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

(72) Inventors: **STICKEL, Juliane**; Quenstedtstrasse 28, 72076 Tübingen (DE). **KOWALEWSKI, Daniel**; Denzenbergstrasse 29, 72074 Tübingen (DE). **RAMMENSEE, Hans-Georg**; Sommerhalde 3, 72070 Tübingen (DE). **STEVANOVIC, Stefan**; Auf der Burg 3, 72074 Tübingen (DE).

(74) Agent: **BOEHMERT & BOEHMERT**; Jan B. Krauss, Pettenkoferstrasse 20 - 22, 80336 Munich (DE).

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(54) Title: NOVEL IMMUNOTHERAPY AGAINST SEVERAL TUMORS OF THE BLOOD, IN PARTICULAR CHRONIC LYMPHOID LEUKEMIA (CLL)

(57) Abstract: The present invention relates to peptides, 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 cytotoxic T cell (CTL) peptide epitopes, alone or in combination with other tumor-associated peptides that serve as active pharmaceutical ingredients of vaccine compositions that stimulate anti-tumor immune responses. The present invention relates to several novel peptide sequences and their variants derived from HLA class I and HLA class II molecules of human tumor cells that can be used in vaccine compositions for eliciting anti-tumor immune responses.

Novel immunotherapy against several tumors of the blood, in particular chronic lymphoid leukemia (CLL)

The present invention relates to peptides, 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 cytotoxic T cell (CTL) peptide epitopes, alone or in combination with other tumor-associated peptides that serve as active pharmaceutical ingredients of vaccine compositions that stimulate anti-tumor immune responses. The present invention relates to several novel peptide sequences and their variants derived from HLA class I and HLA class II molecules of human tumor cells that can be used in vaccine compositions for eliciting anti-tumor immune responses.

Background of the invention

B-cell chronic lymphocytic leukemia (B-CLL), also known as chronic lymphoid leukemia (CLL), is the most common type of leukemia.

Leukemias are cancers of the white blood cells (leukocytes). CLL affects B cell lymphocytes. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection by producing antibodies. In CLL, B cells grow out of control and accumulate in the bone marrow and blood, where they crowd out healthy blood cells. CLL is a stage of small lymphocytic lymphoma (SLL), a type of B-cell lymphoma, which presents primarily in the lymph nodes. CLL and SLL are considered the same underlying disease, just with different appearances.

CLL is a disease of adults, but, in rare cases, it can occur in teenagers and occasionally in children (inherited). Most (>75%) people newly diagnosed with CLL are over the age of 50, and the majority are men, with a median age of 70 years at the time of diagnosis. Though less common, CLL sometimes affects people between 30 and 39 years of age. The incidence of CLL increases very quickly with increasing age.

In the United States, during 2012 about 16,060 new cases are expected to be diagnosed, and 4,580 patients are expected to die from CLL.

CLL is very rare in Asian countries, such as Japan and China, and may account for as few as 10 percent of all leukemias in those regions.

In view of the above, there remains a need for new efficacious and safe treatment option for cancers, in particular chronic lymphoid leukemia (CLL) and other cancers of the blood of different phenotypes which improve the well-being of the patients by not using excessive chemotherapeutic agents or other agents that may lead to severe side effects.

The present invention employs peptides that stimulate the immune system of the patient and act as anti-tumor-agents in a non-invasive fashion.

Summary of the invention

In a first aspect of the present invention, the present invention relates to a peptide comprising an amino acid sequence selected from the group of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016 or a variant sequence thereof which is at least 80%, preferably at least 90%, homologous (preferably at least 80% or at least 90% identical) to SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016, wherein said variant induces T cells cross-reacting with said peptide, or a pharmaceutical acceptable salt thereof, wherein said peptide is not the underlying full-length polypeptide.

The present invention further relates to a peptide of the present invention comprising a sequence that is selected from the group SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016 or a variant thereof, which is at least 80%, preferably at least 90%, homologous (preferably at least 80% or at least 90% identical) to SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016, wherein said peptide or variant thereof has an overall length for SEQ ID NO: 1 to SEQ ID NO: 225 of between 8 and 100, preferably

between 8 and 30, and most preferred of between 8 and 14 amino acids, and for SEQ ID NO: SEQ ID NO: 543 to SEQ ID NO: 1016 of between 12 and 100, preferably between 12 and 30, and most preferred of between 12 to 18 amino acids.

The following tables show the peptides according to the present invention, their respective SEQ ID NO:, and the prospective source (underlying) proteins for these peptides. All peptides in Table 1a and 1b bind to HLA A HLA B or HLA C alleles, peptides in Table 2 bind to HLA-DR alleles (MHC class II). The peptides in table 3 are further useful in the diagnosis and/or treatment of CLL, Acute myelogenous leukemia (AML), and other hematological malignancies, which involve an over-expression or over-presentaion of the respective underlying polypeptide.

Thus, the present invention relates in particular to a peptide of the present invention comprising a sequence according to SEQ ID NO: 543 to SEQ ID NO: 1016 or a variant thereof, which is at least 80%, preferably at least 90%, homologous (preferably at least 80% or at least 90% identical) to SEQ ID NO: 543 to SEQ ID NO: 1016, wherein said peptide or variant thereof has an overall length of between 12 and 100, preferably between 12 and 30, and most preferred of between 12 to 18 amino acids. The present invention relates in particular to a peptide of the present invention consisting of the sequence according to SEQ ID NO: 543 to SEQ ID NO: 1016.

Table 1a: Preferred 49 HLA class I ligandome derived tumor associated antigens (LiTAAs) according to the invention found represented in ≥20% of CLL patient ligandomes (n=30) and the 225 representing HLA ligands (LiTAPs) annotated with respective HLA restriction.

SEQ ID NO:	**Underlying source protein/** HLA ligands	**Number of positive CLLs (frequency [%])**	**HLA**
	APOBEC3D apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D	**13 (43.3)**	
1	AEHPNVTLTI	1	B*40
2	FLAEHPNVTL	8	A*02
3	ILYGRSYTW	1	A*32

SEQ ID NO:	Underlying source protein/ HLA ligands	Number of positive CLLs (frequency [%])	HLA
4	EVAEFLARH	2	A*26
5	RHSNVNLTI	1	C*07
	CDK14 cyclin-dependent kinase 14	**12 (40.0)**	
6	HPDNVKLFL	1	B*35
7	ISDTGELKL	1	C*05
8	KVNGKLVALK	1	A*03
9	NRLSAQAAL	1	B*39
10	TPFTAIREA	1	B*55
11	FGLARAKSV	6	B*08
12	KIADFGLAR	1	A*03
	RASGRF1 Ras protein-specific guanine nucleotide-releasing factor 1	**12 (40.0)**	B*35
13	AAANIIRTL	8	A*02, B*13, B*51
14	GRFKNLREAL	1	B*27
15	MSPFSKATL	2	C*14
16	QEDPGDNQITL	1	B*40
17	SPFSKATL	2	B*08, B*07
	CDCA7L cell division cycle associated 7-like	**11 (36.7)**	
18	DALLKRTM	1	B*08
19	GEDVRSALL	3	B*40
20	KFAEEFYSF	2	A*24
21	YGYDNVKEY	7	C*03, C*12
	CELSR1 cadherin, EGF LAG seven-pass G-type receptor 1	**11 (36.7)**	
22	LEVEERTKPV	1	B*44
23	RDSPINANLRY	1	B*40
24	RPFVIVTA	1	B*55
25	RPIINTPMV	1	B*55
26	SPTSSRTSSL	7	B*07
27	ATSAPLVSR	1	A*11
	AKAP2 A kinase (PRKA) anchor protein 2	**11 (36.7)**	
28	AELRSTASLL	1	B*40
29	APASSHERASM	2	B*07
30	ASRQAPPHI	1	A*30
31	AVKKNPGIAA	2	A*02
32	EEHLESHKKY	2	B*44
33	GEFTSARAV	1	B*49
34	GQSTPRLFSI	1	B*13
35	LVDDPLEY	1	A*01
36	RPKNLMQTL	3	B*07
37	RQAPPHIEL	2	B*13
38	SEAAELRSTA	1	B*50
	CTDP1 CTD phosphatase, subunit 1	**11 (36.7)**	
39	AAVRIGSVL	2	A*02, B*13

SEQ ID NO:	Underlying source protein/ HLA ligands	Number of positive CLLs (frequency [%])	HLA
	Underlying source protein/ HLA ligands	**Number of positive CLLs (frequency [%])**	**HLA**
40	ERAGVVREL	1	C*07
41	GAAVRIGSVL	1	A*02
42	KLYELHVFTF	1	A*32
43	LYELHVFTF	2	A*24, A*23
44	YLNKEIEEA	6	A*02
	DNMBP dynamin binding protein	**10 [33.3]**	
45	DELPKFHQY	2	B*18
46	DVTGQFPSSF	1	A*26
47	EHSRVLQQL	2	B*39:01
48	IKVSKQLL	1	B*08
49	KPRQSSPQL	3	B*07
50	KQLLAALEI	1	B*13
51	RRKDLVLKY	2	B*27
52	RTRDYASLPPK	1	A*03
	TAGAP T-cell activation RhoGTPase activating protein	**10 (33.3)**	
53	APGSVLPRAL	3	B*07
54	DIKEHPLL	1	B*08
55	DSAGPQDAR	1	A*68
56	FQYAKESYI	1	B*13
57	KVLSWPFLM	1	A*32
58	LENDQSLSF	1	B*44
59	SPSRQPQV	1	B*07
60	SRHQSFTTK	3	B*27
61	SSHNASKTL	2	C*12
	ABCA6 ATP-binding cassette, sub-family A (ABC1), member 6	**10 (33.3)**	
62	EEIDTTMRW	1	B*44
63	ILDEKPVII	5	A*02
64	LPQEPRTSL	2	B*07
65	LTYKLPVA	1	B*57
66	NEMELAHSSF	2	B*18
67	REFPEANFEL	1	B*40
68	THHIPDAKL	1	B*38
69	TVKENLSLF	1	A*26
70	VLLKKAVL	1	B*08
	DMXL1 Dmx-like 1	**10 (33.3)**	
71	HLKSIPVSL	2	B*08, B*07
72	KVWYNVENW	1	A*32
73	LPAYRAQLL	1	B*07
74	LSEQTSVPL	1	A*02
75	SLNQWLVSF	1	A*32
76	SMTSLAQKI	1	A*02
77	SSSGLHPPK	2	A*03, A*11, A*68

SEQ ID NO:	Underlying source protein/ HLA ligands	Number of positive CLLs (frequency [%])	HLA
	PARP3 poly (ADP-ribose) polymerase family, member 3	**10 (33.3)**	
78	DLDVKKMPL	4	B*08
79	FYTVIPHNF	3	A*24
80	HHINTDNPSL	2	B*39
81	RVGEVGQSK	2	A*03
	TP53I11 tumor protein p53 inducible protein 11	**8 (26.7)**	
82	AVFDGAQVTSK	7	A*03, A*11
83	SQTDLVSRL	1	B*15
	B4GALT1 UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 1	**8 (26.7)**	
84	VPVPHTTAL	7	B*07
85	YQVLDVQRY	1	B*15
	IRF9 interferon regulatory factor 9	**8 (26.7)**	
86	APFQGDQRSL	2	B*07
87	DVAEPYKVY	1	A*26
88	IVSGQPGTQK	3	A*03
89	TPEQQAAIL	1	B*35
90	VELFRTAYF	1	B*37
	KDM2B lysine (K)-specific demethylase 2B	**8 (26.7)**	
91	EHADDDPSL	1	B*38
92	SEESVKSTTL	2	B*40
93	SPRPPLGSSL	4	B*07
94	SPWWRSSL	1	B*07
95	VYTPVDSLVF	1	A*24
	TBC1D22A TBC1 domain family, member 22A	**8 (26.7)**	
96	APLQRSQSL	6	B*07, B*08
97	DEVHQDTY	1	B*18
98	LPHSATVTL	1	B*07
	ZNF296 zinc finger protein 296	**8 (26.7)**	
99	SEAPEAPLL	1	B*40
100	SPRASGSGL	6	B*07
101	VVGPAAEAK	2	A*03
	BACH2 BTB and CNC homology 1, basic leucine zipper transcription factor 2	**8 (26.7)**	
102	FSITKSVEL	4	A*02
103	GQTKNDLVV	1	B*13
104	LSQEVCRD	2	n.a.
105	RDIQSPEQI	1	B*40
106	REDNSSNSL	1	B*40
107	TEHQEPGL	2	B*40
108	TKNDLVVSL	1	B*39
	PRR12 proline rich 12	**8 (26.7)**	
109	AEEAGGTRL	1	B*40
110	ENVNKKDY	1	A*26

SEQ ID NO:	Underlying source protein/ HLA ligands	Number of positive CLLs (frequency [%])	HLA
	Underlying source protein/ HLA ligands	**Number of positive CLLs (frequency [%])**	**HLA**
111	GLDPNKPPEL	4	A*02
112	RPAGEPYNRKTL	2	B*07
	ZFAND5 zinc finger, AN1-type domain 5	**7 (23.3)**	
113	SASVQRADTSL	5	C*03
114	YGNPRTNGM	2	B*08
	ATP5G1 ATP synthase, H+ transporting, mitochondrial Fo complex, subunit C1	**7 (23.3)**	
115	LIRPVSASF	3	B*07
116	SPVNSSKQPSY	3	B*35
117	QLFSYAILGF	1	A*32
	DMD dystrophin	**7 (23.3)**	
118	DEHLLIQHY	2	B*18
119	KQVASSTGF	1	B*15
120	RDFGPASQHFL	1	B*40
121	RQLGEVASF	2	A*32
122	TEAETTANVL	1	B*40
123	GYLPVQTVL	1	A*24
	ARID5B AT rich interactive domain 5B (MRF1-like)	**7 (23.3)**	
124	GQKEALLKY	1	B*15
125	KPSEERKTI	1	B*07
126	KQTPKVLVV	1	B*13
127	SVIQHVQSF	1	A*26
128	TPIERIPYL	3	B*51
	ZNF638 zinc finger protein 638	**7 (23.3)**	
129	AEVEKNETV	1	B*40
130	EVKEEIPLV	1	B*08
131	KPTSARSGL	2	B*07
132	KYIETTPLTI	1	A*24
133	SEIKTSIEV	1	B*40
134	SVKPTSATK	4	A*03
135	YPNKGVGQA	1	B*55
	DDX46 DEAD (Asp-Glu-Ala-Asp) box polypeptide 46	**7 (23.3)**	
136	ISMKILNSL	2	A*02
137	KTIAFLLPMF	1	A*32
138	RDSIINDF	2	B*37
139	SVKGGGGNEK	1	A*03
140	GIAKTGSGK	1	A*03
	RRM2B ribonucleotide reductase M2 B (TP53 inducible)	**7 (23.3)**	
141	AETTDNVFTL	1	B*40
142	SEYQRFAVM	3	B*37, B*40, B*49
143	TFGERVVAF	1	A*24

SEQ ID NO:		Number of positive CLLs (frequency [%])	HLA
	Underlying source protein/ HLA ligands		
144	NENLVERF	2	B*18
	BLNK B-cell linker	**7 (23.3)**	
145	KITVPASQK	1	A*03
146	KITVPASQKL	7	A*02
147	VPASQKLRQL	2	B*07
	HSH2D hematopoietic SH2 domain containing	**7 (23.3)**	
148	HVGYTLSYK	1	A*03
149	KLPLPLPPRL	3	C*14
150	KPIEPRREL	1	B*07
151	SHSHVGYTL	3	B*38, B*39
	ERP44 endoplasmic reticulum protein 44	**7 (23.3)**	
152	APSEYRYTL	1	B*07
153	APSEYRYTLL	3	B*07
154	EIFQNEVAR	1	A*68
155	KDVLIPGKL	1	B*40
156	VPLVREITF	2	B*08
	METTL7A methyltransferase like 7A	**7 (23.3)**	
157	DPNPNFEKF	1	B*35
158	IQAPLSWEL	1	B*13
159	VIYNEQMASK	3	A*03
160	VLRPGGAFY	2	B*15
	ELP3 elongator acetyltransferase complex subunit 3	**7 (23.3)**	
161	EDPDQDILI	1	B*18
162	HGNLRELAL	3	B*08
163	KLYPTLVIR	4	A*03
164	SEETFRFEL	1	B*40
	NLRP2 NLR family, pyrin domain containing 2	**6 (20.0)**	
165	ELNKLLEEI	3	A*02
166	IPFSNPRVL	2	B*07
167	LLDEGAKLLY	2	A*01
168	SPADAHRNL	1	B*07
	ZC3H12D zinc finger CCCH-type containing 12D	**6 (20.0)**	
169	AELERQAVL	1	B*37
170	GRVPGPLSL	1	B*27
171	SDLARLILL	1	B*27
172	TPIREQHVL	3	B*35
	NELFE negative elongation factor complex member E	**6 (20.0)**	
173	APRKGNTL	1	B*07
174	EEEEALQKKF	1	B*44
175	KENLVDGF	2	B*37
176	VYKENLVDGF	2	A*23, A*24
	ATP6V1C1 ATPase, H+ transporting,	**6 (20.0)**	

SEQ ID NO:	Underlying source protein/ HLA ligands	Number of positive CLLs (frequency [%])	HLA
	lysosomal 42kDa, V1 subunit C1		
177	TLLVVVPKL	6	A*02
	HLA-DMA major histocompatibility complex, class II, DM alpha	**6 (20.0)**	
178	HEIDRYTAI	1	B*40
179	VFTLKPLEF	3	A*23, A*24
180	YWVPRNAL	2	B*08
	TUFM Tu translation elongation factor, mitochondrial	**6 (20.0)**	
181	IGVEHVVVY	5	C*12
182	RDKPHVNV	1	B*37
	EIF6 eukaryotic translation initiation factor 6	**6 (20.0)**	
183	ADVLKVEVF	2	B*37
184	IPVVHASI	1	B*51
185	RDSLIDSLT	1	B*40
186	TVADQVLVGSY	2	A*26
	CKAP4 cytoskeleton-associated protein 4	**6 (20.0)**	
187	AADTERLAL	1	A*02
188	DMKAKVASL	2	B*08
189	HVLEEVQQV	2	B*13
190	KEAADTERL	1	B*40
191	RISEVLQKL	1	A*02
192	TEVRELVSL	2	B*40
	COBLL1 cordon-bleu WH2 repeat protein-like 1	**6 (20.0)**	
193	AIRSGEAAAK	2	A*03
194	APNPAPKEL	4	B*07
195	RQSLLTAI	1	B*13
196	SPEQTLSPL	1	B*35
197	TEHQVPSSV	1	B*40
198	TTYKIVPPK	1	A*03
	TMED4 transmembrane emp24 protein transport domain containing 4	**6 (20.0)**	
199	QLLDQVEQI	4	A*02
200	DETMVIGNY	1	B*18
201	RQYGSEGRFTF	1	B*37
	TNFRSF13C tumor necrosis factor receptor superfamily, member 13C	**6 (20.0)**	
202	SPAPRTAL	6	B*07
	UBL7 ubiquitin-like 7	**6 (20.0)**	
203	GPRPITQSEL	6	B*07
204	KPEPVDKVA	1	B*07
205	TPSSRPASL	4	B*07
	CXorf21 chromosome X open reading frame 21	**6 (20.0)**	
206	DETQVRSLY	2	B*18

SEQ ID NO:	Underlying source protein/ HLA ligands	Number of positive CLLs (frequency [%])	HLA
207	KEEETNSVATL	1	B*40
208	LEQKVVELY	2	B*18
209	NPISNAVLNEY	1	B*35
210	SIKEKSSL	1	B*08
211	TEITEISTPSL	1	B*40
	ASUN asunder spermatogenesis regulator	**6 (20.0)**	
212	GRLNSVNNR	1	B*27
213	SILEDPPSI	3	A*02
214	TPRTNNIEL	2	B*07
	RSL24D1 ribosomal L24 domain containing 1	**6 (20.0)**	
215	DAMKRVEEI	3	B*08
216	DIKEVKQNI	3	B*08
217	GPIYPGHGM	1	B*07
	Q9UII5, ZNF107 zinc finger protein 107	**6 (20.0)**	
218	GDYGRAFNL	2	B*37
219	TRHKIVHTK	2	B*27
220	RIHTGEKPYK	1	A*03
221	KAFNWFSTL	1	A*32
	TRAF3IP3 TRAF3 interacting protein 3	**6 (20.0)**	
222	QSTQRSLAL	2	B*08
223	RDLQMNQALRF	1	B*40
224	RELESQLHVL	2	B*40
225	SEAEKLTLV	1	B*40

Table 1b: Additional peptides according to the invention for CLL - MHC class I

SEQ ID NO:	Amino acid sequence	HLA
226	AAAKPVATK	A*03, A*11
227	ATYHGSFSTK	A*03, A*11
228	FMYDRPLRL	A*02
229	FRVGNVQEL	
230	GVAPFTIAR	A*03, A*11, A*68
231	KMKPLDGSALY	A*30
232	KPAPAKPVA	B*55
233	KPVAAKPAA	n.a.
234	KQFGVAPFTI	B*13
235	QEELVKISL	B*40:01
236	RQLGTVQQVI	B*13
237	RQLINALQI	B*13, A*32

238	RVIGGLLAGQTY	B*15:01
239	SENAFYLSP	n.a.
240	SQAPVLDAI	B*13
241	STRYPPPAV	A*30
242	TEDTLKVYL	B*40:01, B*52
243	VAAKPVATK	A*03
244	VQRVVESL	B*08
245	VRNPSVVVK	B*27
246	GESEVAIKI	B*49, B*52
247	LIYSVGLLLA	A*02
248	SAYPHQLSF	A*32
249	SVIGVFITK	A*03, A*11, A*68
250	AELGNSVQLI	B*49
251	ANMTVTRI	n.a
252	ARISNVEFY	C*07
253	AVFIGNQQF	B*15:01
254	DIELQAENI	A*02
255	DSYTVRVSV	B*51
256	DVKIFVNTI	B*51
257	EIIPKYGSI	A*25
258	EQSKIFIHR	n.a
259	FVDVGLYQY	A*03
260	GHTSTISTL	B*39
261	GRIEYVEVF	C*07
262	GTSIIPFQK	A*11
263	HPFLRGIGY	B*35
264	IPVEIHTA	B*55
265	KIFVNTIAY	B*15:01
266	LPEDKVRIAY	B*35
267	LPFSEGLTV	B*51
268	LPWANKVTI	B*51
269	PWANKVTI	n.a.
270	QAYNRAVTI	B*51
271	RSFPQKMAY	B*15:01
272	RYPIHWHLL	C*07
273	SPQNLRLML	B*07
274	SYFSSPTQR	B*27
275	VQIKSSLI	B*13
276	VYIGHTSTI	C*07
277	YHVPGTGESY	C*07
278	ATNGDLASR	A*31
279	GLHAEVTGVGY	B*15:01
280	HVSSTSSSF	A*32
281	LQADLQNGL	B*13
282	SELPVSEVA	B*45

283	SQTKSVFEI	B*13
284	THIFTSDGL	B*39
285	VIYFPPLQK	A*11
286	YPFSSEQKW	B*35
287	GQYFGELAL	B*13
288	RIIVKNNAK	n.a.
289	RRIIVKNNAK	B*27
290	SFGELALMY	n.a.
291	AFNAPVINR	B*27
292	IMKRNIATY	B*15:01
293	KVVDVIGTK	A*11
294	LPFLKSLEF	B*07, B*35
295	RLKVVDVIGTK	A*03
296	TPRAATITA	B*07, B*51, B*55
297	KPSEKIQVL	B*07
298	VPYPVTTTV	B*35
299	ASFPPFVEK	B*15
300	AFIHISTAY	A*29
301	ATFEKIPFER	A*11
302	KLFEKVKEV	A*02
303	SQMPKLEAF	B*15:01
304	AVLGQHHNY	A*03
305	GPPAHKPR	n.a.
306	RVYDVLVLK	A*03, A*11
307	LPRPQGITV	B*07
308	VLYVGSKTK	A*03
309	KTKEQVTNV	A*11
310	MPVDPDNEAY	B*35
311	AEKTKQGVA	B*40
312	DIADFFTTR	A*68
313	HSYLQRQSV	C*12
314	KEVTLIEEL	B*40:01
315	REDGPGVAL	B*40:01
316	REDPLPPGL	B*40:01
317	SLFGGSQGLRK	A*03
318	AEFQRLKQA	B*50
319	EVIDGVPGKW	A*25
320	IPKAPGKII	B*07, B*08, B*55
321	SHNGSAIRY	A*32
322	TEVTVVGDKL	B*40:01
323	YASVVVKRY	A*28
324	ATDLALYIK	A*11
325	AYHNWRHAF	C*07

326	EPLNIKDAY	B*35
327	KIAATIISF	B*15:01
328	KIFLHIHGL	B*71
329	LEVILKKI	n.a.
330	SEHPLAQLY	B*44
331	VPSAQTLKI	B*51
332	AEYRSYVA	B*45
333	ALAPGRGTLY	A*24
334	GPRGTQAAL	B*07
335	IEDPGTLHI	B*49
336	IEDPGTLHIW	B*44
337	RPIPIAVKY	B*35
338	VEKLLTNW	n.a.
339	FLDPDIGGVAV	A*02
340	HTAPPENKTW	A*30
341	LLDTPVKTQY	A*01
342	NAVKDFTSF	A*03, A*11
343	SGLLQIKKL	n.a.
344	YHDKNIVLL	B*39
345	SVDPKNYPK	A*11, A*03
346	AVGLVLPAK	A*11
347	AVGLVLPAKL	n.a.
348	ALLEVLSQK	A*03
349	HEKQDTLVA	B*45
350	KELELQIGM	B*40:01, B*52
351	MYSDVWKQL	A*24
352	RELQDEKAEL	B*40:01
353	RITDVLDQK	A*11
354	EVIKITGLK	A*68
355	HHVDITKKL	B*39
356	LPFNVKVSV	B*51
357	TLPRVLEI	B*51
358	TVDLPKSPK	A*11
359	AEHGLLLTA	B*45
360	AQAGALLQV	B*13
361	DGGFVLKV	B*51
362	IVYPSGKVY	B*15:01
363	KLDNQVSKV	A*02
364	SENVKLFSA	B*45
365	VQKLQNII	
366	FSTPHGLEV	B*51
367	KRFHQKSDM	B*27
368	KTFGHAVSL	A*32
369	SSNLITHSR	A*31
370	GVIDGHIYAV	A*02
371	IEPAKETTTNV	B*40:01,

		B*44
372	NAPPSEVLL	n.a.
373	SIEPAKETTTNV	A*02
374	AQSQHNQSL	B*13
375	AQSRTNPQV	B*13
376	KMHDKVFAY	A*03
377	TAKAPLSTV	B*51
378	IPTRTVAI	B*51
379	NHDRKHAV	B*39
380	NNHDRKHAV	B*08
381	TPGGTRIIY	B*35
382	EHWPSPETF	A*68
383	EIITNTLSF	A*25
384	EVRGALMSAF	A*25
385	IPRPILVLL	B*07
386	LPNKNRDEL	B*07
387	QRIPAGAVL	B*27
388	AEGPAGGFMVV	B*49
389	AYYRDAEAY	C*07
390	QVNRPLTMR	A*03
391	RHSPVFQVY	A*32
392	SLPVPNSAY	B*15:01
393	TLGPPGTAHLY	B*15:01
394	IEPAKETTTNV	B*40:01, B*44
395	NAPPSEVLL	n.a.
396	SIEPAKETTTNV	A*02
397	DLYSGLNQR	A*68
398	KAKAKPVTR	A*31
399	AVLDKAMKAK	A*03
400	LELSTPLKI	B*49
401	LPLNLDTKY	B*35
402	TVIYRIQAL	A*02
403	DAHIYLNHI	B*51
404	NHIEPLKIQL	B*39
405	AYRPAVHPR	B*27
406	LRAPLEHEL	n.a.
407	RLFMVLLLK	A*03
408	RSPDVLKDF	B*15:01
409	ETAPGVHKR	A*68
410	LYHGYIYTY	A*24
411	GQHVATQHF	B*15:01
412	LNGQLPNL	n.a.
413	LPFPDETHERY	B*35
414	LPHNTHRVV	B*51
415	VVFDSPRNR	A*03
416	YPLGRILI	B*51
417	KEFAEFVTS	B*50
418	VMLDVPIRL	A*02

419	VPMTPLRTV	B*51
420	QIDYKTLVL	B*13
421	VEDPTIVRI	B*40:01, B*44, B*52
422	IPYQDLPHL	B*07
423	DTPFLTGHGR	A*68
424	EFYRALYI	
425	RYYPQILTNK	
426	KAYERHVL	B*08
427	LPSPEFHDY	B*35
428	SLYAHPIEH	A*03
429	LVREPGSQA	B*08
430	RLAGPGSEKY	B*15:01
431	SPGAGRNSVL	B*07
432	SVQSDQGYISR	A*11
433	GVRPPAPSL	B*13
434	IFSEKPVFV	n.a.
435	KASNLLLGF	B*58
436	KRYIFADAY	n.a.
437	RNLQLSLPR	A*31
438	EASEPVALR	A*68
439	RPKVPDQSV	B*07, B*08, B*35
440	VLYENALKL	A*02
441	EVLDKSQTNY	A*25
442	MPSPIPAKY	B*35
443	YGIENFTSV	B*51
444	ARAAQVFFL	B*27
445	EHIVPNAEL	B*39
446	EAFEFVKQR	A*68
447	NHFEGHYQY	n.a.
448	DAYPKNPHL	B*51
449	DVNIKSTER	A*68
450	HINSIKSVF	A*31
451	YESEKVGVA	B*50
452	ENAPTTVSR	A*68
453	RFPHLLAHTY	C*14
454	TLDGSLHAV	A*02
455	RTVLKNLSLLK	A*03
456	FEAKVQAI	B*49
457	FFEAKVQAI	C*12
458	KELQSTFK	n.a.
459	NVSSRFEEEI	A*02
460	EVWNNLGTTK	A*68
461	MIFRSGSLI	n.a.
462	NHALPLPGF	B*39
463	ASVFGTMPLK	A*11

464	REFPDRLVGY	B*44
465	SVFGTMPLK	A*11
466	DEMRFVTQI	n.a.
467	ETVHFATTQW	A*25
468	LPPPATQI	B*51
469	LARDLYAF	C*03, C*12
470	LPGIGLSTSL	B*53
471	MEVILPML	n.a.
472	AILDYILAK	A*03
473	KIASQLSKL	A*02
474	KVTSTTTVK	A*03, A*11
475	YNTLLPYTF	n.a.
476	FLDPRPLTV	A*02
477	SAFADRPAF	C*03
478	AAVPVIISR	A*68
479	EEIGKVAAA	B*45
480	FLKDLVASV	A*02
481	VIISRALEL	C*03
482	APRTTGTPRTSL	B*07
483	ESVGGSPQTK	A*68
484	IPKDKAIL	B*08
485	LPAYGRTTL	B*07
486	HQAAIVSKI	B*13
487	QAAIVSKI	B*51
488	RQKMPEDGL	B*13
489	SVQKSSGVK	A*11
490	DSIGSTVSSER	A*68
491	LPYNNKDRDAL	B*07
492	IYDEIQQEM	C*14
493	AQAKGLIQV	B*13
494	EVSSEIYQW	A*25
495	KWNPVPLSY	A*29
496	NRLLAQQSL	B*27
497	APRPVAVAV	B*07
498	FYRETVQVGR	A*33
499	LLAPRPVAV	A*02
500	GLAALVILK	A*03
501	KIQEVFSSY	B*15:01
502	ASLDKFLSH	A*11
503	ALYATKTLR	A*03
504	MEYVISRI	n.a.
505	VPVGRQPII	B*51
506	KLLIGVIAAV	A*02
507	LPSLIKLD	n.a. (B*51!!)
508	PSLIKLDL	n.a.
509	ARNKELIGK	B*27

510	AVKSNAAAY	B*15:01
511	EVIIPHSGW	A*25
512	SVKEQEAQF	B*15:01
513	APRGLEPIAI	B*07
514	GRFGGVITI	B*27
515	PVAGFFINR	A*68
516	TPKTPSRDA	B*08, B*55
517	VLFGGKVSGA	A*02
518	AEHIESRTL	B*40, B*44
519	DQYPYLKSV	C*12
520	IARNLTQQL	B*07
521	IESRTLAIA	B*50
522	MTSALPIIQK	A*11
523	SLLTSSKGQLQK	A*03
524	TSALPIIQK	A*11, A*03
525	VRLGSLSTK	B*27
526	RINEFSISSF	B*15
527	DEKQQHIVY	B*18
528	DEVYQVTVY	B*18
529	GEISEKAKL	B*40
530	YTMKEVLFY	A*03
531	SQLTTLSFY	B*15
532	LEKQLIEL	B*44
533	ELTLGEFLK	A*68, A*33
534	LTLGEFLK	A*68
535	LTLGEFLKL	A*02
536	TLGEFLKL	A*02
537	ITARPVLW	B*58
538	KLMSPKLYVW	A*32
539	KVSAVTLAY	A*03
540	VEGSGELFRW	B*44
541	RPKSNIVL	B*07
542	RPKSNIVLL	B*07

Table 1c: Additional peptides according to the invention for CLL - MHC class II

SEQ ID NO:	**Amino acid sequence**	**MHC**
543	GEPLSYTRFSLARQ	class II
544	GEPLSYTRFSLARQVD	class II
545	GEPLSYTRFSLARQVDG	class II
546	GGEPLSYTRFSLARQVD	class II
547	GGEPLSYTRFSLARQVDG	class II
548	NPGGYVAYSKAATVTG	class II
549	NPGGYVAYSKAATVTGK	class II

550	NPGGYVAYSKAATVTGKL	class II
551	NSVIIVDKNGRL	class II
552	NSVIIVDKNGRLV	class II
553	NSVIIVDKNGRLVY	class II
554	RVEYHFLSPYVSPK	class II
555	RVEYHFLSPYVSPKE	class II
556	RVEYHFLSPYVSPKESPF	class II
557	SPFRHVFWGSGSHTL	class II
558	SVIIVDKNGRLV	class II
559	VEYHFLSPYVSPK	class II
560	VEYHFLSPYVSPKE	class II
561	LPSQAFEYILYNKG	class II
562	LPSQAFEYILYNKGI	class II
563	LPSQAFEYILYNKGIM	class II
564	LPSQAFEYILYNKGIMG	class II
565	MNGYFLIERGKNM	class II
566	NGYFLIERGKNM	class II
567	PSQAFEYILYNKG	class II
568	PSQAFEYILYNKGI	class II
569	PSQAFEYILYNKGIM	class II
570	EGVQYSYSLFHLM	class II
571	EGVQYSYSLFHLML	class II
572	GVQYSYSLFHLM	class II
573	GVQYSYSLFHLML	class II
574	SIISIHPKIQEHQPR	class II
575	SSIRTSTNSQVDK	class II
576	VLVGYKAVYRIS	class II
577	YSSIRTSTNSQVDK	class II
578	GGGYGSGGGSGGYGSRRF	class II
579	GGSFGGRSSGSP	class II
580	KGGSFGGRSSGSP	class II
581	SGQQQSNYGPMKGGSFGGRSSGSPY	class II
582	SGSPYGGGYGSGGGSGGYGSRRF	class II
583	SPYGGGYGSGGGSGGYGSRRF	class II
584	YGGGYGSGGGSGGYGSRRF	class II
585	GNRINEFSISSF	class II
586	HGNQITSDKVGRKV	class II
587	IPPVNTNLENLYLQ	class II
588	LQVLRLDGNEIKR	class II
589	LQVLRLDGNEIKRS	class II
590	LQVLRLDGNEIKRSA	class II
591	LRELHLDHNQISRVPN	class II
592	LYVRLSHNSLTNNG	class II
593	VPSRMKYVYFQNNQ	class II
594	VPSRMKYVYFQNNQIT	class II
595	VPSRMKYVYFQNNQITS	class II
596	WIALHGNQITSD	class II
597	WIALHGNQITSDK	class II
598	ADDNVSFRWEALGNT	class II

599	ADDNVSFRWEALGNTL	class II
600	DADDNVSFRWEALGNTL	class II
601	DDNVSFRWEALGNT	class II
602	DDNVSFRWEALGNTL	class II
603	DNVSFRWEALGNT	class II
604	DNVSFRWEALGNTL	class II
605	DNVSFRWEALGNTLS	class II
606	DTGSYRAQISTKTSAK	class II
607	DTGSYRAQISTKTSAKL	class II
608	DTITIYSTINHSK	class II
609	EDTGSYRAQISTKTSAK	class II
610	ENDTITIYSTINHSK	class II
611	ENDTITIYSTINHSKESKPT	class II
612	GSYRAQISTKTSAK	class II
613	NDTITIYSTINH	class II
614	NDTITIYSTINHS	class II
615	NDTITIYSTINHSK	class II
616	NVSFRWEALGNTL	class II
617	SPTNNTVYASVTHSNRET	class II
618	TGSYRAQISTKTSAK	class II
619	TPRENDTITIYSTINHSK	class II
620	TPRENDTITIYSTINHSKESKPT	class II
621	VSFRWEALGNTL	class II
622	APIHFTIEKLELNEK	class II
623	DAQFEVIKGQTIE	class II
624	DAQFEVIKGQTIEVR	class II
625	ESYFIPEVRIYDSGT	class II
626	IPEVRIYDSGTY	class II
627	KDKAIVAHNRHGNK	class II
628	KDKAIVAHNRHGNKA	class II
629	NFVILEFPVEEQDR	class II
630	SQPRISYDAQFEVIK	class II
631	SQPRISYDAQFEVIKG	class II
632	YDAQFEVIKGQTIE	class II
633	GNPAYRSFSNSLSQ	class II
634	GPPGEAGYKAFSSLLA	class II
635	GPPGEAGYKAFSSLLASS	class II
636	GPPGEAGYKAFSSLLASSA	class II
637	GPPGEAGYKAFSSLLASSAVSPE	class II
638	GPPGEAGYKAFSSLLASSAVSPEK	class II
639	GYKAFSSLLASSAVSP	class II
640	GYKAFSSLLASSAVSPE	class II
641	KAFSSLLASSAVSPE	class II
642	NPAYRSFSNSLSQ	class II
643	SRDDFQEGREGIVAR	class II
644	SSSSFHPAPGNAQ	class II
645	VARLTESLFLDL	class II
646	VARLTESLFLDLLG	class II
647	VIAGNPAYRSFSN	class II

648	VPQPEPETWEQILRRNVLQ	class II
649	YKAFSSLLASSAVS	class II
650	YKAFSSLLASSAVSP	class II
651	YKAFSSLLASSAVSPE	class II
652	GNQVFSYTANKEIRTDD	class II
653	IEEIVLVDDASERD	class II
654	IEEIVLVDDASERDF	class II
655	LENIYPDSQIPRH	class II
656	LENIYPDSQIPRHY	class II
657	NQVFSYTANKEIR	class II
658	NQVFSYTANKEIRT	class II
659	NQVFSYTANKEIRTDD	class II
660	VHSVINRSPRHMIEE	class II
661	EYVSLYHQPAAM	class II
662	IKAEYKGRVTLKQYPR	class II
663	LNVHSEYEPSWEEQP	class II
664	LPYLFQMPAYASSS	class II
665	LPYLFQMPAYASSSK	class II
666	NFIKAEYKGRVT	class II
667	TNFIKAEYKGRVT	class II
668	TTNFIKAEYKGRVT	class II
669	VTLNVHSEYEPSWEEQP	class II
670	YPRKNLFLVEVTQLTESDS	class II
671	YPRKNLFLVEVTQLTESDSG	class II
672	ADLSSFKSQELN	class II
673	ADLSSFKSQELNER	class II
674	ADLSSFKSQELNERN	class II
675	ADLSSFKSQELNERNE	class II
676	ADLSSFKSQELNERNEA	class II
677	AEQQRLKSQDLELSWNLNG	class II
678	EQQRLKSQDLELSWN	class II
679	ISQELEELRAEQQR	class II
680	ISQELEELRAEQQRLK	class II
681	KGTKQWVHARYA	class II
682	QADLSSFKSQELNER	class II
683	SWNLNGLQADLSSFK	class II
684	TGSWIGLRNLDLKG	class II
685	FGNYNNQSSNFGPMKGGNFGGRS	class II
686	FGPMKGGNFGGRSSGPYGGGGQY	class II
687	GPMKGGNFGGRSSGP	class II
688	GPYGGGGQYFAKP	class II
689	KGGNFGGRSSGP	class II
690	NDFGNYNNQSSNFGP	class II
691	SGPYGGGGQYFAKP	class II
692	DAGSYKAQINQRNFE	class II
693	DAGSYKAQINQRNFEVT	class II
694	DGELIRTQPQRLPQ	class II
695	GELIRTQPQRLPQ	class II
696	NPSDGELIRTQPQRLP	class II

697	NPSDGELIRTQPQRLPQ	class II
698	NPSDGELIRTQPQRLPQL	class II
699	ASNDMYHSRALQVVR	class II
700	ASNDMYHSRALQVVRA	class II
701	EGVRRALDFAVGEYN	class II
702	EGVRRALDFAVGEYNK	class II
703	SNDMYHSRALQVVR	class II
704	VGEYNKASNDMYH	class II
705	VRARKQIVAGVNY	class II
706	VRRALDFAVGEYNKASND	class II
707	VVRARKQIVAGVN	class II
708	VVRARKQIVAGVNY	class II
709	APLEGARFALVRED	class II
710	APVELILSDETLPAPE	class II
711	ELILSDETLPAPE	class II
712	LAPLEGARFALVRE	class II
713	LAPLEGARFALVRED	class II
714	RGEKELLVPRSSTSPD	class II
715	ASKTFTTQETITNAET	class II
716	DQHFRTTPLEKNAPV	class II
717	NTPILVDGKDVMPE	class II
718	NTPILVDGKDVMPEV	class II
719	NTPILVDGKDVMPEVN	class II
720	SNTPILVDGKDVMPE	class II
721	SNTPILVDGKDVMPEVN	class II
722	TPILVDGKDVMP	class II
723	TPILVDGKDVMPE	class II
724	TPILVDGKDVMPEV	class II
725	TPILVDGKDVMPEVN	class II
726	GPLKFLHQDIDSGQG	class II
727	GPLKFLHQDIDSGQGIR	class II
728	LGDIYFKLFRASG	class II
729	TGHLFDLSSLSGRAG	class II
730	VPSPVDCQVTDLAGNE	class II
731	DGLNSLTYQVLDVQRYPL	class II
732	HPVLQRQQLDYGIY	class II
733	LNSLTYQVLDVQR	class II
734	LNSLTYQVLDVQRYP	class II
735	LNSLTYQVLDVQRYPL	class II
736	LPQLVGVSTPLQG	class II
737	LPQLVGVSTPLQGG	class II
738	LPQLVGVSTPLQGGS	class II
739	RLPQLVGVSTPLQGGS	class II
740	SPHKVAIIIPFRNR	class II
741	SPHKVAIIIPFRNRQE	class II
742	SPHKVAIIIPFRNRQEH	class II
743	AIVQAVSAHRHR	class II
744	ARNFERNKAIKVI	class II
745	ARNFERNKAIKVIIA	class II

746	NFERNKAIKVII	class II
747	NFERNKAIKVIIA	class II
748	VAIVQAVSAHRH	class II
749	VAIVQAVSAHRHR	class II
750	VAIVQAVSAHRHRA	class II
751	VAIVQAVSAHRHRAR	class II
752	EEVITLIRSNQQLE	class II
753	EEVITLIRSNQQLEN	class II
754	IPADTFAALKNPNAML	class II
755	LKQLLSDKQQKRQSG	class II
756	LKQLLSDKQQKRQSGQ	class II
757	TPSYVAFTDTER	class II
758	TPSYVAFTDTERL	class II
759	EGLYSRTLAGSIT	class II
760	EGLYSRTLAGSITTPP	class II
761	EKWYIPDPTGKFN	class II
762	GAIAAINSIQHNTR	class II
763	LPILVPSAKKAI	class II
764	LPILVPSAKKAIY	class II
765	LPILVPSAKKAIYM	class II
766	LPILVPSAKKAIYMD	class II
767	LPILVPSAKKAIYMDD	class II
768	VEEGLYSRTLAGSIT	class II
769	WEKWYIPDPTGKFN	class II
770	YKIVNFDPKLLE	class II
771	YKIVNFDPKLLEG	class II
772	YKIVNFDPKLLEGKV	class II
773	LPEFYKTVSPAL	class II
774	VGQFIQDVKNSRST	class II
775	VGQFIQDVKNSRSTD	class II
776	VVGQFIQDVKNSRS	class II
777	VVGQFIQDVKNSRST	class II
778	VVGQFIQDVKNSRSTD	class II
779	VVGQFIQDVKNSRSTDS	class II
780	DNGHLYREDQTSPAPG	class II
781	DNGHLYREDQTSPAPGLR	class II
782	EVQVFAPANALPARSE	class II
783	GHLYREDQTSPAPG	class II
784	LPARSEAAAVQPVIG	class II
785	NGHLYREDQTSPAPG	class II
786	NGHLYREDQTSPAPGL	class II
787	NGHLYREDQTSPAPGLR	class II
788	VFAPANALPARSEAA	class II
789	VQVFAPANALPARSE	class II
790	AIVVSDRDGVPVIK	class II
791	GLHAIVVSDRDGVPV	class II
792	GLHAIVVSDRDGVPVIK	class II
793	HAIVVSDRDGVPV	class II
794	KLPSVEGLHAIVVSDRDG	class II

795	LHAIVVSDRDGVPV	class II
796	LHAIVVSDRDGVPVI	class II
797	LHAIVVSDRDGVPVIK	class II
798	LPSVEGLHAIVVSDR	class II
799	VPVIKVANDNAPE	class II
800	YNTYQVVQFNRLP	class II
801	YNTYQVVQFNRLPL	class II
802	YNTYQVVQFNRLPLV	class II
803	YNTYQVVQFNRLPLVV	class II
804	YYNTYQVVQFNRLP	class II
805	YYNTYQVVQFNRLPL	class II
806	YYNTYQVVQFNRLPLV	class II
807	DKIYFMAGSSRKE	class II
808	DVGTDEEEETAKESTAEKDE	class II
809	EVTFKSILFVPTSAP	class II
810	KSEKFAFQAEVNR	class II
811	LPEFDGKRFQNVAK	class II
812	DGSYRIFSKGASE	class II
813	GSYRIFSKGASE	class II
814	SDGSYRIFSKGASE	class II
815	SVKKMMKDNNLVRH	class II
816	VKKMMKDNNLVRH	class II
817	NNMRIFGEAAEKN	class II
818	VDKVLERDQKLSE	class II
819	VDKVLERDQKLSELD	class II
820	VDKVLERDQKLSELDD	class II
821	VDKVLERDQKLSELDDR	class II
822	VLERDQKLSELDDR	class II
823	ATRSIQVDGKTIKAQ	class II
824	ATRSIQVDGKTIKAQI	class II
825	IGVEFATRSIQVDGK	class II
826	RSIQVDGKTIKA	class II
827	RSIQVDGKTIKAQ	class II
828	RSIQVDGKTIKAQI	class II
829	TRSIQVDGKTIKAQ	class II
830	DIMRVNVDKVLERDQK	class II
831	DIMRVNVDKVLERDQKL	class II
832	IMRVNVDKVLERDQK	class II
833	VDKVLERDQKLSE	class II
834	VDKVLERDQKLSELD	class II
835	VDKVLERDQKLSELDD	class II
836	VDKVLERDQKLSELDDR	class II
837	VLERDQKLSELDDR	class II
838	ATRSIQVDGKTIKAQ	class II
839	ATRSIQVDGKTIKAQI	class II
840	IGVEFATRSIQVDGK	class II
841	RSIQVDGKTIKA	class II
842	RSIQVDGKTIKAQ	class II
843	RSIQVDGKTIKAQI	class II

844	TRSIQVDGKTIKAQ	class II
845	GIRVAPVPLYNS	class II
846	GIRVAPVPLYNSFH	class II
847	NPNGIRVAPVPLYNSFH	class II
848	DDPAIDVCKKLLGKYPN	class II
849	DKQPYSKLPGVSLLKP	class II
850	DKQPYSKLPGVSLLKPL	class II
851	HPRYYISANVTGFK	class II
852	SHPRYYISANVTG	class II
853	SHPRYYISANVTGFK	class II
854	TSHPRYYISANVTG	class II
855	TSHPRYYISANVTGFK	class II
856	ADIFVDPVLHTA	class II
857	ADIFVDPVLHTACA	class II
858	DPGADYRIDRALNEA	class II
859	IAQDYKVSYSLA	class II
860	IAQDYKVSYSLAK	class II
861	ISRDWKLDPVLYRK	class II
862	LIAQDYKVSYSLA	class II
863	RQKLIAQDYKVSYS	class II
864	RQKLIAQDYKVSYSL	class II
865	RQKLIAQDYKVSYSLA	class II
866	RQKLIAQDYKVSYSLAK	class II
867	SALDYRLDPQLQLH	class II
868	SKADIFVDPVLHTA	class II
869	SPSKNYILSVISGSI	class II
870	ETTQLTADSHPSYHTDG	class II
871	SGESLYHVLGLDKNATSDD	class II
872	TTQLTADSHPSYHT	class II
873	TTQLTADSHPSYHTD	class II
874	TTQLTADSHPSYHTDG	class II
875	SVEEFLSEKLERI	class II
876	VEEFLSEKLERI	class II
877	DLSSSILAQSRERVA	class II
878	EKGVRTLTAAAVSGAQ	class II
879	EKGVRTLTAAAVSGAQP	class II
880	EKGVRTLTAAAVSGAQPI	class II
881	KGVRTLTAAAVSGA	class II
882	KGVRTLTAAAVSGAQ	class II
883	VGPFAPGITEKAPEEKK	class II
884	DPPLIALDKDAPLR	class II
885	EIITPDVPFTVDKDG	class II
886	IITPDVPFTVDKDG	class II
887	PPLIALDKDAPLR	class II
888	TNVKKSHKATVHIQ	class II
889	DDNIKTYSDHPE	class II
890	DDNIKTYSDHPEK	class II
891	DSAVFFEQGTTRIG	class II
892	GDKVYVHLKNLASRPY	class II

893	GDKVYVHLKNLASRPYT	class II
894	VHLKNLASRPYT	class II
895	VYVHLKNLASRPY	class II
896	VYVHLKNLASRPYT	class II
897	VYVHLKNLASRPYTFH	class II
898	YVHLKNLASRPY	class II
899	YVHLKNLASRPYT	class II
900	YVHLKNLASRPYTFH	class II
901	SNLIKLAQKVPTAD	class II
902	YDTRTSALSAKS	class II
903	ALMTDPKLITWSPV	class II
904	NDVAWNFEKFLVGPDG	class II
905	QSVYAFSARPLAG	class II
906	QSVYAFSARPLAGGEPV	class II
907	WNFEKFLVGPDG	class II
908	DVGMFVALTKLGQPD	class II
909	VGMFVALTKLGQPD	class II
910	AGVFHVEKNGRY	class II
911	FAGVFHVEKNGRYS	class II
912	GPITITIVNRDGTR	class II
913	NGRYSISRTEAADL	class II
914	RKSRQGSLAMEELK	class II
915	RRKSRQGSLAMEELK	class II
916	EEFKKLTSIKIQNDK	class II
917	INRRMADDNKLFR	class II
918	TATIVMVTNLKERKE	class II
919	ELFYKGIRPAINVG	class II
920	GQKRSTVAQLVKR	class II
921	SDLDAATQQLLSRGV	class II
922	FDFSQNTRVPRLPE	class II
923	GDAPAILFDKEF	class II
924	VTHEIDRYTAIAY	class II
925	GQGYLIKDGKLIKNNA	class II
926	IDTTSKFGHGRFQTM	class II
927	IDVIGVTKGKGYKGVTSRW	class II
928	MGPLKKDRIAKEEGA	class II
929	AAKYQLDPTASISA	class II
930	IAAKYQLDPTASISA	class II
931	IAAKYQLDPTASISAK	class II
932	AGLGRAYALAFAERG	class II
933	DAFGRIDVVVNNAG	class II
934	GLGRAYALAFAER	class II
935	GLGRAYALAFAERG	class II
936	AKFALNGEEFMNFDL	class II
937	AKFALNGEEFMNFDLK	class II
938	ALNGEEFMNFDLK	class II
939	KFALNGEEFMNFDL	class II
940	SDGSFHASSSLTVK	class II
941	EERNLLSVAYKNVVGAR	class II

942	ERNLLSVAYKNVVGAR	class II
943	IAELDTLSEESYKD	class II
944	IAELDTLSEESYKDS	class II
945	ADSYLDEGFLLDKKIG	class II
946	DSYLDEGFLLDKK	class II
947	DSYLDEGFLLDKKIG	class II
948	VDNIIKAAPRKRVPD	class II
949	SPPQFRVNGAISN	class II
950	SPPQFRVNGAISNFE	class II
951	SPPQFRVNGAISNFEE	class II
952	SPPQFRVNGAISNFEEF	class II
953	VGKMFVDVYFQEDKK	class II
954	VGKMFVDVYFQEDKKE	class II
955	DPKRTIAQDYGVLKADE	class II
956	DPKRTIAQDYGVLKADEG	class II
957	PKRTIAQDYGVLKADEG	class II
958	GLFIIDDKGILRQ	class II
959	GLFIIDDKGILRQIT	class II
960	RGLFIIDDKGILR	class II
961	RGLFIIDDKGILRQ	class II
962	RGLFIIDDKGILRQIT	class II
963	GNTVIHLDQALARMR	class II
964	NTVIHLDQALARMR	class II
965	NTVIHLDQALARMRE	class II
966	ENNEIISNIRDSVIN	class II
967	NNEIISNIRDSVIN	class II
968	SPTVQVFSASGKPV	class II
969	SSPTVQVFSASGKPVE	class II
970	AEPNYHSLPSARTDEQ	class II
971	SSILAKTASNIIDVS	class II
972	LEARATAPPAPSAPN	class II
973	ADDLEGEAFLPL	class II
974	ADDLEGEAFLPLR	class II
975	ADDLEGEAFLPLRE	class II
976	GADDLEGEAFLPLR	class II
977	AGREINLVDAHLKSE	class II
978	AGREINLVDAHLKSEQT	class II
979	GREINLVDAHLKSE	class II
980	KPGIVYASLNHSVIG	class II
981	NKPGIVYASLNHSVIG	class II
982	TTLYVTDVKSASERPS	class II
983	APSTYAHLSPAKTPPP	class II
984	APSTYAHLSPAKTPPPP	class II
985	APSTYAHLSPAKTPPPPA	class II
986	RDDLYDQDDSRDFPR	class II
987	TRPYHSLPSEAVFA	class II
988	TRPYHSLPSEAVFAN	class II
989	VAVFTFHNHGRT	class II
990	VAVFTFHNHGRTA	class II

991	VAVFTFHNHGRTANL	class II
992	EDDYIKSWEDNQQGDE	class II
993	ELERIQIQEAAKKKPG	class II
994	ERIQIQEAAKKKP	class II
995	ERIQIQEAAKKKPG	class II
996	ERIQIQEAAKKKPGI	class II
997	LERIQIQEAAKKKPG	class II
998	LSSISQYSGKIK	class II
999	SPAKDSLSFEDF	class II
1000	SPAKDSLSFEDFLDL	class II
1001	INSRFPIPSATDPD	class II
1002	VQHYELLNGQSVFG	class II
1003	DNQYAVLENQKSSH	class II
1004	GPPEIYSDTQFPS	class II
1005	GPPEIYSDTQFPSLQ	class II
1006	TPQGPPEIYSDTQFPS	class II
1007	TPQGPPEIYSDTQFPSLQ	class II
1008	TPQGPPEIYSDTQFPSLQST	class II
1009	ANLQRAYSLAKEQR	class II
1010	NLQRAYSLAKEQR	class II
1011	TPSGITYDRKDIEEH	class II
1012	VSTLNSEDFVLVSR	class II
1013	VSTLNSEDFVLVSRQ	class II
1014	VSTLNSEDFVLVSRQG	class II
1015	GSSFFGELFNQNPE	class II
1016	SGSSFFGELFNQNPE	class II

Table 2: Peptides according to the invention suitable for the (combined) treatment of CLL and/or AML

SEQ ID NO:	**Amino acid sequence**
710	APVELILSDETLPAPE
878	EKGVRTLTAAAVSGAQ
879	EKGVRTLTAAAVSGAQP
533	ELTLGEFLK
476	FLDPRPLTV
892	GDKVYVHLKNLASRPY
111	GLDPNKPPEL
178	HEIDRYTAI
181	IGVEHVVVY
184	IPVVHASI
882	KGVRTLTAAAVSGAQ
363	KLDNQVSKV
42	KLYELHVFTF
163	KLYPTLVIR
137	KTIAFLLPMF
713	LAPLEGARFALVRED
532	LEKQLIEL

734	LNSLTYQVLDVQRYP
736	LPQLVGVSTPLQG
737	LPQLVGVSTPLQGG
738	LPQLVGVSTPLQGGS
534	LTLGEFLK
535	LTLGEFLKL
914	RKSRQGSLAMEELK
739	RLPQLVGVSTPLQGGS
477	SAFADRPAF
164	SEETFRFEL
364	SENVKLFSA
531	SQLTTLSFY
536	TLGEFLKL
186	TVADQVLVGSY
179	VFTLKPLEF
159	VIYNEQMASK
365	VQKLQNII
895	VYVHLKNLASRPY
44	YLNKEIEEA
180	YWVPRNAL

Thus, particularly preferred is at least one peptide according to the present invention selected from the group consisting of SEQ ID NO: 710, 878, 879, 533, 476, 892, 111, 178, 181, 184, 882, 363, 42, 163, 137, 713, 532, 734, 736, 737, 738, 534, 535, 914, 739, 477, 164, 364, 531, 536, 186, 179, 159, 365, 895, 44, and 180, and the use thereof in the treatment of AML and/or CML as described herein.

The present invention furthermore relates to the peptides according to the present invention for use in the treatment of CLLAML As shown in the following table 3, many of the peptides according to the present invention can also be used in other cancerous and proliferative indications.

Table 3: Peptides according to the present invention and their specific uses in other proliferative diseases, optionally in other organs.

Seq ID	Sequence	Tissue and disease
1	AEHPNVTLTI	colon or rectum, spleen, non-Hodgkin's lymphoma
2	FLAEHPNVTL	colon or rectum, spleen, non-Hodgkin's lymphoma
3	ILYGRSYTW	stomach, adenocarcinoma, skin, squamous cell carcinoma
4	EVAEFLARH	colon or rectum, spleen, non-Hodgkin's

		lymphoma
5	RHSNVNLTI	colon or rectum, spleen, non-Hodgkin's lymphoma
6	HPDNVKLFL	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
7	ISDTGELKL	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
8	KVNGKLVALK	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
9	NRLSAQAAL	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
10	TPFTAIREA	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
11	FGLARAKSV	kidney, clear cell renal cell carcinoma,
12	KIADFGLAR	brain, glioblastoma, liver, hepatocellular carcinoma
13	AAANIIRTL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma
14	GRFKNLREAL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma
15	MSPFSKATL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma
16	QEDPGDNQITL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma
17	SPFSKATL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma
18	DALLKRTM	stomach, metastatic, skin, basal cell carcinoma
19	GEDVRSALL	stomach, metastatic, skin, basal cell carcinoma
20	KFAEEFYSF	stomach, metastatic, skin, basal cell carcinoma
21	YGYDNVKEY	stomach, metastatic, skin, basal cell carcinoma
22	LEVEERTKPV	lung, non-small cell lung carcinoma, breast, carcinoma
23	RDSPINANLRY	lung, non-small cell lung carcinoma, breast, carcinoma
24	RPFVIVTA	lung, non-small cell lung carcinoma, breast, carcinoma
25	RPIINTPMV	lung, non-small cell lung carcinoma, breast, carcinoma
26	SPTSSRTSSL	lung, non-small cell lung carcinoma, breast, carcinoma
27	ATSAPLVSR	stomach, metastatic, lung, neuroendocrine carcinoma (non-small cell type)

28	AELRSTASLL	lipoma
29	APASSHERASM	lipoma
30	ASRQAPPHI	lipoma
31	AVKKNPGIAA	lipoma
32	EEHLESHKKY	lipoma
33	GEFTSARAV	lipoma
34	GQSTPRLFSI	lipoma
35	LVDDPLEY	lipoma
36	RPKNLMQTL	lipoma
37	RQAPPHIEL	lipoma
38	SEAAELRSTA	lipoma
39	AAVRIGSVL	colon, adenoma
40	ERAGVVREL	colon, adenoma
41	GAAVRIGSVL	colon, adenoma
42	KLYELHVFTF	colon, adenoma
43	LYELHVFTF	colon, adenoma
44	YLNKEIEEA	colon, adenoma
45	DELPKFHQY	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
46	DVTGQFPSSF	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
47	EHSRVLQQL	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
48	IKVSKQLL	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
49	KPRQSSPQL	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
50	KQLLAALEI	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
51	RRKDLVLKY	stomach, adenocarcinoma, liver, focal nodular hyperplasia
52	RTRDYASLPPK	stomach, adenocarcinoma, white blood cell s, chronic lymphocytic leukemia
53	APGSVLPRAL	stomach, adenocarcinoma, lymph node, Hodgkin's disease
54	DIKEHPLL	stomach, adenocarcinoma, lymph node, Hodgkin's disease
55	DSAGPQDAR	stomach, adenocarcinoma, lymph node, Hodgkin's disease
56	FQYAKESYI	stomach, adenocarcinoma, lymph node, Hodgkin's disease
57	KVLSWPFLM	stomach, adenocarcinoma, lymph node, Hodgkin's disease
58	LENDQSLSF	stomach, adenocarcinoma, lymph node, Hodgkin's disease
59	SPSRQPQV	stomach, adenocarcinoma, lymph node, Hodgkin's disease
60	SRHQSFTTK	stomach, adenocarcinoma, lymph node, Hodgkin's disease
61	SSHNASKTL	stomach, adenocarcinoma, lymph node,

		Hodgkin's disease
62	EEIDTTMRW	liver, hepatocellular carcinoma, lipoma
63	ILDEKPVII	liver, hepatocellular carcinoma, lipoma
64	LPQEPRTSL	liver, hepatocellular carcinoma, lipoma
65	LTYKLPVA	liver, hepatocellular carcinoma, lipoma
66	NEMELAHSSF	liver, hepatocellular carcinoma, lipoma
67	REFPEANFEL	liver, hepatocellular carcinoma, lipoma
68	THHIPDAKL	liver, hepatocellular carcinoma, lipoma
69	TVKENLSLF	liver, hepatocellular carcinoma, lipoma
70	VLLKKAVL	liver, hepatocellular carcinoma, lipoma
71	HLKSIPVSL	kidney, clear cell renal cell carcinoma
72	KVWYNVENW	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
73	LPAYRAQLL	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
74	LSEQTSVPL	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
75	SLNQWLVSF	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
76	SMTSLAQKI	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
77	SSSGLHPPK	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
78	DLDVKKMPL	stomach, metastatic, kidney, carcinoma
79	FYTVIPHNF	stomach, metastatic, kidney, carcinoma
80	HHINTDNPSL	stomach, metastatic, kidney, carcinoma
81	RVGEVGQSK	stomach, metastatic, kidney, carcinoma
82	AVFDGAQVTSK	lung, non-small cell lung carcinoma, kidney, oncocytoma
83	SQTDLVSRL	lung, non-small cell lung carcinoma, kidney, oncocytoma
84	VPVPHTTAL	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
85	YQVLDVQRY	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
86	APFQGDQRSL	colon or rectum, breast, mucinous carcinoma
87	DVAEPYKVY	colon or rectum, breast, mucinous carcinoma
88	IVSGQPGTQK	colon or rectum, breast, mucinous carcinoma
89	TPEQQAAIL	colon or rectum, breast, mucinous carcinoma
90	VELFRTAYF	colon or rectum, breast, mucinous carcinoma
91	EHADDDPSL	brain, cancer, kidney, Wilm's tumor
92	SEESVKSTTL	brain, cancer, kidney, Wilm's tumor
93	SPRPPLGSSL	brain, cancer, kidney, Wilm's tumor

94	SPWWRSSL	brain, cancer, kidney, Wilm's tumor
95	VYTPVDSLVF	brain, cancer, kidney, Wilm's tumor
96	APLQRSQSL	pancreas, adenocarcinoma, kidney, renal cell carcinoma
97	DEVHQDTY	pancreas, adenocarcinoma, kidney, renal cell carcinoma
98	LPHSATVTL	pancreas, adenocarcinoma, kidney, renal cell carcinoma
99	SEAPEAPLL	testis, seminoma
100	SPRASGSGL	testis, seminoma
101	VVGPAAEAK	testis, seminoma
102	FSITKSVEL	non-Hodgkin's lymphoma, small lymphocytic type
103	GQTKNDLVV	non-Hodgkin's lymphoma, small lymphocytic type
104	LSQEVCRD	non-Hodgkin's lymphoma, small lymphocytic type
105	RDIQSPEQI	non-Hodgkin's lymphoma, small lymphocytic type
106	REDNSSNSL	non-Hodgkin's lymphoma, small lymphocytic type
107	TEHQEPGL	non-Hodgkin's lymphoma, small lymphocytic type
108	TKNDLVVSL	non-Hodgkin's lymphoma, small lymphocytic type
109	AEEAGGTRL	breast, carcinoma
110	ENVNKKDY	breast, carcinoma
111	GLDPNKPPEL	breast, carcinoma
112	RPAGEPYNRKTL	breast, carcinoma
113	SASVQRADTSL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical adenoma
114	YGNPRTNGM	stomach, metastatic, breast, carcinoma
115	LIRPVSASF	esophagus, adenocarcinoma
116	SPVNSSKQPSY	esophagus, adenocarcinoma
117	QLFSYAILGF	liver, hepatocellular carcinoma, colon, non-Hodgkin's lymphoma
118	DEHLLIQHY	liver, hepatocellular carcinoma, parotid gland, pleomorphic adenoma
119	KQVASSTGF	liver, hepatocellular carcinoma, parotid gland, pleomorphic adenoma
120	RDFGPASQHFL	liver, hepatocellular carcinoma, parotid gland, pleomorphic adenoma
121	RQLGEVASF	liver, hepatocellular carcinoma, parotid gland, pleomorphic adenoma
122	TEAETTANVL	liver, hepatocellular carcinoma, parotid gland, pleomorphic adenoma
123	GYLPVQTVL	kidney, clear cell renal cell carcinoma, parotid gland, pleomorphic adenoma
124	GQKEALLKY	liver, hepatocellular carcinoma, synovial sarcoma

125	KPSEERKTI	liver, hepatocellular carcinoma, synovial sarcoma
126	KQTPKVLVV	liver, hepatocellular carcinoma, synovial sarcoma
127	SVIQHVQSF	liver, hepatocellular carcinoma, synovial sarcoma
128	TPIERIPYL	liver, hepatocellular carcinoma, synovial sarcoma
129	AEVEKNETV	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
130	EVKEEIPLV	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
131	KPTSARSGL	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
132	KYIETTPLTI	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
133	SEIKTSIEV	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
134	SVKPTSATK	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
135	YPNKGVGQA	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma
136	ISMKILNSL	lung, non-small cell lung carcinoma, thymus, thymoma, benign
137	KTIAFLLPMF	lung, non-small cell lung carcinoma, thymus, thymoma, benign
138	RDSIINDF	lung, non-small cell lung carcinoma, thymus, thymoma, benign
139	SVKGGGGNEK	lung, non-small cell lung carcinoma, thymus, thymoma, benign
140	GIAKTGSGK	lung, non-small cell lung carcinoma, thymus, thymoma, benign
141	AETTDNVFTL	kidney, clear cell renal cell carcinoma, thyroid gland, follicular adenoma
142	SEYQRFAVM	kidney, clear cell renal cell carcinoma, thyroid gland, follicular adenoma
143	TFGERVVAF	kidney, clear cell renal cell carcinoma, thyroid gland, follicular adenoma
144	NENLVERF	stomach, adenocarcinoma, colon, adenocarcinoma
145	KITVPASQK	stomach, adenocarcinoma, colon, non-Hodgkin's lymphoma
146	KITVPASQKL	stomach, adenocarcinoma, colon, non-Hodgkin's lymphoma
147	VPASQKLRQL	stomach, adenocarcinoma, colon, non-Hodgkin's lymphoma
148	HVGYTLSYK	stomach, adenocarcinoma
149	KLPLPLPPRL	stomach, adenocarcinoma
150	KPIEPRREL	stomach, adenocarcinoma
151	SHSHVGYTL	stomach, adenocarcinoma
152	APSEYRYTL	colon or rectum, stomach, mucinous

		adenocarcinoma
		colon or rectum, stomach, mucinous
153	APSEYRYTLL	adenocarcinoma
		colon or rectum, stomach, mucinous
154	EIFQNEVAR	adenocarcinoma
		colon or rectum, stomach, mucinous
155	KDVLIPGKL	adenocarcinoma
		colon or rectum, stomach, mucinous
156	VPLVREITF	adenocarcinoma
		liver, hepatocellular carcinoma, cancer,
157	DPNPNFEKF	liver, focal nodular hyperplasia
		liver, hepatocellular carcinoma, cancer,
158	IQAPLSWEL	liver, focal nodular hyperplasia
		liver, hepatocellular carcinoma, cancer,
159	VIYNEQMASK	liver, focal nodular hyperplasia
		liver, hepatocellular carcinoma, cancer,
160	VLRPGGAFY	liver, focal nodular hyperplasia
		stomach, adenocarcinoma, endometrium,
161	EDPDQDILI	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, endometrium,
162	HGNLRELAL	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, endometrium,
163	KLYPTLVIR	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, endometrium,
164	SEETFRFEL	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, ovary,
165	ELNKLLEEI	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, ovary,
166	IPFSNPRVL	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, ovary,
167	LLDEGAKLLY	adenocarcinoma, endometrioid
		stomach, adenocarcinoma, ovary,
168	SPADAHRNL	adenocarcinoma, endometrioid
		stomach, metastatic, endometrium,
173	APRKGNTL	Mullerian mixed tumor
		stomach, metastatic, endometrium,
174	EEEEALQKKF	Mullerian mixed tumor
		stomach, metastatic, endometrium,
175	KENLVDGF	Mullerian mixed tumor
		stomach, metastatic, endometrium,
176	VYKENLVDGF	Mullerian mixed tumor
		stomach, adenocarcinoma, bone, giant
177	TLLVVVPKL	cell tumor of bone
		kidney, clear cell renal cell carcinoma,
178	HEIDRYTAI	non-Hodgkin's lymphoma
		kidney, clear cell renal cell carcinoma,
179	VFTLKPLEF	non-Hodgkin's lymphoma
		kidney, clear cell renal cell carcinoma,
180	YWVPRNAL	non-Hodgkin's lymphoma
181	IGVEHVVVY	brain, cancer, kidney, oncocytoma
182	RDKPHVNV	brain, cancer, omentum, leiomyosarcoma

183	ADVLKVEVF	stomach, adenocarcinoma, colon, adenocarcinoma
184	IPVVHASI	stomach, adenocarcinoma, colon, adenocarcinoma
185	RDSLIDSLT	stomach, adenocarcinoma, colon, adenocarcinoma
186	TVADQVLVGSY	stomach, adenocarcinoma, colon, adenocarcinoma
187	AADTERLAL	lung, non-small cell lung carcinoma, chondrosarcoma
188	DMKAKVASL	lung, non-small cell lung carcinoma, chondrosarcoma
189	HVLEEVQQV	lung, non-small cell lung carcinoma, chondrosarcoma
190	KEAADTERL	lung, non-small cell lung carcinoma, chondrosarcoma
191	RISEVLQKL	lung, non-small cell lung carcinoma, chondrosarcoma
192	TEVRELVSL	lung, non-small cell lung carcinoma, chondrosarcoma
193	AIRSGEAAAK	liver, hepatocellular carcinoma, pleura, malignant mesothelioma
194	APNPAPKEL	liver, hepatocellular carcinoma, pleura, malignant mesothelioma
195	RQSLLTAI	liver, hepatocellular carcinoma, liver, hepatocellular carcinoma, cancer, pleura, malignant mesothelioma
196	SPEQTLSPL	liver, hepatocellular carcinoma, pleura, malignant mesothelioma
197	TEHQVPSSV	liver, hepatocellular carcinoma, liver, hepatocellular carcinoma, cancer, pleura, malignant mesothelioma
198	TTYKIVPPK	liver, hepatocellular carcinoma, liver, hepatocellular carcinoma, cancer, pleura, malignant mesothelioma
199	QLLDQVEQI	stomach, metastatic thyroid gland, papillary carcinoma
200	DETMVIGNY	stomach, metastatic, rectum, adenocarcinoma
201	RQYGSEGRFTF	kidney, clear cell renal cell carcinoma, rectum, adenocarcinoma
203	GPRPITQSEL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma
204	KPEPVDKVA	stomach, metastatic, lymph node, non-Hodgkin's lymphoma
205	TPSSRPASL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma
212	GRLNSVNNR	kidney, clear cell renal cell carcinoma, leiomyosarcoma
213	SILEDPPSI	kidney, clear cell renal cell carcinoma, leiomyosarcoma

214	TPRTNNIEL	kidney, clear cell renal cell carcinoma, leiomyosarcoma
215	DAMKRVEEI	stomach, adenocarcinoma, ovary, thecoma-fibroma
216	DIKEVKQNI	stomach, adenocarcinoma, ovary, thecoma-fibroma
217	GPIYPGHGM	stomach, adenocarcinoma, ovary, thecoma-fibroma
218	GDYGRAFNL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma
219	TRHKIVHTK	stomach, metastatic, lymph node, non-Hodgkin's lymphoma
220	RIHTGEKPYK	colon or rectum, thyroid gland, nodular hyperplasia
221	KAFNWFSTL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma
222	QSTQRSLAL	liver, hepatocellular carcinoma, uterin cervix, squamous cell carcinoma
223	RDLQMNQALRF	liver, hepatocellular carcinoma, uterin cervix, squamous cell carcinoma
224	RELESQLHVL	liver, hepatocellular carcinoma, uterin cervix, squamous cell carcinoma
225	SEAEKLTLV	liver, hepatocellular carcinoma, uterin cervix, squamous cell carcinoma
226	AAAKPVATK	pancreas, adenocarcinoma, fibromatosis
227	ATYHGSFSTK	pancreas, adenocarcinoma, fibromatosis
228	FMYDRPLRL	pancreas, adenocarcinoma, fibromatosis
229	FRVGNVQEL	pancreas, adenocarcinoma, fibromatosis
230	GVAPFTIAR	pancreas, adenocarcinoma, fibromatosis
231	KMKPLDGSALY	pancreas, adenocarcinoma, fibromatosis
232	KPAPAKPVA	pancreas, adenocarcinoma, fibromatosis
233	KPVAAKPAA	pancreas, adenocarcinoma, fibromatosis
234	KQFGVAPFTI	pancreas, adenocarcinoma, fibromatosis
235	QEELVKISL	pancreas, adenocarcinoma, fibromatosis
236	RQLGTVQQVI	pancreas, adenocarcinoma, fibromatosis
237	RQLINALQI	pancreas, adenocarcinoma, fibromatosis
238	RVIGGLLAGQTY	pancreas, adenocarcinoma, fibromatosis
239	SENAFYLSP	pancreas, adenocarcinoma, fibromatosis
240	SQAPVLDAI	pancreas, adenocarcinoma, fibromatosis
241	STRYPPPAV	pancreas, adenocarcinoma, fibromatosis
242	TEDTLKVYL	pancreas, adenocarcinoma, fibromatosis
243	VAAKPVATK	pancreas, adenocarcinoma, fibromatosis
244	VQRVVESL	pancreas, adenocarcinoma, fibromatosis
245	VRNPSVVVK	pancreas, adenocarcinoma, fibromatosis
246	GESEVAIKI	myometrium, leiomyoma
247	LIYSVGLLLA	myometrium, leiomyoma
248	SAYPHQLSF	myometrium, leiomyoma
249	SVIGVFITK	myometrium, leiomyoma
250	AELGNSVQLI	liver, hepatocellular carcinoma, thyroid

		gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
251	ANMTVTRI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
252	ARISNVEFY	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
253	AVFIGNQQF	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
254	DIELQAENI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
255	DSYTVRVSV	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
256	DVKIFVNTI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
257	EIIPKYGSI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
258	EQSKIFIHR	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
259	FVDVGLYQY	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
260	GHTSTISTL	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
261	GRIEYVEVF	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
262	GTSIIPFQK	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
263	HPFLRGIGY	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
264	IPVEIHTA	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
265	KIFVNTIAY	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
266	LPEDKVRIAY	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
267	LPFSEGLTV	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
268	LPWANKVTI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
269	PWANKVTI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
270	QAYNRAVTI	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
271	RSFPQKMAY	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
272	RYPIHWHLL	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
273	SPQNLRLML	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
274	SYFSSPTQR	gland, nodular hyperplasia
		liver, hepatocellular carcinoma, thyroid
275	VQIKSSLI	gland, nodular hyperplasia

276	VYIGHTSTI	liver, hepatocellular carcinoma, thyroid gland, nodular hyperplasia
277	YHVPGTGESY	liver, hepatocellular carcinoma, thyroid gland, nodular hyperplasia
278	ATNGDLASR	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
279	GLHAEVTGVGY	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
280	HVSSTSSSF	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
281	LQADLQNGL	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
282	SELPVSEVA	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
283	SQTKSVFEI	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
284	THIFTSDGL	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
285	VIYFPPLQK	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
286	YPFSSEQKW	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
287	GQYFGELAL	stomach, gastrointestinal stromal tumor (GIST)
288	RIIVKNNAK	stomach, gastrointestinal stromal tumor (GIST)
289	RRIIVKNNAK	stomach, gastrointestinal stromal tumor (GIST)
290	SFGELALMY	stomach, gastrointestinal stromal tumor (GIST)
291	AFNAPVINR	stomach, gastrointestinal stromal tumor (GIST)
292	IMKRNIATY	stomach, gastrointestinal stromal tumor (GIST)
293	KVVDVIGTK	stomach, gastrointestinal stromal tumor (GIST)
294	LPFLKSLEF	stomach, gastrointestinal stromal tumor (GIST)
295	RLKVVDVIGTK	stomach, gastrointestinal stromal tumor (GIST)
296	TPRAATITA	stomach, gastrointestinal stromal tumor (GIST)
297	KPSEKIQVL	lipoma
298	VPYPVTTTV	lipoma
299	ASFPPFVEK	lipoma
300	AFIHISTAY	colon or rectum, colon, adenocarcinoma
301	ATFEKIPFER	colon or rectum, colon, adenocarcinoma
302	KLFEKVKEV	colon or rectum, colon, adenocarcinoma
303	SQMPKLEAF	colon or rectum, colon, adenocarcinoma
304	AVLGQHHNY	colon or rectum, colon, adenocarcinoma

305	GPPAHKPR	spleen, chronic myeloid leukemia
306	RVYDVLVLK	colon or rectum, colon, adenocarcinoma
307	LPRPQGITV	liver, hepatocellular carcinoma, liver, focal nodular hyperplasia
308	VLYVGSKTK	brain, glioblastoma, schwannoma
309	KTKEQVTNV	brain, glioblastoma, schwannoma
310	MPVDPDNEAY	brain, glioblastoma, schwannoma
311	AEKTKQGVA	brain, glioblastoma, schwannoma
312	DIADFFTTR	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical adenoma
313	HSYLQRQSV	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical adenoma
314	KEVTLIEEL	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical adenoma
315	REDGPGVAL	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical adenoma
316	REDPLPPGL	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical adenoma
317	SLFGGSQGLRK	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical adenoma
318	AEFQRLKQA	intramuscular lipoma
319	EVIDGVPGKW	intramuscular lipoma
320	IPKAPGKII	intramuscular lipoma
321	SHNGSAIRY	intramuscular lipoma
322	TEVTVVGDKL	intramuscular lipoma
323	YASVVVKRY	intramuscular lipoma
324	ATDLALYIK	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
325	AYHNWRHAF	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
326	EPLNIKDAY	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
327	KIAATIISF	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
328	KIFLHIHGL	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
329	LEVILKKI	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
330	SEHPLAQLY	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
331	VPSAQTLKI	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
332	AEYRSYVA	stomach, metastatic adrenal gland, adrenal cortical carcinoma
333	ALAPGRGTLY	stomach, metastatic adrenal gland, adrenal cortical carcinoma
334	GPRGTQAAL	stomach, metastatic adrenal gland, adrenal cortical carcinoma
335	IEDPGTLHI	stomach, metastatic adrenal gland, adrenal cortical carcinoma

336	IEDPGTLHIW	stomach, metastatic adrenal gland, adrenal cortical carcinoma
337	RPIPIAVKY	stomach, metastatic adrenal gland, adrenal cortical carcinoma
338	VEKLLTNW	stomach, metastatic, pancreas, adenocarcinoma
339	FLDPDIGGVAV	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
340	HTAPPENKTW	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
341	LLDTPVKTQY	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
342	NAVKDFTSF	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
343	SGLLQIKKL	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
344	YHDKNIVLL	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
345	SVDPKNYPK	pancreas, adenocarcinoma, colon, adenocarcinoma
346	AVGLVLPAK	liver, hepatocellular carcinoma, cancer, thyroid gland, papillary carcinoma
347	AVGLVLPAKL	liver, hepatocellular carcinoma, cancer, thyroid gland, papillary carcinoma
348	ALLEVLSQK	stomach, adenocarcinoma, breast, carcinoma
349	HEKQDTLVA	kidney, clear cell renal cell carcinoma, spleen, chronic myeloid leukemia
350	KELELQIGM	kidney, clear cell renal cell carcinoma, spleen, chronic myeloid leukemia
351	MYSDVWKQL	kidney, clear cell renal cell carcinoma, spleen, chronic myeloid leukemia
352	RELQDEKAEL	kidney, clear cell renal cell carcinoma, spleen, chronic myeloid leukemia
353	RITDVLDQK	kidney, clear cell renal cell carcinoma, spleen, chronic myeloid leukemia
354	EVIKITGLK	stomach, adenocarcinoma
355	HHVDITKKL	stomach, adenocarcinoma, kidney, carcinoma
356	LPFNVKVSV	stomach, adenocarcinoma, stomach, gastrointestinal stromal tumor (GIST)
357	TLPRVLEI	stomach, adenocarcinoma, bone, giant cell tumor of bone
358	TVDLPKSPK	stomach, adenocarcinoma, thyroid gland, nodular hyperplasia
359	AEHGLLLTA	stomach, metastatic, uterin cervix, adenocarcinoma
360	AQAGALLQV	stomach, metastatic, uterin cervix, adenocarcinoma
361	DGGFVLKV	stomach, metastatic, uterin cervix, adenocarcinoma

362	IVYPSGKVY	stomach, metastatic, uterin cervix, adenocarcinoma
363	KLDNQVSKV	colon or rectum, prostate, benign nodular hyperplasia
364	SENVKLFSA	colon or rectum, prostate, benign nodular hyperplasia
365	VQKLQNII	colon or rectum, prostate, benign nodular hyperplasia
366	FSTPHGLEV	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
367	KRFHQKSDM	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
368	KTFGHAVSL	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
369	SSNLITHSR	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
370	GVIDGHIYAV	stomach, metastatic, leiomyosarcoma
371	IEPAKETTTNV	pancreas, adenocarcinoma, lung, adenocarcinoma
372	NAPPSEVLL	pancreas, adenocarcinoma, lung, adenocarcinoma
373	SIEPAKETTTNV	pancreas, adenocarcinoma, lung, adenocarcinoma
374	AQSQHNQSL	spleen, extramedullary hematopoiesis
375	AQSRTNPQV	spleen, extramedullary hematopoiesis
376	KMHDKVFAY	spleen, extramedullary hematopoiesis
377	TAKAPLSTV	spleen, extramedullary hematopoiesis
378	IPTRTVAI	liver, hepatocellular carcinoma, lipoma
379	NHDRKHAV	liver, hepatocellular carcinoma, lipoma
380	NNHDRKHAV	liver, hepatocellular carcinoma, lipoma
381	TPGGTRIIY	liver, hepatocellular carcinoma, breast, carcinoma
382	EHWPSPETF	bone, non-ossifying fibroma
383	EIITNTLSF	bone, non-ossifying fibroma
384	EVRGALMSAF	bone, non-ossifying fibroma
385	IPRPILVLL	bone, non-ossifying fibroma
386	LPNKNRDEL	bone, non-ossifying fibroma
387	QRIPAGAVL	bone, non-ossifying fibroma
388	AEGPAGGFMVV	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
389	AYYRDAEAY	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
390	QVNRPLTMR	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
391	RHSPVFQVY	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
392	SLPVPNSAY	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia
393	TLGPPGTAHLY	pancreas, adenocarcinoma, spleen, chronic myeloid leukemia

394	IEPAKETTTNV	pancreas, adenocarcinoma, lung, adenocarcinoma
395	NAPPSEVLL	pancreas, adenocarcinoma, lung, adenocarcinoma
396	SIEPAKETTTNV	pancreas, adenocarcinoma, lung, adenocarcinoma
397	DLYSGLNQR	lymph node, Hodgkin's disease
398	KAKAKPVTR	lymph node, Hodgkin's disease
399	AVLDKAMKAK	liver, hepatocellular carcinoma, liver, hepatic adenoma
400	LELSTPLKI	liver, hepatocellular carcinoma, liver, hepatic adenoma
401	LPLNLDTKY	liver, hepatocellular carcinoma, liver, hepatic adenoma
402	TVIYRIQAL	liver, hepatocellular carcinoma, liver, hepatic adenoma
403	DAHIYLNHI	stomach, adenocarcinoma, pancreas, microcystic adenoma
404	NHIEPLKIQL	stomach, adenocarcinoma, pancreas, microcystic adenoma
405	AYRPAVHPR	thyroid gland, nodular hyperplasia
406	LRAPLEHEL	thyroid gland, nodular hyperplasia
407	RLFMVLLLK	thyroid gland, nodular hyperplasia
408	RSPDVLKDF	thyroid gland, nodular hyperplasia
409	ETAPGVHKR	stomach, metastatic, non-Hodgkin's lymphoma
410	LYHGYIYTY	stomach, metastatic, non-Hodgkin's lymphoma
415	VVFDSPRNR	liver, hepatocellular carcinoma, pancreas, adenocarcinoma
416	YPLGRILI	lung, non-small cell lung carcinoma, pancreas, adenocarcinoma
417	KEFAEFVTS	pancreas, adenocarcinoma, pancreas, adenocarcinoma
418	VMLDVPIRL	pancreas, adenocarcinoma, pancreas, adenocarcinoma
419	VPMTPLRTV	liver, hepatocellular carcinoma, cancer, rectum, adenocarcinoma
420	QIDYKTLVL	stomach, metastatic, leiomyosarcoma
421	VEDPTIVRI	stomach, metastatic, leiomyosarcoma
422	IPYQDLPHL	kidney, clear cell renal cell carcinoma, lipoma
423	DTPFLTGHGR	stomach, adenocarcinoma, bone, non-ossifying fibroma
424	EFYRALYI	stomach, adenocarcinoma, bone, non-ossifying fibroma
425	RYYPQILTNK	stomach, adenocarcinoma, bone, non-ossifying fibroma
426	KAYERHVL	intestines, malignant carcinoid tumor
427	LPSPEFHDY	intestines, malignant carcinoid tumor

428	SLYAHPIEH	intestines, malignant carcinoid tumor
429	LVREPGSQA	kidney, clear cell renal cell carcinoma, lymph node, Hodgkin's disease
430	RLAGPGSEKY	kidney, clear cell renal cell carcinoma, lymph node, Hodgkin's disease
431	SPGAGRNSVL	kidney, clear cell renal cell carcinoma, lymph node, Hodgkin's disease
432	SVQSDQGYISR	kidney, clear cell renal cell carcinoma, lymph node, Hodgkin's disease
433	GVRPPAPSL	liver, hepatocellular carcinoma, kidney, carcinoma
434	IFSEKPVFV	liver, hepatocellular carcinoma, kidney, carcinoma
435	KASNLLLGF	liver, hepatocellular carcinoma, kidney, carcinoma
436	KRYIFADAY	liver, hepatocellular carcinoma, kidney, carcinoma
437	RNLQLSLPR	liver, hepatocellular carcinoma, kidney, carcinoma
438	EASEPVALR	brain, glioblastoma, liver, hepatic adenoma
439	RPKVPDQSV	brain, glioblastoma, liver, hepatic adenoma
440	VLYENALKL	spleen, extramedullary hematopoiesis
441	EVLDKSQTNY	liver, hepatocellular carcinoma, endometrium, hyperplasia
442	MPSPIPAKY	liver, hepatocellular carcinoma, endometrium, hyperplasia
443	YGIENFTSV	liver, hepatocellular carcinoma, endometrium, hyperplasia
444	ARAAQVFFL	colon or rectum, kidney, renal cell carcinoma
445	EHIVPNAEL	colon or rectum, kidney, renal cell carcinoma
446	EAFEFVKQR	stomach, adenocarcinoma, breast, carcinoma
447	NHFEGHYQY	stomach, adenocarcinoma, breast, carcinoma
448	DAYPKNPHL	stomach, adenocarcinoma, liver, hepatocellular carcinoma
449	DVNIKSTER	stomach, adenocarcinoma, liver, hepatocellular carcinoma
450	HINSIKSVF	stomach, adenocarcinoma, liver, hepatocellular carcinoma
451	YESEKVGVA	stomach, adenocarcinoma, liver, hepatocellular carcinoma
452	ENAPTTVSR	stomach, adenocarcinoma, adrenal gland, adrenal cortical adenoma
453	RFPHLLAHTY	stomach, adenocarcinoma, adrenal gland, adrenal cortical adenoma
454	TLDGSLHAV	stomach, adenocarcinoma, adrenal gland,

		adrenal cortical adenoma
455	RTVLKNLSLLK	liver, hepatocellular carcinoma, pancreas, microcystic adenoma
456	FEAKVQAI	stomach, adenocarcinoma, metastatic adenocarcinoma of stomach
457	FFEAKVQAI	stomach, adenocarcinoma, metastatic adenocarcinoma of stomach
458	KELQSTFK	stomach, adenocarcinoma, metastatic adenocarcinoma of stomach
459	NVSSRFEEEI	stomach, adenocarcinoma, metastatic adenocarcinoma of stomach
460	EVWNNLGTTK	brain, cancer, lymph node, malignant melanoma
461	MIFRSGSLI	brain, cancer, lymph node, malignant melanoma
462	NHALPLPGF	brain, cancer, lymph node, malignant melanoma
463	ASVFGTMPLK	kidney, polycystic kidney disease
464	REFPDRLVGY	kidney, polycystic kidney disease
465	SVFGTMPLK	kidney, polycystic kidney disease
466	DEMRFVTQI	lung, non-small cell lung carcinoma, testis, mixed germ cell tumor
467	ETVHFATTQW	lung, non-small cell lung carcinoma, testis, mixed germ cell tumor
468	LPPPATQI	lung, non-small cell lung carcinoma, testis, mixed germ cell tumor
469	LARDLYAF	liver, hepatocellular carcinoma, neuroblastoma
470	LPGIGLSTSL	liver, hepatocellular carcinoma, neuroblastoma
471	MEVILPML	liver, hepatocellular carcinoma, neuroblastoma
472	AILDYILAK	stomach, metastatic, lung, neuroendocrine carcinoma (non-small cell type)
473	KIASQLSKL	stomach, metastatic, lung, neuroendocrine carcinoma (non-small cell type)
474	KVTSTTTVK	stomach, metastatic, lung, neuroendocrine carcinoma (non-small cell type)
475	YNTLLPYTF	stomach, metastatic, lung, neuroendocrine carcinoma (non-small cell type)
476	FLDPRPLTV	pancreas, adenocarcinoma, myometrium, leiomyoma
477	SAFADRPAF	pancreas, adenocarcinoma, myometrium, leiomyoma
478	AAVPVIISR	lymph node, papillary carcinoma of thyroid
479	EEIGKVAAA	lymph node, papillary carcinoma of thyroid
480	FLKDLVASV	lymph node, papillary carcinoma of thyroid
481	VIISRALEL	lymph node, papillary carcinoma of thyroid
482	APRTTGTPRTSL	kidney, oncocytoma
483	ESVGGSPQTK	kidney, oncocytoma

484	IPKDKAIL	kidney, oncocytoma
485	LPAYGRTTL	kidney, oncocytoma
486	HQAAIVSKI	stomach, adenocarcinoma, kidney, angiomyolipoma
487	QAAIVSKI	stomach, adenocarcinoma, kidney, angiomyolipoma
488	RQKMPEDGL	stomach, adenocarcinoma, kidney, angiomyolipoma
489	SVQKSSGVK	stomach, adenocarcinoma, kidney, angiomyolipoma
490	DSIGSTVSSER	stomach, adenocarcinoma
491	LPYNNKDRDAL	stomach, adenocarcinoma
492	IYDEIQQEM	colon or rectum, colon, adenoma
493	AQAKGLIQV	thymus, thymoma, benign
494	EVSSEIYQW	thymus, thymoma, benign
495	KWNPVPLSY	thymus, thymoma, benign
496	NRLLAQQSL	thymus, thymoma, benign
497	APRPVAVAV	stomach, adenocarcinoma
498	FYRETVQVGR	stomach, adenocarcinoma
499	LLAPRPVAV	stomach, adenocarcinoma
500	GLAALVILK	stomach, adenocarcinoma, neurofibroma
501	KIQEVFSSY	stomach, adenocarcinoma, neurofibroma
502	ASLDKFLSH	spleen, chronic myeloid leukemia
503	ALYATKTLR	colon or rectum, pancreas, microcystic adenoma
504	MEYVISRI	colon or rectum, pancreas, microcystic adenoma
505	VPVGRQPII	colon or rectum, pancreas, microcystic adenoma
506	KLLIGVIAAV	stomach, metastatic, colon, adenocarcinoma
507	LPSLIKLD	stomach, metastatic, colon, adenocarcinoma
508	PSLIKLDL	stomach, metastatic, colon, adenocarcinoma
509	ARNKELIGK	stomach, adenocarcinoma
510	AVKSNAAAY	stomach, adenocarcinoma
511	EVIIPHSGW	stomach, adenocarcinoma
512	SVKEQEAQF	stomach, adenocarcinoma
513	APRGLEPIAI	liver, hepatocellular carcinoma, liver, focal nodular hyperplasia
514	GRFGGVITI	liver, hepatocellular carcinoma, liver, focal nodular hyperplasia
518	AEHIESRTL	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
519	DQYPYLKSV	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
520	IARNLTQQL	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
521	IESRTLAIA	kidney, clear cell renal cell carcinoma,

		liver, focal nodular hyperplasia
522	MTSALPIIQK	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
523	SLLTSSKGQLQK	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
524	TSALPIIQK	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
525	VRLGSLSTK	kidney, clear cell renal cell carcinoma, liver, focal nodular hyperplasia
526	RINEFSISSF	chondrosarcoma
527	DEKQQHIVY	liver, hepatocellular carcinoma, synovial sarcoma
528	DEVYQVTVY	liver, hepatocellular carcinoma, synovial sarcoma
529	GEISEKAKL	liver, hepatocellular carcinoma, synovial sarcoma
530	YTMKEVLFY	liver, hepatocellular carcinoma, synovial sarcoma
531	SQLTTLSFY	lung, non-small cell lung carcinoma, omentum, adenocarcinoma
532	LEKQLIEL	stomach, adenocarcinoma, rectum, adenocarcinoma
533	ELTLGEFLK	stomach, metastatic, ovary, Mullerian mixed tumor
534	LTLGEFLK	stomach, metastatic, ovary, Mullerian mixed tumor
535	LTLGEFLKL	stomach, metastatic, ovary, Mullerian mixed tumor
536	TLGEFLKL	stomach, metastatic, ovary, Mullerian mixed tumor
537	ITARPVLW	non-Hodgkin's lymphoma
538	KLMSPKLYVW	non-Hodgkin's lymphoma
539	KVSAVTLAY	non-Hodgkin's lymphoma
540	VEGSGELFRW	non-Hodgkin's lymphoma
541	RPKSNIVL	non-Hodgkin's lymphoma
542	RPKSNIVLL	non-Hodgkin's lymphoma
543	GEPLSYTRFSLARQ	lung, non-small cell lung carcinoma, lung, adenocarcinoma
544	GEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
545	GEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
546	GGEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
547	GGEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
548	NPGGYVAYSKAATVTG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
549	NPGGYVAYSKAATVTGK	lung, non-small cell lung carcinoma, lung, adenocarcinoma

550	NPGGYVAYSKAATVTGKL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
551	NSVIIVDKNGRL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
552	NSVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
553	NSVIIVDKNGRLVY	lung, non-small cell lung carcinoma, lung, adenocarcinoma
554	RVEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
555	RVEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
556	RVEYHFLSPYVSPKESPF	lung, non-small cell lung carcinoma, lung, adenocarcinoma
557	SPFRHVFWGSGSHTL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
558	SVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
559	VEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
560	VEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
561	LPSQAFEYILYNKG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
562	LPSQAFEYILYNKGI	lung, non-small cell lung carcinoma, lung, adenocarcinoma
563	LPSQAFEYILYNKGIM	lung, non-small cell lung carcinoma, lung, adenocarcinoma
564	LPSQAFEYILYNKGIMG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
565	MNGYFLIERGKNM	lung, non-small cell lung carcinoma, lung, adenocarcinoma
566	NGYFLIERGKNm	lung, non-small cell lung carcinoma, lung, adenocarcinoma
567	PSQAFEYILYNKG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
568	PSQAFEYILYNKGI	lung, non-small cell lung carcinoma, lung, adenocarcinoma
569	PSQAFEYILYNKGIM	lung, non-small cell lung carcinoma, lung, adenocarcinoma
570	EGVQYSYSLFHLM	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
571	EGVQYSYSLFHLML	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
572	GVQYSYSLFHLM	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
573	GVQYSYSLFHLML	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
574	SIISIHPKIQEHQPR	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
575	SSIRTSTNSQVDK	stomach, metastatic, stomach,

		gastrointestinal stromal tumor (GIST)
576	VLVGYKAVYRIS	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
577	YSSIRTSTNSQVDK	stomach, metastatic, stomach, gastrointestinal stromal tumor (GIST)
578	GGGYGSGGGSGGYGSRR F	colon or rectum, thymus, thymoma, malignant
579	GGSFGGRSSGSP	colon or rectum, thymus, thymoma, malignant
580	KGGSFGGRSSGSP	colon or rectum, thymus, thymoma, malignant
581	SGQQQSNYGPMKGGSFG GRSSGSPY	colon or rectum, thymus, thymoma, malignant
582	SGSPYGGGYGSGGGSGG YGSRRF	colon or rectum, thymus, thymoma, malignant
583	SPYGGGYGSGGGSGGYG SRRF	colon or rectum, thymus, thymoma, malignant
584	YGGGYGSGGGSGGYGSR RF	colon or rectum, thymus, thymoma, malignant
585	GNRINEFSISSF	chondrosarcoma
586	HGNQITSDKVGRKV	chondrosarcoma
587	IPPVNTNLENLYLQ	chondrosarcoma
588	LQVLRLDGNEIKR	chondrosarcoma
589	LQVLRLDGNEIKRS	chondrosarcoma
590	LQVLRLDGNEIKRSA	chondrosarcoma
591	LRELHLDHNQISRVPN	chondrosarcoma
592	LYVRLSHNSLTNNG	chondrosarcoma
593	VPSRMKYVYFQNNQ	chondrosarcoma
594	VPSRMKYVYFQNNQIT	chondrosarcoma
595	VPSRMKYVYFQNNQITS	chondrosarcoma
596	WIALHGNQITSD	chondrosarcoma
597	WIALHGNQITSDK	chondrosarcoma
598	ADDNVSFRWEALGNT	chondrosarcoma
599	ADDNVSFRWEALGNTL	colon or rectum
600	DADDNVSFRWEALGNTL	colon or rectum
601	DDNVSFRWEALGNT	colon or rectum
602	DDNVSFRWEALGNTL	colon or rectum
603	DNVSFRWEALGNT	colon or rectum
604	DNVSFRWEALGNTL	colon or rectum
605	DNVSFRWEALGNTLS	colon or rectum
606	DTGSYRAQISTKTSAK	colon or rectum
607	DTGSYRAQISTKTSAKL	colon or rectum
608	DTITIYSTINHSK	colon or rectum
609	EDTGSYRAQISTKTSAK	colon or rectum
610	ENDTITIYSTINHSK	colon or rectum
611	ENDTITIYSTINHSKESKPT	colon or rectum
612	GSYRAQISTKTSAK	colon or rectum
613	NDTITIYSTINH	colon or rectum
614	NDTITIYSTINHS	colon or rectum

615	NDTITIYSTINHSK	colon or rectum
616	NVSFRWEALGNTL	colon or rectum
617	SPTNNTVYASVTHSNRET	colon or rectum
618	TGSYRAQISTKTSAK	colon or rectum
619	TPRENDTITIYSTINHSK	colon or rectum
620	TPRENDTITIYSTINHSKESKPT	colon or rectum
621	VSFRWEALGNTL	colon or rectum
622	APIHFTIEKLELNEK	lipoma
623	DAQFEVIKGQTIE	lipoma
624	DAQFEVIKGQTIEVR	lipoma
625	ESYFIPEVRIYDSGT	lipoma
626	IPEVRIYDSGTY	lipoma
627	KDKAIVAHNRHGNK	lipoma
628	KDKAIVAHNRHGNKA	lipoma
629	NFVILEFPVEEQDR	lipoma
630	SQPRISYDAQFEVIK	lipoma
631	SQPRISYDAQFEVIKG	lipoma
632	YDAQFEVIKGQTIE	lipoma
633	GNPAYRSFSNSLSQ	colon or rectum, kidney, angiomyolipoma
634	GPPGEAGYKAFSSLLA	colon or rectum, kidney, angiomyolipoma
635	GPPGEAGYKAFSSLLASS	colon or rectum, kidney, angiomyolipoma
636	GPPGEAGYKAFSSLLASSA	colon or rectum, kidney, angiomyolipoma
637	GPPGEAGYKAFSSLLASSAVSPE	colon or rectum, kidney, angiomyolipoma
638	GPPGEAGYKAFSSLLASSAVSPEK	colon or rectum, kidney, angiomyolipoma
639	GYKAFSSLLASSAVSP	colon or rectum, kidney, angiomyolipoma
640	GYKAFSSLLASSAVSPE	colon or rectum, kidney, angiomyolipoma
641	KAFSSLLASSAVSPE	colon or rectum, kidney, angiomyolipoma
642	NPAYRSFSNSLSQ	colon or rectum, kidney, angiomyolipoma
643	SRDDFQEGREGIVAR	colon or rectum, kidney, angiomyolipoma
644	SSSSFHPAPGNAQ	colon or rectum, kidney, angiomyolipoma
645	VARLTESLFLDL	colon or rectum, kidney, angiomyolipoma
646	VARLTESLFLDLLG	colon or rectum, kidney, angiomyolipoma
647	VIAGNPAYRSFSN	colon or rectum, kidney, angiomyolipoma
648	VPQPEPETWEQILRRNVLQ	colon or rectum, kidney, angiomyolipoma
649	YKAFSSLLASSAVS	colon or rectum, kidney, angiomyolipoma
650	YKAFSSLLASSAVSP	colon or rectum, kidney, angiomyolipoma
651	YKAFSSLLASSAVSPE	colon or rectum, kidney, angiomyolipoma,
652	GNQVFSYTANKEIRTDD	colon or rectum, urinary bladder, transitional cell carcinoma
653	IEEIVLVDDASERD	colon or rectum, urinary bladder, transitional cell carcinoma
654	IEEIVLVDDASERDF	colon or rectum, urinary bladder, transitional cell carcinoma
655	LENIYPDSQIPRH	colon or rectum, urinary bladder, transitional cell carcinoma

656	LENIYPDSQIPRHY	colon or rectum, urinary bladder, transitional cell carcinoma
657	NQVFSYTANKEIR	colon or rectum, urinary bladder, transitional cell carcinoma
658	NQVFSYTANKEIRT	colon or rectum, urinary bladder, transitional cell carcinoma
659	NQVFSYTANKEIRTDD	colon or rectum, urinary bladder, transitional cell carcinoma
660	VHSVINRSPRHMIEE	colon or rectum, urinary bladder, transitional cell carcinoma
661	EYVSLYHQPAAM	non-Hodgkin's lymphoma
662	IKAEYKGRVTLKQYPR	non-Hodgkin's lymphoma
663	LNVHSEYEPSWEEQP	non-Hodgkin's lymphoma
664	LPYLFQmPAYASSS	non-Hodgkin's lymphoma
665	LPYLFQmPAYASSSK	non-Hodgkin's lymphoma
666	NFIKAEYKGRVT	non-Hodgkin's lymphoma
667	TNFIKAEYKGRVT	non-Hodgkin's lymphoma
668	TTNFIKAEYKGRVT	non-Hodgkin's lymphoma
669	VTLNVHSEYEPSWEEQP	non-Hodgkin's lymphoma
670	YPRKNLFLVEVTQLTESDS	non-Hodgkin's lymphoma
671	YPRKNLFLVEVTQLTESDS G	non-Hodgkin's lymphoma
672	ADLSSFKSQELN	lymph node, papillary carcinoma of thyroid
673	ADLSSFKSQELNER	lymph node, papillary carcinoma of thyroid
674	ADLSSFKSQELNERN	lymph node, papillary carcinoma of thyroid
675	ADLSSFKSQELNERNE	lymph node, papillary carcinoma of thyroid
676	ADLSSFKSQELNERNEA	lymph node, papillary carcinoma of thyroid
677	AEQQRLKSQDLELSWNLN G	lymph node, papillary carcinoma of thyroid, metastatic
678	EQQRLKSQDLELSWN	lymph node, papillary carcinoma of thyroid
679	ISQELEELRAEQQR	lymph node, papillary carcinoma of thyroid
680	ISQELEELRAEQQRLK	lymph node, papillary carcinoma of thyroid
681	KGTKQWVHARYA	lymph node, papillary carcinoma of thyroid
682	QADLSSFKSQELNER	lymph node, papillary carcinoma of thyroid, metastatic
683	SWNLNGLQADLSSFK	lymph node, papillary carcinoma of thyroid
684	TGSWIGLRNLDLKG	lymph node, papillary carcinoma of thyroid
685	FGNYNNQSSNFGPMKGGN FGGRS	pancreas, adenocarcinoma, thymus, thymoma, malignant
686	FGPMKGGNFGGRSSGPYG GGGQY	pancreas, adenocarcinoma, thymus, thymoma, malignant
687	GPMKGGNFGGRSSGP	pancreas, adenocarcinoma, thymus, thymoma, malignant
688	GPYGGGGQYFAKP	pancreas, adenocarcinoma, thymus, thymoma, malignant
689	KGGNFGGRSSGP	pancreas, adenocarcinoma, thymus, thymoma, malignant
690	NDFGNYNNQSSNFGP	pancreas, adenocarcinoma, thymus, thymoma, malignant

691	SGPYGGGGQYFAKP	pancreas, adenocarcinoma, thymus, thymoma, malignant
692	DAGSYKAQINQRNFE	lung, non-small cell lung carcinoma, lymph node, non-Hodgkin's lymphoma
693	DAGSYKAQINQRNFEVT	lung, non-small cell lung carcinoma, lymph node, non-Hodgkin's lymphoma
694	DGELIRTQPQRLPQ	pancreas, adenocarcinoma, intramuscular lipoma
695	GELIRTQPQRLPQ	pancreas, adenocarcinoma, intramuscular lipoma
696	NPSDGELIRTQPQRLP	pancreas, adenocarcinoma, intramuscular lipoma
697	NPSDGELIRTQPQRLPQ	pancreas, adenocarcinoma, intramuscular lipoma
698	NPSDGELIRTQPQRLPQL	pancreas, adenocarcinoma, intramuscular lipoma
699	ASNDMYHSRALQVVR	colon or rectum, bone, giant cell tumor of bone
700	ASNDMYHSRALQVVRA	colon or rectum, bone, giant cell tumor of bone
701	EGVRRALDFAVGEYN	colon or rectum, bone, giant cell tumor of bone
702	EGVRRALDFAVGEYNK	colon or rectum, bone, giant cell tumor of bone
703	SNDMYHSRALQVVR	colon or rectum, bone, giant cell tumor of bone
704	VGEYNKASNDMYH	colon or rectum, bone, giant cell tumor of bone
705	VRARKQIVAGVNY	colon or rectum, bone, giant cell tumor of bone
706	VRRALDFAVGEYNKASND	colon or rectum, bone, giant cell tumor of bone
707	VVRARKQIVAGVN	colon or rectum, bone, giant cell tumor of bone
708	VVRARKQIVAGVNY	colon or rectum, bone, giant cell tumor of bone
709	APLEGARFALVRED	liver, hepatocellular carcinoma
710	APVELILSDETLPAPE	liver, hepatocellular carcinoma
711	ELILSDETLPAPE	liver, hepatocellular carcinoma
712	LAPLEGARFALVRE	liver, hepatocellular carcinoma
713	LAPLEGARFALVRED	liver, hepatocellular carcinoma
714	RGEKELLVPRSSTSPD	liver, hepatocellular carcinoma
715	ASKTFTTQETITNAET	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
716	DQHFRTTPLEKNAPV	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
717	NTPILVDGKDVMPE	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
718	NTPILVDGKDVMPEV	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
719	NTPILVDGKDVMPEVN	kidney, clear cell renal cell carcinoma,

		kidney, angiomyolipoma
720	SNTPILVDGKDVMPE	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
721	SNTPILVDGKDVMPEVN	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
722	TPILVDGKDVMP	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
723	TPILVDGKDVMPE	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
724	TPILVDGKDVMPEV	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
725	TPILVDGKDVMPEVN	kidney, clear cell renal cell carcinoma, kidney, angiomyolipoma
726	GPLKFLHQDIDSGQG	kidney, renal cell carcinoma
727	GPLKFLHQDIDSGQGIR	kidney, renal cell carcinoma
728	LGDIYFKLFRASG	kidney, renal cell carcinoma
729	TGHLFDLSSLSGRAG	kidney, renal cell carcinoma
730	VPSPVDCQVTDLAGNE	kidney, renal cell carcinoma
731	DGLNSLTYQVLDVQRYPL	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
732	HPVLQRQQLDYGIY	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
733	LNSLTYQVLDVQR	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
734	LNSLTYQVLDVQRYP	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
735	LNSLTYQVLDVQRYPL	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
736	LPQLVGVSTPLQG	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
737	LPQLVGVSTPLQGG	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
738	LPQLVGVSTPLQGGS	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
739	RLPQLVGVSTPLQGGS	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
740	SPHKVAIIIPFRNR	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
741	SPHKVAIIIPFRNRQE	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type

		kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma,
742	SPHKVAIIIPFRNRQEH	endometrioid type
743	AIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
744	ARNFERNKAIKVI	non-Hodgkin's lymphoma, peripheral T cell type
745	ARNFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
746	NFERNKAIKVII	non-Hodgkin's lymphoma, peripheral T cell type
747	NFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
748	VAIVQAVSAHRH	non-Hodgkin's lymphoma, peripheral T cell type
749	VAIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
750	VAIVQAVSAHRHRA	non-Hodgkin's lymphoma, peripheral T cell type
751	VAIVQAVSAHRHRAR	non-Hodgkin's lymphoma, peripheral T cell type
752	EEVITLIRSNQQLE	lung, non-small cell lung carcinoma, pancreas, adenocarcinoma
753	EEVITLIRSNQQLEN	lung, non-small cell lung carcinoma, pancreas, adenocarcinoma
754	IPADTFAALKNPNAML	lung, non-small cell lung carcinoma, pancreas, adenocarcinoma
755	LKQLLSDKQQKRQSG	lung, non-small cell lung carcinoma, pancreas, adenocarcinoma
756	LKQLLSDKQQKRQSGQ	lung, non-small cell lung carcinoma, pancreas, adenocarcinoma
757	TPSYVAFTDTER	pancreas, adenocarcinoma, rectum, adenocarcinoma
758	TPSYVAFTDTERL	pancreas, adenocarcinoma, rectum, adenocarcinoma
759	EGLYSRTLAGSIT	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
760	EGLYSRTLAGSITTPP	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
761	EKWYIPDPTGKFN	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
762	GAIAAINSIQHNTR	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
763	LPILVPSAKKAI	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
764	LPILVPSAKKAIY	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
765	LPILVPSAKKAIYM	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
766	LPILVPSAKKAIYMD	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia

767	LPILVPSAKKAIYMDD	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
768	VEEGLYSRTLAGSIT	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
769	WEKWYIPDPTGKFN	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
770	YKIVNFDPKLLE	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
771	YKIVNFDPKLLEG	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
772	YKIVNFDPKLLEGKV	liver, hepatocellular carcinoma, cancer, thyroid gland, nodular hyperplasia
773	LPEFYKTVSPAL	colon or rectum, endometrium, adenocarcinoma, endometrioid type
774	VGQFIQDVKNSRST	colon or rectum, endometrium, adenocarcinoma, endometrioid type
775	VGQFIQDVKNSRSTD	colon or rectum, endometrium, adenocarcinoma, endometrioid type
776	VVGQFIQDVKNSRS	colon or rectum, endometrium, adenocarcinoma, endometrioid type
777	VVGQFIQDVKNSRST	colon or rectum, endometrium, adenocarcinoma, endometrioid type
778	VVGQFIQDVKNSRSTD	colon or rectum, endometrium, adenocarcinoma, endometrioid type
779	VVGQFIQDVKNSRSTDS	colon or rectum, endometrium, adenocarcinoma, endometrioid type
780	DNGHLYREDQTSPAPG	pancreas, adenocarcinoma, kidney, angiomyolipoma
781	DNGHLYREDQTSPAPGLR	pancreas, adenocarcinoma, kidney, angiomyolipoma
782	EVQVFAPANALPARSE	pancreas, adenocarcinoma, kidney, angiomyolipoma
783	GHLYREDQTSPAPG	pancreas, adenocarcinoma, kidney, angiomyolipoma
784	LPARSEAAAVQPVIG	pancreas, adenocarcinoma, kidney, angiomyolipoma
785	NGHLYREDQTSPAPG	pancreas, adenocarcinoma, kidney, angiomyolipoma
786	NGHLYREDQTSPAPGL	pancreas, adenocarcinoma, kidney, angiomyolipoma
787	NGHLYREDQTSPAPGLR	pancreas, adenocarcinoma, kidney, angiomyolipoma
788	VFAPANALPARSEAA	pancreas, adenocarcinoma, kidney, angiomyolipoma
789	VQVFAPANALPARSE	pancreas, adenocarcinoma, kidney, angiomyolipoma
790	AIVVSDRDGVPVIK	stomach, adenocarcinoma, parathyroid gland, adenoma
791	GLHAIVVSDRDGVPV	stomach, adenocarcinoma, parathyroid gland, adenoma
792	GLHAIVVSDRDGVPVIK	stomach, adenocarcinoma, parathyroid

		gland, adenoma stomach, adenocarcinoma, parathyroid
793	HAIVVSDRDGVPV	gland, adenoma stomach, adenocarcinoma, parathyroid
794	KLPSVEGLHAIVVSDRDG	gland, adenoma stomach, adenocarcinoma, parathyroid
795	LHAIVVSDRDGVPV	gland, adenoma stomach, adenocarcinoma, parathyroid
796	LHAIVVSDRDGVPVI	gland, adenoma stomach, adenocarcinoma, parathyroid
797	LHAIVVSDRDGVPVIK	gland, adenoma stomach, adenocarcinoma, parathyroid
798	LPSVEGLHAIVVSDR	gland, adenoma stomach, adenocarcinoma, parathyroid
799	VPVIKVANDNAPE	gland, adenoma stomach, adenocarcinoma, parathyroid
800	YNTYQVVQFNRLP	gland, adenoma stomach, adenocarcinoma, parathyroid
801	YNTYQVVQFNRLPL	gland, adenoma stomach, adenocarcinoma, parathyroid
802	YNTYQVVQFNRLPLV	gland, adenoma stomach, adenocarcinoma, parathyroid
803	YNTYQVVQFNRLPLVV	gland, adenoma stomach, adenocarcinoma, parathyroid
804	YYNTYQVVQFNRLP	gland, adenoma stomach, adenocarcinoma, parathyroid
805	YYNTYQVVQFNRLPL	gland, adenoma stomach, adenocarcinoma, parathyroid
806	YYNTYQVVQFNRLPLV	gland, adenoma liver, hepatocellular carcinoma, thyroid
807	DKIYFmAGSSRKE	gland, nodular hyperplasia liver, hepatocellular carcinoma, thyroid
808	DVGTDEEEETAKESTAEKD E	gland, nodular hyperplasia liver, hepatocellular carcinoma, thyroid
809	EVTFKSILFVPTSAP	gland, nodular hyperplasia liver, hepatocellular carcinoma, thyroid
810	KSEKFAFQAEVNR	gland, nodular hyperplasia liver, hepatocellular carcinoma, thyroid
811	LPEFDGKRFQNVAK	gland, nodular hyperplasia
812	DGSYRIFSKGASE	colon or rectum, liposarcoma
813	GSYRIFSKGASE	colon or rectum, liposarcoma
814	SDGSYRIFSKGASE	colon or rectum, liposarcoma
815	SVKKMMKDNNLVRH	colon or rectum, liver, hepatocellular carcinoma
816	VKKMMKDNNLVRH	colon or rectum, liver, hepatocellular carcinoma
817	NNmRIFGEAAEKN	stomach, adenocarcinoma, thyroid gland, papillary carcinoma
818	VDKVLERDQKLSE	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid
819	VDKVLERDQKLSELD	lung, non-small cell lung carcinoma, lymph

		node, papillary carcinoma of thyroid
		lung, non-small cell lung carcinoma, lymph
820	VDKVLERDQKLSELDD	node, papillary carcinoma of thyroid
		stomach, adenocarcinoma, lymph node,
821	VDKVLERDQKLSELDDR	papillary carcinoma of thyroid
		lung, non-small cell lung carcinoma, lymph
822	VLERDQKLSELDDR	node, papillary carcinoma of thyroid
		stomach, adenocarcinoma, kidney,
823	ATRSIQVDGKTIKAQ	angiomyolipoma
		stomach, adenocarcinoma, kidney,
824	ATRSIQVDGKTIKAQI	angiomyolipoma
		stomach, adenocarcinoma, kidney,
825	IGVEFATRSIQVDGK	angiomyolipoma
		stomach, adenocarcinoma, kidney,
826	RSIQVDGKTIKA	angiomyolipoma
		stomach, adenocarcinoma, kidney,
827	RSIQVDGKTIKAQ	angiomyolipoma
		stomach, adenocarcinoma, kidney,
828	RSIQVDGKTIKAQI	angiomyolipoma
		stomach, adenocarcinoma, kidney,
829	TRSIQVDGKTIKAQ	angiomyolipoma
		stomach, adenocarcinoma, medullary
830	DIMRVNVDKVLERDQK	carcinoma of thyroid origin
		stomach, adenocarcinoma, medullary
831	DIMRVNVDKVLERDQKL	carcinoma of thyroid origin
		lung, non-small cell lung carcinoma, lymph
832	IMRVNVDKVLERDQK	node, Hodgkin's disease
		lung, non-small cell lung carcinoma, lymph
833	VDKVLERDQKLSE	node, papillary carcinoma of thyroid
		lung, non-small cell lung carcinoma, lymph
834	VDKVLERDQKLSELD	node, papillary carcinoma of thyroid
		lung, non-small cell lung carcinoma, lymph
835	VDKVLERDQKLSELDD	node, papillary carcinoma of thyroid
		stomach, adenocarcinoma, lymph node,
836	VDKVLERDQKLSELDDR	papillary carcinoma of thyroid
		lung, non-small cell lung carcinoma, lymph
837	VLERDQKLSELDDR	node, papillary carcinoma of thyroid
838	ATRSIQVDGKTIKAQ	stomach, adenocarcinoma
		stomach, adenocarcinoma, kidney,
839	ATRSIQVDGKTIKAQI	angiomyolipoma
		stomach, adenocarcinoma, kidney,
840	IGVEFATRSIQVDGK	angiomyolipoma
		stomach, adenocarcinoma, kidney,
841	RSIQVDGKTIKA	angiomyolipoma
		stomach, adenocarcinoma, kidney,
842	RSIQVDGKTIKAQ	angiomyolipoma
		stomach, adenocarcinoma, kidney,
843	RSIQVDGKTIKAQI	angiomyolipoma
		stomach, adenocarcinoma, kidney,
844	TRSIQVDGKTIKAQ	angiomyolipoma
845	GIRVAPVPLYNS	lung, non-small cell lung carcinoma, liver,

		hepatocellular carcinoma
846	GIRVAPVPLYNSFH	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
847	NPNGIRVAPVPLYNSFH	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
848	DDPAIDVCKKLLGKYPN	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
849	DKQPYSKLPGVSLLKP	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
850	DKQPYSKLPGVSLLKPL	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
851	HPRYYISANVTGFK	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
852	SHPRYYISANVTG	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
853	SHPRYYISANVTGFK	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
854	TSHPRYYISANVTG	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
855	TSHPRYYISANVTGFK	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
856	ADIFVDPVLHTA	kidney, renal cell carcinoma
857	ADIFVDPVLHTACA	kidney, renal cell carcinoma
858	DPGADYRIDRALNEA	kidney, renal cell carcinoma
859	IAQDYKVSYSLA	kidney, renal cell carcinoma
860	IAQDYKVSYSLAK	kidney, renal cell carcinoma
861	ISRDWKLDPVLYRK	kidney, renal cell carcinoma
862	LIAQDYKVSYSLA	kidney, renal cell carcinoma
863	RQKLIAQDYKVSYS	kidney, renal cell carcinoma
864	RQKLIAQDYKVSYSL	kidney, renal cell carcinoma
865	RQKLIAQDYKVSYSLA	kidney, renal cell carcinoma
866	RQKLIAQDYKVSYSLAK	kidney, renal cell carcinoma
867	SALDYRLDPQLQLH	kidney, renal cell carcinoma
868	SKADIFVDPVLHTA	kidney, renal cell carcinoma
869	SPSKNYILSVISGSI	kidney, renal cell carcinoma
870	ETTQLTADSHPSYHTDG	stomach, metastatic, skin, squamous cell carcinoma
871	SGESLYHVLGLDKNATSDD	stomach, metastatic, skin, squamous cell carcinoma
872	TTQLTADSHPSYHT	stomach, metastatic, skin, squamous cell carcinoma
873	TTQLTADSHPSYHTD	stomach, metastatic, skin, squamous cell carcinoma
874	TTQLTADSHPSYHTDG	stomach, metastatic, skin, squamous cell carcinoma
875	SVEEFLSEKLERI	pancreas, adenocarcinoma, liver, hepatic adenoma
876	VEEFLSEKLERI	pancreas, adenocarcinoma, liver, hepatic adenoma
877	DLSSSILAQSRERVA	pancreas, adenocarcinoma, bone, giant

		cell tumor of bone
		pancreas, adenocarcinoma, bone, giant
878	EKGVRTLTAAAVSGAQ	cell tumor of bone
		pancreas, adenocarcinoma, bone, giant
879	EKGVRTLTAAAVSGAQP	cell tumor of bone
		pancreas, adenocarcinoma, bone, giant
880	EKGVRTLTAAAVSGAQPI	cell tumor of bone
		pancreas, adenocarcinoma, bone, giant
881	KGVRTLTAAAVSGA	cell tumor of bone
		pancreas, adenocarcinoma, bone, giant
882	KGVRTLTAAAVSGAQ	cell tumor of bone
		pancreas, adenocarcinoma, bone, giant
883	VGPFAPGITEKAPEEKK	cell tumor of bone
		brain, glioblastoma, parotid gland,
884	DPPLIALDKDAPLR	pleomorphic adenoma
		brain, glioblastoma, parotid gland,
885	EIITPDVPFTVDKDG	pleomorphic adenoma
		brain, glioblastoma, parotid gland,
886	IITPDVPFTVDKDG	pleomorphic adenoma
		brain, glioblastoma, parotid gland,
887	PPLIALDKDAPLR	pleomorphic adenoma
		brain, glioblastoma, parotid gland,
888	TNVKKSHKATVHIQ	pleomorphic adenoma
		kidney, clear cell renal cell carcinoma,
889	DDNIKTYSDHPE	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
890	DDNIKTYSDHPEK	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
891	DSAVFFEQGTTRIG	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
892	GDKVYVHLKNLASRPY	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
893	GDKVYVHLKNLASRPYT	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
894	VHLKNLASRPYT	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
895	VYVHLKNLASRPY	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
896	VYVHLKNLASRPYT	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
897	VYVHLKNLASRPYTFH	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
898	YVHLKNLASRPY	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
899	YVHLKNLASRPYT	liver, hepatocellular carcinoma
		kidney, clear cell renal cell carcinoma,
900	YVHLKNLASRPYTFH	liver, hepatocellular carcinoma
901	SNLIKLAQKVPTAD	liver, hepatocellular carcinom
902	YDTRTSALSAKS	liver, hepatocellular carcinoma
903	ALMTDPKLITWSPV	bone, non-ossifying fibroma
904	NDVAWNFEKFLVGPDG	bone, non-ossifying fibroma

905	QSVYAFSARPLAG	bone, non-ossifying fibroma
906	QSVYAFSARPLAGGEPV	bone, non-ossifying fibroma
907	WNFEKFLVGPDG	colon or rectum, bone, non-ossifying fibroma
908	DVGMFVALTKLGQPD	stomach, adenocarcinoma, uterin cervix, squamous cell carcinoma
909	VGMFVALTKLGQPD	stomach, adenocarcinoma, uterin cervix, squamous cell carcinoma
910	AGVFHVEKNGRY	stomach, adenocarcinoma, colon, adenocarcinoma
911	FAGVFHVEKNGRYS	stomach, adenocarcinoma, colon, adenocarcinoma
912	GPITITIVNRDGTR	stomach, adenocarcinoma, colon, adenocarcinoma
913	NGRYSISRTEAADL	stomach, adenocarcinoma, colon, adenocarcinoma
914	RKSRQGSLAMEELK	rectum, adenocarcinoma
915	RRKSRQGSLAMEELK	rectum, adenocarcinoma
916	EEFKKLTSIKIQNDK	brain, glioblastoma, small Intestine, gastrointestinal stromal tumor (GIST)
917	INRRMADDNKLFR	brain, glioblastoma, small Intestine, gastrointestinal stromal tumor (GIST)
918	TATIVMVTNLKERKE	brain, glioblastoma, small Intestine, gastrointestinal stromal tumor (GIST)
919	ELFYKGIRPAINVG	liver, hepatocellular carcinoma, kidney, oncocytoma
920	GQKRSTVAQLVKR	liver, hepatocellular carcinoma, kidney, oncocytoma
921	SDLDAATQQLLSRGV	liver, hepatocellular carcinoma, kidney, oncocytoma
922	FDFSQNTRVPRLPE	kidney, clear cell renal cell carcinoma, non-Hodgkin's lymphoma
923	GDAPAILFDKEF	kidney, clear cell renal cell carcinoma, non-Hodgkin's lymphoma
924	VTHEIDRYTAIAY	kidney, clear cell renal cell carcinoma, non-Hodgkin's lymphoma
929	AAKYQLDPTASISA	kidney, oncocytoma
930	IAAKYQLDPTASISA	kidney, oncocytoma
931	IAAKYQLDPTASISAK	kidney, oncocytoma
932	AGLGRAYALAFAERG	liver, hepatocellular carcinoma, hepatic adenoma
933	DAFGRIDVVVNNAG	liver, hepatocellular carcinoma, hepatic adenoma
934	GLGRAYALAFAER	liver, hepatocellular carcinoma, hepatic adenoma
935	GLGRAYALAFAERG	liver, hepatocellular carcinoma, hepatic adenoma
936	AKFALNGEEFMNFDL	liver, hepatocellular carcinoma, liposarcoma
937	AKFALNGEEFMNFDLK	liver, hepatocellular carcinoma, liposarcoma

938	ALNGEEFMNFDLK	liver, hepatocellular carcinoma, liposarcoma
939	KFALNGEEFMNFDL	liver, hepatocellular carcinoma, liposarcoma
940	SDGSFHASSSLTVK	liver, hepatocellular carcinoma, liposarcoma
941	EERNLLSVAYKNVVGAR	colon or rectum, esophagus, adenocarcinoma
942	ERNLLSVAYKNVVGAR	colon or rectum, esophagus, adenocarcinoma
943	IAELDTLSEESYKD	colon or rectum, Vulva, squamous cell carcinoma
944	IAELDTLSEESYKDS	colon or rectum, Vulva, squamous cell carcinoma
945	ADSYLDEGFLLDKKIG	lung, non-small cell lung carcinoma, ovary, Mullerian mixed tumor
946	DSYLDEGFLLDKK	lung, non-small cell lung carcinoma, ovary, Mullerian mixed tumor
947	DSYLDEGFLLDKKIG	lung, non-small cell lung carcinoma, ovary, Mullerian mixed tumor
948	VDNIIKAAPRKRVPD	lung, non-small cell lung carcinoma, ovary, Mullerian mixed tumor
949	SPPQFRVNGAISN	colon or rectum, ovary, granulosa cell tumor
950	SPPQFRVNGAISNFE	colon or rectum, ovary, granulosa cell tumor
951	SPPQFRVNGAISNFEE	colon or rectum, ovary, granulosa cell tumor
952	SPPQFRVNGAISNFEEF	colon or rectum, ovary, granulosa cell tumor
953	VGKMFVDVYFQEDKK	colon or rectum, ovary, granulosa cell tumor
954	VGKMFVDVYFQEDKKE	colon or rectum, ovary, granulosa cell tumor
955	DPKRTIAQDYGVLKADE	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
956	DPKRTIAQDYGVLKADEG	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
957	PKRTIAQDYGVLKADEG	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
958	GLFIIDDKGILRQ	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
959	GLFIIDDKGILRQIT	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
960	RGLFIIDDKGILR	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
961	RGLFIIDDKGILRQ	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
962	RGLFIIDDKGILRQIT	lung, non-small cell lung carcinoma, thyroid gland, nodular hyperplasia
963	GNTVIHLDQALARMR	brain, glioblastoma, lung, small cell

		carcinoma
964	NTVIHLDQALARMR	brain, glioblastoma, lung, small cell carcinoma
965	NTVIHLDQALARMRE	brain, glioblastoma, lung, small cell carcinoma
966	ENNEIISNIRDSVIN	stomach, adenocarcinoma, kidney, oncocytoma
967	NNEIISNIRDSVIN	stomach, adenocarcinoma, kidney, oncocytoma
968	SPTVQVFSASGKPV	stomach, adenocarcinoma, kidney, oncocytoma
969	SSPTVQVFSASGKPVE	stomach, adenocarcinoma, kidney, oncocytoma
970	AEPNYHSLPSARTDEQ	thyroid gland, follicular adenoma
971	SSILAKTASNIIDVS	thyroid gland, follicular adenoma
973	ADDLEGEAFLPL	stomach, adenocarcinoma, spleen, chronic myeloid leukemia
974	ADDLEGEAFLPLR	stomach, adenocarcinoma, spleen, chronic myeloid leukemia
975	ADDLEGEAFLPLRE	stomach, adenocarcinoma, spleen, chronic myeloid leukemia
976	GADDLEGEAFLPLR	stomach, adenocarcinoma, spleen, chronic myeloid leukemia
977	AGREINLVDAHLKSE	lymph node, Hodgkin's disease
978	AGREINLVDAHLKSEQT	lymph node, Hodgkin's disease
979	GREINLVDAHLKSE	lymph node, Hodgkin's disease
980	KPGIVYASLNHSVIG	lymph node, Hodgkin's disease
981	NKPGIVYASLNHSVIG	lymph node, Hodgkin's disease
982	TTLYVTDVKSASERPS	lymph node, Hodgkin's disease
983	APSTYAHLSPAKTPPP	stomach, adenocarcinoma, pancreas, adenocarcinoma
984	APSTYAHLSPAKTPPPP	stomach, adenocarcinoma, pancreas, adenocarcinoma
985	APSTYAHLSPAKTPPPPA	stomach, adenocarcinoma, pancreas, adenocarcinoma
986	RDDLYDQDDSRDFPR	stomach, adenocarcinoma, pancreas, adenocarcinoma
987	TRPYHSLPSEAVFA	adrenal gland, adrenal cortical adenoma
988	TRPYHSLPSEAVFAN	adrenal gland, adrenal cortical adenoma
989	VAVFTFHNHGRT	adrenal gland, adrenal cortical adenoma
990	VAVFTFHNHGRTA	adrenal gland, adrenal cortical adenoma
991	VAVFTFHNHGRTANL	adrenal gland, adrenal cortical adenoma
992	EDDYIKSWEDNQQGDE	brain, glioblastoma, pleura, malignant mesothelioma
993	ELERIQIQEAAKKKPG	brain, glioblastoma, pleura, malignant mesothelioma
994	ERIQIQEAAKKKP	brain, glioblastoma, pleura, malignant mesothelioma
995	ERIQIQEAAKKKPG	brain, glioblastoma, pleura, malignant mesothelioma

996	ERIQIQEAAKKKPGI	brain, glioblastoma, pleura, malignant mesothelioma
997	LERIQIQEAAKKKPG	brain, glioblastoma, pleura, malignant mesothelioma
998	LSSISQYSGKIK	brain, glioblastoma, pleura, malignant mesothelioma
999	SPAKDSLSFEDF	rectum, adenocarcinoma
1000	SPAKDSLSFEDFLDL	rectum, adenocarcinoma
1001	INSRFPIPSATDPD	brain, glioblastoma, brain, oligodendroglioma
1002	VQHYELLNGQSVFG	brain, glioblastoma, brain, oligodendroglioma
1003	DNQYAVLENQKSSH	colon or rectum, pleura, malignant mesothelioma
1004	GPPEIYSDTQFPS	colon or rectum, pleura, malignant mesothelioma
1005	GPPEIYSDTQFPSLQ	colon or rectum, pleura, malignant mesothelioma
1006	TPQGPPEIYSDTQFPS	colon or rectum, pleura, malignant mesothelioma
1007	TPQGPPEIYSDTQFPSLQ	colon or rectum, pleura, malignant mesothelioma
1008	TPQGPPEIYSDTQFPSLQS T	colon or rectum, pleura, malignant mesothelioma
1009	ANLQRAYSLAKEQR	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical carcinoma
1010	NLQRAYSLAKEQR	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical carcinoma
1011	TPSGITYDRKDIEEH	kidney, clear cell renal cell carcinoma, adrenal gland, adrenal cortical carcinoma
1012	VSTLNSEDFVLVSR	brain, glioblastoma, kidney, angiomyolipoma
1013	VSTLNSEDFVLVSRQ	brain, glioblastoma, kidney, angiomyolipoma
1014	VSTLNSEDFVLVSRQG	brain, glioblastoma, kidney, angiomyolipoma
1015	GSSFFGELFNQNPE	brain, glioblastoma, thyroid gland, papillary carcinoma
1016	SGSSFFGELFNQNPE	brain, glioblastoma, thyroid gland, papillary carcinoma

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 adrenal cortical adenoma; non-ossifying fibroma; brain cancer and a proliferative disease selected from kidney oncocytoma, kidney Wilm's tumor, lymph node malignant melanoma, and omentum leiomyosarcoma; glioblastoma and a proliferative disease selected from oligodendroglioma, kidney angiomyolipoma, liver hepatic adenoma, liver

hepatocellular carcinoma, lung small cell carcinoma, parotid gland pleomorphic adenoma, pleura malignant mesothelioma, schwannoma, small intestine gastrointestinal stromal tumor (GIST), and thyroid gland papillary carcinoma; breast carcinoma; chondrosarcoma; colonal or rectal cancer and a proliferative disease selected from bone giant cell tumor of bone, bone, non-ossifying fibroma, breast mucinous carcinoma, colon adenocarcinoma, colon adenoma, endometrium adenocarcinoma endometrioid type, esophagus adenocarcinoma, kidney angiomyolipoma, kidney renal cell carcinoma, liposarcoma, liver hepatocellular carcinoma, ovary granulosa cell tumor, pancreas microcystic adenoma, pleura malignant mesothelioma, prostate benign nodular hyperplasia, spleen non-Hodgkin's lymphoma, stomach mucinous adenocarcinoma, thymus thymoma, malignant, thyroid gland nodular hyperplasia, urinary bladder, transitional cell carcinoma, and vulva squamous cell carcinoma; colon adenoma; esophagus adenocarcinoma; intestines malignant carcinoid tumor; intramuscular lipoma; kidney clear cell renal cell carcinoma and a proliferative disease selected from adrenal gland, adrenal cortical carcinoma, endometrium adenocarcinoma endometrioid type, endometrium adenocarcinoma endometrioid type, kidney angiomyolipoma leiomyosarcoma, lipoma liver hepatocellular carcinoma, lymph node Hodgkin's disease, non-Hodgkin's lymphoma, pancreas adenocarcinoma, parotid gland pleomorphic adenoma, prostate adenocarcinoma, rectum adenocarcinoma, spleen chronic myeloid leukemia, spleen non-Hodgkin's lymphoma, and thyroid gland follicular adenoma; kidney oncocytoma; kidney polycystic kidney disease; kidney renal cell carcinoma; lipoma; liver hepatocellular carcinoma and a proliferative disease selected from, adrenal gland adrenal cortical adenoma, breast carcinoma, liver focal nodular hyperplasia, cancer rectum adenocarcinoma, cancer thyroid gland, nodular hyperplasia, cancer thyroid gland, papillary carcinoma, colon non-Hodgkin's lymphoma, endometrium hyperplasia, hepatic adenoma, kidney carcinoma, kidney oncocytoma, lipoma, liposarcoma, liver focal nodular hyperplasia, liver hepatic adenoma, pleura malignant mesothelioma, neuroblastoma, pancreas adenocarcinoma, pancreas microcystic adenoma, parotid gland pleomorphic adenoma, pleura malignant mesothelioma, synovial sarcoma, thyroid gland nodular hyperplasia, and uterine cervix squamous cell carcinoma; lung, non-small cell lung carcinoma, and a proliferative disease selected from breast carcinoma, chondrosarcoma, kidney oncocytoma, liver hepatocellular carcinoma, lung adenocarcinoma, lymph node Hodgkin's disease,

lymph node non-Hodgkin's lymphoma, lymph node papillary carcinoma of thyroid, omentum adenocarcinoma, ovary Mullerian mixed tumor, pancreas adenocarcinoma, testis mixed germ cell tumor, thymus thymoma benign, and thyroid gland, nodular hyperplasia; lymph node Hodgkin's disease; lymph node papillary carcinoma of thyroid; lymph node papillary carcinoma of thyroid metastatic; myometrium leiomyoma; non-Hodgkin's lymphoma; non-Hodgkin's lymphoma, peripheral T cell type or small lymphocytic type; pancreas adenocarcinoma and a proliferative disease selected from bone giant cell tumor of bone, colon adenocarcinoma, fibromatosis, intramuscular lipoma, kidney angiomyolipoma, kidney renal cell carcinoma, liver hepatic adenoma, lung adenocarcinoma, myometrium leiomyoma, non-Hodgkin's lymphoma small lymphocytic type, pancreas adenocarcinoma, prostate benign nodular hyperplasia, rectum adenocarcinoma, spleen chronic myeloid leukemia, and thymus, thymoma, malignant; rectum adenocarcinoma; spleen chronic myeloid leukemia; spleen extramedullary hematopoiesis; stomach, adenocarcinoma and a proliferative disease selected from , adrenal gland adrenal cortical adenoma, bone giant cell tumor of bone, bone non-ossifying fibroma, breast carcinoma, colon adenocarcinoma, colon non-Hodgkin's lymphoma, endometrium adenocarcinoma endometrioid, kidney angiomyolipoma, kidney carcinoma, kidney oncocytoma, liver, focal nodular hyperplasia, liver hepatocellular carcinoma, lymph node Hodgkin's disease, lymph node papillary carcinoma of thyroid, medullary carcinoma of thyroid origin, metastatic adenocarcinoma of stomach, neurofibroma, ovary thecoma-fibroma, pancreas adenocarcinoma, pancreas microcystic adenoma, parathyroid gland adenoma, rectum adenocarcinoma, skin squamous cell carcinoma, spleen chronic myeloid leukemia, stomach gastrointestinal stromal tumor (GIST), thyroid gland nodular hyperplasia, thyroid gland papillary carcinoma, uterin cervix squamous cell carcinoma, and white blood cells chronic lymphocytic leukemia; stomach gastrointestinal stromal tumor (GIST); stomach cancer metastatic and a proliferative disease selected from adrenal gland adrenal cortical carcinoma, thyroid gland papillary carcinoma, skin, squamous cell carcinoma, breast carcinoma, colon adenocarcinoma , endometrium Mullerian mixed tumor, kidney carcinoma, leiomyosarcoma, lung neuroendocrine carcinoma (non-small cell type), lymph node non-Hodgkin's lymphoma, non-Hodgkin's lymphoma, ovary Mullerian mixed tumor, pancreas adenocarcinoma, rectum adenocarcinoma, skin basal cell carcinoma, stomach gastrointestinal stromal tumor (GIST), and uterine cervix adenocarcinoma;

testis seminoma; thymus benign thymoma; thyroid gland follicular adenoma; and thyroid gland nodular hyperplasia.

Another preferred aspect of the present invention relates to the use of the peptides according to the present invention for the - preferably combined – preferred immunotherapy of diseases according to the following table 4.

Table 4: Preferred peptides according to the present invention and diseases to be treated

Seq ID	Sequence	Tissue and disease
22	LEVEERTKPV	lung, non-small cell lung carcinoma, breast, carcinoma
23	RDSPINANLRY	lung, non-small cell lung carcinoma, breast, carcinoma
24	RPFVIVTA	lung, non-small cell lung carcinoma, breast, carcinoma
25	RPIINTPMV	lung, non-small cell lung carcinoma, breast, carcinoma
26	SPTSSRTSSL	lung, non-small cell lung carcinoma, breast, carcinoma
27	ATSAPLVSR	stomach, metastatic, lung, neuroendocrine carcinoma
114	YGNPRTNGM	stomach, metastatic, breast, carcinoma
102	FSITKSVEL	non-Hodgkin's lymphoma, small lymphocytic type
103	GQTKNDLVV	non-Hodgkin's lymphoma, small lymphocytic type
104	LSQEVCRD	non-Hodgkin's lymphoma, small lymphocytic type
105	RDIQSPEQI	non-Hodgkin's lymphoma, small lymphocytic type
106	REDNSSNSL	non-Hodgkin's lymphoma, small lymphocytic type
107	TEHQEPGL	non-Hodgkin's lymphoma, small lymphocytic type
108	TKNDLVVSL	non-Hodgkin's lymphoma, small lymphocytic type
977	AGREINLVDAHLKSE	lymph node, Hodgkin's disease
979	GREINLVDAHLKSE	lymph node, Hodgkin's disease
980	KPGIVYASLNHSVIG	lymph node, Hodgkin's disease
220	RIHTGEKPYK	colon or rectum, thyroid gland, nodular hyperplasia
53	APGSVLPRAL	lymph node, Hodgkin's disease
54	DIKEHPLL	lymph node, Hodgkin's disease
55	DSAGPQDAR	lymph node, Hodgkin's disease

56	FQYAKESYI	lymph node, Hodgkin's disease
57	KVLSWPFLM	lymph node, Hodgkin's disease
58	LENDQSLSF	lymph node, Hodgkin's disease
59	SPSRQPQV	lymph node, Hodgkin's disease
60	SRHQSFTTK	lymph node, Hodgkin's disease
61	SSHNASKTL	lymph node, Hodgkin's disease
1003	DNQYAVLENQKSSH	colon or rectum, pleura, malignant mesothelioma,
1004	GPPEIYSDTQFPS	colon or rectum, pleura, malignant mesothelioma,
1005	GPPEIYSDTQFPSLQ	colon or rectum, pleura, malignant mesothelioma,
1006	TPQGPPEIYSDTQFPS	colon or rectum, pleura, malignant mesothelioma,
1007	TPQGPPEIYSDTQFPSLQ	colon or rectum, pleura, malignant mesothelioma,
1008	TPQGPPEIYSDTQFPSLQST	colon or rectum, pleura, malignant mesothelioma,
91	EHADDDPSL	kidney, Wilm's tumor
92	SEESVKSTTL	kidney, Wilm's tumor
93	SPRPPLGSSL	kidney, Wilm's tumor
94	SPWWRSSL	kidney, Wilm's tumor
95	VYTPVDSLVF	kidney, Wilm's tumor
18	DALLKRTM	stomach, metastatic, skin, basal cell carcinoma
19	GEDVRSALL	stomach, metastatic, skin, basal cell carcinoma
20	KFAEEFYSF	stomach, metastatic, skin, basal cell carcinoma
21	YGYDNVKEY	stomach, metastatic, skin, basal cell carcinoma
661	EYVSLYHQPAAM	non-Hodgkin's lymphoma, peripheral T cell type
664	LPYLFQMPAYASSS	non-Hodgkin's lymphoma, peripheral T cell type
665	LPYLFQMPAYASSSK	non-Hodgkin's lymphoma, peripheral T cell type
666	NFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
667	TNFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
668	TTNFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
780	DNGHLYREDQTSPAPG	kidney, angiomyolipoma
781	DNGHLYREDQTSPAPGLR	kidney, angiomyolipoma
782	EVQVFAPANALPARSE	kidney, angiomyolipoma
783	GHLYREDQTSPAPG	kidney, angiomyolipoma
784	LPARSEAAAVQPVIG	kidney, angiomyolipoma
785	NGHLYREDQTSPAPG	kidney, angiomyolipoma
786	NGHLYREDQTSPAPGL	kidney, angiomyolipoma
787	NGHLYREDQTSPAPGLR	kidney, angiomyolipoma
788	VFAPANALPARSEAA	kidney, angiomyolipoma
789	VQVFAPANALPARSE	kidney, angiomyolipoma
178	HEIDRYTAI	non-Hodgkin's lymphoma, follicular type,
179	VFTLKPLEF	non-Hodgkin's lymphoma, follicular type,
180	YWVPRNAL	non-Hodgkin's lymphoma, follicular type,
694	DGELIRTQPQRLPQ	pancreas, adenocarcinoma, intramuscular lipoma
695	GELIRTQPQRLPQ	pancreas, adenocarcinoma, intramuscular lipoma

696	NPSDGELIRTQPQRLP	pancreas, adenocarcinoma, intramuscular lipoma
697	NPSDGELIRTQPQRLPQ	pancreas, adenocarcinoma, intramuscular lipoma
698	NPSDGELIRTQPQRLPQL	pancreas, adenocarcinoma, intramuscular lipoma
922	FDFSQNTRVPRLPE	non-Hodgkin's lymphoma, follicular type
923	GDAPAILFDKEF	non-Hodgkin's lymphoma, follicular type
924	VTHEIDRYTAIAY	non-Hodgkin's lymphoma, follicular type
692	DAGSYKAQINQRNFE	lymph node, non-Hodgkin's lymphoma
693	DAGSYKAQINQRNFEVT	lymph node, non-Hodgkin's lymphoma
1	AEHPNVTLTI	spleen, non-Hodgkin's lymphoma
2	FLAEHPNVTL	spleen, non-Hodgkin's lymphoma
4	EVAEFLARH	spleen, non-Hodgkin's lymphoma
5	RHSNVNLTI	spleen, non-Hodgkin's lymphoma
222	QSTQRSLAL	uterine cervix, squamous cell carcinoma
223	RDLQMNQALRF	uterine cervix, squamous cell carcinoma
224	RELESQLHVL	uterine cervix, squamous cell carcinoma
225	SEAEKLTLV	uterine cervix, squamous cell carcinoma
6	HPDNVKLFL	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
7	ISDTGELKL	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
8	KVNGKLVALK	pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
9	NRLSAQAAL	pancreas, pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
10	TPFTAIREA	pancreas, pancreas, adenocarcinoma, non-Hodgkin's lymphoma, small lymphocytic type
11	FGLARAKSV	kidney, clear cell renal cell carcinoma, kidney, renal cell carcinoma, clear cell type
12	KIADFGLAR	brain, glioblastoma, liver, hepatocellular carcinoma
812	DGSYRIFSKGASE	colon or rectum, liposarcoma
813	GSYRIFSKGASE	colon or rectum, liposarcoma
814	SDGSYRIFSKGASE	colon or rectum, liposarcoma
815	SVKKMMKDNNLVRH	colon or rectum, liver, hepatocellular carcinoma
816	VKKMMKDNNLVRH	colon or rectum, liver, hepatocellular carcinoma
145	KITVPASQK	colon, non-Hodgkin's lymphoma
146	KITVPASQKL	colon, non-Hodgkin's lymphoma
147	VPASQKLRQL	colon, non-Hodgkin's lymphoma
537	ITARPVLW	non-Hodgkin's lymphoma, diffuse large B-cell type
538	KLMSPKLYVW	non-Hodgkin's lymphoma, diffuse large B-cell type
539	KVSAVTLAY	non-Hodgkin's lymphoma, diffuse large B-cell type
540	VEGSGELFRW	non-Hodgkin's lymphoma, diffuse large B-cell type
672	ADLSSFKSQELN	lymph node, papillary carcinoma of thyroid,

		metastatic
673	ADLSSFKSQELNER	lymph node, papillary carcinoma of thyroid, metastatic
674	ADLSSFKSQELNERN	lymph node, papillary carcinoma of thyroid, metastatic
679	ISQELEELRAEQQR	lymph node, papillary carcinoma of thyroid, metastatic
680	ISQELEELRAEQQRLK	lymph node, papillary carcinoma of thyroid, metastatic
681	KGTKQWVHARYA	lymph node, papillary carcinoma of thyroid, metastatic
682	QADLSSFKSQELNER	lymph node, papillary carcinoma of thyroid, metastatic
684	TGSWIGLRNLDLKG	lymph node, papillary carcinoma of thyroid, metastatic
743	AIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
744	ARNFERNKAIKVI	non-Hodgkin's lymphoma, peripheral T cell type
745	ARNFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
746	NFERNKAIKVII	non-Hodgkin's lymphoma, peripheral T cell type
747	NFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
748	VAIVQAVSAHRH	non-Hodgkin's lymphoma, peripheral T cell type
749	VAIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
750	VAIVQAVSAHRHRA	non-Hodgkin's lymphoma, peripheral T cell type
818	VDKVLERDQKLSE	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
819	VDKVLERDQKLSELD	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
820	VDKVLERDQKLSELDD	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
821	VDKVLERDQKLSELDDR	stomach, diffuse subtype adenocarcinoma, lymph node, papillary carcinoma of thyroid, metastatic
822	VLERDQKLSELDDR	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
833	VDKVLERDQKLSE	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
834	VDKVLERDQKLSELD	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, etastatic
835	VDKVLERDQKLSELDD	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
836	VDKVLERDQKLSELDDR	stomach, diffuse subtype adenocarcinoma, lymph node, papillary carcinoma of thyroid, metastatic
837	VLERDQKLSELDDR	lung, non-small cell lung carcinoma, lymph node, papillary carcinoma of thyroid, metastatic
848	DDPAIDVCKKLLGKYPN	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
849	DKQPYSKLPGVSLLKP	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
850	DKQPYSKLPGVSLLKPL	kidney, clear cell renal cell carcinoma, pancreas,

		adenocarcinoma
851	HPRYYISANVTGFK	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
852	SHPRYYISANVTG	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
853	SHPRYYISANVTGFK	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
854	TSHPRYYISANVTG	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
855	TSHPRYYISANVTGFK	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
908	DVGMFVALTKLGQPD	stomach, differentiated subtype adenocarcinoma, uterine cervix, squamous cell carcinoma,
909	VGMFVALTKLGQPD	stomach, differentiated subtype adenocarcinoma, uterine cervix, squamous cell carcinoma
1015	GSSFFGELFNQNPE	brain, glioblastoma, thyroid gland, papillary carcinoma
1016	SGSSFFGELFNQNPE	brain, glioblastoma, thyroid gland, papillary carcinoma
466	DEMRFVTQI	testis, mixed germ cell tumor
467	ETVHFATTQW	testis, mixed germ cell tumor
468	LPPPATQI	testis, mixed germ cell tumor
633	GNPAYRSFSNSLSQ	kidney, angiomyolipoma
634	GPPGEAGYKAFSSLLA	kidney, angiomyolipoma
635	GPPGEAGYKAFSSLLASS	kidney, angiomyolipoma
636	GPPGEAGYKAFSSLLASSA	kidney, angiomyolipoma
637	GPPGEAGYKAFSSLLASSAVSPE	kidney, angiomyolipoma
638	GPPGEAGYKAFSSLLASSAVSPEK	kidney, angiomyolipoma
639	GYKAFSSLLASSAVSP	kidney, angiomyolipoma
640	GYKAFSSLLASSAVSPE	kidney, angiomyolipoma
641	KAFSSLLASSAVSPE	kidney, angiomyolipoma
642	NPAYRSFSNSLSQ	kidney, angiomyolipoma
643	SRDDFQEGREGIVAR	kidney, angiomyolipoma
644	SSSSFHPAPGNAQ	kidney, angiomyolipoma
645	VARLTESLFLDL	kidney, angiomyolipoma
646	VARLTESLFLDLLG	kidney, angiomyolipoma
647	VIAGNPAYRSFSN	kidney, angiomyolipoma
648	VPQPEPETWEQILRRNVLQ	kidney, angiomyolipoma
649	YKAFSSLLASSAVS	kidney, angiomyolipoma
650	YKAFSSLLASSAVSP	kidney, angiomyolipoma
651	YKAFSSLLASSAVSPE	kidney, angiomyolipoma
992	EDDYIKSWEDNQQGDE	pleura, malignant mesothelioma
993	ELERIQIQEAAKKKPG	pleura, malignant mesothelioma
994	ERIQIQEAAKKKP	pleura, malignant mesothelioma
995	ERIQIQEAAKKKPG	pleura, malignant mesothelioma
996	ERIQIQEAAKKKPGI	pleura, malignant mesothelioma

997	LERIQIQEAAKKKPG	pleura, malignant mesothelioma
998	LSSISQYSGKIK	pleura, malignant mesothelioma
941	EERNLLSVAYKNVVGAR	colon or rectum, esophagus, adenocarcinoma,
942	ERNLLSVAYKNVVGAR	colon or rectum, esophagus, adenocarcinoma,
943	IAELDTLSEESYKD	colon or rectum, vulva, squamous cell carcinoma,
944	IAELDTLSEESYKDS	colon or rectum, vulva, squamous cell carcinoma,
218	GDYGRAFNL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma, small lymphocytic type
219	TRHKIVHTK	stomach, metastatic, lymph node, non-Hodgkin's lymphoma, small lymphocytic type
221	KAFNWFSTL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma, small lymphocytic type
541	RPKSNIVL	non-Hodgkin's lymphoma, diffuse large B-cell type
542	RPKSNIVLL	non-Hodgkin's lymphoma, diffuse large B-cell type
1001	INSRFPIPSATDPD	brain, glioblastoma, brain, oligodendroglioma,
1002	VQHYELLNGQSVFG	brain, glioblastoma, brain, oligodendroglioma,
910	AGVFHVEKNGRY	stomach, diffuse subtype adenocarcinoma, colon, adenocarcinoma
911	FAGVFHVEKNGRYS	stomach, diffuse subtype adenocarcinoma, colon, adenocarcinoma
912	GPITITIVNRDGTR	stomach, diffuse subtype adenocarcinoma, colon, adenocarcinoma
913	NGRYSISRTEAADL	stomach, diffuse subtype adenocarcinoma, colon, adenocarcinoma
45	DELPKFHQY	stomach, adenocarcinoma, white blood cells, chronic lymphocytic leukemia
46	DVTGQFPSSF	white blood cells, chronic lymphocytic leukemia
47	EHSRVLQQL	white blood cells, chronic lymphocytic leukemia
48	IKVSKQLL	white blood cells, chronic lymphocytic leukemia
49	KPRQSSPQL	white blood cells, chronic lymphocytic leukemia
50	KQLLAALEI	white blood cells, chronic lymphocytic leukemia
51	RRKDLVLKY	liver, focalnodular hyperplasia
52	RTRDYASLPPK	white blood cells, chronic lymphocytic leukemia
124	GQKEALLKY	liver, hepatocellular carcinoma, synovial sarcoma
125	KPSEERKTI	liver, hepatocellular carcinoma, synovial sarcoma
126	KQTPKVLVV	liver, hepatocellular carcinoma, synovial sarcoma
127	SVIQHVQSF	liver, hepatocellular carcinoma, synovial sarcoma
128	TPIERIPYL	liver, hepatocellular carcinoma, synovial sarcoma
773	LPEFYKTVSPAL	colon or rectum, endometrium, adenocarcinoma, endometrioid type

774	VGQFIQDVKNSRST	colon or rectum, endometrium, adenocarcinoma, endometrioid type
775	VGQFIQDVKNSRSTD	colon or rectum, endometrium, adenocarcinoma, endometrioid type
776	VVGQFIQDVKNSRS	colon or rectum, endometrium, adenocarcinoma, endometrioid type
777	VVGQFIQDVKNSRST	colon or rectum, endometrium, adenocarcinoma, endometrioid type
778	VVGQFIQDVKNSRSTD	colon or rectum, endometrium, adenocarcinoma, endometrioid type
779	VVGQFIQDVKNSRSTDS	colon or rectum, endometrium, adenocarcinoma, endometrioid type
685	FGNYNNQSSNFGPMKGGN FGGRS	pancreas, adenocarcinoma, thymus, thymoma, malignant
686	FGPMKGGNFGGRSSGPYG GGGQY	pancreas, adenocarcinoma, thymus, thymoma, malignant
687	GPMKGGNFGGRSSGP	pancreas, adenocarcinoma, thymus, thymoma, malignant
688	GPYGGGGQYFAKP	pancreas, adenocarcinoma, thymus, thymoma, malignant
689	KGGNFGGRSSGP	pancreas, adenocarcinoma, thymus, thymoma, malignant
690	NDFGNYNNQSSNFGP	pancreas, adenocarcinoma, thymus, thymoma, malignant
691	SGPYGGGGQYFAKP	pancreas, adenocarcinoma, thymus, thymoma, malignant
13	AAANIIRTL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma
14	GRFKNLREAL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma,
15	MSPFSKATL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma,
16	QEDPGDNQITL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma,
17	SPFSKATL	liver, hepatocellular carcinoma, adrenal gland, adrenal cortical carcinoma,
129	AEVEKNETV	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
130	EVKEEIPLV	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
131	KPTSARSGL	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
132	KYIETTPLTI	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
133	SEIKTSIEV	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
134	SVKPTSATK	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
135	YPNKGVGQA	kidney, clear cell renal cell carcinoma, spleen, non-Hodgkin's lymphoma, follicular type
966	ENNEIISNIRDSVIN	stomach, adenocarcinoma, kidney, oncocytoma

967	NNEIISNIRDSVIN	stomach, adenocarcinoma, kidney, oncocytoma
968	SPTVQVFSASGKPV	stomach, adenocarcinoma, kidney, oncocytoma
969	SSPTVQVFSASGKPVE	stomach, adenocarcinoma, kidney, oncocytoma
830	DIMRVNVDKVLERDQK	stomach, diffuse subtype adenocarcinoma, Medullary carcinoma of thyroid Origin
831	DIMRVNVDKVLERDQKL	stomach, diffuse subtype adenocarcinoma, medullary carcinoma
832	IMRVNVDKVLERDQK	lung, non-small cell lung carcinoma, lymph node, Hodgkin's disease
752	EEVITLIRSNQQLE	pancreas, adenocarcinoma
753	EEVITLIRSNQQLEN	pancreas, adenocarcinoma
754	IPADTFAALKNPNAML	pancreas, adenocarcinoma
755	LKQLLSDKQQKRQSG	pancreas, adenocarcinoma
756	LKQLLSDKQQKRQSGQ	pancreas, adenocarcinoma
118	DEHLLIQHY	parotid gland, pleomorphic adenoma
119	KQVASSTGF	parotid gland, pleomorphic adenoma
120	RDFGPASQHFL	parotid gland, pleomorphic adenoma
121	RQLGEVASF	parotid gland, pleomorphic adenoma
122	TEAETTANVL	parotid gland, pleomorphic adenoma
123	GYLPVQTVL	kidney, clear cell renal cell carcinoma, parotid gland, pleomorphic adenoma
987	TRPYHSLPSEAVFA	adrenal gland, adrenal cortical adenoma
988	TRPYHSLPSEAVFAN	adrenal gland, adrenal cortical adenoma
989	VAVFTFHNHGRT	adrenal gland, adrenal cortical adenoma
990	VAVFTFHNHGRTA	adrenal gland, adrenal cortical adenoma
991	VAVFTFHNHGRTANL	adrenal gland, adrenal cortical adenoma
339	FLDPDIGGVAV	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
340	HTAPPENKTW	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
341	LLDTPVKTQY	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
342	NAVKDFTSF	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
343	SGLLQIKKL	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
344	YHDKNIVLL	kidney, clear cell renal cell carcinoma, pancreas, adenocarcinoma
71	HLKSIPVSL	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
72	KVWYNVENW	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
73	LPAYRAQLL	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
74	LSEQTSVPL	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
75	SLNQWLVSF	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
76	SMTSLAQKI	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma

77	SSSGLHPPK	kidney, clear cell renal cell carcinoma, prostate, adenocarcinoma
578	GGGYGSGGGSGGYGSRRF	colon or rectum, thymus, thymoma, malignant,
579	GGSFGGRSSGSP	colon or rectum, thymus, thymoma, malignant
580	KGGSFGGRSSGSP	colon or rectum, thymus, thymoma, malignant
581	SGQQQSNYGPMKGGSFGG RSSGSPY	colon or rectum, thymus, thymoma, malignant
582	SGSPYGGGYGSGGGSGGY GSRRF	colon or rectum, thymus, thymoma, malignant
583	SPYGGGYGSGGGSGGYGS RRF	colon or rectum, thymus, thymoma, malignant
584	YGGGYGSGGGSGGYGSRR F	colon or rectum, thymus, thymoma, malignant
84	VPVPHTTAL	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
85	YQVLDVQRY	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
731	DGLNSLTYQVLDVQRYPL	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
732	HPVLQRQQLDYGIY	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
733	LNSLTYQVLDVQR	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
734	LNSLTYQVLDVQRYP	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
735	LNSLTYQVLDVQRYPL	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
736	LPQLVGVSTPLQG	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
737	LPQLVGVSTPLQGG	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
738	LPQLVGVSTPLQGGS	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
739	RLPQLVGVSTPLQGGS	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
740	SPHKVAIIIPFRNR	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
741	SPHKVAIIIPFRNRQE	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid

		type
742	SPHKVAIIIPFRNRQEH	kidney, clear cell renal cell carcinoma, endometrium, adenocarcinoma, endometrioid type
527	DEKQQHIVY	liver, hepatocellular carcinoma, synovial sarcoma
528	DEVYQVTVY	liver, hepatocellular carcinoma, synovial sarcoma
529	GEISEKAKL	liver, hepatocellular carcinoma, synovial sarcoma
530	YTMKEVLFY	liver, hepatocellular carcinoma, synovial sarcoma
203	GPRPITQSEL	lymph node, non-Hodgkin's lymphoma, marginal zone B-cell type
204	KPEPVDKVA	lymph node, non-Hodgkin's lymphoma
205	TPSSRPASL	lymph node, non-Hodgkin's lymphoma
949	SPPQFRVNGAISN	ovary, granulosa cell tumor
950	SPPQFRVNGAISNFE	ovary, granulosa cell tumor
951	SPPQFRVNGAISNFEE	ovary, granulosa cell tumor
952	SPPQFRVNGAISNFEEF	ovary, granulosa cell tumor
953	VGKMFVDVYFQEDKK	ovary, granulosa cell tumor
954	VGKmFVDVYFQEDKKE	ovary, granulosa cell tumor
916	EEFKKLTSIKIQNDK	brain, glioblastoma, small intestine, gastrointestinal stromal tumor (GIST)
917	INRRMADDNKLFR	brain, glioblastoma, small intestine, gastrointestinal stromal tumor (GIST)
918	TATIVMVTNLKERKE	brain, glioblastoma, small intestine, gastrointestinal stromal tumor (GIST)
526	RINEFSISSF	chondrosarcoma
585	GNRINEFSISSF	chondrosarcoma
586	HGNQITSDKVGRKV	chondrosarcoma
587	IPPVNTNLENLYLQ	chondrosarcoma
588	LQVLRLDGNEIKR	chondrosarcoma
589	LQVLRLDGNEIKRS	chondrosarcoma
590	LQVLRLDGNEIKRSA	chondrosarcoma
592	LYVRLSHNSLTNNG	chondrosarcoma
596	WIALHGNQITSD	chondrosarcoma
597	WIALHGNQITSDK	chondrosarcoma
165	ELNKLLEEI	ovary, adenocarcinoma
166	IPFSNPRVL	ovary, adenocarcinoma
167	LLDEGAKLLY	ovary, adenocarcinoma
168	SPADAHRNL	ovary, adenocarcinoma
96	APLQRSQSL	kidney, renal cell carcinoma, clear cell type
97	DEVHQDTY	kidney, renal cell carcinoma, clear cell type
98	LPHSATVTL	kidney, renal cell carcinoma, clear cell type
152	APSEYRYTL	stomach, mucinous adenocarcinoma
153	APSEYRYTLL	stomach, mucinous adenocarcinoma
154	EIFQNEVAR	stomach, mucinous adenocarcinoma
155	KDVLIPGKL	stomach, mucinous adenocarcinoma
156	VPLVREITF	stomach, mucinous adenocarcinoma

62	EEIDTTMRW	liver, hepatocellular carcinoma, lipoma
63	ILDEKPVII	liver, hepatocellular carcinoma, lipoma
64	LPQEPRTSL	liver, hepatocellular carcinoma, lipoma
65	LTYKLPVA	liver, hepatocellular carcinoma, lipoma
66	NEMELAHSSF	liver, hepatocellular carcinoma, lipoma
67	REFPEANFEL	liver, hepatocellular carcinoma, lipoma
68	THHIPDAKL	liver, hepatocellular carcinoma, lipoma
69	TVKENLSLF	liver, hepatocellular carcinoma, lipoma
70	VLLKKAVL	liver, hepatocellular carcinoma, lipoma
136	ISMKILNSL	lung, non-small cell lung carcinoma, thymus, thymoma
137	KTIAFLLPMF	lung, non-small cell lung carcinoma, thymus, thymoma
138	RDSIINDF	lung, non-small cell lung carcinoma, thymus, thymoma
139	SVKGGGGNEK	lung, non-small cell lung carcinoma, thymus, thymoma
140	GIAKTGSGK	lung, non-small cell lung carcinoma, thymus, thymoma
503	ALYATKTLR	pancreas, microcystic adenoma
504	MEYVISRI	pancreas, microcystic adenoma
505	VPVGRQPII	pancreas, microcystic adenoma
278	ATNGDLASR	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
279	GLHAEVTGVGY	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
280	HVSSTSSSF	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
281	LQADLQNGL	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
282	SELPVSEVA	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
283	SQTKSVFEI	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
284	THIFTSDGL	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
285	VIYFPPLQK	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
286	YPFSSEQKW	pancreas, adenocarcinoma, prostate, benign nodular hyperplasia
78	DLDVKKMPL	kidney, carcinoma
79	FYTVIPHNF	kidney, carcinoma
80	HHINTDNPSL	kidney, carcinoma
81	RVGEVGQSK	kidney, carcinoma
28	AELRSTASLL	lipoma
29	APASSHERASM	lipoma
30	ASRQAPPHI	lipoma
31	AVKKNPGIAA	lipoma
32	EEHLESHKKY	lipoma
33	GEFTSARAV	lipoma

34	GQSTPRLFSI	lipoma
35	LVDDPLEY	lipoma
36	RPKNLMQTL	lipoma
37	RQAPPHIEL	lipoma
38	SEAAELRSTA	lipoma
490	DSIGSTVSSER	stomach, adenocarcinoma, signet ring cell type,
491	LPYNNKDRDAL	stomach, adenocarcinoma, signet ring cell type,
215	DAMKRVEEI	ovary, thecoma-fibroma
216	DIKEVKQNI	ovary, thecoma-fibroma
217	GPIYPGHGM	ovary, thecoma-fibroma
963	GNTVIHLDQALARMR	lung, small cell carcinoma
964	NTVIHLDQALARMR	lung, small cell carcinoma
965	NTVIHLDQALARMRE	lung, small cell carcinoma
187	AADTERLAL	chondrosarcoma
188	DMKAKVASL	chondrosarcoma
189	HVLEEVQQV	chondrosarcoma
190	KEAADTERL	chondrosarcoma
191	RISEVLQKL	chondrosarcoma
192	TEVRELVSL	chondrosarcoma
875	SVEEFLSEKLERI	liver, hepatic adenoma
876	VEEFLSEKLERI	liver, hepatic adenoma
973	ADDLEGEAFLPL	spleen, chronic myeloid leukemia
974	ADDLEGEAFLPLR	spleen, chronic myeloid leukemia
975	ADDLEGEAFLPLRE	spleen, chronic myeloid leukemia
976	GADDLEGEAFLPLR	spleen, chronic myeloid leukemia
141	AETTDNVFTL	kidney, clear cell renal cell carcinoma, thyroid gland, follicular adenoma
142	SEYQRFAVM	kidney, clear cell renal cell carcinoma, thyroid gland, follicular adenoma
143	TFGERVVAF	kidney, clear cell renal cell carcinoma, thyroid gland, follicular adenoma
144	NENLVERF	stomach, colon, adenocarcinoma, mucinous type
117	QLFSYAILGF	liver, hepatocellular carcinoma, colon, non-Hodgkin's lymphoma
845	GIRVAPVPLYNS	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
846	GIRVAPVPLYNSFH	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
847	NPNGIRVAPVPLYNSFH	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
478	AAVPVIISR	lymph node, papillary carcinoma of thyroid, metastatic
479	EEIGKVAAA	lymph node, papillary carcinoma of thyroid, metastatic
480	FLKDLVASV	lymph node, papillary carcinoma of thyroid, metastatic
481	VIISRALEL	lymph node, papillary carcinoma of thyroid, metastatic
420	QIDYKTLVL	stomach, metastatic, leiomyosarcoma
421	VEDPTIVRI	stomach, metastatic, leiomyosarcoma

543	GEPLSYTRFSLARQ	lung, non-small cell lung carcinoma, lung, adenocarcinoma
544	GEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
545	GEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
546	GGEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
547	GGEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
548	NPGGYVAYSKAATVTG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
549	NPGGYVAYSKAATVTGK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
550	NPGGYVAYSKAATVTGKL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
551	NSVIIVDKNGRL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
552	NSVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
553	NSVIIVDKNGRLVY	lung, non-small cell lung carcinoma, lung, adenocarcinoma
554	RVEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
555	RVEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
556	RVEYHFLSPYVSPKESPF	lung, non-small cell lung carcinoma, lung, adenocarcinoma
557	SPFRHVFWGSGSHTL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
558	SVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
559	VEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
560	VEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
388	AEGPAGGFMVV	spleen, chronic myeloid leukemia
389	AYYRDAEAY	spleen, chronic myeloid leukemia
390	QVNRPLTMR	spleen, chronic myeloid leukemia
391	RHSPVFQVY	spleen, chronic myeloid leukemia
392	SLPVPNSAY	spleen, chronic myeloid leukemia
393	TLGPPGTAHLY	spleen, chronic myeloid leukemia
308	VLYVGSKTK	schwannoma
309	KTKEQVTNV	schwannoma
310	MPVDPDNEAY	schwannoma
311	AEKTKQGVA	schwannoma
446	EAFEFVKQR	stomach, adenocarcinoma, breast, carcinoma
447	NHFEGHYQY	stomach, adenocarcinoma, breast, carcinoma

Another more preferred aspect of the present invention relates to the use of the peptides according to the present invention for the - preferably combined – more preferred immunotherapy of diseases according to the following table 5.

Table 5: More preferred peptides according to the present invention and diseases to be treated

Seq ID	Sequence	Tissue and disease
22	LEVEERTKPV	breast, carcinoma
23	RDSPINANLRY	breast, carcinoma
24	RPFVIVTA	breast, carcinoma
25	RPIINTPMV	breast, carcinoma
26	SPTSSRTSSL	breast, carcinoma
27	ATSAPLVSR	lung, neuroendocrine carcinoma
114	YGNPRTNGM	breast, carcinoma
102	FSITKSVEL	non-Hodgkin's lymphoma, small lymphocytic type
103	GQTKNDLVV	non-Hodgkin's lymphoma, small lymphocytic type
104	LSQEVCRD	non-Hodgkin's lymphoma, small lymphocytic type
105	RDIQSPEQI	non-Hodgkin's lymphoma, small lymphocytic type
106	REDNSSNSL	non-Hodgkin's lymphoma, small lymphocytic type
107	TEHQEPGL	non-Hodgkin's lymphoma, small lymphocytic type
108	TKNDLVVSL	non-Hodgkin's lymphoma, small lymphocytic type
977	AGREINLVDAHLKSE	lymph node, Hodgkin's disease
978	AGREINLVDAHLKSEQT	lymph node, Hodgkin's disease
979	GREINLVDAHLKSE	lymph node, Hodgkin's disease
980	KPGIVYASLNHSVIG	lymph node, Hodgkin's disease
981	NKPGIVYASLNHSVIG	lymph node, Hodgkin's disease
982	TTLYVTDVKSASERPS	lymph node, Hodgkin's disease
220	RIHTGEKPYK	thyroid gland, nodular hyperplasia
53	APGSVLPRAL	lymph node, Hodgkin's disease
54	DIKEHPLL	lymph node, Hodgkin's disease
55	DSAGPQDAR	lymph node, Hodgkin's disease
56	FQYAKESYI	lymph node, Hodgkin's disease
57	KVLSWPFLM	lymph node, Hodgkin's disease
58	LENDQSLSF	lymph node, Hodgkin's disease
59	SPSRQPQV	lymph node, Hodgkin's disease
60	SRHQSFTTK	lymph node, Hodgkin's disease
61	SSHNASKTL	lymph node, Hodgkin's disease
1003	DNQYAVLENQKSSH	pleura, malignant mesothelioma
1004	GPPEIYSDTQFPS	pleura, malignant mesothelioma
1005	GPPEIYSDTQFPSLQ	pleura, malignant mesothelioma
1006	TPQGPPEIYSDTQFPS	pleura, malignant mesothelioma
1007	TPQGPPEIYSDTQFPSLQ	pleura, malignant mesothelioma
1008	TPQGPPEIYSDTQFPSLQST	pleura, malignant mesothelioma
91	EHADDDPSL	kidney, Wilm's tumor

92	SEESVKSTTL	kidney, Wilm's tumor
93	SPRPPLGSSL	kidney, Wilm's tumor
94	SPWWRSSL	kidney, Wilm's tumor
95	VYTPVDSLVF	kidney, Wilm's tumor
18	DALLKRTM	skin, basal cell carcinoma
19	GEDVRSALL	skin, basal cell carcinoma
20	KFAEEFYSF	skin, basal cell carcinoma
21	YGYDNVKEY	skin, basal cell carcinoma
661	EYVSLYHQPAAM	non-Hodgkin's lymphoma, peripheral T cell type,
662	IKAEYKGRVTLKQYPR	non-Hodgkin's lymphoma, peripheral T cell type
663	LNVHSEYEPSWEEQP	non-Hodgkin's lymphoma, peripheral T cell type
664	LPYLFQmPAYASSS	non-Hodgkin's lymphoma, peripheral T cell type
665	LPYLFQmPAYASSSK	non-Hodgkin's lymphoma, peripheral T cell type
666	NFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
667	TNFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
668	TTNFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
669	VTLNVHSEYEPSWEEQP	non-Hodgkin's lymphoma, peripheral T cell type
670	YPRKNLFLVEVTQLTESDS	non-Hodgkin's lymphoma, peripheral T cell type
671	YPRKNLFLVEVTQLTESDS G	non-Hodgkin's lymphoma, peripheral T cell type
780	DNGHLYREDQTSPAPG	kidney, angiomyolipoma
781	DNGHLYREDQTSPAPGLR	kidney, angiomyolipoma
782	EVQVFAPANALPARSE	kidney, angiomyolipoma
783	GHLYREDQTSPAPG	kidney, angiomyolipoma
784	LPARSEAAAVQPVIG	kidney, angiomyolipoma
785	NGHLYREDQTSPAPG	kidney, angiomyolipoma
786	NGHLYREDQTSPAPGL	kidney, angiomyolipoma
787	NGHLYREDQTSPAPGLR	kidney, angiomyolipoma
788	VFAPANALPARSEAA	kidney, angiomyolipoma
789	VQVFAPANALPARSE	kidney, angiomyolipoma
178	HEIDRYTAI	non-Hodgkin's lymphoma
179	VFTLKPLEF	non-Hodgkin's lymphoma
180	YWVPRNAL	non-Hodgkin's lymphoma
694	DGELIRTQPQRLPQ	intramuscular lipoma
695	GELIRTQPQRLPQ	intramuscular lipoma
696	NPSDGELIRTQPQRLP	intramuscular lipoma
697	NPSDGELIRTQPQRLPQ	intramuscular lipoma
698	NPSDGELIRTQPQRLPQL	intramuscular lipoma
922	FDFSQNTRVPRLPE	non-Hodgkin's lymphoma
923	GDAPAILFDKEF	non-Hodgkin's lymphoma
924	VTHEIDRYTAIAY	non-Hodgkin's lymphoma
692	DAGSYKAQINQRNFE	lymph node, non-Hodgkin's lymphoma
693	DAGSYKAQINQRNFEVT	lymph node, non-Hodgkin's lymphoma
1	AEHPNVTLTI	spleen, non-Hodgkin's lymphoma
2	FLAEHPNVTL	spleen, non-Hodgkin's lymphoma
4	EVAEFLARH	spleen, non-Hodgkin's lymphoma
5	RHSNVNLTI	spleen, non-Hodgkin's lymphoma
222	QSTQRSLAL	uterine cervix, squamous cell carcinoma
223	RDLQMNQALRF	uterine cervix, squamous cell carcinoma

224 RELESQLHVL	uterine cervix, squamous cell carcinoma
225 SEAEKLTLV	uterine cervix, squamous cell carcinoma
6 HPDNVKLFL	non-Hodgkin's lymphoma, small lymphocytic type
7 ISDTGELKL	non-Hodgkin's lymphoma, small lymphocytic type
8 KVNGKLVALK	non-Hodgkin's lymphoma, small lymphocytic type
9 NRLSAQAAL	non-Hodgkin's lymphoma, small lymphocytic type
10 TPFTAIREA	non-Hodgkin's lymphoma, small lymphocytic type
11 FGLARAKSV	kidney, renal cell carcinoma, clear cell type
12 KIADFGLAR	liver, hepatocellular carcinoma
812 DGSYRIFSKGASE	liposarcoma
813 GSYRIFSKGASE	liposarcoma
814 SDGSYRIFSKGASE	liposarcoma
815 SVKKMMKDNNLVRH	liver, hepatocellular carcinoma
816 VKKMMKDNNLVRH	liver, hepatocellular carcinoma
145 KITVPASQK	colon, non-Hodgkin's lymphoma
146 KITVPASQKL	colon, non-Hodgkin's lymphoma
147 VPASQKLRQL	colon, non-Hodgkin's lymphoma
537 ITARPVLW	non-Hodgkin's lymphoma, diffuse large B-cell type
538 KLMSPKLYVW	non-Hodgkin's lymphoma, diffuse large B-cell type
539 KVSAVTLAY	non-Hodgkin's lymphoma, diffuse large B-cell type
540 VEGSGELFRW	non-Hodgkin's lymphoma, diffuse large B-cell type
672 ADLSSFKSQELN	lymph node, papillary carcinoma of thyroid, metastatic
673 ADLSSFKSQELNER	lymph node, papillary carcinoma of thyroid, metastatic
674 ADLSSFKSQELNERN	lymph node, papillary carcinoma of thyroid, metastatic
675 ADLSSFKSQELNERNE	lymph node, papillary carcinoma of thyroid, metastatic
676 ADLSSFKSQELNERNEA	lymph node, papillary carcinoma of thyroid, metastatic
677 AEQQRLKSQDLELSWNLNG	lymph node, papillary carcinoma of thyroid, metastatic
678 EQQRLKSQDLELSWN	lymph node, papillary carcinoma of thyroid, metastatic
679 ISQELEELRAEQQR	lymph node, papillary carcinoma of thyroid, metastatic
680 ISQELEELRAEQQRLK	lymph node, papillary carcinoma of thyroid, metastatic
681 KGTKQWVHARYA	lymph node, papillary carcinoma of thyroid, metastatic
682 QADLSSFKSQELNER	lymph node, papillary carcinoma of thyroid, metastatic
683 SWNLNGLQADLSSFK	lymph node, papillary carcinoma of thyroid, metastatic
684 TGSWIGLRNLDLKG	lymph node, papillary carcinoma of thyroid, metastatic
743 AIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
744 ARNFERNKAIKVI	non-Hodgkin's lymphoma, peripheral T cell type
745 ARNFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type

746	NFERNKAIKVII	non-Hodgkin's lymphoma, peripheral T cell type
747	NFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
748	VAIVQAVSAHRH	non-Hodgkin's lymphoma, peripheral T cell type
749	VAIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
750	VAIVQAVSAHRHRA	non-Hodgkin's lymphoma, peripheral T cell type
751	VAIVQAVSAHRHRAR	non-Hodgkin's lymphoma, peripheral T cell type
818	VDKVLERDQKLSE	lymph node, papillary carcinoma of thyroid, metastatic
819	VDKVLERDQKLSELD	lymph node, papillary carcinoma of thyroid, metastatic
820	VDKVLERDQKLSELDD	lymph node, papillary carcinoma of thyroid, metastatic
821	VDKVLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
822	VLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
833	VDKVLERDQKLSE	lymph node, papillary carcinoma of thyroid, metastatic
834	VDKVLERDQKLSELD	lymph node, papillary carcinoma of thyroid, metastatic
835	VDKVLERDQKLSELDD	lymph node, papillary carcinoma of thyroid, metastatic
836	VDKVLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
837	VLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
848	DDPAIDVCKKLLGKYPN	pancreas, adenocarcinoma
849	DKQPYSKLPGVSLLKP	pancreas, adenocarcinoma
850	DKQPYSKLPGVSLLKPL	pancreas, adenocarcinoma
851	HPRYYISANVTGFK	pancreas, adenocarcinoma
852	SHPRYYISANVTG	pancreas, adenocarcinoma
853	SHPRYYISANVTGFK	pancreas, adenocarcinoma
854	TSHPRYYISANVTG	pancreas, adenocarcinoma
855	TSHPRYYISANVTGFK	pancreas, adenocarcinoma
908	DVGMFVALTKLGQPD	uterine cervix, squamous cell carcinoma
909	VGmFVALTKLGQPD	uterine cervix, squamous cell carcinoma
1015	GSSFFGELFNQNPE	thyroid gland, papillary carcinoma
1016	SGSSFFGELFNQNPE	thyroid gland, papillary carcinoma
466	DEMRFVTQI	testis, mixed germ cell tumor
467	ETVHFATTQW	testis, mixed germ cell tumor
468	LPPPATQI	testis, mixed germ cell tumor
633	GNPAYRSFSNSLSQ	kidney, angiomyolipoma
634	GPPGEAGYKAFSSLLA	kidney, angiomyolipoma
635	GPPGEAGYKAFSSLLASS	kidney, angiomyolipoma
636	GPPGEAGYKAFSSLLASSA	kidney, angiomyolipoma
637	GPPGEAGYKAFSSLLASSAVSPE	kidney, angiomyolipoma
639	GYKAFSSLLASSAVSP	kidney, angiomyolipoma
640	GYKAFSSLLASSAVSPE	kidney, angiomyolipoma

641	KAFSSLLASSAVSPE	kidney, angiomyolipoma
642	NPAYRSFSNSLSQ	kidney, angiomyolipoma
643	SRDDFQEGREGIVAR	kidney, angiomyolipoma
644	SSSSFHPAPGNAQ	kidney, angiomyolipoma
645	VARLTESLFLDL	kidney, angiomyolipoma
646	VARLTESLFLDLLG	kidney, angiomyolipoma
647	VIAGNPAYRSFSN	kidney, angiomyolipoma
648	VPQPEPETWEQILRRNVLQ	kidney, angiomyolipoma
649	YKAFSSLLASSAVS	kidney, angiomyolipoma
650	YKAFSSLLASSAVSP	kidney, angiomyolipoma
651	YKAFSSLLASSAVSPE	kidney, angiomyolipoma
992	EDDYIKSWEDNQQGDE	pleura, malignant mesothelioma
993	ELERIQIQEAAKKKPG	pleura, malignant mesothelioma
994	ERIQIQEAAKKKP	pleura, malignant mesothelioma
995	ERIQIQEAAKKKPG	pleura, malignant mesothelioma
996	ERIQIQEAAKKKPGI	pleura, malignant mesothelioma
997	LERIQIQEAAKKKPG	pleura, malignant mesothelioma
998	LSSISQYSGKIK	pleura, malignant mesothelioma,
941	EERNLLSVAYKNVVGAR	esophagus, adenocarcinoma
942	ERNLLSVAYKNVVGAR	esophagus, adenocarcinoma
943	IAELDTLSEESYKD	vulva, squamous cell carcinoma
944	IAELDTLSEESYKDS	vulva, squamous cell carcinoma
218	GDYGRAFNL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma, small lymphocytic type
219	TRHKIVHTK	stomach, metastatic, lymph node, non-Hodgkin's lymphoma, small lymphocytic type
221	KAFNWFSTL	stomach, metastatic, lymph node, non-Hodgkin's lymphoma, small lymphocytic type
541	RPKSNIVL	non-Hodgkin's lymphoma, diffuse large B-cell type
542	RPKSNIVLL	non-Hodgkin's lymphoma, diffuse large B-cell type
1001	INSRFPIPSATDPD	brain, glioblastoma, brain, oligodendroglioma,
1002	VQHYELLNGQSVFG	brain, glioblastoma, brain, oligodendroglioma,
910	AGVFHVEKNGRY	colon, adenocarcinoma, mucinous type
911	FAGVFHVEKNGRYS	colon, adenocarcinoma, mucinous type
912	GPITITIVNRDGTR	colon, adenocarcinoma, mucinous type
913	NGRYSISRTEAADL	colon, adenocarcinoma, mucinous type
45	DELPKFHQY	white blood cells, chronic lymphocytic leukemia
46	DVTGQFPSSF	white blood cells, chronic lymphocytic leukemia
47	EHSRVLQQL	white blood cells, chronic lymphocytic leukemia
48	IKVSKQLL	white blood cells, chronic lymphocytic leukemia
49	KPRQSSPQL	white blood cells, chronic lymphocytic leukemia
50	KQLLAALEI	white blood cells, chronic lymphocytic leukemia
51	RRKDLVLKY	liver, focalnodular hyperplasia
52	RTRDYASLPPK	white blood cells, chronic lymphocytic leukemia
124	GQKEALLKY	synovial sarcoma
125	KPSEERKTI	synovial sarcoma
126	KQTPKVLVV	synovial sarcoma
127	SVIQHVQSF	synovial sarcoma

128 TPIERIPYL	synovial sarcoma
773 LPEFYKTVSPAL	endometrium, adenocarcinoma, endometrioid type
774 VGQFIQDVKNSRST	endometrium, adenocarcinoma, endometrioid type
775 VGQFIQDVKNSRSTD	endometrium, adenocarcinoma, endometrioid type
776 VVGQFIQDVKNSRS	endometrium, adenocarcinoma, endometrioid type
777 VVGQFIQDVKNSRST	endometrium, adenocarcinoma, endometrioid type
778 VVGQFIQDVKNSRSTD	endometrium, adenocarcinoma, endometrioid type
779 VVGQFIQDVKNSRSTDS	endometrium, adenocarcinoma, endometrioid type
687 GPMKGGNFGGRSSGP	thymus, thymoma, malignant
688 GPYGGGGQYFAKP	thymus, thymoma, malignant
689 KGGNFGGRSSGP	thymus, thymoma, malignant
690 NDFGNYNNQSSNFGP	thymus, thymoma, malignant
691 SGPYGGGGQYFAKP	thymus, thymoma, malignant
13 AAANIIRTL	adrenal gland, adrenal cortical carcinoma
14 GRFKNLREAL	adrenal gland, adrenal cortical carcinoma
15 MSPFSKATL	adrenal gland, adrenal cortical carcinoma
16 QEDPGDNQITL	adrenal gland, adrenal cortical carcinoma
17 SPFSKATL	adrenal gland, adrenal cortical carcinoma
129 AEVEKNETV	spleen, non-Hodgkin's lymphoma
130 EVKEEIPLV	spleen, non-Hodgkin's lymphoma
131 KPTSARSGL	spleen, non-Hodgkin's lymphoma
132 KYIETTPLTI	spleen, non-Hodgkin's lymphoma
133 SEIKTSIEV	spleen, non-Hodgkin's lymphoma
134 SVKPTSATK	spleen, non-Hodgkin's lymphoma
135 YPNKGVGQA	spleen, non-Hodgkin's lymphoma
966 ENNEIISNIRDSVIN	kidney, oncocytoma
967 NNEIISNIRDSVIN	kidney, oncocytoma
968 SPTVQVFSASGKPV	kidney, oncocytoma
969 SSPTVQVFSASGKPVE	kidney, oncocytoma
830 DIMRVNVDKVLERDQK	Medullary carcinoma of thyroid origin
831 DIMRVNVDKVLERDQKL	Medullary carcinoma of thyroid origin
832 IMRVNVDKVLERDQK	lymph node, Hodgkin's disease
752 EEVITLIRSNQQLE	pancreas, adenocarcinoma,
753 EEVITLIRSNQQLEN	pancreas, adenocarcinoma,
754 IPADTFAALKNPNAML	pancreas, adenocarcinoma
755 LKQLLSDKQQKRQSG	pancreas, adenocarcinoma
756 LKQLLSDKQQKRQSGQ	pancreas, adenocarcinoma
339 FLDPDIGGVAV	pancreas, adenocarcinoma
340 HTAPPENKTW	pancreas, adenocarcinoma
341 LLDTPVKTQY	pancreas, adenocarcinoma
342 NAVKDFTSF	pancreas, adenocarcinoma
343 SGLLQIKKL	pancreas, adenocarcinoma
344 YHDKNIVLL	pancreas, adenocarcinoma
71 HLKSIPVSL	prostate, adenocarcinoma
72 KVWYNVENW	prostate, adenocarcinoma
73 LPAYRAQLL	prostate, adenocarcinoma
74 LSEQTSVPL	prostate, adenocarcinoma
75 SLNQWLVSF	prostate, adenocarcinoma
76 SMTSLAQKI	prostate, adenocarcinoma

77	SSSGLHPPK	prostate, adenocarcinoma
578	GGGYGSGGGSGGYGSRRF	thymus, thymoma, malignant
579	GGSFGGRSSGSP	thymus, thymoma, malignant
580	KGGSFGGRSSGSP	thymus, thymoma, malignant
583	SPYGGGYGSGGGSGGYGSRRF	thymus, thymoma, malignant
584	YGGGYGSGGGSGGYGSRRF	thymus, thymoma, malignant
84	VPVPHTTAL	endometrium, adenocarcinoma
85	YQVLDVQRY	endometrium, adenocarcinoma
731	DGLNSLTYQVLDVQRYPL	endometrium, adenocarcinoma
732	HPVLQRQQLDYGIY	endometrium, adenocarcinoma
733	LNSLTYQVLDVQR	endometrium, adenocarcinoma
734	LNSLTYQVLDVQRYP	endometrium, adenocarcinoma
735	LNSLTYQVLDVQRYPL	endometrium, adenocarcinoma
736	LPQLVGVSTPLQG	endometrium, adenocarcinoma
737	LPQLVGVSTPLQGG	endometrium, adenocarcinoma
738	LPQLVGVSTPLQGGS	endometrium, adenocarcinoma
739	RLPQLVGVSTPLQGGS	endometrium, adenocarcinoma
740	SPHKVAIIIPFRNR	endometrium, adenocarcinoma
741	SPHKVAIIIPFRNRQE	endometrium, adenocarcinoma
742	SPHKVAIIIPFRNRQEH	endometrium, adenocarcinoma
527	DEKQQHIVY	synovial sarcoma
528	DEVYQVTVY	synovial sarcoma
529	GEISEKAKL	synovial sarcoma
530	YTMKEVLFY	synovial sarcoma
203	GPRPITQSEL	lymph node, non-Hodgkin's lymphoma, marginal Zone B-cell type
204	KPEPVDKVA	lymph node, non-Hodgkin's lymphoma, marginal Zone B-cell type
205	TPSSRPASL	lymph node, non-Hodgkin's lymphoma, marginal Zone B-cell type
949	SPPQFRVNGAISN	ovary, granulosa cell tumor
950	SPPQFRVNGAISNFE	ovary, granulosa cell tumor
951	SPPQFRVNGAISNFEE	ovary, granulosa cell tumor
952	SPPQFRVNGAISNFEEF	ovary, granulosa cell tumor
953	VGKMFVDVYFQEDKK	ovary, granulosa cell tumor
954	VGKmFVDVYFQEDKKE	ovary, granulosa cell tumor
916	EEFKKLTSIKIQNDK	small intestine, gastrointestinal stromal tumor (GIST)
917	INRRMADDNKLFR	small intestine, gastrointestinal stromal tumor (GIST)
918	TATIVMVTNLKERKE	small intestine, gastrointestinal stromal tumor (GIST)
526	RINEFSISSF	connective tissues, chondrosarcoma
585	GNRINEFSISSF	connective tissues, chondrosarcoma
586	HGNQITSDKVGRKV	connective tissues, chondrosarcoma
587	IPPVNTNLENLYLQ	connective tissues, chondrosarcoma
588	LQVLRLDGNEIKR	connective tissues, chondrosarcoma

589 LQVLRLDGNEIKRS	connective tissues, chondrosarcoma
590 LQVLRLDGNEIKRSA	connective tissues, chondrosarcoma
591 LRELHLDHNQISRVPN	connective tissues, chondrosarcoma
592 LYVRLSHNSLTNNG	connective tissues, chondrosarcoma,
593 VPSRMKYVYFQNNQ	connective tissues, chondrosarcoma
594 VPSRMKYVYFQNNQIT	connective tissues, chondrosarcoma
595 VPSRMKYVYFQNNQITS	connective tissues, chondrosarcoma
596 WIALHGNQITSD	connective tissues, chondrosarcoma
597 WIALHGNQITSDK	connective tissues, chondrosarcoma
165 ELNKLLEEI	ovary, adenocarcinoma, endometrioid type
166 IPFSNPRVL	ovary, adenocarcinoma, endometrioid type
167 LLDEGAKLLY	ovary, adenocarcinoma, endometrioid type
168 SPADAHRNL	ovary, adenocarcinoma, endometrioid type
96 APLQRSQSL	kidney, renal cell carcinoma, clear cell type
97 DEVHQDTY	kidney, renal cell carcinoma, clear cell type
98 LPHSATVTL	kidney, renal cell carcinoma, clear cell type
152 APSEYRYTL	stomach, mucinous adenocarcinoma
153 APSEYRYTLL	stomach, mucinous adenocarcinoma
154 EIFQNEVAR	stomach, mucinous adenocarcinoma
155 KDVLIPGKL	stomach, mucinous adenocarcinoma
156 VPLVREITF	stomach, mucinous adenocarcinoma
136 ISMKILNSL	thymus, thymoma, benign
137 KTIAFLLPMF	thymus, thymoma, benign
138 RDSIINDF	thymus, thymoma, benign
139 SVKGGGGNEK	thymus, thymoma, benign
140 GIAKTGSGK	thymus, thymoma, benign
503 ALYATKTLR	pancreas, microcystic adenoma
504 MEYVISRI	pancreas, microcystic adenoma
505 VPVGRQPII	pancreas, microcystic adenoma
278 ATNGDLASR	prostate, benign nodular hyperplasia
279 GLHAEVTGVGY	prostate, benign nodular hyperplasia
280 HVSSTSSSF	prostate, benign nodular hyperplasia
281 LQADLQNGL	prostate, benign nodular hyperplasia
282 SELPVSEVA	prostate, benign nodular hyperplasia
283 SQTKSVFEI	prostate, benign nodular hyperplasia
284 THIFTSDGL	prostate, benign nodular hyperplasia
285 VIYFPPLQK	prostate, benign nodular hyperplasia
286 YPFSSEQKW	prostate, benign nodular hyperplasia
963 GNTVIHLDQALARMR	lung, small cell carcinoma
964 NTVIHLDQALARMR	lung, small cell carcinoma
965 NTVIHLDQALARMRE	lung, small cell carcinoma
187 AADTERLAL	connective tissues, chondrosarcoma
188 DMKAKVASL	connective tissues, chondrosarcoma
189 HVLEEVQQV	connective tissues, chondrosarcoma
190 KEAADTERL	connective tissues, chondrosarcoma
191 RISEVLQKL	connective tissues, chondrosarcoma
192 TEVRELVSL	
973 ADDLEGEAFLPL	spleen, chronic myeloid leukemia
974 ADDLEGEAFLPLR	spleen, chronic myeloid leukemia

975 ADDLEGEAFLPLRE	spleen, chronic myeloid leukemia
976 GADDLEGEAFLPLR	spleen, chronic myeloid leukemia
141 AETTDNVFTL	thyroid gland, follicular adenoma
142 SEYQRFAVM	thyroid gland, follicular adenoma
143 TFGERVVAF	thyroid gland, follicular adenoma
144 NENLVERF	stomach, colon, adenocarcinoma, mucinous type
117 QLFSYAILGF	colon, non-Hodgkin's lymphoma
845 GIRVAPVPLYNS	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
846 GIRVAPVPLYNSFH	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
847 NPNGIRVAPVPLYNSFH	lung, non-small cell lung carcinoma, liver, hepatocellular carcinoma
478 AAVPVIISR	lymph node, papillary carcinoma of thyroid, metastatic
479 EEIGKVAAA	lymph node, papillary carcinoma of thyroid, metastatic
480 FLKDLVASV	lymph node, papillary carcinoma of thyroid, metastatic
481 VIISRALEL	lymph node, papillary carcinoma of thyroid, metastatic
420 QIDYKTLVL	leiomyosarcoma
421 VEDPTIVRI	leiomyosarcoma
543 GEPLSYTRFSLARQ	lung, non-small cell lung carcinoma, lung, adenocarcinoma
544 GEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
545 GEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
546 GGEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
547 GGEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
548 NPGGYVAYSKAATVTG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
549 NPGGYVAYSKAATVTGK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
550 NPGGYVAYSKAATVTGKL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
551 NSVIIVDKNGRL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
552 NSVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
553 NSVIIVDKNGRLVY	lung, non-small cell lung carcinoma, lung, adenocarcinoma
554 RVEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
555 RVEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
556 RVEYHFLSPYVSPKESPF	lung, non-small cell lung carcinoma, lung,

		adenocarcinoma
557	SPFRHVFWGSGSHTL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
558	SVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
559	VEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
560	VEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
388	AEGPAGGFmVV	spleen, chronic myeloid leukemia
389	AYYRDAEAY	spleen, chronic myeloid leukemia
390	QVNRPLTMR	spleen, chronic myeloid leukemia
391	RHSPVFQVY	spleen, chronic myeloid leukemia
392	SLPVPNSAY	spleen, chronic myeloid leukemia
393	TLGPPGTAHLY	spleen, chronic myeloid leukemia
308	VLYVGSKTK	schwannoma
309	KTKEQVTNV	schwannoma
310	MPVDPDNEAY	schwannoma
311	AEKTKQGVA	schwannoma
446	EAFEFVKQR	stomach, diffuse subtype adenocarcinoma, breast, carcinoma
447	NHFEGHYQY	stomach, diffuse subtype adenocarcinoma, breast, carcinoma

Finally a most preferred aspect of the present invention relates to the use of the peptides according to the present invention for the - preferably combined – most preferred immunotherapy of diseases according to the following table 6.

Table 6: Most preferred peptides according to the present invention and diseases to be treated

Seq ID	Sequence	Tissue and disease
22	LEVEERTKPV	breast, carcinoma
23	RDSPINANLRY	breast, carcinoma
24	RPFVIVTA	breast, carcinoma
25	RPIINTPMV	breast, carcinoma
26	SPTSSRTSSL	breast, carcinoma
27	ATSAPLVSR	lung, neuroendocrine carcinoma (non-small cell type)
114	YGNPRTNGM	breast, carcinoma
102	FSITKSVEL	non-Hodgkin's lymphoma, small lymphocytic type
103	GQTKNDLVV	non-Hodgkin's lymphoma, small lymphocytic type
104	LSQEVCRD	non-Hodgkin's lymphoma, small lymphocytic type
105	RDIQSPEQI	non-Hodgkin's lymphoma, small lymphocytic

		type
106	REDNSSNSL	non-Hodgkin's lymphoma, small lymphocytic type
107	TEHQEPGL	non-Hodgkin's lymphoma, small lymphocytic type
108	TKNDLVVSL	non-Hodgkin's lymphoma, small lymphocytic type
977	AGREINLVDAHLKSE	lymph node, Hodgkin's disease
978	AGREINLVDAHLKSEQT	lymph node, Hodgkin's disease
979	GREINLVDAHLKSE	lymph node, Hodgkin's disease
980	KPGIVYASLNHSVIG	lymph node, Hodgkin's disease
981	NKPGIVYASLNHSVIG	lymph node, Hodgkin's disease
982	TTLYVTDVKSASERPS	lymph node, Hodgkin's disease
220	RIHTGEKPYK	colon or rectum, thyroid gland, nodular hyperplasia
53	APGSVLPRAL	lymph node, Hodgkin's disease
54	DIKEHPLL	lymph node, Hodgkin's disease
55	DSAGPQDAR	lymph node, Hodgkin's disease
56	FQYAKESYI	lymph node, Hodgkin's disease
57	KVLSWPFLM	lymph node, Hodgkin's disease
58	LENDQSLSF	lymph node, Hodgkin's disease
59	SPSRQPQV	lymph node, Hodgkin's disease
60	SRHQSFTTK	lymph node, Hodgkin's disease
61	SSHNASKTL	lymph node, Hodgkin's disease
100 3	DNQYAVLENQKSSH	pleura, malignant mesothelioma
100 4	GPPEIYSDTQFPS	pleura, malignant mesothelioma
100 5	GPPEIYSDTQFPSLQ	pleura, malignant mesothelioma
100 6	TPQGPPEIYSDTQFPS	pleura, malignant mesothelioma
100 7	TPQGPPEIYSDTQFPSLQ	pleura, malignant mesothelioma
100 8	TPQGPPEIYSDTQFPSLQS T	pleura, malignant mesothelioma
661	EYVSLYHQPAAM	non-Hodgkin's lymphoma, peripheral T cell type
662	IKAEYKGRVTLKQYPR	non-Hodgkin's lymphoma, peripheral T cell type
663	LNVHSEYEPSWEEQP	non-Hodgkin's lymphoma, peripheral T cell type
664	LPYLFQMPAYASSS	non-Hodgkin's lymphoma, peripheral T cell type
665	LPYLFQMPAYASSSK	non-Hodgkin's lymphoma, peripheral T cell type
666	NFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
667	TNFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type

668	TTNFIKAEYKGRVT	non-Hodgkin's lymphoma, peripheral T cell type
669	VTLNVHSEYEPSWEEQP	non-Hodgkin's lymphoma, peripheral T cell type
670	YPRKNLFLVEVTQLTESDS	non-Hodgkin's lymphoma, peripheral T cell type
671	YPRKNLFLVEVTQLTESDS G	non-Hodgkin's lymphoma, peripheral T cell type
780	DNGHLYREDQTSPAPG	kidney, angiomyolipoma
781	DNGHLYREDQTSPAPGLR	kidney, angiomyolipoma
782	EVQVFAPANALPARSE	kidney, angiomyolipoma
783	GHLYREDQTSPAPG	kidney, angiomyolipoma
784	LPARSEAAAVQPVIG	kidney, angiomyolipoma
785	NGHLYREDQTSPAPG	kidney, angiomyolipoma
786	NGHLYREDQTSPAPGL	kidney, angiomyolipoma
787	NGHLYREDQTSPAPGLR	kidney, angiomyolipoma
788	VFAPANALPARSEAA	kidney, angiomyolipoma
789	VQVFAPANALPARSE	kidney, angiomyolipoma
222	QSTQRSLAL	uterine cervix, squamous cell carcinoma
223	RDLQMNQALRF	uterine cervix, squamous cell carcinoma
224	RELESQLHVL	uterine cervix, squamous cell carcinoma
225	SEAEKLTLV	uterine cervix, squamous cell carcinoma
12	KIADFGLAR	liver, hepatocellular carcinoma
812	DGSYRIFSKGASE	colon or rectum
813	GSYRIFSKGASE	colon or rectum
814	SDGSYRIFSKGASE	colon or rectum
815	SVKKMMKDNNLVRH	colon or rectum, liver, hepatocellular carcinoma
816	VKKMMKDNNLVRH	colon or rectum, liver, hepatocellular carcinoma
743	AIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
744	ARNFERNKAIKVI	non-Hodgkin's lymphoma, peripheral T cell type
745	ARNFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
746	NFERNKAIKVII	non-Hodgkin's lymphoma, peripheral T cell type
747	NFERNKAIKVIIA	non-Hodgkin's lymphoma, peripheral T cell type
748	VAIVQAVSAHRH	non-Hodgkin's lymphoma, peripheral T cell type
749	VAIVQAVSAHRHR	non-Hodgkin's lymphoma, peripheral T cell type
750	VAIVQAVSAHRHRA	non-Hodgkin's lymphoma, peripheral T cell type
751	VAIVQAVSAHRHRAR	non-Hodgkin's lymphoma, peripheral T cell type
818	VDKVLERDQKLSE	lymph node, papillary carcinoma of thyroid, metastatic

819	VDKVLERDQKLSELD	lymph node, papillary carcinoma of thyroid, metastatic
820	VDKVLERDQKLSELDD	lymph node, papillary carcinoma of thyroid, metastatic
821	VDKVLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
822	VLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
833	VDKVLERDQKLSE	lymph node, papillary carcinoma of thyroid, metastatic
834	VDKVLERDQKLSELD	lymph node, papillary carcinoma of thyroid, metastatic
835	VDKVLERDQKLSELDD	lymph node, papillary carcinoma of thyroid, metastatic
836	VDKVLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
837	VLERDQKLSELDDR	lymph node, papillary carcinoma of thyroid, metastatic
908	DVGMFVALTKLGQPD	uterine cervix, squamous cell carcinoma
909	VGmFVALTKLGQPD	uterine cervix, squamous cell carcinoma
218	GDYGRAFNL	lymph node, non-Hodgkin's lymphoma, small lymphocytic type
219	TRHKIVHTK	lymph node, non-Hodgkin's lymphoma, small lymphocytic type
221	KAFNWFSTL	lymph node, non-Hodgkin's lymphoma, small lymphocytic type
541	RPKSNIVL	non-Hodgkin's lymphoma, diffuse large B-cell type
542	RPKSNIVLL	non-Hodgkin's lymphoma, diffuse large B-cell type
752	EEVITLIRSNQQLE	pancreas, adenocarcinoma
753	EEVITLIRSNQQLEN	pancreas, adenocarcinoma
754	IPADTFAALKNPNAML	pancreas, adenocarcinoma
755	LKQLLSDKQQKRQSG	pancreas, adenocarcinoma
756	LKQLLSDKQQKRQSGQ	pancreas, adenocarcinoma
71	HLKSIPVSL	prostate, adenocarcinoma
72	KVWYNVENW	prostate, adenocarcinoma
73	LPAYRAQLL	prostate, adenocarcinoma
74	LSEQTSVPL	prostate, adenocarcinoma
75	SLNQWLVSF	prostate, adenocarcinoma
76	SMTSLAQKI	prostate, adenocarcinoma
77	SSSGLHPPK	prostate, adenocarcinoma
527	DEKQQHIVY	synovial sarcoma
528	DEVYQVTVY	synovial sarcoma
529	GEISEKAKL	synovial sarcoma
530	YTMKEVLFY	synovial sarcoma
165	ELNKLLEEI	ovary, adenocarcinoma, endometrioid type
166	IPFSNPRVL	ovary, adenocarcinoma, endometrioid type
167	LLDEGAKLLY	ovary, adenocarcinoma, endometrioid type

168	SPADAHRNL	ovary, adenocarcinoma, endometrioid type
96	APLQRSQSL	kidney, renal cell carcinoma, clear cell type
97	DEVHQDTY	kidney, renal cell carcinoma, clear cell type
98	LPHSATVTL	kidney, renal cell carcinoma, clear cell type
278	ATNGDLASR	prostate, benign nodular hyperplasia
279	GLHAEVTGVGY	prostate, benign nodular hyperplasia
280	HVSSTSSSF	prostate, benign nodular hyperplasia
281	LQADLQNGL	prostate, benign nodular hyperplasia
282	SELPVSEVA	prostate, benign nodular hyperplasia
283	SQTKSVFEI	prostate, benign nodular hyperplasia
284	THIFTSDGL	prostate, benign nodular hyperplasia
285	VIYFPPLQK	prostate, benign nodular hyperplasia
286	YPFSSEQKW	prostate, benign nodular hyperplasia
973	ADDLEGEAFLPL	spleen, chronic myeloid leukemia
974	ADDLEGEAFLPLR	spleen, chronic myeloid leukemia
975	ADDLEGEAFLPLRE	spleen, chronic myeloid leukemia
976	GADDLEGEAFLPLR	spleen, chronic myeloid leukemia
141	AETTDNVFTL	thyroid gland, follicular adenoma
142	SEYQRFAVM	thyroid gland, follicular adenoma
143	TFGERVVAF	thyroid gland, follicular adenoma
144	NENLVERF	colon, adenocarcinoma, mucinous type
845	GIRVAPVPLYNS	liver, hepatocellular carcinoma
846	GIRVAPVPLYNSFH	liver, hepatocellular carcinoma
847	NPNGIRVAPVPLYNSFH	liver, hepatocellular carcinoma
478	AAVPVIISR	lymph node, papillary carcinoma of thyroid, metastatic
479	EEIGKVAAA	lymph node, papillary carcinoma of thyroid, metastatic
480	FLKDLVASV	lymph node, papillary carcinoma of thyroid, metastatic
481	VIISRALEL	lymph node, papillary carcinoma of thyroid, metastatic
420	QIDYKTLVL	leiomyosarcoma
421	VEDPTIVRI	leiomyosarcoma
543	GEPLSYTRFSLARQ	lung, non-small cell lung carcinoma, lung, adenocarcinoma
544	GEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
545	GEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
546	GGEPLSYTRFSLARQVD	lung, non-small cell lung carcinoma, lung, adenocarcinoma
547	GGEPLSYTRFSLARQVDG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
548	NPGGYVAYSKAATVTG	lung, non-small cell lung carcinoma, lung, adenocarcinoma
549	NPGGYVAYSKAATVTGK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
550	NPGGYVAYSKAATVTGKL	lung, non-small cell lung carcinoma, lung,

		adenocarcinoma
551	NSVIIVDKNGRL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
552	NSVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
553	NSVIIVDKNGRLVY	lung, non-small cell lung carcinoma, lung, adenocarcinoma
554	RVEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
555	RVEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma
556	RVEYHFLSPYVSPKESPF	lung, non-small cell lung carcinoma, lung, adenocarcinoma
557	SPFRHVFWGSGSHTL	lung, non-small cell lung carcinoma, lung, adenocarcinoma
558	SVIIVDKNGRLV	lung, non-small cell lung carcinoma, lung, adenocarcinoma
559	VEYHFLSPYVSPK	lung, non-small cell lung carcinoma, lung, adenocarcinoma
560	VEYHFLSPYVSPKE	lung, non-small cell lung carcinoma, lung, adenocarcinoma

B4GALT1 encodes a type II membrane-bound glycoprotein that appears to have exclusive specificity for the donor substrate UDP-galactose (RefSeq). B4GALT1 was shown to be up-regulated in a variety of highly metastatic cell lines such as human lung cancer and ovarian cancer cell lines and was described as a valuable candidate biomarker of invasive phenotype of colorectal cancer (Poeta et al., 2012; Zhou et al., 2012).

CP encodes a metalloprotein that binds most of the copper in plasma and is involved in the peroxidation of Fe(II)transferrin to Fe(III) transferrin (RefSeq).

CST3 encodes a member of the cystatin superfamily, which encompasses proteins that contain multiple cystatin-like sequences (RefSeq).

CTSH encodes a lysosomal cysteine proteinase, which is important in the overall degradation of lysosomal proteins (RefSeq). CTSH expression is increased in pathologic conditions including breast carcinoma, melanoma, gliomas, colorectal carcinoma and prostate carcinoma. CTSH-mediated processing of talin is thought to promote cancer cell progression by affecting integrin activation and adhesion strength (Jevnikar et al., 2013).

DNAJC5 encodes a member of the J protein family. J proteins function in many cellular processes by regulating the ATPase activity of 70 kDa heat shock proteins (RefSeq).

FAIM3 also known as TOSO encodes an Fc receptor for IgM (RefSeq). FAIM3 was identified as being over-expressed and associated with anti-apoptotic characteristics in chronic lymphocytic leukemia and it is regulated by B-cell receptor activation. These studies show that FAIM3 could be used as a prognostic marker for high-risk chronic lymphocytic leukemia (Pallasch et al., 2008; Yi et al., 2011; Yu et al., 2011).

FCER2 encodes a B-cell specific antigen and a low-affinity receptor for IgE. It has essential roles in B cell growth and differentiation, and the regulation of IgE production (RefSeq).

FMOD encodes a member of the family of small interstitial proteoglycans. The encoded protein possesses a central region containing leucine-rich repeats with 4 keratan sulfate chains, flanked by terminal domains containing disulphide bonds (RefSeq). FMOD was shown to be highly over-expressed in chronic lymphocytic leukemia cells. Hence, FMOD might serve as potential tumor-associated antigen in chronic lymphocytic leukemia (Mayr et al., 2005).

GALNT1 encodes a member of the UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase (GalNAc-T) family of enzymes (RefSeq). Studies have revealed that GALNT1 expression correlates with the degree of proliferation and recurrence in human breast cancer, ovarian cancer and bladder carcinoma. The latter suggests the use of GALNT1 as a clinical prognostic marker in human bladder carcinoma (Ding et al., 2012).

GLT8D1 encodes a member of the glycosyltransferase family (RefSeq). Studies revealed that GLT8D1 was ubiquitously up-regulated in the majority of human cancers, such as brain, liver, breast, lung, stomach, pancreas, colon, kidney, bladder, prostate and testis. GLT8D1-induced differentially methylated genes have strong

potential as epigenetic biomarkers for early cancer screening, diagnostic, prognostic and therapeutic interventions (Teh et al., 2012).

GPI encodes a member of the glucose phosphate isomerase protein family (RefSeq). The GPI gene has been identified to be hypoxia inducible in human pancreatic cancer. The use of GPI inhibitors such as erythrose-4-phosphate diminishes the migratory and invasive capacities in bi-dimensional cultures of several breast cancer cell lines, suggesting that GPI inhibition could be a selective strategy to block tumor metastasis (Yoon et al., 2001; Gallardo-Perez et al., 2014).

GPX1 encodes a member of the glutathione peroxidase family (RefSeq). The GPX1 rs1050450 C > T polymorphism was associated with an increased risk of bladder cancer, but not prostate cancer. High expression of GPX1 in breast cancer cells of patients correlated with a worse clinical outcome and reduced overall survival of patients who underwent chemotherapy, implying that GPX1 could be used as a prognostic marker for these patients (Jardim et al., 2013; Men et al., 2014).

TFRC encodes the transferrin receptor and it is located on chromosome 3q29 (RefSeq). The expression rate of TFRC in oral squamous cell carcinoma was significantly higher than that in dysplasia, suggesting that oral squamous cell carcinoma disease progression might be related to TFRC expression. Anti-TFRC antibody blocked the interaction between transferrin and TFRC and, consequently, iron uptake. The resulting iron deprivation inhibited cell growth and induced apoptosis (Nagai et al., 2014).

UGCG encodes an enzyme that catalyzes the first glycosylation step in the biosynthesis of glycosphingolipids, which are membrane components containing lipid and sugar moieties (RefSeq). Studies have shown that UGCG is over-expressed in leukemia, breast cancer, renal cell cancer and papillary thyroid carcinomas. UGCG up-regulates MDR1 expression through activation of cSrc and beta-catenin signaling (Zhang et al., 2013; Liu et al., 2010).

The present invention furthermore relates to the 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 -II.

The present invention further relates to the peptides according to the present invention wherein said peptides (each) consist or consist essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

A peptide consisting essentially of the amino acid sequence as indicated 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, compared to the non-modified peptide. In another peptide consisting essentially of the amino acid sequence, one or two amino acids are exchanged with their conservative exchange partners (see herein below as well) 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, compared to the non-modified peptide.

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

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

The present invention further relates to a nucleic acid, encoding the peptides according to the present invention.

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

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

The present invention further relates to a peptide according to the present invention according to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, a nucleic acid according to the present invention or an expression vector according to the present invention for use in medicine.

The present invention further relates to antibodies according to the present invention that are specific for a peptide according to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, and methods of making them.

The present invention further relates to T-cell receptors (TCR), in particular soluble TCR (sTCRs) targeting the peptides according to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016 and/or complexes of said peptides according to the present invention with MHC, and methods of making them.

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.

The present invention further relates to the host cell according to the present invention wherein the antigen presenting cell is a dendritic cell.

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

The present invention further relates to an *in vitro* method for producing activated cytotoxic T lymphocytes (CTL), the method comprising contacting in vitro CTL with antigen loaded human class I or II MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate said CTL in an antigen specific manner, wherein said antigen is any peptide according to the present invention.

The present invention further relates to the 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 by contacting a sufficient amount of the antigen with an antigen-presenting cell.

The present invention further relates to the method according to the present invention, wherein the antigen-presenting cell comprises an expression vector capable of expressing said peptide containing SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016, or said variant amino acid sequence.

The present invention further relates to activated cytotoxic T lymphocytes (CTL), produced by the method according to the present invention, which selectively recognize a cell which aberrantly expresses a polypeptide comprising an amino acid sequence according to the present invention.

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

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

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

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

The present invention further relates to a use according to the present invention, wherein said cancer cells are cells of haematological malignancies, such as, CLL or AML cells.

The present invention further relates to particular marker proteins and biomarkers based on the peptides according to the present invention that can be used in the diagnosis and/or prognosis of haematological malignancies, in particular chronic lymphoid leukemia (CLL) cells.

Further, the present invention relates to the use of these novel targets for cancer treatment.

Further, the present invention relates to a method for producing a personalized anti-cancer vaccine for an individual patient using a database ("warehouse") of prescreened tumour associated peptides.

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

Specific elements of the cellular immune response are capable of specifically recognising and destroying tumor cells. The isolation of cytotoxic T-cells (CTL) from tumor-infiltrating cell populations or from peripheral blood suggests that such cells play an important role in natural immune defences against cancer. CD8-positive T-

cells in particular, which recognise 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).

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

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 S, et al. Survey of naturally occurring CD4+ T cell responses against NY-ESO-1 in cancer patients: correlation with antibody responses. Proc Natl Acad Sci U S A. 2003 Jul 22;100(15):8862-7). At the tumor site, T helper cells, support a CTL friendly cytokine milieu Mortara L, et al. CIITA-induced MHC class II expression in mammary adenocarcinoma leads to a Th1 polarization of the tumor microenvironment, tumor rejection, and specific antitumor memory. Clin Cancer Res. 2006 Jun 1;12(11 Pt 1):3435-43) and attract effector cells, e.g. CTLs, NK cells, macrophages, granulocytes (Hwang ML, et al. Cognate memory CD4+ T cells

generated with dendritic cell priming influence the expansion, trafficking, and differentiation of secondary CD8+ T cells and enhance tumor control. J Immunol. 2007 Nov 1;179(9):5829-38).

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 surprisingly been found to express MHC class II molecules (Dengjel J, et al. Unexpected abundance of HLA class II presented peptides in primary renal cell carcinomas. Clin Cancer Res. 2006 Jul 15;12(14 Pt 1):4163-70).

It was shown in mammalian animal models, e.g., mice, that even in the absence of CTL effector cells (i.e., 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).

Additionally, it was shown that CD4-positive T cells recognizing peptides from tumor-associated antigens presented by HLA class II molecules can counteract tumor progression via the induction of antibody (Ab) responses.

In contrast to tumor-associated peptides binding to HLA class I molecules, only a small number of class II ligands of tumor associated antigens (TAA) have been described to date.

Since the constitutive expression of HLA class II molecules is usually limited to cells of the immune system, the possibility of isolating class II peptides directly from primary tumors was not considered possible. However, Dengjel et al. were successful in identifying a number of MHC Class II epitopes directly from tumors (WO 2007/028574, EP 1 760 088 B1; (Dengjel et al., 2006).

The antigens that are recognized by the tumor specific cytotoxic T lymphocytes, that is, their epitopes, 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, up-regulated in cells of the respective tumor.

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+ CTLs (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.

The present invention also relates to two new and very useful MHC class II peptides (according to SEQ ID NO: 543 to SEQ ID NO: 1016). These peptides are particularly useful in the diagnosis and/or treatment of CLL and other cancers over-expressing and / or over – presenting the antigens the peptides are derived from respectively, such as AML.

The present invention also relates to so-called length variants of the inventive MHC class II peptides according to SEQ ID NO: 543 to SEQ ID NO: 1016.

The length variants are generally N- and/or C-terminally extended (between 1 and 5, preferably 1 to 10 amino acids) or N- and/or C-terminally shortened (between 1 and 5 amino acids) peptides, which still can bind to MHC, and elicit a cellular immune response as described herein. As is known in the state of the art, peptides binding to class II proteins are not constrained in size and can vary from 11 to 30 amino acids in length. The peptide binding groove in the MHC class II molecules is open at both ends, which enables binding of peptides with relatively longer length. Though the "core" nine residues long segment contributes the most to the recognition of the peptide, the flanking regions are also important for the specificity of the peptide to the class II allele (see, for example, Meydan C, et al., Prediction of peptides binding to MHC class I and II alleles by temporal motif mining. BMC Bioinformatics. 2013; 14 Suppl 2: S13). Using the many software tools as available (e.g. as described above), the person of skill in the art will be able to identify the binding motif, and thus identify the possibilities for extensions and/or deletions of the MHC class II peptides according to Table 1c, in order to create length variants.

For a peptide to trigger (elicit) a cellular immune response, it must bind to an MHC-molecule. This process is dependent on the allele of the MHC-molecule and specific polymorphisms of the amino acid sequence of the peptide. MHC-class-I-binding peptides are usually 8-12 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.

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

The antigens that are recognized by the tumor specific cytotoxic T lymphocytes, that is, their epitopes, 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, up-regulated in cells of the respective tumor.

The current classification of tumor associated antigens comprises the following major groups:
a) Cancer-testis antigens: The first TAAs ever identified that can be recognized by T cells belong to this class, which was originally called cancer-testis (CT) antigens because of the expression of its members in histologically different human tumors and, among normal tissues, only in spermatocytes/spermatogonia of testis and, occasionally, in placenta. Since the cells of testis do not express class I and II HLA molecules, these antigens cannot be recognized by T cells in normal tissues and can therefore be considered as immunologically tumor-specific. Well-known examples for CT antigens are the MAGE family members or NY-ESO-1.
b) Differentiation antigens: These TAAs are shared between tumors and the normal tissue from which the tumor arose; most are found in melanomas and normal melanocytes. Many of these melanocyte lineage-related proteins are involved in the biosynthesis of melanin and are therefore not tumor specific but nevertheless are widely used for cancer immunotherapy. Examples include, but are not limited to, tyrosinase and Melan-A/MART-1 for melanoma or PSA for prostate cancer.

c) Overexpressed TAAs: Genes encoding widely expressed TAAs have been detected in histologically different types of tumors as well as in many normal tissues, generally with lower expression levels. It is possible that many of the epitopes processed and potentially presented by normal tissues are below the threshold level for T-cell recognition, while their overexpression in tumor cells can trigger an anticancer response by breaking previously established tolerance. Prominent examples for this class of TAAs are Her-2/neu, Survivin, Telomerase or WT1.
d) Tumor specific antigens: These unique TAAs arise from mutations of normal genes (such as β-catenin, CDK4, etc.). Some of these molecular changes are associated with neoplastic transformation and/or progression. Tumor specific antigens are generally able to induce strong immune responses without bearing the risk for autoimmune reactions against normal tissues. On the other hand, these TAAs are in most cases only relevant to the exact tumor on which they were identified and are usually not shared between many individual tumors.
e) TAAs arising from abnormal post-translational modifications: Such TAAs may arise from proteins which are neither specific nor overexpressed in tumors but nevertheless become tumor associated by posttranslational processes primarily active in tumors. Examples for this class arise from altered glycosylation patterns leading to novel epitopes in tumors as for MUC1 or events like protein splicing during degradation which may or may not be tumor specific.
f) Oncoviral proteins: These TAAs are viral proteins that may play a critical role in the oncogenic process and, because they are foreign (not of human origin), they can evoke a T-cell response. Examples of such proteins are the human papilloma type 16 virus proteins, E6 and E7, which are expressed in cervical carcinoma.

For proteins to be recognized by cytotoxic T-lymphocytes as tumor-specific or -associated antigens, and to be used in a therapy, particular prerequisites must be fulfilled. The antigen should be expressed mainly by tumor cells and not or in comparably small amounts by normal healthy tissues or in another 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 a function e.g. in cell cycle control or suppression of apoptosis. Additionally, downstream targets of the proteins directly causative for a transformation may be upregulated und thus may be indirectly tumor-associated. Such indirect tumor-associated antigens may also be targets of a vaccination approach (Singh-Jasuja et al., 2004). In both cases it is essential that epitopes are present in the amino acid sequence of the antigen, since such a peptide ("immunogenic peptide") that is derived from a tumor associated antigen should lead to an *in vitro* or *in vivo* T-cell-response.

Basically, any peptide able to bind a 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 with a corresponding TCR and the absence of immunological tolerance for this particular epitope.

Therefore, TAAs are a starting point for the development of a tumor vaccine. The methods for identifying and characterizing the TAAs are based on the use of CTL that can be isolated from patients or healthy subjects, or they are based on the generation of differential transcription profiles or differential peptide expression patterns between tumors and normal tissues.

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

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

T-helper cells 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 T_{H1} 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.

The inventors identified a novel category of ligandome-derived tumor-associated antigens (LiTAAs), which were frequently and exclusively detected in CLL patients. Specific immune recognition of the corresponding HLA ligands (LiTAPs) was observed exclusively in CLL patients, remarkably showing a direct correlation with the frequency of HLA restricted presentation. Furthermore, retrospective survival analysis of 33 CLL patients indicated a potential association of LiTAP-specific immune responses with improved overall survival in CLL patients.

Uses against further cancers are disclosed in the following description of the proteins of the peptides according to the invention.

Detailed description of the invention

As used herein and except as noted otherwise all terms are defined as given below.

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 and in case of MHC class II peptides they can be as long as 15, 16, 17, 18, 19 or 20 amino acids in length.

Furthermore, the term “peptide” shall include salts of a series of amino acid residues, connected one to the other typically by peptide bonds between the alpha-amino and carbonyl groups of the adjacent amino acids. Preferably, the salts are pharmaceutical acceptable salts of the peptides, such as, for example, the chloride or acetate (trifluoroacetate) salts.

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

The term “the peptides of the present invention” shall include the peptides consisting of or comprising a peptide as defined above according to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016.

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

A peptide, oligopeptide, protein or polynucleotide coding for such a molecule is “immunogenic” (and thus is an “immunogen” within the present invention), if it is capable of inducing an immune response. In the case of the present invention, immunogenicity is more specifically defined as the ability to induce a T-cell response. Thus, an “immunogen” would be a molecule that is capable of inducing an immune response, and in the case of the present invention, a molecule capable of inducing a T-cell response. In another aspect, the immunogen can be the peptide, the complex

of the peptide with MHC, oligopeptide, and/or protein that is used to raise specific antibodies or TCRs against it.

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

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

Table 7: Expression frequencies F of HLA*A02 and the most frequent HLA-DR serotypes. Frequencies are deduced from haplotype frequencies G_f within the American population adapted from Mori et al. (Mori M, et al. HLA gene and haplotype frequencies in the North American population: the National Marrow Donor Program Donor Registry. Transplantation. 1997 Oct 15;64(7):1017-27) employing the Hardy-Weinberg formula $F=1-(1-G_f)^2$. Combinations of A*02 with certain HLA-DR alleles might be enriched or less frequent than expected from their single frequencies due to linkage disequilibrium. For details refer to Chanock et al. (S.J. Chanock, et al (2004) HLA-A, -B, -Cw, -DQA1 and DRB1 in an African American population from Bethesda, USA Human Immunology, 65: 1223-1235).

	Expression frequencies of HLA*02 and HLA-DR serotypes within North American subpopulations			
HLA Allele	Caucasian American	African American	Asian American	Latin American
A*02	49.1%	34.1%	43.2%	48.3%
DR1	19.4%	13.2%	6.8%	15.3%
DR2	28.2%	29.8%	33.8%	21.2%
DR3	20.6%	24.8%	9.2%	15.2%

DR4	30.7%	11.1%	28.6%	36.8%
DR5	23.3%	31.1%	30.0%	20.0%
DR6	26.7%	33.7%	25.1%	31.1%
DR7	24.8%	19.2%	13.4%	20.2%
DR8	5.7%	12.1%	12.7%	18.6%
DR9	2.1%	5.8%	18.6%	2.1%

Therefore, for therapeutic and diagnostic purposes a peptide that binds with appropriate affinity to several different HLA class II receptors is highly desirable. A peptide binding to several different HLA class II molecules is called a promiscuous binder.

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

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

The term ”nucleotide sequence“ refers to a heteropolymer of deoxyribonucleotides.

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

As used herein the term “a nucleotide coding (or encoding) for a peptide” refers to a nucleotide sequence coding for the peptide including artificial (man-made) start and stop codons compatible for the biological system the sequence is going to be expressed by.

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

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

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

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

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

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

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

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 that generates an immune response (i.e., has immunogenic activity) when administered, alone or optionally with a suitable

adjuvant, to an animal, such as a mammal, for example, a rabbit or a mouse, and also including a human, such immune response taking the form of stimulating a T-cell response within the recipient animal, such as a human. Alternatively, the "active fragment" may also be used to induce a T-cell response *in vitro*.

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

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

Percent Identity = 100 [1 -(C/R)]

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

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

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.

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

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

Less conservative substitutions might involve the replacement of one amino acid by another that has similar characteristics but is somewhat different in size, such as

replacement of an alanine by an isoleucine residue. Highly non-conservative replacements might involve substituting an acidic amino acid for one that is polar, or even for one that is basic in character. Such “radical” substitutions cannot, however, be dismissed as potentially ineffective since chemical effects are not totally predictable and radical substitutions might well give rise to serendipitous effects not otherwise predictable from simple chemical principles.

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, amino acids possessing non-standard R groups (i.e., R groups other than those found in the common 20 amino acids of natural proteins) may also be used for substitution purposes to produce immunogens and immunogenic polypeptides according to the present invention.

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

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 depicted from table 8:

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

The amino acids for the elongation can be the peptides of the original sequence of the protein or any other amino acid. The elongation can be used to enhance the stability or solubility of the peptides.

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

Preferably, when the CTLs 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 pM, and most preferably no more than about 10 pM. It is also preferred that the substituted peptide be recognized by CTLs from more than one individual, at least two, and more preferably three individuals.

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 4 residues from the reference peptide, as long as they have substantially identical antigenic activity.

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 now 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 explored for cancer immunotherapy.

Specific elements of the cellular immune response are capable of specifically recognizing and destroying tumor cells. The isolation of cytotoxic T-cells (CTL) from tumor-infiltrating cell populations or from peripheral blood suggests that such cells play an important role in natural immune defences 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 12 residues derived from proteins or defect ribosomal products (DRIPS) located in the cytosols, play an important role in this response. The MHC-molecules of the human are also designated as human leukocyte-antigens (HLA).

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

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

Considering the severe side-effects and expense associated with treating cancer better prognosis and diagnostic methods are desperately needed. Therefore, there is a need to identify other factors representing biomarkers for cancer in general and

CLL in particular. Furthermore, there is a need to identify factors that can be used in the treatment of cancer in general and CLL in particular.

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.

The source gene/protein (also designated “full-length protein” or “underlying protein”) from which the peptides are derived were shown to be highly overexpressed in diseased (e.g. cancerous) compared with normal tissues. “Normal tissues” in relation to this invention shall particularly mean a blood sample from a healthy donor and sub-populations of blood cells,especially white blood cells, (see example 2, and figure 2) demonstrating a high degree of tumor association of the source genes. Moreover, the peptides themselves are strongly over-presented on tumor tissue – “tumor tissue” in relation to this invention shall mean a blood sample from a patient suffering from CLL and sub-populations of blood cells,especially white blood cells, but not on normal tissues (see example 3 and Figure 3).

HLA-bound peptides can be recognized by the immune system, specifically T lymphocytes/T cells. T cells can destroy the cells presenting the recognized HLA/peptide complex, e.g. cells presenting the peptides of the present invention that are derived from their underlying proteins.

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, in particular sTCRs, according to the present invention (see example 4 and figure 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.

A “pharmaceutical composition” is a composition suitable for administration to a human being in a medical setting. Preferably, said pharmaceutical composition is sterile and produced according to the GMP guidelines.

The pharmaceutical compositions comprise the peptides either in the free form or in the form of a pharmaceutically acceptable salt (see also above). As used herein, "a pharmaceutically acceptable salt" refers to a derivative of the disclosed peptides wherein the peptide is modified by making acid or base salts of the agent. For example, acid salts are prepared from the free base (typically wherein the neutral form of the drug has a neutral $–NH_2$ group) involving reaction with a suitable acid. Suitable acids for preparing acid salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methane sulfonic acid, ethane sulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid phosphoric acid and the like. Conversely, preparation of basic salts of acid moieties which may be present on a peptide are prepared using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine or the like.

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

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 (leukimea) cells and since it was determined that these peptides are not or at lower levels present in normal tissues (such as white blood cells), these peptides can be used to diagnose the presence of a cancer.

The presence of claimed peptides 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 sample is malignant or generally diseased, or can be usesd 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. Thus, presence of peptides shows that this mechanism is not exploited by the analyzed cells.

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

The peptides of the present invention can be used to generate and develop specific antibodies against MHC/peptide complexes. These can be used for therapy,

targeting toxins or radioactive substances to the diseased tissue. Another use of these antibodies can be targeting radionuclides to the diseased tissue for imaging purposes such as PET. This use can help to detect small metastases or to determine the size and precise localization of diseased tissues.

Therefore, it is a further aspect of the invention to provide a method for producing a recombinant antibody specifically binding to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, 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.

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.

Yet another aspect of the present invention then relates to a method of producing said antibody specifically binding to a human major histocompatibility complex (MHC) class I or II being complexed with a HLA-restricted antigen, the method comprising: immunizing a genetically engineered non-human mammal comprising cells expressing said human major histocompatibility complex (MHC) class I or II with a soluble form of a MHC class I or II molecule being complexed with said HLA-restricted antigen; isolating mRNA molecules from antibody producing cells of said non-human mammal; producing a phage display library displaying protein molecules encoded by said mRNA molecules; and isolating at least one phage from said phage display library, said at least one phage displaying said antibody specifically bindable to said human major histocompatibility complex (MHC) class I or II being complexed

with said HLA-restricted antigen. Respective methods for producing such antibodies and single chain class I major histocompatibility complexes, as well as other tools for the production of these antibodies are disclosed in WO 03/068201, WO 2004/084798, WO 01/72768, WO 03/070752, and Cohen CJ, et al. Recombinant antibodies with MHC-restricted, peptide-specific, T-cell receptor-like specificity: new tools to study antigen presentation and TCR-peptide-MHC interactions. J Mol Recognit. 2003 Sep-Oct;16(5):324-32.; Denkberg G, et al. Selective targeting of melanoma and APCs using a recombinant antibody with TCR-like specificity directed toward a melanoma differentiation antigen. J Immunol. 2003 Sep 1;171(5):2197-207; and Cohen CJ, et al. Direct phenotypic analysis of human MHC class I antigen presentation: visualization, quantitation, and in situ detection of human viral epitopes using peptide-specific, MHC-restricted human recombinant antibodies. J Immunol. 2003 Apr 15; 170(8):4349-61, which for the purposes of the present invention are all explicitly incorporated by reference in their entireties.

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

It is a further aspect of the invention to provide a method for producing a soluble T-cell receptor 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 N, et al. Monoclonal TCR-redirected tumor cell killing. *Nat Med* 2012 Jun;18(6):980-987). For the purpose of stabilization of T-cell receptors during phage display and in case of practical use as drug, alpha and beta chain can be linked e.g. by non-native disulfide bonds, other covalent bonds (single-chain T-cell receptor), or by dimerization domains (see Boulter JM, et al. Stable, soluble T-cell receptor molecules for crystallization and therapeutics. Protein Eng 2003 Sep;16(9):707-711.; Card KF, et al. A soluble single-chain T-cell receptor IL-2 fusion protein retains MHC-restricted peptide specificity and IL-2 bioactivity. Cancer Immunol Immunother 2004 Apr;53(4):345-357; and Willcox BE, et al. Production of soluble alphabeta T-cell receptor heterodimers suitable for biophysical analysis of

ligand binding. Protein Sci 1999 Nov; 8 (11):2418-2423). The T-cell receptor can be linked to toxins, drugs, cytokines (see 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.

In addition, they can be used to verify a pathologist's diagnosis of a cancer based on a biopsied sample.

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 (J. Pinheiro, et al. The nlme Package: Linear and Nonlinear Mixed Effects Models. 2007) adjusting for multiple testing by False Discovery Rate (Y. Benjamini and Y. Hochberg. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society. Series B (Methodological), Vol.57 (No.1):289-300, 1995).

For the identification and relative quantitation of HLA ligands by mass spectrometry, HLA molecules from shock-frozen tissue samples were purified and HLA-associated peptides were isolated. The isolated peptides were separated and sequences were identified by online nano-electrospray-ionization (nanoESI) liquid chromatography-mass spectrometry (LC-MS) experiments. The resulting peptide sequences were verified by comparison of the fragmentation pattern of natural TUMAPs recorded from CLL 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 CLL patients.

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.

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.

HLA-peptide complexes from CLL tissue samples were purified and HLA-associated peptides were isolated and analysed 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.

All TUMAPs contained in the application at hand were identified with this approach on primary CLL samples confirming their presentation on primary CLL.

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

The present invention therefore relates to a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO:

527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016 or a variant thereof which is at least 90% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016 or a variant thereof that induces T cells cross-reacting with said peptide, wherein said peptide is not the underlying full-length polypeptide.

The present invention further relates to a peptide comprising a sequence that is selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1024 or a variant thereof which is at least 90% homologous (preferably identical) to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016, wherein said peptide or variant has an overall length of between 8 and 100, preferably between 8 and 30, and most preferred between 8 and 14 amino acids.

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

The present invention further relates to the peptides according to the invention wherein the peptide consists or consists essentially of an amino acid sequence according to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016.

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

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

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

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

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

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

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

The present invention further relates to the host cell according to the invention that is an antigen presenting cell.

The present invention further relates to the host cell according to the invention wherein the antigen presenting cell is a dendritic cell.

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

The present invention further relates to an *in vitro* method for producing activated cytotoxic T lymphocytes (CTL), the method comprising contacting *in vitro* CTL with antigen loaded human class I or II MHC molecules expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate said CTL in an antigen specific manner, wherein said antigen is any peptide according to the invention.

The present invention further relates to the method as described, wherein said antigen is loaded onto class I or II MHC molecules expressed on the surface of a

suitable antigen-presenting cell by contacting a sufficient amount of the antigen with an antigen-presenting cell.

The present invention further relates to the method according to the invention, wherein the antigen-presenting cell comprises an expression vector capable of expressing said peptide containing SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 527 to SEQ ID NO: 551 or SEQ ID NO: 552 to SEQ ID NO: 1016 or said variant amino acid sequence.

The present invention further relates to activated cytotoxic T lymphocytes (CTL), produced by the method according to the invention, which selectively recognise a cell which aberrantly expresses a polypeptide comprising an amino acid sequence described.

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 invention, the method comprising administering to the patient an effective number of cytotoxic T lymphocytes (CTL) according to the invention.

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

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

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

The present invention further relates to a use according to the invention, wherein said cancer cells are CLL cells or other non solid tumor cells.

The present invention further relates to particular marker proteins and biomarkers that can be used in the prognosis of CLL.

Further, the present invention relates to the use of the novel targets as described in accordance with the present invention for cancer treatment.

The term “antibody” or ”antibodies“ is used herein in a broad sense and includes both polyclonal and monoclonal antibodies. In addition to intact or “full” immunoglobulin molecules, also included in the term ”antibodies“ are fragments or polymers of those immunoglobulin molecules and humanized versions of immunoglobulin molecules, so long as they exhibit any of the desired properties (e.g., specific binding of an CLL marker polypeptide, delivery of a toxin to an CLL (leukimea) cells expressing a CLL marker gene at an increased level, and/or inhibiting the activity of a CLL marker polypeptide) according to the invention.

Whenever possible, the antibodies of the invention may be purchased from commercial sources. The antibodies of the invention may also be generated using well-known methods. The skilled artisan will understand that either full length 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.

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: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016 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.

One of skill in the art will realize that the generation of two or more different sets of monoclonal or polyclonal antibodies maximizes the likelihood of obtaining an antibody with the specificity and affinity required for its intended use (e.g., ELISA, immunohistochemistry, *in vivo* imaging, immunotoxin therapy). The antibodies are tested for their desired activity by known methods, in accordance with the purpose for which the antibodies are to be used (e.g., ELISA, immunohistochemistry, immunotherapy, etc.; for further guidance on the generation and testing of antibodies, see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988, new 2nd edition 2013). For example, the antibodies may be tested in ELISA assays or Western blots. After their initial *in vitro* characterization, antibodies intended for therapeutic or *in vivo* diagnostic use are tested according to known clinical testing methods.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a substantially homogeneous population of antibodies, i.e.; the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired antagonistic activity (U.S. Pat. No. 4,816,567, which is hereby incorporated in its entirety).

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

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in 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).

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 a $F(ab')_2$ fragment and a pFc' fragment.

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

The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues

from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (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.

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

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

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

Effective dosages and schedules for administering the antibodies may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of antibodies that must be administered will vary depending on, for example, the subject that will receive the antibody, the route of administration, the particular type of antibody used and other drugs being administered. A typical daily dosage of the antibody used alone might range from about 1 (µg/kg to up to 100 mg/kg of body weight or more per day, depending on the factors mentioned above. Following administration of an antibody for treating CLL, the efficacy of the therapeutic antibody can be assessed in various ways well known to the skilled practitioner. s secondary to CLL

Because the peptides as mentioned in the Tables above (specifically the ones associated with CLL) of the invention and thus their underlying polypeptides are highly expressed in CLL, and are expressed at rather to extremely low levels in normal cells, the inhibition of a protein selected from the group consisting of

APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3 expression or of the activity thereof may be preferably integrated into a therapeutic strategy for treating or preventing CLL.

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

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

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

An alternative strategy for inhibiting the function of a protein selected from the group consisting of APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3 using gene therapy involves intracellular expression of an anti-protein antibody or a portion of an anti-protein antibody. For example, the gene (or gene fragment) encoding a monoclonal antibody that specifically binds to a protein selected from the group consisting of APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3 and inhibits its biological activity is placed under the transcriptional control of a specific (e.g., tissue- or tumor-specific) gene regulatory sequence, within a nucleic acid expression vector. The vector is then administered to the subject such that it is taken up by CLL cells or other cells, which then secrete the anti-protein antibody, and thereby block biological activity of the respective polypeptide. Preferably, proteins are present on the cellular surface of CLL cancer cells.

In the methods described above, which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), the nucleic acids of the present invention can be in the form of naked DNA or the nucleic acids can be in a vector for delivering the nucleic acids to the cells for inhibition of CLL tumor marker protein expression. The vector can be a commercially available preparation, such as an adenovirus vector (Quantum Biotechnologies, Inc. (Laval, Quebec, Canada). Delivery of the nucleic acid or vector to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as LIPOFECTIN, LIPOFECTAMINE (GIBCO-25 BRL, Inc., Gaithersburg, Md.), SUPERFECT (Qiagen, Inc. Hilden, Germany) and TRANSFECTAM (Promega Biotec, Inc., Madison, Wis.,

US), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this invention can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, US) as well as by means of a SONOPORATION machine (ImaRx Pharmaceutical Corp., Tucson, Arizona, US).

As one example, vector delivery can be via a viral system, such as a retroviral vector system that can package a recombinant retroviral genome. The recombinant retrovirus can then be used to infect and thereby deliver to the infected cells antisense nucleic acid that inhibits expression of a protein selected from the group consisting of APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3. The exact method of introducing the altered nucleic acid into mammalian cells is, of course, not limited to the use of retroviral vectors. Other techniques are widely available for this procedure including the use of adenoviral vectors, adeno-associated viral (AAV) vectors, lentiviral vectors, pseudotyped retroviral vectors. Physical transduction techniques can also be used, such as liposome delivery and receptor-mediated and other endocytosis mechanisms. This invention can be used in conjunction with any of these or other commonly used gene transfer methods.

The antibodies may also be used for *in vivo* diagnostic assays. Generally, the antibody is labeled with a radionucleotide (such as ^{111}In, ^{99}Tc, ^{14}C, ^{131}I, ^{3}H, ^{32} P or ^{35} S) so that the tumor can be localized using immunoscintiography. In one embodiment, antibodies or fragments thereof bind to the extracellular domains of two or more targets of a protein selected from the group consisting of APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-

DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3, and the affinity value (Kd) is less than 1 x 10μM.

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

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: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016 or a variant thereof which is 90% homologous to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, 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 and / or class II.

In the present invention, the term ”homologous“ refers to the degree of identity (see Percent Identity above) between sequences of two amino acid sequences, i.e. peptide or polypeptide sequences. The aforementioned ”homology“ is determined by

comparing two sequences aligned under optimal conditions over the sequences to be compared. Such a sequence homology can be calculated by creating an alignment using, for example, the ClustalW algorithm. Commonly available sequence analysis software, more specifically, Vector NTI, GENETYX or other analysis tools are provided by public databases.

A person skilled in the art will be able to assess, whether T cells induced by a variant of a specific peptide will be able to cross-react with the peptide itself (Fong L, et al. Altered peptide ligand vaccination with Flt3 ligand expanded dendritic cells for tumor immunotherapy. Proc Natl Acad Sci USA. 2001 Jul 17;98(15):8809-14; Zaremba S, et al. Identification of an enhancer agonist cytotoxic T lymphocyte peptide from human carcinoembryonic antigen. Cancer Res. 1997 Oct 15;57(20):4570-7; Colombetti S, et al. Impact of orthologous melan-A peptide immunizations on the anti-self melan-A/HLA-A2 T cell cross-reactivity. J Immunol. 2006 Jun 1;176(11):6560-7; Appay V, et al. Decreased specific CD8+ T cell cross-reactivity of antigen recognition following vaccination with Melan-A peptide. Eur J Immunol. 2006 Jul;36(7):1805-14).

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: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016. 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 CTL.

These CTL 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 (Godkin A, et al. Use of eluted peptide sequence data to identify the binding

characteristics of peptides to the insulin-dependent diabetes susceptibility allele HLA-DQ8 (DQ 3.2). Int Immunol. 1997 Jun;9(6):905-11) and databases (Rammensee H. et al. SYFPEITHI: database for MHC ligands and peptide motifs. Immunogenetics. 1999 Nov;50(3-4):213-9), 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: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, 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 CTL, 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.

The amino acid residues that do not substantially contribute to interactions with the T-cell receptor can be modified by replacement with another amino acid whose incorporation does not substantially affect T-cell reactivity and does not eliminate binding to the relevant MHC. Thus, apart from the proviso given, the peptide of the 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.

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

Accordingly, the present invention also 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 class II binding peptides the length can also be 15, 16, 17, 18, 19, 20, 21 or 22 amino acids.

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

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: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

"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: 225, SEQ ID NO: 226: to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016 or a variant thereof contains additional N- and/or C-terminally located stretches of amino acids that are not necessarily forming part of the peptide that functions as an epitope for MHC molecules epitope.

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

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

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

A non-peptide bond is, for example, $-CH_2-NH$, $-CH_2S-$, $-CH_2CH_2-$, $-CH=CH-$, $-COCH_2-$, $-CH(OH)CH_2-$, and $-CH_2SO-$. United States Patent 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 $NaCNBH_3$.

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.

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.

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, 2005, 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) for more extensive methodology relating to chemical modification of proteins.

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

Selective reduction of disulfide bonds in proteins is also common. Disulfide bonds can be formed and oxidized during the heat treatment of biopharmaceuticals.

Woodward's Reagent K may be used to modify specific glutamic acid residues. N-(3-(dimethylamino)propyl)-N'-ethylcarbodiimide can be used to form intra-molecular crosslinks between a lysine residue and a glutamic acid residue.

For example, diethylpyrocarbonate is a reagent for the modification of histidyl residues in proteins. Histidine can also be modified using 4-hydroxy-2-nonenal.

The reaction of lysine residues and other α-amino groups is, for example, useful in binding of peptides to surfaces or the cross-linking of proteins/peptides. Lysine is the site of attachment of poly(ethylene)glycol and the major site of modification in the glycosylation of proteins.

Methionine residues in proteins can be modified with e.g. iodoacetamide, bromoethylamine, and chloramine T.

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

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

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

A peptide or variant, wherein the peptide is modified or includes non-peptide bonds is a preferred embodiment of the invention. Generally, peptides and variants (at least those containing peptide linkages between amino acid residues) may be synthesized by the Fmoc-polyamide mode of solid-phase peptide synthesis as disclosed by Lukas et al. (Solid-phase peptide synthesis under continuous-flow conditions. Proc Natl Acad Sci U S A. May 1981; 78(5): 2791–2795) and references 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/1hydroxybenzotriazole mediated coupling procedure. All coupling and deprotection reactions are monitored using ninhydrin, trinitrobenzene sulphonic acid or isotin test procedures. Upon completion of synthesis, peptides are cleaved from the resin support with concomitant removal of side-chain protecting groups by treatment with 95% trifluoroacetic acid containing a 50 % scavenger mix. Scavengers commonly used include ethandithiol, phenol, anisole and water, the exact choice depending on the constituent amino acids of the peptide being synthesized. Also a combination of solid phase and solution phase methodologies for the synthesis of peptides is possible (see, for example, Bruckdorfer et al., 2004, and the references as cited therein).

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

Purification may be performed by any one, or a combination of, techniques such as re-crystallization, size exclusion chromatography, ion-exchange chromatography,

hydrophobic interaction chromatography and (usually) reverse-phase high performance liquid chromatography using e.g. acetonitril/water gradient separation.

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.

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.

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

Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc. New Haven, CN, USA.

A desirable method of modifying the DNA encoding the polypeptide of the invention employs the polymerase chain reaction as disclosed by Saiki RK, et al. (Diagnosis of

sickle cell anemia and beta-thalassemia with enzymatically amplified DNA and nonradioactive allele-specific oligonucleotide probes. N Engl J Med. 1988 Sep 1;319(9):537-41). This method may be used for introducing the DNA into a suitable vector, for example by engineering in suitable restriction sites, or it may be used to modify the DNA in other useful ways as is known in the art. If viral vectors are used, pox- or adenovirus vectors are preferred.

The DNA (or in the case of retroviral vectors, RNA) may then be expressed in a suitable host to produce a polypeptide comprising the peptide or variant of the invention. Thus, the DNA encoding the peptide or variant of the invention may be used in accordance with known techniques, appropriately modified in view of the teachings contained herein, to construct an expression vector, which is then used to transform an appropriate host cell for the expression and production of the polypeptide of the invention. Such techniques include those disclosed in US Patent 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.

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.

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

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

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

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

A typical mammalian cell vector plasmid for constitutive expression comprises the CMV or SV40 promoter with a suitable poly A tail and a resistance marker, such as neomycin. One example is pSVL available from Pharmacia, Piscataway, NJ, USA. An example of an inducible mammalian expression vector is pMSG, also available from Pharmacia. Useful yeast plasmid vectors are pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers HIS3, TRP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps). CMV promoter-based vectors (for example from Sigma-Aldrich) provide transient or stable expression, cytoplasmic expression or secretion, and N-terminal or C-terminal tagging in various combinations of FLAG, 3xFLAG, c-*myc* or MAT. These fusion proteins allow for detection, purification and analysis of recombinant protein. Dual-tagged fusions provide flexibility in detection.

The strong human cytomegalovirus (CMV) promoter regulatory region drives constitutive protein expression levels as high as 1 mg/L in COS cells. For less potent cell lines, protein levels are typically ~0.1 mg/L. The presence of the SV40 replication origin will result in high levels of DNA replication in SV40 replication permissive COS cells. CMV vectors, for example, can contain the pMB1 (derivative of pBR322) origin

for replication in bacterial cells, the b-lactamase gene for ampicillin resistance selection in bacteria, hGH polyA, and the f1 origin. Vectors containing the preprotrypsin leader (PPT) sequence can direct the secretion of FLAG fusion proteins into the culture medium for purification using ANTI-FLAG antibodies, resins, and plates. Other vectors and expression systems are well known in the art for use with a variety of host cells.

In another embodiment two or more peptides or peptide variants of the invention are encoded and thus expressed in a successive order (similar to "beads on a string" constructs). In doing so, the peptides or peptide variants may be linked or fused together by stretches of linker amino acids, such as for example LLLLLL, or may be linked without any additional peptide(s) between them.

The present invention also relates to a host cell transformed with a polynucleotide vector construct of the present invention. The host cell can be either prokaryotic or eukaryotic. Bacterial cells may be preferred prokaryotic host cells in some circumstances and typically are a strain of E. coli such as, for example, the E. coli strains DH5 available from Bethesda Research Laboratories Inc., Bethesda, MD, USA, and RR1 available from the American Type Culture Collection (ATCC) of Rockville, MD, USA (No ATCC 31343). Preferred eukaryotic host cells include yeast, insect and mammalian cells, preferably vertebrate cells such as those from a mouse, rat, monkey or human fibroblastic and colon cell lines. Yeast host cells include YPH499, YPH500 and YPH501, which are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Preferred mammalian host cells include Chinese hamster ovary (CHO) cells available from the ATCC as CCL61, NIH Swiss mouse embryo cells NIH/3T3 available from the ATCC as CRL 1658, monkey kidney-derived COS-1 cells available from the ATCC as CRL 1650 and 293 cells which are human embryonic kidney cells. Preferred insect cells are Sf9 cells which can be transfected with baculovirus expression vectors. An overview regarding the choice of suitable host cells for expression can be found in, for example, the textbook of Paulina Balbás and Argelia Lorence "Methods in Molecular Biology Recombinant Gene Expression, Reviews and Protocols," Part One, Second Edition, ISBN 978-1-58829-262-9, and other literature known to the person of skill.

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

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

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

In a preferred embodiment the host cell is an antigen presenting cell, in particular a dendritic cell or antigen presenting cell. APCs loaded with a recombinant fusion protein containing prostatic acid phosphatase (PAP) were approved by the U.S. Food and Drug Administration (FDA) on April 29, 2010, to treat asymptomatic or minimally symptomatic metastatic HRPC (Sipuleucel-T) (Small EJ, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006 Jul

1;24(19):3089-94. Rini et al. Combination immunotherapy with prostatic acid phosphatase pulsed antigen-presenting cells (provenge) plus bevacizumab in patients with serologic progression of prostate cancer after definitive local therapy. Cancer. 2006 Jul 1;107(1):67-74).

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

In another embodiment the peptide, the nucleic acid or the expression vector of the invention are used in medicine. For example, the peptide or its variant may be prepared for intravenous (i.v.) injection, sub-cutaneous (s.c.) injection, intradermal (i.d.) injection, intraperitoneal (i.p.) injection, intramuscular (i.m.) injection. Preferred methods of peptide injection include s.c., i.d., i.p., i.m., and i.v. Preferred methods of DNA injection include i.d., i.m., s.c., i.p. and i.v. Doses of e.g. between 50 µg and 1.5 mg, preferably 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 Nature Medicine 18, 1254–1261 (2012)).

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

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

The human peptide loading deficient cell line T2 is available from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, USA under Catalogue No CRL 1992; the Drosophila cell line Schneider line 2 is available from

the ATCC under Catalogue No CRL 19863; the mouse RMA-S cell line is described in Karre et al 1985 (Ljunggren, H.-G., and K. Karre. 1985. J. Exp. Med. 162:1745).

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

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

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: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, or a variant amino acid sequence thereof.

A number of other methods may be used for generating CTL *in vitro*. For example, autologous tumor-infiltrating lymphocytes can be used in the generation of CTL. Plebanski et al (1995) (Induction of peptide-specific primary cytotoxic T lymphocyte responses from human peripheral blood.Eur J Immunol. 1995 Jun;25(6):1783-7) make use of autologous peripheral blood lymphocytes (PLBs) in the preparation of CTL. Furthermore, the production of autologous CTL 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 CTL. In addition, macrophages pulsed with peptide or polypeptide, or infected with recombinant virus, may be used in the preparation of autologous CTL. S. Walter et al. 2003 (Cutting edge: predetermined avidity of human CD8 T cells expanded on calibrated MHC/anti-CD28-coated microspheres.J Immunol. 2003 Nov 15;171(10):4974-8) 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.

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. (1994) Development of cowpea mosaic virus as a high-yielding system for the presentation of foreign peptides.Virology. 1994 Aug 1;202(2):949-55) which describes the development of cowpea mosaic virus as a high-yielding system for the presentation of foreign peptides.

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

Activated T cells, which are produced by the above method, will selectively recognize a cell that aberrantly expresses a polypeptide that comprises an amino acid sequence of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

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.

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

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

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

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

Protocols for this so-called adoptive transfer of T cells are well known in the art. Reviews can be found in: Gattinoni L, et al. Adoptive immunotherapy for cancer: building on success. Nat Rev Immunol. 2006 May;6(5):383-93. Review. and Morgan RA, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. Science. 2006 Oct 6;314(5796):126-9).

Any molecule of the invention, i.e. the peptide, nucleic acid, antibody, expression vector, cell, activated CTL, 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).

Preferably, the medicament of the present invention is a vaccine. It may be administered directly into the patient, into the affected organ or systemically i.d., i.m., s.c., i.p. and i.v., or applied ex vivo to cells derived from the patient or a human cell line which are subsequently administered to the patient, or used *in vitro* to select a subpopulation of immune cells derived from the patient, which are then re-administered to the patient. If the nucleic acid is administered to cells *in vitro*, it may be useful for the cells to be transfected so as to co-express immune-stimulating cytokines, such as interleukin-2. The peptide may be substantially pure, or combined with an immune-stimulating adjuvant (see below) or used in combination with immune-stimulatory cytokines, or be administered with a suitable delivery system, for example liposomes. The peptide may also be conjugated to a suitable carrier such as keyhole limpet haemocyanin (KLH) or mannan (see WO 95/18145 and Longenecker, 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 CTLs is more efficient in the presence of help provided by CD4 T-helper cells. Thus, for MHC Class I epitopes that stimulate CD8 CTL the fusion partner or sections of a hybrid molecule suitably provide epitopes which stimulate CD4-positive T cells. CD4- and CD8-stimulating epitopes are well known in the art and include those identified in the present invention.

In one aspect, the vaccine comprises at least one peptide having the amino acid sequence set forth SEQ ID No. 1 to SEQ ID No. 1016, 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.

In another aspect, the vaccine comprises at least one peptide having the amino acid sequence set forth in SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, 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.

The polynucleotide may be substantially pure, or contained in a suitable vector or delivery system. The nucleic acid may be DNA, cDNA, PNA, RNA or a combination thereof. Methods for designing and introducing such a nucleic acid are well known in the art. An overview is provided by e.g. (Pascolo et al., Human peripheral blood mononuclear cells transfected with messenger RNA stimulate antigen-specific cytotoxic T-lymphocytes in vitro.Cell Mol Life Sci. 2005 Aug;62(15):1755-62). Polynucleotide vaccines are easy to prepare, but the mode of action of these vectors in inducing an immune response is not fully understood. Suitable vectors and delivery systems include viral DNA and/or RNA, such as systems based on adenovirus, vaccinia virus, retroviruses, herpes virus, adeno-associated virus or hybrids containing elements of more than one virus. Non-viral delivery systems include cationic lipids and cationic polymers and are well known in the art of DNA delivery. Physical delivery, such as via a “gene-gun” may also be used. The peptide or peptides encoded by the nucleic acid may be a fusion protein, for example with an epitope that stimulates T cells for the respective opposite CDR as noted above.

The medicament of the invention may also include one or more adjuvants. Adjuvants are substances that non-specifically enhance or potentiate the immune response (e.g., immune responses mediated by CTLs and helper-T (T_H) cells to an antigen, and would thus be considered useful in the medicament of the present invention. Suitable adjuvants include, but are not limited to, 1018 ISS, aluminium salts, AMPLIVAX®, AS15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, flagellin or TLR5 ligands derived from flagellin, FLT3 ligand, GM-CSF, IC30, IC31, Imiquimod (ALDARA®), resiquimod, ImuFact IMP321, Interleukins as IL-2, IL-13, IL-21, Interferon-alpha or -beta, or pegylated derivatives thereof, IS Patch, ISS,

ISCOMATRIX, ISCOMs, JuvImmune®, LipoVac, MALP2, MF59, monophosphoryl lipid A, Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, water-in-oil and oil-in-water emulsions, OK-432, OM-174, OM-197-MP-EC, ONTAK, OspA, PepTel® vector system, poly(lactid co-glycolid) [PLG]-based and dextran microparticles, talactoferrin SRL172, 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 The Yin and Yang of T cell costimulation.Science. 1995 Nov 10;270(5238):932-3. Review). 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, 1996 Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells Nat Med. 1996 Oct;2(10):1096-103).

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 T_{H1} cells and strong cytotoxic T-lymphocyte (CTL) generation, even in the absence of CD4 T cell help. The T_{H1} 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 T_{H2} 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). US 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.

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

Preferred adjuvants are 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.

In a preferred embodiment, the pharmaceutical composition according to the invention the adjuvant is selected from the group consisting of colony-stimulating

factors, such as Granulocyte Macrophage Colony Stimulating Factor (GM-CSF, sargramostim), cyclophosphamide, imiquimod, resiquimod, and interferon-alpha.

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

In a preferred embodiment of the pharmaceutical composition according to the invention, the adjuvant is cyclophosphamide, imiquimod or resiquimod.

Even more preferred adjuvants are Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, poly-ICLC (Hiltonol®) and anti-CD40 mAB or combinations thereof.

This composition is used for parenteral administration, such as subcutaneous, intradermal, intramuscular or oral administration. For this, the peptides and optionally other molecules are dissolved or suspended in a pharmaceutically acceptable, preferably aqueous carrier. In addition, the composition can contain excipients, such as buffers, binding agents, blasting agents, diluents, flavours, lubricants, etc. The peptides can also be administered together with immune stimulating substances, such as cytokines. An extensive listing of excipients that can be used in such a composition, can be, for example, taken from A. Kibbe, Handbook of Pharmaceutical Excipients, 3rd Ed., 2000, American Pharmaceutical Association and pharmaceutical press. The composition can be used for a prevention, prophylaxis and/or therapy of adenomateous or cancerous diseases. Exemplary formulations can be found in, for example, EP2112253.

Nevertheless depending on the number and the physico-chemical characteristics of the peptides of the invention further research is needed to provide formulations for specific combinations of peptides, especially combinations with more than 20 peptides that are stable for more than 12 to 18 months.

The present invention provides a medicament that useful in treating cancer, in particular AML, Chronic lymphoid leukemia (CLL) and other hematological malignancies.

The present invention is further directed at a kit comprising:
(a) a container containing a pharmaceutical composition as described above, in solution or in lyophilized form;
(b) optionally a second container containing a diluent or reconstituting solution for the lyophilized formulation; and
(c) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.

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

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

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

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

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

Preferably, kits of the invention include a formulation of the invention packaged for use in combination with the co-administration of a second compound (such as adjuvants (e.g. GM-CSF), a chemotherapeutic agent, a natural product, a hormone or antagonist, an anti-angiogenesis agent or inhibitor, a 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.

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

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

Since the peptides of the invention were isolated from CLL, the medicament of the invention is preferably used to treat CLL. In a preferred embodiment, since the peptides of the invention derived from a protein selected from the group consisting of APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3 were isolated from CLL, and thus the medicament of the invention is preferably used to treat CLL.

The present invention further includes 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. Preferably, 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.

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.

As used herein, the term “warehouse” shall refer to a group of peptides that have been pre-screened for immunogenicity and over-presentation in a particular tumour 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 tumour-associated peptides which were highly overexpressed in the tumour tissue of several HLA-A, HLA-B and HLA-C positive CLL patients analyzed (see tables above). It contains MHC class I and MHC class II peptides. In addition to the tumor associated peptides collected from several GBM tissues, the warehouse may contain an HLA-A*02 and an HLA-A*24 marker peptide. 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, it functions as an important positive control peptide 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 population.

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

1. HLA ligands from the malignant material were identified by mass spectrometry
2. Genome-wide messenger ribonucleic acid (mRNA) expression analysis by microarrays was used to identify genes over-expressed in the malignant tissue (CLL) compared with a range of normal organs and tissues
3. Identified HLA ligands were compared to gene expression data. Peptides encoded by selectively expressed or over-expressed genes as detected in step 2 were considered suitable TUMAP candidates for a multi-peptide vaccine.
4. Literature research was performed in order to identify additional evidence supporting the relevance of the identified peptides as TUMAPs

5. The relevance of over-expression at the mRNA level was confirmed by redetection of selected TUMAPs from step 3 on tumor tissue and lack of (or infrequent) detection on healthy tissues

6. 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.

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

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

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

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

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

In addition to, or as an alternative to, selecting peptides using a warehousing (database) model, TUMAPs may be identified in the patient *de novo* and then included in the vaccine. As one example, candidate TUMAPs may be identified in the patient by (a1) comparing expression data from the tumor sample to expression data from a sample of normal tissue corresponding to the tissue type of the tumor sample to identify proteins that are over-expressed or aberrantly expressed in the tumor sample; and (a2) correlating the expression data with sequences of MHC ligands bound to MHC class I and/or class II molecules in the tumor sample to identify MHC ligands derived from 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 tumour 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 tumour 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, tumour mRNA is sequenced for direct quantification of gene expression and validation that mutated genes are expressed in the patients' tumours. The resultant millions of sequence reads are processed through software algorithms. The output list contains mutations and gene expression. Tumour-specific somatic mutations are determined by comparison with the PBMC-derived germline variations and prioritized.. The *de novo* identified peptides may then be tested for immunogenicity as described above for the warehouse, and candidate TUMAPs possessing suitable immunogenicity are selected for inclusion in the vaccine.

In one exemplary embodiment, the peptides included in the vaccine are identified by: (a) identifying tumour-associated peptides (TUMAPs) presented by a tumor sample from the individual patient by the methdos 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 tumour-associated peptide identified in the patient; and (d) optionally, selecting at least one peptide identified *de novo* in (a) confirming its immunogenicity.

In one exemplary embodiment, the peptides included in the vaccine are identified by: (a) identifying tumour-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.

Once the peptides are selected, the vaccine is manufactured.

The vaccine preferably is a liquid formulation consisting of the individual peptides dissolved in 33% DMSO.
Each peptide to be included into a product is dissolved in DMSO. The concentration of the single peptide solutions has to be chosen depending on the number of peptides to be included into the product. The single peptide-DMSO solutions are

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

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

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

Figure 1 shows the HLA surface expression of primary CLL samples. (a) HLA class I and (b) HLA class II expression of $CD5^+CD19^+$ CLL cells compared to autologous $CD5^-CD19^+$ B cells in 7 primary CLL samples. Data are expressed as mean ± s.d. of triplicate experiments. (c) Mean HLA class I and (d) HLA class II expression $CD5^+CD19^+$ CLL cells compared to autologous $CD5^-CD19^+$ B cells (n=7). * $P<0.01$ Abbreviations: UPN, uniform patient number

Figure 2 shows the identification of a novel category of tumor-associated antigens by HLA ligandome profiling. (a) Overlap of HLA class I ligand source proteins of primary CLL samples (n=30) and HV PBMC (n=30). (b) Comparative profiling of HLA class I ligand source proteins based on the frequency of HLA restricted representation in CLL and HV PBMC ligandomes. Frequencies [%] of CLL patients/HVs positive for HLA restricted presentation of the respective source protein (x-axis) are indicated on the y-axis. The box on the left-hand side highlights the subset of source proteins showing CLL-exclusive representation in >20% of patients (LiTAAs: ligandome-derived tumor-associated antigens). (c) Representation of published CLL-associated antigens in HLA class I ligandomes. Bars indicate relative representation [%] of respective antigens by HLA class I ligands in CLL and HV PBMC. Dashed lines separate the antigens into three groups according to their degree of CLL-association.

(d) Source protein overlaps of CLL samples from different stages of disease (Binet A (n=9), Binet B (n=7), Binet C (n=14)). (e) Heatmap analysis of the representation frequencies [%] of LiTAAs across different disease stages (Binet A-C, as in (d)) (f) Heatmap analysis of LiTAA representation [%] on primary CLL samples with del17p (n=5) and without del17p (n=25). Abbreviations: CLL, chronic lymphocytic leukemia; HV, healthy volunteer

Figure 3 shows that LiTAAs are specifically recognized by CLL patient immune responses. (a) HLA class I LiTAAs and corresponding LiTAPs (3 HLA-A*03, 5 HLA-A*02, 5 HLA-B*07) functionally evaluated in IFNγ ELISPOT assays. Absolute numbers and frequencies of peptide-specific immune recognition by CLL patient PBMC are summarized in the right hand column. (b) Example of A*03 LiTAPs evaluated in ELISPOT using HV PBMC as a control. An EBV epitope mix containing 4 frequently recognized peptides (....) was used as positive control, HIV GAG_{18-26} A*03 peptide served as negative control. (c) Example of ELISPOT assays using HLA-A*03 LiTAPs (n=3) on PBMC of 3 different CLL patients. Results are shown for immunoreactive LiTAPs. EBV epitope mix served as positive control, HIV GAG_{18-26} A*03 peptide as negative control. (d) Example of HLA-A*03 benign tissue-derived LiBAPs (n=3) tested on CLL patient PBMC as internal control for the target selection strategy. EBV epitope mix served as positive control, HIV GAG_{18-26} A*03 peptide as negative control. (e) Scatterplot of the allele-adjusted frequencies of LiTAP presentation in CLL ligandomes (as detected by MS) and the corresponding allele-adjusted frequencies of immune recognition by CLL patient PBMC in IFNγ ELISPOT. Data points are shown for the 14/15 LiTAPs showing immune recognition. Abbreviations: LiTAP, ligandome-derived tumor-associated peptide; HV, healthy volunteer; neg., negative; pos., positive; UPN, uniform patient number; LiBAP, ligandome-derived benign tissue-associated peptide; MS, mass spectrometry .

Figure 4 shows the identification of additional/synergistic HLA class II LiTAAs and LiTAPs. (a) Overlap of HLA class II ligand source proteins of primary CLL samples (n=20) and HV PBMC (n=13). (b) Comparative profiling of HLA class II ligand source proteins based on the frequency of HLA restricted representation in CLL and HV PBMC ligandomes. Frequencies [%] of CLL patients/HVs positive for HLA restricted presentation of the respective source protein (x-axis) are indicated on the y-axis. The

box on the left-hand side highlights the subset of source proteins showing CLL-exclusive representation in >20% of patients (LiTAAs: ligandome-derived tumor-associated antigens). (c) HLA class II LiTAAs and corresponding LiTAPs (n=6) functionally evaluated in IFNγ ELISPOT assays. Absolute numbers and frequencies of peptide-specific immune recognition by CLL patient PBMC are summarized in the right hand column. (d) Example of HLA class II LiTAPs evaluated in ELISPOT using HV PBMC as a control. PHA was used as positive control. $FLNA_{1669-1683}$ HLA-DR peptide served as negative control. (e) Example of ELISPOT assays using HLA class II LiTAPs (n=6) on PBMC of 3 different CLL patients. Results are shown for immunoreactive LiTAPs. PHA was used as positive control, $FLNA_{1669-1683}$ HLA-DR peptide served as negative control. (f) Overlap analysis of CLL-exclusive HLA class I and HLA class II ligand source proteins for shared/synergistic vaccine targets. (g) Heatmap analysis of the 132 shared HLA class I/II LiTAAs (identified in (d)). The two source proteins showing representation in ≥20% of both, HLA class I and II CLL patient ligandomes are specified.

Figure 5 shows the longitudinal HLA class I ligandome analysis of CLL patients undergoing chemo-/immunotherapy. Volcano-Plots of the relative abundances of ligands in the HLA class I ligandomes of patients after treatment compared to their respective abundance prior to therapy (ratio post therapy/pre therapy). Dashed lines indicate the thresholds for significant changes in abundance (>2-fold ratio, $p<0.05$), with significantly up-regulated ligands in the upper-right and significantly down-regulated ligands in the upper-left. Frequencies of significantly regulated ligands are specified in the respective quadrants. LiTAPs showing significant regulation over the course of therapy are marked in red and their sequences are specified. (a) Analysis of a CLL patient ligandome prior to therapy and 48h/24h after treatment with rituximab/bendamustin ($375mg/m^2$ / $90mg/m^2$). 1/28 (3.6%) of detectable LiTAPs showed significant changes in abundance. (b) Analysis of a CLL patient ligandome prior to therapy and after the first 7 days of treatment with alemtuzumab (3 doses of alemtuzumab, 10 mg, 20 mg and 30mg on day 1, 3 and 5; ligandome analysis on day 7). 3/24 (12.5%) of detectable LiTAPs showed significant changes in abundance. (c) Analysis of a CLL patient ligandome prior to therapy and 24h after treatment with 300 mg ofatumumab. 2/10 (20.0%) of detectable LiTAPs showed significant changes in abundance.

Figure 6 shows the retrospective survival analysis of CLL patients with respect to their immune recognition of LiTAPs. (a) Kaplan Meier plot of the overall survival of 44 CLL patients. (b) Overall survival of subjects evaluated for LiTAP-specific immune responses grouped as follows: black, CLL patients showing immune responses to >1 LiTAPs (n=10). Red, CLL patients showing immune reactions to 0-1 LiTAPs (n=34).

Figure 7 shows the saturation analysis of HLA class I ligand source protein identifications in CLL patients. Number of unique HLA ligand source protein identifications as a function of total HLA ligand source protein identifications in 30 CLL patients. Exponential regression allowed for the robust calculation (R^2=0.9912) of the maximum attainable number of different source protein identifications (dashed line). The dotted line depicts the source proteome coverage achieved in our CLL patient cohort.

Figure 8 shows that HLA-A*02 and B*07 LiTAPs are specifically recognized by CLL patient immune responses. (a) Example of HLA-A*02 (n=3) and (d) HLA-B*07 (n=3) benign tissue-derived LiBAPs tested on CLL patient PBMC as internal control for the target selection strategy. EBV epitope mix served as positive control, HIV $XX_{xx\text{-}xx}$ A*02 and HIV $XX_{xx\text{-}xx}$ HLA-B*07 peptide served as negative control, respectively. (b) Example of HLA-A*02 (n=6) and (e) HLA-B*07 (n=5) LiTAPs evaluated in ELISPOT assays using HV PBMC as a control. Positive and negative controls as described in (a). (c) Example of ELISPOT assays using HLA-A*02 (n=6) and (f) HLA-B*07 (n=5) LiTAPs on PBMC of 3 different HLA-matched CLL patients, each. Results are shown for immunoreactive LiTAPs. Positive and negative controls as described in (a). Abbreviations: LiBAP, ligandome-derived benign tissue-associated peptide; LiTAP, ligandome-derived tumor-associated peptide; HV, healthy volunteer; neg., negative; pos., positive; UPN, uniform patient number.

Figure 9 shows the intracellular cytokine and tetramer staining of HLA-A*03 LiTAP specific CLL patient T cells. (a) Intracellular staining for IFNγ and TNFα of $P_{A*03}{}^3$ ($DMXL1_{1271\text{-}1279}$ SSSGLHPPK (SEQ ID NO: 77) stimulated CLL patient PBMC. PMA/ionomycin served as positive control, HIV $GAG_{18\text{-}26}$ A*03 peptide as negative control. (b) Tetramer staining of CLL patient $CD8^+$ T cells with $P_{A*03}{}^3$ ($DMXL1_{1271\text{-}1279}$

SSSGLHPPK (SEQ ID NO: 77)) tetramers. As control, tetramer staining with the non-recognized $P_{A*02}{}^{1}$ ($ABCA6_{1270-1278}$ ILDEKPVII (SEQ ID NO: 63) in the same patient is shown.

Figure 10 shows the quantification of HLA surface expression on primary CLL cells from patients undergoing chemo-/immunotherapy. HLA surface expression on $CD5^{+}CD19^{+}$ CLL cells was quantified by flow cytometry, before and after therapy. Data are expressed as mean ± s.d. of triplicate experiments. (a) HLA class I and (b) HLA class II surface expression on primary CLL cells of 4 patients prior to therapy and 24h after treatment with rituximab. (c) HLA class I and (d) HLA class II surface expression on primary CLL cells of a patient prior to therapy, 72h (10mg) and 7d (60mg) after treatment with alemtuzumab. *P<0.01 Abbreviations: UPN, uniform patient number; h, hour; d, day.

Figure 11 shows the over-presentation of peptide ILDEKPVII in normal tissues as compared to CLL samples. Shown are only samples on which the peptide was detected. The test panel included 12 CLL samples and the following normal samples: 1 x adipose tissue, 3 x adrenal gland, 6 x artery, 5 x bone marrow, 7 x brain, 3 x breast, 5 x nerve, 13 x colon, 7 x esophagus, 2 x gallbladder, 5 x heart, 12 x kidney, 20 x liver, 44 x lung, 3 x lymph node, 4 x peripheral blood mononuclear cells, 2 x ovary, 6 x pancreas, 1 x peritoneum, 3 x pituitary, 2 x placenta, 3 x pleura, 3 x prostate, 6 x rectum, 7 x salivary gland, 4 x skeletal muscle, 5 x skin, 3 x small intestine, 4 x spleen, 5 x stomach, 4 x testis, 3 x thymus, 3 x thyroid gland, 3 x trachea, 2 x ureter, 5 x urinary bladder, 2 x uterus, 2 x vein.

EXAMPLES

EXAMPLE 1:

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

Tissue samples

Patients' tumor samples were provided by University of Tübingen, Tübingen, Germany. Written informed consents of all patients had been given. For ligandome analysis, PBMC from CLL patients (>80% CLL cell frequency) as well as PBMC from

healthy volunteers (HVs) were isolated by density gradient centrifugation. Informed consent was obtained in accordance with the Helsinki protocol. This study was performed according to the guidelines of the local ethics committee. HLA typing was carried out by the Department of Hematology and Oncology, Tübingen. Samples were stored at -80°C until further use.

Quantification of HLA surface expression

For comparison with healthy autologous B lymphocytes, quantification of HLA surface expression was performed in patient samples containing at least 0.5% $CD5^-$ $CD19^+$ normal B cells. HLA surface expression was analyzed using the QIFIKIT® quantitative flow cytometric assay (Dako) according to the manufacturer's instructions. In brief, triplicates of each sample were stained with the pan-HLA class I specific monoclonal antibody (mAb) W6/32, HLA-DR specific mAb L243 (both produced in house) or IgG isotype control (BioLegend), respectively. Surface marker staining was carried out with directly labeled CD3 (BD), CD5 (BD) and CD19 (BD) antibodies. 7-AAD (BioLegend) was added as viability marker immediately prior to flow cytometric analysis on a FACSCanto Analyzer (BD).

Isolation of HLA peptides from tissue samples

HLA class I and II molecules were isolated employing standard immunoaffinity purification as described previously. In brief, snap-frozen cell pellets were lysed in 10 mM CHAPS/PBS (AppliChem, St. Louis, MO, USA/Gibco, Carlsbad, CA, USA) containing 1x protease inhibitor (Complete, Roche, Basel, Switzerland). HLA molecules were single-step purified using the pan-HLA class I specific mAb W6/32 and the pan-HLA class II specific mAb Tü39 respectively, covalently linked to CNBr-activated sepharose (GE Healthcare, Chalfont St Giles, UK). HLA:peptide complexes were eluted by repeated addition of 0.2% trifluoroacetic acid (TFA, Merck, Whitehouse Station, NJ, USA). Elution fractions E1-E8 were pooled and free HLA ligands were isolated by ultrafiltration using centrifugal filter units (Amicon, Millipore, Billerica, MA, USA). HLA ligands were extracted and desalted from the filtrate using ZipTip C18 pipette tips (Millipore). Extracted peptides were eluted in 35 µl of 80% acetonitrile (ACN, Merck)/0.2% TFA, centrifuged to complete dryness and resuspended in 25 µl of 1% ACN/0.05% TFA. Samples were stored at -20 °C until analysis by LC-MS/MS.

Analysis of HLA ligands by LC-MS/MS

Peptide samples were separated by reversed-phase liquid chromatography (nanoUHPLC, UltiMate 3000 RSLCnano,ThermoFisher, Waltham, MA, USA) and subsequently analyzed in an on-line coupled LTQ Orbitrap XL hybrid mass spectrometer (ThermoFisher). Samples were analyzed in 5 technical replicates. Sample volumes of 5 µl (sample shares of 20%) were injected onto a 75 µm x 2 cm trapping column (Acclaim PepMap RSLC, ThermoFisher) at 4 µl/min for 5.75 min. Peptide separation was subsequently performed at 50°C and a flow rate of 175 nl/min on a 50 µm x 50 cm separation column (Acclaim PepMap RSLC, ThermoFisher) applying a gradient ranging from 2.4-32.0% of ACN over the course of 140 min. Eluting peptides were ionized by nanospray ionization and analyzed in the mass spectrometer implementing a top 5 CID (collision induced dissociation) method generating fragment spectra for the 5 most abundant precursor ions in the survey scans. Resolution was set to 60,000. For HLA class I ligands, the mass range was limited to 400-650 m/z with charge states 2 and 3 permitted for fragmentation. For HLA class II, a mass range of 300-1,500 m/z was analyzed with charge states ≥2 allowed for fragmentation.

Database Search and Spectral Annotation

For data processing, the software Proteome Discoverer (v1.3, ThermoFisher) was used to integrate the search results of the Mascot search engine (Mascot 2.2.04, Matrix Science) against the human proteome as comprised in the Swiss-Prot database (www.uniprot.org, release: September 27th 2013; 20,279 reviewed protein sequences contained). The search combined data of technical replicates and was not restricted by enzymatic specificity. Precursor mass tolerance was set to 5 ppm, fragment mass tolerance to 0.5 Da. Oxidized methionine was allowed as a dynamic modification. False discovery rates (FDR) were determined by the Percolator algorithm based on processing against a decoy database consisting of the shuffled target database. FDR was set at a target value of q≤0.05 (5% FDR). Peptide-spectrum matches (PSMs) with q≤0.05 were filtered according to additional, orthogonal parameters, to ensure spectral quality and validity. Mascot scores were filtered to ≥20. For HLA class I, peptide lengths were limited to 8-12 amino acids (aa) of length. For HLA class II, peptides were limited to 12-25 aa length. Protein grouping

was disabled, allowing for multiple annotations of peptides (e.g. conserved sequences mapping into multiple proteins). For quality control, yield thresholds of ≥300 unique HLA class I ligands and ≥100 unique HLA class II ligands per sample were applied. HLA annotation was performed using SYFPEITHI (www.syfpeithi.de) or an extended in-house database.

Longitudinal analysis of CLL patient ligandomes over the course of therapy

For label-free quantification (LFQ) of the relative HLA ligand abundances over the course of therapy, the injected peptide amounts of paired samples were normalized and LC-MS/MS analysis was performed in 5 technical replicates for each sample.

In brief, relative amounts of substance of paired samples were calculated from average precursor ion intensities determined in dose-finding mass spectrometry runs and adjusted accordingly by dilution. Relative quantification of HLA ligands was performed by calculating the area under the curve of the corresponding precursor extracted ion chromatograms (XIC) using Proteome Discoverer 1.3. The ratios of the mean areas of the individual peptides in the 5 LFQ-MS runs of each sample were calculated and two-tailed *t*-tests were performed using an in-house Matlab script (v8.2, Mathworks).

Peptide synthesis

The automated peptide synthesizer EPS221 (Abimed) was used to synthesize peptides using the 9-fluorenylmethyl-oxycarbonyl/tert-butyl (Fmoc/tBu) strategy as described. Synthetic peptides were used for validation of LC-MS/MS identifications as well as for functional experiments.

Amplification of peptide-specific T cells

PBMC from CLL patients and healthy volunteers were cultured in RPMI1640 medium (Gibco) supplemented with 10% pooled human serum (PHS, produced in-house), 100 mM β-mercaptoethanol (Roth, Karlsruhe, Germany) and 1% penicillin/streptomycin (GE). For $CD8^+$ T cell stimulation, PBMC were thawed and pulsed with 1 µg/ml per peptide. Peptide-pulsed PBMC (5-6 x 10^6 cells/ml) were cultured at 37°C and 5% CO_2 for 12 days. On day 0 and day 1.5 ng/ml IL-4 (R&D Systems, Minneapolis, MN, USA) and 5 ng/ml IL-7 (Promokine, Heidelberg,

Germany) were added to the culture medium. On days 3, 5, 7 and 9, 2 ng/ml IL-2 (R&D Systems) were added to the culture medium. Peptide-stimulated PBMC were functionally characterized by ELISPOT assays on day 12 and by intracellular cytokine staining on day 13 respectively. For $CD4^+$ T-cell stimulation, culture was performed as described for $CD8^+$ T cells with 2 modifications: pulsing was carried out with 10 µg/ml of HLA class II peptide and no IL-4 and IL-7 was added.

IFN-γ ELISPOT assay

IFN-γ ELISPOT assays were carried out as described previously (33). In brief, 96-well nitrocellulose plates (Millipore) were coated with 1 mg/ml IFN-γ mAb (Mabtech, Cincinnati, OH, USA) and incubated over night at 4 °C. Plates were blocked with 10% PHS for 2 h at 37 °C. 5 x 10^5 cells/well of pre-stimulated PBMC were pulsed with 1 µg/ml (HLA class I) or 2.5 µg/ml (HLA class II) peptide and incubated for 24-26 h. Readout was performed according to manufacturer's instructions. Spots were counted using an ImmunoSpot S5 analyzer (CTL, Shaker Heights, OH, USA). T cell responses were considered to be positive when >15 spots/well were counted and the mean spot count per well was at least 3-fold higher than the mean number of spots in the negative control wells (according to the cancer immunoguiding program (CIP) guidelines).

Intracellular IFN-γ and TNF-α staining

The frequency and functionality of peptide-specific $CD8^+$ T cells was analyzed by intracellular IFN-γ and TNF-α staining. PBMC were pulsed with 1 µg/ml of individual peptide and incubated in the presence of 10 µg/ml Brefeldin A (Sigma, St. Louis, MO, USA) and 10 µg/ml GolgiStop (BD) for 6-8 h. Cells were labeled using Cytofix/Cytoperm (BD), CD8-PECy7 (Beckman Coulter, Fullerton, CA, USA), CD4-APC (BD Bioscience), TNF-α-PE (Beckman Coulter) and IFN-γ-FITC (BD). Samples were analyzed on a FACS Canto II.

The frequency of peptide-specific $CD8^+$ T cells was determined by staining with anti-CD8 and HLA:peptide-tetramer-PE

Results

Primary CLL cells display no loss or down-regulation of HLA expression compared to autologous normal B cells

HLA loss or down-regulation in malignancies may pose a major limitation for T cell based immunotherapy. Therefore, as a first step, the inventors determined the HLA expression levels on $CD19^+CD5^+$ CLL cells compared to autologous $CD19^+CD5^-$ B lymphocytes. HLA surface levels were quantified by flow cytometry in a panel of 7 CLL patients. HLA surface expression levels revealed patient-individual heterogeneity with total HLA class I molecule counts ranging from ~42,500-288,500 molecules/cell on CLL cells and ~32,000-256,500 molecules/cell on normal B cells. Patient individual analysis of HLA surface expression in triplicates revealed small, albeit significant differences in expression levels ($P<0.01$) for 4/7 patients (Fig. 1a). HLA-DR expression ranged from ~29,000-100,500 on CLL cells and ~19,500-79,500 on B cells. Minor differences in HLA-DR levels ($P<0.01$) were detected for 5/7 patients. Statistical analysis of mean HLA surface expression on CLL cells compared to normal B cells showed no significant differences in HLA class I and II expression (Fig. 1c, d). Taken together, these data demonstrate high levels of HLA class I and II expression on CLL cells without evidence of HLA loss or down-regulation compared to normal B cells.

LC-MS/MS identifies a vast array of naturally presented HLA class I & II ligands

Mapping the HLA class I ligandomes of 30 CLL patients, the inventors were able to identify a total of 18,844 different peptides representing 7,377 source proteins, attaining >95% of maximum attainable coverage (Figure 7). The numbers of different peptides identified per patient ranged from 345-2,497 (mean 1,131). Overall, peptides restricted by more than 30 different HLA-A and -B alleles (covering >99% of the Caucasian population_ENREF_27) were identified in this study. In the HV cohort of 30 PBMC donors, a total of 17,322 unique peptides representing 7,180 different source proteins were identified (>90% coverage). The HLA allele distribution in the HV cohort covered 100% of HLA-A and >80% of HLA-B alleles in the CLL patient cohort.

Analysis of the HLA class II ligandomes was performed for 20 CLL patients. A total of 5,059 unique peptides representing 1,486 source proteins was identified. The HLA class II HV cohort of 13 PBMC donors yielded 2,046 different peptides representing 756 source proteins.

Comparative profiling of HLA class I ligandomes reveals a multitude of CLL-associated antigens

In order to identify novel CLL-associated antigens, the inventors compared the HLA ligand source proteomes of the CLL and HV cohorts. Overlap analysis of HLA source proteins revealed 2,148 proteins (29.1% of the mapped CLL source proteome) to be exclusively represented in the HLA ligandome of CLL (Fig. 2a). With the aim of designing a broadly applicable off-the-shelf peptide vaccine, the inventors subsequently prioritized the selection of potential targets according to the following criteria:

CLL-exclusivity was defined as paramount criterion, followed by ranking of antigens according to frequency of representation in CLL ligandomes (Fig. 2b). Our platform highlighted 49 source proteins (0.7% of the CLL source proteome) represented by 225 different HLA ligands showing CLL-exclusive representation in ≥20% of CLL patients. Applying the same antigen ranking strategy to HV PBMC exclusive antigens, a set of 71 ligandome-derived benign tissue-associated antigens (LiBAAs) and the 298 corresponding ligands (LiBAPs) were identified for use as internal control in immunological assays.

Apart from broadly represented CLL-LiTAAs suited for the design of off-the-shelf vaccines, a second panel of 2,099 CLL-exclusive antigens with representation frequencies <20% was identified by our platform. These targets lend themselves as repositories for more individualized therapeutic approaches.

Detection of naturally presented HLA class I ligands derived from established CLL-associated antigens by LC-MS/MS

Alongside the identification of novel CLL-associated antigens, a secondary approach focused on the ranking of the few established CLL-antigens within the present dataset of naturally presented HLA ligands. The inventors were able to identify 28 different HLA ligands representing 8 described CLL-associated antigens. Of note, only Fibromodulin ($FMOD_{324-333}$, RINEFSISSF, HLA-A*23 (SEQ ID NO: 526) showed CLL-exclusive representation, ranking at #437 of CLL-antigens in the present dataset, due to low frequency of representation in the CLL patient cohort. The remaining seven antigens showed representation, both on CLL and HV PBMC, thus failing to fulfill the paramount criterion of CLL-exclusivity. However, for CD19, CD20,

RHAMM and PRAME, CLL-associated overrepresentation of varying degrees was detected (Fig. 2c).

Comparative ligandome profiling identifies LiTAAs shared among different disease stages and risk strata

In order to assess the applicability of the novel targets across different stages of disease, the inventors performed subset-specific ligandome profiling comparing patients in disease stages Binet A (n=9), B (n=7) and C (n=14). Overlap analysis of the 2,148 CLL-exclusive source proteins found 550 (25.6%) of them shared among at least two stages, with a core group of 137 proteins (6.1%) represented in patients of all three stages of disease (Fig. 2d). Of note, 45/49 (91.8%) of LiTAAs belong to the core group of shared source proteins represented in all three subsets. Heatmap analysis of the representation frequencies of all 49 LiTAAs across Binet stages A, B and C is shown in Fig. 2e.

Another focus was placed on determining the representation of LiTAAs in the subsets of high-risk patients carrying the 17p13 deletion (del17p, n=5) as compared to patients without this genetic aberration (no del17p, n=25). The inventors found 77.7% of the identified LiTAAs to be represented in both subsets (Fig. 2f). Together, these data support the devised strategy of cohort-comprising analysis of HLA ligandomes for selection of broadly applicable targets.

Functional characterization of HLA class I LiTAPs reveals CLL-associated immunoreactivity

In order to evaluate the immunogenicity and specificity of our HLA class I LiTAPs, the inventors next performed 12-day recall IFNγ ELISPOT assays. A panel of 15 LiTAPs (6 A*02, 4 A*03 and 5 B*07 LiTAPs) was implemented for stimulation of HLA-matched PBMC obtained from CLL patients and healthy volunteers (Fig. 3a). The inventors observed IFNγ secretion for 14/15 (93.3%) of tested LiTAPs in CLL patients (3/4 A*03 (Fig. 3c), 6/6 A*02 and 5/5 B*07 LiTAPs (Fig. 8 c,f)), but not in healthy controls (0/10, Fig. 3b, Fig. 8 b,e). These findings were confirmed exemplarily for $P_{A*03}{}^{3}$ ($DMXL1_{1271-1279}$ SSSGLHPPK) by tetramer staining of $CD8^{+}$ T cells and intracellular cytokine staining for IFNγ and TNFα (Fig. 9 a,b). ELISPOT assays using HLA-matched benign tissue-derived LiBAPs were performed to control for the CLL-

specificity of the observed LiTAP-directed immune recognition in CLL patients. The inventors tested a panel of 9 LiBAPs (3 A*02, 3 A*03, 3*B*07) and observed no significant IFNγ secretion in any of the tested CLL patients (0/7 A*03 (Fig. 3d), 0/10 $A*02^+$ and 0/5 B*07 (Fig. 8 a,d)).

For the 14/15 LiTAPs showing immune recognition in 1 or more patients, the inventors calculated the allele-adjusted frequencies of HLA restricted presentation (as detected by LC-MS/MS) and the frequencies of immunoreactivity (as detected by ELISPOT) in CLL patients. Strikingly, a linear correlation of these two parameters was observed (Pearson's r=0.77, R^2=0.59, Fig. 3 e). These findings suggest two main points: First, tumor-exclusive representation is prerequisite for immune recognition. Secondly, frequency of immune recognition can be directly deduced from the frequency of HLA restricted presentation for immunoreactive LiTAPs. Together, these data demonstrate the efficacy of our approach identifying immunologically relevant targets for CLL-specific peptide vaccines.

HLA class II ligandome analysis identifies additional $CD4^+$ T cell epitopes for synergistic vaccine design

Because of the important indirect and direct roles $CD4^+$ T cells play in anti-cancer immune responses, optimal vaccine design calls for the inclusion of additional HLA class II epitopes. The inventors performed overlap analysis of CLL and HV PBMC ligandomes and identified 937 proteins (63.0% of the identified CLL source proteins) to be exclusively represented in the ligandomes of CLL patients (Fig. 4 a). Applying the same antigen-ranking strategy as described for HLA class I, the inventors identified 73 HLA class II LiTAAs represented by 460 corresponding LiTAPs (Fig. 4 b). Functional characterization of a panel of 7 HLA class II LiTAPs (Fig. 4c) in IFNγ ELISPOT assays revealed significant IFNγ secretion for 6/7 (85.7%) LiTAPs in CLL patients (Fig. 4e), but not in healthy controls (0/10, Fig. 4d). Next, the inventors performed combined analysis of HLA class I and II ligandomes in order to identify shared, synergistic targets. Overlap analysis of CLL-exclusive source proteins revealed 132 proteins to be represented both in HLA class I and II ligandomes (Fig. 4f). Heatmap analysis identified 2 proteins displaying representation frequencies ≥20% in both ligandomes (B4GALT1 (26.7% class I/30.0% class II), HLA-DMA (20.0% class I/20% class II), Fig. 4g). Strikingly, one of the class I LiTAPs (HLA-

$DMA_{206-214}$, HEIDRYTAI, B*18) was revealed to be completely embedded in the corresponding HLA class II LiTAP (VTHEIDRYTAIAY (SEQ ID No. 924)). Together, the inventors identified a panel of class II LiTAPs, which could be verified as T cell epitopes, as well as an array of potentially synergistic HLA class II ligands covering class I LiTAAs.

Longitudinal analysis of CLL patient ligandomes under different therapeutic regimens

The scope of peptide based immunotherapy is maintenance therapy and eradication of MRD. As a consequence, peptide vaccination in CLL would take place after standard chemo-/immunotherapy. Therefore, the inventors analyzed HLA expression and performed ligandome profiling across different time points of CLL patients undergoing different therapeutic regimens.

The inventors quantified HLA class I and II surface expression in 4 patients undergoing rituximab treatment (Rt_{0h}, Rt_{24h}) and 1 patient receiving alemtuzumab (At_{0h}, At_{72h}, At_{7d}, Fig. 10 a-d). HLA surface expression showed patient-individual heterogeneity with no significant changes in mean HLA class I (Rt_{0h}=50,500, Rt_{24h}=48,000; At_{0h}=42,500, At_{7d}=61,500) and HLA class II (Rt_{0h}=36,500, Rt_{24h}=27,500; At_{0h}=47,000, At_{7d}=55,500) expression over the course of either therapeutic regimen.

Longitudinal HLA class I ligandome profiling was performed in single patients undergoing rituximab-bendamustin, alemtuzumab or ofatumumab treatment, respectively (Fig. 5a-c). Differential presentation (≥2-fold change, $p \leq 0.05$) was observed for 11.1% of HLA class I ligands under rituximab-bendamustin treatment, for 21.6% of ligands under ofatumumab treatment and for 33.6% of ligands under alemtuzumab treatment. Overall, LiTAPs representing 8/49 (16.3%) LiTAAs were revealed to be differentially presented over the course of therapy. Taken together, these data demonstrate stable expression of surface HLA and robust presentation of LiTAPs over the course of different therapies.

Immune responses against LiTAPs might be associated with improved overall survival of CLL patients

As a last step, the inventors performed retrospective survival analysis of 33 CLL patients (Fig. 6a) analyzed by ELISPOT assays comparing cases with 0-1 LiTAP-specific (n=23) versus >1 LiTAP-specific (n=10) T cell responses (Fig. 6 b). In the low-responding cohort 6/23 (26.1%) of patients, in the high-responding cohort 0/11 of patients died. Overall survival seems to be prolonged in the cohort showing >1 immune reactions.

EXAMPLE 2

Synthesis of peptides

All peptides were synthesized using standard and well-established solid phase peptide synthesis using the Fmoc-strategy. After purification by preparative RP-HPLC, ion-exchange procedure was performed to incorporate physiological compatible counter ions (for example trifluoro-acetate, acetate, ammonium or chloride).

Identity and purity of each individual peptide have been determined by mass spectrometry and analytical RP-HPLC. After ion-exchange procedure the peptides were obtained as white to off-white lyophilizates in purities of 90% to 99.7%.

All TUMAPs are preferably administered as trifluoro-acetate salts or acetate salts, other salt-forms are also possible. For the measurements of example 4, trifluoro-acetate salts of the peptides were used.

EXAMPLE 3

MHC Binding Assays

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

generally described in Rodenko et al. (Rodenko et al., Nat Protoc. **1** (2006): 1120-1132).

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

MHC class I binding scores for the peptides as tested were; <20 % = +; 20 % - 49 % = ++; 50 % - 75 %= +++; >= 75 % = ++++

Seq ID NO.	sequence	Peptide exchange
229	FRVGNVQEL	++++
239	SENAFYLSP	++++

EXAMPLE 4

***In vitro* immunogenicity for MHC class I presented peptides**

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

***In vitro* priming of CD8+ T cells**

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

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

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

The purified co-stimulatory mouse IgG2a anti human CD28 Ab 9.3 (Jung et al., Proc Natl Acad Sci USA **84** (1987): 4611-4615) was chemically biotinylated using Sulfo-N-hydroxysuccinimidobiotin as recommended by the manufacturer (Perbio, Bonn, Germany). Beads used were 5.6 µm diameter streptavidin coated polystyrene particles (Bangs Laboratories, Illinois, USA).

pMHC used for positive and negative control stimulations were A*0201/MLA-001 (peptide ELAGIGILTV (SEQ ID NO. 1017) from modified Melan-A/MART-1) and A*0201/DDX5-001 (YLLPAIVHI from DDX5, SEQ ID NO. 1018), respectively.

800.000 beads / 200 µl were coated in 96-well plates in the presence of 4 x 12.5 ng different biotin-pMHC, washed and 600 ng biotin anti-CD28 were added subsequently in a volume of 200 µl. Stimulations were initiated in 96-well plates by co-incubating $1x10^6$ CD8+ T cells with $2x10^5$ 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., Nat.Protoc. **7** (2012): 891-902) with minor modifications encompassing coupling to 5 different fluorochromes. Finally, multimeric analyses were performed by staining the cells with Live/dead near IR dye (Invitrogen, Karlsruhe, Germany), CD8-FITC antibody clone SK1 (BD, Heidelberg, Germany) and fluorescent pMHC multimers. For analysis, a BD LSRII SORP cytometer equipped with appropriate lasers and filters was used. Peptide specific cells were calculated as percentage of total CD8+ cells. Evaluation of multimeric analysis was done using the FlowJo software (Tree Star, Oregon, USA). *In vitro* priming of specific multimer+ CD8+ lymphocytes was detected by by comparing to negative control stimulations. Immunogenicity for a given antigen was detected if at least one evaluable *in vitro* stimulated well of one healthy donor was found to contain a specific CD8+ T-cell line after *in vitro* stimulation (i.e. this well contained at least 1% of specific multimer+ among CD8+ T-cells and the percentage of specific multimer+ cells was at least 10x the median of the negative control stimulations).

In vitro immunogenicity for CLL peptides

For tested HLA class I peptides, *in vitro* immunogenicity could be demonstrated by generation of peptide specific T-cell lines. As an exemplary result, peptide KFAEEFYSF (SEQ ID NO. 20) led to *in vitro* T-cell responses in 2 of 5 tested donors.

EXAMPLE 5

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

Tissue samples:

In addition to the samples used for identification of peptides, an independent sample set comprising both normal and tumor (CLL) tissues was used for analysis / confirmation of HLA-A*02-associated peptides of the invention. Written informed consents of all patients had been given before surgery or autopsy. Tissues were shock-frozen immediately after excision and stored until isolation of TUMAPs at -70°C or below.

Isolation of HLA peptides from tissue samples

HLA peptide pools from shock-frozen tissue samples were obtained by immune precipitation from solid tissues according to a slightly modified protocol (Falk et al., Nature **351** (1991): 290-296; Seeger et al., Immunogenetics **49** (1999): 571-576) using the HLA-A*02-specific antibody BB7.2, the HLA-A, -B, C-specific antibody W6/32, CNBr-activated sepharose, acid treatment, and ultrafiltration.

Mass spectrometry analyses

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

Label-free relative LC-MS quantitation was performed by ion counting i.e. by extraction and analysis of LC-MS features (Mueller et al., Proteomics. **7** (2007): 3470-3480). 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., J

Proteome.Res **7** (2008): 51-61; Sturm et al., BMC.Bioinformatics. **9** (2008): 163). 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. The presentation profile of an exemplary over-presented peptide is shown in Figure 11.

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Claims

1. A peptide of between 9 and 100 amino acids in length, comprising an amino acid sequence that is at least 80% identical to a sequence selected from SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016, or a pharmaceutically acceptable salt thereof.

2. The peptide according to claim 1, wherein said peptide has the ability to bind to a human major histocompatibility complex (MHC) class-I molecule and/or a human major histocompatibility complex (MHC) class-II molecule.

3. The peptide according to claim 1, wherein said peptide is between 9 and 30 amino acids in length.

4. The peptide according to claim 1, comprising an N-terminal and/or C-terminal amino acid extension of no more than 10 amino acids in length.

5. The peptide according to any one of claims 1 to 3, selected from the group consisting of:
(a) a peptide consisting of an amino acid sequence that is to at least 80% identical to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016;
(b) the peptide of (a) having an N-terminal extension of the core sequence not more than 10 amino acids in length; and
(c) the peptide of (a) or (b), having a C-terminal extension not more than 10 amino acids in length.

6. The peptide according to any of claims 1 to 5, wherein said amino acid sequence is to at least 90% identical to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

7. The peptide according to any of claims 1 to 6, wherein said amino acid sequence is at least 95% identical to SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

8. The peptide according to any of claims 1 to 6, wherein said amino acid sequence comprises any of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

9. The peptide according to claim 1 or 2, wherein said amino acid sequence consists of any of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

10. The peptide according to any of Claims 1 to 9, wherein said peptide is modified and/or includes non-peptide bonds.

11. A T-cell receptor that is reactive with an HLA ligand having at least 80% identity to an amino acid sequence selected from the group consisting SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542, and SEQ ID NO: 543 to SEQ ID NO: 1016.

12. The T-cell receptor according to claim 11, wherein said amino acid sequence is to least 90%, or to at least 95% identical to SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016.

13. The T-cell receptor according to claim 11 or 12, wherein said amino acid sequence comprises any of SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016.

14. The T-cell receptor according to any of claims 11 to 13, wherein said amino acid sequence consists of any of SEQ ID NO: 1 to SEQ ID NO: 225, SEQ ID NO: 226 to SEQ ID NO: 542 or SEQ ID NO: 543 to SEQ ID NO: 1016.

15. A fusion protein, comprising
(a) an amino acid sequence that is to at least 80% identical to SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016; and
(b) N-terminal amino acids 1-80 of HLA-DR antigen-associated invariant chain (Ii).

16. The fusion protein according to claim 15, wherein said amino acid sequence of (a) is at least 90%, preferably at least 95% identical to SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016.

17. The fusion protein according to claim 16, wherein said amino acid sequence of (a) comprises SEQ ID NO: 1 to SEQ ID NO: 225 or SEQ ID NO: 543 to SEQ ID NO: 1016.

18. A nucleic acid, encoding for:
(a) the peptide according to any of Claims 1 to 10;
(b) the T cell receptor according to any claims 11 to 14; or
(c) the fusion protein according to claims 15 to 17.

19. The nucleic acid according to Claim 18, which is DNA, cDNA, PNA, RNA, or combinations thereof.

20. An expression vector comprising a nucleic acid according to Claim 18 or 19.

21. A host cell comprising the nucleic acid according to Claim 18 or 19, or the expression vector according to Claim 20.

22. The host cell according to Claim 21 that is an antigen presenting cell, for example a dendritic cell.

23. A method for producing the peptide according to any one of Claims 1 to 10, the T cell receptor according to any of Claims 12 to 14, or the fusion protein according to any of Claims 15 to 17, said method comprising culturing the host cell according to Claim 21, and isolating said peptide, said T cell receptor, or said fusion protein from said host cell and/or its culture medium.

24. An *in vitro* method for producing activated cytotoxic T lymphocytes (CTL), the method comprising contacting *in vitro* a CTL with antigen loaded human class I or II MHC molecules expressed on the surface of a suitable antigen-presenting cell for a

period of time sufficient to activate said CTL in an antigen specific manner, wherein said antigen is said peptide according to any one of claims 1 to 10.

25. The method according to Claim 24, wherein said 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.

26. The method according to Claim 25, wherein said antigen-presenting cell comprises an expression vector capable of expressing said peptide according to any one of claims 1 to 9.

27. An activated cytotoxic T lymphocyte (CTL), produced by the method according to any one of Claims 24 to 26.

28. A method of killing target cancer cells in a patient, the method comprising administering to said patient an effective number of cytotoxic T lymphocytes (CTL) according to Claim 27.

29. Use of the peptide according to any one of Claims 1 to 10, the T cell receptor according to any of Claims 12 to 14, the fusion protein according to any of Claims 15 to 17, the nucleic acid according to Claim 18 or 19, the expression vector according to claim 20, the host cell according to Claims 22 or 23, or the activated cytotoxic T lymphocyte according to claim 27 as a medicament, or in the manufacture of a medicament.

30. The use according to claim 29, wherein said medicament is a vaccine.

31. The use according to Claim 29 or 30, wherein said medicament is active against cancer.

32. The use according to any of Claims 29 to 31, wherein said cancer is chronic lymphatic leukemia (CLL) and/or acute myeloid leukemia (AML).

33. A pharmaceutical composition comprising at least one active ingredient selected from the group consisting of the peptide according to any one of Claims 1 to 10, the T cell receptor according to any of Claims 12 to 14, the fusion protein according to any of Claims 15 to 17, the nucleic acid according to Claim 18 or 19, the expression vector according to claim 20, the host cell according to Claims 22 or 23, and the activated cytotoxic T lymphocyte according to claim 27, and
a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising at least one active ingredient selected from the group consisting of
a) a peptide having the ability to bind to a human major histocompatibility complex (MHC) class-I molecule and/or a human major histocompatibility complex (MHC) class-II molecule, and wherein said peptide is derived from a protein selected from the group consisting of APOBEC3D, CDK14, RASGRF1, CDCA7L, CELSR1, AKAP2, CTDP1, DNMBP, TAGAP, ABCA6, DMXL1, PARP3, TP53I11, B4GALT1, IRF9, KDM2B, TBC1D22A, ZNF296, BACH2, PRR12, ZFAND5, ATP5G1, DMD, ARID5B, ZNF638, DDX46, RRM2B, BLNK, HSH2D, ERP44, METTL7A, ELP3, NLRP2, ZC3H12D, NELFE, ATP6V1C1, HLA-DMA, TUFM, EIF6, CKAP4, COBLL1, TMED4, TNFRSF13C, UBL7, CXorf21, ASUN, SL24D1, and TRAF3IP3;
b) a T-cell receptor reactive with a peptide according to (a);
c) a fusion protein comprising a peptide according to (a), and the N-terminal amino acids 1 to 80 of the HLA-DR antigen-associated invariant chain (Ii);
d) a nucleic acid encoding for any of a) to c) or an expression vector comprising said nucleic acid,
e) a host cell comprising the expression vector of d, and
f) an activated cytotoxic T-lymphocyte (CTL), obtained by a method comprising contacting *in vitro* CTL with a peptide according to a) expressed on the surface of a suitable antigen-presenting cell for a period of time sufficient to activate said CTL in an antigen specific manner; and
a pharmaceutically acceptable carrier.

35. A method for killing target cells in a patient, said method comprising administering to the patient an effective amount of the pharmaceutical composition according to Claim 34.

36. A method for identifying a tumor-associated peptide as suitable for inclusion in a peptide-based vaccine, said method comprising:
(a) eluting and identifying naturally presented HLA ligands from at least one primary tumor sample and from at least one corresponding normal tissue sample,
(b) generating a ligandome for said at least tumor sample and for said at least normal tissue sample based on said HLA ligands as identified; and
(c) selecting at least one HLA ligand as suitable for inclusion that a) is derived from an antigen exclusively presented by cells of said at least one tumor sample and b) exhibits a high frequency of presentation in said ligandome for said at least one tumor sample.

37. The method according to Claim 36, wherein said frequency of presentation is selected from at least 5%, at least 10%, and at least 20%.

38. The method according to Claims 36 or 37, wherein a plurality of samples is used, and a plurality of ligandomes is generated.

39. The method according to any of Claims 36 to 38, wherein a tumor sample from an individual patient is used in step (a).

40. The method according to any of Claims 36 to 39, wherein said selecting in step (c) comprises comparing said ligandome with a database of peptides that have been prescreened for immunogenicity and overpresentation in tumors as compared to corresponding non tumor tissue.

41. The method according to any of Claims 36 to 40, wherein said identifying comprises eluting bound peptides from MHC molecules from said tumor sample, and sequencing of said eluted peptides.

42. The method according to any of Claims 36 to 41, wherein said at least normal tissue sample corresponds in tissue type to the tumor sample from the patient.

43. The method according to any of Claims 40 to 42, wherein said peptides included in the database are identified by a method comprising:
1) identifying HLA ligands from said tumor material by mass spectrometry;
2) identifying genes that are over-expressed in the tumor material by comparison with a range of normal tissues using genome-wide messenger ribonucleic acid (mRNA) expression analysis using microarrays;
3) comparing the HLA ligands as identified with the gene expression data;
4) selecting peptides encoded by genes that are specifically expressed or over-expressed as detected in step b);
5) confirming the relevance of the over-expression at the mRNA level by redetection of selected HLA ligands from step c) on tumor tissue in contrast to normal tissues; and
6) performing *in vitro* immunogenicity assays using human T cells from the patient or healthy donors in order to assess, whether an induction of *in vivo* T-cell responses by the peptides as selected can be achieved.

44. The method according to any of Claims 40 to 43, wherein the immunogenicity of the peptides included in the database is determined by a method selected from the group of *in vitro* immunogenicity assays, patient immune-monitoring for individual HLA binding, MHC multimer staining, ELISPOT assays, and intracellular cytokine staining.

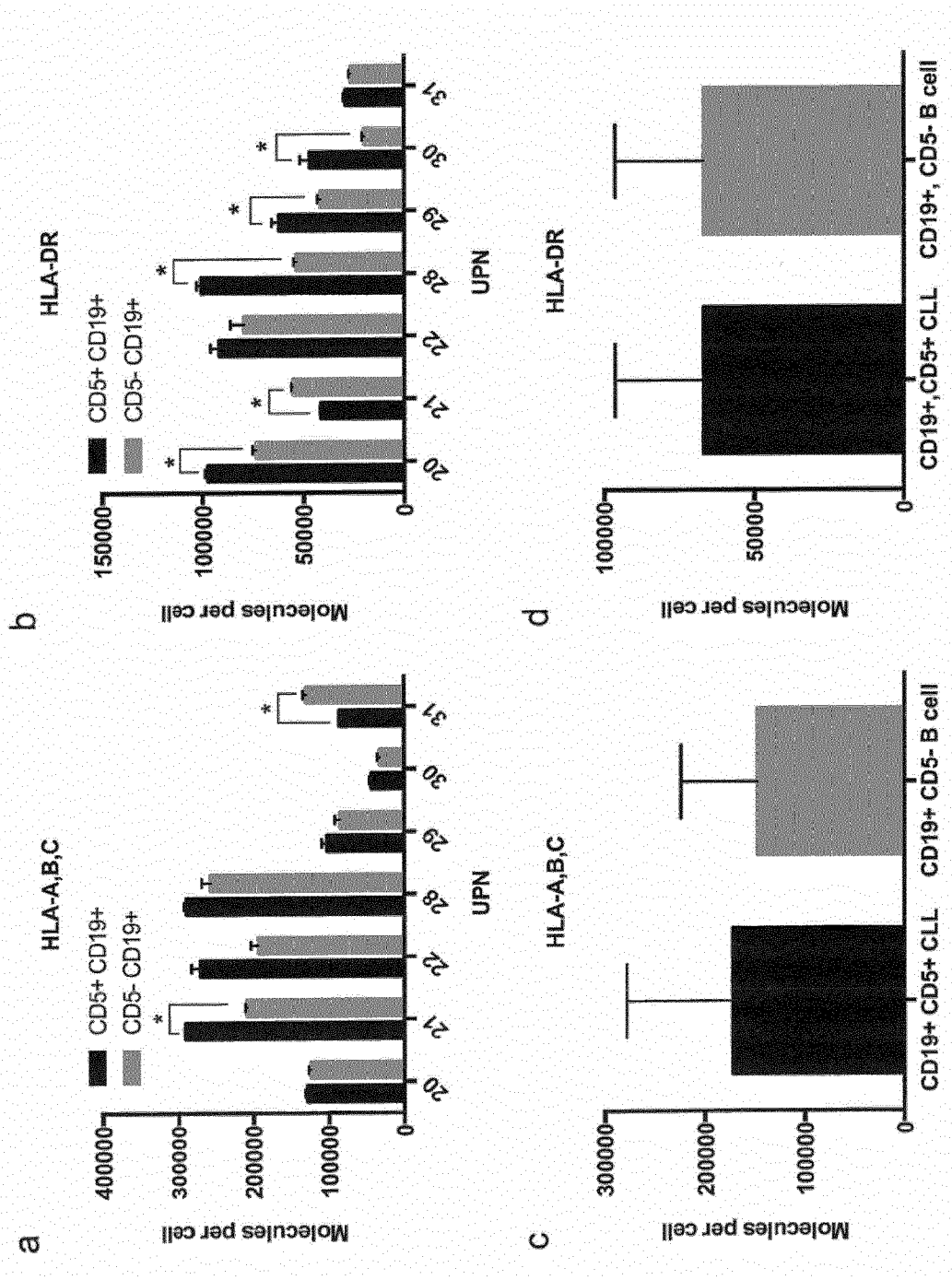
45. The method according to any of Claims 40 to 44, wherein the database comprises the peptides SEQ ID NO: 1 to SEQ ID NO: 1016.

46. The method according to any of Claims 40 to 45, further comprising the step of identifying at least one peptide having at least one mutation that is unique for said tumor sample compared with normal corresponding tissue from said individual patient, and optionally, selecting said peptide for inclusion into the vaccine.

47. The method according to Claim 46, wherein said at least one mutation is identified by whole genome sequencing.

48. The method according to any of Claims 36 to 47, further comprising the step of producing a peptide-based vaccine comprising at least one tumor-associated peptide as selected according to (c), wherein said peptide-based vaccine is preferably personalized.

Figure 1


a
HLA-A,B,C
CD5+ CD19+
CD5- CD19+
Molecules per cell
400000
300000
200000
100000
0
20
27
28
29
30
37
UPN
*
b
HLA-DR
CD5+ CD19+
CD5- CD19+
Molecules per cell
150000
100000
50000
0
20
27
28
29
30
37
UPN
*
c
HLA-A,B,C
Molecules per cell
300000
200000
100000
0
CD19+ CD5+ CLL
CD19+ CD5- B cell
d
HLA-DR
Molecules per cell
100000
50000
0
CD19+,CD5+ CLL
CD19+, CD5- B cell

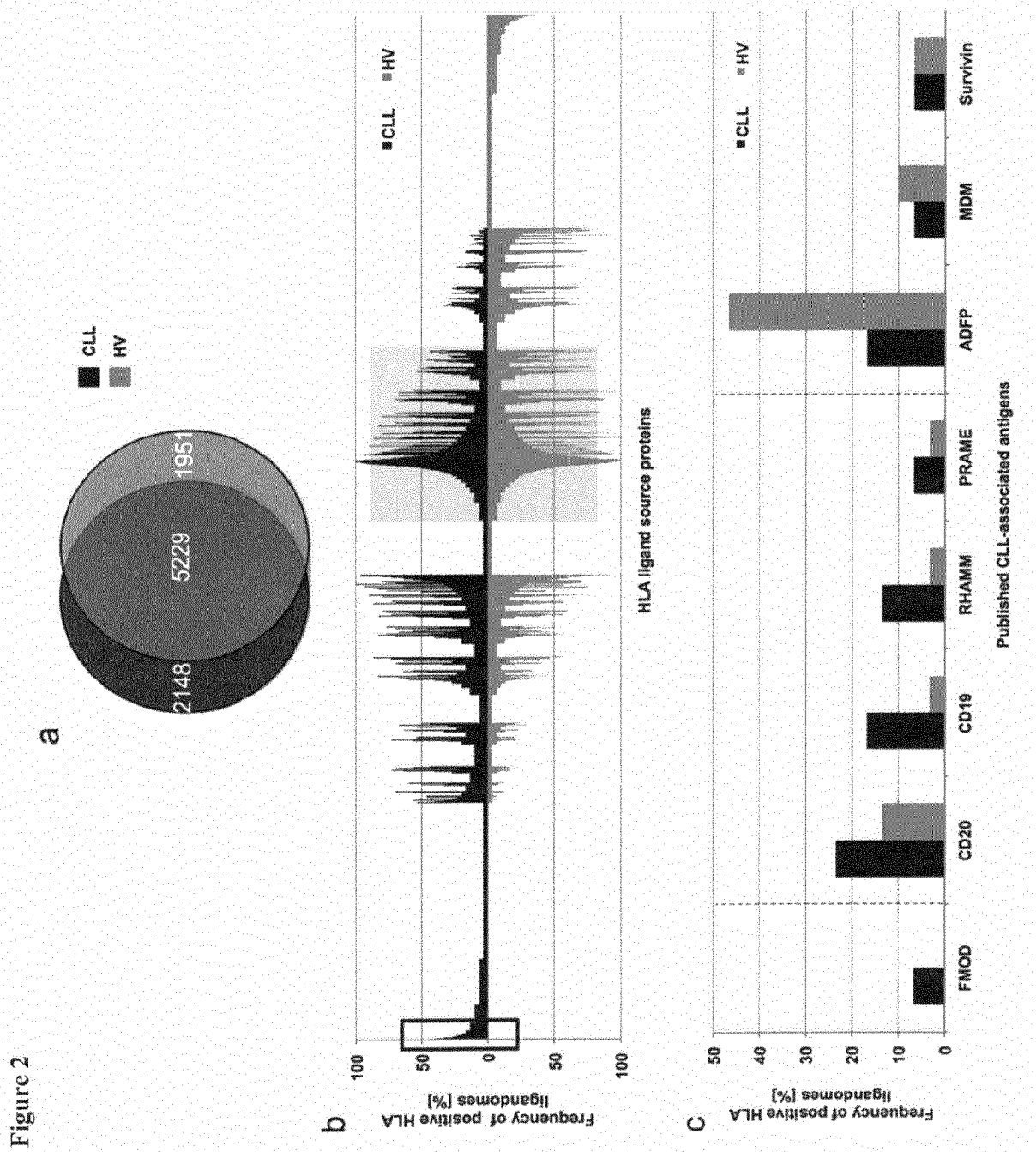

a
CLL
HV
2148
5229
1951
b
CLL
HV
Frequency of positive HLA ligandomes [%]
100
50
0
50
100
HLA ligand source proteins
c
CLL
HV
Frequency of positive HLA ligandomes [%]
50
40
30
20
10
0
FMOD
CD20
CD19
RHAMM
PRAME
ADFP
MDM
Survivin
Published CLL-associated antigens

Figure 2

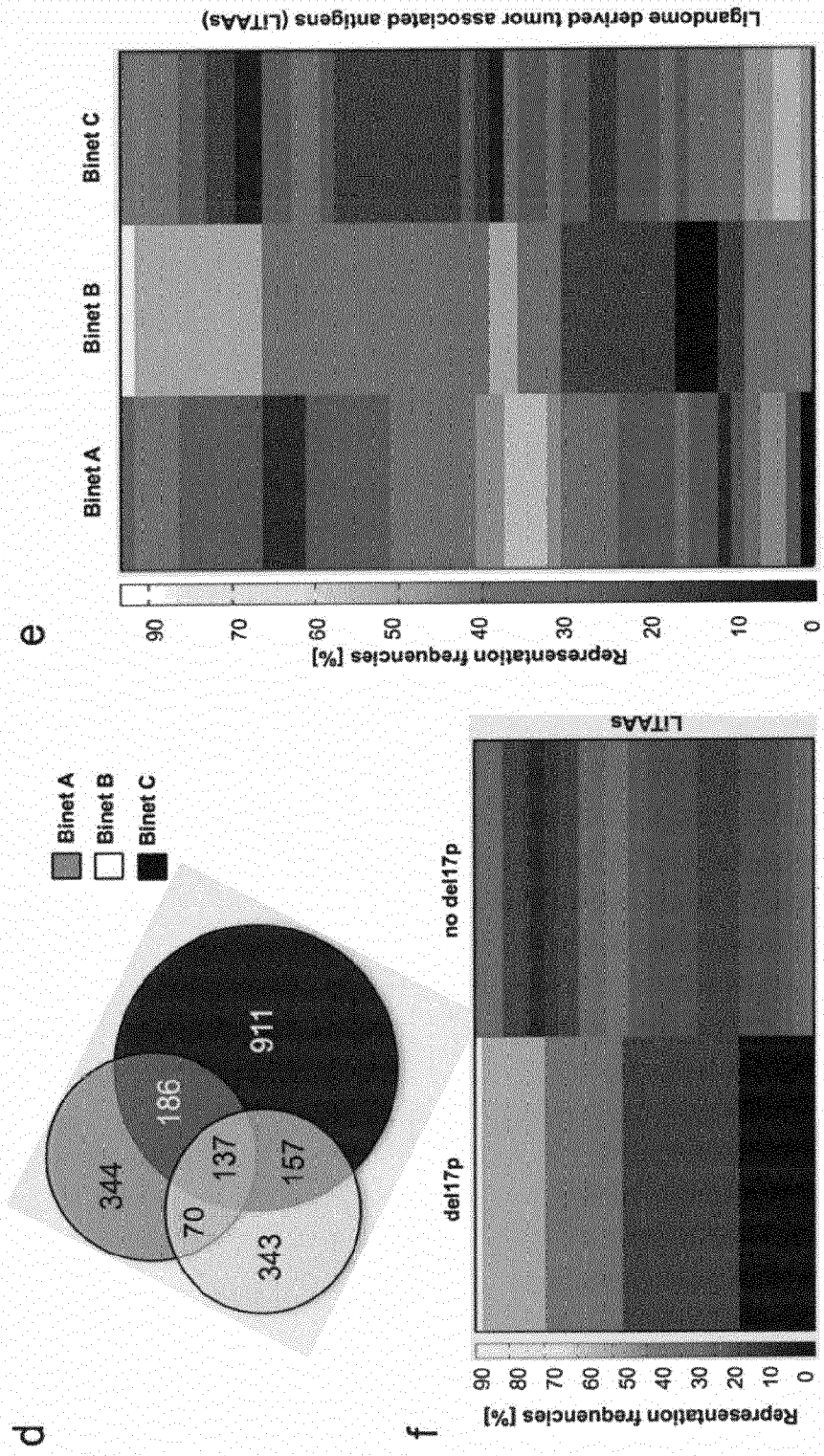


Figure 2 cont.:

Figure 3

a

Peptide	Sequence	Source protein	CD8+ T-cell response in CLL
P_{A*03}^{1}	YGYDNVKEY	CDCA7L	2/13 (15,3%)
P_{A*03}^{2}	AVFDGAQVTSK	TP53I11	3/13 (23,0%)
P_{A*03}^{3}	SSSGLHPPK	DMXL1	4/13 (30,8%)
P_{A*02}^{1}	ILDEKPVII	ABCA6	2/11 (18,2%)
P_{A*02}^{2}	YLNKEIEEA	CTDP1	3/11 (27,3%)
P_{A*02}^{3}	SILEDPPSI	ASUN	3/11 (27,3%)
P_{A*02}^{4}	DLDVKKMPL	PARP3	2/11 (18,2%)
P_{A*02}^{5}	QLLDQVEQI	TMED4	3/11 (27,3%)
P_{A*02}^{6}	AAANIIRTL	RASGRF1	1/11 (9,1%)
P_{B*07}^{1}	SPRPPLGSSL	KDM2B	4/6 (66,7%)
P_{B*07}^{2}	APLQRSQSL	TBC1D22A	4/7 (57,1%)
P_{B*07}^{3}	SPTSSRTSSL	CELSR1	3/6 (50%)
P_{B*07}^{4}	KPRQSSPQL	DNMBP	3/6 (50%)
P_{B*07}^{5}	SASVQRADTSL	ZFAND5	4/14 (28,6%)

b

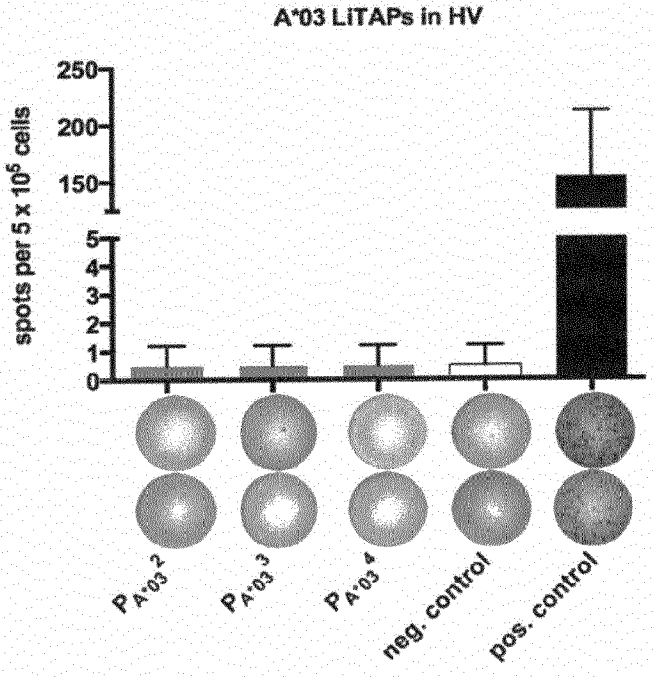
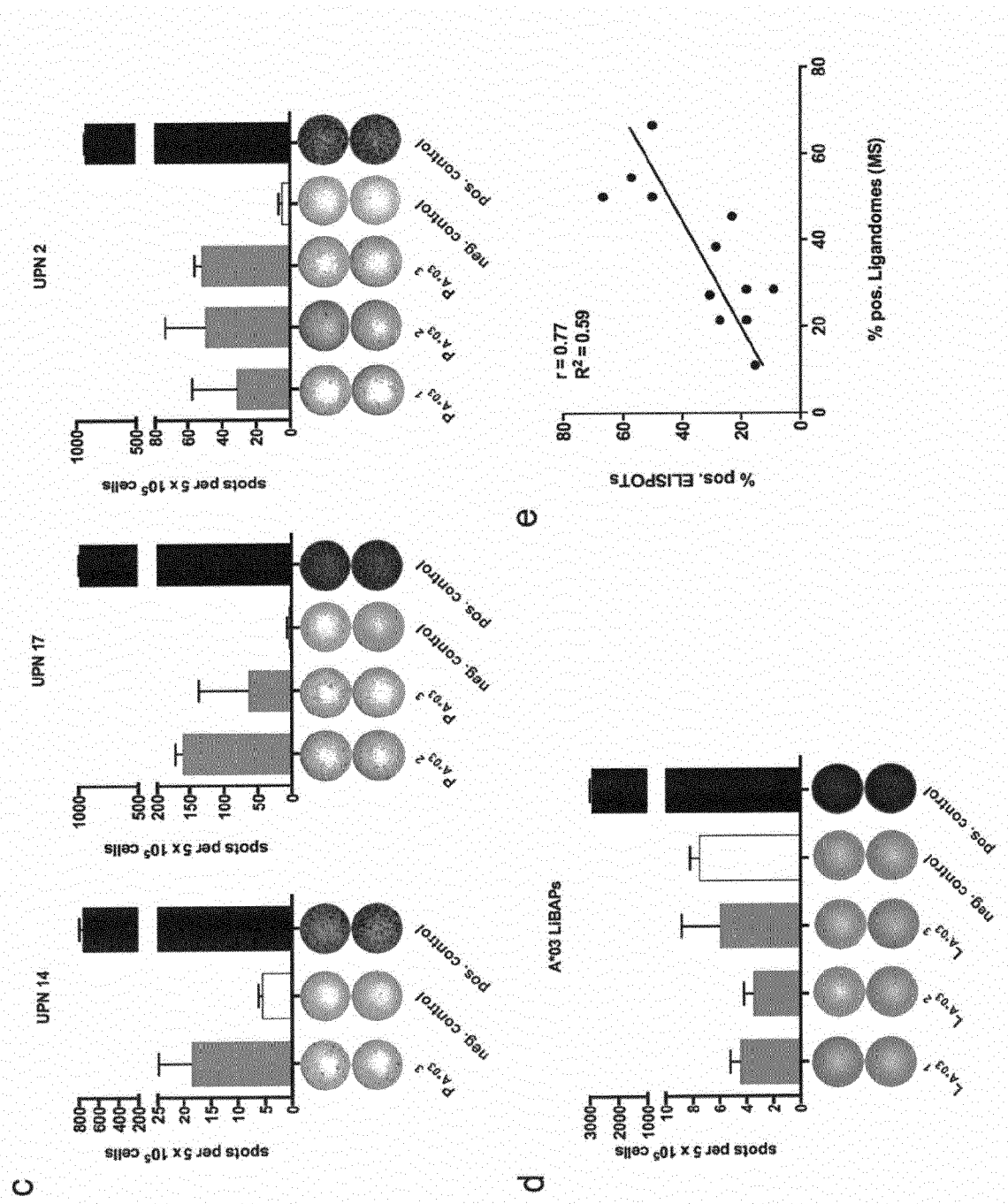


Figure 3 cont.:



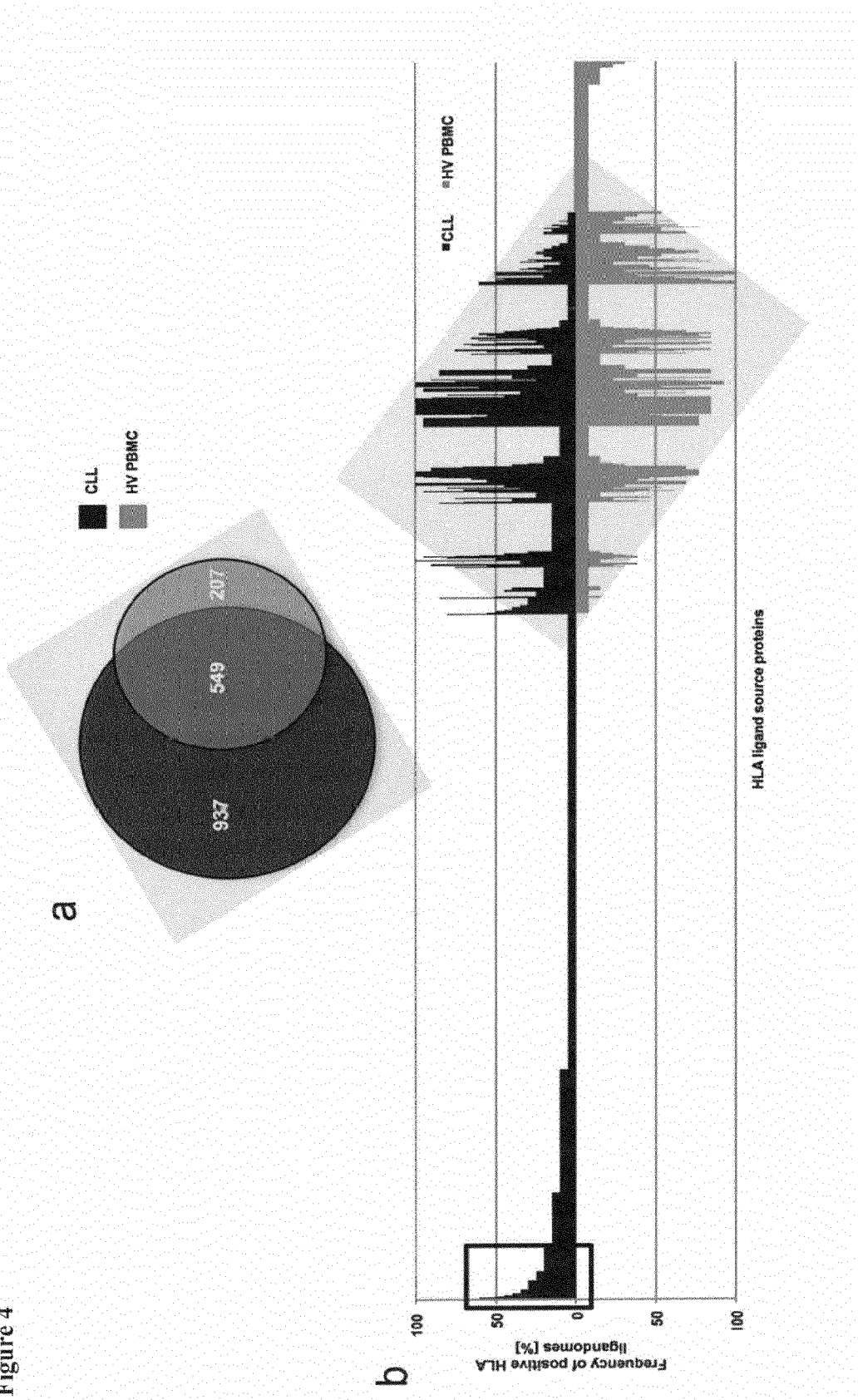
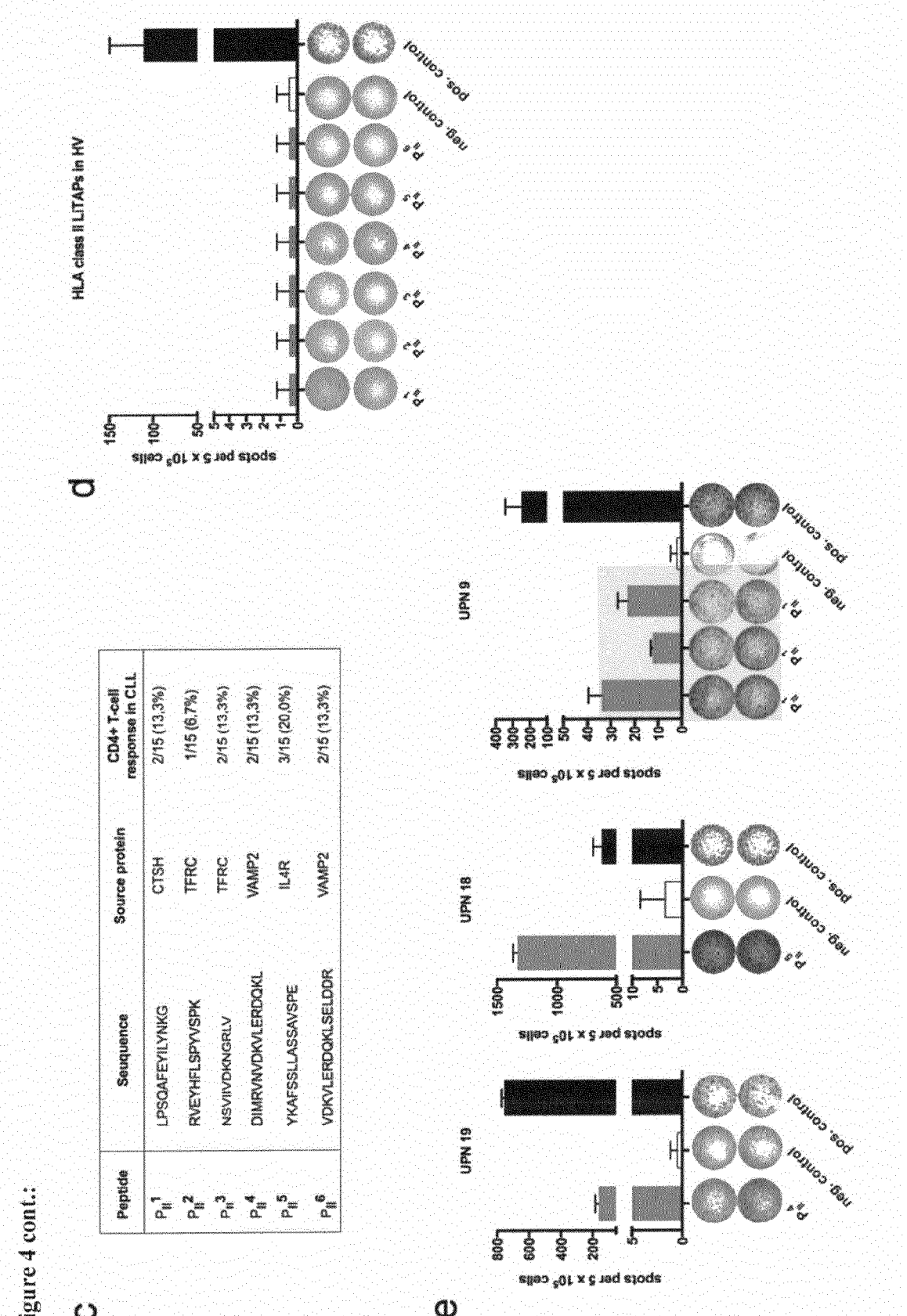

a
CLL
HV PBMC
937
549
207
b
CLL
HV PBMC
Frequency of positive HLA ligandomes [%]
100
50
0
50
100
HLA ligand source proteins

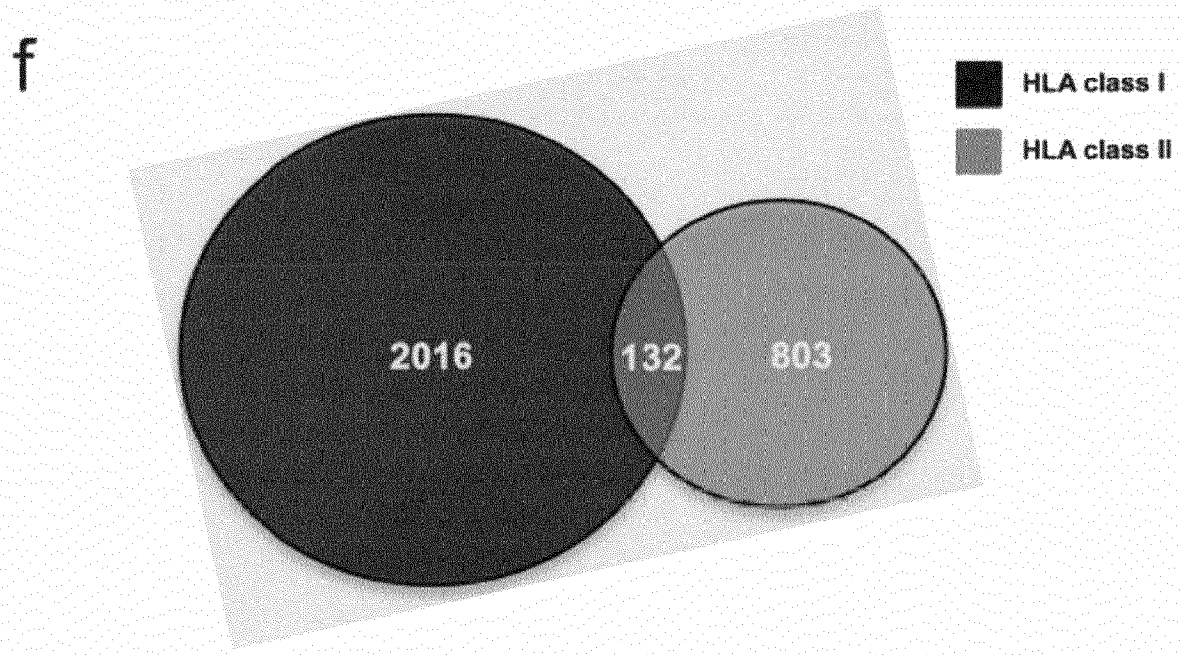
Figure 4

Figure 4 cont.:



Peptide	Sequence	Source protein	CD4+ T-cell response in CLL
P_{II}^1	LPSQAFEYILYNKG	CTSH	2/15 (13,3%)
P_{II}^2	RVEYHFLSPYVSPK	TFRC	1/15 (6,7%)
P_{II}^3	NSVIIVDKNGRLV	TFRC	2/15 (13,3%)
P_{II}^4	DIMRVAVDKVLERDQKL	VAMP2	2/15 (13,3%)
P_{II}^5	YKAFSSLLASSAVSPE	IL4R	3/15 (20,0%)
P_{II}^6	VDKVLERDQKLSELDDR	VAMP2	2/15 (13,3%)

Figure 4 cont.:



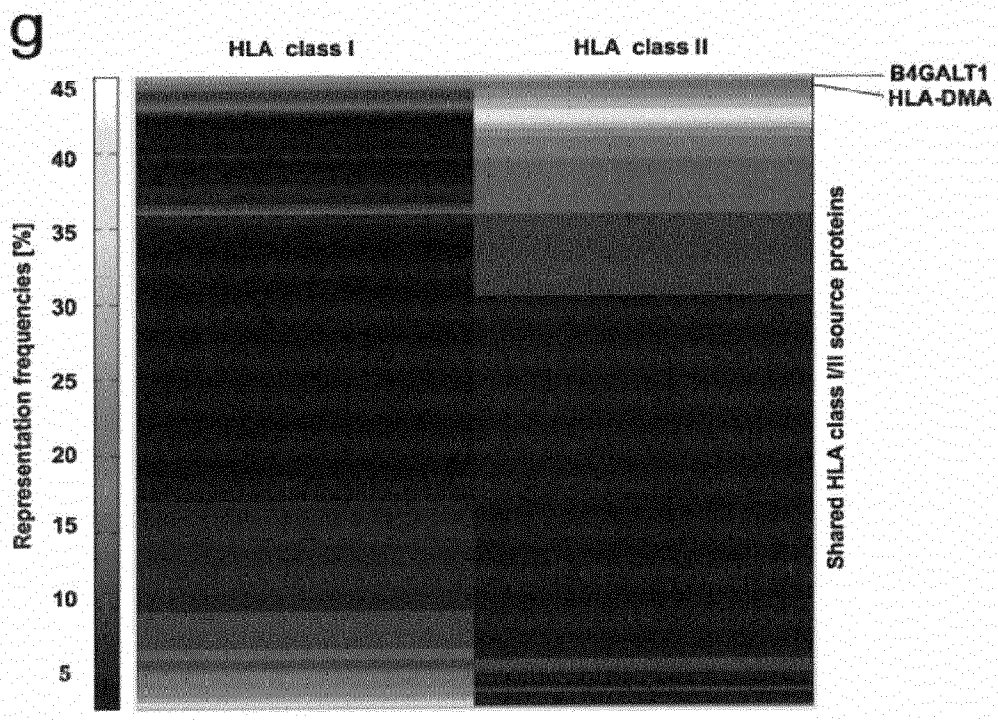
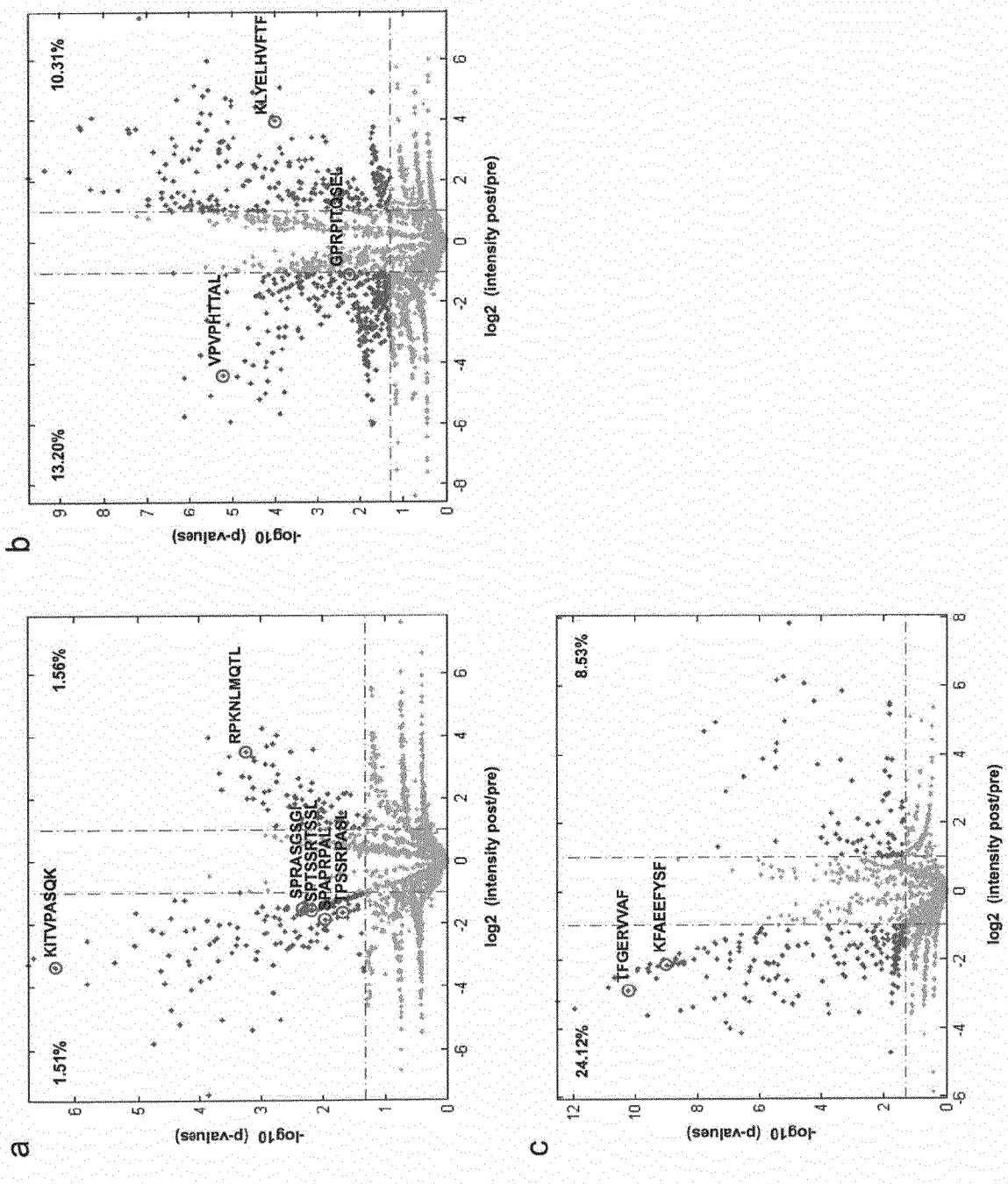


Figure 5


a
1.51%
1.56%
KITVPASQK
RPKNLMQTL
SPRASGSGK
SPTSSRTSSL
SPAPRPALL
TPSSRPASL
-log10 (p-values)
log2 (intensity post/pre)
b
13.20%
10.31%
VPVPHTTAL
KLYELHVFTF
GPRPTASEL
-log10 (p-values)
log2 (intensity post/pre)
c
24.12%
8.53%
TFGERVVAF
KFAEEFYSF
-log10 (p-values)
log2 (intensity post/pre)

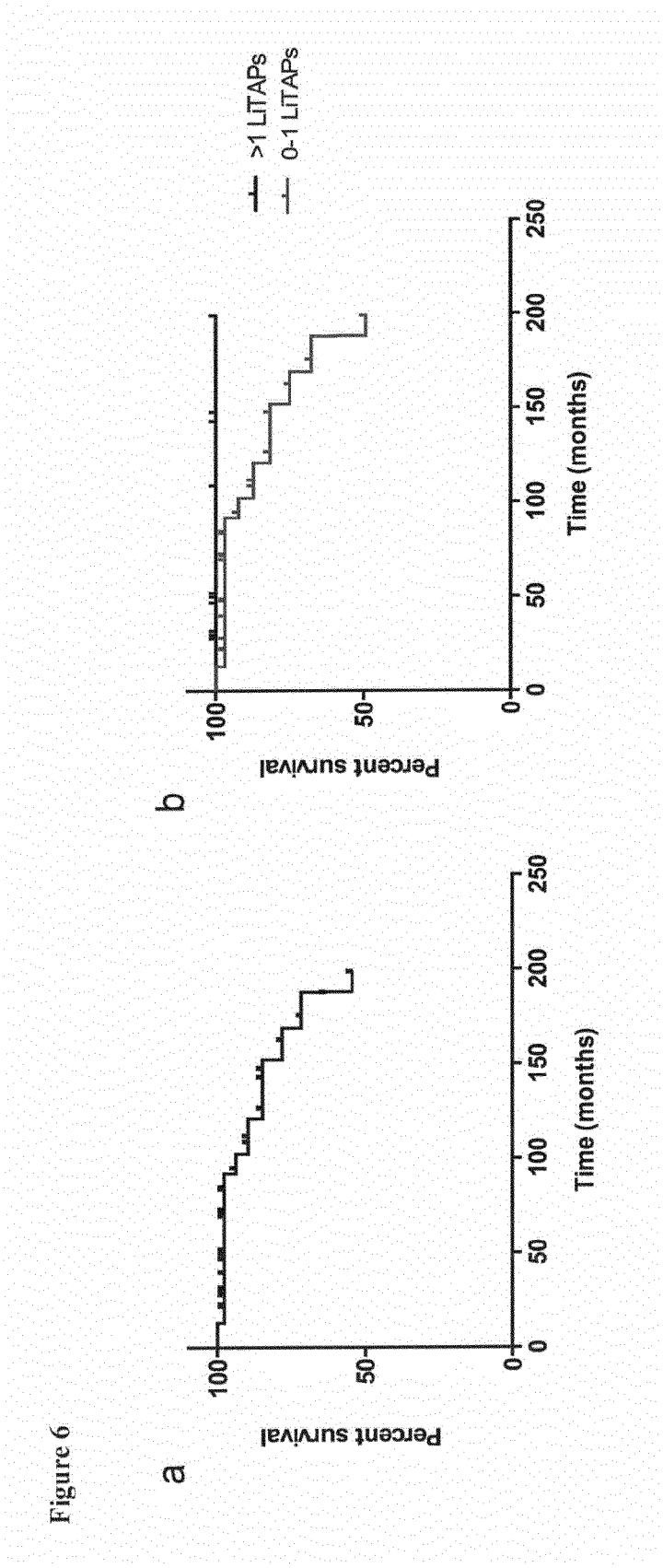

a
Percent survival
100
50
0
0
50
100
150
200
250
Time (months)
b
Percent survival
100
50
0
0
50
100
150
200
250
Time (months)
>1 LITAPs
0-1 LITAPs

Figure 6

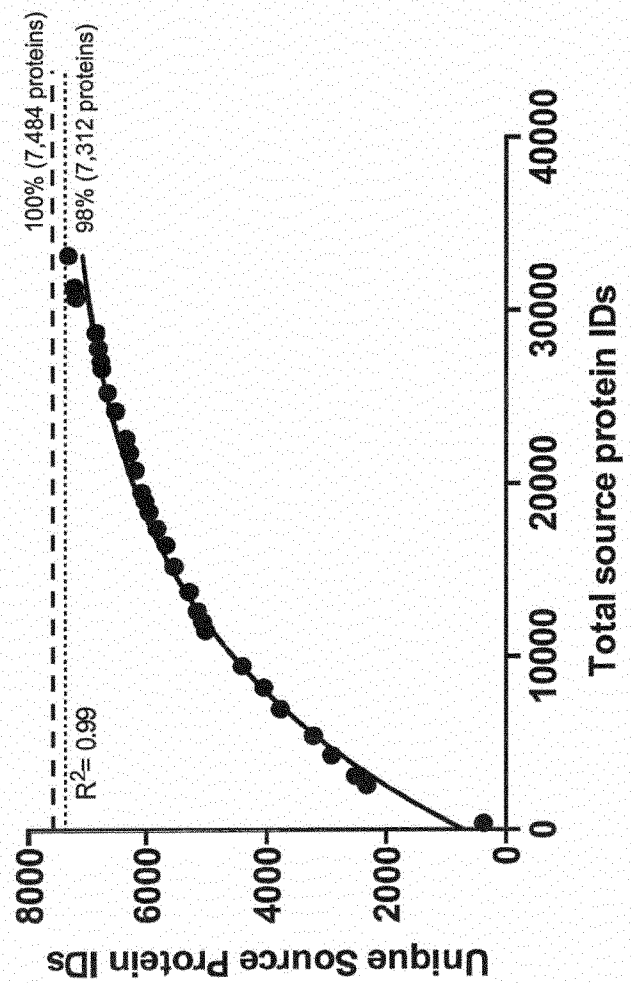

100% (7,484 proteins)
98% (7,312 proteins)
R2= 0.99
Unique Source Protein IDs
Total source protein IDs
0
2000
4000
6000
8000
10000
20000
30000
40000

Figure 7

Figure 8

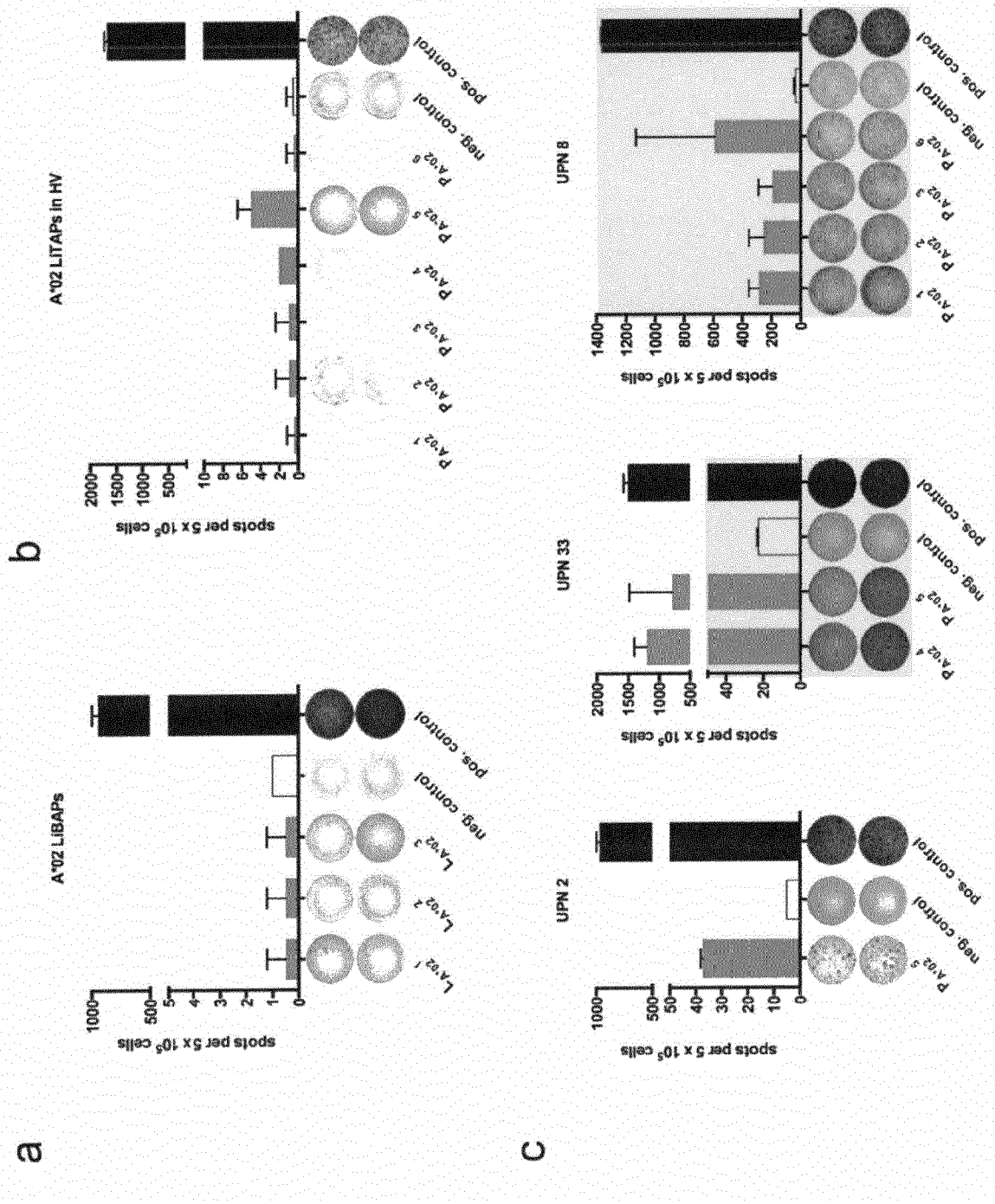

a
A*02 LiBAPs
spots per 5 x 10^5 cells
pos. control
neg. control
L-A*02 1
L-A*02 2
L-A*02 3
b
A*02 LiTAPs in HV
spots per 5 x 10^5 cells
pos. control
neg. control
P-A*02 8
P-A*02 5
P-A*02 4
P-A*02 3
P-A*02 2
P-A*02 1
c
UPN 2
UPN 33
UPN 8
spots per 5 x 10^5 cells
pos. control
neg. control
P-A*02 5
P-A*02 4
P-A*02 3
P-A*02 2
P-A*02 1

Figure 8 cont.:

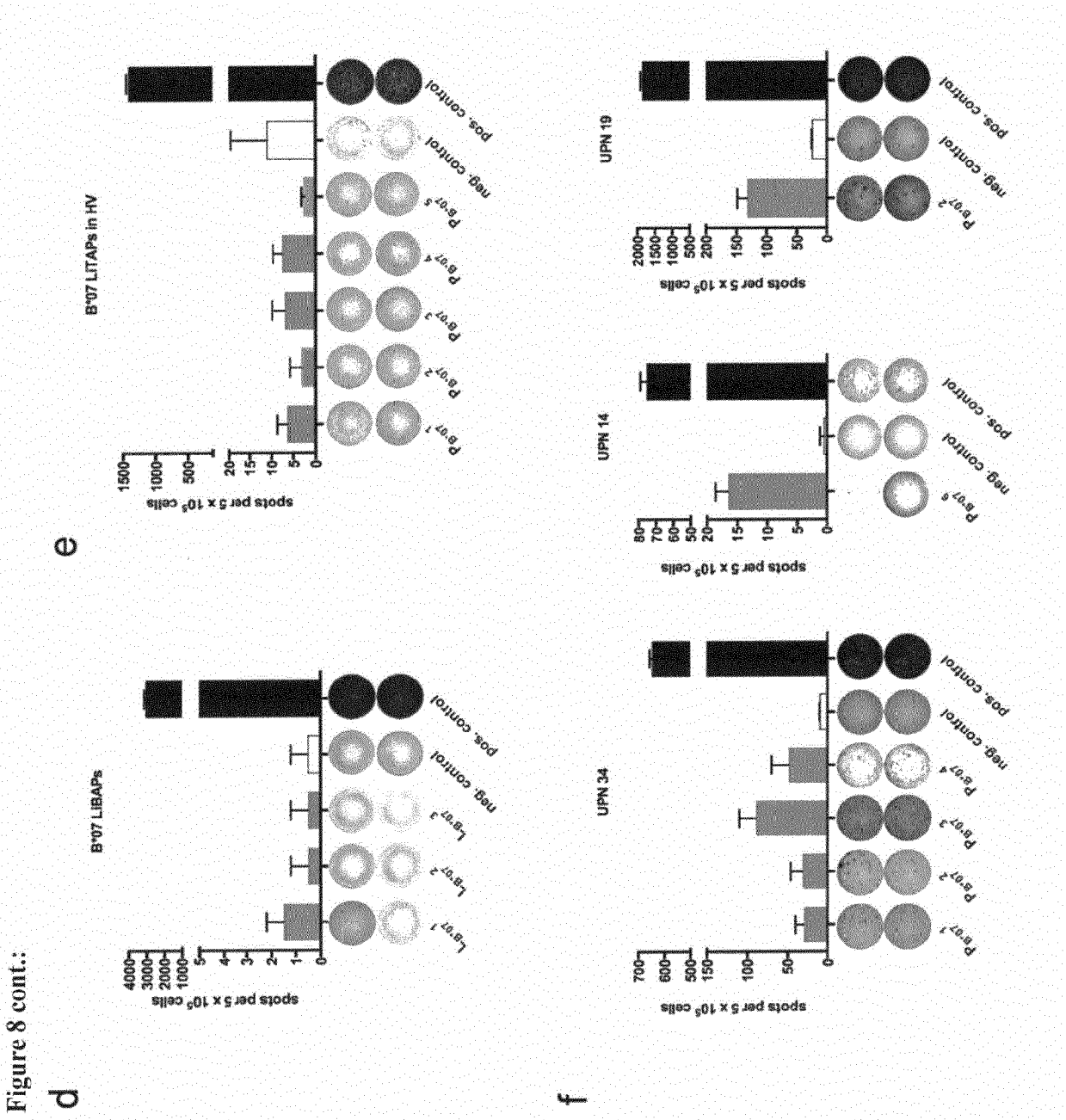


Figure 9

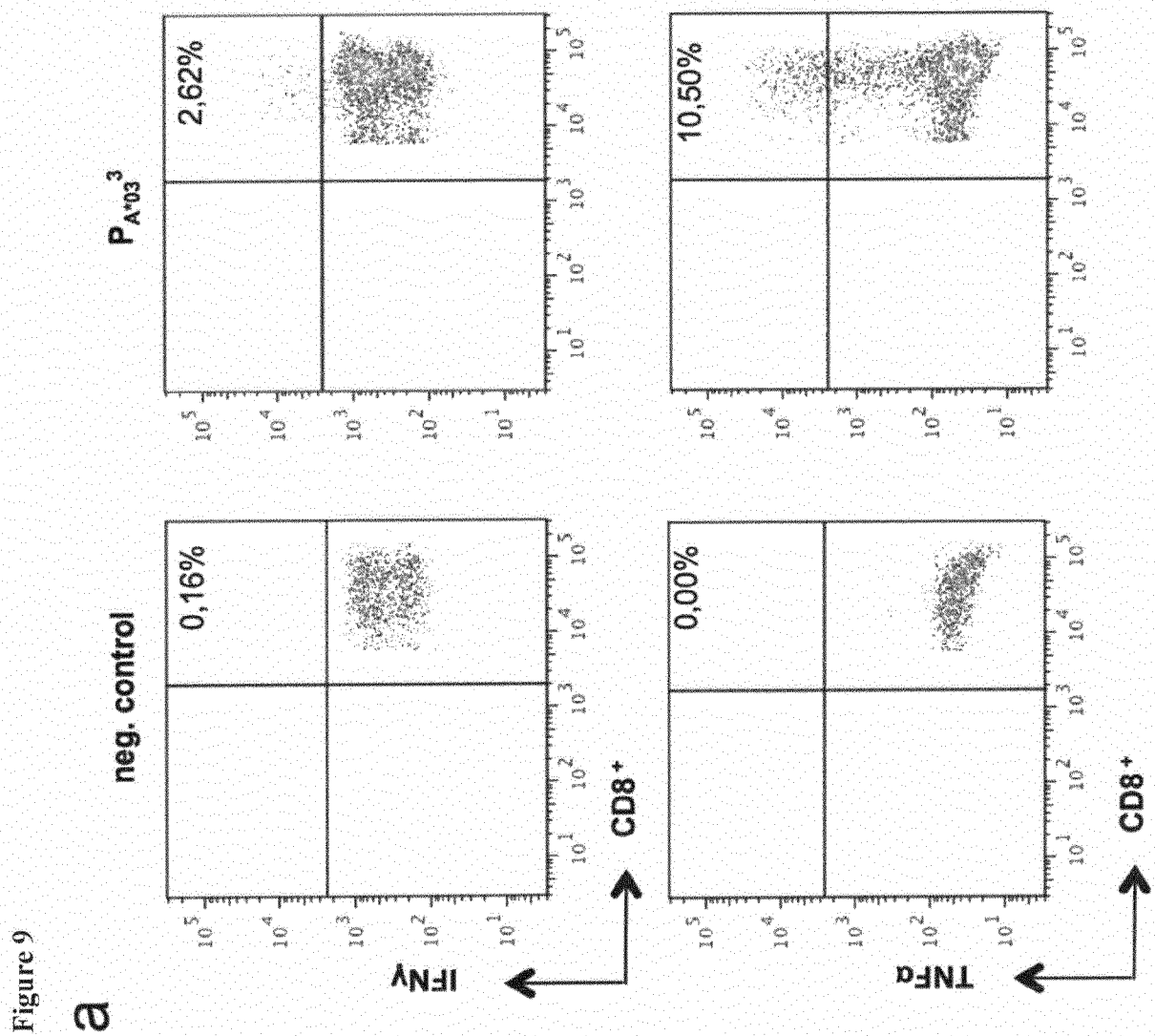


Figure 9 cont.:

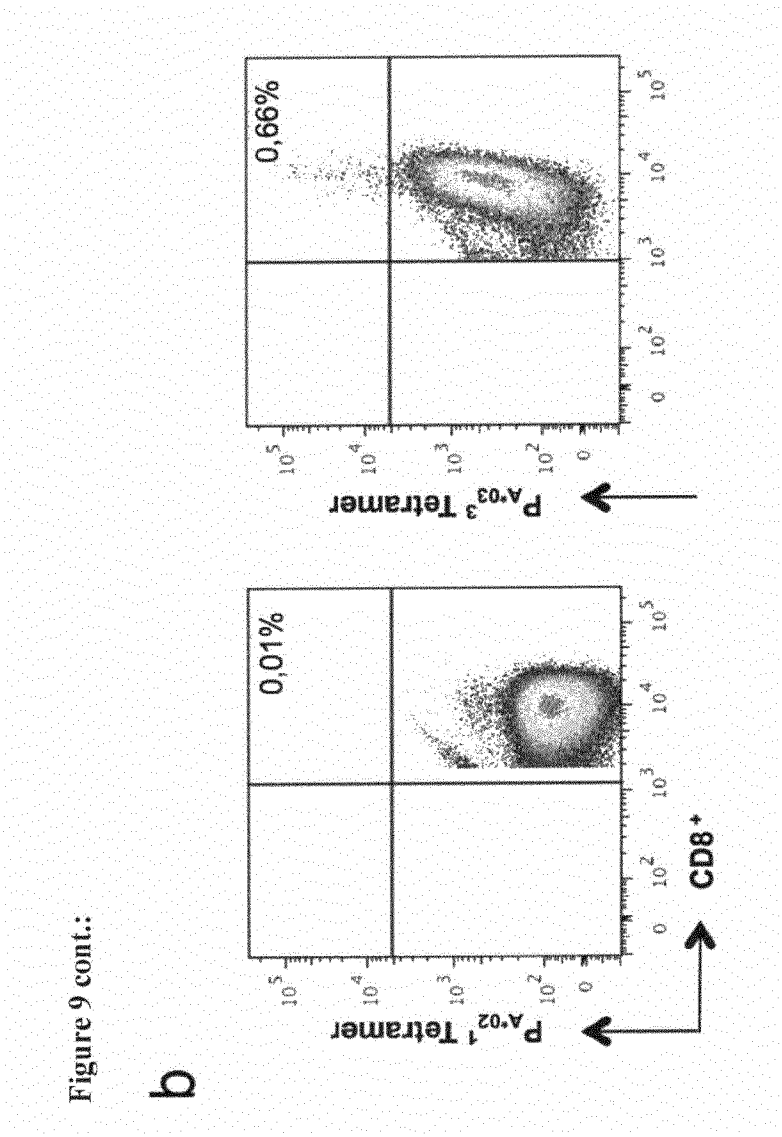
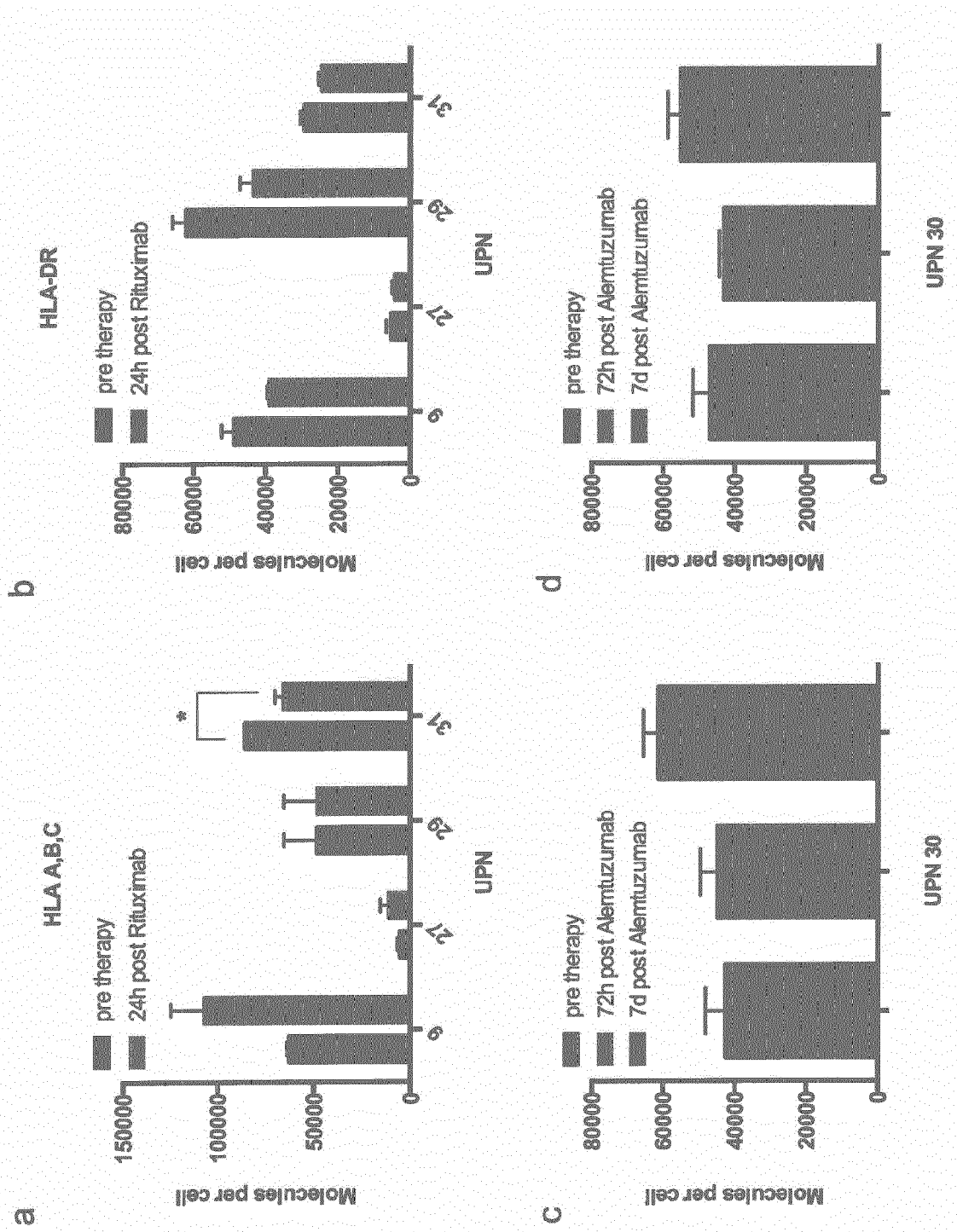


Figure 10


a
HLA A,B,C
pre therapy
24h post Rituximab
Molecules per cell
150000
100000
50000
0
6
21
29
31
*
UPN
b
HLA-DR
pre therapy
24h post Rituximab
Molecules per cell
80000
60000
40000
20000
0
6
21
29
31
UPN
c
pre therapy
72h post Alemtuzumab
7d post Alemtuzumab
Molecules per cell
80000
60000
40000
20000
0
UPN 30
d
pre therapy
72h post Alemtuzumab
7d post Alemtuzumab
Molecules per cell
80000
60000
40000
20000
0
UPN 30

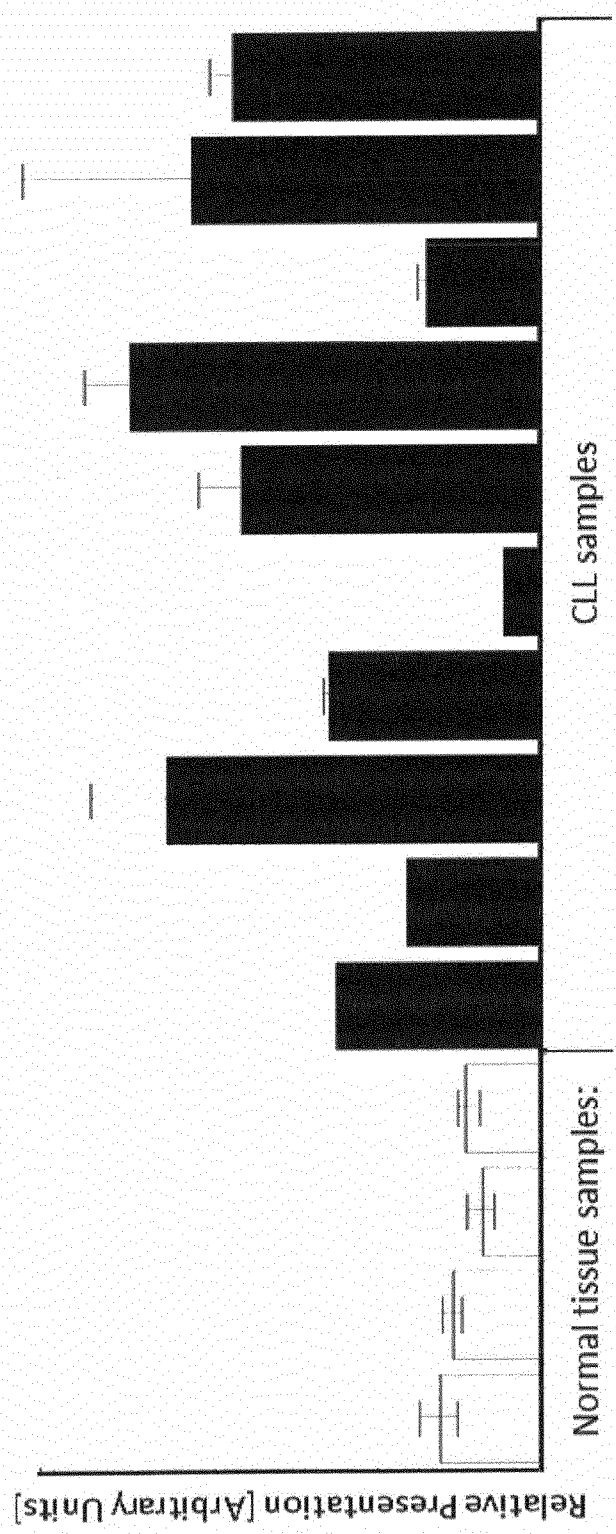

Relative Presentation [Arbitrary Units]
Normal tissue samples:
3 x liver, 1 x lymph node
CLL samples

Figure 11