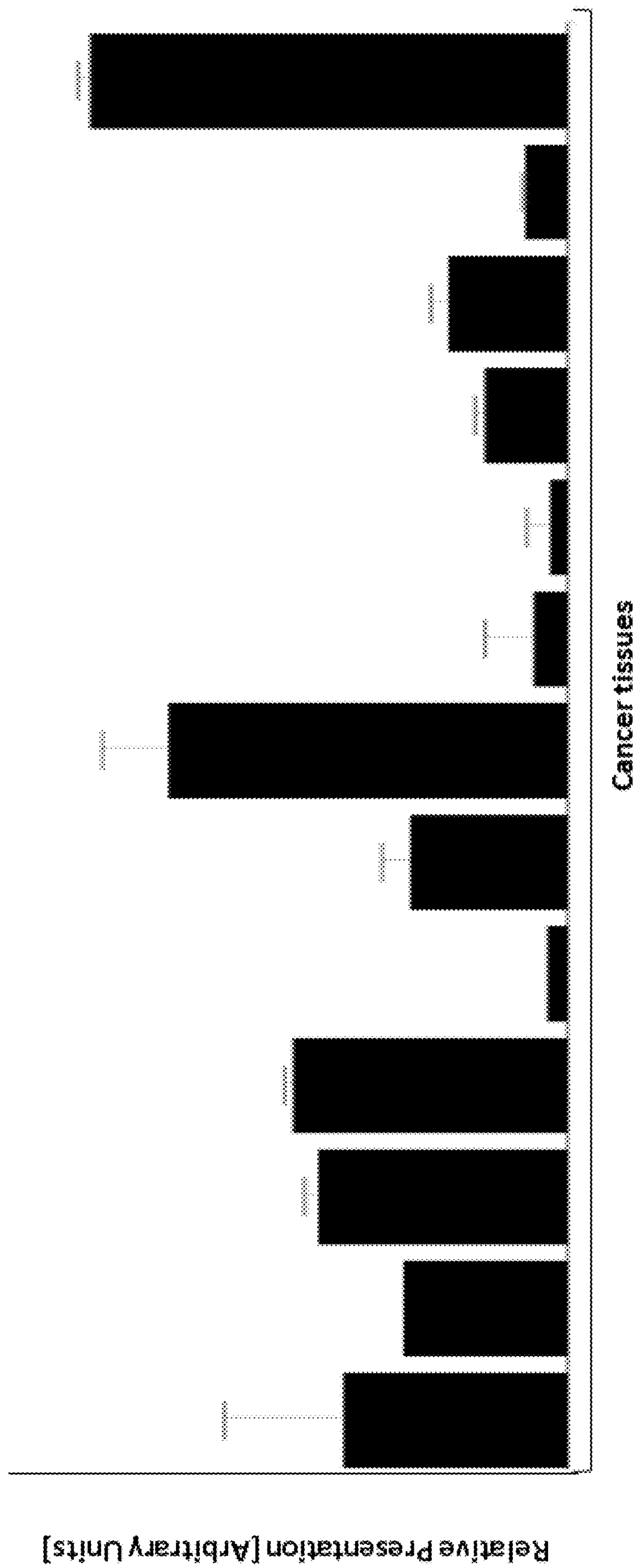
SEQ ID NO: 164




Peptide detected on

10 cell lines, 1 primary culture, 1 normal tissue (1 adrenal gland), 36 cancer tissues (12 brain cancers, 1 colon cancer, 2 head and neck cancers, 2 kidney cancers, 3 leukocytic leukemia cancers, 1 liver cancer, 5 lung cancers, 1 myeloid cell cancer, 1 ovarian cancer, 1 rectum cancer, 1 skin cancer, 2 stomach cancers, 2 urinary bladder cancers, 2 uterus cancers) (from left to right)

Figure 1N
Peptide: TLDTSKLYV (A*02)
SEQ ID NO: 167

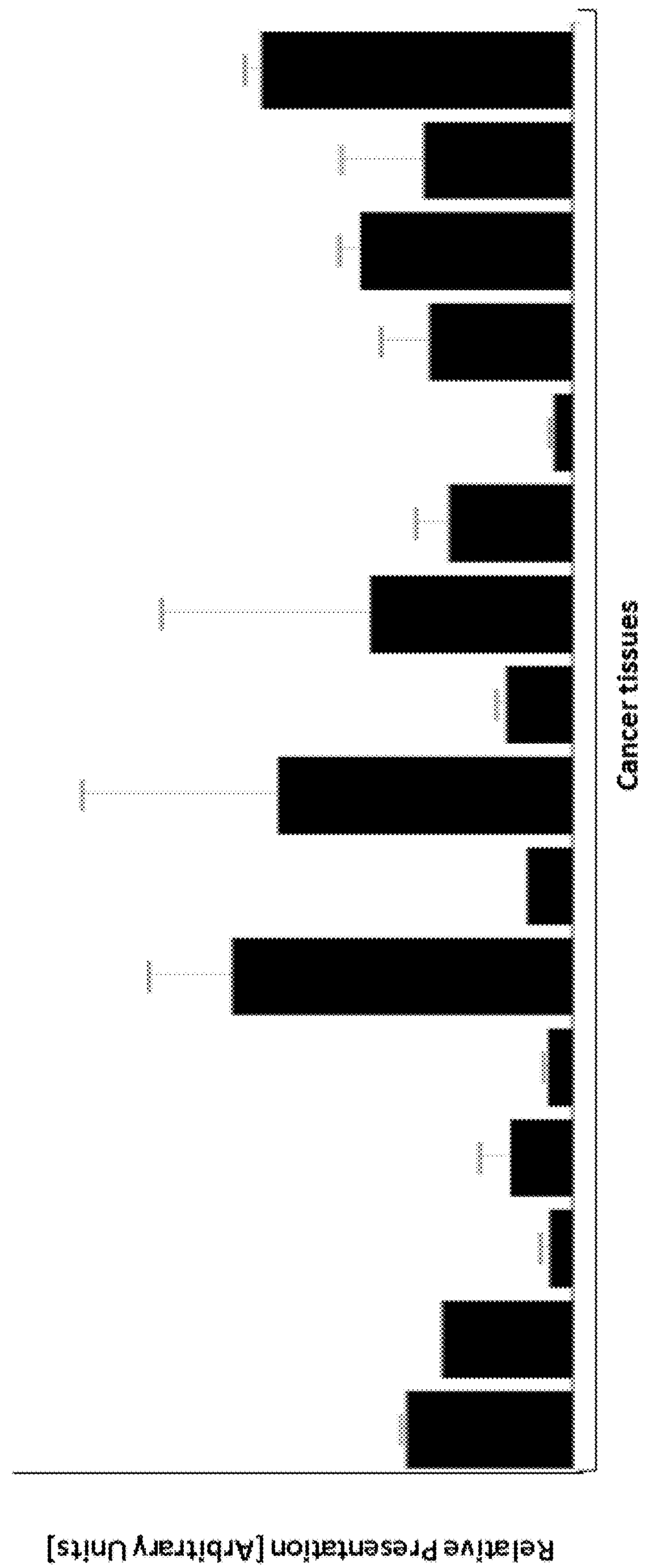



Peptide detected on
13 cancer tissues (1 brain cancer, 8 leukocytic leukemia cancers, 4 lymph node cancers) (from left to right)

Figure 10

Peptide: YLLDQSFVM (A*02)

SEQ ID NO: 168

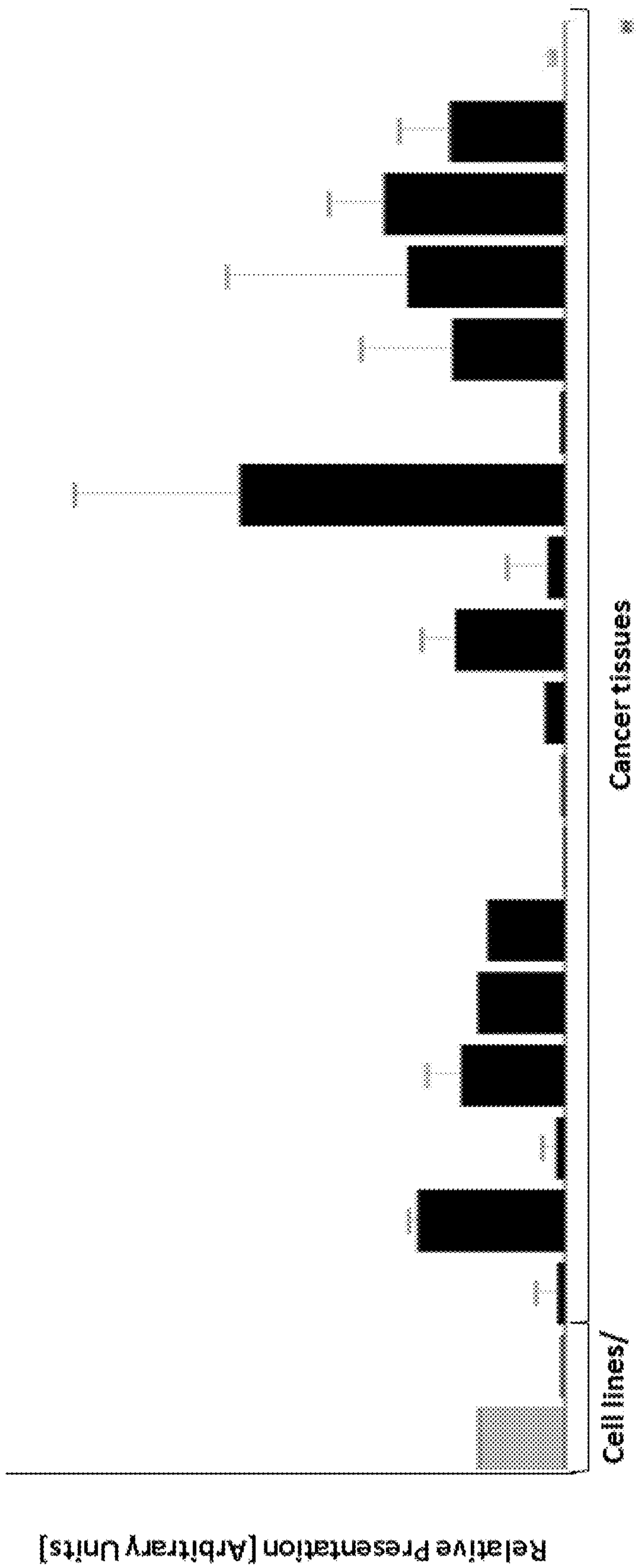



Peptide detected on
16 cancer tissues (10 leukocytic leukemia cancers, 6 lymph node cancers) (from left to right)

Figure 1P

Peptide: YIQEYLTLL (A*02)

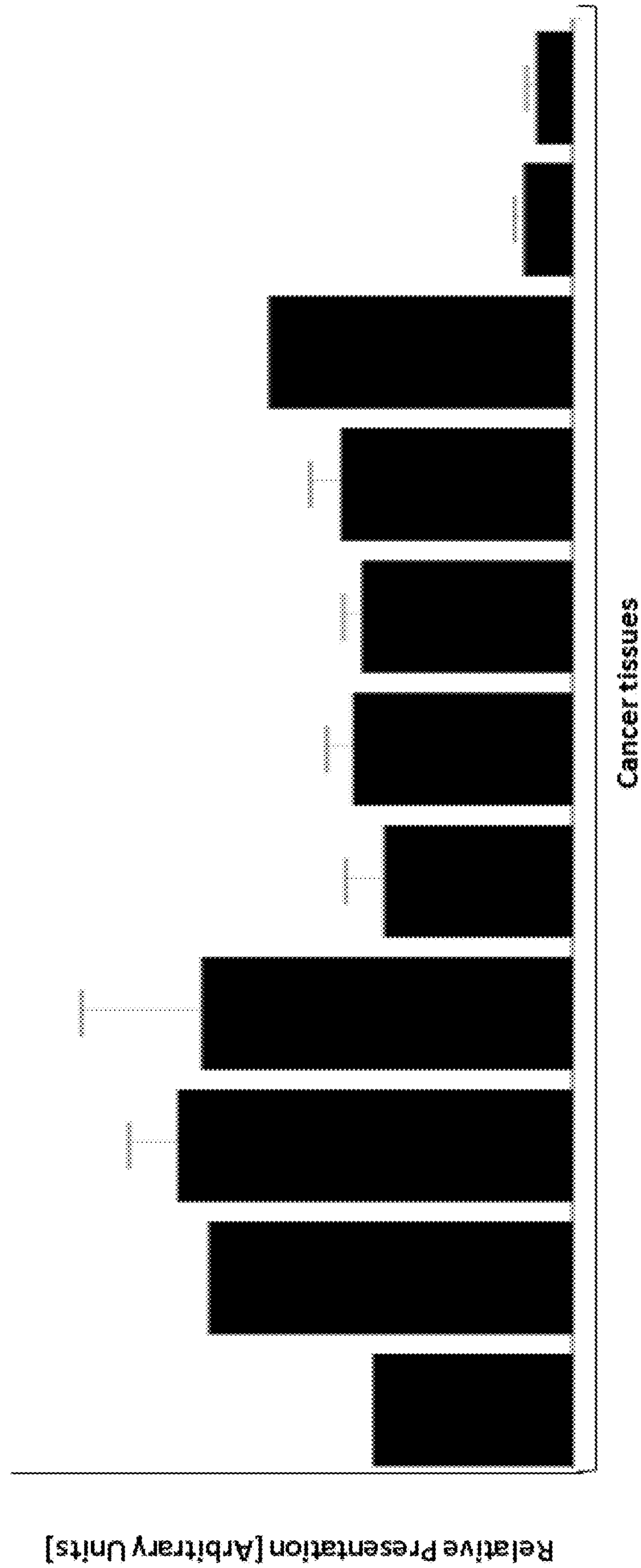
SEQ ID NO: 192




Peptide detected on

2 cell lines, 18 cancer tissues (1 colon cancer, 1 head and neck cancer, 1 kidney cancer, 4 leukocytic leukemia cancers, 5 lung cancers, 3 lymph node cancers, 1 myeloid cell cancer, 1 stomach cancer, 1 urinary bladder cancer) (from left to right)

Figure 1Q
Peptide: YLQEVPILTL (A*02)
SEQ ID NO: 197

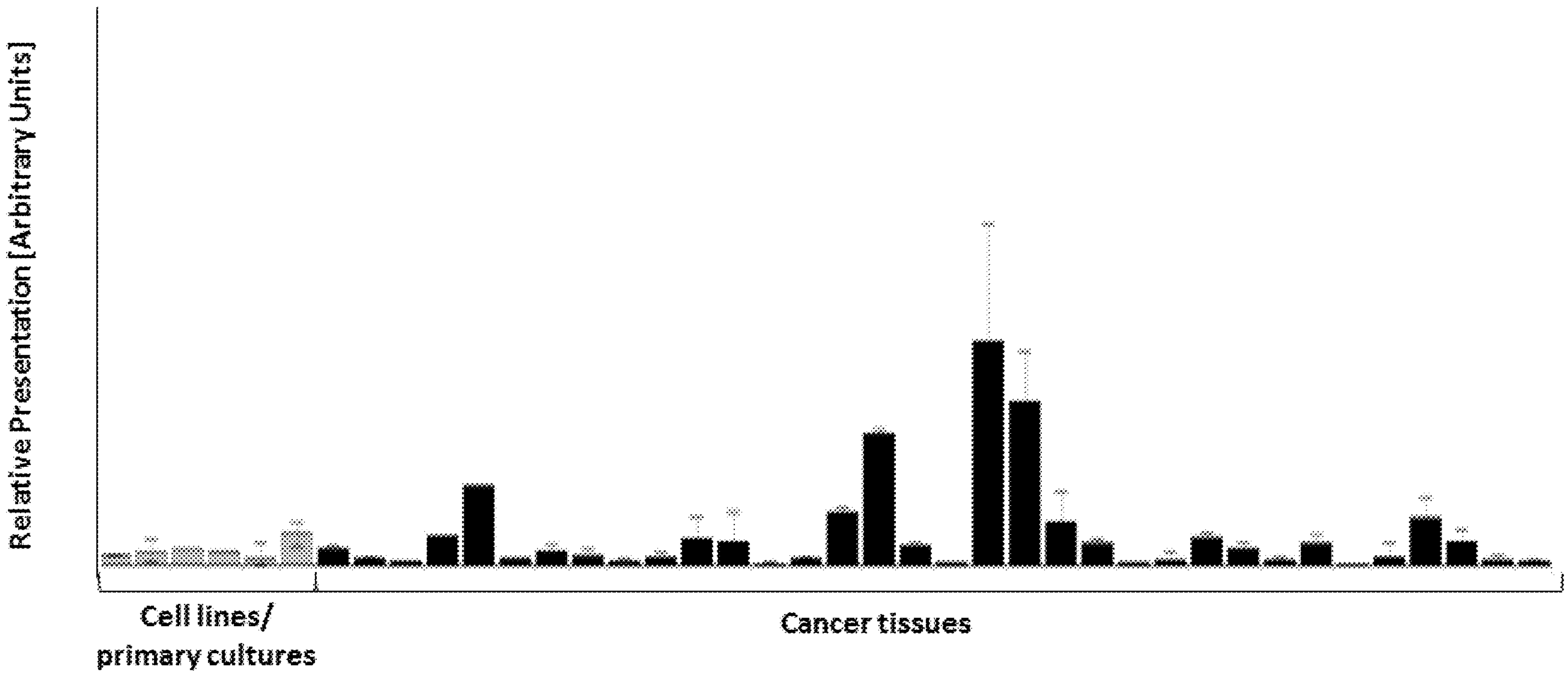



Peptide detected on
11 cancer tissues (5 leukocytic leukemia cancers, 4 lymph node cancers, 1 skin cancer, 1 uterus cancer) (from left to right)

Figure 1R

Peptide: YMFEEVPIVI (A*02)

SEQ ID NO: 200

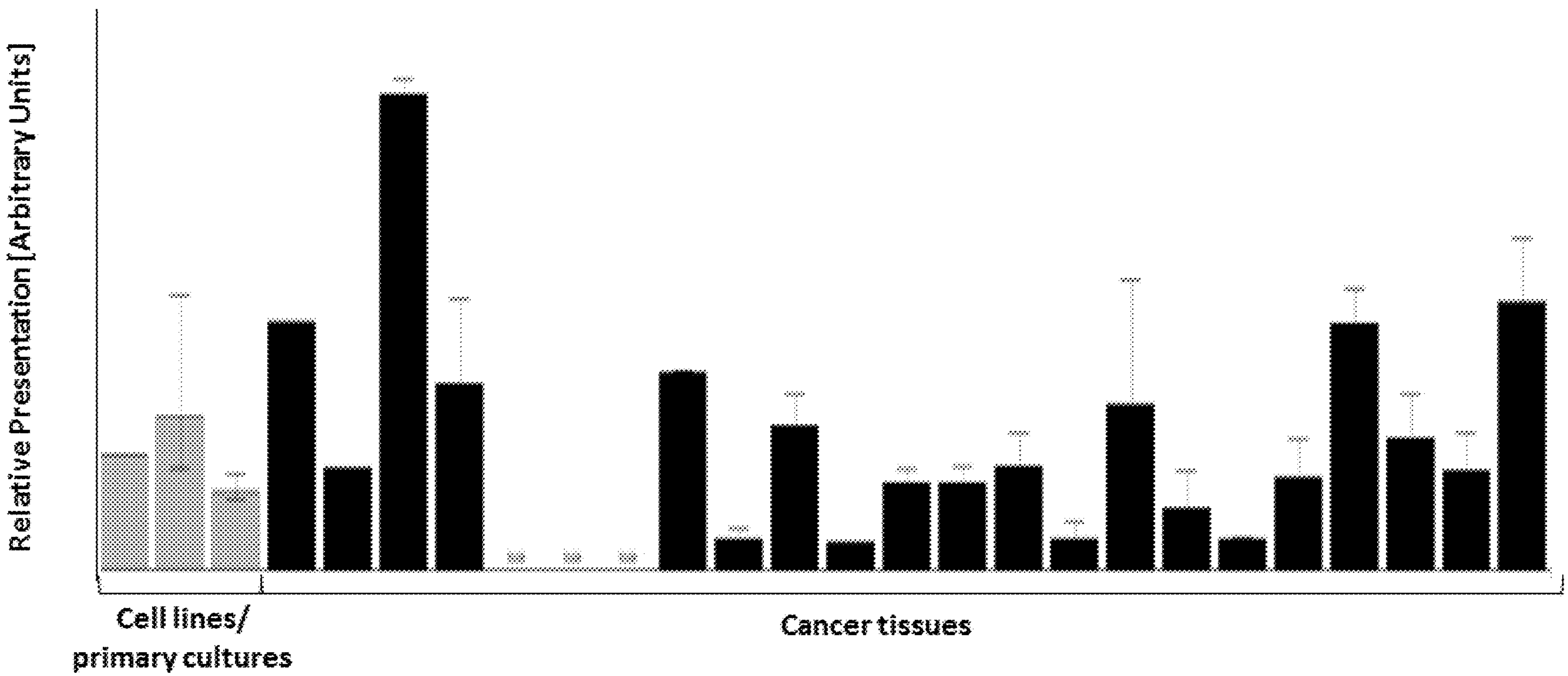



Peptide detected on
4 cell lines, 2 primary cultures, 34 cancer tissues (1 bile duct cancer, 2 breast cancers, 1 colon cancer, 1 esophageal cancer, 1 gallbladder cancer, 5 head and neck cancers, 2 leukocytic leukemia cancers, 2 liver cancers, 9 lung cancers, 4 lymph node cancers, 2 ovarian cancers, 1 rectum cancer, 2 skin cancers, 1 urinary bladder cancer) (from left to right)

Figure 1S

Peptide: LIDVKPLGV (A*02)

SEQ ID NO: 211




Peptide detected on

3 cell lines, 23 cancer tissues (5 brain cancers, 1 breast cancer, 1 esophageal cancer, 1 head and neck cancer, 1 kidney cancer, 3 leukocytic leukemia cancers, 2 liver cancers, 2 lung cancers, 4 lymph node cancers, 1 ovarian cancer, 1 prostate cancer, 1 skin cancer) (from left to right)

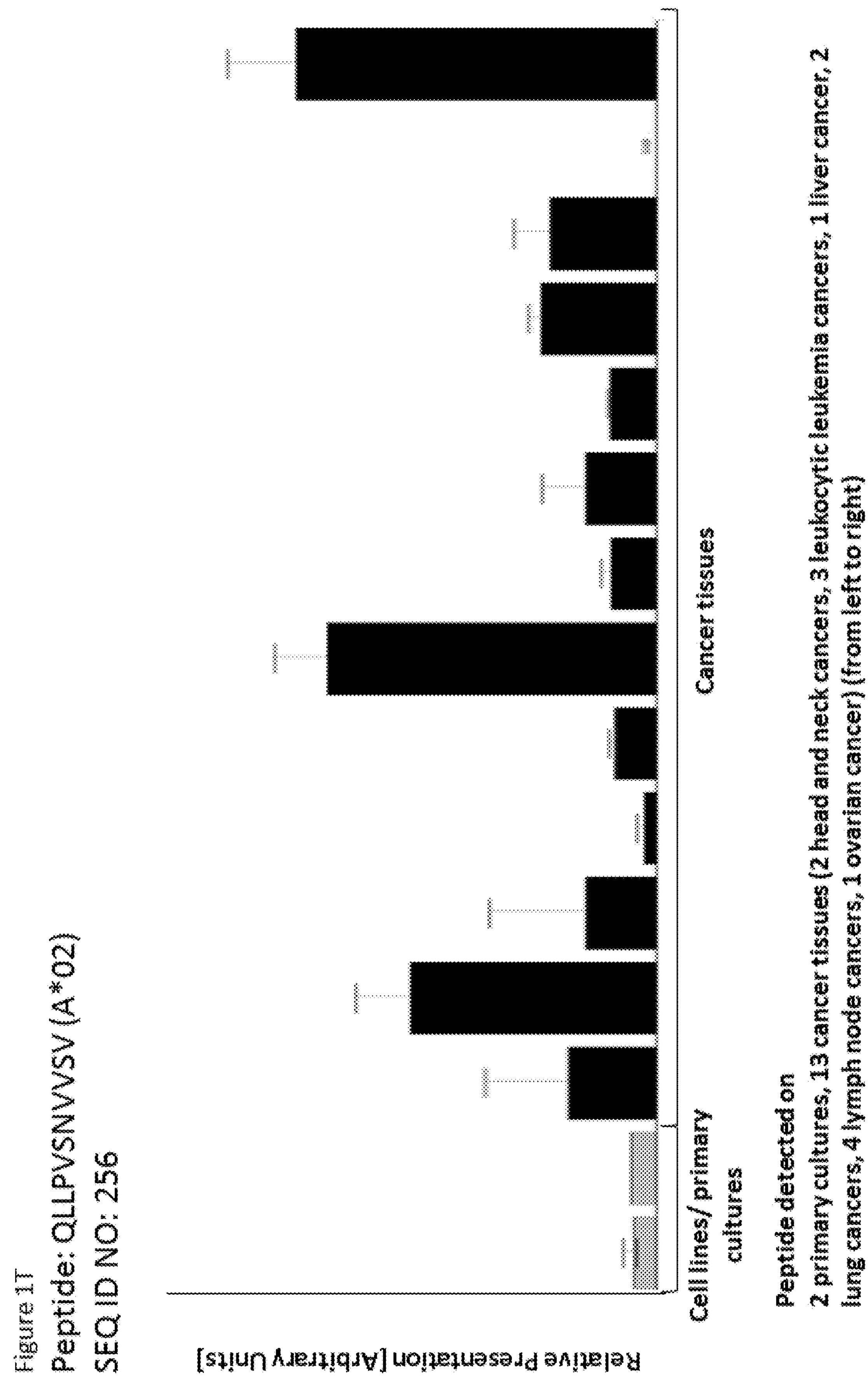
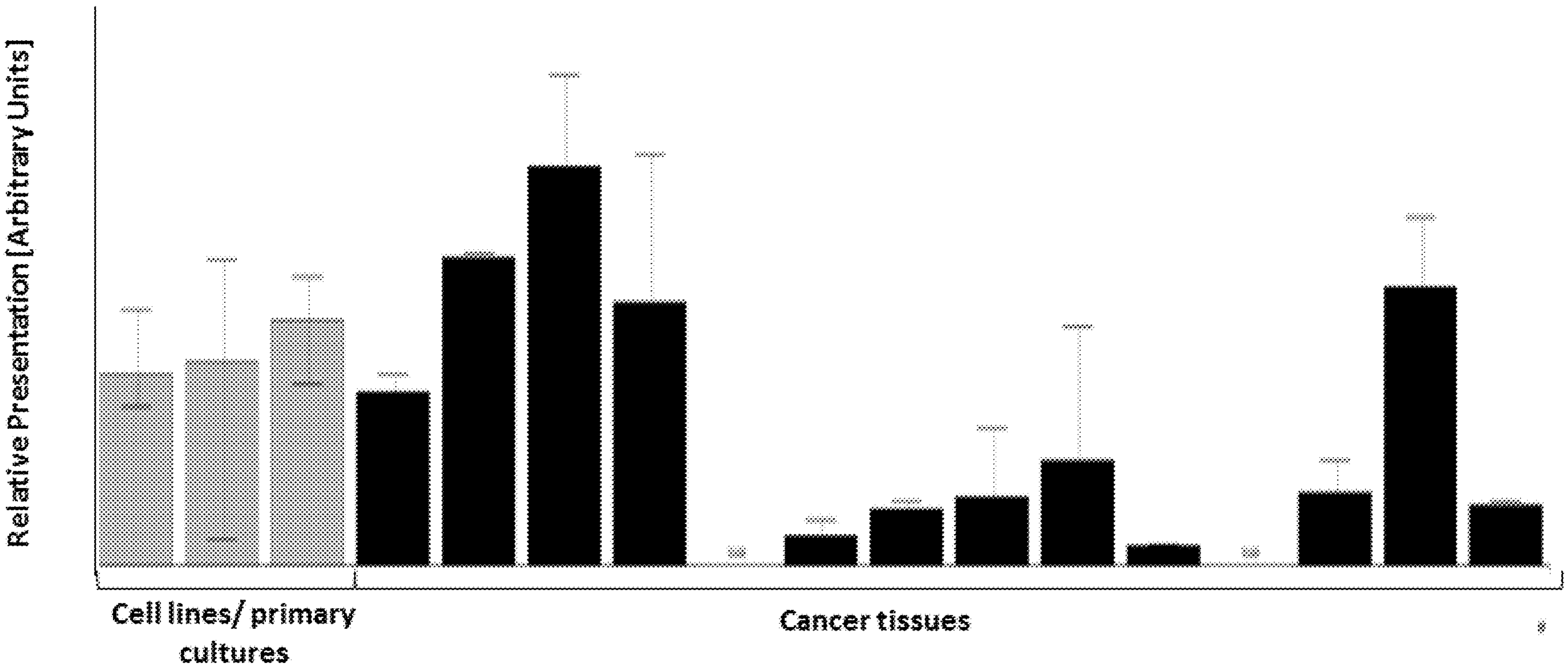


Figure 1T
Peptide: QLLPVSNVVSV (A*02)
SEQ ID NO: 256
Relative Presentation [Arbitrary Units]
Cell lines/ primary cultures
Cancer tissues
Peptide detected on
2 primary cultures, 13 cancer tissues (2 head and neck cancers, 3 leukocytic leukemia cancers, 1 liver cancer, 2 lung cancers, 4 lymph node cancers, 1 ovarian cancer) (from left to right)

Figure 1U

Peptide: LLYNSTDPTL (A*02)

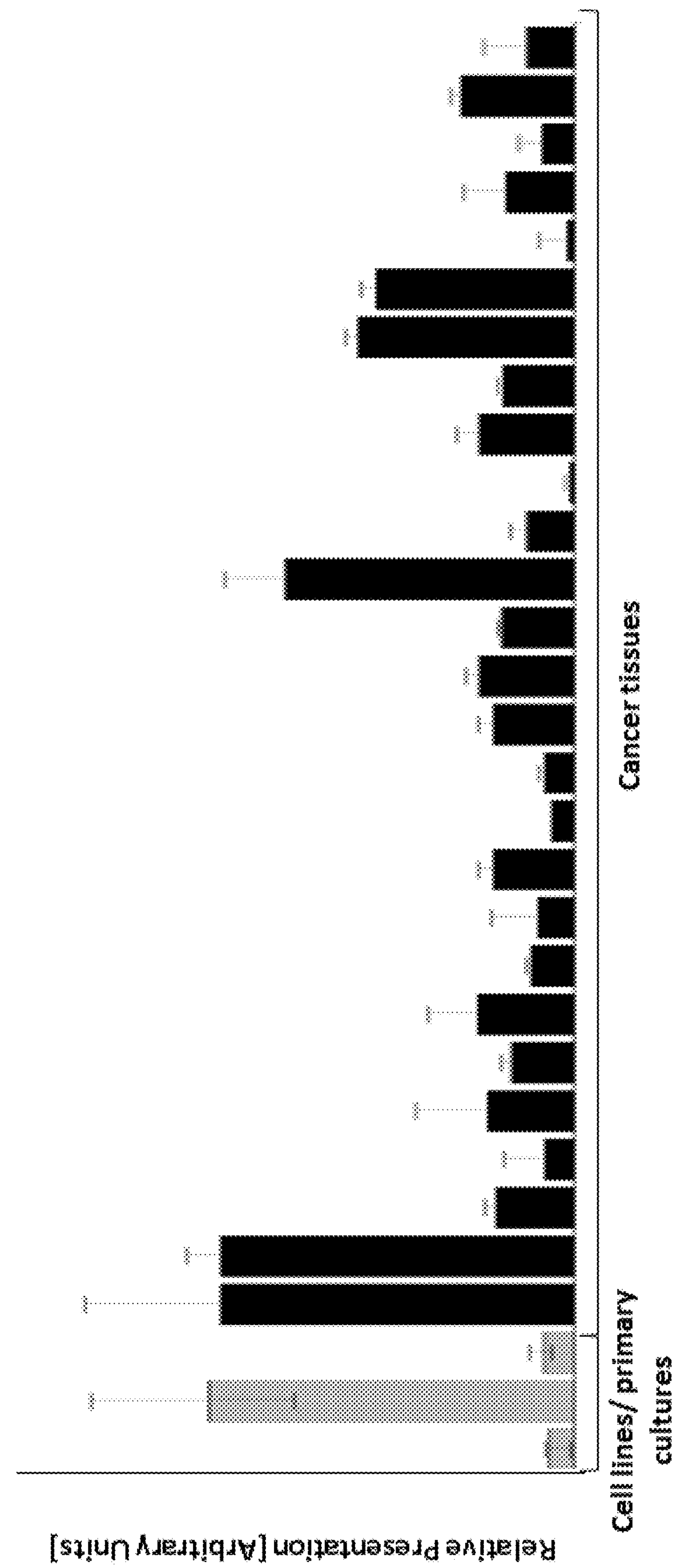
SEQ ID NO: 312




Peptide detected on

1 cell line, 2 primary cultures, 14 cancer tissues (1 colon cancer, 4 leukocytic leukemia cancers, 2 lung cancers, 5 lymph node cancers, 1 ovarian cancer, 1 urinary bladder cancer) (from left to right)

Figure 1V
Peptide: VLLPQETAEIHL (A*02)
SEQ ID NO: 328




Peptide detected on
3 primary cultures, 27 cancer tissues (1 breast cancer, 1 colon cancer, 5 leukocytic leukemia cancers, 5 lung cancers, 7 lymph node cancers, 2 ovarian cancers, 2 skin cancers, 1 stomach cancer, 3 urinary bladder cancers)
(from left to right)

Figure 2A

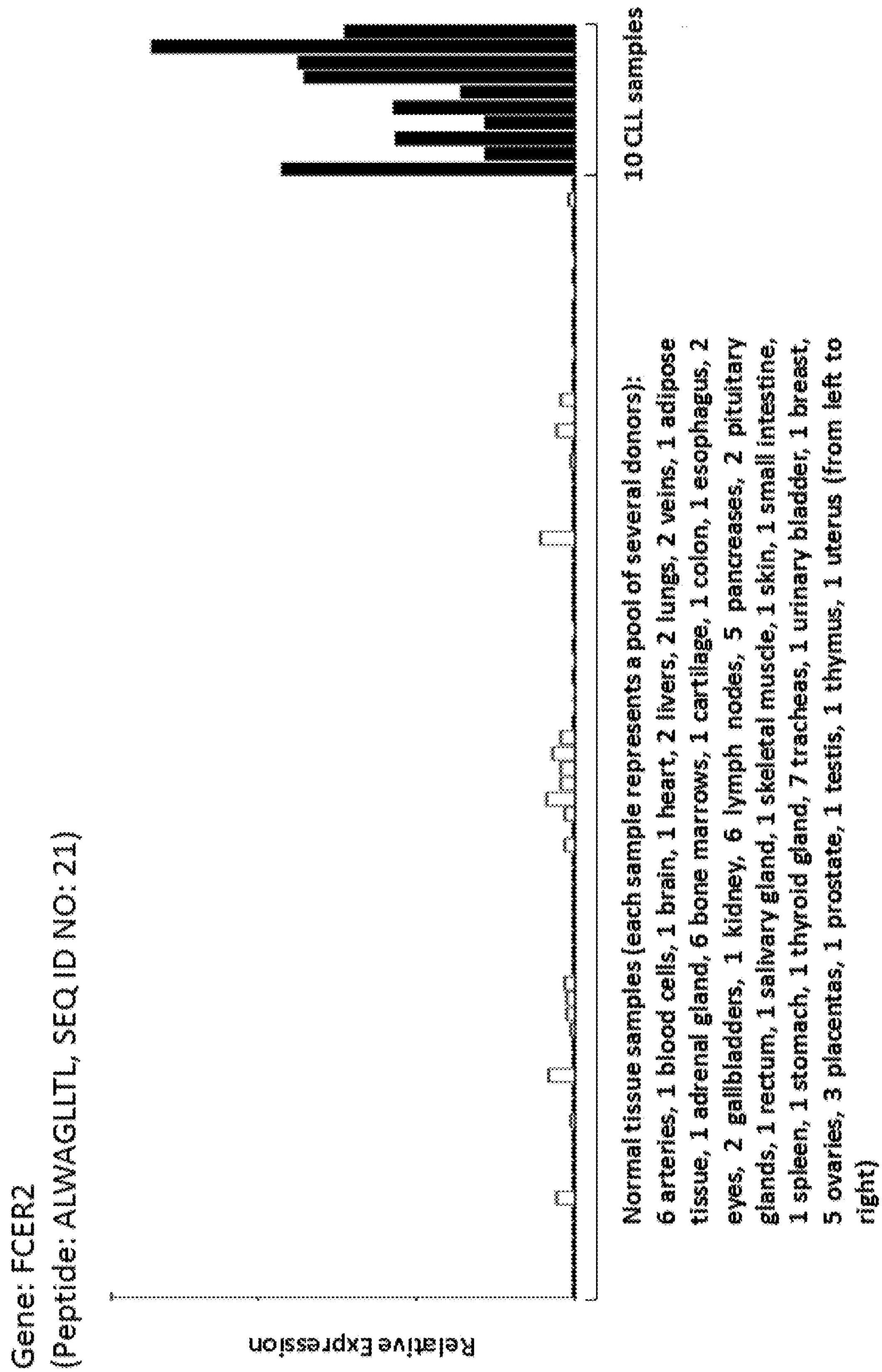
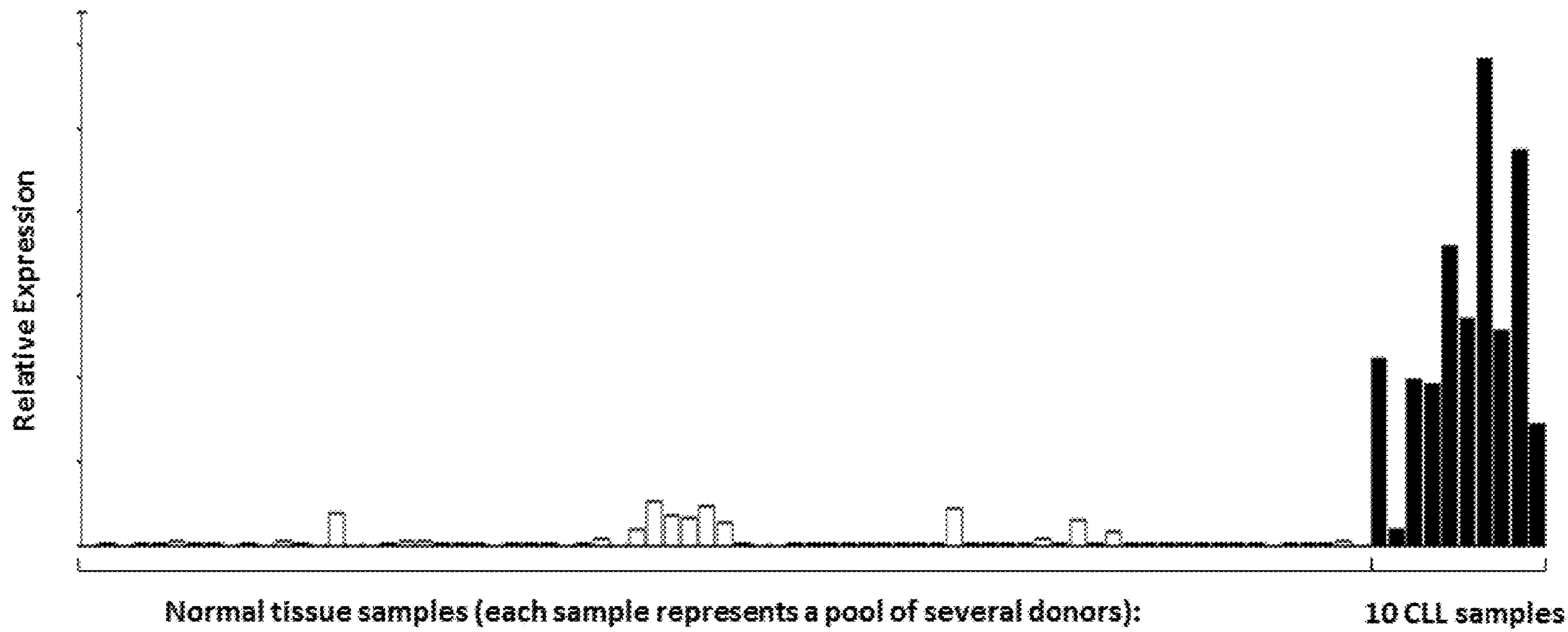

Gene: FCER2
(Peptide: ALWAGLLTL, SEQ ID NO: 21)
Relative Expression
10 CLL samples
Normal tissue samples (each sample represents a pool of several donors):
6 arteries, 1 blood cells, 1 brain, 1 heart, 2 livers, 2 lungs, 2 veins, 1 adipose tissue, 1 adrenal gland, 6 bone marrows, 1 cartilage, 1 colon, 1 esophagus, 2 eyes, 2 gallbladders, 1 kidney, 6 lymph nodes, 5 pancreases, 2 pituitary glands, 1 rectum, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 thyroid gland, 7 tracheas, 1 urinary bladder, 1 breast, 5 ovaries, 3 placentas, 1 prostate, 1 testis, 1 thymus, 1 uterus (from left to right)

Figure 2B

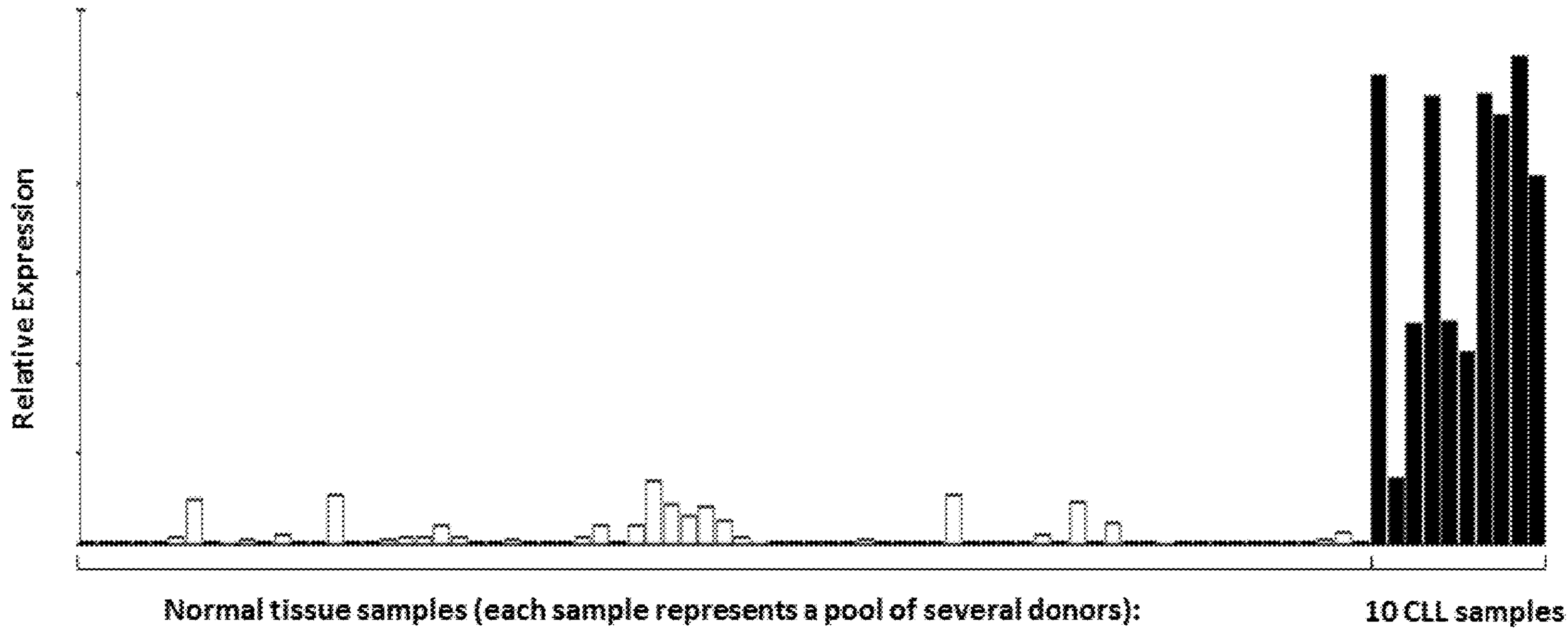
Gene: CLEC17A
(Peptide: GLKHDIARV, SEQ ID NO: 71)




Normal tissue samples (each sample represents a pool of several donors): 6 arteries, 1 blood cells, 1 brain, 1 heart, 2 livers, 2 lungs, 2 veins, 1 adipose tissue, 1 adrenal gland, 6 bone marrows, 1 cartilage, 1 colon, 1 esophagus, 2 eyes, 2 gallbladders, 1 kidney, 6 lymph nodes, 5 pancreases, 2 pituitary glands, 1 rectum, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 thyroid gland, 7 tracheas, 1 urinary bladder, 1 breast, 5 ovaries, 3 placentas, 1 prostate, 1 testis, 1 thymus, 1 uterus (from left to right)

Figure 2C

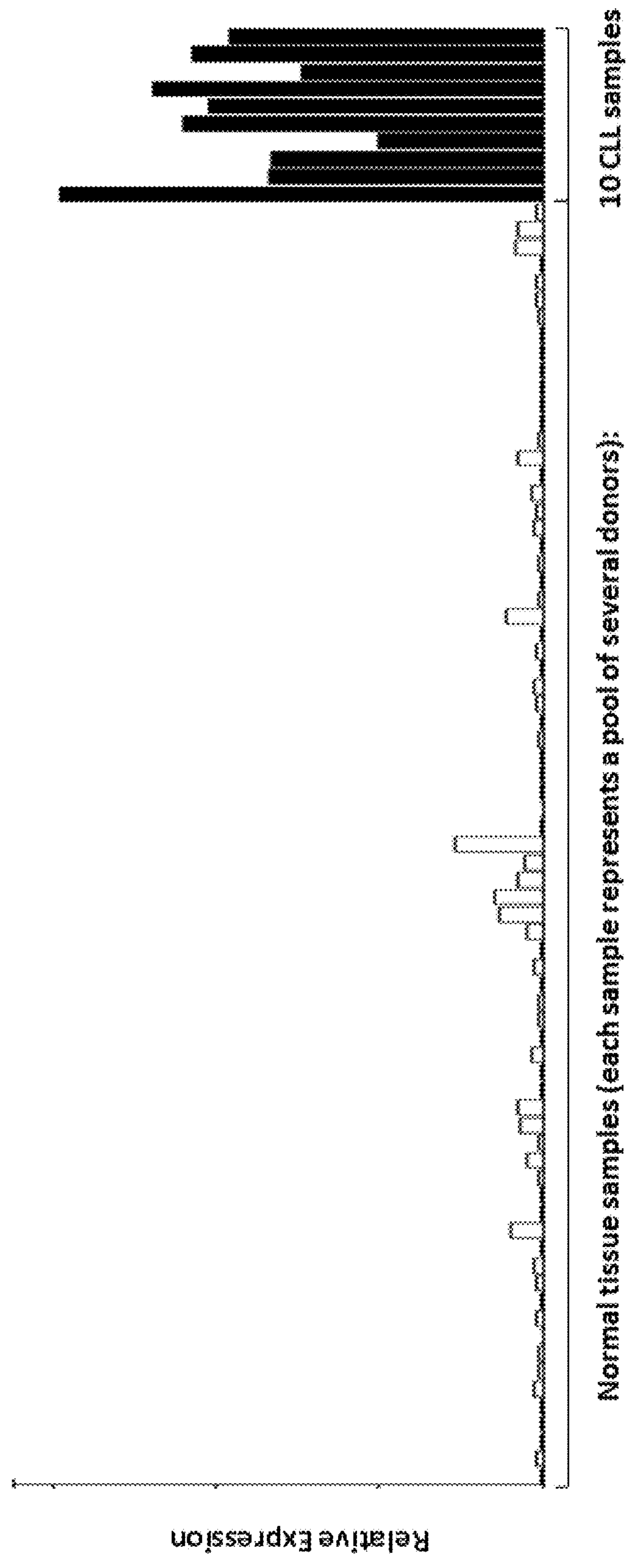
Gene: PAX5
(Peptide: GLDDMKANL, SEQ ID NO: 65)




Normal tissue samples (each sample represents a pool of several donors): 6 arteries, 1 blood cells, 1 brain, 1 heart, 2 livers, 2 lungs, 2 veins, 1 adipose tissue, 1 adrenal gland, 6 bone marrows, 1 cartilage, 1 colon, 1 esophagus, 2 eyes, 2 gallbladders, 1 kidney, 6 lymph nodes, 5 pancreases, 2 pituitary glands, 1 rectum, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 thyroid gland, 7 tracheas, 1 urinary bladder, 1 breast, 5 ovaries, 3 placentas, 1 prostate, 1 testis, 1 thymus, 1 uterus (from left to right)

Figure 2D

Gene: KIAA0226L
(Peptide: GIIDGSPRL, SEQ ID NO: 62)




Normal tissue samples (each sample represents a pool of several donors):
6 arteries, 1 blood cells, 1 brain, 1 heart, 2 livers, 2 lungs, 2 veins, 1 adipose tissue, 1 adrenal gland, 6 bone marrows, 1 cartilage, 1 colon, 1 esophagus, 2 eyes, 2 gallbladders, 1 kidney, 6 lymph nodes, 5 pancreases, 2 pituitary glands, 1 rectum, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 thyroid gland, 7 tracheas, 1 urinary bladder, 1 breast, 5 ovaries, 3 placentas, 1 prostate, 1 testis, 1 thymus, 1 uterus (from left to right)

FIGURE 3A

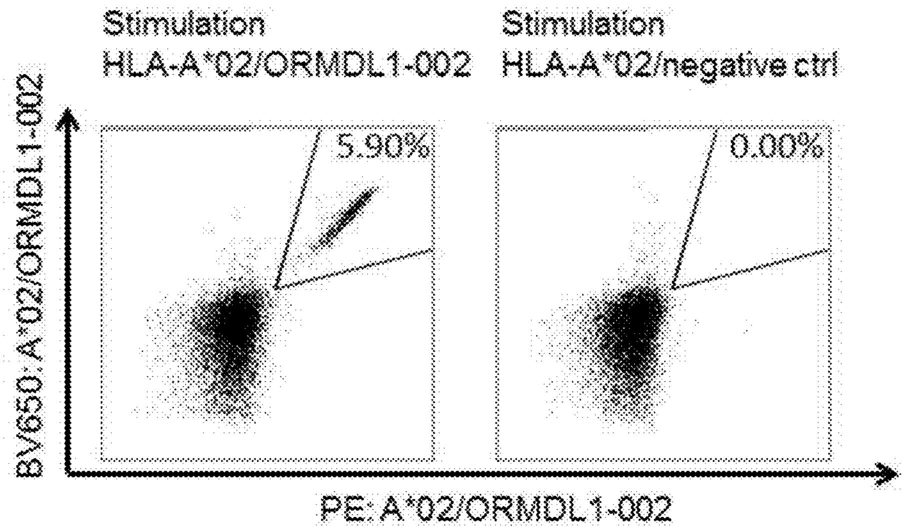



FIGURE 3B

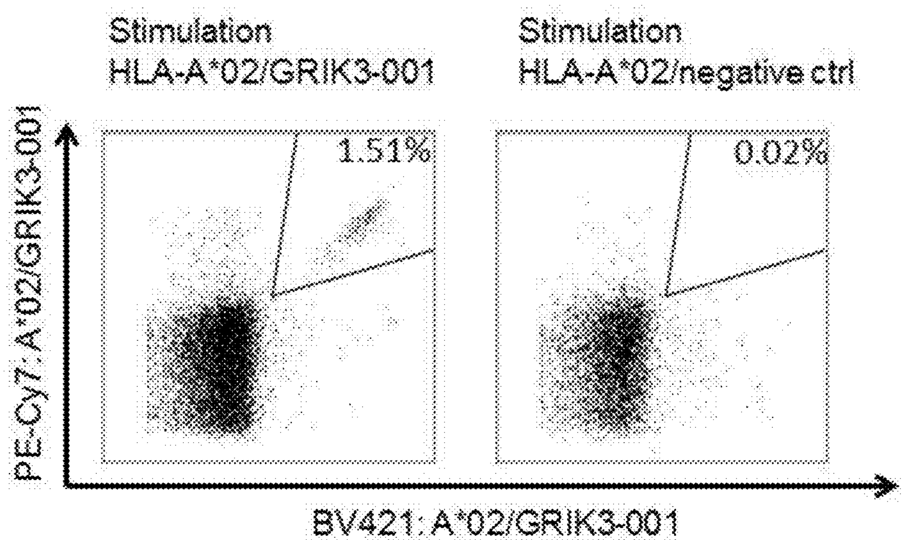


FIGURE 3 C

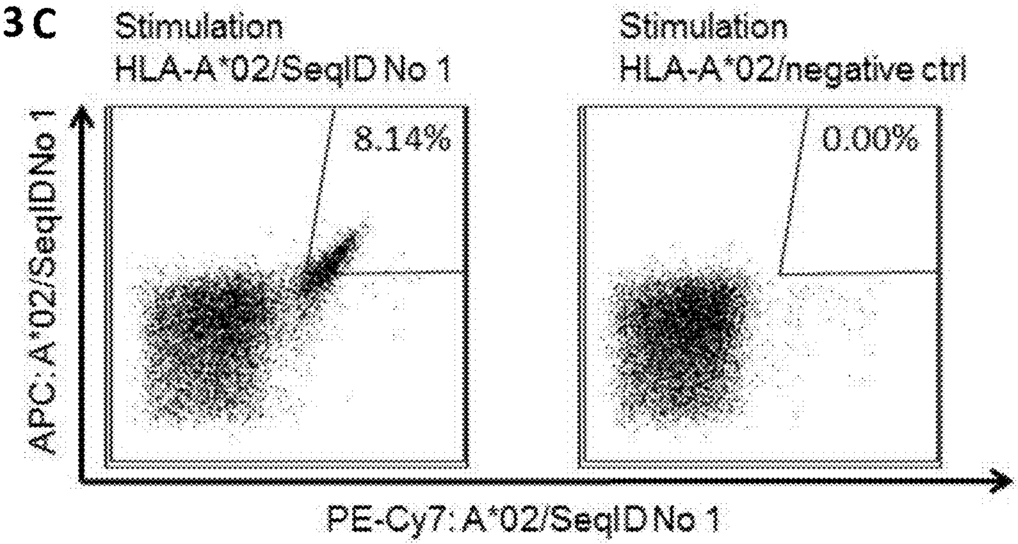



FIGURE 3D

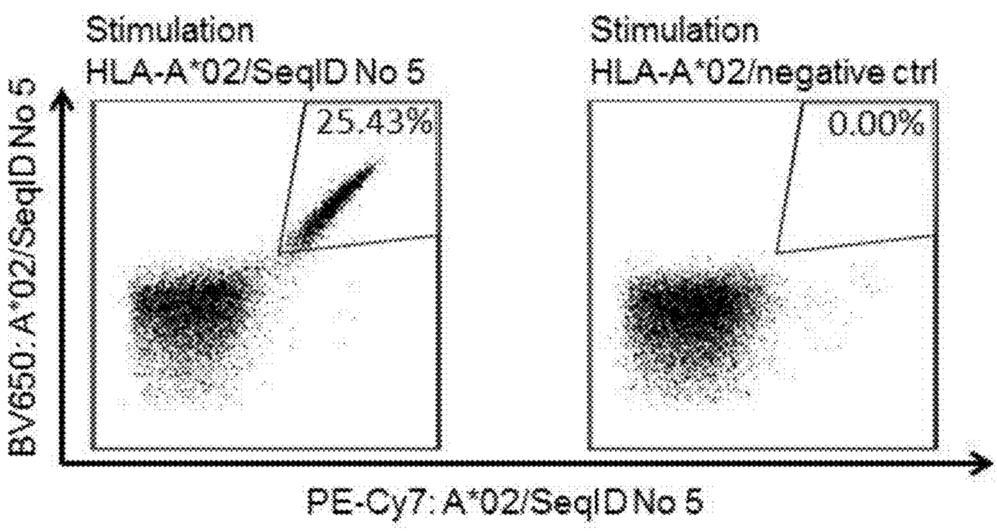


FIGURE 3E

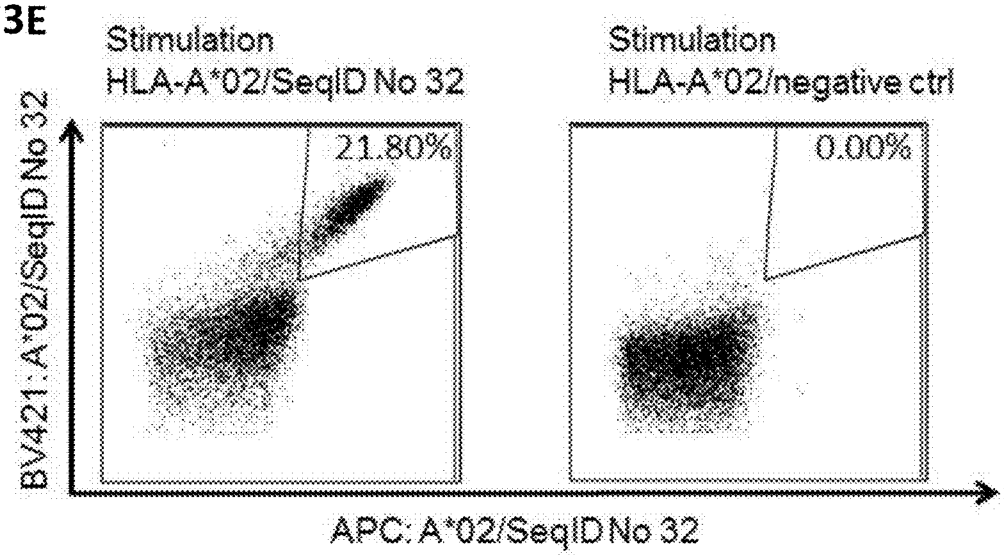
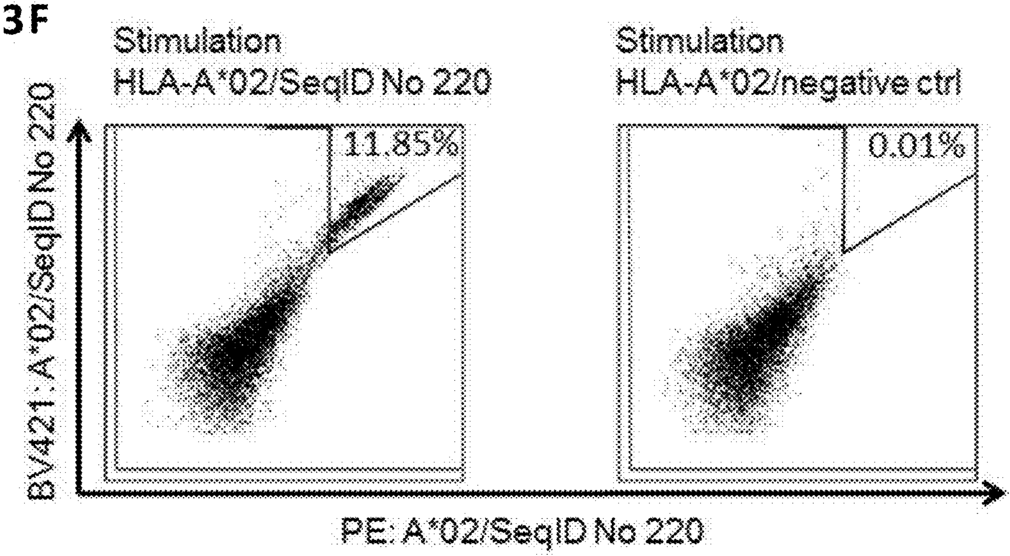



FIGURE 3F



# NOVEL PEPTIDES AND COMBINATION OF PEPTIDES FOR USE IN IMMUNOTHERAPY AGAINST CLL AND OTHER CANCERS

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application is a continuation of U.S. application Ser. No. 16/415,671, filed 17 May 2019, which is a continuation of U.S. application Ser. No. 15/375,070, filed 9 Dec. 2016, now U.S. Pat. No. 10,398,766, issued 3 Sep. 2019, which claims the benefit of U.S. Provisional Application Ser. No. 62/265,615, filed 10 Dec. 2015, and Great Britain Application No. 1521746.6, filed 10 Dec. 2015, the content of each of these applications is herein incorporated by reference in their entirety.

**[0002]** This application also is related to PCT/EP2016/078718 filed 24 Nov. 2016, the content of which is incorporated herein by reference in its entirety.

## REFERENCE TO SEQUENCE LISTING SUBMITTED AS A COMPLIANT ASCII TEXT FILE (.TXT)

**[0003]** Pursuant to the EFS-Web legal framework and 37 CFR §§ 1.821-825 (see MPEP § 2442.03(a)), a Sequence Listing in the form of an ASCII-compliant text file (entitled "2912919-058011_Sequence_Listing_ST25.txt" created on 21 Oct. 2019, and 82,332 bytes in size) is submitted concurrently with the instant application, and the entire contents of the Sequence Listing are incorporated herein by reference.

## FIELD

**[0004]** 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.

**[0005]** The present invention relates to several novel peptide sequences and their variants derived from HLA class I 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

**[0006]** Chronic lymphocytic leukemia (CLL) is a B-cell neoplasm with morphologically mature, immunologically not completely matured B lymphocytes. CLL is diagnosed when at least 5000 B lymphocytes/µl are present in peripheral blood, whereof up to 55% are immature. Abnormal B cells show a characteristic phenotype expressing CD19, dim CD20, dim CD5, CD23, CD79a and dim IgM or dim IgD (Gribben, 2010).

**[0007]** Two different staging systems are used to classify CLL: The Rai system and the Binet system. The Rai staging system comprises five stages (0-IV) that classify the disease according to the progressive accumulation of abnormal cells. The Binet system uses three stages (A, B, C) to rank the disease according to the number of involved sites (http://www.cancer.gov/cancertopics/pdq/treatment/CLL/Patient).

**[0008]** CLL is primarily a disease of the elderly. The mean age at diagnosis is 72 years for sporadic cases and 58 years for familial cases. The incidence of CLL is higher in males than in females, with a male:female ratio of about 2:1 (Cartwright et al., 2002).

**[0009]** CLL is the most common leukemia in the Western world where it comprises about ⅓rd of all leukemias. Incidence rates are similar in the US and Europe, and estimated new cases are about 16,000 per year. CLL is more common in Caucasians than in Africans, rarer in Hispanics and Native Americans and seldom in Asians. In people of Asian origin, CLL incidence rates are 3-fold lower than in Caucasians (Gunawardana et al., 2008).

**[0010]** The five-year overall survival for patients with CLL is about 79% (http://www.cancernet/cancer-types/leukernia-chronic-lymphocytic-cll/statistics). The prognosis for individual patients depends on the stage at the time of diagnosis and the occurrence of several prognostic factors. Following the Rai system, patients with stage 0 show a median survival of 10 years or more, while patients at stage I/II have a median survival of 7 years and patients at stage III/IV 0.75-4 years (Gribben, 2010). Several factors are associated with poor prognosis in CLL. These include high expression levels of ZAP-70 or CD38, an IgVH unmutated status and the cytogenetic aberrations del 17p or del 11q (Gribben, 2010).

**[0011]** While CLL is not curable at present, many patients show only slow progression of the disease or worsening of symptoms. As patients do not benefit from an early onset of treatment, the initial approach is "watch and wait" (Richards et al., 1999). For patients with symptomatic or rapidly progressing disease, several treatment options are available. These include chemotherapy, targeted therapy, immune-based therapies like monoclonal antibodies, CARs and active immunotherapy, and stern cell transplants.

**[0012]** Chemotherapeutic drugs used for CLL treatment are mostly alkylating agents like chlorambucil and cyclophosphamide or purine analogues like fludarabine. The German CLL Study Group (GCLLSG) CCL4 demonstrated that fludarabine/cyclophosphamide combinational therapy is superior to sole fludarabine treatment (complete remission (CR) of 24% vs.7%) (Eichhorst et al., 2006).

**[0013]** Ibrutinib and idelalisib are kinase inhibitors that target molecules in the B-cell receptor signaling cascade. Ibrutinib inhibits Bruton's tyrosine kinase (BTK), a src-related cytoplasmic tyrosine kinase important for B-cell maturation, and is used for initial or second-line therapy (Byrd et al., 2013; O'Brien et al., 2014). Idelalisib is a PI3K-delta inhibitor used in combination with rituximab in refractory CLL (Furman et al., 2014).

**[0014]** Hematopoietic stem cell transplants (HSCTs) can be considered for patients with poor prognosis, e.g. patients with del 17p or p53 mutations. HSCTs can either be allogeneic, where the transplanted cells are donated from an HLA-matched person, or autologous, where the patients' own stem cells are re-infused after chemotherapy (Schetelig et al., 2008).

[0015] Monoclonal antibodies are widely used in hematologic malignancies. This is due to the knowledge of suitable antigens based on the good characterization of immune cell surface molecules and the accessibility of tumor cells in blood or bone marrow. Common monoclonal antibodies used in CLL therapy target either CD20 or CD52. Rituximab, the first monoclonal anti-CD20 antibody originally approved by the FDA for treatment of NHLs, is now widely used in CLL therapy. Combinational treatment with rituximab/fludarabine/cyclophosphamide leads to higher CR rates and improved overall survival (OS) than the combination fludarabine/cyclophosphamide and has become the preferred treatment option (GCLLSG CLLR) (Hallek et al., 2008). Ofatumomab targets CD20 and is used for therapy of refractory CLL patients (Wierda et al., 2011). Obinutuzumab is another monoclonal anti-CD20 antibody used in first-line treatment in combination with chlorambucil (Goede et al., 2014).

[0016] Alemtuzumab is an anti-CD52 antibody used for treatment of patients with chemotherapy-resistant disease or patients with poor prognostic factors as del 17p or p53 mutations (Parikh et al., 2011). Novel monoclonal antibodies target CD37 (otlertuzumab, BI 836826, IMGN529 and (177)Lu-tetulomab) or CD40 (dacetuzumab and lucatumumab) and are tested in pre-clinical settings (Robak and Robak, 2014).

[0017] Several completed and ongoing trials are based on engineered autologous chimeric antigen receptor (CAR)-modified T cells with CD19 specificity (Maus et al., 2014). So far, only the minority of patients showed detectable or persistent CARs. One partial response (PR) and two complete responses (CR) have been detected in the CAR T-cell trials by Porter et al. and Kalos et al. (Kalos et al., 2011; Porter et al., 2011).

[0018] Active immunotherapy includes the following strategies: gene therapy, whole modified tumor cell vaccines, DC-based vaccines and TAA-derived peptide vaccines.

[0019] Approaches in gene therapy make use of autologous genetically modified tumor cells. These B-CLL cells are transfected with immuno-(co-)stimulatory genes like IL-2, IL-12, TNF-alpha, GM-CSF, CD80, CD40L, LFA-3 and ICAM-1 to improve antigen presentation and T cell activation (Carballido et al., 2012). While specific T-cell responses and reduction in tumor cells are readily observed, immune responses are only transient.

[0020] Several studies have used autologous DCs as antigen presenting cells to elicit anti-tumor responses. DCs have been loaded ex vivo with tumor associated peptides, whole tumor cell lysate, tumor-derived RNA or DNA. Another strategy uses whole tumor cells for fusion with DCs and generation of DC—B-CLL-cell hybrids. Transfected DCs initiated both CD4+ and CD8+ T-cell responses (Muller et al., 2004). Fusion hybrids and DCs loaded with tumor cell lysate or apoptotic bodies increased tumor-specific CD8+ T-cell responses. Patients that showed a clinical response had increased IL-12 serum levels and reduced numbers of Tregs (Palma et al., 2008).

[0021] Different approaches use altered tumor cells to initiate or increase CLL-specific immune responses. An example for this strategy is the generation of trioma cells: B-CLL cells are fused to anti-Fc receptor expressing hybridoma cells that have anti-APC specificity. Trioma cells induced CLL-specific T-cell responses in vitro (Kronenberger et al., 2008). Another strategy makes use of irradiated autologous CLL cells with *Bacillus* Calmette-Guérin as an adjuvant as a vaccine. Several patients showed a reduction in leukocyte levels or stable disease (Hus et al., 2008). Besides isolated CLL cells, whole blood from CLL patients has been used as a vaccine after preparation in a blood treatment unit. The vaccine elicited CLL-specific T-cell responses and led to partial clinical responses or stable disease in several patients (Spaner et al., 2005).

[0022] Several TAAs are overexpressed in CLL and are suitable for vaccinations. These include fibromodulin (Mayr et al., 2005), RHAMM/CD168 (Giannopoulos et al., 2006), MDM2 (Mayr et al., 2006), hTERT (Counter et al., 1995), the oncofetal antigen-immature laminin receptor protein (OFAiLRP) (Siegel et al., 2003), adipophilin (Schmidt et al., 2004), survivin (Granziero et al., 2001), KW1 to KW14 (Krackhardt et al., 2002) and the tumor-derived IgVHCDR3 region (Harig et al., 2001; Carballido et al., 2012).

[0023] A phase I clinical trial was conducted using the RHAMM-derived R3 peptide as a vaccine. 5 of 6 patients had detectable R3-specific CD8+ T-cell responses (Giannopoulos et al., 2010).

[0024] 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 CLL in particular. There is also a need to identify factors representing biomarkers for cancer in general and CLL in particular, leading to better diagnosis of cancer, assessment of prognosis, and prediction of treatment success.

[0025] 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.

[0026] The current classification of tumor associated antigens (TAAs) comprises the following major groups:

[0027] 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.

[0028] 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.

[0029] 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.

**[0030]** d) Tumor-specific antigens: These unique TAAs arise from mutations of normal genes (such as β-catenin, CDK4, etc.). Some of these molecular changes are associated with neoplastic transformation and/or progression. Tumor-specific antigens are generally able to induce strong immune responses without bearing the risk for autoimmune reactions against normal tissues. On the other hand, these TAAs are in most cases only relevant to the exact tumor on which they were identified and are usually not shared between many individual tumors. Tumor-specificity (or -association) of a peptide may also arise if the peptide originates from a tumor-(-associated) exon in case of proteins with tumor-specific (-associated) isoforms.

**[0031]** 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.

**[0032]** 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.

**[0033]** 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.

**[0034]** 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.

**[0035]** MHC class I molecules can be found on most nucleated cells. They present peptides that result from proteolytic cleavage of predominantly endogenous proteins, defective ribosomal products (DRIPs) and larger peptides. 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.

**[0036]** 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.

**[0037]** 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).

**[0038]** 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).

**[0039]** Elongated (longer) peptides of the invention can act as MHC class II active epitopes.

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

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

**[0042]** 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).

**[0043]** 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.

**[0044]** For an MHC class I peptide to trigger (elicit) a cellular immune response, it also must bind to an MHC-molecule. This process is dependent on the allele of the MHC-molecule and specific polymorphisms of the amino acid sequence of the peptide. MHC-class-I-binding peptides are usually 8-12 amino acid residues in length and usually contain two conserved residues ("anchors") in their sequence that interact with the corresponding binding groove of the MHC-molecule. In this way, each MHC allele has a "binding motif" determining which peptides can bind specifically to the binding groove.

**[0045]** 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).

**[0046]** 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 und thus may be indirectly tumor-associated. Such indirect tumor-associated antigens may also be targets of a vaccination approach (Singh-Jasuja et al., 2004). It is essential that epitopes are present in the amino acid sequence of the antigen, in order to ensure that such a peptide ("immunogenic peptide"), being derived from a tumor associated antigen, leads to an in vitro or in vivo T-cell-response.

**[0047]** 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.

**[0048]** 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.

**[0049]** 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.

**[0050]** 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").

**[0051]** 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

**[0052]** 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: 385 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: 385, 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.

**[0053]** 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: 385 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: 385, 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.

**[0054]** 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. All peptides in Table 1 and Table 2 bind to HLA-A*02. The peptides in Table 2 have been disclosed before in large listings as results of high-throughput screenings with high error rates or calculated using algorithms, but have not been associated with cancer at all before. The peptides in Table 3 are additional peptides that may be useful in combination with the other peptides of the invention. The peptides in Table 4 are furthermore useful in the diagnosis and/or treatment of various other malignancies that involve an over-expression or over-presentation of the respective underlying polypeptide.

TABLE 1

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 1 | AIPPSFASIFL | 3507 | IGHM |
| 2 | ALHRPDVYL | 3507 | IGHM |
| 3 | VIAELPPKV | 3507 | IGHM |
| 4 | VIAELPPKVSV | 3507 | IGHM |
| 5 | ALIFKIASA | 4214 | MAP3K1 |
| 6 | ALDTLEDDMTI | 2222 | FDFT1 |
| 7 | ALLERTGYTL | 10236, 10492 | HNRNPR, SYNCRIP |
| 8 | ALAASALPALV | 6124 | RPL4 |
| 9 | ALCDTLITV | 27033 | ZBTB32 |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 10 | FVYGESVEL | 27033 | ZBTB32 |
| 11 | ALFTFJPLTV | 54665 | RSBN1 |
| 12 | ALGEDEITL | 25909, 285116 | AHCTF1, AHCTF1P1 |
| 13 | VVDGMPPGV | 2969, 2970 | GTF2I, GTF2IP1 |
| 14 | ALLRLLPGL | 25920 | COBRA1 |
| 15 | ALPEVSVEA | 79649 | MAP7D3 |
| 16 | ALPGGAAVAAV | 79697 | C14orf169 |
| 17 | ALTKTNLQL | 9750 | FAM65B |
| 18 | LLGEFSIKM | 9750 | FAM65B |
| 19 | QVMEKLAAV | 9750 | FAM65B |
| 20 | ALVDPGPDFVV | 546 | ATRX |
| 21 | ALWAGLLTL | 2208 | FCER2 |
| 22 | ALWDPVIEL | 27340 | UTP20 |
| 23 | ALYLTEVFL | 55024 | BANK1 |
| 24 | AMAGDVVYA | 160365 | CLECL1 |
| 25 | ATYSGLESQSV | 3185 | HNRNPF |
| 26 | AVLLVLPLV | 11322 | TMC6 |
| 27 | AVLGLVWLL | 11322 | TMC6 |
| 28 | AVLHLLLSV | 1535 | CYBA |
| 29 | AVLQAVTAV | 58155 | PTBP2 |
| 30 | ELLEGSEIYL | 147007, 23098 | TMEM199, SARM1 |
| 31 | ELMHGVAGV | 165631 | PARP15 |
| 32 | FIDKFTPPV | 3117, 3122 | HLA-DQA1, HLA-DRA |
| 33 | FIINSSNIFL | 253959 | RALGAPA1 |
| 34 | YLPYIFPNI | 253959 | RALGAPA1 |
| 35 | FILPSSLYL | 81539 | SLC38A1 |
| 36 | FILTHVDQL | 257106 | ARHGAP30 |
| 37 | FIMEGGAMVL | 4174 | MCM5 |
| 38 | FIMEGGAMV | 4174 | MCM5 |
| 39 | FLDALLTDV | 79915 | ATAD5 |
| 40 | FLDEDDMSL | 23141 | ANKLE2 |
| 41 | FLDPSLDPLL | 58508, 85318 | MLL3, BAGE3 |
| 42 | FLEEGGVVTV | 5810 | RAD1 |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 43 | FLLGPEALSFA | 55183 | RIF1 |
| 44 | FLLSINDFL | 157680 | VPS13B |
| 45 | FLPELPADLEA | 11064 | CNTRL |
| 46 | YIIDSAQAV | 11064 | CNTRL |
| 47 | FLSDQPEPYL | 160518, 23258 | DENND5B, DENND5A |
| 48 | FLSPQQPPLL | 8621 | CDK13 |
| 49 | FLTDLFAQL | 55671 | SMEK1 |
| 50 | FLFEPVVKAFL | 55671 | SMEK1 |
| 51 | FLVEAPHDWDL | 9790 | BMS1 |
| 52 | FLVETGFLHV | 100268168, 114987, 4602 | WDR31, MYB |
| 53 | FLWQHVELVL | 55181 | SMG8 |
| 54 | FLYPFPLALF | 440026 | TMEM41B |
| 55 | FMEPTLLML | 23 | ABCF1 |
| 56 | FVFEAPYTL | 139818 | DOCK11 |
| 57 | GLSEISLRL | 139818 | DOCK11 |
| 58 | YIQQGIFSV | 139818 | DOCK11 |
| 59 | FVFGDENGTVSL | 79084 | WDR77 |
| 60 | FVLDHEDGLNL | 4926 | NUMA1 |
| 61 | FVYFIVREV | 285527 | FRYL |
| 62 | GIIDGSPRL | 80183 | KIAA0226L |
| 63 | SLAHVAGCEL | 80183 | KIAA0226L |
| 64 | KLLESVASA | 80183 | KIAA0226L |
| 65 | GLDDMKANL | 5079 | PAX5 |
| 66 | SLAGGLDDMKA | 5079 | PAX5 |
| 67 | GLDDVTVEV | 51019 | CCDC53 |
| 68 | GLDQQFAGLDL | 1654 | DDX3X |
| 69 | GLHQREIFL | 9922 | IQSEC1 |
| 70 | FVPDTPVGV | 9922 | IQSEC1 |
| 71 | GLKHDIARV | 388512 | CLEC17A |
| 72 | GLLDAGKMYV | 911 | CD1C |
| 73 | GLLEVISALQL | 9816 | URB2 |
| 74 | GLLRASFLL | 11344, 54106 | TWF2, TLR9 |
| 75 | GLSIFAQDLRL | 11344, 54106 | TWF2, TLR9 |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 76 | GLLRIIPYL | 23352 | UBR4 |
| 77 | GLLRLTWFL | 11214 | AKAP13 |
| 78 | GLPSFLTEV | 100532732, 4439 | MSH5-SAPCD1, MSH5 |
| 79 | GLQAKIQEA | 23224 | SYNE2 |
| 80 | VLIEDELEEL | 23224 | SYNE2 |
| 81 | WLVGQEFEL | 23224 | SYNE2 |
| 82 | GLQSGVDIGV | 1265 | CNN2 |
| 83 | GQGEVLVYV | 2316 | FLNA |
| 84 | GVMDVNTAL | 391370, 6206 | RPS12P4, RPS12 |
| 85 | HLMLHTAAL | 80012 | PHC3 |
| 86 | HLYPGAVTI | 55103 | RALGPS2 |
| 87 | HQIEAVDGEEL | 10567 | RABAC1 |
| 88 | ILDEIGADVQA | 29920 | PYCR2 |
| 89 | ILDFGTFQL | 54832 | VPS13C |
| 90 | VIADLGLIRV | 54832 | VPS13C |
| 91 | ILDLNTYNV | 5336 | PLCG2 |
| 92 | ILEPLNPLL | 9330 | GTF3C3 |
| 93 | ILFNTQINI | 64801 | ARV1 |
| 94 | ILFPLRFTL | 9675 | TTI1 |
| 95 | ILGYMAHEHKV | 6530 | SLC6A2 |
| 96 | ILIDKTSFV | 951 | CD37 |
| 97 | LLFATQITL | 951 | CD37 |
| 98 | SLIKYFLFV | 951 | CD37 |
| 99 | ILIFHSVAL | 84636 | GPR174 |
| 100 | ILNNEVFAI | 26999 | CYFIP2 |
| 101 | ILVVIEPLL | 23451 | SF3B1 |
| 102 | IQDRAVPSL | 3930 | LBR |
| 103 | KLGGTPAPA | 5218 | CDK14 |
| 104 | KLILLDTPLFL | 253190, 94009 | SERHL2, SERHL |
| 105 | KLMNDIADI | 472 | ATM |
| 106 | FMASHLDYL | 472 | ATM |
| 107 | ILYNLYDLL | 472 | ATM |
| 108 | VIYTLIHYI | 472 | ATM |
| 109 | KLWEGLTELV | 10235 | RASGRP2 |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 110 | LLFDHLEPMEL | 10235 | RASGRP2 |
| 111 | KLWNVAAPLYL | 92105 | INTS4 |
| 112 | KTLDVDATYEI | 3978 | LIG1 |
| 113 | KVPAEEVLVAV | 91782 | CHMP7 |
| 114 | LIPEGPPQV | 64224 | HERPUD2 |
| 115 | LLFDKLYLL | 25885 | POLR1A |
| 116 | LLIGATMQV | 23225 | NUP210 |
| 117 | LLILENILL | 23225 | NUP210 |
| 118 | RLLILENILL | 23225 | NUP210 |
| 119 | VLPAEFFEV | 23225 | NUP210 |
| 120 | AIDAALTSV | 23225 | NUP210 |
| 121 | RLYEITIEV | 23225 | NUP210 |
| 122 | LLIPVVPGV | 55178 | RNMTL1 |
| 123 | LLLAEAELLTL | 57724 | EPG5 |
| 124 | LLLEETEKQAV | 92154, 9788 | MTSS1L, MTSS1 |
| 125 | LLLEIGEVGKLFV | 23158 | TBC1D9 |
| 126 | LLPEGGITAI | 9904 | RBM19 |
| 127 | LLPTAPTTV | 55729 | ATF7IP |
| 128 | LLSEEEYHL | 9793 | CKAP5 |
| 129 | LLVGTLDVV | 23061, 23158 | TBC1D9B, TBC1D9 |
| 130 | LLVLIPVYL | 23344 | ESYT1 |
| 131 | LQALEVLKI | 27304 | MOCS3 |
| 132 | LVYEAIIMV | 27250 | PDCD4 |
| 133 | YLLSGDISEA | 27250 | PDCD4 |
| 134 | MLLEHGITLV | 200576 | PIKFYVE |
| 135 | MTAGFSTIAGSV | 64078 | SLC28A3 |
| 136 | NLDKLWTLV | 389435, 6157 | RPL27AP6, RPL27A |
| 137 | NLIKTVIKL | 25816 | TNFAIP8 |
| 138 | NLLDIDAPVTV | 5530 | PPP3CA |
| 139 | NLTDVVEKL | 120892 | LRRK2 |
| 140 | QIAELPATSV | 401145 | CCSER1 |
| 141 | QILSEIVEA | 10724 | MGEA5 |
| 142 | QLDEPAPQV | 387032, 80317 | ZKSCAN4, ZKSCAN3 |
| 143 | QLLDTYFTL | 7405 | UVRAG |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 144 | QLPPFPREL | 8498 | RANBP3 |
| 145 | SALDTITTV | 3832 | KIF11 |
| 146 | SIIEGPIIKL | 23347 | SMCHD1 |
| 147 | SILETVATL | 253714 | MMS22L |
| 148 | SIVASLITV | 221188 | GPR114 |
| 149 | SLDNGGYYI | 4067 | LYN |
| 150 | SLFDQPLSII | 117289 | TAGAP |
| 151 | SLFDSAYGA | 2313 | FLI1 |
| 152 | SLIRILQTI | 160518 | DENND5B |
| 153 | SLLAELHVL | 115352 | FCRL3 |
| 154 | SLLAELHVLTV | 115352 | FCRL3 |
| 155 | SLMLEVPAL | 1756 | DMD |
| 156 | SLNIGDVQL | 973 | CD79A |
| 157 | SLNIRDFTM | 147694, 7565 | ZNF548, ZNF17 |
| 158 | SLPEAPLDV | 29123 | ANKRD11 |
| 159 | SLQEEKLIYV | 84668 | FAM126A |
| 160 | SLSFLVPSL | 9631 | NUP155 |
| 161 | SMDDGMINV | 7011 | TEP1 |
| 162 | SMKDDLENV | 3688 | ITGB1 |
| 163 | SQLDISEPYKV | 3394 | IRF8 |
| 164 | SVHKGFAFV | 101060301, 3183, 343069, 440563, 649330 | HNRNPC, HNRNPCL1 |
| 165 | TLDDDLDTV | 51092 | SIDT2 |
| 166 | TLDPNQVSL | 85464 | SSH2 |
| 167 | TLDTSKLYV | 5923 | RASGRF1 |
| 168 | YLLDQSFVM | 5923 | RASGRF1 |
| 169 | TLLLGLTEV | 55423 | SIRPG |
| 170 | TLTFRVETV | 51379 | CRLF3 |
| 171 | TLVPPAALISI | 6907 | TBL1X |
| 172 | TLYDMLASI | 10973 | ASCC3 |
| 173 | TVIENIHTI | 23358 | USP24 |
| 174 | VLAELPIIVV | 8295 | TRRAP |
| 175 | FTVPRVVAV | 8295 | TRRAP |
| 176 | VLAEQNIIPSA | 54855 | FAM46C |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 177 | VLDDRELLL | 23178 | PASK |
| 178 | VLFFNVQEV | 57536 | KIAA1328 |
| 179 | VLLGLEMTL | 1606 | DGKA |
| 180 | LLKDGPEIGL | 1606 | DGKA |
| 181 | VLLSIPFVSV | 94103 | ORMDL3 |
| 182 | VLLSVPGPPV | 2264 | FGFR4 |
| 183 | VLMPTVYQQGV | 54472 | TOLLIP |
| 184 | VLSHNLYTV | 50619 | DEF6 |
| 185 | VMDDQRDLI | 972 | CD74 |
| 186 | VMDPTKILI | 255967 | PAN3 |
| 187 | VMDTHLVNI | 9779 | TBC1D5 |
| 188 | VMGDIPAAV | 4678 | NASP |
| 189 | VMLEMTPEL | 3112, 6891 | HLA-DOB, TAP2 |
| 190 | VVMGTVPRL | 1729 | DIAPH1 |
| 191 | YIFDGSDGGV | 5287 | PIK3C2B |
| 192 | YIQEYLTLL | 57674 | RNF213 |
| 193 | YLDLSNNRL | 81793 | TLR10 |
| 194 | YLDNVLAEL | 1840, 23220 | DTX1, DTX4 |
| 195 | YLGGFALSV | 6850 | SYK |
| 196 | YLLLQTYVL | 51259 | TMEM216 |
| 197 | YLQEVPILTL | 1633 | DCK |
| 198 | YLTFLPAEV | 64135 | IFIH1 |
| 199 | YLVELSSLL | 80279 | CDK5RAP3 |
| 200 | YMFEEVPIVI | 8667 | EIF3H |
| 201 | YQLELHGIEL | 5698 | PSMB9 |
| 202 | YVDDVFLRV | 10347 | ABCA7 |
| 203 | ALLSSQLAL | 8925 | HERC1 |
| 204 | GLLQINDKIAL | 5000 | ORC4 |
| 205 | GLSQANFTL | 10288, 10859, 10990, 11024, 11025, 11026, 11027, 23547, 79166, 79168 | LILRB2, LILRB1, LILRB5, LILRA1, LILRB3, LILRA3, LILRA2, LILRA4, LILRP2, LILRA6 |
| 206 | HMQDVRVLL | 84824 | FCRLA |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 207 | IIADLDTTIMFA | 7094, 83660 | TLN1, TLN2 |
| 208 | ILLKTEGINL | 166379 | BBS12 |
| 209 | ILQAELPSL | 57508 | INTS2 |
| 210 | KLLVQDFFL | 8564 | KMO |
| 211 | LIDVKPLGV | 134510 | UBLCP1 |
| 212 | NIIEAINELLV | 8892 | EIF2B2 |
| 213 | RLLYQLVFL | 3566 | IL4R |
| 214 | RLQELTEKL | 255394 | TCP11L2 |
| 215 | VMQDIVYKL | 84759 | PCGF1 |
| 216 | WLAGDVPAA | 24148 | PRPF6 |
| 217 | ALDEPPYLTV | 51742 | ARID4B |
| 218 | ALGEEWKGYVV | 6194, 728131 | RPS6 |
| 219 | ALLNLLESA | 5788 | PTPRC |
| 220 | ALPEILFAKV | 643 | CXCR5 |
| 221 | ALVSTIIMV | 80228 | ORAI2 |
| 222 | ALWELSLKI | 2889 | RAPGEF1 |
| 223 | ALWVSQPPEI | 259197 | NCR3 |
| 224 | AMEALVVEV | 1660 | DHX9 |
| 225 | ILQERELLPV | 1660 | DHX9 |
| 226 | AMNISVPQV | 23387 | SIK3 |
| 227 | FLAEASVMTQL | 1445 | CSK |
| 228 | FLGGLSPGV | 2968 | GTF2H4 |
| 229 | FLLNLQNCHL | 55608 | ANKRD10 |
| 230 | FLQDSKVIFV | 4772 | NFATC1 |
| 231 | FLYIRQLAI | 26155, 401010 | NOC2L |
| 232 | FMHQIIDQV | 79789 | CLMN |
| 233 | GIIDINVRL | 51163 | DBR1 |
| 234 | GLDDAEYAL | 7376 | NR1H2 |
| 235 | GLDDLLLFL | 8914 | TIMELESS |
| 236 | GLLESGRHYL | 9744 | ACAP1 |
| 237 | GLQENLDVVV | 8881 | CDC16 |
| 238 | GLVETELQL | 55690 | PACS1 |
| 239 | ILAGEMLSV | 7203 | CCT3 |
| 240 | ILARDILEI | 5714 | PSMD8 |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 241 | ILGDILLKV | 79831 | KDM8 |
| 242 | ILLGIQELL | 7329 | UBE2I |
| 243 | ILPTLEKELFL | 79886 | CAAP1 |
| 244 | ILQALAVHL | 54936 | ADPRHL2 |
| 245 | KIMDYSLLLGV | 23396 | PIP5K1C |
| 246 | KLDETGVAL | 7155 | TOP2B |
| 247 | KLKDRLPSI | 81606 | LBH |
| 248 | KTVEPPISQV | 57466 | SCAF4 |
| 249 | LLPTGVFQV | 51131 | PHF11 |
| 250 | LLVQEPDGLMV | 404734, 54882 | ANKHD1-EIF4EBP3, ANKHD1 |
| 251 | LLYDNVPGA | 11262 | SP140 |
| 252 | NLLDPGSSYLL | 5074 | PAWR |
| 253 | NLWSVDGEVTV | 92017 | SNX29 |
| 254 | QLIPKLIFL | 57705 | WDFY4 |
| 255 | YLFEEAISM | 57705 | WDFY4 |
| 256 | QLLPVSNVVSV | 55374 | TMCO6 |
| 257 | RIINGIIISV | 84329 | HVCN1 |
| 258 | RLDYITAEI | 10471 | PFDN6 |
| 259 | RLLDEQFAVL | 9026 | HIP1R |
| 260 | SLDDVEGMSV | 80196 | RNF34 |
| 261 | SLVEAQGWLV | 161176 | SYNE3 |
| 262 | SLWNAGTSV | 3495 | IGHD |
| 263 | SQWEDIHVV | 55843 | ARHGAP15 |
| 264 | TILDYINVV | 89790, 89858 | SIGLEC10, SIGLEC12 |
| 265 | TLLADDLEIKL | 2124 | EVI2B |
| 266 | TLLDQLDTQL | 8678 | BECN1 |
| 267 | TLLDWQDSL | 8289 | ARID1A |
| 268 | TLLQVFHLL | 63892 | THADA |
| 269 | TLTDEQFLV | 738 | VPS51 |
| 270 | TVLPVPPLSV | 5430 | POLR2A |
| 271 | VIRNIVEAA | 100128168, 100996747, 389472, 441502, 6231, 643003, 728937, 729188 | RPS26P39, RPS26P32, RPS26P11, RPS26, RPS26P28, RPS26P25, RPS26P58 |

TABLE 1-continued

Peptides according to the present invention.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 272 | VLDELPPLI | 55832, 91689 | CAND1, C22orf32 |
| 273 | VLGEYSYLL | 23431 | AP4E1 |
| 274 | VLLEYHIAYL | 8087 | FXR1 |
| 275 | VLLFIEHSV | 134265, 7805 | AFAP1L1, LAPTM5 |
| 276 | VLNDGAPNV | 117246 | FTSJ3 |
| 277 | VMILKLPFL | 25929 | GEMIN5 |
| 278 | YLDDLLPKL | 89910 | UBE3B |
| 279 | YMAPEVVEA | 2872 | MKNK2 |
| 280 | YTLDSLYWSV | 81887 | LAS1L |

J = phospho-serine

**[0055]** KIAA0226L (also known as C13orf18) encodes KIAA0226-like and is located on chromosome 13q14.13 (RefSeq, 2002). KIAA0226L is thought to be a tumor suppressor gene and is hyper-methylated in cervical cancer. Re-activation of KIAA0226L leads to decreased cell growth, viability, and colony formation (Huisman et al., 2015; Eijsink et al., 2012; Huisman et al., 2013). The methylation pattern of KIAA0226L can be used to differ between precursor lesions and normal cervix cancer (Milutin et al., 2015). The methylation pattern of KIAA0226L cannot be used as specific biomarker for cervical cancer (Sohrabi et al., 2014). Re-activation of KIAA0226L partially de-methylates its promotor region and also decreases repressive histone methylations (Huisman et al., 2013).

**[0056]** FCRL3, also known as FCRH3 or IRTA3, encodes Fc receptor like 3, one of several FC receptor-like glycoproteins of the immunoglobulin receptor superfamily which may play a role in regulation of the immune system (RefSeq, 2002). FCRL3 is up-regulated on CD4+CD26-T cells in S6zary syndrome patients with a high tumor burden, suggesting that FCRL3 expression correlates with a high circulating tumor burden (Wysocka et al., 2014). FCRL3 is up-regulated in chronic lymphocytic leukemia (Poison et al., 2006). FCRL3 is a potential marker with prognostic relevance in chronic lymphocytic leukemia (Zucchetto et al., 2011)

TABLE 2

Additional peptides according to the present invention with no prior known cancer association.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 281 | NLLDDRGMTAL | 146206 | RLTPR |
| 282 | LLRDGIELV | 152926 | PPM1K |
| 283 | ILQPMDIHV | 54832 | VPS13C |
| 284 | LLSAAEPVPA | 974 | CD79B |
| 285 | GVATAGCVNEV | 3394 | IRF8 |
| 286 | FLLEDLSQKL | 2177 | FANCD2 |
| 287 | FLWEEKFNSL | 10750 | GRAP |
| 288 | GLAESTGLLAV | 50855, 84552 | PARD6A, PARD6G |
| 289 | ILEEQPMDMLL | 84301 | DDI2 |
| 290 | LANPHELSL | 84301 | DDI2 |
| 291 | ILLNEDDLVTI | 57724 | EPG5 |
| 292 | AAALIIHHV | 25942 | SIN3A |
| 293 | ALDIMIPMV | 4217 | MAP3K5 |
| 294 | ALLDQLHTLL | 8202 | NCOA3 |
| 295 | ALLQKLQQL | 122618 | PLD4 |
| 296 | FIAPTGHSL | 23157, 55752 | SEPT6, SEPT11 |
| 297 | FLVEPQEDTRL | 8237 | USP11 |
| 298 | IILPVEVEV | 23505 | TMEM131 |
| 299 | ILEENIPVL | 55653 | BCAS4 |
| 300 | ILLNPAYDVYL | 23225 | NUP210 |
| 301 | AASPIITLV | 23225 | NUP210 |
| 302 | ILQDLTFVHL | 2889 | RAPGEF1 |
| 303 | ILSQPTPSL | 29028 | ATAD2 |
| 304 | LAIVPVNTL | 23132 | RAD54L2 |
| 305 | LLFPQIEGIKI | 26263 | FBXO22 |
| 306 | VVAEELENV | 26263 | FBXO22 |
| 307 | LLLTKPTEA | 5336 | PLCG2 |
| 308 | SLYDVSRMYV | 5336 | PLCG2 |
| 309 | ILYGTQFVL | 5336 | PLCG2 |
| 310 | LLSTLHLLV | 64098 | PARVG |
| 311 | LLVDVEPKV | 100129492, 6632 | SNRPD1 |
| 312 | LLYNSTDPTL | 64005 | MYO1G |
| 313 | LMADLEGLHL | 8546 | AP3B1 |
| 314 | LMKDCEAEV | 5518 | PPP2R1A |
| 315 | LVYEAPETV | 57448 | BIRC6 |
| 316 | MLLEHGITL | 200576 | PIKFYVE |

TABLE 2 -continued

Additional peptides according to the present invention with no prior known cancer association.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 317 | NLLAHIWAL | 58513 | EPS15L1 |
| 318 | NLQVTQPTV | 100505503, 402057, 442216, 6218 | RPS17L, RPS17P16, RPS17P5, RPS17 |
| 319 | QVIPQLQTV | 6671 | SP4 |
| 320 | TIAPVTVAV | 6671 | SP4 |
| 321 | RLLEFELAQL | 6093 | ROCK1 |
| 322 | SLASIHVPL | 23163 | GGA3 |
| 323 | SLDLFNCEV | 10541, 23520, 646791, 647020, 723972, 8125 | ANP32B, ANP32C, ANP32BP1, ANP32AP1, ANP32A |
| 324 | SLYSALQQA | 11190 | CEP250 |
| 325 | TLENGVPCV | 23240 | KIAA0922 |
| 326 | VLAFLVHEL | 11176 | BAZ2A |
| 327 | VLIKWFPEV | 54509 | RHOF |
| 328 | VLLPQETAEIHL | 5292 | PIM1 |
| 329 | VLMDGSVKL | 11184 | MAP4K1 |
| 330 | VLMWEIYSL | 695 | BTK |
| 331 | VLWELAHLPTL | 23358 | USP24 |
| 332 | VMIQHVENL | 4033 | LRMP |
| 333 | VTLEFPQLIRV | 126382 | NR2C2AP |
| 334 | YLLEEKIASL | 51199 | NIN |
| 335 | YLYQEQYFI | 10668 | CGRRF1 |
| 336 | YMAVTTQEV | 79840 | NHEJ1 |
| 337 | YMYEKESEL | 22806 | IKZF3 |
| 338 | FLDMTNWNL | 64771 | C6orf106 |
| 339 | GLWGTVVNI | 25914 | RTTN |
| 340 | KLLEEICNL | 10075 | HUWE1 |
| 341 | LLAELPASVHA | 2319 | FLOT2 |
| 342 | SLITPLQAV | 5591 | PRKDC |
| 343 | ILLEALDCI | 158078, 1915 | EEF1A1P5, EEF1A1 |
| 344 | VLAFENPQV | 25852 | ARMC8 |
| 345 | YLIEPDVELQRI | 25852 | ARMC8 |
| 346 | VLVQVSPSL | 23404 | EXOSC2 |
| 347 | YLGPVSPSL | 4154 | MBNL1 |

TABLE 2 -continued

Additional peptides according to the present invention with no prior known cancer association.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 348 | ALAKPPVVSV | 57634 | EP400 |
| 349 | ALATHILSL | 11215 | AKAP11 |
| 350 | ALEDRVWEL | 285025 | CCDC141 |
| 351 | ALSEKLARL | 115106 | HAUS1 |
| 352 | ALVFELHYV | 57705 | WDFY4 |
| 353 | ATPMPTPSV | 55206 | SBNO1 |
| 354 | FIMDDPAGNSYL | 8882 | ZNF259 |
| 355 | FIWPMLIHI | 11325 | DDX42 |
| 356 | FLHDHQAEL | 259197 | NCR3 |
| 357 | FLIQEIKTL | 23352 | UBR4 |
| 358 | FLTDYLNDL | 54880 | BCOR |
| 359 | FMQDPMEVFV | 10212 | DDX39A |
| 360 | HLIDTNKIQL | 55619 | DOCK10 |
| 361 | ILQEFESKL | 2074, 267004 | ERCC6, PGBD3 |
| 362 | ILTELGGFEV | 51366 | UBR5 |
| 363 | ITTEVVNELYV | 57222 | ERGIC1 |
| 364 | KMDWIFHTI | 5290 | PIK3CA |
| 365 | LISPLLLPV | 144132 | DNHD1 |
| 366 | LLSETCVTI | 23469 | PHF3 |
| 367 | NLWSLVAKV | 9889 | ZBED4 |
| 368 | QLQPTDALLCV | 125950 | RAVER1 |
| 369 | RLLDLENSLLGL | 54899 | PXK |
| 370 | SIFASPESV | 10285 | SMNDC1 |
| 371 | SLADDSVLERL | 23195 | MDN1 |
| 372 | SLFGPLPGPGPALV | 9595 | CYTIP |
| 373 | TLLADQGEIRV | 9219 | MTA2 |
| 374 | VLSVITEEL | 55621 | TRMT1 |
| 375 | VLWFKPVEL | 55720 | TSR1 |
| 376 | VLYNQRVEEI | 6730 | SRP68 |
| 377 | VVDGTCVAV | 57589 | KIAA1432 |
| 378 | YILGKFFAL | 8914 | TIMELESS |
| 379 | YLAELVTPIL | 1981 | EIF4G1 |
| 380 | YLDRKLLTL | 6850 | SYK |
| 381 | YLLEENKIKL | 139818 | DOCK11 |

TABLE 2 -continued

Additional peptides according to the present invention with no prior known cancer association.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 382 | YLLPLLQRL | 55794 | DDX28 |
| 383 | YLLREWVNL | 23019 | CNOT1 |
| 384 | YMIGSEVGNYL | 6598 | SMARCB1 |
| 385 | YTIPLAIKL | 128869 | PIGU |

TABLE 3

Peptides useful for e.g. personalized cancer therapies.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 386 | FLGDYVENL | 54832 | VPS13C |
| 387 | YLILSSHQL | 1269 | CNR2 |
| 388 | GLLSALENV | 1269 | CNR2 |
| 389 | GLAALAVHL | 2175 | FANCA |
| 390 | GLEERLYTA | 29933 | GPR132 |
| 391 | FLLEREQLL | 165055 | CCDC138 |
| 392 | FLWERPTLLV | 79922 | MRM1 |
| 393 | FVMEGEPPKL | 348654 | GEN1 |
| 394 | ILSTEIFGV | 79703 | C11orf80 |
| 395 | ALYGKLLKL | 157680 | VPS13B |
| 396 | TLLGKQVTL | 157680 | VPS13B |
| 397 | FLPPEHTIVYI | 9896 | FIG4 |
| 398 | FLAELPGSLSL | 5326 | PLAGL2 |
| 399 | ALAAPDIVPAL | 79886 | CAAP1 |
| 400 | ALFQPHLINV | 10097 | ACTR2 |
| 401 | AMADKMDMSL | 10189 | ALYREF |
| 402 | LLVSNLDFGV | 10189 | ALYREF |
| 403 | FIMPATVADATAV | 23352 | UBR4 |
| 404 | FLQPDLDSL | 10514 | MYBBP1A |
| 405 | FLVEKQPPQV | 6778 | STAT6 |
| 406 | FLWPKEVEL | 146206 | RLTPR |
| 407 | FMIDASVHPTL | 221960, 51622 | CCZ1B, CCZ1 |
| 408 | FMVDNEAIYDI | 10376, 112714, 113457, 51807, 7277, 7278, 7846, 84790 | TUBA1B, TUBA3E, TUBA3D, TUBA8, TUBA4A, TUBA3C, TUBA1A, TUBA1C |
| 409 | GLDAATATV | 9869 | SETDB1 |
| 410 | GLFDGVPTTA | 122618 | PLD4 |
| 411 | GLFEDVTQPGILL | 23140 | ZZEF1 |
| 412 | ILGTEDLIVEV | 79719 | AAGAB |

TABLE 3 -continued

| Peptides useful for e.g. personalized cancer therapies. | | | |
|---|---|---|---|
| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
| 413 | ILLEHGADPNL | 22852 | ANKRD26 |
| 414 | ILSVVNSQL | 80183 | KIAA0226L |
| 415 | ILVTSIFFL | 643 | CXCR5 |
| 416 | IMEDIILTL | 1656 | DDX6 |
| 417 | IQIGEETVITV | 2316 | FLNA |
| 418 | IVTEIISEI | 64151 | NCAPG |
| 419 | LLNEILEQV | 64151 | NCAPG |
| 420 | KLIDDQDISISL | 80208 | SPG11 |
| 421 | KLWTGGLDNTV | 7088, 7090, 7091 | TLE1, TLE3, TLE4 |
| 422 | KQFEGTVEI | 675 | BRCA2 |
| 423 | LLIGTDVSL | 9730 | VPRBP |
| 424 | LLPPLESLATV | 5518 | PPP2R1A |
| 425 | LLSDVRFVL | 53339 | BTBD1 |
| 426 | LLWGNLPEI | 653820, 729533 | FAM72B, FAM72A |
| 427 | LLYDAVHIV | 2899 | GRIK3 |
| 428 | LMYPYIYHV | 54954 | FAM1200 |
| 429 | NLLETKLQL | 219988 | PATL1 |
| 430 | QLIEKNWLL | 56992 | KIF15 |
| 431 | RMVAEIQNV | 11262 | 5P140 |
| 432 | SAVDFIRTL | 9263 | STK17A |
| 433 | SILDRDDIFV | 8237 | USP11 |
| 434 | SIQQSIERLLV | 4809 | NHP2L1 |
| 435 | SLFNQEVQI | 100528032, 22914, 8302 | KLRK1, KLRC4 |
| 436 | SLFSSLEPQIQPV | 23029 | RBM34 |
| 437 | SLEPQIQPV | 23029 | RBM34 |
| 438 | SLFIGEKAVLL | 23029 | RBM34 |
| 439 | SLLDLHTKV | 27340 | UTP20 |
| 440 | SLLEQGKEPWMV | 147949, 163087, 342892, 374899, 84503 | ZNF583, ZNF383, ZNF850, ZNF829, ZNF527 |
| 441 | SLLEVNEASSV | 149628 | PYHIN1 |
| 442 | SLNDLEKDVMLL | 6597 | SMARCA4 |
| 443 | SLTIDGIYYV | 1659 | DHX8 |
| 444 | SMSGYDQVL | 3187, 3188 | HNRNPH1, HNRNPH2 |
| 445 | VIIKGLEEITV | 3832 | KIF11 |
| 446 | VILTSSPFL | 10800 | CYSLTR1 |
| 447 | VLDDSIYLV | 57565 | KLHL14 |

TABLE 3 -continued

Peptides useful for e.g. personalized cancer therapies.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 448 | VMNDRLYAI | 57565 | KLHL14 |
| 449 | LLDAMNYHL | 57565 | KLHL14 |
| 450 | VLGPGPPPL | 254359 | ZDHHC24 |
| 451 | VLIEYNFSI | 55215 | FANCI |
| 452 | VLLSLLEKV | 1130 | LYST |
| 453 | SLLPLVWKI | 1130 | LYST |
| 454 | VLMDEGAVLTL | 54596 | L1TD1 |
| 455 | VLPDPEVLEAV | 57326 | PBXIP1 |
| 456 | YAAPGGLIGV | 1968, 255308 | E1F253 |
| 457 | YIMEPSIFNTL | 51497 | TH1L |
| 458 | YIQEHLLQI | 10625 | IVNS1ABP |
| 459 | YLDFSNNRL | 51284 | TLR7 |
| 460 | YLEDGFAYV | 5558 | PRIM2 |
| 461 | YLLNLNHLGL | 23471 | TRAM1 |
| 462 | YVLPKLYVKL | 100128168, 100996747, 441502, 6231, 643003, 644166, 644928, 644934, 646753, 728937, 729188 | RP526P39, RPS26P11, RP526, RP526P28, RP526P20, RP526P15, RP526P50, RP526P2, RP526P25, RP526P58 |
| 463 | ALMAVVSGL | 55103 | RALGPS2 |
| 464 | ALSDETKNNWEV | 5591 | PRKDC |
| 465 | FLYDEIEAEVNL | 23191, 26999 | CYFIP1, CYFIP2 |
| 466 | FLYDEIEAEV | 23191, 26999 | CYFIP1, CYFIP2 |
| 467 | IMQDFPAEIFL | 25914 | RTTN |
| 468 | KIQEILTQV | 10643 | IGF2BP3 |
| 469 | SLDGTELQL | 284114 | TMEM102 |
| 470 | TLTNIIHNL | 94101 | ORMDL1 |
| 471 | VLLAAGPSAA | 23225 | NUP210 |
| 472 | YLFESEGLVL | 283431 | GAS2L3 |
| 473 | ALADDDFLTV | 4173 | MCM4 |
| 474 | ALADLIEKELSV | 4850 | CNOT4 |
| 475 | ALDDMISTL | 7203 | CC13 |
| 476 | ALITEVVRL | 26005 | C2CD3 |
| 477 | ALLDQTKTLAESAL | 7094 | TLN1 |
| 478 | AMFESSQNVLL | 64328 | XPO4 |
| 479 | YLAHFIEGL | 64328 | XPO4 |
| 480 | FLAEDPKVTL | 60489 | APOBEC3G |
| 481 | FLIDTSASM | 203522, 26512 | DDX26B, IN156 |

TABLE 3 -continued

| Peptides useful for e.g. personalized cancer therapies. | | | |
|---|---|---|---|
| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
| 482 | FLTDLEDLTL | 26151 | NAT9 |
| 483 | FLTEMVHFI | 93517 | SDR42E1 |
| 484 | FLVDGPRVQL | 90204 | ZSWIM1 |
| 485 | GLLDCPIFL | 2177 | FANCD2 |
| 486 | GLLDLPFRVGV | 23347 | SMCHD1 |
| 487 | GLSDGNPSL | 79684 | MSANTD2 |
| 488 | GVYDGEEHSV | 4113 | MAGEB2 |
| 489 | HLANIVERL | 117854, 445372, 53840 | TRIM6, TRIM6-TRIM34, TRIM34 |
| 490 | ILDEKPVII | 23460 | ABCA6 |
| 491 | ILFSEDSTKLFV | 84916 | CIRH1A |
| 492 | ILLDDNMQIRL | 5261 | PHKG2 |
| 493 | LIIDQADIYL | 27042 | DIEXF |
| 494 | LLGDSSFFL | 283254 | HARBI1 |
| 495 | LLLDEEGTFSL | 27013 | CNPPD1 |
| 496 | LLVEQPPLAGV | 4773 | NFATC2 |
| 497 | LLWDVPAPSL | 1388, 7148 | ATF6B, TNXB |
| 498 | LTAPPEALLMV | 79050 | NOC4L |
| 499 | NLMEMVAQL | 55636 | CHD7 |
| 500 | QIITSVVSV | 5378 | PMS1 |
| 501 | QLALKVEGV | 25896 | IN157 |
| 502 | QLLDETSAITL | 10915 | TCERG1 |
| 503 | QLYEEPDTKL | 10270 | AKAP8 |
| 504 | RLYSGISGLEL | 84172 | POLR1B |
| 505 | RVLEVGALQAV | 25885 | POLR1A |
| 506 | SLLPLDDIVRV | 3708, 3709 | ITPR1, ITPR2 |
| 507 | SLLTEQDLWTV | 90806 | ANGEL2 |
| 508 | SVDSAPAAV | 10635 | RAD51AP1 |
| 509 | TLQEVVTGV | 55750 | AGK |
| 510 | TVDVATPSV | 8924 | HERC2 |
| 511 | VLAYFLPEA | 4171 | MCM2 |
| 512 | VLISVLQAI | 26999 | CYFIP2 |
| 513 | YLIPFTGIVGL | 26001 | RNF167 |
| 514 | YLLDDGTLVV | 8872 | CDC123 |
| 515 | YLMPGFIHL | 168400, 55510 | DDX53, DDX43 |
| 516 | YLPDIIKDQKA | 5496 | PPM1G |
| 517 | YLQLTQSEL | 283237 | TTC9C |

TABLE 3 -continued

Peptides useful for e.g. personalized cancer therapies.

| SEQ ID No. | Sequence | GeneID(s) | Official Gene Symbol(s) |
|---|---|---|---|
| 518 | YLTEVFLHVV | 55024 | BANK1 |
| 519 | YLVEGRFSV | 55125 | CEP192 |
| 520 | YLVYILNEL | 51202 | DDX47 |
| 521 | YLYGQTTTYL | 7153 | TOP2A |
| 522 | YVLTQPPSV | 28796, 28815, 28831, 3537, 3538 | IGLV3-21, IGLV2-14, IGLJ3, IGLC1, IGLC2 |

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0057]** FIGS. **1**A-**1**V describe relative presentation of various peptides of the present disclosure.

**[0058]** FIGS. **2**A-**2**D describe relative expression of various peptides of the present disclosure.

**[0059]** FIGS. **3**A-**3**F describe simulation graphs of various peptides of the present disclosure.

## DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

**[0060]** 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, acute myelogenous leukemia, bile duct cancer, brain cancer, breast cancer, colorectal carcinoma, esophageal cancer, gallbladder cancer, gastric cancer, hepatocellular cancer, Merkel cell carcinoma, melanoma, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small cell lung cancer, urinary bladder cancer, glioblastoma, renal cell carcinoma, hepatocellular carcinoma, testis cancer, and uterine cancer. 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: 385. More preferred are the peptides—alone or in combination—selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 202 (see Table 1), and their uses in the immunotherapy of CLL, acute myelogenous leukemia, bile duct cancer, brain cancer, breast cancer, colorectal carcinoma, esophageal cancer, gallbladder cancer, gastric cancer, hepatocellular cancer, Merkel cell carcinoma, melanoma, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small cell lung cancer, urinary bladder cancer, glioblastoma, renal cell carcinoma, hepatocellular carcinoma, testis cancer, and uterine cancer, and preferably CLL.

**[0061]** As shown in the following Tables 4A and B, many of the peptides according to the present invention are also found on other tumor types and can, thus, also be used in the immunotherapy of other indications. Also, refer to FIGS. **1**A-**1**V and Example 1.

TABLE 4A

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 1 | AIPPSFASIFL | NHL |
| 2 | ALHRPDVYL | NHL |
| 3 | VIAELPPKV | NHL |
| 5 | ALIFKIASA | AML, BRCA |
| 7 | ALLERTGYTL | HCC, NHL |
| 8 | ALAASALPALV | AML |
| 9 | ALCDTLITV | NHL |
| 10 | FVYGESVEL | NHL |
| 12 | ALGEDEITL | NHL, AML, Melanoma |
| 13 | VVDGMPPGV | NHL |
| 14 | ALLRLLPGL | NHL, AML |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 15 | ALPEVSVEA | NHL, AML, Melanoma |
| 19 | QVMEKLAAV | NHL |
| 20 | ALVDPGPDFVV | NHL |
| 21 | ALWAGLLTL | NHL |
| 22 | ALWDPVIEL | NHL |
| 24 | AMAGDVVYA | NHL |
| 25 | ATYSGLESQSV | Melanoma |
| 26 | AVLLVLPLV | NHL |
| 27 | AVLGLVWLL | NSCLC, NHL, Uterine Cancer |
| 28 | AVLHLLLSV | NHL, BRCA |
| 29 | AVLQAVTAV | SCLC, NHL, AML, Melanoma, OC, Gallbladder Cancer, Bile Duct Cancer |
| 30 | ELLEGSEIYL | NHL |
| 32 | FIDKFTPPV | NHL |
| 33 | FIINSSNIFL | NHL |
| 35 | FILPSSLYL | RCC, NHL, AML, Gallbladder Cancer, Bile Duct Cancer |
| 37 | FIMEGGAMVL | AML |
| 38 | FIMEGGAMV | NHL |
| 39 | FLDALLTDV | SCLC, NHL, AML, Melanoma |
| 40 | FLDEDDMSL | SCLC, NHL, Urinary bladder cancer |
| 42 | FLEEGGVVTV | NHL, Melanoma |
| 43 | FLLGPEALSFA | NHL, AML |
| 44 | FLLSINDFL | Melanoma |
| 45 | FLPELPADLEA | NHL, Melanoma |
| 46 | YIIDSAQAV | NHL |
| 48 | FLSPQQPPLL | NHL |
| 49 | FLTDLFAQL | NHL |
| 52 | FLVETGFLHV | Melanoma |
| 55 | FMEPTLLML | NHL, Urinary bladder cancer |
| 56 | FVFEAPYTL | NHL, AML |
| 57 | GLSEISLRL | NHL, AML, Melanoma |
| 58 | YIQQGIFSV | NHL |
| 59 | FVFGDENGTVSL | NHL, Esophageal Cancer, Urinary bladder cancer, Uterine Cancer |
| 60 | FVLDHEDGLNL | Melanoma, Esophageal Cancer |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 62 | GIIDGSPRL | NHL |
| 63 | SLAHVAGCEL | NHL |
| 64 | KLLESVASA | NHL |
| 66 | SLAGGLDDMKA | NHL |
| 67 | GLDDVTVEV | HCC, NHL, Melanoma, Esophageal Cancer, OC, Gallbladder Cancer, Bile Duct Cancer |
| 68 | GLDQQFAGLDL | RCC, HCC, NHL, Melanoma |
| 69 | GLHQREIFL | NHL |
| 70 | FVPDTPVGV | NHL |
| 71 | GLKHDIARV | NHL |
| 72 | GLLDAGKMYV | NHL, Melanoma |
| 74 | GLLRASFLL | NHL, AML, BRCA |
| 75 | GLSIFAQDLRL | NHL |
| 76 | GLLRIIPYL | NHL |
| 78 | GLPSFLTEV | HCC, NHL, AML, Melanoma |
| 79 | GLQAKIQEA | NHL, Esophageal Cancer, Uterine Cancer |
| 80 | VLIEDELEEL | NHL |
| 81 | WLVGQEFEL | NHL |
| 82 | GLQSGVDIGV | NHL |
| 83 | GQGEVLVYV | SCLC, GC, Esophageal Cancer |
| 86 | HLYPGAVTI | HCC, NHL |
| 87 | HQIEAVDGEEL | GC, NHL, Esophageal Cancer |
| 88 | ILDEIGADVQA | PC, NHL |
| 89 | ILDFGTFQL | NHL |
| 91 | ILDLNTYNV | NHL |
| 92 | ILEPLNPLL | NHL |
| 93 | ILFNTQINI | SCLC, NHL, AML, Melanoma, OC |
| 94 | ILFPLRFTL | NSCLC, RCC, CRC, NHL, Melanoma, OC |
| 96 | ILIDKTSFV | NHL |
| 97 | LLFATQITL | NHL |
| 98 | SLIKYFLFV | NHL |
| 99 | ILIFHSVAL | NHL, AML |
| 100 | ILNNEVFAI | NHL, AML |
| 101 | ILVVIEPLL | NHL |
| 102 | IQDRAVPSL | AML |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 103 | KLGGTPAPA | NHL |
| 105 | KLMNDIADI | NHL |
| 109 | KLWEGLTELV | AML |
| 110 | LLFDHLEPMEL | NHL |
| 111 | KLWNVAAPLYL | OC |
| 112 | KTLDVDATYEI | HCC, NHL, Melanoma, Esophageal Cancer, OC |
| 113 | KVPAEEVLVAV | NHL |
| 116 | LLIGATMQV | SCLC, NHL, AML |
| 117 | LLILENILL | NHL, AML, Melanoma |
| 118 | RLLILENILL | NHL |
| 119 | VLPAEFFEV | NHL, AML, Urinary bladder cancer, Uterine Cancer |
| 120 | AIDAALTSV | NHL, AML |
| 121 | RLYEITIEV | SCLC, NHL, AML, BRCA, OC |
| 122 | LLIPVVPGV | NSCLC, NHL |
| 124 | LLLEETEKQAV | RCC, HCC |
| 125 | LLLEIGEVGKLFV | NHL |
| 126 | LLPEGGITAI | NHL |
| 127 | LLPTAPTTV | NHL |
| 130 | LLVLIPVYL | NHL, Melanoma |
| 133 | YLLSGDISEA | NHL |
| 136 | NLDKLWTLV | GC, Esophageal Cancer |
| 137 | NLIKTVIKL | NHL |
| 138 | NLLDIDAPVTV | SCLC, NHL |
| 139 | NLTDVVEKL | RCC, NHL |
| 141 | QILSEIVEA | NHL, Melanoma |
| 145 | SALDTITTV | NHL |
| 146 | SIIEGPIIKL | NHL, Urinary bladder cancer |
| 147 | SILETVATL | NHL, AML |
| 148 | SIVASLITV | NHL, AML |
| 149 | SLDNGGYYI | NHL |
| 150 | SLFDQPLSII | NHL |
| 151 | SLFDSAYGA | AML |
| 152 | SLIRILQTI | HCC |
| 153 | SLLAELHVL | NHL |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 154 | SLLAELHVLTV | NHL |
| 155 | SLMLEVPAL | HCC, NHL |
| 156 | SLNIGDVQL | NHL |
| 157 | SLNIRDFTM | AML |
| 158 | SLPEAPLDV | NHL, AML, Uterine Cancer |
| 159 | SLQEEKLIYV | Brain Cancer, NHL, MCC, Melanoma, Esophageal Cancer, Urinary bladder cancer |
| 160 | SLSFLVPSL | NHL, AML, Urinary bladder cancer |
| 161 | SMDDGMINV | CRC, NHL, Gallbladder Cancer, Bile Duct Cancer NSCLC, SCLC, RCC, HCC, NHL, BRCA, Melanoma, |
| 162 | SMKDDLENV | Esophageal Cancer, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer |
| 163 | SQLDISEPYKV | NHL |
| 164 | SVHKGFAFV | NSCLC, RCC, Brain Cancer, GC, AML, Esophageal Cancer, Urinary bladder cancer, Uterine Cancer |
| 165 | TLDDDLDTV | NHL |
| 166 | TLDPNQVSL | AML |
| 167 | TLDTSKLYV | NHL |
| 168 | YLLDQSFVM | NHL |
| 169 | TLLLGLTEV | NHL, Melanoma |
| 170 | TLTFRVETV | NHL, Melanoma |
| 172 | TLYDMLASI | CRC, NHL, AML, Melanoma |
| 175 | FTVPRVVAV | NHL |
| 177 | VLDDRELLL | NHL |
| 178 | VLFFNVQEV | SCLC, NHL |
| 179 | VLLGLEMTL | NHL, Esophageal Cancer |
| 180 | LLKDGPEIGL | NHL |
| 181 | VLLSIPFVSV | HCC, NHL |
| 183 | VLMPTVYQQGV | AML |
| 185 | VMDDQRDLI | AML |
| 186 | VMDPTKILI | AML, Urinary bladder cancer |
| 187 | VMDTHLVNI | NHL, Urinary bladder cancer |
| 188 | VMGDIPAAV | NHL, AML, Gallbladder Cancer, Bile Duct Cancer |
| 189 | VMLEMTPEL | SCLC, PC, NHL, BRCA, Melanoma, Gallbladder Cancer, Bile Duct Cancer |
| 190 | VVMGTVPRL | NHL, AML |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 192 | YIQEYLTLL | NHL |
| 193 | YLDLSNNRL | NHL |
| 194 | YLDNVLAEL | NHL |
| 195 | YLGGFALSV | NHL, AML |
| 196 | YLLLQTYVL | NHL |
| 197 | YLQEVPILTL | NHL, Melanoma |
| 199 | YLVELSSLL | HCC, NHL, AML |
| 200 | YMFEEVPIVI | NSCLC, SCLC, CRC, HCC, NHL, Melanoma, Esophageal Cancer, OC, Urinary bladder cancer, Gallbladder Cancer, Bile Duct Cancer |
| 201 | YQLELHGIEL | Esophageal Cancer |
| 202 | YVDDVFLRV | Urinary bladder cancer |
| 203 | ALLSSQLAL | NHL |
| 204 | GLLQINDKIAL | SCLC, RCC, HCC, Melanoma, OC, Urinary bladder cancer |
| 205 | GLSQANFTL | NHL |
| 207 | IIADLDTTIMFA | SCLC, NHL, Melanoma, OC |
| 208 | ILLKTEGINL | NHL, BRCA, OC, Urinary bladder cancer |
| 209 | ILQAELPSL | NHL |
| 210 | KLLVQDFFL | HCC, NHL |
| 211 | LIDVKPLGV | NHL, BRCA, Melanoma |
| 212 | NIIEAINELLV | NHL, BRCA, Melanoma |
| 213 | RLLYQLVFL | NHL, Esophageal Cancer, Urinary bladder cancer, Gallbladder Cancer, Bile Duct Cancer |
| 214 | RLQELTEKL | NHL, AML |
| 215 | VMQDIVYKL | NHL, Esophageal Cancer, Urinary bladder cancer |
| 216 | WLAGDVPAA | SCLC, NHL |
| 217 | ALDEPPYLTV | NHL, Melanoma |
| 218 | ALGEEWKGYVV | Esophageal Cancer |
| 219 | ALLNLLESA | NHL, AML, OC |
| 220 | ALPEILFAKV | NHL |
| 221 | ALVSTIIMV | NHL, AML |
| 222 | ALWELSLKI | NHL |
| 223 | ALWVSQPPEI | NHL |
| 224 | AMEALVVEV | NHL |
| 225 | ILQERELLPV | NHL, Melanoma, OC, Urinary bladder cancer |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 227 | FLAEASVMTQL | NHL |
| 228 | FLGGLSPGV | NHL, Esophageal Cancer |
| 229 | FLLNLQNCHL | NHL |
| 230 | FLQDSKVIFV | NHL |
| 231 | FLYIRQLAI | AML |
| 232 | FMHQIIDQV | RCC, CRC, Melanoma |
| 233 | GIIDINVRL | PC, NHL, Melanoma, Esophageal Cancer, Urinary bladder cancer, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer |
| 234 | GLDDAEYAL | NHL, AML, Melanoma, Urinary bladder cancer |
| 235 | GLDDLLLFL | SCLC, PC, NHL, AML, Urinary bladder cancer, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer |
| 236 | GLLESGRHYL | NHL, AML |
| 237 | GLQENLDVVV | SCLC, NHL, Melanoma, Uterine Cancer |
| 238 | GLVETELQL | NHL, AML |
| 239 | ILAGEMLSV | NHL, AML, Melanoma, Gallbladder Cancer, Bile Duct Cancer |
| 240 | ILARDILEI | NHL, Urinary bladder cancer |
| 241 | ILGDILLKV | AML |
| 242 | ILLGIQELL | NHL, AML |
| 243 | ILPTLEKELFL | AML |
| 244 | ILQALAVHL | NHL, AML, OC |
| 245 | KIMDYSLLLGV | SCLC, RCC, OC |
| 246 | KLDETGVAL | HCC, NHL, AML, Melanoma |
| 247 | KLKDRLPSI | NHL |
| 248 | KTVEPPISQV | NHL |
| 249 | LLPTGVFQV | Urinary bladder cancer |
| 250 | LLVQEPDGLMV | SCLC, HCC, Melanoma, Urinary bladder cancer |
| 251 | LLYDNVPGA | NHL |
| 252 | NLLDPGSSYLL | Esophageal Cancer |
| 253 | NLWSVDGEVTV | NHL |
| 254 | QLIPKLIFL | NHL, Melanoma |
| 255 | YLFEEAISM | NHL |
| 257 | RIINGIIISV | NHL |
| 258 | RLDYITAEI | RCC, NHL, AML, Melanoma |
| 260 | SLDDVEGMSV | NHL, Gallbladder Cancer, Bile Duct Cancer |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 261 | SLVEAQGWLV | NHL |
| 263 | SQWEDIHVV | NHL, AML |
| 264 | TILDYINVV | Brain Cancer, NHL, AML, BRCA, OC, Uterine Cancer |
| 265 | TLLADDLEIKL | Esophageal Cancer |
| 266 | TLLDQLDTQL | NHL, OC, Urinary bladder cancer |
| 267 | TLLDWQDSL | NHL, AML, Melanoma |
| 268 | TLLQVFHLL | NHL |
| 269 | TLTDEQFLV | NHL, AML |
| 271 | VIRNIVEAA | GC, CRC, PC, AML, Esophageal Cancer |
| 272 | VLDELPPLI | SCLC, NHL |
| 273 | VLGEYSYLL | NHL |
| 274 | VLLEYHIAYL | NSCLC, SCLC, HCC, NHL, Urinary bladder cancer |
| 275 | VLLFIEHSV | NHL |
| 276 | VLNDGAPNV | NSCLC, SCLC, NHL, Melanoma, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer |
| 278 | YLDDLLPKL | PC, NHL |
| 280 | YTLDSLYWSV | NHL |
| 281 | NLLDDRGMTAL | NHL, AML |
| 282 | LLRDGIELV | NHL, Melanoma, OC |
| 283 | ILQPMDIHV | NHL |
| 284 | LLSAAEPVPA | NHL |
| 286 | FLLEDLSQKL | NHL |
| 288 | GLAESTGLLAV | NHL |
| 290 | LANPHELSL | AML |
| 291 | ILLNEDDLVTI | SCLC, NHL, Melanoma |
| 292 | AAALIIHHV | Urinary bladder cancer |
| 294 | ALLDQLHTLL | NHL |
| 295 | ALLQKLQQL | NHL |
| 296 | FIAPTGHSL | SCLC, NHL, AML, BRCA |
| 297 | FLVEPQEDTRL | NHL, Melanoma |
| 298 | IILPVEVEV | SCLC, NHL, AML, Urinary bladder cancer |
| 299 | ILEENIPVL | NHL |
| 300 | ILLNPAYDVYL | NHL, Melanoma |
| 303 | ILSQPTPSL | NHL, AML, Melanoma, OC |
| 304 | LAIVPVNTL | AML |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 305 | LLFPQIEGIKI | NHL, Melanoma |
| 306 | VVAEELENV | NHL, Melanoma, OC |
| 307 | LLLTKPTEA | NHL |
| 308 | SLYDVSRMYV | NHL |
| 309 | ILYGTQFVL | NHL |
| 310 | LLSTLHLLV | NHL |
| 311 | LLVDVEPKV | NSCLC, SCLC, RCC, HCC, PC, NHL, AML, Melanoma |
| 312 | LLYNSTDPTL | NHL |
| 313 | LMADLEGLHL | Melanoma, Urinary bladder cancer |
| 314 | LMKDCEAEV | NHL |
| 316 | MLLEHGITL | NHL |
| 317 | NLLAHIWAL | AML |
| 320 | TIAPVTVAV | NHL |
| 321 | RLLEFELAQL | SCLC, CRC, NHL, OC |
| 322 | SLASIHVPL | NHL |
| 323 | SLDLFNCEV | NHL |
| 324 | SLYSALQQA | NHL |
| 325 | TLENGVPCV | NHL |
| 326 | VLAFLVHEL | Esophageal Cancer |
| 327 | VLIKWFPEV | NHL |
| 328 | VLLPQETAEIHL | NHL, BRCA, Melanoma, OC, Urinary bladder cancer |
| 329 | VLMDGSVKL | NHL |
| 330 | VLMWEIYSL | NHL |
| 332 | VMIQHVENL | NHL |
| 333 | VTLEFPQLIRV | SCLC, HCC, NHL |
| 334 | YLLEEKIASL | NHL |
| 335 | YLYQEQYFI | SCLC, NHL, AML, Urinary bladder cancer |
| 337 | YMYEKESEL | NHL |
| 338 | FLDMTNWNL | HCC, NHL, Melanoma, OC, Urinary bladder cancer |
| 339 | GLWGTVVNI | NHL, AML, Melanoma, Uterine Cancer |
| 341 | LLAELPASVHA | HCC, NHL, Urinary bladder cancer |
| 342 | SLITPLQAV | NHL, AML, Urinary bladder cancer, Gallbladder Cancer, Bile Duct Cancer |
| 343 | ILLEALDCI | NHL, AML, Melanoma, Esophageal Cancer |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 344 | VLAFENPQV | Esophageal Cancer |
| 346 | VLVQVSPSL | RCC, NHL, AML, Gallbladder Cancer, Bile Duct Cancer |
| 347 | YLGPVSPSL | NHL |
| 348 | ALAKPPVVSV | SCLC, HCC, Melanoma, Esophageal Cancer |
| 349 | ALATHILSL | NHL, Urinary bladder cancer |
| 350 | ALEDRVWEL | NHL, Esophageal Cancer |
| 351 | ALSEKLARL | HCC, NHL, AML, Urinary bladder cancer |
| 352 | ALVFELHYV | NHL |
| 353 | ATPMPTPSV | SCLC, NHL |
| 354 | FIMDDPAGNSYL | CRC, NHL, AML, Melanoma, Esophageal Cancer, Urinary bladder cancer, Gallbladder Cancer, Bile Duct Cancer |
| 357 | FLIQEIKTL | NHL, OC, Urinary bladder cancer |
| 358 | FLTDYLNDL | NHL |
| 359 | FMQDPMEVFV | Melanoma |
| 360 | HLIDTNKIQL | NHL |
| 362 | ILTELGGFEV | NHL |
| 363 | ITTEVVNELYV | NHL, Melanoma |
| 364 | KMDWIFHTI | Urinary bladder cancer |
| 365 | LISPLLLPV | NHL, AML, Melanoma, Urinary bladder cancer |
| 367 | NLWSLVAKV | NSCLC, NHL, AML, Melanoma, OC |
| 369 | RLLDLENSLLGL | AML |
| 370 | SIFASPESV | Melanoma, Esophageal Cancer, Urinary bladder cancer |
| 371 | SLADDSVLERL | RCC, HCC, NHL, AML, Esophageal Cancer, Urinary bladder cancer |
| 373 | TLLADQGEIRV | NHL, Melanoma |
| 374 | VLSVITEEL | NHL, AML |
| 375 | VLWFKPVEL | NSCLC, HCC, NHL, Melanoma, Esophageal Cancer |
| 376 | VLYNQRVEEI | Urinary bladder cancer |
| 377 | VVDGTCVAV | NHL, Melanoma |
| 378 | YILGKFFAL | NHL, AML |
| 379 | YLAELVTPIL | NSCLC, SCLC, NHL, Melanoma |
| 380 | YLDRKLLTL | NHL |
| 381 | YLLEENKIKL | NHL |
| 382 | YLLPLLQRL | NHL, AML |
| 383 | YLLREWVNL | HCC, NHL |

TABLE 4A -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows for selected peptides on which additional tumor types they were found and either over-presented on more than 5% of the measured tumor samples, or presented on more than 5% of the measured tumor samples with a ratio of geometric means tumor vs normal tissues being larger than 3.

| SEQ ID No. | Sequence | Other relevant organs/diseases |
|---|---|---|
| 384 | YMIGSEVGNYL | NHL, Urinary bladder cancer |
| 385 | YTIPLAIKL | NHL, AML, BRCA, Esophageal Cancer |

Over-presentation is defined as higher presentation on the tumor sample as compared to the normal sample with highest presentation.
Normal tissues against which over-presentation was tested were:
adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary gland, pleura, salivary gland, skeletal muscle, skin, small intestine, pleen, stomach, thymus, thyroid gland, trachea, ureter, and urinary bladder.
NSCLC = non-small cell lung cancer,
SCLC = small cell lung cancer,
RCC = kidney cancer,
CRC = colon or rectum cancer,
GC = stomach cancer,
HCC = liver cancer,
PC = pancreatic cancer,
PrC = prostate cancer, leukemia,
BRCA = breast cancer,
MCC = Merkel cell carcinoma,
NHL = Non Hodgkin lymphoma

**[0062]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 1, 2, 3, 7, 9, 10, 13, 14, 15, 19, 20, 21,22, 24, 26, 27, 28, 29, 30, 32, 33, 35, 38, 39, 40, 42, 43, 45, 46, 48, 49, 55, 56, 57, 58, 59, 62, 63, 64, 66, 67, 68, 69, 70, 71,72, 74, 75, 76, 78, 79, 80, 81, 82, 86, 87, 88, 89, 91, 92, 93, 94, 96, 97, 98, 99, 100, 101, 103, 105, 110, 112, 113, 116, 117, 118, 119, 120, 121,122, 125, 126, 127, 130, 133, 137, 138, 139, 141,145, 146, 147, 148, 149, 150, 153, 154, 155, 156, 158, 159, 160, 161,162, 163, 165, 167, 168, 169, 170, 172, 175, 177, 178, 179, 180, 181,187, 188, 189, 190, 192, 193, 194, 195, 196, 197, 199, 200, 203, 205, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 219, 220, 221, 222, 223, 224, 225, 227, 228, 229, 230, 233, 234, 235, 236, 237, 238, 239, 240, 242, 244, 246, 247, 248, 251,253, 254, 255, 257, 258, 260, 261,263, 264, 266, 267, 268, 269, 272, 273, 274, 275, 276, 278, 280, 281,282, 283, 284, 286, 288, 290, 291,294, 295, 296, 297, 298, 299, 300, 303, 305, 306, 307, 308, 309, 310, 311,312, 314, 316, 320, 321,322, 323, 324, 325, 327, 328, 329, 330, 332, 333, 334, 335, 337, 338, 339, 341, 342, 343, 346, 347, 349, 350, 351,352, 353, 354, 357, 358, 360, 362, 363, 365, 367, 371, 373, 374, 375, 377, 378, 379, 380, 381, 382, 383, 384, and 385 for the—in one preferred embodiment combined—treatment of NHL.

**[0063]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 5, 8, 12, 14, 15, 29, 35, 37, 39, 43, 56, 57, 74, 78, 93, 99, 100, 102, 109, 116, 117, 119, 120, 121, 147, 148, 151,157, 158, 160, 164, 166, 172, 183, 185, 186, 188, 190, 195, 199, 214, 219,221, 231,234, 235, 236, 238, 239, 241, 242, 243, 244, 246, 258, 263, 264, 267, 269, 271, 281, 290, 296, 298, 303, 304, 311,317, 335, 339, 342, 343, 346, 351,354, 365, 367, 369, 374, 378, 382, and 385 for the—in one preferred embodiment combined—treatment of AML.

**[0064]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 5, 28, 74, 121, 162, 208, 211, 212, 264, 296, 328, and 385 for the—in one preferred embodiment combined—treatment of BRCA.

**[0065]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 7, 67, 68, 78, 86, 112, 124, 152, 155, 162, 181,199,200, 204, 210, 246, 250,274, 311,333,338,341,348, 351, 371, 375, and 383 for the—in one preferred embodiment combined—treatment of HCC.

**[0066]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 12, 15, 25, 29, 39, 42, 44, 45, 52, 57, 60, 67, 68, 72, 78, 93, 94, 112, 117, 130, 141,159, 162, 169, 170, 172, 189, 197, 200, 204, 207, 211,212, 217, 225, 232, 233, 234, 237, 239, 246, 250, 254, 258, 267, 276, 282, 291,297, 300, 303, 305, 306, 311,313, 328, 338, 339, 343, 348, 354, 359, 363, 365, 367, 370, 373, 375, 377, and 379 for the—in one preferred embodiment combined—treatment of melanoma.

**[0067]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 27, 94, 122, 162, 164, 200, 274, 276, 311, 367, 375, and 379 for the—in one preferred embodiment combined—treatment of NSCLC.

**[0068]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 27, 59, 79, 119, 158, 162, 164, 233, 235, 237, 264, 276, and 339 for the—in one preferred embodiment combined—treatment of uterine cancer.

**[0069]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 29, 67, 93, 94, 111,112, 200, 204, 207, 208, 219, 225, 244, 245, 264, 266, 282, 303, 306, 321,328, 338, 357, and 367 for the—in one preferred embodiment combined—treatment of ovarian cancer (OC).

**[0070]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 29, 35, 67, 161, 162, 188, 189, 200, 213, 233, 235, 239, 260, 276, 342, 346, and 354 for the—in one preferred embodiment combined—treatment of gallbladder cancer and/or bile duct cancer.

**[0071]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 35, 68, 94, 124, 139, 162, 164, 197, 204, 232, 245, 258, 311, 346, and 371 for the—in one preferred embodiment combined—treatment of RCC.

**[0072]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 39, 40, 83, 93, 121,138, 162, 178, 189, 200, 204, 207, 216, 235, 237, 245, 250, 272, 274, 276, 291,296, 298, 311, 321, 333, 335, 348, 353, and 379 for the—in one preferred embodiment combined—treatment of SCLC.

**[0073]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 40, 55, 59, 119, 146, 159, 160, 164, 186, 187, 200,202, 204, 208, 213, 215,225,233,234, 235, 240, 249, 250, 266, 274, 292, 298, 313, 328, 335, 338, 341, 342, 349, 351,354, 357, 364, 365, 370, 371, 376, and 384 for the—in one preferred embodiment combined—treatment of urinary bladder cancer.

**[0074]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 59, 60, 67, 79, 83, 87, 112, 136, 159, 162, 164, 179, 200, 201, 213, 215, 218, 228, 233, 252, 265, 271, 326, 343, 344, 348, 350, 354, 370, 371, 375, and 385 for the—in one preferred embodiment combined—treatment of esophageal cancer.

**[0075]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 83, 87, 136, 164, and 271 for the—in one preferred embodiment combined—treatment of gastric cancer (GC).

**[0076]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 88, 189, 233, 235, 271, 278, and 311 for the—in one preferred embodiment combined—treatment of pancreatic cancer (PC).

**[0077]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 94, 161, 172, 200, 232, 271, 321, and 354 for the—in one preferred embodiment combined—treatment of colorectal cancer (CRC).

**[0078]** Thus, another aspect of the present invention relates to the use of the peptide according to the present invention according to SEQ ID No. 159 for the treatment of MCC.

**[0079]** 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 CLL, acute myelogenous leukemia, bile duct cancer, brain cancer, breast cancer, colorectal carcinoma, esophageal cancer, gallbladder cancer, gastric cancer, hepatocellular cancer, Merkel cell carcinoma, melanoma, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small cell lung cancer, urinary bladder cancer and uterine cancer.

**[0080]** Table 4B: Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over-presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3. Over-presentation is defined as higher presentation on the tumour sample as compared to the normal sample with highest presentation. Normal tissues against which over-presentation was tested were: adipose tissue, adrenal gland, artery, bone marrow, brain, central nerve, colon, duodenum, oesophagus, eye, gallbladder, heart, kidney, liver, lung, lymph node, mononuclear white blood cells, pancreas, parathyroid gland, peripheral nerve, peritoneum, pituitary, pleura, rectum, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, ureter, urinary bladder, vein.

TABLE 4B

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 5 | ALIFKIASA | Uterine Cancer |
| 7 | ALLERTGYTL | Uterine Cancer, AML |
| 8 | ALAASALPALV | AML, HNSCC |
| 11 | ALFTFSPLTV | AML, HNSCC, NHL, NSCLC, OC, SCLC |

TABLE 4B -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 13 | VVDGMPPGV | BRCA, Uterine Cancer |
| 14 | ALLRLLPGL | BRCA, Melanoma HNSCC |
| 15 | ALPEVSVEA | Esophageal Cancer |
| 25 | ATYSGLESQSV | AML |
| 26 | AVLLVLPLV | NHL, NSCLC |
| 27 | AVLGLVWLL | HNSCC |
| 29 | AVLQAVTAV | Uterine Cancer |
| 30 | ELLEGSEIYL | CRC, BRCA, Melanoma, Uterine Cancer |
| 35 | FILPSSLYL | SCLC, Uterine Cancer |
| 37 | FIMEGGAMVL | NHL |
| 38 | FIMEGGAMV | HNSCC |
| 40 | FLDEDDMSL | HNSCC |
| 41 | FLDPSLDPLL | Uterine Cancer |
| 42 | FLEEGGVVTV | SCLC, AML |
| 44 | FLLSINDFL | RCC, Uterine Cancer, AML, NHL |
| 45 | FLPELPADLEA | NSCLC, Uterine Cancer, OC |
| 48 | FLSPQQPPLL | HNSCC |
| 49 | FLTDLFAQL | NHL, Melanoma |
| 51 | FLVEAPHDWDL | Uterine Cancer |
| 55 | FMEPTLLML | HNSCC |
| 58 | YIQQGIFSV | NHL, NSCLC |
| 59 | FVFGDENGTVSL | SCLC, HNSCC |
| 67 | GLDDVTVEV | AML |
| 68 | GLDQQFAGLDL | BRCA, OC, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer, HNSCC |
| 76 | GLLRIIPYL | RCC |
| 82 | GLQSGVDIGV | AML, Esophageal Cancer, PC |
| 83 | GQGEVLVYV | NHL |
| 84 | GVMDVNTAL | AML, HCC, HNSCC, NHL, NSCLC, GC, RCC |
| 86 | HLYPGAVTI | AML |
| 87 | HQIEAVDGEEL | PC |
| 89 | ILDFGTFQL | BRCA |
| 90 | VIADLGLIRV | Melanoma |
| 91 | ILDLNTYNV | AML |

TABLE 4B -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 93 | ILFNTQINI | Uterine Cancer, HNSCC |
| 94 | ILFPLRFTL | Gallbladder Cancer, Bile Duct Cancer, AML, HNSCC |
| 101 | ILVVIEPLL | Uterine Cancer |
| 107 | ILYNLYDLL | Melanoma |
| 108 | VIYTLIHYI | BRCA, Melanoma |
| 111 | KLWNVAAPLYL | Melanoma |
| 112 | KTLDVDATYEI | Uterine Cancer |
| 113 | KVPAEEVLVAV | NHL, NSCLC |
| 114 | LIPEGPPQV | AML, HNSCC |
| 115 | LLFDKLYLL | Uterine Cancer |
| 118 | RLLILENILL | HNSCC |
| 119 | VLPAEFFEV | SCLC |
| 124 | LLLEETEKQAV | HNSCC |
| 125 | LLLEIGEVGKLFV | BRCA |
| 126 | LLPEGGITAI | SCLC, HCC, Melanoma, Uterine Cancer, HNSCC |
| 127 | LLPTAPTTV | SCLC |
| 128 | LLSEEEYHL | Urinary Bladder Cancer, NHL, HNSCC |
| 130 | LLVLIPVYL | Uterine Cancer |
| 136 | NLDKLWTLV | AML, CRC, Melanoma, NSCLC, Brain Cancer |
| 138 | NLLDIDAPVTV | Uterine Cancer, AML |
| 141 | QILSEIVEA | Uterine Cancer |
| 145 | SALDTITTV | NSCLC, RCC, GC, HCC, AML |
| 146 | SIIEGPIIKL | HNSCC |
| 147 | SILETVATL | Melanoma |
| 152 | SLIRILQTI | SCLC |
| 156 | SLNIGDVQL | AML |
| 159 | SLQEEKLIYV | HNSCC |
| 160 | SLSFLVPSL | Uterine Cancer |
| 161 | SMDDGMINV | SCLC, Melanoma, Uterine Cancer, AML, HNSCC |
| 162 | SMKDDLENV | PC, OC, HNSCC |
| 164 | SVHKGFAFV | CRC, Melanoma, HNSCC |
| 172 | TLYDMLASI | SCLC, Urinary Bladder Cancer, Uterine Cancer |
| 173 | TVIENIHTI | CRC, HCC, Melanoma, NHL, NSCLC, OC, Esophageal Cancer, GC, RCC |

TABLE 4B -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 174 | VLAELPIIVV | NSCLC, OC |
| 176 | VLAEQNIIPSA | NSCLC, SCLC, GC, Melanoma, NHL, HNSCC |
| 179 | VLLGLEMTL | HNSCC |
| 181 | VLLSIPFVSV | Melanoma, Gallbladder Cancer, Bile Duct Cancer |
| 184 | VLSHNLYTV | NHL |
| 187 | VMDTHLVNI | CRC, Melanoma, Uterine Cancer |
| 188 | VMGDIPAAV | Urinary Bladder Cancer, HNSCC |
| 189 | VMLEMTPEL | HNSCC |
| 190 | VVMGTVPRL | Melanoma |
| 191 | YIFDGSDGGV | Uterine Cancer |
| 192 | YIQEYLTLL | SCLC, Urinary Bladder Cancer, AML, HNSCC |
| 197 | YLQEVPILTL | Uterine Cancer |
| 198 | YLTFLPAEV | BRCA, Uterine Cancer |
| 199 | YLVELSSLL | Melanoma |
| 200 | YMFEEVPIVI | BRCA, HNSCC |
| 201 | YQLELHGIEL | NHL |
| 202 | YVDDVFLRV | AML, HNSCC |
| 203 | ALLSSQLAL | NHL, AML, NSCLC |
| 204 | GLLQINDKIAL | BRCA, Uterine Cancer, AML |
| 208 | ILLKTEGINL | Melanoma, HNSCC |
| 211 | LIDVKPLGV | RCC, Brain Cancer, HCC, Esophageal Cancer, HNSCC |
| 212 | NIIEAINELLV | Uterine Cancer, AML, HNSCC |
| 215 | VMQDIVYKL | HNSCC |
| 216 | WLAGDVPAA | AML, HNSCC |
| 217 | ALDEPPYLTV | AML |
| 218 | ALGEEWKGYVV | AML |
| 221 | ALVSTIIMV | Brain Cancer |
| 224 | AMEALVVEV | AML |
| 226 | AMNISVPQV | AML, PrC, Brain Cancer, Gallbladder Cancer, CCC, HNSCC, NHL, NSCLC, OC, SCLC, Uterine Cancer |
| 228 | FLGGLSPGV | SCLC, BRCA, Uterine Cancer, AML, HNSCC |
| 231 | FLYIRQLAI | Uterine Cancer |
| 232 | FMHQIIDQV | Uterine Cancer |
| 234 | GLDDAEYAL | Uterine Cancer, HNSCC |

TABLE 4B -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 235 | GLDDLLLFL | BRCA, HNSCC |
| 237 | GLQENLDVVV | AML |
| 239 | ILAGEMLSV | SCLC, HCC |
| 240 | ILARDILEI | Melanoma |
| 242 | ILLGIQELL | BRCA |
| 247 | KLKDRLPSI | HCC |
| 257 | RIINGIIISV | AML |
| 258 | RLDYITAEI | GC, Uterine Cancer |
| 260 | SLDDVEGMSV | SCLC, HNSCC |
| 261 | SLVEAQGWLV | AML |
| 264 | TILDYINVV | HNSCC |
| 266 | TLLDQLDTQL | CRC, BRCA, Uterine Cancer |
| 268 | TLLQVFHLL | Uterine Cancer |
| 269 | TLTDEQFLV | BRCA |
| 272 | VLDELPPLI | BRCA, Uterine Cancer, HNSCC |
| 273 | VLGEYSYLL | NHL, HNSCC |
| 274 | VLLEYHIAYL | Melanoma, HNSCC |
| 275 | VLLFIEHSV | Melanoma |
| 279 | YMAPEVVEA | HNSCC, NHL, NSCLC, SCLC, Uterine Cancer |
| 280 | YTLDSLYWSV | SCLC, BRCA, Melanoma, HNSCC |
| 286 | FLLEDLSQKL | Uterine Cancer |
| 289 | ILEEQPMDMLL | Uterine Cancer |
| 293 | ALDIMIPMV | AML, CRC, Brain Cancer, Gallbladder Cancer, CCC, HNSCC, Melanoma, NHL, NSCLC, OC, Brain Cancer, RCC, SCLC, Urinary Bladder Cancer, Uterine Cancer |
| 294 | ALLDQLHTLL | AML |
| 298 | IILPVEVEV | CRC, HNSCC |
| 299 | ILEENIPVL | Uterine Cancer, AML |
| 303 | ILSQPTPSL | Uterine Cancer |
| 305 | LLFPQIEGIKI | Urinary Bladder Cancer, HNSCC |
| 306 | VVAEELENV | RCC |
| 311 | LLVDVEPKV | Uterine Cancer, HNSCC |
| 312 | LLYNSTDPTL | Urinary Bladder Cancer |
| 313 | LMADLEGLHL | Uterine Cancer, AML |

TABLE 4B -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 317 | NLLAHIWAL | NHL |
| 321 | RLLEFELAQL | Brain Cancer, PrC, Uterine Cancer, AML, HNSCC |
| 323 | SLDLFNCEV | Uterine Cancer, AML |
| 324 | SLYSALQQA | SCLC, Uterine Cancer, AML |
| 326 | VLAFLVHEL | Esophageal Cancer, NSCLC, RCC |
| 327 | VLIKWFPEV | Uterine Cancer |
| 333 | VTLEFPQLIRV | BRCA |
| 334 | YLLEEKIASL | AML |
| 335 | YLYQEQYFI | CRC, Brain Cancer, Gallbladder Cancer, CCC, NSCLC, UterineCancer |
| 336 | YMAVTTQEV | Uterine Cancer |
| 339 | GLWGTVVNI | HNSCC |
| 340 | KLLEEICNL | Melanoma, Uterine Cancer, AML, NHL |
| 342 | SLITPLQAV | HNSCC |
| 343 | TLLEALDCI | GC, Uterine Cancer, HNSCC |
| 344 | VLAFENPQV | HNSCC |
| 346 | VLVQVSPSL | HNSCC |
| 348 | ALAKPPVVSV | NSCLC, Urinary Bladder Cancer, NHL, HNSCC |
| 349 | ALATHILSL | HCC, Melanoma |
| 351 | ALSEKLARL | CRC, HNSCC, Melanoma, NSCLC, OC, PC, Brain Cancer, RCC, Uterine Cancer |
| 353 | ATPMPTPSV | BRCA, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer, AML, HNSCC |
| 354 | FIMDDPAGNSYL | Brain Cancer, HNSCC |
| 355 | FIWPMLIHI | Melanoma, Uterine Cancer |
| 357 | FLIQEIKTL | HCC |
| 358 | FLTDYLNDL | AML |
| 359 | FMQDPMEVFV | Melanoma, NHL, NSCLC, OC |
| 360 | HLIDTNKIQL | NHL, NSCLC |
| 361 | ILQEFESKL | AML, NHL |
| 362 | ILTELGGFEV | AML, PrC, BRCA, PC, CRC, HCC, HNSCC, Melanoma, NSCLC, OC, Esophageal Cancer, GC, RCC, SCLC, Urinary Bladder Cancer, Uterine Cancer |
| 363 | ITTEVVNELYV | BRCA |
| 365 | LISPLLLPV | SCLC, Uterine Cancer, HNSCC |
| 367 | NLWSLVAKV | Uterine Cancer |

TABLE 4B -continued

Peptides according to the present invention and their specific uses in other proliferative diseases, especially in other cancerous diseases. The table shows, like Table 4A, for selected peptides on which additional tumour types they were found showing over presentation (including specific presentation) on more than 5% of the measured tumour samples, or presentation on more than 5% of the measured tumour samples with a ratio of geometric means tumour vs normal tissues being larger than 3.

| SEQ ID NO. | Sequence | Additional Entities |
|---|---|---|
| 368 | QLQPTDALLCV | Uterine Cancer |
| 370 | SIFASPESV | Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer, AML, HNSCC |
| 374 | VLSVITEEL | SCLC, HCC, PrC, Urinary Bladder Cancer, Uterine Cancer |
| 375 | VLWFKPVEL | BRCA, OC, Uterine Cancer, Gallbladder Cancer, Bile Duct Cancer, HNSCC |
| 377 | VVDGTCVAV | BRCA, Uterine Cancer, HNSCC |
| 378 | YILGKFFAL | Melanoma, Esophageal Cancer |
| 379 | YLAELVTPIL | HCC, BRCA, Uterine Cancer, AML, HNSCC |
| 383 | YLLREWVNL | Melanoma, Uterine Cancer |
| 384 | YMIGSEVGNYL | SCLC, Uterine Cancer |
| 385 | YTIPLAIKL | CRC |

Over-presentation is defined as higher presentation on the tumour sample as compared to the normal sample with highest presentation.
Normal tissues against which over-presentation was tested were:
adipose tissue, adrenal gland, artery, bone marrow, brain, central nerve, colon, duodenum, oesophagus, eye, gallbladder, heart, kidney, liver, lung, lymph node, mononuclear white blood cells, pancreas, parathyroid gland, peripheral nerve, peritoneum, pituitary, pleura, rectum, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, ureter, urinary bladder, vein.
NSCLC = non-small cell lung cancer,
SCLC = small cell lung cancer,
RCC = kidney cancer,
CRC = colon or rectum cancer,
GC = stomach cancer,
HCC = liver cancer,
PC = pancreatic cancer,
PrC = prostate cancer,
BRCA = breast cancer,
NHL = non-Hodgkin lymphoma,
AML = acute myeloid leukemia,
OC = ovarian cancer,
HNSCC = head and neck squamous cell carcinoma,
CCC = cholangiocarcinoma.

**[0081]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 5, 7, 13, 29, 30, 35, 41, 44, 45, 51, 68, 93, 101, 112, 115, 126, 130, 138, 141, 160, 161, 172, 187, 191, 197, 198, 204, 212, 226, 228, 231,232, 234, 258, 266, 268, 272, 279, 286, 289, 293, 299, 303, 311,313, 321,323, 324, 327, 335, 336, 340, 343, 351,353, 355, 362, 365, 367, 368, 370, 374, 375, 377, 379, 383, and 384 for the—in one preferred embodiment combined—treatment of uterine cancer.

**[0082]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 7, 8, 11, 25, 42, 44, 67, 82, 84, 86, 91,94, 114, 136, 138, 145, 156, 161, 192, 202, 203, 204, 212, 216, 217, 218, 224, 226, 237, 257, 261,293, 294, 299, 313, 321,323, 324, 334, 340, 353, 358, 361, 362, 370, and 379 for the—in one preferred embodiment combined—treatment of AML.

**[0083]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 8, 11, 14, 27, 38, 40, 48, 55, 59, 68, 84, 93, 94, 114, 118, 124, 126, 128, 146, 159, 161, 162, 164, 176, 179, 188, 189, 192, 200, 202, 208, 211,212, 215, 216, 226, 228, 234, 235, 260, 264, 272, 273, 274, 279, 280, 293, 298, 305, 311,321,339, 342, 343, 344, 346, 348, 351,353, 354, 362, 365, 370, 375, 377, and 379 for the—in one preferred embodiment combined—treatment of HNSCC.

**[0084]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 11, 26, 37, 44, 49, 58, 83, 84, 113, 128, 173, 176, 184, 201, 203, 226, 273, 279, 293, 317, 340, 348, 359, 360, and 361 for the—in one preferred embodiment combined—treatment of NHL.

**[0085]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 11, 26, 45, 58, 84, 113, 136, 145, 173, 174, 176, 203, 226, 279, 293, 326, 335, 348, 351, 359, 360, and 362 for the—in one preferred embodiment combined—treatment of NSCLC.

**[0086]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 11, 45, 68, 162, 173, 174, 226, 293, 351, 359, 362, and 375 for the—in one preferred embodiment combined—treatment of OC.

**[0087]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 11, 35, 42, 59, 119, 126, 127, 152, 161,172, 176, 192, 226, 228, 239, 260, 280, 293, 324, 362, 365, 374, and 384 for the—in one preferred embodiment combined—treatment of SCLC.

**[0088]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 13, 14, 30, 68, 89, 108, 125, 198,200,204, 228,235,242, 266, 269, 272, 280,333,353,362, 363, 375, 377, and 379 for the—in one preferred embodiment combined—treatment of BRCA.

**[0089]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 14, 30, 49, 90, 107, 108, 111,126, 136, 147, 161,164, 173, 176, 181,187, 190, 199,208,240,274, 275, 280, 293, 340, 349, 351, 355, 359, 362, 378, and 383 for the—in one preferred embodiment combined—treatment of melanoma.

**[0090]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 15, 82, 173, 211, 326, 362, and 378 for the—in one preferred embodiment combined—treatment of esophageal cancer.

**[0091]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 30, 136, 164, 173, 187, 266, 293, 298, 335, 351, 362, 363, and 385 for the—in one preferred embodiment combined—treatment of CRC.

**[0092]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 44, 76, 84, 145, 173, 211, 293, 306, 326, 351, and 362 for the—in one preferred embodiment combined—treatment of RCC.

**[0093]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 68, 94, 181, 226, 293, 335, 353, 370, and 375 for the—in one preferred embodiment combined—treatment of gallbladder cancer and/or bile duct cancer and/or cholangiocarcinoma.

**[0094]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 82, 87, 162, 351, and 362 for the—in one preferred embodiment combined—treatment of PC.

**[0095]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 84, 145, 173, 176, 258, 343, and 362 for the—in one preferred embodiment combined—treatment of GC.

**[0096]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 84, 126, 145, 173, 211, 239, 247, 349, 357, 362, 374, and 379 for the—in one preferred embodiment combined—treatment of HCC.

**[0097]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 136, 211, 221, 226, 293, 321, 335, 351, and 354 for the—in one preferred embodiment combined—treatment of brain cancer.

**[0098]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 128, 172, 188, 192, 293, 305, 312, 321, 348, 362, and 374 for the—in one preferred embodiment combined—treatment of urinary bladder cancer.

**[0099]** Thus, another aspect of the present invention relates to the use of at least one peptide according to the present invention according to any one of SEQ ID No. 226, 321, 362, and 374 for the—in one preferred embodiment combined—treatment of PrC.

**[0100]** 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.

**[0101]** 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: 385.

**[0102]** The present invention further relates to the peptides according to the present invention, wherein said peptide is modified and/or includes non-peptide bonds.

**[0103]** 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 (li), or fused to (or into the sequence of) an antibody, such as, for example, an antibody that is specific for dendritic cells.

**[0104]** 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.

**[0105]** The present invention further relates to an expression vector capable of expressing and/or expressing a nucleic acid according to the present invention.

**[0106]** 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.

**[0107]** 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.

**[0108]** 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 methods of making these, as well as NK cells or other cells bearing said TCR or cross-reacting with said TCRs.

**[0109]** The antibodies and TCRs are additional embodiments of the immunotherapeutic use of the peptides according to the invention at hand.

**[0110]** 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 invention further relates to the host cell according to the present invention that is an antigen presenting cell, and preferably is a dendritic cell.

**[0111]** 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.

**[0112]** 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.

**[0113]** 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.: 385, preferably containing SEQ ID No. 1 to SEQ ID No. 202, or a variant amino acid sequence.

**[0114]** 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.

**[0115]** 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.

**[0116]** 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 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.

**[0117]** Preferably, said medicament is a cellular therapy, a vaccine or a protein based on a soluble TCR or antibody.

**[0118]** The present invention further relates to a use according to the present invention, wherein said cancer cells are CLL, acute myelogenous leukemia, bile duct cancer, brain cancer, breast cancer, colorectal carcinoma, esophageal cancer, gallbladder cancer, gastric cancer, hepatocellular cancer, Merkel cell carcinoma, melanoma, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small cell lung cancer, urinary bladder cancer and uterine cancer, and preferably CLL cells.

**[0119]** 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 CLL. 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.

**[0120]** 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.

**[0121]** 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.

**[0122]** 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.

**[0123]** 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).

**[0124]** As used herein and except as noted otherwise all terms are defined as given below.

**[0125]** 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.

**[0126]** The term "peptide" is used herein to designate a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. The peptides are preferably 9 amino acids in length, but can be as short as 8 amino acids in length, and as long as 10, 11, 12, 13, or 14 or longer, and in case of MHC class II peptides (elongated variants of the peptides of the invention) they can be as long as 15, 16, 17, 18, 19 or 20 or more amino acids in length.

**[0127]** 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.

[0128] 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.

[0129] 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.

[0130] The term "full length polypeptide" means a complete protein (amino acid chain) or complete subunit (amino acid chain) of a multimeric protein.

[0131] A peptide, oligopeptide, protein or polynucleotide coding for such a molecule is "immunogenic" (and thus is an "immunogen" within the present invention), if it is capable of inducing an immune response. In the case of the present invention, immunogenicity is more specifically defined as the ability to induce a T-cell response. Thus, an "immunogen" would be a molecule that is capable of inducing an immune response, and in the case of the present invention, a molecule capable of inducing a T-cell response. In another aspect, the immunogen can be the peptide, the complex of the peptide with MHC, oligopeptide, and/or protein that is used to raise specific antibodies or TCRs against it.

[0132] 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.

[0133] 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 5

Expression frequencies F of HLA-A*02 and HLA-A*24 and the most frequent HLA-DR serotypes. Frequencies are deduced from haplotype frequencies Gf within the American population adapted from Mori et al. (Mori et al., 1997) employing the Hardy-Weinberg formula $F = 1 - (1-Gf)^2$. Combinations of A*02 or A*24 with certain HLA-DR alleles might be enriched or less frequent than expected from their single frequencies due to linkage disequilibrium. For details refer to Chanock et al. (Chanock et al., 2004).

| Allele | Population | Calculated phenotype from allele frequency |
|---|---|---|
| A*02 | Caucasian (North America) | 49.1% |
| A*02 | African American (North America) | 34.1% |
| A*02 | Asian American (North America) | 43.2% |
| A*02 | Latin American (North American) | 48.3% |
| DR1 | Caucasian (North America) | 19.4% |
| DR2 | Caucasian (North America) | 28.2% |
| DR3 | Caucasian (North America) | 20.6% |
| DR4 | Caucasian (North America) | 30.7% |
| DR5 | Caucasian (North America) | 23.3% |
| DR6 | Caucasian (North America) | 26.7% |
| DR7 | Caucasian (North America) | 24.8% |
| DR8 | Caucasian (North America) | 5.7% |
| DR9 | Caucasian (North America) | 2.1% |
| DR1 | African (North) American | 13.20% |
| DR2 | African (North) American | 29.80% |
| DR3 | African (North) American | 24.80% |
| DR4 | African (North) American | 11.10% |
| DR5 | African (North) American | 31.10% |
| DR6 | African (North) American | 33.70% |
| DR7 | African (North) American | 19.20% |
| DR8 | African (North) American | 12.10% |
| DR9 | African (North) American | 5.80% |
| DR1 | Asian (North) American | 6.80% |
| DR2 | Asian (North) American | 33.80% |
| DR3 | Asian (North) American | 9.20% |
| DR4 | Asian (North) American | 28.60% |
| DR5 | Asian (North) American | 30.00% |
| DR6 | Asian (North) American | 25.10% |
| DR7 | Asian (North) American | 13.40% |
| DR8 | Asian (North) American | 12.70% |
| DR9 | Asian (North) American | 18.60% |
| DR1 | Latin (North) American | 15.30% |
| DR2 | Latin (North) American | 21.20% |
| DR3 | Latin (North) American | 15.20% |
| DR4 | Latin (North) American | 36.80% |
| DR5 | Latin (North) American | 20.00% |
| DR6 | Latin (North) American | 31.10% |
| DR7 | Latin (North) American | 20.20% |
| DR8 | Latin (North) American | 18.60% |
| DR9 | Latin (North) American | 2.10% |
| A*24 | Philippines | 65% |
| A*24 | Russia Nenets | 61% |
| A*24:02 | Japan | 59% |
| A*24 | Malaysia | 58% |
| A*24:02 | Philippines | 54% |
| A*24 | India | 47% |
| A*24 | South Korea | 40% |
| A*24 | Sri Lanka | 37% |
| A*24 | China | 32% |
| A*24:02 | India | 29% |
| A*24 | Australia West | 22% |
| A*24 | USA | 22% |
| A*24 | Russia Samara | 20% |
| A*24 | South America | 20% |
| A*24 | Europe | 18% |

[0134] The peptides of the invention, preferably when included into a vaccine of the invention as described herein bind to A*02. 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 positive, whereas no selection for MHC class II allotypes is necessary due to the pan-binding nature of these peptides.

[0135] 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.allelefrequencies.net).

**[0136]** In a preferred embodiment, the term "nucleotide sequence" refers to a heteropolymer of deoxyribonucleotides.

**[0137]** 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.

**[0138]** 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.

**[0139]** 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.

**[0140]** The term "coding region" refers to that portion of a gene which either naturally or normally codes for the expression product of that gene in its natural genomic environment, i.e., the region coding in vivo for the native expression product of the gene.

**[0141]** 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.

**[0142]** 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).

**[0143]** 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.

**[0144]** 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.

**[0145]** 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.

**[0146]** The term "promoter" means a region of DNA involved in binding of RNA polymerase to initiate transcription.

**[0147]** 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.

**[0148]** 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.

**[0149]** 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 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.

**[0150]** 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.

**[0151]** 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:

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

**[0152]** 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

**[0153]** (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

**[0154]** (ii) each gap in the Reference Sequence and

**[0155]** (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

**[0156]** (iiii) the alignment has to start at position 1 of the aligned sequences; and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

**[0157]** 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.

**[0158]** 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: 385 or a variant thereof which is 88% homologous to SEQ ID NO: 1 to SEQ ID NO: 385, 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.

**[0159]** 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.

**[0160]** 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).

**[0161]** 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: 385. 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.

**[0162]** 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 385, 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.

**[0163]** 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."

**[0164]** 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, lie, Val, Cys); and Group 5-large, aromatic residues (Phe, Tyr, Trp).

**[0165]** 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.

**[0166]** 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.

**[0167]** 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.

**[0168]** 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.

**[0169]** The amino acid residues that do not substantially contribute to interactions with the T-cell receptor can be modified by replacement with other amino acids 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.

TABLE 6

Variants and motif of the peptides according to SEQ ID NO: 2, 5, 8, 62, and 53

| | Position | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| SEQ ID NO. 2 | A | L | H | R | P | D | V | Y | L | | |
| Variants | | | | | | | | | V | | |
| | | | | | | | | | I | | |
| | | | | | | | | | A | | |
| | | M | | | | | | | | | |
| | | M | | | | | | | V | | |
| | | M | | | | | | | I | | |
| | | M | | | | | | | A | | |
| | | A | | | | | | | | | |
| | | A | | | | | | | V | | |
| | | A | | | | | | | I | | |
| | | A | | | | | | | A | | |
| | | V | | | | | | | | | |
| | | V | | | | | | | V | | |
| | | V | | | | | | | I | | |
| | | V | | | | | | | A | | |
| | | T | | | | | | | | | |
| | | T | | | | | | | V | | |
| | | T | | | | | | | I | | |
| | | T | | | | | | | A | | |
| | | Q | | | | | | | | | |
| | | Q | | | | | | | V | | |
| | | Q | | | | | | | I | | |
| | | Q | | | | | | | A | | |
| SEQ ID NO 5 | A | L | I | F | K | I | A | S | A | | |
| Variants | | | | | | | | | L | | |
| | | | | | | | | | I | | |
| | | | | | | | | | V | | |
| | | M | | | | | | | | | |
| | | M | | | | | | | L | | |
| | | M | | | | | | | I | | |
| | | M | | | | | | | V | | |

TABLE 6 -continued

Variants and motif of the peptides according to SEQ ID NO: 2, 5, 8, 62, and 53

| | Position | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| | | A | | | | | | | | | |
| | | A | | | | | | | L | | |
| | | A | | | | | | | I | | |
| | | A | | | | | | | V | | |
| | | V | | | | | | | | | |
| | | V | | | | | | | L | | |
| | | V | | | | | | | I | | |
| | | V | | | | | | | V | | |
| | | T | | | | | | | | | |
| | | T | | | | | | | L | | |
| | | T | | | | | | | I | | |
| | | T | | | | | | | V | | |
| | | Q | | | | | | | | | |
| | | Q | | | | | | | L | | |
| | | Q | | | | | | | I | | |
| | | Q | | | | | | | V | | |
| SEQ ID NO. 8 | A | L | A | A | S | A | L | P | A | L | V |
| Variants | | | | | | | | | | | I |
| | | | | | | | | | | | L |
| | | | | | | | | | | | A |
| | | M | | | | | | | | | |
| | | M | | | | | | | | | I |
| | | M | | | | | | | | | L |
| | | M | | | | | | | | | A |
| | | A | | | | | | | | | |
| | | A | | | | | | | | | I |
| | | A | | | | | | | | | L |
| | | A | | | | | | | | | A |
| | | V | | | | | | | | | |
| | | V | | | | | | | | | I |
| | | V | | | | | | | | | L |
| | | V | | | | | | | | | A |
| | | T | | | | | | | | | |
| | | T | | | | | | | | | I |
| | | T | | | | | | | | | L |
| | | T | | | | | | | | | A |
| | | Q | | | | | | | | | |
| | | Q | | | | | | | | | I |
| | | Q | | | | | | | | | L |
| | | Q | | | | | | | | | A |
| SEQ ID 62 | G | I | I | D | G | S | P | R | L | | |
| Variants | | L | | | | | | | V | | |
| | | L | | | | | | | I | | |
| | | L | | | | | | | | | |
| | | L | | | | | | | A | | |
| | | M | | | | | | | V | | |
| | | M | | | | | | | I | | |
| | | M | | | | | | | | | |
| | | M | | | | | | | A | | |
| | | A | | | | | | | V | | |
| | | A | | | | | | | I | | |
| | | A | | | | | | | | | |
| | | A | | | | | | | A | | |
| | | V | | | | | | | V | | |
| | | V | | | | | | | I | | |
| | | V | | | | | | | | | |
| | | V | | | | | | | A | | |
| | | T | | | | | | | V | | |
| | | T | | | | | | | I | | |
| | | T | | | | | | | | | |
| | | T | | | | | | | A | | |
| | | Q | | | | | | | V | | |
| | | Q | | | | | | | I | | |
| | | Q | | | | | | | | | |
| | | Q | | | | | | | A | | |

TABLE 6 -continued

| Variants and motif of the peptides according to SEQ ID NO: 2, 5, 8, 62, and 53 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Position | | | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| SEQ ID 153 | S | L | L | A | | L | H | V | L | | |
| Variants | | | | | | | | | V | | |
| | | | | | | | | | I | | |
| | | | | | | | | | A | | |
| | | M | | | | | | | V | | |
| | | M | | | | | | | I | | |
| | | M | | | | | | | | | |
| | | M | | | | | | | A | | |
| | | A | | | | | | | V | | |
| | | A | | | | | | | I | | |
| | | A | | | | | | | | | |
| | | A | | | | | | | A | | |
| | | V | | | | | | | V | | |
| | | V | | | | | | | I | | |
| | | V | | | | | | | | | |
| | | V | | | | | | | A | | |
| | | T | | | | | | | V | | |
| | | T | | | | | | | I | | |
| | | T | | | | | | | | | |
| | | T | | | | | | | A | | |
| | | Q | | | | | | | V | | |
| | | Q | | | | | | | I | | |
| | | Q | | | | | | | | | |
| | | Q | | | | | | | A | | |

**[0170]** 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.

**[0171]** 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 7.

TABLE 7

| 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 |

**[0172]** 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.

**[0173]** 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.

**[0174]** 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.

**[0175]** 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 or 22 amino acids.

**[0176]** 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.

**[0177]** 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 μM, more preferably no more than about 1 nM, and still more preferably no more than about 100 μM, and most preferably no more than about 10 μM. It is also preferred that the substituted peptide be recognized by T cells from more than one individual, at least two, and more preferably three individuals.

[0178] 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: 385.

[0179] "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 385 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.

[0180] 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.

[0181] 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.

[0182] 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 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.

[0183] A non-peptide bond is, for example, —$CH_2$—NH, —$CH_2S$—, —$CH_2CH_2$-, —CH═CH—, —$COCH_2$—, —CH(OH)$CH_2$—, and —$CH_2SO$—. U.S. Pat. No. 4,897,445 provides a method for the solid phase synthesis of non-peptide bonds (—$CH_2$—NH) in polypeptide chains which involves polypeptides synthesized by standard procedures and the non-peptide bond synthesized by reacting an amino aldehyde and an amino acid in the presence of $NaCNBH_3$.

[0184] Peptides comprising the sequences described above may be synthesized with additional chemical groups present at their amino and/or carboxy termini, to enhance the stability, bioavailability, and/or affinity of the peptides. For example, hydrophobic groups such as carbobenzoxyl, dansyl, 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] Histidine can also be modified using 4-hydroxy-2-nonenal. The reaction of lysine residues and other a-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.

[0190] 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).

[0191] 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.

[0192] A peptide or variant, wherein the peptide is modified or includes non-peptide bonds is a preferred embodiment of the invention.

[0193] 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: 385 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 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 $(NH_4)_3PO_4$, $(NH_4)_2HPO_4$, $(NH_4)H_2PO_4$, $(NH_4)_2SO_4$, $NH_4CH_3COO$, $NH_4Cl$, $NH_4Br$, $NH_4NO_3$, $NH_4ClO_4$, $NH_4I$, $NH_4SCN$, $Rb_3PO_4$, $Rb_2HPO_4$, $RbH_2PO_4$, $Rb_2SO_4$, $Rb_4CH_3COO$, $Rb_4Cl$, $Rb_4Br$, $Rb_4NO_3$, $Rb_4ClO_4$, $Rb_4I$, $Rb_4SCN$, $K_3PO_4$, $K_2HPO_4$, $KH_2PO_4$, $K_2SO_4$, $KCH_3COO$, 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, $Cu_2SO_4$, $Mg_3(PO_4)_2$, $Mg_2HPO_4$, $Mg(H_2PO_4)_2$, $Mg_2SO_4$, $Mg(CH_3COO)_2$, $MgCl_2$, $MgBr_2$, $Mg(NO_3)_2$, $Mg(ClO_4)_2$, $MgI_2$, $Mg(SCN)_2$, $MnCl_2$, $Ca_3(PO_4)$, $Ca_2HPO_4$, $Ca(H_2PO_4)_2$, $CaSO_4$, $Ca(CH_3COO)_2$, $CaCl_2$, $CaBr_2$, $Ca(NO_3)_2$, $Ca(ClO_4)_2$, $CaI_2$, $Ca(SCN)_2$, $Ba_3(PO_4)_2$, $Ba_2HPO_4$, $Ba(H_2PO_4)_2$, $BaSO_4$, $Ba(CH_3COO)_2$, $BaCl_2$, $BaBr_2$, $Ba(NO_3)_2$, $Ba(ClO_4)_2$, $BaI_2$, and $Ba(SCN)_2$. 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.

[0194] 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), 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-dicyclohexyl-carbodiimide/1 hydroxybenzotriazole 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.

[0195] 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).

[0196] 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).

[0197] 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.

[0198] 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. In order to select over-presented peptides, a presentation profile is calculated showing the median sample presentation as well as replicate variation. The profile juxtaposes samples of the tumor entity of interest to a baseline of normal tissue samples. Each of these profiles can then be consolidated into an over-presentation score by calculating the p-value of a Linear Mixed-Effects Model (Pinheiro et al., 2015) adjusting for multiple testing by False Discovery Rate (Benjamini and Hochberg, 1995) (cf. Example 1, FIGS. **1A-1V**).

[0199] For the identification and relative quantitation of HLA ligands by mass spectrometry, HLA molecules from shock-frozen tissue samples were purified and HLA-associated peptides were isolated. The isolated peptides were separated and sequences were identified by online nano-electrospray-ionization (nanoESI) liquid chromatography-mass spectrometry (LC-MS) experiments. The resulting peptide sequences were verified by comparison of the fragmentation pattern of natural tumor-associated peptides (TUMAPs) recorded from CLL samples (N=17 A*02-positive samples) with the fragmentation patterns of corresponding synthetic reference peptides of identical sequences. Since the peptides were directly identified as ligands of HLA molecules of primary tumors, these results provide direct evidence for the natural processing and presentation of the identified peptides on primary cancer tissue obtained from 16 CLL patients.

[0200] 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.

[0201] Presentation levels including error estimates for each peptide and sample were established. Peptides exclusively presented on tumor tissue and peptides over-presented in tumor versus non-cancerous tissues and organs have been identified.

[0202] HLA-peptide complexes from CLL tissue samples were purified and HLA-associated peptides were isolated and analyzed by LC-MS (see examples). All TUMAPs contained in the present application were identified with this approach on primary CLL samples confirming their presentation on primary CLL.

[0203] TUMAPs identified on multiple CLL and normal tissues were quantified using ion-counting of label-free LC-MS data. The method assumes that LC-MS signal areas of a peptide correlate with its abundance in the sample. All quantitative signals of a peptide in various LC-MS experiments were normalized based on central tendency, averaged per sample and merged into a bar plot, called presentation profile. The presentation profile consolidates different analysis methods like protein database search, spectral clustering, charge state deconvolution (decharging) and retention time alignment and normalization.

[0204] Furthermore, the discovery platform Technique XPRESIDENT® v2.x (see for example PCT/EP2011/056056 and PCT/EP2015/079873) allows the direct absolute quantitation of MHC-, preferably HLA-restricted, peptide levels on cancer or other infected tissues.

[0205] Briefly, the total cell count was calculated from the total DNA content of the analyzed tissue sample. The total peptide amount for a TUMAP in a tissue sample was measured by nanoLC-MS/MS as the ratio of the natural TUMAP and a known amount of an isotope-labelled version of the TUMAP, the so-called internal standard. The efficiency of TUMAP isolation was determined by spiking peptide:MHC complexes of all selected TUMAPs into the tissue lysate at the earliest possible point of the TUMAP isolation procedure and their detection by nanoLC-MS/MS following completion of the peptide isolation procedure. The total cell count and the amount of total peptide were calculated from triplicate measurements per tissue sample. The peptide-specific isolation efficiencies were calculated as an average from 10 spike experiments each measured as a triplicate (see Example 6 and Table 12). Besides over-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, FIGS. 3A-3F). An additional source of normal tissue data was a database of publicly available RNA expression data from around 3000 normal tissue samples (Lonsdale, 2013). 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.

[0206] The present invention provides peptides that are useful in treating cancers/tumors, preferably CLL 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 CLL samples.

[0207] 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 adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, and urinary bladder cells or other normal tissue cells, demonstrating a high degree of tumor association of the source genes (see Example 2).

[0208] Moreover, the peptides themselves are strongly over-presented on tumor tissue—"tumor tissue" in relation to this invention shall mean a sample from a patient suffering from CLL, but not on normal tissues (see Example 1).

[0209] 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. CLL 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 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. 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.

**[0210]** 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 nucleic acids, vectors and host cells for expressing TCRs and peptides of the present description; and methods of using the same.

**[0211]** 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.

**[0212]** 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.

**[0213]** 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.

**[0214]** 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 (TRDD/TRDJ) region, and the term "TCR delta constant domain" refers to the extracellular TRDC region, or to a C-terminal truncated TRDC sequence.

**[0215]** TCRs of the present description preferably bind to an peptide-HLA molecule complex with a binding affinity (KD) of about 100 μM or less, about 50 μM or less, about 25 M or less, or about 10 μM or less. More preferred are high affinity TCRs having binding affinities of about 1 μM 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.

**[0216]** 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 μM or less.

**[0217]** 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.

**[0218]** 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.

**[0219]** 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.

**[0220]** 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.

**[0221]** 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 pepides can be enhanced by methods well known in the art.

[0222] 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 HLA-A*02-negative healthy donors with A2/peptide monomers, incubating the PBMCs with tetramer-phyco-erythrin (PE) and isolating the high avidity T-cells by fluo-rescence activated cell sorting (FACS)-Calibur analy-sis.

[0223] 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 TCRap 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.

[0224] 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.

[0225] 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 sys-tems.

[0226] 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.

[0227] 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) promoter. In a preferred embodiment, the promoter is heterologous to the nucleic acid being expressed.

[0228] 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).

[0229] 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.

[0230] 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 bi-cistronic constructs in a single vector, which has been shown to be capable of over-coming 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).

[0231] 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 "op-timal" 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, has been shown to significantly enhance TCR-alpha and TCR-beta gene expression (Scholten et al., 2006).

[0232] 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 de-creasing 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 (CD3 fusion). (Schmitt et al. 2009).

[0233] In an embodiment, a host cell is engineered to express a TCR of the present description.

[0234] 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.

[0235] 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.

[0236] 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.

**[0237]** In an especially preferred embodiment, the pharmaceutical compositions comprise the peptides as salts of acetic acid (acetates), trifluoro acetates or hydrochloric acid (chlorides).

**[0238]** 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 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.

**[0239]** 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. 385, 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.

**[0240]** 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.

**[0241]** 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.

**[0242]** The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

**[0243]** 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, Conn., USA. A desirable method of modifying the DNA encoding the polypeptide of the invention employs the polymerase chain reaction as disclosed by Saiki R K, et al. (Saiki et al., 1988).

**[0244]** 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.

**[0245]** 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 U.S. Pat. Nos. 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.

**[0246]** The DNA (or in the case of retroviral vectors, RNA) encoding the polypeptide constituting the compound of the invention may be joined to a wide variety of other DNA sequences for introduction into an appropriate host. The companion DNA will depend upon the nature of the host, the manner of the introduction of the DNA into the host, and whether episomal maintenance or integration is desired.

**[0247]** 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.

[0248] Alternatively, the gene for such selectable trait can be on another vector, which is used to co-transform the desired host cell.

[0249] 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.

[0250] 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.

[0251] 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.

[0252] One example is pSVL available from Pharmacia, Piscataway, N.J., USA. An example of an inducible mammalian expression vector is pMSG, also available from Pharmacia.

[0253] Useful yeast plasmid vectors are pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, Calif. 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (Ylps) and incorporate the yeast selectable markers HIS3, TRP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps). 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, 3×FLAG, 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.

[0254] 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.

[0255] 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.

[0256] 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).

[0257] 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, Calif. 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 Balbas 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.

[0258] 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.

[0259] 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 and is well known in the art for transforming yeast cell, bacterial cells, insect cells and vertebrate cells.

[0260] 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.

[0261] 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.

[0262] 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 Apr. 29, 2010, to treat asymptomatic or minimally symptomatic metastatic HRPC (Sipuleucel-T) (Rini et al., 2006; Small et al., 2006).

**[0263]** 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.

**[0264]** In another embodiment, the peptide, the nucleic acid or the expression vector of the invention are used in medicine. For example, the peptide or its variant may be prepared for intravenous (i.v.) injection, sub-cutaneous (s.c.) injection, intradermal (i.d.) injection, intraperitoneal (i.p.) injection, intramuscular (i.m.) injection. Preferred methods of peptide injection include s.c., i.d., i.p., i.m., and i.v. Preferred methods of DNA injection include i.d., i.m., s.c., i.p. and i.v. Doses of e.g. between 50 μg and 1.5 mg, preferably 125 μg to 500 μg, of peptide or DNA may be given and will depend on the respective peptide or DNA. Dosages of this range were successfully used in previous trials (Walter et al., 2012).

**[0265]** 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).

**[0266]** 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.

**[0267]** 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.

**[0268]** 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, Juvlmmune®, 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, 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).

**[0269]** 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 experiments (Krieg, 2006). U.S. Pat. No. 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.

**[0270]** Other examples for useful adjuvants include, but are not limited to chemically modified CpGs (e.g. CpR, Idera), dsRNA analogues such as Poly(l:C) and derivates thereof (e.g.

**[0271]** AmpliGen®, Hiltonol®, poly-(ICLC), poly(IC—R), poly(l: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.

**[0272]** Preferred adjuvants are anti-CD40, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, interferon-alpha, CpG oligonucleotides and derivates, poly-(I:C) and derivates, RNA, sildenafil, and particulate formulations with PLG or virosomes.

**[0273]** 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.

**[0274]** In a preferred embodiment, the pharmaceutical composition according to the invention the adjuvant is selected from the group consisting of colony-stimulating factors, such as Granulocyte Macrophage Colony Stimulating Factor (GM-CSF, sargramostim), cyclophosphamide, imiquimod and resiquimod. In a preferred embodiment of the pharmaceutical composition according to the invention, the adjuvant is cyclophosphamide, imiquimod or resiquimod. Even more preferred adjuvants are Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, poly-ICLC (Hiltonol®) and anti-CD40 mAB, or combinations thereof.

**[0275]** 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).

**[0276]** 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.

**[0277]** 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.

**[0278]** 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.

**[0279]** 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 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).

**[0280]** 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.

**[0281]** "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.

**[0282]** 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 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, anti-CD28. For further information on polypeptide scaffolds see for example the background section of WO 2014/071978A1 and the references cited therein.

**[0283]** 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.

**[0284]** Furthermore, aptamers recognizing specific tumor cell lines have been identified.

**[0285]** 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, this renders the aptamers applicable as so-called broad-spectrum diagnostics and therapeutics.

**[0286]** Further, investigation of cell-binding behavior with flow cytometry showed that the aptamers revealed very good apparent affinities that are within the nanomolar range.

**[0287]** 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.

**[0288]** 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 385, according to the invention at hand with the MHC molecule, using the cell-SELEX (Systematic Evolution of Ligands by Exponential enrichment) technique.

**[0289]** 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.

**[0290]** This use can help to detect small metastases or to determine the size and precise localization of diseased tissues.

**[0291]** Therefore, it is a further aspect of the invention to provide a method for producing a recombinant antibody specifically binding to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, the method comprising: immunizing a genetically engineered non-human mammal comprising cells expressing said human major histocompatibility complex (MHC) class I or II with a soluble form of a MHC class I or II molecule being complexed with said HLA-restricted antigen; isolating mRNA molecules from antibody producing cells of said non-human mammal; producing a phage display library displaying protein molecules encoded by said mRNA molecules; and isolating at least one phage from said phage display library, said at least one phage displaying said antibody specifically binding to said human major histocompatibility complex (MHC) class I or II being complexed with said HLA-restricted antigen.

**[0292]** It is a further aspect of the invention to provide an antibody that specifically binds to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, wherein the antibody preferably is a polyclonal antibody, monoclonal antibody, bi-specific antibody and/or a chimeric antibody.

**[0293]** 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.

**[0294]** 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.

**[0295]** 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: 385, or a variant thereof which is at least 88% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 385 or a variant thereof that induces T cells cross-reacting with said peptide, wherein said peptide is not the underlying full-length polypeptide.

**[0296]** 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: 385 or a variant thereof which is at least 88% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 385, 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.

**[0297]** 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.

**[0298]** 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: 385.

**[0299]** The present invention further relates to the peptides according to the invention, wherein the peptide is (chemically) modified and/or includes non-peptide bonds.

**[0300]** 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 (li), 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.

**[0301]** The present invention further relates to the nucleic acid according to the invention that is DNA, cDNA, PNA, RNA or combinations thereof.

**[0302]** The present invention further relates to an expression vector capable of expressing a nucleic acid according to the present invention.

**[0303]** 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 CLL.

**[0304]** 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.

[0305] 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.

[0306] 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.

[0307] 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.

[0308] The present invention further relates to the method according to the 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: 385 or said variant amino acid sequence.

[0309] 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.

[0310] 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 according to the present invention.

[0311] 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.

[0312] 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.

[0313] The present invention further relates to a use according to the invention, wherein said cancer cells are CLL cells or other solid or hematological tumor cells such as acute myelogenous leukemia, bile duct cancer, brain cancer, breast cancer, colorectal carcinoma, esophageal cancer, gallbladder cancer, gastric cancer, hepatocellular cancer, Merkel cell carcinoma, melanoma, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small cell lung cancer, urinary bladder cancer and uterine cancer. 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 CLL. The present invention also relates to the use of these novel targets for cancer treatment.

[0314] The term "antibody" or "antibodies" is used herein in a broad sense and includes both polyclonal and monoclonal antibodies. In addition to intact or "full" immunoglobulin molecules, also included in the term "antibodies" are fragments (e.g. CDRs, Fv, Fab and Fc fragments) or polymers of those immunoglobulin molecules and humanized versions of immunoglobulin molecules, as long as they exhibit any of the desired properties (e.g., specific binding of a CLL marker (poly)peptide, delivery of a toxin to a CLL cell expressing a cancer marker gene at an increased level, and/or inhibiting the activity of a CLL marker polypeptide) according to the invention.

[0315] 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 CLL 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.

[0316] 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: 385 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 CLL marker polypeptide used to generate the antibody according to the invention.

[0317] 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-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.

[0318] 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 (U.S. Pat. No. 4,816,567, which is hereby incorporated in its entirety).

[0319] 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 U.S. Pat. No. 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).

**[0320]** In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art. For instance, digestion can be performed using papain. Examples of papain digestion are described in WO 94/29348 and U.S. Pat. No. 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.

**[0321]** 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.

**[0322]** 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.

**[0323]** 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.

**[0324]** The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

**[0325]** 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.

**[0326]** 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 (U.S. Pat. No. 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.

**[0327]** 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.

**[0328]** Antibodies of the invention are preferably administered to a subject in a pharmaceutically acceptable carrier. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of antibody being administered.

**[0329]** 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.

**[0330]** 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.

[0331] A typical daily dosage of the antibody used alone might range from about 1 (μg/kg to up to 100 mg/kg of body weight or more per day, depending on the factors mentioned above.

[0332] Following administration of an antibody, preferably for treating CLL, the efficacy of the therapeutic antibody can be assessed in various ways well known to the skilled practitioner. For instance, the size, number, and/or distribution of cancer in a subject receiving treatment may be monitored using standard tumor imaging techniques. A therapeutically-administered antibody that arrests tumor growth, results in tumor shrinkage, and/or prevents the development of new tumors, compared to the disease course that would occurs in the absence of antibody administration, is an efficacious antibody for treatment of cancer.

[0333] 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), 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.

[0334] 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.

[0335] The antibodies or TCRs may also be used for in vivo diagnostic assays. Generally, the antibody is labeled with a radionucleotide (such as $^{111}$1n, $^{99}$Tc, $^{14}$C, $^{131}$I, $^{3}$H, $^{32}$P or $^{35}$S) SO that the tumor can be localized using immunoscintiography. In one embodiment, antibodies or fragments thereof bind to the extracellular domains of two or more targets of a protein selected from the group consisting of the above-mentioned proteins, and the affinity value (Kd) is less than 1×10 μM.

[0336] Antibodies for diagnostic use may be labeled with probes suitable for detection by various imaging methods. Methods for detection of probes include, but are not limited to, fluorescence, light, confocal and electron microscopy; magnetic resonance imaging and spectroscopy; fluoroscopy, computed tomography and positron emission tomography.

[0337] 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.

[0338] 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.

[0339] 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, Md. 20852, USA under Catalogue No CRL 1992; the *Drosophila* cell line Schneider line 2 is available from the ATCC under Catalogue No CRL 19863; the mouse RMA-S cell line is described in Ljunggren et al. (Ljunggren and Karre, 1985).

[0340] 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.

[0341] In case of a MHC class I epitope being used as an antigen, the T cells are CD8-positive T cells.

[0342] 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: 385, or a variant amino acid sequence thereof.

[0343] 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.

[0344] 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.

[0345] 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 elicit high- or low-avidity antigen-specific T cell responses with high efficiency from blood samples. Apart from MHC:peptide complexes, aAPCs should carry other proteins with co-stimulatory activity like anti-CD28 antibodies coupled to their surface. Furthermore, such aAPC-based systems often require the addition of appropriate soluble factors, e. g. cytokines, like interleukin-12.

**[0346]** 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, 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.

**[0347]** 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.

**[0348]** 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 385.

**[0349]** Preferably, the T cell recognizes the cell by interacting through its TCR with the HLA/peptide-complex (for example, binding). The T cells are useful in a method of killing target cells in a patient whose target cells aberrantly express a polypeptide comprising an amino acid sequence of the invention wherein the patient is administered an effective number of the activated T cells. The T cells that are administered to the patient may be derived from the patient and activated as described above (i.e. they are autologous T cells). Alternatively, the T cells are not from the patient but are from another individual. Of course, it is preferred if the individual is a healthy individual. By "healthy individual" the inventors mean that the individual is generally in good health, preferably has a competent immune system and, more preferably, is not suffering from any disease that can be readily tested for, and detected.

**[0350]** 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)).

**[0351]** 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.

**[0352]** 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.

**[0353]** T cells may be obtained by methods known in the art, e.g. those described above.

**[0354]** Protocols for this so-called adoptive transfer of T cells are well known in the art. Reviews can be found in: Gattioni 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.

**[0355]** 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).

**[0356]** 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.

**[0357]** 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.

**[0358]** 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.

**[0359]** 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).

**[0360]** 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.

[0361] 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.

[0362] 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.

[0363] 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.

[0364] 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.

[0365] Since the peptides of the invention were isolated from CLL, the medicament of the invention is preferably used to treat CLL.

[0366] 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.

[0367] 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.

[0368] 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 CLL 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 CLL tissues, the warehouse may contain HLA-A*02 and HLA-A*24 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.

[0369] 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, CLL samples from patients and blood from healthy donors were analyzed in a stepwise approach:

[0370] 1. HLA ligands from the malignant material were identified by mass spectrometry

[0371] 2. Genome-wide messenger ribonucleic acid (mRNA) expression analysis was used to identify genes over-expressed in the malignant tissue (CLL) compared with a range of normal organs and tissues

[0372] 3. Identified HLA ligands were compared to gene expression data. Peptides over-presented or selectively 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.

[0373] 4. Literature research was performed in order to identify additional evidence supporting the relevance of the identified peptides as TUMAPs

[0374] 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.

[0375] 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 CLL patients.

[0376] 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.

[0377] 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.

**[0378]** In one 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.

**[0379]** 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.

**[0380]** 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.

**[0381]** 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 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.

**[0382]** 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.

**[0383]** 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.

**[0384]** 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; and (b) selecting at least one peptide identified de novo in (a) and confirming its immunogenicity.

**[0385]** 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.

**[0386]** 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.

**[0387]** 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.

**[0388]** 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 CLL 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.

**[0389]** 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 biomarker for CLL. 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 of malignant cells escape immuno-surveillance.

**[0390]** Thus, presence of peptides shows that this mechanism is not exploited by the analyzed cells.

**[0391]** 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.

**[0392]** 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

**[0393]** FIGS. **1**A to **1**V show the overpresentation of various peptides in normal tissues (white bars) and CLL (black bars). FIG. **1**A) Gene: IGHM, Peptide: ALHRPDVYL (SEQ ID NO.: 2). Tissues from left to right: 2 adipose tissues, 3 adrenal glands, 4 blood cells, 10 blood vessels, 6 bone marrows, 7 brains, 6 breasts, 2 cartilages, 2 eyes, 3 gallbladders, 6 hearts, 14 kidneys, 19 large intestines, 20 livers, 45 lungs, 6 lymph nodes, 7 nerves, 3 ovaries, 10 pancreases, 3 parathyroid glands, 1 peritoneum, 5 pituitary glands, 6 placentas, 3 pleuras, 3 prostates, 7 salivary glands, 5 skeletal muscles, 6 skins, 4 small intestines, 9 spleens, 5 stomachs, 6 testes, 2 thymi, 3 thyroid glands, 9 tracheas, 3 ureters, 6 urinary bladders, 2 uteri, 6 esophagi, 17 chronic lymphocytic leukemia samples. The peptide has additionally been detected on 2/21 non-Hodgkin lymphoma samples. FIG. **1**B) Gene: IGHM, Peptide: VIAELPPKV (SEQ ID NO.: 3). Tissues from left to right: 2 adipose tissues, 3 adrenal glands, 4 blood cells, 10 blood vessels, 6 bone marrows, 7 brains, 6 breasts, 2 cartilages, 2 eyes, 3 gallbladders, 6 hearts, 14 kidneys, 19 large intestines, 20 livers, 45 lungs, 6 lymph nodes, 7 nerves, 3 ovaries, 10 pancreases, 3 parathyroid glands, 1 peritoneum, 5 pituitary glands, 6 placentas, 3 pleuras, 3 prostates, 7 salivary glands, 5 skeletal muscles, 6 skins, 4 small intestines, 9 spleens, 5 stomachs, 6 testes, 2 thymi, 3 thyroid glands, 9 tracheas, 3 ureters, 6 urinary bladders, 2 uteri, 6 esophagi, 17 chronic lymphocytic leukemia samples. The peptide has additionally been detected on 5/21 non-Hodgkin lymphoma samples and 1/90 lung cancers. FIG. **1**C), Gene: IGHM, Peptide: VIAELPPKVSV (SEQ ID No.: 4), Tissues from left to right: 2 adipose tissues, 3 adrenal glands, 4 blood cells, 10 blood vessels, 6 bone marrows, 7 brains, 6 breasts, 2 cartilages, 2 eyes, 3 gallbladders, 6 hearts, 14 kidneys, 19 large intestines, 20 livers, 45 lungs, 6 lymph nodes, 7 nerves, 3 ovaries, 10 pancreases, 3 parathyroid glands, 1 peritoneum, 5 pituitary glands, 6 placentas, 3 pleuras, 3 prostates, 7 salivary glands, 5 skeletal muscles, 6 skins, 4 small intestines, 9 spleens, 5 stomachs, 6 testes, 2 thymi, 3 thyroid glands, 9 tracheas, 3 ureters, 6 urinary bladders, 2 uteri, 6 esophagi, 17 chronic lymphocytic leukemia samples. FIG. **1**D), Gene: NUP210, Peptide: RLYEITIEV (SEQ ID No.: 121). Samples from left to right: 1 PBMC culture, 1 benign prostate, 8 normal tissues (3 lungs, 4 spleens, 1 trachea), 49 cancer tissues (2 brain cancers, 2 breast cancers, 1 colon cancer, 13 leukocytic leukemia cancers, 13 lung cancers, 8 lymph node cancers, 1 myeloid cells cancer, 4 ovarian cancers, 2 skin cancers, 1 urinary bladder cancer, 2 uterus cancers). Discrepancies regarding the list of tumor types between FIG. **1**D and table 4 may be due to the more stringent selection criteria applied in table 4 (for details please refer to table 4). The normal tissue panel and the cancer cell lines and xenografts tested were the same as in FIGS. **1**A-**1**C. FIG. **1**E), Gene: COBRA1, Peptide: ALLRLLPGL (SEQ ID No.: 14). Samples from left to right: 1 cell line, 11 cancer tissues (1 breast cancer, 1 colon cancer, 1 head and neck cancer, 2 leukocytic leukemia cancers, 1 liver cancer, 1 lung cancer, 2 lymph node cancers, 1 myeloid cell cancer, 1 skin cancer). FIG. **1**F), Gene: KIAA0226L, Peptide: GIIDGSPRL (SEQ ID No.: 62). Samples from left to right: 2 normal tissues (1 lymph node, 1 spleen), 18 cancer tissues (2 colon cancers, 9 leukocytic leukemia cancers, 6 lymph node cancers, 1 rectum cancer). FIG. **1**G), Gene: DDX3X, Peptide: GLDQQFAGLDL (SEQ ID No.: 68). Samples from left to right: 1 cell line, 2 primary cultures, 21 cancer tissues (1 bile duct cancer, 1 brain cancer, 1 breast cancer, 1 head and neck cancer, 2 kidney cancers, 3 leukocytic leukemia cancers, 2 liver cancers, 2 lung cancers, 2 lymph node cancers, 3 ovarian cancers, 1 rectum cancer, 1 skin cancer, 1 uterus cancer). FIG. **1**H), Gene: LIG1, Peptide: KTLDVDATYEI (SEQ ID No.: 112). Samples from left to right: 2 cell lines, 1 primary culture, 13 cancer tissues (1 esophageal cancer, 2 leukocytic leukemia cancers, 1 liver cancer, 3 lung cancers, 2 lymph node cancers, 2 ovarian cancers, 1 skin cancer, 1 uterus cancer). FIG. **1**I), Gene: SMCHD1, Peptide: SIIEGPIIKL (SEQ ID No.: 146). Samples from left to right: 14 cancer tissues (1 head and neck cancer, 3 leukocytic leukemia cancers, 6 lung cancers, 1 lymph node cancer, 1 ovarian cancer, 2 urinary bladder cancers). FIG. **1**J), Gene: MMS22L, Peptide: SILETVATL (SEQ ID No.: 147). Samples from left to right: 1 primary culture, 11 cancer tissues (1 colon cancer, 4 leukocytic leukemia cancers, 1 lung cancer, 3 lymph node cancers, 1 myeloid cell cancer, 1 skin cancer). FIG. **1**K), Gene: FCRL3, Peptide: SLLAELHVL (SEQ ID No.: 153). Samples from left to right: 1 cell line, 9 normal tissues (1 lymph node, 1 rectum, 7 spleens), 27 cancer tissues (1 breast cancer, 1 kidney cancer, 10 leukocytic leukemia cancers, 14 lymph node cancers, 1 skin cancer). FIG. **1**L), Gene: FAM126A, Peptide:

SLQEEKLIYV (SEQ ID No.: 159). Samples from left to right: 2 cell lines, 23 cancer tissues (5 brain cancers, 1 breast cancer, 1 esophageal cancer, 3 head and neck cancers, 2 leukocytic leukemia cancers, 5 lung cancers, 3 lymph node cancers, 1 skin cancer, 2 urinary bladder cancers). FIG. **1**M), Gene: HNRNPC, Peptide: SVHKGFAFV (SEQ ID No.: 164). Samples from left to right: 10 cell lines, 1 primary culture, 1 normal tissue (1 adrenal gland), 36 cancer tissues (12 brain cancers, 1 colon cancer, 2 head and neck cancers, 2 kidney cancers, 3 leukocytic leukemia cancers, 1 liver cancer, 5 lung cancers, 1 myeloid cell cancer, 1 ovarian cancer, 1 rectum cancer, 1 skin cancer, 2 stomach cancers, 2 urinary bladder cancers, 2 uterus cancers). FIG. **1**N), Gene: RASGRF1, Peptide: TLDTSKLYV (SEQ ID No.: 167). Samples from left to right: 13 cancer tissues (1 brain cancer, 8 leukocytic leukemia cancers, 4 lymph node cancers). FIG. **1**O), Gene: RASGRF1, Peptide: YLLDQSFVM (SEQ ID No.: 168). Samples from left to right: 16 cancer tissues (10 leukocytic leukemia cancers, 6 lymph node cancers). FIG. **1**P), Gene: RNF213, Peptide: YIQEYLTLL (SEQ ID No.: 192). Samples from left to right: 2 cell lines, 18 cancer tissues (1 colon cancer, 1 head and neck cancer, 1 kidney cancer, 4 leukocytic leukemia cancers, 5 lung cancers, 3 lymph node cancers, 1 myeloid cell cancer, 1 stomach cancer, 1 urinary bladder cancer). FIG. **1**Q), Gene: DCK, Peptide: YLQEVPILTL (SEQ ID No.: 197). Samples from left to right: 11 cancer tissues (5 leukocytic leukemia cancers, 4 lymph node cancers, 1 skin cancer, 1 uterus cancer). FIG. **1**R), Gene: EIF3H, Peptide: YMFEEVPIVI (SEQ ID No.: 200). Samples from left to right: 4 cell lines, 2 primary cultures, 34 cancer tissues (1 bile duct cancer, 2 breast cancers, 1 colon cancer, 1 esophageal cancer, 1 gallbladder cancer, 5 head and neck cancers, 2 leukocytic leukemia cancers, 2 liver cancers, 9 lung cancers, 4 lymph node cancers, 2 ovarian cancers, 1 rectum cancer, 2 skin cancers, 1 urinary bladder cancer). FIG. **1**S), Gene: UBLCP1, Peptide: LIDVKPLGV (SEQ ID No.: 211). Samples from left to right: 3 cell lines, 23 cancer tissues (5 brain cancers, 1 breast cancer, 1 esophageal cancer, 1 head and neck cancer, 1 kidney cancer, 3 leukocytic leukemia cancers, 2 liver cancers, 2 lung cancers, 4 lymph node cancers, 1 ovarian cancer, 1 prostate cancer, 1 skin cancer). FIG. **1**T), Gene: TMCO6, Peptide: QLLPVSNVVSV (SEQ ID No.: 256). Samples from left to right: 2 primary cultures, 13 cancer tissues (2 head and neck cancers, 3 leukocytic leukemia cancers, 1 liver cancer, 2 lung cancers, 4 lymph node cancers, 1 ovarian cancer). FIG. **1**U), Gene: MYO1G, Peptide: LLYNSTDPTL (SEQ ID No.: 312). Samples from left to right: 1 cell line, 2 primary cultures, 14 cancer tissues (1 colon cancer, 4 leukocytic leukemia cancers, 2 lung cancers, 5 lymph node cancers, 1 ovarian cancer, 1 urinary bladder cancer). FIG. **1**V), Gene: PIM1, Peptide: VLLPQETAEIHL (SEQ ID No.: 328). Samples from left to right: 3 primary cultures, 27 cancer tissues (1 breast cancer, 1 colon cancer, 5 leukocytic leukemia cancers, 5 lung cancers, 7 lymph node cancers, 2 ovarian cancers, 2 skin cancers, 1 stomach cancer, 3 urinary bladder cancers). FIGS. **2**A to **2**D show exemplary expression profiles of source genes of the present invention that are highly over-expressed or exclusively expressed in CLL in a panel of normal tissues (white bars) and 17 CLL samples (black bars). Tissues from left to right: 6 arteries, 1 blood cells, 1 brain, 1 heart, 2 livers, 2 lungs, 2 veins, 1 adipose tissue, 1 adrenal gland, 6 bone marrows, 1 cartilage, 1 colon, 1 esophagus, 2 eyes, 2 gallbladders, 1 kidney, 6 lymph nodes, 5 pancreases, 2 pituitary glands, 1 rectum, 1 salivary gland, 1 skeletal muscle, 1 skin, 1 small intestine, 1 spleen, 1 stomach, 1 thyroid gland, 7 tracheas, 1 urinary bladder, 1 breast, 5 ovaries, 3 placentas, 1 prostate, 1 testis, 1 thymus, 1 uterus, 10 chronic lymphocytic leukemia samples. FIG. **2**A) Gene symbol: FCER2; FIG. **2**B) Gene symbol: KIAA0226L; FIG. **2**C) Gene symbol: PAX5; FIG. **2**D) Gene symbol: CLEC17A.

**[0394]** FIGS. **3**A-**3**F show exemplary immunogenicity data: flow cytometry results after peptide-specific multimer staining. CD8+ T cells were primed using artificial APCs coated with anti-CD28 mAb and HLA-A*02 in complex with SeqID No 1 peptide (FIG. **3**C, left panel), SeqID No 5 peptide (FIG. **3**D left panel), SeqID No 32 peptide (FIG. **3**E, left panel) and SeqID No 220 peptide (FIG. **3**F, 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 1 (FIG. **3**C), A*02/SeqID No 5 (D), A*02/SeqID No 32 (FIG. **3**E) or A*02/SeqID No 220 (FIG. **3**F). Right panels (FIGS. **3**C, **3**D, **3**E and **3**F) 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.

## EXAMPLES

### Example 1

**[0395]** Identification and quantitation of tumor associated peptides presented on the cell surface Tissue samples Patients' tumor tissues were obtained from: ProteoGenex Inc. (Culver City, Calif., USA); University Hospital Bonn (Bonn, Germany); University Hospital Tubingen (Tubingen, Germany).

**[0396]** Normal tissues were obtained from Asterand (Detroit, Mich., USA & Royston, Herts, UK); Bio-Options Inc. (Brea, Calif., USA); BioServe (Beltsville, Md., USA); Capital BioScience Inc. (Rockville, Md., USA); Geneticist Inc. (Glendale, Calif., USA); Kyoto Prefectural University of Medicine (KPUM) (Kyoto, Japan); ProteoGenex Inc. (Culver City, Calif., USA); Tissue Solutions Ltd (Glasgow, UK); University Hospital Geneva (Geneva, Switzerland); University Hospital Heidelberg (Heidelberg, Germany); University Hospital Munich (Munich, Germany); University Hospital TObingen (TObingen, Germany).

**[0397]** 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.

**[0398]** Isolation of HLA Peptides from Tissue Samples

**[0399]** 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, CNBr-activated sepharose, acid treatment, and ultrafiltration.

[0400] Mass Spectrometry Analyses

[0401] The HLA peptide pools as obtained were separated according to their hydrophobicity by reversed-phase chromatography (nanoAcquity UPLC system, Waters) and the eluting peptides were analyzed in LTQ-velos and fusion hybrid mass spectrometers (ThermoElectron) equipped with an ESI source. Peptide pools were loaded directly onto the analytical fused-silica micro-capillary column (75 μm i.d.× 250 mm) packed with 1.7 μm C18 reversed-phase material (Waters) applying a flow rate of 400 nL per minute. Subsequently, the peptides were separated using a two-step 180 minute-binary gradient from 10% to 33% B at a flow rate of 300 nL per minute. The gradient was composed of Solvent A (0.1% formic acid in water) and solvent B (0.1% formic acid in acetonitrile). A gold coated glass capillary (PicoTip, New Objective) was used for introduction into the nanoESI source. The LTQ-Orbitrap mass spectrometers were operated in the data-dependent mode using a TOP5 strategy. In brief, a scan cycle was initiated with a full scan of high mass accuracy in the orbitrap (R=30 000), which was followed by MS/MS scans also in the orbitrap (R=7500) on the 5 most abundant precursor ions with dynamic exclusion of previously selected ions. Tandem mass spectra were interpreted by SEQUEST and additional manual control. The identified peptide sequence was assured by comparison of the generated natural peptide fragmentation pattern with the fragmentation pattern of a synthetic sequence-identical reference peptide.

[0402] Label-free relative LC-MS quantitation was performed by ion counting i.e. by extraction and analysis of LC-MS features (Mueller et al., 2007). The method assumes that the peptide's LC-MS signal area correlates with its abundance in the sample. Extracted features were further processed by charge state deconvolution and retention time alignment (Mueller et al., 2008; Sturm et al., 2008). Finally, all LC-MS features were cross-referenced with the sequence identification results to combine quantitative data of different samples and tissues to peptide presentation profiles. The quantitative data were normalized in a two-tier fashion according to central tendency to account for variation within technical and biological replicates. Thus each identified peptide can be associated with quantitative data allowing relative quantification between samples and tissues. In addition, all quantitative data acquired for peptide candidates was inspected manually to assure data consistency and to verify the accuracy of the automated analysis. For each peptide, a presentation profile was calculated showing the mean sample presentation as well as replicate variations. The profiles juxtapose CLL samples to a baseline of normal tissue samples. Presentation profiles of exemplary over-presented peptides are shown in FIGS. 1A-1V. Presentation scores for exemplary peptides are shown in Table 8.

[0403] Table 8: Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a

TABLE 8

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 1 | AIPPSFASIFL | +++ |
| 2 | ALHRPDVYL | +++ |
| 3 | VIAELPPKV | +++ |
| 4 | VIAELPPKVSV | +++ |
| 5 | ALIFKIASA | +++ |
| 6 | ALDTLEDDMTI | +++ |
| 7 | ALLERTGYTL | +++ |
| 8 | ALAASALPALV | +++ |
| 9 | ALCDTLITV | +++ |
| 10 | FVYGESVEL | +++ |
| 11 | ALFTFJPLTV | +++ |
| 12 | ALGEDEITL | +++ |
| 13 | VVDGMPPGV | ++ |
| 14 | ALLRLLPGL | + |
| 15 | ALPEVSVEA | + |
| 16 | ALPGGAAVAAV | ++ |
| 17 | ALTKTNLQL | +++ |
| 18 | LLGEFSIKM | +++ |
| 19 | QVMEKLAAV | + |
| 20 | ALVDPGPDFVV | + |
| 21 | ALWAGLLTL | +++ |
| 22 | ALWDPVIEL | +++ |
| 23 | ALYLTEVFL | +++ |
| 24 | AMAGDVVYA | +++ |
| 25 | ATYSGLESQSV | + |
| 27 | AVLGLVWLL | ++ |
| 28 | AVLHLLLSV | +++ |
| 29 | AVLQAVTAV | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 30 | ELLEGSEIYL | + |
| 31 | ELMHGVAGV | ++ |
| 32 | FIDKFTPPV | +++ |
| 33 | FIINSSNIFL | +++ |
| 35 | FILPSSLYL | +++ |
| 36 | FILTHVDQL | +++ |
| 37 | FIMEGGAMVL | +++ |
| 39 | FLDALLTDV | +++ |
| 40 | FLDEDDMSL | + |
| 41 | FLDPSLDPLL | +++ |
| 43 | FLLGPEALSFA | +++ |
| 45 | FLPELPADLEA | ++ |
| 47 | FLSDQPEPYL | ++ |
| 48 | FLSPQQPPLL | +++ |
| 49 | FLTDLFAQL | + |
| 50 | FLFEPVVKAFL | +++ |
| 51 | FLVEAPHDWDL | ++ |
| 52 | FLVETGFLHV | +++ |
| 53 | FLWQHVELVL | +++ |
| 54 | FLYPFPLALF | +++ |
| 56 | FVFEAPYTL | +++ |
| 57 | GLSEISLRL | +++ |
| 58 | YIQQGIFSV | ++ |
| 59 | FVFGDENGTVSL | +++ |
| 60 | FVLDHEDGLNL | ++ |
| 61 | FVYFIVREV | +++ |
| 62 | GIIDGSPRL | + |
| 63 | SLAHVAGCEL | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 64 | KLLESVASA | ++ |
| 65 | GLDDMKANL | +++ |
| 66 | SLAGGLDDMKA | +++ |
| 68 | GLDQQFAGLDL | +++ |
| 69 | GLHQREIFL | +++ |
| 70 | FVPDTPVGV | ++ |
| 71 | GLKHDIARV | +++ |
| 72 | GLLDAGKMYV | +++ |
| 73 | GLLEVISALQL | +++ |
| 74 | GLLRASFLL | +++ |
| 76 | GLLRIIPYL | ++ |
| 77 | GLLRLTWFL | ++ |
| 78 | GLPSFLTEV | +++ |
| 79 | GLQAKIQEA | +++ |
| 80 | VLIEDELEEL | +++ |
| 81 | WLVGQEFEL | +++ |
| 82 | GLQSGVDIGV | + |
| 83 | GQGEVLVYV | + |
| 86 | HLYPGAVTI | +++ |
| 88 | ILDEIGADVQA | +++ |
| 89 | ILDFGTFQL | +++ |
| 90 | VIADLGLIRV | +++ |
| 92 | ILEPLNPLL | +++ |
| 93 | ILFNTQINI | +++ |
| 94 | ILFPLRFTL | +++ |
| 95 | ILGYMAHEHKV | +++ |
| 96 | ILIDKTSFV | + |
| 97 | LLFATQITL | + |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 98 | SLIKYFLFV | +++ |
| 99 | ILIFHSVAL | +++ |
| 100 | ILNNEVFAI | + |
| 101 | ILVVIEPLL | +++ |
| 102 | IQDRAVPSL | +++ |
| 103 | KLGGTPAPA | ++ |
| 104 | KLILLDTPLFL | +++ |
| 105 | KLMNDIADI | +++ |
| 106 | FMASHLDYL | +++ |
| 107 | ILYNLYDLL | ++ |
| 108 | VIYTLIHYI | + |
| 109 | KLWEGLTELV | ++ |
| 112 | KTLDVDATYEI | +++ |
| 113 | KVPAEEVLVAV | + |
| 114 | LIPEGPPQV | +++ |
| 115 | LLFDKLYLL | +++ |
| 116 | LLIGATMQV | +++ |
| 117 | LLILENILL | ++ |
| 118 | RLLILENILL | +++ |
| 119 | VLPAEFFEV | +++ |
| 121 | RLYEITIEV | ++ |
| 122 | LLIPVVPGV | ++ |
| 123 | LLLAEAELLTL | +++ |
| 124 | LLLEETEKQAV | ++ |
| 125 | LLLEIGEVGKLFV | ++ |
| 126 | LLPEGGITAI | +++ |
| 127 | LLPTAPTTV | +++ |
| 128 | LLSEEEYHL | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 129 | LLVGTLDVV | + |
| 130 | LLVLIPVYL | +++ |
| 131 | LQALEVLKI | +++ |
| 132 | LVYEAIIMV | +++ |
| 133 | YLLSGDISEA | +++ |
| 134 | MLLEHGITLV | +++ |
| 135 | MTAGFSTIAGSV | +++ |
| 137 | NLIKTVIKL | + |
| 138 | NLLDIDAPVTV | ++ |
| 139 | NLTDVVEKL | +++ |
| 140 | QIAELPATSV | +++ |
| 141 | QILSEIVEA | ++ |
| 142 | QLDEPAPQV | +++ |
| 144 | QLPPFPREL | +++ |
| 145 | SALDTITTV | +++ |
| 146 | SIIEGPIIKL | +++ |
| 147 | SILETVATL | +++ |
| 148 | SIVASLITV | +++ |
| 149 | SLDNGGYYI | +++ |
| 153 | SLLAELHVL | ++ |
| 154 | SLLAELHVLTV | ++ |
| 155 | SLMLEVPAL | +++ |
| 157 | SLNIRDFTM | +++ |
| 160 | SLSFLVPSL | +++ |
| 162 | SMKDDLENV | +++ |
| 163 | SQLDISEPYKV | + |
| 164 | SVHKGFAFV | +++ |
| 165 | TLDDDLDTV | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 166 | TLDPNQVSL | +++ |
| 167 | TLDTSKLYV | +++ |
| 168 | YLLDQSFVM | +++ |
| 169 | TLLLGLTEV | +++ |
| 170 | TLTFRVETV | +++ |
| 171 | TLVPPAALISI | +++ |
| 172 | TLYDMLASI | +++ |
| 174 | VLAELPIIVV | +++ |
| 175 | FTVPRVVAV | ++ |
| 176 | VLAEQNIIPSA | +++ |
| 177 | VLDDRELLL | +++ |
| 178 | VLFFNVQEV | +++ |
| 179 | VLLGLEMTL | +++ |
| 181 | VLLSIPFVSV | + |
| 182 | VLLSVPGPPV | +++ |
| 185 | VMDDQRDLI | + |
| 186 | VMDPTKILI | +++ |
| 187 | VMDTHLVNI | +++ |
| 189 | VMLEMTPEL | +++ |
| 190 | VVMGTVPRL | +++ |
| 191 | YIFDGSDGGV | +++ |
| 192 | YIQEYLTLL | +++ |
| 193 | YLDLSNNRL | +++ |
| 194 | YLDNVLAEL | + |
| 195 | YLGGFALSV | +++ |
| 197 | YLQEVPILTL | +++ |
| 198 | YLTFLPAEV | +++ |
| 199 | YLVELSSLL | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 200 | YMFEEVPIVI | +++ |
| 201 | YQLELHGIEL | +++ |
| 202 | YVDDVFLRV | +++ |
| 204 | GLLQINDKIAL | ++ |
| 205 | GLSQANFTL | + |
| 206 | HMQDVRVLL | +++ |
| 208 | ILLKTEGINL | ++ |
| 209 | ILQAELPSL | ++ |
| 210 | KLLVQDFFL | +++ |
| 211 | LIDVKPLGV | +++ |
| 212 | NIIEAINELLV | ++ |
| 213 | RLLYQLVFL | ++ |
| 214 | RLQELTEKL | + |
| 215 | VMQDIVYKL | + |
| 217 | ALDEPPYLTV | + |
| 218 | ALGEEWKGYVV | + |
| 219 | ALLNLLESA | ++ |
| 221 | ALVSTIIMV | + |
| 225 | ILQERELLPV | + |
| 226 | AMNISVPQV | + |
| 227 | FLAEASVMTQL | ++ |
| 228 | FLGGLSPGV | ++ |
| 229 | FLLNLQNCHL | ++ |
| 231 | FLYIRQLAI | + |
| 232 | FMHQIIDQV | + |
| 234 | GLDDAEYAL | + |
| 235 | GLDDLLLFL | + |
| 236 | GLLESGRHYL | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 237 | GLQENLDVVV | + |
| 238 | GLVETELQL | + |
| 240 | ILARDILEI | ++ |
| 241 | ILGDILLKV | + |
| 242 | ILLGIQELL | ++ |
| 243 | ILPTLEKELFL | + |
| 244 | ILQALAVHL | ++ |
| 245 | KIMDYSLLLGV | + |
| 248 | KTVEPPISQV | + |
| 249 | LLPTGVFQV | + |
| 251 | LLYDNVPGA | + |
| 254 | QLIPKLIFL | +++ |
| 255 | YLFEEAISM | + |
| 258 | RLDYITAEI | ++ |
| 259 | RLLDEQFAVL | + |
| 260 | SLDDVEGMSV | ++ |
| 261 | SLVEAQGWLV | ++ |
| 263 | SQWEDIHVV | ++ |
| 264 | TILDYINVV | +++ |
| 266 | TLLDQLDTQL | + |
| 267 | TLLDWQDSL | + |
| 268 | TLLQVFHLL | ++ |
| 270 | TVLPVPPLSV | +++ |
| 271 | VIRNIVEAA | ++ |
| 273 | VLGEYSYLL | + |
| 275 | VLLFIEHSV | + |
| 276 | VLNDGAPNV | + |
| 277 | VMILKLPFL | + |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 278 | YLDDLLPKL | ++ |
| 280 | YTLDSLYWSV | + |
| 281 | NLLDDRGMTAL | +++ |
| 282 | LLRDGIELV | +++ |
| 283 | ILQPMDIHV | +++ |
| 284 | LLSAAEPVPA | +++ |
| 286 | FLLEDLSQKL | +++ |
| 287 | FLWEEKFNSL | +++ |
| 289 | ILEEQPMDMLL | +++ |
| 290 | LANPHELSL | +++ |
| 291 | ILLNEDDLVTI | +++ |
| 292 | AAALIIHHV | + |
| 294 | ALLDQLHTLL | + |
| 297 | FLVEPQEDTRL | ++ |
| 298 | IILPVEVEV | +++ |
| 299 | ILEENIPVL | ++ |
| 300 | ILLNPAYDVYL | ++ |
| 302 | ILQDLTFVHL | + |
| 304 | LAIVPVNTL | +++ |
| 305 | LLFPQIEGIKI | + |
| 307 | LLLTKPTEA | ++ |
| 308 | SLYDVSRMYV | +++ |
| 309 | ILYGTQFVL | + |
| 310 | LLSTLHLLV | + |
| 311 | LLVDVEPKV | + |
| 312 | LLYNSTDPTL | +++ |
| 314 | LMKDCEAEV | ++ |
| 316 | MLLEHGITL | +++ |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 317 | NLLAHIWAL | + |
| 318 | NLQVTQPTV | +++ |
| 320 | TIAPVTVAV | + |
| 322 | SLASIHVPL | +++ |
| 323 | SLDLFNCEV | +++ |
| 327 | VLIKWFPEV | +++ |
| 328 | VLLPQETAEIHL | ++ |
| 329 | VLMDGSVKL | + |
| 330 | VLMWEIYSL | ++ |
| 331 | VLWELAHLPTL | +++ |
| 332 | VMIQHVENL | +++ |
| 334 | YLLEEKIASL | +++ |
| 336 | YMAVTTQEV | +++ |
| 337 | YMYEKESEL | ++ |
| 338 | FLDMTNWNL | + |
| 339 | GLWGTVVNI | + |
| 340 | KLLEEICNL | ++ |
| 341 | LLAELPASVHA | ++ |
| 342 | SLITPLQAV | +++ |
| 343 | TLLEALDCI | ++ |
| 344 | VLAFENPQV | ++ |
| 345 | YLIEPDVELQRI | + |
| 346 | VLVQVSPSL | +++ |
| 347 | YLGPVSPSL | + |
| 349 | ALATHILSL | ++ |
| 350 | ALEDRVWEL | + |
| 351 | ALSEKLARL | + |
| 352 | ALVFELHYV | + |

TABLE 8-continued

Presentation scores. The table lists peptides that are very highly over-presented on tumors compared to a panel of normal tissues (+++), highly over-presented on tumors compared to a panel of normal tissues (++) or over-presented on tumors compared to a panel of normal tissues (+). The panel of normal tissues considered relevant for comparison with tumors consisted of: adipose tissue, adrenal gland, blood cells, blood vessel, bone marrow, brain, breast, esophagus, eye, gallbladder, heart, kidney, large intestine, liver, lung, lymph node, nerve, pancreas, parathyroid gland, peritoneum, pituitary, pleura, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea, ureter, urinary bladder.

| SEQ ID No. | Sequence | Peptide Presentation |
|---|---|---|
| 353 | ATPMPTPSV | ++ |
| 354 | FIMDDPAGNSYL | + |
| 355 | FIWPMLIHI | +++ |
| 356 | FLHDHQAEL | + |
| 357 | FLIQEIKTL | ++ |
| 358 | FLTDYLNDL | + |
| 359 | FMQDPMEVFV | ++ |
| 360 | HLIDTNKIQL | + |
| 362 | ILTELGGFEV | + |
| 363 | ITTEVVNELYV | + |
| 364 | KMDWIFHTI | + |
| 365 | LISPLLLPV | ++ |
| 367 | NLWSLVAKV | ++ |
| 368 | QLQPTDALLCV | + |
| 371 | SLADDSVLERL | + |
| 372 | SLFGPLPGPGPALV | + |
| 374 | VLSVITEEL | ++ |
| 375 | VLWFKPVEL | ++ |
| 377 | VVDGTCVAV | + |
| 378 | YILGKFFAL | + |
| 379 | YLAELVTPIL | + |
| 380 | YLDRKLLTL | + |
| 382 | YLLPLLQRL | +++ |
| 383 | YLLREWVNL | +++ |
| 384 | YMIGSEVGNYL | + |
| 385 | YTIPLAIKL | +++ |

Example 2

**[0404]** Expression profiling of genes encoding the peptides of the invention 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.

**[0405]** RNA Sources and Preparation

**[0406]** 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.

**[0407]** Total RNA from healthy human tissues for RNASeq experiments was obtained from: Asterand (Detroit, Mich., USA & Royston, Herts, UK); BioCat GmbH (Heidelberg, Germany); BioServe (Beltsville, Md., USA); Geneticist Inc. (Glendale, Calif., USA); Istituto Nazionale Tumori "Pascale" (Naples, Italy); ProteoGenex Inc. (Culver City, Calif., USA); University Hospital Heidelberg (Heidelberg, Germany).

**[0408]** Total RNA from tumor tissues for RNASeq experiments was obtained from: Tissue Solutions Ltd (Glasgow, UK); University Hospital Bonn (Bonn, 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).

**[0409]** RNAseq Experiments

**[0410]** Gene expression analysis of—tumor and normal tissue RNA samples was performed by next generation sequencing (RNAseq) by CeGaT (TObingen, Germany). Briefly, sequencing libraries are prepared using the Illumina HiSeq v4 reagent kit according to the provider's protocol (Illumina Inc, San Diego, Calif., USA), which includes RNA fragmentation, cDNA conversion and addition of sequencing adaptors. Libraries derived from multiple samples are mixed equimolarly 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 CLL are shown in FIGS. 3A-3F. Expression scores for further exemplary genes are shown in Table 9.

TABLE 9

Expression scores. The table lists peptides from genes that are very highly over-expressed in tumors compared to a panel of normal tissues (+++), highly over-expressed in tumors compared to a panel of normal tissues (++) or over-expressed in 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, artery, blood cells, bone marrow, brain, cartilage, colon, esophagus, eye, gallbladder, heart, kidney, liver, lung, lymph node, pancreas, pituitary, rectum, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, urinary bladder, and vein. 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.

| SEQ ID No | Sequence | Gene Expression |
|---|---|---|
| 1 | AIPPSFASIFL | ++ |
| 2 | ALHRPDVYL | ++ |
| 3 | VIAELPPKV | +++ |
| 4 | VIAELPPKVSV | +++ |
| 5 | ALIFKIASA | +++ |
| 9 | ALCDTLITV | +++ |
| 10 | FVYGESVEL | +++ |
| 17 | ALTKTNLQL | +++ |
| 18 | LLGEFSIKM | +++ |
| 19 | QVMEKLAAV | +++ |
| 21 | ALWAGLLTL | +++ |
| 24 | AMAGDVVYA | +++ |
| 31 | ELMHGVAGV | +++ |
| 46 | YIIDSAQAV | ++ |
| 62 | GIIDGSPRL | +++ |
| 63 | SLAHVAGCEL | +++ |
| 64 | KLLESVASA | +++ |
| 65 | GLDDMKANL | +++ |
| 66 | SLAGGLDDMKA | +++ |
| 71 | GLKHDIARV | +++ |
| 74 | GLLRASFLL | ++ |
| 75 | GLSIFAQDLRL | ++ |
| 85 | HLMLHTAAL | + |
| 86 | HLYPGAVTI | +++ |
| 91 | ILDLNTYNV | + |
| 96 | ILIDKTSFV | +++ |
| 97 | LLFATQITL | +++ |

TABLE 9-continued

Expression scores. The table lists peptides from genes that are very highly over-expressed in tumors compared to a panel of normal tissues (+++), highly over-expressed in tumors compared to a panel of normal tissues (++) or over-expressed in 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, artery, blood cells, bone marrow, brain, cartilage, colon, esophagus, eye, gallbladder, heart, kidney, liver, lung, lymph node, pancreas, pituitary, rectum, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, urinary bladder, and vein. 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.

| SEQ ID No | Sequence | Gene Expression |
|---|---|---|
| 98 | SLIKYFLFV | +++ |
| 105 | KLMNDIADI | ++ |
| 106 | FMASHLDYL | + |
| 107 | ILYNLYDLL | ++ |
| 108 | VIYTLIHYI | + |
| 113 | KVPAEEVLVAV | ++ |
| 116 | LLIGATMQV | + |
| 117 | LLILENILL | ++ |
| 118 | RLLILENILL | ++ |
| 119 | VLPAEFFEV | ++ |
| 120 | AIDAALTSV | ++ |
| 121 | RLYEITIEV | ++ |
| 127 | LLPTAPTTV | + |
| 137 | NLIKTVIKL | + |
| 146 | SIIEGPIIKL | +++ |
| 149 | SLDNGGYYI | +++ |
| 150 | SLFDQPLSII | +++ |
| 153 | SLLAELHVL | +++ |
| 154 | SLLAELHVLTV | +++ |
| 156 | SLNIGDVQL | +++ |
| 163 | SQLDISEPYKV | +++ |
| 177 | VLDDRELLL | ++ |
| 189 | VMLEMTPEL | +++ |
| 193 | YLDLSNNRL | + |
| 195 | YLGGFALSV | ++ |
| 205 | GLSQANFTL | +++ |
| 206 | HMQDVRVLL | +++ |

TABLE 9-continued

Expression scores. The table lists peptides from genes that are very highly over-expressed in tumors compared to a panel of normal tissues (+++), highly over-expressed in tumors compared to a panel of normal tissues (++) or over-expressed in 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, artery, blood cells, bone marrow, brain, cartilage, colon, esophagus, eye, gallbladder, heart, kidney, liver, lung, lymph node, pancreas, pituitary, rectum, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, urinary bladder, and vein. 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.

| SEQ ID No | Sequence | Gene Expression |
|---|---|---|
| 213 | RLLYQLVFL | +++ |
| 220 | ALPEILFAKV | ++ |
| 221 | ALVSTIIMV | + |
| 223 | ALWVSQPPEI | ++ |
| 235 | GLDDLLLFL | + |
| 251 | LLYDNVPGA | +++ |
| 254 | QLIPKLIFL | +++ |
| 255 | YLFEEAISM | +++ |
| 257 | RIINGIIISV | +++ |
| 262 | SLWNAGTSV | ++ |
| 275 | VLLFIEHSV | ++ |
| 284 | LLSAAEPVPA | +++ |
| 285 | GVATAGCVNEV | +++ |
| 286 | FLLEDLSQKL | ++ |
| 294 | ALLDQLHTLL | + |
| 299 | ILEENIPVL | ++ |
| 300 | ILLNPAYDVYL | ++ |
| 301 | AASPIITLV | + |
| 307 | LLLTKPTEA | ++ |
| 308 | SLYDVSRMYV | + |
| 309 | ILYGTQFVL | ++ |
| 312 | LLYNSTDPTL | + |
| 319 | QVIPQLQTV | ++ |
| 320 | TIAPVTVAV | ++ |
| 330 | VLMWEIYSL | ++ |
| 332 | VMIQHVENL | +++ |
| 337 | YMYEKESEL | +++ |

TABLE 9-continued

Expression scores. The table lists peptides from genes that are very highly over-expressed in tumors compared to a panel of normal tissues (+++), highly over-expressed in tumors compared to a panel of normal tissues (++) or over-expressed in 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, artery, blood cells, bone marrow, brain, cartilage, colon, esophagus, eye, gallbladder, heart, kidney, liver, lung, lymph node, pancreas, pituitary, rectum, salivary gland, skeletal muscle, skin, small intestine, spleen, stomach, thyroid gland, trachea, urinary bladder, and vein. 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.

| SEQ ID No | Sequence | Gene Expression |
|---|---|---|
| 352 | ALVFELHYV | +++ |
| 356 | FLHDHQAEL | + |
| 360 | HLIDTNKIQL | + |
| 378 | YILGKFFAL | + |
| 380 | YLDRKLLTL | ++ |

## Example 3

**[0411]** In Vitro Immunogenicity for MHC Class I Presented Peptides

**[0412]** 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*0201 restricted TUMAPs of the invention, demonstrating that these peptides are T-cell epitopes against which CD8+ precursor T cells exist in humans (Table 10).

**[0413]** In Vitro Priming of CD8+ T Cells

**[0414]** In order to perform in vitro stimulations by artificial antigen presenting cells loaded with peptide-MHC complex (pMHC) and anti-CD28 antibody, the inventors first isolated CD8+ T cells from fresh HLA-A*02 leukapheresis products via positive selection using CD8 microbeads (Miltenyi Biotec, Bergisch-Gladbach, Germany) of healthy donors obtained from the University clinics Mannheim, Germany, after informed consent.

**[0415]** 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, Nirnberg, Germany) were also added to the TCM at this step.

**[0416]** 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.

**[0417]** 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).

**[0418]** pMHC used for positive and negative control stimulations were A*0201/MLA-001 (peptide ELAGIGILTV (SEQ ID NO. 523) from modified Melan-A/MART-1) and A*0201/DDX5-001 (YLLPAIVHI from DDX5, SEQ ID NO. 524), respectively.

**[0419]** 800.000 beads/200 μl were coated in 96-well plates in the presence of 4×12.5 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 $1\times10^6$ CD8+ T cells with $2\times10^5$ 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 10× the median of the negative control stimulations).

**[0420]** In Vitro Immunogenicity for CLL Peptides

**[0421]** 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 two peptides of the invention are shown in FIGS. 3A-3F together with corresponding negative controls. Results for two peptides from the invention are summarized in Table 10A, others in Table 10B.

TABLE 10A

| 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 |
| 427 | LLYDAVHIV | ++ |
| 521 | YLYGQTTTYL | ++ |

TABLE 10B

| In vitro immunogenicity of additional HLA class I peptides of the invention Exemplary results of in vitro immunogenicity experiments conducted by the applicant for HLA-A*02 restricted peptides of the invention. Results of in vitro immunogenicity experiments are indicated. Percentage of positive wells and donors (among evaluable) are summarized as indicated <20% = +; 20%-49% = ++; 50%-69% = +++; >= 70% = ++++ | | |
|---|---|---|
| SEQ ID NO: | Sequence | Wells positive +%+ |
| 1 | AIPPSFASIFL | "+++" |
| 2 | ALHRPDVYL | "+" |
| 5 | ALIFKIASA | "+++" |
| 17 | ALTKTNLQL | "+" |
| 26 | AVLLVLPLV | "+" |
| 32 | FIDKFTPPV | "++++" |
| 49 | FLTDLFAQL | "++" |
| 54 | FLYPFPLALF | "+" |
| 56 | FVFEAPYTL | "++" |
| 57 | GLSEISLRL | "+" |
| 69 | GLHQREIFL | "+" |
| 81 | WLVGQEFEL | "+" |
| 86 | HLYPGAVTI | "+" |
| 96 | ILIDKTSFV | "+" |
| 100 | ILNNEVFAI | "++" |
| 101 | ILVVIEPLL | "+" |
| 102 | IQDRAVPSL | "+" |
| 112 | KTLDVDATYEI | "+" |
| 114 | LIPEGPPQV | "+" |
| 154 | SLLAELHVLTV | "+" |
| 192 | YIQEYLTLL | "+" |
| 197 | YLQEVPILTL | "+" |
| 200 | YMFEEVPIVI | "+" |

TABLE 10B-continued

| In vitro immunogenicity of additional HLA class I peptides of the invention Exemplary results of in vitro immunogenicity experiments conducted by the applicant for HLA-A*02 restricted peptides of the invention. Results of in vitro immunogenicity experiments are indicated. Percentage of positive wells and donors (among evaluable) are summarized as indicated <20% = +; 20%-49% = ++; 50%-69% = +++; >= 70% = ++++ | | |
|---|---|---|
| SEQ ID NO: | Sequence | Wells positive +%+ |
| 201 | YQLELHGIEL | "+" |
| 202 | YVDDVFLRV | "++" |
| 220 | ALPEILFAKV | "++" |
| 240 | ILARDILEI | "+" |
| 281 | NLLDDRGMTAL | "+" |
| 282 | LLRDGIELV | "++" |
| 307 | LLLTKPTEA | "+" |
| 320 | TIAPVTVAV | "+" |
| 322 | SLASIHVPL | "+" |
| 323 | SLDLFNCEV | "+" |
| 329 | VLMDGSVKL | "+++" |
| 332 | VMIQHVENL | "+" |
| 380 | YLDRKLLTL | "++++" |

Example 4

**[0422]** Synthesis of Peptides

**[0423]** All peptides were synthesized using standard and well-established solid phase peptide synthesis using the Fmoc-strategy. Identity and purity of each individual peptide have been determined by mass spectrometry and analytical RP-HPLC. The peptides were obtained as white to off-white lyophilizates (trifluoro acetate salt) in purities of >50%. All TUMAPs are preferably administered as trifluoro-acetate salts or acetate salts, other salt-forms are also possible.

Example 5

**[0424]** MHC Binding Assays

**[0425]** 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 (μ2m) of stabilized MHC complexes. The assay was performed as generally described in Rodenko et al. (Rodenko et al., 2006).

**[0426]** 96 well MAXISorp plates (NUNC) were coated over night with 2 ug/ml streptavidin in PBS at room temperature, washed 4× and blocked for 1 h 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 1 h at 37° C., washed four times, incubated with 2 ug/ml HRP conjugated anti-β2m for 1h at 37° C., washed again and detected with TMB solution that is stopped with $NH_2SO_4$. Absorption was measured at 450 nm. 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 11

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 | Sequence | Peptide Exchange |
|---|---|---|
| 1 | AIPPSFASIFL | "+++" |
| 2 | ALHRPDVYL | "+++" |
| 3 | VIAELPPKV | "++" |
| 4 | VIAELPPKVSV | "+++" |
| 5 | ALIFKIASA | "+++" |
| 6 | ALDTLEDDMTI | "+++" |
| 7 | ALLERTGYTL | "+++" |
| 8 | ALAASALPALV | "+++" |
| 9 | ALCDTLITV | "+++" |
| 10 | FVYGESVEL | "+++" |
| 11 | ALFTFJPLTV | "+++" |
| 12 | ALGEDEITL | "+++" |
| 13 | VVDGMPPGV | "+++" |
| 14 | ALLRLLPGL | "+++" |
| 15 | ALPEVSVEA | "+++" |
| 16 | ALPGGAAVAAV | "++++" |
| 17 | ALTKTNLQL | "+++" |
| 18 | LLGEFSIKM | "+++" |
| 19 | QVMEKLAAV | "+++" |
| 20 | ALVDPGPDFVV | "+++" |
| 21 | ALWAGLLTL | "+++" |
| 22 | ALWDPVIEL | "+++" |
| 23 | ALYLTEVFL | "++++" |
| 24 | AMAGDVVYA | "+++" |
| 25 | ATYSGLESQSV | "++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 26 | AVLLVLPLV | "+++" |
| 27 | AVLGLVWLL | "+++" |
| 28 | AVLHLLLSV | "++" |
| 29 | AVLQAVTAV | "+++" |
| 30 | ELLEGSEIYL | "+++" |
| 31 | ELMHGVAGV | "+++" |
| 32 | FIDKFTPPV | "++++" |
| 34 | YLPYIFPN I | "+++" |
| 35 | FILPSSLYL | "+++" |
| 36 | FILTHVDQL | "++++" |
| 37 | FIMEGGAMVL | "++++" |
| 38 | FIMEGGAMV | "+++" |
| 39 | FLDALLTDV | "+++" |
| 40 | FLDEDDMSL | "++" |
| 41 | FLDPSLDPLL | "+++" |
| 42 | FLEEGGVVTV | "+++" |
| 43 | FLLGPEALSFA | "++++" |
| 44 | FLLSINDFL | "+++" |
| 45 | FLPELPADLEA | "+++" |
| 46 | YIIDSAQAV | "+++" |
| 47 | FLSDQPEPYL | "++" |
| 48 | FLSPQQPPLL | "+++" |
| 49 | FLTDLFAQL | "++++" |
| 50 | FLFEPVVKAFL | "+++" |
| 51 | FLVEAPHDWDL | "++++" |
| 52 | FLVETGFLHV | "++++" |
| 53 | FLWQHVELVL | "+++" |
| 54 | FLYPFPLALF | "+++" |
| 55 | FMEPTLLML | "+++" |
| 56 | FVFEAPYTL | "+++" |
| 57 | GLSEISLRL | "++++" |
| 58 | YIQQGIFSV | "+++" |
| 59 | FVFGDENGTVSL | "+++" |
| 60 | FVLDHEDGLNL | "+++" |
| 61 | FVYFIVREV | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 62 | GIIDGSPRL | "+++" |
| 63 | SLAHVAGCEL | "+++" |
| 64 | KLLESVASA | "+++" |
| 65 | GLDDMKANL | "++" |
| 66 | SLAGGLDDMKA | "+++" |
| 67 | GLDDVTVEV | "++" |
| 68 | GLDQQFAGLDL | "+" |
| 69 | GLHQREIFL | "+++" |
| 70 | FVPDTPVGV | "+++" |
| 71 | GLKHDIARV | "+++" |
| 72 | GLLDAGKMYV | "+++" |
| 73 | GLLEVISALQL | "+++" |
| 74 | GLLRASFLL | "++" |
| 75 | GLSIFAQDLRL | "++" |
| 76 | GLLRIIPYL | "+++" |
| 78 | GLPSFLTEV | "+++" |
| 79 | GLQAKIQEA | "+++" |
| 80 | VLIEDELEEL | "++" |
| 81 | WLVGQEFEL | "+++" |
| 82 | GLQSGVDIGV | "+++" |
| 83 | GQGEVLVYV | "+++" |
| 84 | GVMDVNTAL | "++" |
| 85 | HLMLHTAAL | "++++" |
| 86 | HLYPGAVTI | "+++" |
| 87 | HQIEAVDGEEL | "++" |
| 88 | ILDEIGADVQA | "+++" |
| 89 | ILDFGTFQL | "+++" |
| 90 | VIADLGLIRV | "+++" |
| 91 | ILDLNTYNV | "+++" |
| 92 | ILEPLNPLL | "+++" |
| 93 | ILFNTQINI | "+++" |
| 94 | ILFPLRFTL | "+++" |
| 95 | ILGYMAHEHKV | "++" |
| 96 | ILIDKTSFV | "+++" |
| 97 | LLFATQITL | "++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 98 | SLIKYFLFV | "+" |
| 99 | ILIFHSVAL | "+++" |
| 100 | ILNNEVFAI | "+++" |
| 101 | ILVVIEPLL | "++++" |
| 102 | IQDRAVPSL | "++" |
| 103 | KLGGTPAPA | "++" |
| 104 | KLILLDTPLFL | "+++" |
| 105 | KLMNDIADI | "++" |
| 106 | FMASHLDYL | "+++" |
| 107 | ILYNLYDLL | "+++" |
| 108 | VIYTLIHYI | "+++" |
| 109 | KLWEGLTELV | "+++" |
| 110 | LLFDHLEPMEL | "+++" |
| 111 | KLWNVAAPLYL | "+++" |
| 112 | KTLDVDATYEI | "+++" |
| 113 | KVPAEEVLVAV | "+++" |
| 114 | LIPEGPPQV | "+++" |
| 115 | LLFDKLYLL | "+++" |
| 116 | LLIGATMQV | "+++" |
| 117 | LLILENILL | "+++" |
| 118 | RLLILENILL | "+++" |
| 119 | VLPAEFFEV | "+++" |
| 120 | AIDAALTSV | "+++" |
| 121 | RLYEITIEV | "++++" |
| 122 | LLIPVVPGV | "+++" |
| 123 | LLLAEAELLTL | "++" |
| 124 | LLLEETEKQAV | "+++" |
| 125 | LLLEIGEVGKLFV | "+++" |
| 126 | LLPEGGITAI | "+++" |
| 127 | LLPTAPTTV | "+++" |
| 128 | LLSEEEYHL | "+++" |
| 130 | LLVLIPVYL | "+" |
| 131 | LQALEVLKI | "+" |
| 132 | LVYEAIIMV | "+++" |
| 133 | YLLSGDISEA | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 134 | MLLEHGITLV | "++++" |
| 135 | MTAGFSTIAGSV | "+" |
| 136 | NLDKLWTLV | "++" |
| 137 | NLIKTVIKL | "+++" |
| 138 | NLLDIDAPVTV | "+++" |
| 139 | NLTDVVEKL | "+++" |
| 140 | QIAELPATSV | "+++" |
| 141 | QILSEIVEA | "++" |
| 142 | QLDEPAPQV | "++" |
| 143 | QLLDTYFTL | "+++" |
| 145 | SALDTITTV | "+++" |
| 146 | SIIEGPIIKL | "+++" |
| 147 | SILETVATL | "+++" |
| 148 | SIVASLITV | "+++" |
| 149 | SLDNGGYYI | "+++" |
| 150 | SLFDQPLSII | "+++" |
| 151 | SLFDSAYGA | "+++" |
| 152 | SLIRILQTI | "+++" |
| 153 | SLLAELHVL | "+++" |
| 154 | SLLAELHVLTV | "++++" |
| 155 | SLMLEVPAL | "+++" |
| 156 | SLNIGDVQL | "+++" |
| 157 | SLNIRDFTM | "+++" |
| 158 | SLPEAPLDV | "+++" |
| 159 | SLQEEKLIYV | "+++" |
| 160 | SLSFLVPSL | "+++" |
| 161 | SMDDGMINV | "+++" |
| 162 | SMKDDLENV | "++" |
| 163 | SQLDISEPYKV | "+++" |
| 164 | SVHKGFAFV | "+++" |
| 165 | TLDDDLDTV | "++" |
| 166 | TLDPNQVSL | "++" |
| 167 | TLDTSKLYV | "+++" |
| 168 | YLLDQSFVM | "++++" |
| 169 | TLLLGLTEV | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 170 | TLTFRVETV | "+++" |
| 171 | TLVPPAALISI | "+++" |
| 172 | TLYDMLASI | "+++" |
| 173 | TVIENIHTI | "++" |
| 174 | VLAELPIIVV | "+++" |
| 175 | FTVPRVVAV | "+++" |
| 176 | VLAEQNIIPSA | "+++" |
| 177 | VLDDRELLL | "+++" |
| 178 | VLFFNVQEV | "+++" |
| 179 | VLLGLEMTL | "+++" |
| 180 | LLKDGPEIGL | "++" |
| 181 | VLLSIPFVSV | "+++" |
| 182 | VLLSVPGPPV | "+++" |
| 183 | VLMPTVYQQGV | "+++" |
| 184 | VLSHNLYTV | "+++" |
| 185 | VMDDQRDLI | "++" |
| 186 | VMDPTKILI | "++++" |
| 187 | VMDTHLVNI | "++++" |
| 188 | VMGDIPAAV | "++" |
| 189 | VMLEMTPEL | "+++" |
| 190 | VVMGTVPRL | "+++" |
| 191 | YIFDGSDGGV | "+++" |
| 192 | YIQEYLTLL | "+++" |
| 193 | YLDLSNNRL | "+++" |
| 194 | YLDNVLAEL | "++++" |
| 195 | YLGGFALSV | "++++" |
| 196 | YLLLQTYVL | "+" |
| 197 | YLQEVPILTL | "++++" |
| 198 | YLTFLPAEV | "+++" |
| 199 | YLVELSSLL | "++++" |
| 200 | YMFEEVPIVI | "++++" |
| 201 | YQLELHGIEL | "++++" |
| 202 | YVDDVFLRV | "++++" |
| 203 | ALLSSQLAL | "+++" |
| 204 | GLLQINDKIAL | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 205 | GLSQANFTL | "+++" |
| 206 | HMQDVRVLL | "+++" |
| 207 | IIADLDTTIMFA | "+++" |
| 208 | ILLKTEGINL | "+++" |
| 209 | ILQAELPSL | "+++" |
| 210 | KLLVQDFFL | "+++" |
| 211 | LIDVKPLGV | "+++" |
| 214 | RLQELTEKL | "+++" |
| 215 | VMQDIVYKL | "+++" |
| 216 | WLAGDVPAA | "+++" |
| 217 | ALDEPPYLTV | "+++" |
| 218 | ALGEEWKGYVV | "++" |
| 219 | ALLNLLESA | "+++" |
| 220 | ALPEILFAKV | "+++" |
| 221 | ALVSTIIMV | "+" |
| 222 | ALWELSLKI | "+++" |
| 223 | ALWVSQPPEI | "+++" |
| 224 | AMEALVVEV | "+++" |
| 225 | ILQERELLPV | "+++" |
| 226 | AMNISVPQV | "+++" |
| 227 | FLAEASVMTQL | "+++" |
| 228 | FLGGLSPGV | "+++" |
| 229 | FLLNLQNCHL | "++++" |
| 230 | FLQDSKVIFV | "+++" |
| 231 | FLYIRQLAI | "+++" |
| 232 | FMHQIIDQV | "++++" |
| 233 | GIIDINVRL | "++" |
| 234 | GLDDAEYAL | "++" |
| 235 | GLDDLLLFL | "+++" |
| 236 | GLLESGRHYL | "+++" |
| 237 | GLQENLDVVV | "++++" |
| 238 | GLVETELQL | "+++" |
| 239 | ILAGEMLSV | "+++" |
| 240 | ILARDILEI | "+++" |
| 241 | ILGDILLKV | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 242 | ILLGIQELL | "+++" |
| 243 | ILPTLEKELFL | "+++" |
| 244 | ILQALAVHL | "+++" |
| 245 | KIMDYSLLLGV | "++++" |
| 246 | KLDETGVAL | "++" |
| 247 | KLKDRLPSI | "++" |
| 248 | KTVEPPISQV | "++" |
| 249 | LLPTGVFQV | "+++" |
| 250 | LLVQEPDGLMV | "+++" |
| 251 | LLYDNVPGA | "+++" |
| 252 | NLLDPGSSYLL | "+++" |
| 253 | NLWSVDGEVTV | "+++" |
| 254 | QLIPKLIFL | "+++" |
| 255 | YLFEEAISM | "+++" |
| 256 | QLLPVSNVVSV | "+++" |
| 258 | RLDYITAEI | "+++" |
| 259 | RLLDEQFAVL | "+++" |
| 260 | SLDDVEGMSV | "+++" |
| 261 | SLVEAQGWLV | "+++" |
| 262 | SLWNAGTSV | "+++" |
| 263 | SQWEDIHVV | "+++" |
| 264 | TILDYINVV | "+++" |
| 265 | TLLADDLEIKL | "+++" |
| 266 | TLLDQLDTQL | "++" |
| 267 | TLLDWQDSL | "+++" |
| 268 | TLLQVFHLL | "+++" |
| 269 | TLTDEQFLV | "++" |
| 270 | TVLPVPPLSV | "+++" |
| 271 | VIRNIVEAA | "++" |
| 272 | VLDELPPLI | "+++" |
| 273 | VLGEYSYLL | "+++" |
| 274 | VLLEYHIAYL | "+++" |
| 275 | VLLFIEHSV | "+++" |
| 276 | VLNDGAPNV | "+++" |
| 277 | VMILKLPFL | "++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 278 | YLDDLLPKL | "+++" |
| 279 | YMAPEVVEA | "+++" |
| 280 | YTLDSLYWSV | "+++" |
| 281 | NLLDDRGMTAL | "+++" |
| 282 | LLRDGIELV | "+++" |
| 283 | ILQPMDIHV | "+++" |
| 284 | LLSAAEPVPA | "++" |
| 285 | GVATAGCVNEV | "++++" |
| 286 | FLLEDLSQKL | "+++" |
| 287 | FLWEEKFNSL | "++++" |
| 288 | GLAESTGLLAV | "+++" |
| 289 | ILEEQPMDMLL | "+++" |
| 291 | ILLNEDDLVTI | "+++" |
| 292 | AAALIIHHV | "+++" |
| 293 | ALDIMIPMV | "+++" |
| 294 | ALLDQLHTLL | "++++" |
| 295 | ALLQKLQQL | "+++" |
| 296 | FIAPTGHSL | "++" |
| 297 | FLVEPQEDTRL | "+++" |
| 298 | IILPVEVEV | "+++" |
| 299 | ILEENIPVL | "+++" |
| 300 | ILLNPAYDVYL | "+++" |
| 301 | AASPIITLV | "+++" |
| 302 | ILQDLTFVHL | "+++" |
| 303 | ILSQPTPSL | "+++" |
| 304 | LAIVPVNTL | "+" |
| 305 | LLFPQIEGIKI | "+++" |
| 306 | VVAEELENV | "++" |
| 307 | LLLTKPTEA | "+++" |
| 308 | SLYDVSRMYV | "++++" |
| 309 | ILYGTQFVL | "+++" |
| 310 | LLSTLHLLV | "+++" |
| 311 | LLVDVEPKV | "+++" |
| 312 | LLYNSTDPTL | "+++" |
| 313 | LMADLEGLHL | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 314 | LMKDCEAEV | "+++" |
| 315 | LVYEAPETV | "+++" |
| 316 | MLLEHGITL | "+++" |
| 317 | NLLAHIWAL | "+++" |
| 318 | NLQVTQPTV | "+++" |
| 319 | QVIPQLQTV | "+++" |
| 320 | TIAPVTVAV | "++++" |
| 321 | RLLEFELAQL | "+++" |
| 322 | SLASIHVPL | "+++" |
| 323 | SLDLFNCEV | "++++" |
| 324 | SLYSALQQA | "+++" |
| 325 | TLENGVPCV | "+++" |
| 326 | VLAFLVHEL | "++++" |
| 327 | VLIKWFPEV | "++++" |
| 328 | VLLPQETAEIHL | "++++" |
| 329 | VLMDGSVKL | "++++" |
| 330 | VLMWEIYSL | "+++" |
| 331 | VLWELAHLPTL | "+++" |
| 332 | VMIQHVENL | "+++" |
| 333 | VTLEFPQLIRV | "+++" |
| 334 | YLLEEKIASL | "+++" |
| 335 | YLYQEQYFI | "+++" |
| 336 | YMAVTTQEV | "++++" |
| 337 | YMYEKESEL | "++" |
| 338 | FLDMTNWNL | "++++" |
| 339 | GLWGTVVNI | "+++" |
| 340 | KLLEEICNL | "++++" |
| 341 | LLAELPASVHA | "+++" |
| 342 | SLITPLQAV | "+++" |
| 344 | VLAFENPQV | "+++" |
| 345 | YLIEPDVELQRI | "+++" |
| 346 | VLVQVSPSL | "+++" |
| 347 | YLGPVSPSL | "+++" |
| 348 | ALAKPPVVSV | "+++" |
| 349 | ALATHILSL | "+++" |

TABLE 11-continued

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 | Sequence | Peptide Exchange |
|---|---|---|
| 350 | ALEDRVWEL | "+++" |
| 351 | ALSEKLARL | "+++" |
| 352 | ALVFELHYV | "+++" |
| 353 | ATPMPTPSV | "++" |
| 354 | FIMDDPAGNSYL | "+++" |
| 355 | FIWPMLIHI | "+++" |
| 356 | FLHDHQAEL | "++" |
| 357 | FLIQEIKTL | "+++" |
| 358 | FLTDYLNDL | "+++" |
| 359 | FMQDPMEVFV | "+++" |
| 360 | HLIDTNKIQL | "+++" |
| 361 | ILQEFESKL | "+++" |
| 362 | ILTELGGFEV | "+++" |
| 363 | ITTEVVNELYV | "+++" |
| 364 | KMDWIFHTI | "+++" |
| 365 | LISPLLLPV | "+++" |
| 367 | NLWSLVAKV | "+++" |
| 369 | RLLDLENSLLGL | "+++" |
| 370 | SIFASPESV | "+++" |
| 371 | SLADDSVLERL | "+++" |
| 372 | SLFGPLPGPGPALV | "+++" |
| 373 | TLLADQGEIRV | "++" |
| 374 | VLSVITEEL | "+++" |
| 375 | VLWFKPVEL | "+++" |
| 376 | VLYNQRVEEI | "+++" |
| 377 | VVDGTCVAV | "+++" |
| 378 | YILGKFFAL | "+++" |
| 379 | YLAELVTPIL | "+++" |
| 380 | YLDRKLLTL | "+++" |
| 381 | YLLEENKIKL | "+++" |
| 382 | YLLPLLQRL | "++++" |
| 383 | YLLREWVNL | "++++" |
| 384 | YMIGSEVGNYL | "++++" |
| 385 | YTIPLAIKL | "+++" |

Example 6

**[0427]** Absolute Quantitation of Tumor Associated Peptides Presented on the Cell Surface.

**[0428]** The generation of binders, such as antibodies and/or TCRs, is a laborious process, which may be conducted only for a number of selected targets. In the case of tumor-associated and -specific peptides, selection criteria include but are not restricted to exclusiveness of presentation and the density of peptide presented on the cell surface. In addition to the isolation and relative quantitation of peptides as described in EXAMPLE 1, the inventors did analyze absolute peptide copies per cell as described in patent x. The quantitation of TUMAP copies per cell in solid tumor samples requires the absolute quantitation of the isolated TUMAP, the efficiency of TUMAP isolation, and the cell count of the tissue sample analyzed. An overview on our experimental approach is described below.

**[0429]** Peptide Quantitation by nanoLC-MS/MS

**[0430]** For an accurate quantitation of peptides by mass spectrometry, a calibration curve was generated for each peptide using the internal standard method. The internal standard is a double-isotope-labelled variant of each peptide, i.e. two isotope-labelled amino acids were included in TUMAP synthesis. It differs from the tumor-associated peptide only in its mass but shows no difference in other physicochemical properties (Anderson et al., 2012). The internal standard was spiked to each MS sample and all MS signals were normalized to the MS signal of the internal standard to level out potential technical variances between MS experiments. The calibration curves were prepared in at least three different matrices, i.e. HLA peptide eluates from natural samples similar to the routine MS samples, and each preparation was measured in duplicate MS runs. For evaluation, MS signals were normalized to the signal of the internal standard and a calibration curve was calculated by logistic regression. For the quantitation of tumor-associated peptides from tissue samples, the respective samples were also spiked with the internal standard; the MS signals were normalized to the internal standard and quantified using the peptide calibration curve.

**[0431]** Efficiency of Peptide/MHC Isolation

**[0432]** As for any protein purification process, the isolation of proteins from tissue samples is associated with a certain loss of the protein of interest. To determine the efficiency of TUMAP isolation, peptide/MHC complexes were generated for all TUMAPs selected for absolute quantitation. To be able to discriminate the spiked from the natural peptide/MHC complexes, single-isotope-labelled versions of the TUMAPs were used, i.e. one isotope-labelled amino acid was included in TUMAP synthesis. These complexes were spiked into the freshly prepared tissue lysates, i.e. at the earliest possible point of the TUMAP isolation procedure, and then captured like the natural peptide/MHC complexes in the following affinity purification. Measuring the recovery of the single-labelled TUMAPs therefore allows conclusions regarding the efficiency of isolation of individual natural TUMAPs.

**[0433]** The efficiency of isolation was analyzed in a low number of samples and was comparable among these tissue samples. In contrast, the isolation efficiency differs between individual peptides. This suggests that the isolation efficiency, although determined in only a limited number of tissue samples, may be extrapolated to any other tissue preparation. However, it is necessary to analyze each

TUMAP individually as the isolation efficiency may not be extrapolated from one peptide to others.

**[0434]** Determination of the Cell Count in Solid, Frozen Tissue

**[0435]** In order to determine the cell count of the tissue samples subjected to absolute peptide quantitation, the inventors applied DNA content analysis. This method is applicable to a wide range of samples of different origin and, most importantly, frozen samples (Alcoser et al., 2011; Forsey and Chaudhuri, 2009; Silva et al., 2013). During the peptide isolation protocol, a tissue sample is processed to a homogenous lysate, from which a small lysate aliquot is taken. The aliquot is divided in three parts, from which DNA is isolated (QiaAmp DNA Mini Kit, Qiagen, Hilden, Germany). The total DNA content from each DNA isolation is quantified using a fluorescence-based DNA quantitation assay (Qubit dsDNA HS Assay Kit, Life Technologies, Darmstadt, Germany) in at least two replicates.

**[0436]** In order to calculate the cell number, a DNA standard curve from aliquots of single healthy blood cells, with a range of defined cell numbers, has been generated. The standard curve is used to calculate the total cell content from the total DNA content from each DNA isolation. The mean total cell count of the tissue sample used for peptide isolation is extrapolated considering the known volume of the lysate aliquots and the total lysate volume.

**[0437]** Peptide Copies Per Cell

**[0438]** With data of the aforementioned experiments, the inventors calculated the number of TUMAP copies per cell by dividing the total peptide amount by the total cell count of the sample, followed by division through isolation efficiency. Copy cell number for selected peptides are shown in Table 12.

TABLE 12

Absolute copy numbers. The table lists the results of absolute peptide quantitation in NSCLC tumor samples. The median number of copies per cell are indicated for each peptide: <100 = +; >=100 = ++; >=1,000 +++; >=10,000 = ++++. The number of samples, in which evaluable, high quality MS data are available, is indicated.

| Seq ID | Sequence | Copu Number Category | Number of quantifiable samples |
|---|---|---|---|
| 62 | GIIDGSPRL | + | 17 |
| 153 | SLLAELHVL | ++ | 17 |

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Ala Ile Pro Pro Ser Phe Ala Ser Ile Phe Leu
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Ala Leu His Arg Pro Asp Val Tyr Leu
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Val Ile Ala Glu Leu Pro Pro Lys Val
1               5


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

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

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Ala Val Leu Gln Ala Val Thr Ala Val
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Glu Leu Leu Glu Gly Ser Glu Ile Tyr Leu
1               5                   10

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<400> SEQUENCE: 31

Glu Leu Met His Gly Val Ala Gly Val
1               5

<210> SEQ ID NO 32
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<400> SEQUENCE: 32

Phe Ile Asp Lys Phe Thr Pro Pro Val
1               5

<210> SEQ ID NO 33
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<212> TYPE: PRT
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<400> SEQUENCE: 33

Phe Ile Ile Asn Ser Ser Asn Ile Phe Leu
1               5                   10

<210> SEQ ID NO 34
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Tyr Leu Pro Tyr Ile Phe Pro Asn Ile
1               5

<210> SEQ ID NO 35
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Phe Ile Leu Pro Ser Ser Leu Tyr Leu
1               5

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Phe Ile Leu Thr His Val Asp Gln Leu
1               5

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<400> SEQUENCE: 37

Phe Ile Met Glu Gly Gly Ala Met Val Leu
1               5                   10

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Phe Ile Met Glu Gly Gly Ala Met Val
1               5

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Phe Leu Asp Ala Leu Leu Thr Asp Val
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Phe Leu Asp Glu Asp Asp Met Ser Leu
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Phe Leu Asp Pro Ser Leu Asp Pro Leu Leu
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Phe Leu Glu Glu Gly Gly Val Val Thr Val
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Phe Leu Leu Gly Pro Glu Ala Leu Ser Phe Ala
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Phe Leu Leu Ser Ile Asn Asp Phe Leu
1 5

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Phe Leu Pro Glu Leu Pro Ala Asp Leu Glu Ala
1 5 10

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Tyr Ile Ile Asp Ser Ala Gln Ala Val
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Phe Leu Ser Asp Gln Pro Glu Pro Tyr Leu
1               5                   10

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Phe Leu Ser Pro Gln Gln Pro Pro Leu Leu
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Phe Leu Thr Asp Leu Phe Ala Gln Leu
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Phe Leu Val Glu Thr Gly Phe Leu His Val
1               5                   10

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Phe Leu Trp Gln His Val Glu Leu Val Leu
1               5                   10

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Phe Leu Tyr Pro Phe Pro Leu Ala Leu Phe
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Phe Met Glu Pro Thr Leu Leu Met Leu
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Phe Val Phe Glu Ala Pro Tyr Thr Leu
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Gly Leu Ser Glu Ile Ser Leu Arg Leu
1               5

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Tyr Ile Gln Gln Gly Ile Phe Ser Val
1               5

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Phe Val Phe Gly Asp Glu Asn Gly Thr Val Ser Leu
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Phe Val Leu Asp His Glu Asp Gly Leu Asn Leu
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Phe Val Tyr Phe Ile Val Arg Glu Val
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Gly Ile Ile Asp Gly Ser Pro Arg Leu
1               5

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Ser Leu Ala His Val Ala Gly Cys Glu Leu
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Lys Leu Leu Glu Ser Val Ala Ser Ala
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Gly Leu Asp Asp Met Lys Ala Asn Leu
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Ser Leu Ala Gly Gly Leu Asp Asp Met Lys Ala
1               5                   10

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Gly Leu Asp Asp Val Thr Val Glu Val

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1               5

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Gly Leu Asp Gln Gln Phe Ala Gly Leu Asp Leu
1               5                   10

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Gly Leu His Gln Arg Glu Ile Phe Leu
1               5

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Phe Val Pro Asp Thr Pro Val Gly Val
1               5

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Gly Leu Lys His Asp Ile Ala Arg Val
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Gly Leu Leu Asp Ala Gly Lys Met Tyr Val
1               5                   10

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Gly Leu Leu Glu Val Ile Ser Ala Leu Gln Leu
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Gly Leu Leu Arg Ala Ser Phe Leu Leu
1               5

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Gly Leu Ser Ile Phe Ala Gln Asp Leu Arg Leu
1               5                   10

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Gly Leu Leu Arg Ile Ile Pro Tyr Leu
1               5

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Gly Leu Leu Arg Leu Thr Trp Phe Leu
1               5

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Gly Leu Pro Ser Phe Leu Thr Glu Val
1               5

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Gly Leu Gln Ala Lys Ile Gln Glu Ala
1               5

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

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His Gln Ile Glu Ala Val Asp Gly Glu Glu Leu
1 5 10

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<400> SEQUENCE: 88

Ile Leu Asp Glu Ile Gly Ala Asp Val Gln Ala
1 5 10

<210> SEQ ID NO 89
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Ile Leu Asp Phe Gly Thr Phe Gln Leu
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Val Ile Ala Asp Leu Gly Leu Ile Arg Val
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Ile Leu Asp Leu Asn Thr Tyr Asn Val
1 5

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Ile Leu Glu Pro Leu Asn Pro Leu Leu
1 5

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Ile Leu Phe Asn Thr Gln Ile Asn Ile
1 5

<210> SEQ ID NO 94
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Ile Leu Phe Pro Leu Arg Phe Thr Leu
1 5

<210> SEQ ID NO 95
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<400> SEQUENCE: 95

Ile Leu Gly Tyr Met Ala His Glu His Lys Val
1 5 10

<210> SEQ ID NO 96
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Ile Leu Ile Asp Lys Thr Ser Phe Val
1 5

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Leu Leu Phe Ala Thr Gln Ile Thr Leu
1 5

<210> SEQ ID NO 98
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<400> SEQUENCE: 98

Ser Leu Ile Lys Tyr Phe Leu Phe Val
1 5

<210> SEQ ID NO 99
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Ile Leu Ile Phe His Ser Val Ala Leu
1 5

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Ile Leu Asn Asn Glu Val Phe Ala Ile
1 5

<210> SEQ ID NO 101
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Ile Leu Val Val Ile Glu Pro Leu Leu
1 5

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Ile Gln Asp Arg Ala Val Pro Ser Leu
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<210> SEQ ID NO 103
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<400> SEQUENCE: 103

Lys Leu Gly Gly Thr Pro Ala Pro Ala
1               5

<210> SEQ ID NO 104
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Lys Leu Ile Leu Leu Asp Thr Pro Leu Phe Leu
1               5                   10

<210> SEQ ID NO 105
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<400> SEQUENCE: 105

Lys Leu Met Asn Asp Ile Ala Asp Ile
1               5

<210> SEQ ID NO 106
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Phe Met Ala Ser His Leu Asp Tyr Leu
1               5

<210> SEQ ID NO 107
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Ile Leu Tyr Asn Leu Tyr Asp Leu Leu
1               5

<210> SEQ ID NO 108
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Val Ile Tyr Thr Leu Ile His Tyr Ile
1               5

<210> SEQ ID NO 109
<211> LENGTH: 10

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Lys Leu Trp Glu Gly Leu Thr Glu Leu Val
1 5 10

<210> SEQ ID NO 110
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Leu Leu Phe Asp His Leu Glu Pro Met Glu Leu
1 5 10

<210> SEQ ID NO 111
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Lys Leu Trp Asn Val Ala Ala Pro Leu Tyr Leu
1 5 10

<210> SEQ ID NO 112
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Lys Thr Leu Asp Val Asp Ala Thr Tyr Glu Ile
1 5 10

<210> SEQ ID NO 113
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Lys Val Pro Ala Glu Glu Val Leu Val Ala Val
1 5 10

<210> SEQ ID NO 114
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Leu Ile Pro Glu Gly Pro Pro Gln Val
1 5

<210> SEQ ID NO 115
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Leu Leu Phe Asp Lys Leu Tyr Leu Leu
1 5

<210> SEQ ID NO 116

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Leu Leu Ile Gly Ala Thr Met Gln Val
1               5

<210> SEQ ID NO 117
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Leu Leu Ile Leu Glu Asn Ile Leu Leu
1               5

<210> SEQ ID NO 118
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Arg Leu Leu Ile Leu Glu Asn Ile Leu Leu
1               5                   10

<210> SEQ ID NO 119
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Val Leu Pro Ala Glu Phe Phe Glu Val
1               5

<210> SEQ ID NO 120
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Ala Ile Asp Ala Ala Leu Thr Ser Val
1               5

<210> SEQ ID NO 121
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

Arg Leu Tyr Glu Ile Thr Ile Glu Val
1               5

<210> SEQ ID NO 122
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Leu Leu Ile Pro Val Val Pro Gly Val
1               5

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<210> SEQ ID NO 123
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Leu Leu Leu Ala Glu Ala Glu Leu Leu Thr Leu
1 5 10

<210> SEQ ID NO 124
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Leu Leu Leu Glu Glu Thr Glu Lys Gln Ala Val
1 5 10

<210> SEQ ID NO 125
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

Leu Leu Leu Glu Ile Gly Glu Val Gly Lys Leu Phe Val
1 5 10

<210> SEQ ID NO 126
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Leu Leu Pro Glu Gly Gly Ile Thr Ala Ile
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Leu Leu Pro Thr Ala Pro Thr Thr Val
1 5

<210> SEQ ID NO 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Leu Leu Ser Glu Glu Glu Tyr His Leu
1 5

<210> SEQ ID NO 129
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Leu Leu Val Gly Thr Leu Asp Val Val
1 5

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<210> SEQ ID NO 130
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Leu Leu Val Leu Ile Pro Val Tyr Leu
1               5

<210> SEQ ID NO 131
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Leu Gln Ala Leu Glu Val Leu Lys Ile
1               5

<210> SEQ ID NO 132
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Leu Val Tyr Glu Ala Ile Ile Met Val
1               5

<210> SEQ ID NO 133
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Tyr Leu Leu Ser Gly Asp Ile Ser Glu Ala
1               5                   10

<210> SEQ ID NO 134
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Met Leu Leu Glu His Gly Ile Thr Leu Val
1               5                   10

<210> SEQ ID NO 135
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Met Thr Ala Gly Phe Ser Thr Ile Ala Gly Ser Val
1               5                   10

<210> SEQ ID NO 136
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Asn Leu Asp Lys Leu Trp Thr Leu Val
1               5

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<210> SEQ ID NO 137
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Asn Leu Ile Lys Thr Val Ile Lys Leu
1 5

<210> SEQ ID NO 138
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Asn Leu Leu Asp Ile Asp Ala Pro Val Thr Val
1 5 10

<210> SEQ ID NO 139
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Asn Leu Thr Asp Val Val Glu Lys Leu
1 5

<210> SEQ ID NO 140
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Gln Ile Ala Glu Leu Pro Ala Thr Ser Val
1 5 10

<210> SEQ ID NO 141
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

Gln Ile Leu Ser Glu Ile Val Glu Ala
1 5

<210> SEQ ID NO 142
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Gln Leu Asp Glu Pro Ala Pro Gln Val
1 5

<210> SEQ ID NO 143
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Gln Leu Leu Asp Thr Tyr Phe Thr Leu

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1 5

<210> SEQ ID NO 144
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

Gln Leu Pro Pro Phe Pro Arg Glu Leu
1 5

<210> SEQ ID NO 145
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Ser Ala Leu Asp Thr Ile Thr Thr Val
1 5

<210> SEQ ID NO 146
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

Ser Ile Ile Glu Gly Pro Ile Ile Lys Leu
1 5 10

<210> SEQ ID NO 147
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Ser Ile Leu Glu Thr Val Ala Thr Leu
1 5

<210> SEQ ID NO 148
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

Ser Ile Val Ala Ser Leu Ile Thr Val
1 5

<210> SEQ ID NO 149
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Ser Leu Asp Asn Gly Gly Tyr Tyr Ile
1 5

<210> SEQ ID NO 150
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

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Ser Leu Phe Asp Gln Pro Leu Ser Ile Ile
1               5                   10

<210> SEQ ID NO 151
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Ser Leu Phe Asp Ser Ala Tyr Gly Ala
1               5

<210> SEQ ID NO 152
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Ser Leu Ile Arg Ile Leu Gln Thr Ile
1               5

<210> SEQ ID NO 153
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Ser Leu Leu Ala Glu Leu His Val Leu
1               5

<210> SEQ ID NO 154
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Ser Leu Leu Ala Glu Leu His Val Leu Thr Val
1               5                   10

<210> SEQ ID NO 155
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

Ser Leu Met Leu Glu Val Pro Ala Leu
1               5

<210> SEQ ID NO 156
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Ser Leu Asn Ile Gly Asp Val Gln Leu
1               5

<210> SEQ ID NO 157
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

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Ser Leu Asn Ile Arg Asp Phe Thr Met
1 5

<210> SEQ ID NO 158
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Ser Leu Pro Glu Ala Pro Leu Asp Val
1 5

<210> SEQ ID NO 159
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Ser Leu Gln Glu Glu Lys Leu Ile Tyr Val
1 5 10

<210> SEQ ID NO 160
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Ser Leu Ser Phe Leu Val Pro Ser Leu
1 5

<210> SEQ ID NO 161
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Ser Met Asp Asp Gly Met Ile Asn Val
1 5

<210> SEQ ID NO 162
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Ser Met Lys Asp Asp Leu Glu Asn Val
1 5

<210> SEQ ID NO 163
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Ser Gln Leu Asp Ile Ser Glu Pro Tyr Lys Val
1 5 10

<210> SEQ ID NO 164
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 164

Ser Val His Lys Gly Phe Ala Phe Val
1 5

<210> SEQ ID NO 165
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Thr Leu Asp Asp Asp Leu Asp Thr Val
1 5

<210> SEQ ID NO 166
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Thr Leu Asp Pro Asn Gln Val Ser Leu
1 5

<210> SEQ ID NO 167
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

Thr Leu Asp Thr Ser Lys Leu Tyr Val
1 5

<210> SEQ ID NO 168
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

Tyr Leu Leu Asp Gln Ser Phe Val Met
1 5

<210> SEQ ID NO 169
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

Thr Leu Leu Leu Gly Leu Thr Glu Val
1 5

<210> SEQ ID NO 170
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Thr Leu Thr Phe Arg Val Glu Thr Val
1 5

<210> SEQ ID NO 171
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 171

Thr Leu Val Pro Pro Ala Ala Leu Ile Ser Ile
1               5                   10

<210> SEQ ID NO 172
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Thr Leu Tyr Asp Met Leu Ala Ser Ile
1               5

<210> SEQ ID NO 173
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Thr Val Ile Glu Asn Ile His Thr Ile
1               5

<210> SEQ ID NO 174
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Val Leu Ala Glu Leu Pro Ile Ile Val Val
1               5                   10

<210> SEQ ID NO 175
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Phe Thr Val Pro Arg Val Val Ala Val
1               5

<210> SEQ ID NO 176
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Val Leu Ala Glu Gln Asn Ile Ile Pro Ser Ala
1               5                   10

<210> SEQ ID NO 177
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Val Leu Asp Asp Arg Glu Leu Leu Leu
1               5

<210> SEQ ID NO 178
<211> LENGTH: 9
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Val Leu Phe Phe Asn Val Gln Glu Val
1               5

<210> SEQ ID NO 179
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Val Leu Leu Gly Leu Glu Met Thr Leu
1               5

<210> SEQ ID NO 180
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Leu Leu Lys Asp Gly Pro Glu Ile Gly Leu
1               5                   10

<210> SEQ ID NO 181
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Val Leu Leu Ser Ile Pro Phe Val Ser Val
1               5                   10

<210> SEQ ID NO 182
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Val Leu Leu Ser Val Pro Gly Pro Pro Val
1               5                   10

<210> SEQ ID NO 183
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Val Leu Met Pro Thr Val Tyr Gln Gln Gly Val
1               5                   10

<210> SEQ ID NO 184
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Val Leu Ser His Asn Leu Tyr Thr Val
1               5

<210> SEQ ID NO 185
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Val Met Asp Asp Gln Arg Asp Leu Ile
1               5

<210> SEQ ID NO 186
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Val Met Asp Pro Thr Lys Ile Leu Ile
1               5

<210> SEQ ID NO 187
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Val Met Asp Thr His Leu Val Asn Ile
1               5

<210> SEQ ID NO 188
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

Val Met Gly Asp Ile Pro Ala Ala Val
1               5

<210> SEQ ID NO 189
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

Val Met Leu Glu Met Thr Pro Glu Leu
1               5

<210> SEQ ID NO 190
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Val Val Met Gly Thr Val Pro Arg Leu
1               5

<210> SEQ ID NO 191
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Tyr Ile Phe Asp Gly Ser Asp Gly Gly Val
1               5                   10

<210> SEQ ID NO 192

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Tyr Ile Gln Glu Tyr Leu Thr Leu Leu
1               5

<210> SEQ ID NO 193
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

Tyr Leu Asp Leu Ser Asn Asn Arg Leu
1               5

<210> SEQ ID NO 194
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

Tyr Leu Asp Asn Val Leu Ala Glu Leu
1               5

<210> SEQ ID NO 195
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Tyr Leu Gly Gly Phe Ala Leu Ser Val
1               5

<210> SEQ ID NO 196
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

Tyr Leu Leu Leu Gln Thr Tyr Val Leu
1               5

<210> SEQ ID NO 197
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Tyr Leu Gln Glu Val Pro Ile Leu Thr Leu
1               5                   10

<210> SEQ ID NO 198
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Tyr Leu Thr Phe Leu Pro Ala Glu Val
1               5

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<210> SEQ ID NO 199
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Tyr Leu Val Glu Leu Ser Ser Leu Leu
1 5

<210> SEQ ID NO 200
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Tyr Met Phe Glu Glu Val Pro Ile Val Ile
1 5 10

<210> SEQ ID NO 201
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Tyr Gln Leu Glu Leu His Gly Ile Glu Leu
1 5 10

<210> SEQ ID NO 202
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

Tyr Val Asp Asp Val Phe Leu Arg Val
1 5

<210> SEQ ID NO 203
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

Ala Leu Leu Ser Ser Gln Leu Ala Leu
1 5

<210> SEQ ID NO 204
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Gly Leu Leu Gln Ile Asn Asp Lys Ile Ala Leu
1 5 10

<210> SEQ ID NO 205
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Gly Leu Ser Gln Ala Asn Phe Thr Leu
1 5

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<210> SEQ ID NO 206
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

His Met Gln Asp Val Arg Val Leu Leu
1 5

<210> SEQ ID NO 207
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Ile Ile Ala Asp Leu Asp Thr Thr Ile Met Phe Ala
1 5 10

<210> SEQ ID NO 208
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

Ile Leu Leu Lys Thr Glu Gly Ile Asn Leu
1 5 10

<210> SEQ ID NO 209
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

Ile Leu Gln Ala Glu Leu Pro Ser Leu
1 5

<210> SEQ ID NO 210
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

Lys Leu Leu Val Gln Asp Phe Phe Leu
1 5

<210> SEQ ID NO 211
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

Leu Ile Asp Val Lys Pro Leu Gly Val
1 5

<210> SEQ ID NO 212
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212

Asn Ile Ile Glu Ala Ile Asn Glu Leu Leu Val
1 5 10

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<210> SEQ ID NO 213
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

Arg Leu Leu Tyr Gln Leu Val Phe Leu
1               5

<210> SEQ ID NO 214
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Arg Leu Gln Glu Leu Thr Glu Lys Leu
1               5

<210> SEQ ID NO 215
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

Val Met Gln Asp Ile Val Tyr Lys Leu
1               5

<210> SEQ ID NO 216
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

Trp Leu Ala Gly Asp Val Pro Ala Ala
1               5

<210> SEQ ID NO 217
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

Ala Leu Asp Glu Pro Pro Tyr Leu Thr Val
1               5                   10

<210> SEQ ID NO 218
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

Ala Leu Gly Glu Glu Trp Lys Gly Tyr Val Val
1               5                   10

<210> SEQ ID NO 219
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

Ala Leu Leu Asn Leu Leu Glu Ser Ala

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1 5

<210> SEQ ID NO 220
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Ala Leu Pro Glu Ile Leu Phe Ala Lys Val
1 5 10

<210> SEQ ID NO 221
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

Ala Leu Val Ser Thr Ile Ile Met Val
1 5

<210> SEQ ID NO 222
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Ala Leu Trp Glu Leu Ser Leu Lys Ile
1 5

<210> SEQ ID NO 223
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

Ala Leu Trp Val Ser Gln Pro Pro Glu Ile
1 5 10

<210> SEQ ID NO 224
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

Ala Met Glu Ala Leu Val Val Glu Val
1 5

<210> SEQ ID NO 225
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

Ile Leu Gln Glu Arg Glu Leu Leu Pro Val
1 5 10

<210> SEQ ID NO 226
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

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Ala Met Asn Ile Ser Val Pro Gln Val
1 5

<210> SEQ ID NO 227
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

Phe Leu Ala Glu Ala Ser Val Met Thr Gln Leu
1 5 10

<210> SEQ ID NO 228
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

Phe Leu Gly Gly Leu Ser Pro Gly Val
1 5

<210> SEQ ID NO 229
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Phe Leu Leu Asn Leu Gln Asn Cys His Leu
1 5 10

<210> SEQ ID NO 230
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

Phe Leu Gln Asp Ser Lys Val Ile Phe Val
1 5 10

<210> SEQ ID NO 231
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

Phe Leu Tyr Ile Arg Gln Leu Ala Ile
1 5

<210> SEQ ID NO 232
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

Phe Met His Gln Ile Ile Asp Gln Val
1 5

<210> SEQ ID NO 233
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

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Gly Ile Ile Asp Ile Asn Val Arg Leu
1 5

<210> SEQ ID NO 234
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

Gly Leu Asp Asp Ala Glu Tyr Ala Leu
1 5

<210> SEQ ID NO 235
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

Gly Leu Asp Asp Leu Leu Leu Phe Leu
1 5

<210> SEQ ID NO 236
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Gly Leu Leu Glu Ser Gly Arg His Tyr Leu
1 5 10

<210> SEQ ID NO 237
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Gly Leu Gln Glu Asn Leu Asp Val Val Val
1 5 10

<210> SEQ ID NO 238
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

Gly Leu Val Glu Thr Glu Leu Gln Leu
1 5

<210> SEQ ID NO 239
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

Ile Leu Ala Gly Glu Met Leu Ser Val
1 5

<210> SEQ ID NO 240
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 240

Ile Leu Ala Arg Asp Ile Leu Glu Ile
1               5

<210> SEQ ID NO 241
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

Ile Leu Gly Asp Ile Leu Leu Lys Val
1               5

<210> SEQ ID NO 242
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

Ile Leu Leu Gly Ile Gln Glu Leu Leu
1               5

<210> SEQ ID NO 243
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

Ile Leu Pro Thr Leu Glu Lys Glu Leu Phe Leu
1               5                   10

<210> SEQ ID NO 244
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

Ile Leu Gln Ala Leu Ala Val His Leu
1               5

<210> SEQ ID NO 245
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

Lys Ile Met Asp Tyr Ser Leu Leu Leu Gly Val
1               5                   10

<210> SEQ ID NO 246
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

Lys Leu Asp Glu Thr Gly Val Ala Leu
1               5

<210> SEQ ID NO 247
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 247

Lys Leu Lys Asp Arg Leu Pro Ser Ile
1 5

<210> SEQ ID NO 248
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

Lys Thr Val Glu Pro Pro Ile Ser Gln Val
1 5 10

<210> SEQ ID NO 249
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

Leu Leu Pro Thr Gly Val Phe Gln Val
1 5

<210> SEQ ID NO 250
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

Leu Leu Val Gln Glu Pro Asp Gly Leu Met Val
1 5 10

<210> SEQ ID NO 251
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

Leu Leu Tyr Asp Asn Val Pro Gly Ala
1 5

<210> SEQ ID NO 252
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

Asn Leu Leu Asp Pro Gly Ser Ser Tyr Leu Leu
1 5 10

<210> SEQ ID NO 253
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

Asn Leu Trp Ser Val Asp Gly Glu Val Thr Val
1 5 10

<210> SEQ ID NO 254
<211> LENGTH: 9
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

Gln Leu Ile Pro Lys Leu Ile Phe Leu
1               5

<210> SEQ ID NO 255
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

Tyr Leu Phe Glu Glu Ala Ile Ser Met
1               5

<210> SEQ ID NO 256
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

Gln Leu Leu Pro Val Ser Asn Val Val Ser Val
1               5                   10

<210> SEQ ID NO 257
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

Arg Ile Ile Asn Gly Ile Ile Ile Ser Val
1               5                   10

<210> SEQ ID NO 258
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

Arg Leu Asp Tyr Ile Thr Ala Glu Ile
1               5

<210> SEQ ID NO 259
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

Arg Leu Leu Asp Glu Gln Phe Ala Val Leu
1               5                   10

<210> SEQ ID NO 260
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

Ser Leu Asp Asp Val Glu Gly Met Ser Val
1               5                   10

<210> SEQ ID NO 261
<211> LENGTH: 10

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

Ser Leu Val Glu Ala Gln Gly Trp Leu Val
1               5                   10

<210> SEQ ID NO 262
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

Ser Leu Trp Asn Ala Gly Thr Ser Val
1               5

<210> SEQ ID NO 263
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

Ser Gln Trp Glu Asp Ile His Val Val
1               5

<210> SEQ ID NO 264
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

Thr Ile Leu Asp Tyr Ile Asn Val Val
1               5

<210> SEQ ID NO 265
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

Thr Leu Leu Ala Asp Asp Leu Glu Ile Lys Leu
1               5                   10

<210> SEQ ID NO 266
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

Thr Leu Leu Asp Gln Leu Asp Thr Gln Leu
1               5                   10

<210> SEQ ID NO 267
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

Thr Leu Leu Asp Trp Gln Asp Ser Leu
1               5

<210> SEQ ID NO 268

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

Thr Leu Leu Gln Val Phe His Leu Leu
1               5

<210> SEQ ID NO 269
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

Thr Leu Thr Asp Glu Gln Phe Leu Val
1               5

<210> SEQ ID NO 270
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

Thr Val Leu Pro Val Pro Pro Leu Ser Val
1               5                   10

<210> SEQ ID NO 271
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

Val Ile Arg Asn Ile Val Glu Ala Ala
1               5

<210> SEQ ID NO 272
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

Val Leu Asp Glu Leu Pro Pro Leu Ile
1               5

<210> SEQ ID NO 273
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

Val Leu Gly Glu Tyr Ser Tyr Leu Leu
1               5

<210> SEQ ID NO 274
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

Val Leu Leu Glu Tyr His Ile Ala Tyr Leu
1               5                   10

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<210> SEQ ID NO 275
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

Val Leu Leu Phe Ile Glu His Ser Val
1 5

<210> SEQ ID NO 276
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

Val Leu Asn Asp Gly Ala Pro Asn Val
1 5

<210> SEQ ID NO 277
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

Val Met Ile Leu Lys Leu Pro Phe Leu
1 5

<210> SEQ ID NO 278
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

Tyr Leu Asp Asp Leu Leu Pro Lys Leu
1 5

<210> SEQ ID NO 279
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

Tyr Met Ala Pro Glu Val Val Glu Ala
1 5

<210> SEQ ID NO 280
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

Tyr Thr Leu Asp Ser Leu Tyr Trp Ser Val
1 5 10

<210> SEQ ID NO 281
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

Asn Leu Leu Asp Asp Arg Gly Met Thr Ala Leu
1 5 10

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<210> SEQ ID NO 282
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

Leu Leu Arg Asp Gly Ile Glu Leu Val
1               5

<210> SEQ ID NO 283
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

Ile Leu Gln Pro Met Asp Ile His Val
1               5

<210> SEQ ID NO 284
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

Leu Leu Ser Ala Ala Glu Pro Val Pro Ala
1               5                   10

<210> SEQ ID NO 285
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

Gly Val Ala Thr Ala Gly Cys Val Asn Glu Val
1               5                   10

<210> SEQ ID NO 286
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

Phe Leu Leu Glu Asp Leu Ser Gln Lys Leu
1               5                   10

<210> SEQ ID NO 287
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

Phe Leu Trp Glu Glu Lys Phe Asn Ser Leu
1               5                   10

<210> SEQ ID NO 288
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

Gly Leu Ala Glu Ser Thr Gly Leu Leu Ala Val
1               5                   10

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<210> SEQ ID NO 289
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

Ile Leu Glu Glu Gln Pro Met Asp Met Leu Leu
1               5                   10

<210> SEQ ID NO 290
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

Leu Ala Asn Pro His Glu Leu Ser Leu
1               5

<210> SEQ ID NO 291
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

Ile Leu Leu Asn Glu Asp Asp Leu Val Thr Ile
1               5                   10

<210> SEQ ID NO 292
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

Ala Ala Ala Leu Ile Ile His His Val
1               5

<210> SEQ ID NO 293
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

Ala Leu Asp Ile Met Ile Pro Met Val
1               5

<210> SEQ ID NO 294
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

Ala Leu Leu Asp Gln Leu His Thr Leu Leu
1               5                   10

<210> SEQ ID NO 295
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

Ala Leu Leu Gln Lys Leu Gln Gln Leu

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1               5

<210> SEQ ID NO 296
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

Phe Ile Ala Pro Thr Gly His Ser Leu
1               5

<210> SEQ ID NO 297
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

Phe Leu Val Glu Pro Gln Glu Asp Thr Arg Leu
1               5                   10

<210> SEQ ID NO 298
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

Ile Ile Leu Pro Val Glu Val Glu Val
1               5

<210> SEQ ID NO 299
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

Ile Leu Glu Glu Asn Ile Pro Val Leu
1               5

<210> SEQ ID NO 300
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

Ile Leu Leu Asn Pro Ala Tyr Asp Val Tyr Leu
1               5                   10

<210> SEQ ID NO 301
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

Ala Ala Ser Pro Ile Ile Thr Leu Val
1               5

<210> SEQ ID NO 302
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

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Ile Leu Gln Asp Leu Thr Phe Val His Leu
1 5 10

<210> SEQ ID NO 303
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

Ile Leu Ser Gln Pro Thr Pro Ser Leu
1 5

<210> SEQ ID NO 304
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

Leu Ala Ile Val Pro Val Asn Thr Leu
1 5

<210> SEQ ID NO 305
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

Leu Leu Phe Pro Gln Ile Glu Gly Ile Lys Ile
1 5 10

<210> SEQ ID NO 306
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

Val Val Ala Glu Glu Leu Glu Asn Val
1 5

<210> SEQ ID NO 307
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

Leu Leu Leu Thr Lys Pro Thr Glu Ala
1 5

<210> SEQ ID NO 308
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

Ser Leu Tyr Asp Val Ser Arg Met Tyr Val
1 5 10

<210> SEQ ID NO 309
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

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Ile Leu Tyr Gly Thr Gln Phe Val Leu
1               5

<210> SEQ ID NO 310
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

Leu Leu Ser Thr Leu His Leu Leu Val
1               5

<210> SEQ ID NO 311
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

Leu Leu Val Asp Val Glu Pro Lys Val
1               5

<210> SEQ ID NO 312
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

Leu Leu Tyr Asn Ser Thr Asp Pro Thr Leu
1               5                   10

<210> SEQ ID NO 313
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

Leu Met Ala Asp Leu Glu Gly Leu His Leu
1               5                   10

<210> SEQ ID NO 314
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

Leu Met Lys Asp Cys Glu Ala Glu Val
1               5

<210> SEQ ID NO 315
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

Leu Val Tyr Glu Ala Pro Glu Thr Val
1               5

<210> SEQ ID NO 316
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 316

Met Leu Leu Glu His Gly Ile Thr Leu
1 5

<210> SEQ ID NO 317
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

Asn Leu Leu Ala His Ile Trp Ala Leu
1 5

<210> SEQ ID NO 318
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

Asn Leu Gln Val Thr Gln Pro Thr Val
1 5

<210> SEQ ID NO 319
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

Gln Val Ile Pro Gln Leu Gln Thr Val
1 5

<210> SEQ ID NO 320
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

Thr Ile Ala Pro Val Thr Val Ala Val
1 5

<210> SEQ ID NO 321
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

Arg Leu Leu Glu Phe Glu Leu Ala Gln Leu
1 5 10

<210> SEQ ID NO 322
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

Ser Leu Ala Ser Ile His Val Pro Leu
1 5

<210> SEQ ID NO 323
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 323

Ser Leu Asp Leu Phe Asn Cys Glu Val
1 5

<210> SEQ ID NO 324
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

Ser Leu Tyr Ser Ala Leu Gln Gln Ala
1 5

<210> SEQ ID NO 325
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

Thr Leu Glu Asn Gly Val Pro Cys Val
1 5

<210> SEQ ID NO 326
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

Val Leu Ala Phe Leu Val His Glu Leu
1 5

<210> SEQ ID NO 327
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

Val Leu Ile Lys Trp Phe Pro Glu Val
1 5

<210> SEQ ID NO 328
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

Val Leu Leu Pro Gln Glu Thr Ala Glu Ile His Leu
1 5 10

<210> SEQ ID NO 329
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

Val Leu Met Asp Gly Ser Val Lys Leu
1 5

<210> SEQ ID NO 330
<211> LENGTH: 9
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

Val Leu Met Trp Glu Ile Tyr Ser Leu
1 5

<210> SEQ ID NO 331
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

Val Leu Trp Glu Leu Ala His Leu Pro Thr Leu
1 5 10

<210> SEQ ID NO 332
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

Val Met Ile Gln His Val Glu Asn Leu
1 5

<210> SEQ ID NO 333
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

Val Thr Leu Glu Phe Pro Gln Leu Ile Arg Val
1 5 10

<210> SEQ ID NO 334
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

Tyr Leu Leu Glu Glu Lys Ile Ala Ser Leu
1 5 10

<210> SEQ ID NO 335
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

Tyr Leu Tyr Gln Glu Gln Tyr Phe Ile
1 5

<210> SEQ ID NO 336
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

Tyr Met Ala Val Thr Thr Gln Glu Val
1 5

<210> SEQ ID NO 337
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

Tyr Met Tyr Glu Lys Glu Ser Glu Leu
1               5

<210> SEQ ID NO 338
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

Phe Leu Asp Met Thr Asn Trp Asn Leu
1               5

<210> SEQ ID NO 339
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

Gly Leu Trp Gly Thr Val Val Asn Ile
1               5

<210> SEQ ID NO 340
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

Lys Leu Leu Glu Glu Ile Cys Asn Leu
1               5

<210> SEQ ID NO 341
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

Leu Leu Ala Glu Leu Pro Ala Ser Val His Ala
1               5                   10

<210> SEQ ID NO 342
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

Ser Leu Ile Thr Pro Leu Gln Ala Val
1               5

<210> SEQ ID NO 343
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

Thr Leu Leu Glu Ala Leu Asp Cys Ile
1               5

<210> SEQ ID NO 344

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<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

Val Leu Ala Phe Glu Asn Pro Gln Val
1               5

<210> SEQ ID NO 345
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

Tyr Leu Ile Glu Pro Asp Val Glu Leu Gln Arg Ile
1               5                   10

<210> SEQ ID NO 346
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

Val Leu Val Gln Val Ser Pro Ser Leu
1               5

<210> SEQ ID NO 347
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

Tyr Leu Gly Pro Val Ser Pro Ser Leu
1               5

<210> SEQ ID NO 348
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

Ala Leu Ala Lys Pro Pro Val Val Ser Val
1               5                   10

<210> SEQ ID NO 349
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

Ala Leu Ala Thr His Ile Leu Ser Leu
1               5

<210> SEQ ID NO 350
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

Ala Leu Glu Asp Arg Val Trp Glu Leu
1               5

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<210> SEQ ID NO 351
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

Ala Leu Ser Glu Lys Leu Ala Arg Leu
1 5

<210> SEQ ID NO 352
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

Ala Leu Val Phe Glu Leu His Tyr Val
1 5

<210> SEQ ID NO 353
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

Ala Thr Pro Met Pro Thr Pro Ser Val
1 5

<210> SEQ ID NO 354
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

Phe Ile Met Asp Asp Pro Ala Gly Asn Ser Tyr Leu
1 5 10

<210> SEQ ID NO 355
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

Phe Ile Trp Pro Met Leu Ile His Ile
1 5

<210> SEQ ID NO 356
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

Phe Leu His Asp His Gln Ala Glu Leu
1 5

<210> SEQ ID NO 357
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

Phe Leu Ile Gln Glu Ile Lys Thr Leu
1 5

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<210> SEQ ID NO 358
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

Phe Leu Thr Asp Tyr Leu Asn Asp Leu
1               5


<210> SEQ ID NO 359
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

Phe Met Gln Asp Pro Met Glu Val Phe Val
1               5                   10


<210> SEQ ID NO 360
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 360

His Leu Ile Asp Thr Asn Lys Ile Gln Leu
1               5                   10


<210> SEQ ID NO 361
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

Ile Leu Gln Glu Phe Glu Ser Lys Leu
1               5


<210> SEQ ID NO 362
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

Ile Leu Thr Glu Leu Gly Gly Phe Glu Val
1               5                   10


<210> SEQ ID NO 363
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

Ile Thr Thr Glu Val Val Asn Glu Leu Tyr Val
1               5                   10


<210> SEQ ID NO 364
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

Lys Met Asp Trp Ile Phe His Thr Ile
1               5
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<210> SEQ ID NO 365
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

Leu Ile Ser Pro Leu Leu Leu Pro Val
1               5

<210> SEQ ID NO 366
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

Leu Leu Ser Glu Thr Cys Val Thr Ile
1               5

<210> SEQ ID NO 367
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

Asn Leu Trp Ser Leu Val Ala Lys Val
1               5

<210> SEQ ID NO 368
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

Gln Leu Gln Pro Thr Asp Ala Leu Leu Cys Val
1               5                   10

<210> SEQ ID NO 369
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 369

Arg Leu Leu Asp Leu Glu Asn Ser Leu Leu Gly Leu
1               5                   10

<210> SEQ ID NO 370
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

Ser Ile Phe Ala Ser Pro Glu Ser Val
1               5

<210> SEQ ID NO 371
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

Ser Leu Ala Asp Asp Ser Val Leu Glu Arg Leu

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1 5 10

<210> SEQ ID NO 372
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

Ser Leu Phe Gly Pro Leu Pro Gly Pro Gly Pro Ala Leu Val
1 5 10

<210> SEQ ID NO 373
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

Thr Leu Leu Ala Asp Gln Gly Glu Ile Arg Val
1 5 10

<210> SEQ ID NO 374
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

Val Leu Ser Val Ile Thr Glu Glu Leu
1 5

<210> SEQ ID NO 375
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

Val Leu Trp Phe Lys Pro Val Glu Leu
1 5

<210> SEQ ID NO 376
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

Val Leu Tyr Asn Gln Arg Val Glu Glu Ile
1 5 10

<210> SEQ ID NO 377
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

Val Val Asp Gly Thr Cys Val Ala Val
1 5

<210> SEQ ID NO 378
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

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Tyr Ile Leu Gly Lys Phe Phe Ala Leu
1               5

<210> SEQ ID NO 379
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

Tyr Leu Ala Glu Leu Val Thr Pro Ile Leu
1               5                   10

<210> SEQ ID NO 380
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

Tyr Leu Asp Arg Lys Leu Leu Thr Leu
1               5

<210> SEQ ID NO 381
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

Tyr Leu Leu Glu Glu Asn Lys Ile Lys Leu
1               5                   10

<210> SEQ ID NO 382
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

Tyr Leu Leu Pro Leu Leu Gln Arg Leu
1               5

<210> SEQ ID NO 383
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

Tyr Leu Leu Arg Glu Trp Val Asn Leu
1               5

<210> SEQ ID NO 384
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

Tyr Met Ile Gly Ser Glu Val Gly Asn Tyr Leu
1               5                   10

<210> SEQ ID NO 385
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

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Tyr Thr Ile Pro Leu Ala Ile Lys Leu
1               5

<210> SEQ ID NO 386
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

Phe Leu Gly Asp Tyr Val Glu Asn Leu
1               5

<210> SEQ ID NO 387
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

Tyr Leu Ile Leu Ser Ser His Gln Leu
1               5

<210> SEQ ID NO 388
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

Gly Leu Leu Ser Ala Leu Glu Asn Val
1               5

<210> SEQ ID NO 389
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

Gly Leu Ala Ala Leu Ala Val His Leu
1               5

<210> SEQ ID NO 390
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

Gly Leu Glu Glu Arg Leu Tyr Thr Ala
1               5

<210> SEQ ID NO 391
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

Phe Leu Leu Glu Arg Glu Gln Leu Leu
1               5

<210> SEQ ID NO 392
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 392

Phe Leu Trp Glu Arg Pro Thr Leu Leu Val
1 5 10

<210> SEQ ID NO 393
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

Phe Val Met Glu Gly Glu Pro Pro Lys Leu
1 5 10

<210> SEQ ID NO 394
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

Ile Leu Ser Thr Glu Ile Phe Gly Val
1 5

<210> SEQ ID NO 395
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

Ala Leu Tyr Gly Lys Leu Leu Lys Leu
1 5

<210> SEQ ID NO 396
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

Thr Leu Leu Gly Lys Gln Val Thr Leu
1 5

<210> SEQ ID NO 397
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

Phe Leu Pro Pro Glu His Thr Ile Val Tyr Ile
1 5 10

<210> SEQ ID NO 398
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Phe Leu Ala Glu Leu Pro Gly Ser Leu Ser Leu
1 5 10

<210> SEQ ID NO 399
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 399

Ala Leu Ala Ala Pro Asp Ile Val Pro Ala Leu
1 5 10

<210> SEQ ID NO 400
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

Ala Leu Phe Gln Pro His Leu Ile Asn Val
1 5 10

<210> SEQ ID NO 401
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

Ala Met Ala Asp Lys Met Asp Met Ser Leu
1 5 10

<210> SEQ ID NO 402
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

Leu Leu Val Ser Asn Leu Asp Phe Gly Val
1 5 10

<210> SEQ ID NO 403
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

Phe Ile Met Pro Ala Thr Val Ala Asp Ala Thr Ala Val
1 5 10

<210> SEQ ID NO 404
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

Phe Leu Gln Pro Asp Leu Asp Ser Leu
1 5

<210> SEQ ID NO 405
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

Phe Leu Val Glu Lys Gln Pro Pro Gln Val
1 5 10

<210> SEQ ID NO 406
<211> LENGTH: 9
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

Phe Leu Trp Pro Lys Glu Val Glu Leu
1 5

<210> SEQ ID NO 407
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

Phe Met Ile Asp Ala Ser Val His Pro Thr Leu
1 5 10

<210> SEQ ID NO 408
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

Phe Met Val Asp Asn Glu Ala Ile Tyr Asp Ile
1 5 10

<210> SEQ ID NO 409
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

Gly Leu Asp Ala Ala Thr Ala Thr Val
1 5

<210> SEQ ID NO 410
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

Gly Leu Phe Asp Gly Val Pro Thr Thr Ala
1 5 10

<210> SEQ ID NO 411
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

Gly Leu Phe Glu Asp Val Thr Gln Pro Gly Ile Leu Leu
1 5 10

<210> SEQ ID NO 412
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

Ile Leu Gly Thr Glu Asp Leu Ile Val Glu Val
1 5 10

<210> SEQ ID NO 413
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

Ile Leu Leu Glu His Gly Ala Asp Pro Asn Leu
1 5 10

<210> SEQ ID NO 414
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

Ile Leu Ser Val Val Asn Ser Gln Leu
1 5

<210> SEQ ID NO 415
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

Ile Leu Val Thr Ser Ile Phe Phe Leu
1 5

<210> SEQ ID NO 416
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

Ile Met Glu Asp Ile Ile Leu Thr Leu
1 5

<210> SEQ ID NO 417
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

Ile Gln Ile Gly Glu Glu Thr Val Ile Thr Val
1 5 10

<210> SEQ ID NO 418
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 418

Ile Val Thr Glu Ile Ile Ser Glu Ile
1 5

<210> SEQ ID NO 419
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

Leu Leu Asn Glu Ile Leu Glu Gln Val
1 5

<210> SEQ ID NO 420

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<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

Lys Leu Ile Asp Asp Gln Asp Ile Ser Ile Ser Leu
1               5                   10

<210> SEQ ID NO 421
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

Lys Leu Trp Thr Gly Gly Leu Asp Asn Thr Val
1               5                   10

<210> SEQ ID NO 422
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

Lys Gln Phe Glu Gly Thr Val Glu Ile
1               5

<210> SEQ ID NO 423
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

Leu Leu Ile Gly Thr Asp Val Ser Leu
1               5

<210> SEQ ID NO 424
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

Leu Leu Pro Pro Leu Glu Ser Leu Ala Thr Val
1               5                   10

<210> SEQ ID NO 425
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

Leu Leu Ser Asp Val Arg Phe Val Leu
1               5

<210> SEQ ID NO 426
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 426

Leu Leu Trp Gly Asn Leu Pro Glu Ile
1               5

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<210> SEQ ID NO 427
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 427

Leu Leu Tyr Asp Ala Val His Ile Val
1               5

<210> SEQ ID NO 428
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 428

Leu Met Tyr Pro Tyr Ile Tyr His Val
1               5

<210> SEQ ID NO 429
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 429

Asn Leu Leu Glu Thr Lys Leu Gln Leu
1               5

<210> SEQ ID NO 430
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 430

Gln Leu Ile Glu Lys Asn Trp Leu Leu
1               5

<210> SEQ ID NO 431
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 431

Arg Met Val Ala Glu Ile Gln Asn Val
1               5

<210> SEQ ID NO 432
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 432

Ser Ala Val Asp Phe Ile Arg Thr Leu
1               5

<210> SEQ ID NO 433
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 433

Ser Ile Leu Asp Arg Asp Asp Ile Phe Val
1               5                   10

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<210> SEQ ID NO 434
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 434

Ser Ile Gln Gln Ser Ile Glu Arg Leu Leu Val
1 5 10

<210> SEQ ID NO 435
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 435

Ser Leu Phe Asn Gln Glu Val Gln Ile
1 5

<210> SEQ ID NO 436
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 436

Ser Leu Phe Ser Ser Leu Glu Pro Gln Ile Gln Pro Val
1 5 10

<210> SEQ ID NO 437
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 437

Ser Leu Glu Pro Gln Ile Gln Pro Val
1 5

<210> SEQ ID NO 438
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 438

Ser Leu Phe Ile Gly Glu Lys Ala Val Leu Leu
1 5 10

<210> SEQ ID NO 439
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 439

Ser Leu Leu Asp Leu His Thr Lys Val
1 5

<210> SEQ ID NO 440
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 440

Ser Leu Leu Glu Gln Gly Lys Glu Pro Trp Met Val
1 5 10

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<210> SEQ ID NO 441
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 441

Ser Leu Leu Glu Val Asn Glu Ala Ser Ser Val
1               5                   10

<210> SEQ ID NO 442
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 442

Ser Leu Asn Asp Leu Glu Lys Asp Val Met Leu Leu
1               5                   10

<210> SEQ ID NO 443
<211> LENGTH: 10
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 443

Ser Leu Thr Ile Asp Gly Ile Tyr Tyr Val
1               5                   10

<210> SEQ ID NO 444
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 444

Ser Met Ser Gly Tyr Asp Gln Val Leu
1               5

<210> SEQ ID NO 445
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 445

Val Ile Ile Lys Gly Leu Glu Glu Ile Thr Val
1               5                   10

<210> SEQ ID NO 446
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 446

Val Ile Leu Thr Ser Ser Pro Phe Leu
1               5

<210> SEQ ID NO 447
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 447

Val Leu Asp Asp Ser Ile Tyr Leu Val

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1 5

<210> SEQ ID NO 448
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 448

Val Met Asn Asp Arg Leu Tyr Ala Ile
1 5

<210> SEQ ID NO 449
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 449

Leu Leu Asp Ala Met Asn Tyr His Leu
1 5

<210> SEQ ID NO 450
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 450

Val Leu Gly Pro Gly Pro Pro Pro Leu
1 5

<210> SEQ ID NO 451
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 451

Val Leu Ile Glu Tyr Asn Phe Ser Ile
1 5

<210> SEQ ID NO 452
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 452

Val Leu Leu Ser Leu Leu Glu Lys Val
1 5

<210> SEQ ID NO 453
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 453

Ser Leu Leu Pro Leu Val Trp Lys Ile
1 5

<210> SEQ ID NO 454
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 454

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Val Leu Met Asp Glu Gly Ala Val Leu Thr Leu
1               5                   10

<210> SEQ ID NO 455
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 455

Val Leu Pro Asp Pro Glu Val Leu Glu Ala Val
1               5                   10

<210> SEQ ID NO 456
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 456

Tyr Ala Ala Pro Gly Gly Leu Ile Gly Val
1               5                   10

<210> SEQ ID NO 457
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 457

Tyr Ile Met Glu Pro Ser Ile Phe Asn Thr Leu
1               5                   10

<210> SEQ ID NO 458
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 458

Tyr Ile Gln Glu His Leu Leu Gln Ile
1               5

<210> SEQ ID NO 459
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 459

Tyr Leu Asp Phe Ser Asn Asn Arg Leu
1               5

<210> SEQ ID NO 460
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 460

Tyr Leu Glu Asp Gly Phe Ala Tyr Val
1               5

<210> SEQ ID NO 461
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 461

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Tyr Leu Leu Asn Leu Asn His Leu Gly Leu
1 5 10

<210> SEQ ID NO 462
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

Tyr Val Leu Pro Lys Leu Tyr Val Lys Leu
1 5 10

<210> SEQ ID NO 463
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 463

Ala Leu Met Ala Val Val Ser Gly Leu
1 5

<210> SEQ ID NO 464
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

Ala Leu Ser Asp Glu Thr Lys Asn Asn Trp Glu Val
1 5 10

<210> SEQ ID NO 465
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

Phe Leu Tyr Asp Glu Ile Glu Ala Glu Val Asn Leu
1 5 10

<210> SEQ ID NO 466
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 466

Phe Leu Tyr Asp Glu Ile Glu Ala Glu Val
1 5 10

<210> SEQ ID NO 467
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 467

Ile Met Gln Asp Phe Pro Ala Glu Ile Phe Leu
1 5 10

<210> SEQ ID NO 468
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 468

Lys Ile Gln Glu Ile Leu Thr Gln Val
1 5

<210> SEQ ID NO 469
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 469

Ser Leu Asp Gly Thr Glu Leu Gln Leu
1 5

<210> SEQ ID NO 470
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

Thr Leu Thr Asn Ile Ile His Asn Leu
1 5

<210> SEQ ID NO 471
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 471

Val Leu Leu Ala Ala Gly Pro Ser Ala Ala
1 5 10

<210> SEQ ID NO 472
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 472

Tyr Leu Phe Glu Ser Glu Gly Leu Val Leu
1 5 10

<210> SEQ ID NO 473
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 473

Ala Leu Ala Asp Asp Asp Phe Leu Thr Val
1 5 10

<210> SEQ ID NO 474
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 474

Ala Leu Ala Asp Leu Ile Glu Lys Glu Leu Ser Val
1 5 10

<210> SEQ ID NO 475
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 475

Ala Leu Asp Asp Met Ile Ser Thr Leu
1               5

<210> SEQ ID NO 476
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 476

Ala Leu Ile Thr Glu Val Val Arg Leu
1               5

<210> SEQ ID NO 477
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 477

Ala Leu Leu Asp Gln Thr Lys Thr Leu Ala Glu Ser Ala Leu
1               5                   10

<210> SEQ ID NO 478
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 478

Ala Met Phe Glu Ser Ser Gln Asn Val Leu Leu
1               5                   10

<210> SEQ ID NO 479
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 479

Tyr Leu Ala His Phe Ile Glu Gly Leu
1               5

<210> SEQ ID NO 480
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 480

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

<210> SEQ ID NO 481
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 481

Phe Leu Ile Asp Thr Ser Ala Ser Met
1               5

<210> SEQ ID NO 482
<211> LENGTH: 10
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 482

Phe Leu Thr Asp Leu Glu Asp Leu Thr Leu
1 5 10

<210> SEQ ID NO 483
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 483

Phe Leu Thr Glu Met Val His Phe Ile
1 5

<210> SEQ ID NO 484
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484

Phe Leu Val Asp Gly Pro Arg Val Gln Leu
1 5 10

<210> SEQ ID NO 485
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 485

Gly Leu Leu Asp Cys Pro Ile Phe Leu
1 5

<210> SEQ ID NO 486
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 486

Gly Leu Leu Asp Leu Pro Phe Arg Val Gly Val
1 5 10

<210> SEQ ID NO 487
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 487

Gly Leu Ser Asp Gly Asn Pro Ser Leu
1 5

<210> SEQ ID NO 488
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 488

Gly Val Tyr Asp Gly Glu Glu His Ser Val
1 5 10

<210> SEQ ID NO 489
<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 489

His Leu Ala Asn Ile Val Glu Arg Leu
1               5

<210> SEQ ID NO 490
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 490

Ile Leu Asp Glu Lys Pro Val Ile Ile
1               5

<210> SEQ ID NO 491
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 491

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

<210> SEQ ID NO 492
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 492

Ile Leu Leu Asp Asp Asn Met Gln Ile Arg Leu
1               5                   10

<210> SEQ ID NO 493
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 493

Leu Ile Ile Asp Gln Ala Asp Ile Tyr Leu
1               5                   10

<210> SEQ ID NO 494
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 494

Leu Leu Gly Asp Ser Ser Phe Phe Leu
1               5

<210> SEQ ID NO 495
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 495

Leu Leu Leu Asp Glu Glu Gly Thr Phe Ser Leu
1               5                   10

<210> SEQ ID NO 496

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<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 496

Leu Leu Val Glu Gln Pro Pro Leu Ala Gly Val
1               5                   10

<210> SEQ ID NO 497
<211> LENGTH: 10
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 497

Leu Leu Trp Asp Val Pro Ala Pro Ser Leu
1               5                   10

<210> SEQ ID NO 498
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 498

Leu Thr Ala Pro Pro Glu Ala Leu Leu Met Val
1               5                   10

<210> SEQ ID NO 499
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 499

Asn Leu Met Glu Met Val Ala Gln Leu
1               5

<210> SEQ ID NO 500
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 500

Gln Ile Ile Thr Ser Val Val Ser Val
1               5

<210> SEQ ID NO 501
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 501

Gln Leu Ala Leu Lys Val Glu Gly Val
1               5

<210> SEQ ID NO 502
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 502

Gln Leu Leu Asp Glu Thr Ser Ala Ile Thr Leu
1               5                   10

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<210> SEQ ID NO 503
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 503

Gln Leu Tyr Glu Glu Pro Asp Thr Lys Leu
1               5                   10

<210> SEQ ID NO 504
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 504

Arg Leu Tyr Ser Gly Ile Ser Gly Leu Glu Leu
1               5                   10

<210> SEQ ID NO 505
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 505

Arg Val Leu Glu Val Gly Ala Leu Gln Ala Val
1               5                   10

<210> SEQ ID NO 506
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 506

Ser Leu Leu Pro Leu Asp Asp Ile Val Arg Val
1               5                   10

<210> SEQ ID NO 507
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 507

Ser Leu Leu Thr Glu Gln Asp Leu Trp Thr Val
1               5                   10

<210> SEQ ID NO 508
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 508

Ser Val Asp Ser Ala Pro Ala Ala Val
1               5

<210> SEQ ID NO 509
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 509

Thr Leu Gln Glu Val Val Thr Gly Val
1               5

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<210> SEQ ID NO 510
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 510

Thr Val Asp Val Ala Thr Pro Ser Val
1               5

<210> SEQ ID NO 511
<211> LENGTH: 9
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 511

Val Leu Ala Tyr Phe Leu Pro Glu Ala
1               5

<210> SEQ ID NO 512
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 512

Val Leu Ile Ser Val Leu Gln Ala Ile
1               5

<210> SEQ ID NO 513
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 513

Tyr Leu Ile Pro Phe Thr Gly Ile Val Gly Leu
1               5                   10

<210> SEQ ID NO 514
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 514

Tyr Leu Leu Asp Asp Gly Thr Leu Val Val
1               5                   10

<210> SEQ ID NO 515
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 515

Tyr Leu Met Pro Gly Phe Ile His Leu
1               5

<210> SEQ ID NO 516
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 516

Tyr Leu Pro Asp Ile Ile Lys Asp Gln Lys Ala
1               5                   10

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<210> SEQ ID NO 517
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 517

Tyr Leu Gln Leu Thr Gln Ser Glu Leu
1               5

<210> SEQ ID NO 518
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 518

Tyr Leu Thr Glu Val Phe Leu His Val Val
1               5                   10

<210> SEQ ID NO 519
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 519

Tyr Leu Val Glu Gly Arg Phe Ser Val
1               5

<210> SEQ ID NO 520
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 520

Tyr Leu Val Tyr Ile Leu Asn Glu Leu
1               5

<210> SEQ ID NO 521
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 521

Tyr Leu Tyr Gly Gln Thr Thr Thr Tyr Leu
1               5                   10

<210> SEQ ID NO 522
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 522

Tyr Val Leu Thr Gln Pro Pro Ser Val
1               5

<210> SEQ ID NO 523
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 523

Glu Leu Ala Gly Ile Gly Ile Leu Thr Val

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1               5                   10

<210> SEQ ID NO 524
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 524

Tyr Leu Leu Pro Ala Ile Val His Ile
1               5
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**1**. A method of eliciting an immune response in a patient who has cancer, comprising administering to the patient a composition comprising a population of activated T cells that kill the cancer cells that present a peptide consisting of the amino acid sequence of SEQ ID NO: 52, 1-51, 53-65, 67-85, or 87-522,

wherein said cancer is selected from the group consisting of glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell and small cell lung cancer, non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer, gallbladder cancer and cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, head and neck squamous cell carcinoma, and uterine cancer.

**2**. The method of claim **1**, wherein the activated T cells are produced by contacting in vitro T cells with the peptide loaded onto human class I MHC molecules expressed on the surface of an antigen-presenting cell for a period of time sufficient to activate said T cells.

**3**. The method of claim **1**, wherein the T cells are autologous to the patient.

**4**. The method of claim **1**, wherein the T cells are obtained from a healthy donor.

**5**. The method of claim **1**, wherein the T cells are obtained from tumor infiltrating lymphocytes or peripheral blood mononuclear cells.

**6**. The method of claim **1**, wherein the activated T cells are expanded in vitro.

**7**. The method of claim **1**, wherein the peptide is in a complex with a class I MHC molecule.

**8**. The method of claim **2**, wherein the antigen presenting cell is infected with recombinant virus expressing the peptide.

**9**. The method of claim **8**, wherein the antigen presenting cell is a dendritic cell or a macrophage.

**10**. The method of claim **1**, wherein the population of activated T cells comprises CD8-positive cells.

**11**. The method of claim **1**, wherein the composition further comprises an adjuvant.

**12**. The method of claim **11**, wherein the adjuvant is selected from anti-CD40 antibody, imiquimod, resiquimod, GM-CSF, cyclophosphamide, sunitinib, bevacizumab, interferon-alpha, interferon-beta, CpG oligonucleotides and derivatives, poly-(I:C) and derivatives, RNA, sildenafil, particulate formulation with poly(lactide co-glycolide) (PLG), virosomes, interleukin (IL)-1, IL-2, IL-4, IL-7, IL-12, IL-13, IL-15, IL-21, and IL-23.

**13**. The method of claim **1**, wherein the immune response comprises a cytotoxic T cell response.

**14**. The method of claim **1**, wherein the cancer is chronic lymphocytic leukemia.

**15**. The method of claim **1**, wherein the cancer is melanoma.

**16**. The method of claim **11**, wherein the adjuvant comprises IL-2.

**17**. The method of claim **11**, wherein the adjuvant comprises IL-7.

**18**. The method of claim **11**, wherein the adjuvant comprises IL-15.

**19**. The method of claim **11**, wherein the adjuvant comprises IL-21.

**20**. A method of eliciting an immune response in a patient who has glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell and small cell lung cancer, non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer, gallbladder cancer and cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, head and neck squamous cell carcinoma, and/or uterine cancer, comprising administering to said patient a composition comprising a peptide in the form of a pharmaceutically acceptable salt, wherein said peptide consists of the amino acid sequence of SEQ ID NO: 52, 1-51, 53-65, 67-85, or 87-522, thereby inducing a T-cell response to the glioblastoma, breast cancer, colorectal cancer, renal cell carcinoma, chronic lymphocytic leukemia, hepatocellular carcinoma, non-small cell and small cell lung cancer, non-Hodgkin lymphoma, acute myeloid leukemia, ovarian cancer, pancreatic cancer, prostate cancer, esophageal cancer, gallbladder cancer and cholangiocarcinoma, melanoma, gastric cancer, testis cancer, urinary bladder cancer, head and neck squamous cell carcinoma, and/or uterine cancer, wherein the T cell response is a cytotoxic T cell response.

* * * * *