

Table 1 Class I HLA-restricted cancer/testis antigens. These antigens were found to be expressed by normal spermatocytes and/or spermatogonia of testis. Occasionally, *MAGE-3*, *MAGE-4* and the *GAGE* genes were found to be expressed also in placenta [38, 40]. The NY-ESO-1 antigen was found to be expressed also in normal ovary cells [30].

Gene	HLA allele	Peptide epitope	Author [Ref]	Tissue distribution among tumors ^a
<i>BAGE</i>	Cw16	AARAVFLAL	Boël <i>et al.</i> , 1995 [16]	Melanoma, myeloma (stage III); lung, bladder, and breast carcinomas; H/N SCC ^b , NSCLC ^b .
<i>CAMEL</i>	A2	MLMAQEALAFI	Aarnoudse <i>et al.</i> , 1999 [1]	Melanoma, myeloma (stage III); NSCLC, H/N SCC, esophageal SCC, infiltrating bladder carcinoma, prostate and breast carcinoma; sarcoma.
<i>DAM-6, -10</i> (<i>MAGE-B1, B2</i>)	A2	FLWGPWAYA	Fleischhauer <i>et al.</i> , 1998 [52]	Melanoma, skin tumors, mammary and ovarian carcinomas [115] - lung carcinoma [39, 115] - seminomas [39].
<i>GAGE-1, -2, -8</i>	Cw6	YRPRPRRY	Van den Eynde <i>et al.</i> , 1995 [186] De Backer <i>et al.</i> , 1999 [40]	Melanoma; myeloma (stage III), lung carcinoma, H/N SCC, esophageal SCC; infiltrating bladder carcinoma, prostate ^b and breast ^b carcinomas; sarcoma ^b .
<i>GAGE-3, -4, -5, -6, -7B</i>	A29	YYWPRPRRY	De Backer <i>et al.</i> , 1999 [40]	Similar to <i>GAGE-1, -2, -8</i> .
<i>IL-13Rα2</i>	A*0201	WLPFGFILI	Okano <i>et al.</i> , 2002 [133]	Glioblastoma multiforme.
<i>MAGE-A1</i>	A1	EADPTGHSY	Traversari <i>et al.</i> , 1992 [181]	Melanoma, myeloma (stage III), lung carcinoma, H/N SCC, esophageal SCC, superficial and infiltrating bladder carcinoma; prostate ^b , colorectal ^b and breast ^b carcinomas, sarcoma ^b . For minor pattern of expressions, also see ref [41, 42, 188].
	A3	SLFRAVITK	Chaux <i>et al.</i> , 1999 [28]	
	A24	NYKHCFPEI	Fujie <i>et al.</i> , 1999 [53]	

	A28	EVYDGREHSA	Chaux <i>et al.</i> , 1999 [28]	
	B37	REPVTKAEML	Tanzarella <i>et al.</i> , 1999 [171]	
	B53	DPARYEFLW	Chaux <i>et al.</i> , 1999 [28]	
	Cw2	SAFPTTINF	Chaux <i>et al.</i> , 1999 [28]	
	Cw3	SAYGEPRKL ^c	Chaux <i>et al.</i> , 1999 [28]	
	Cw16	SAYGEPRKL ^c	van der Bruggen <i>et al.</i> , 1994 [190]	
<i>MAGE-A2</i>	A2	KMVELVHFL	Visseren <i>et al.</i> , 1997 [193]	The same as <i>MAGE-A1</i> .
	A2	YLQLVFGIEV	Visseren <i>et al.</i> , 1997 [193]	
	A24	EYLQLVFGI	Tahara <i>et al.</i> , 1999 [168]	
	B37	REPVTKAEML	Tanzarella <i>et al.</i> , 1999 [171]	
<i>MAGE-A3</i>	A1	EADPIGHLY	Gaugler <i>et al.</i> , 1994 [56]	The same as <i>MAGE-A1</i> .
	A2	FLWGPRALV	van der Bruggen <i>et al.</i> , 1994 [189]	
	A24	TFPDLESEF	Oiso <i>et al.</i> , 1999 [131]	
	A24	IMPKAGLLI	Tanaka <i>et al.</i> , 1997 [169]	
	B44	MEVDPIGHLY	Herman <i>et al.</i> , 1996 [68] Fleischhauer <i>et al.</i> , 1996 [51]	
	B52	WQYFFPVIF	Russo <i>et al.</i> , 2000 [154]	
	B37	REPVTKAEML	Tanzarella <i>et al.</i> , 1999 [171]	
	B*3501	EVDPIGHLY	Benlalam <i>et al.</i> , 2003 [14]	
<i>MAGE-A4</i>	A2	GVYDGREHTV	Duffour <i>et al.</i> , 1999 [48]	The same as <i>MAGE-A1</i> .
<i>MAGE-A6</i>	A34	MVKISGGPR	Zorn and Hercend, 1999 [220]	The same as <i>MAGE-A1</i> .
	B37	REPVTKAEML	Tanzarella <i>et al.</i> , 1999 [171]	
	B*3501	EVDPIGHVY	Benlalam <i>et al.</i> , 2003 [14]	

<i>MAGE-A10</i>	A2	GLYDGMEHL	Huang <i>et al.</i> , 1999 [73]	The same as <i>MAGE-A1</i> , with the exception of breast and colorectal carcinomas.
<i>MAGE-A12</i>	Cw7	VRIGHLYIL	Panelli <i>et al.</i> , 2000 [136] Heidecker <i>et al.</i> , 2000 [67]	The same as <i>MAGE-A1</i> .
<i>NA88-A</i>	B13	MTQGQHFLQKV	Moreau-Aubry <i>et al.</i> , 2000 [120]	Melanoma.
<i>NY-ESO-1</i>	A2	SLLMWITQCFL	Jäger <i>et al.</i> , 1998 [77]	The same as <i>CAMEL</i> .
	A2	SLLMWITQC	Jäger <i>et al.</i> , 1998 [77]	
	A2	QLSLLMWIT	Jäger <i>et al.</i> , 1998 [77]	
	B*3501	MPFATPMEA	Benlalam <i>et al.</i> , 2003 [14]	
<i>NY-ESO-1a (CAG-3)</i>	A31	ASGPGGGAPR	Wang <i>et al.</i> , 1998 [204]	
<i>SSX-2</i>	A2	KASEKIFYV	Ayyoub <i>et al.</i> , 2002 [8]	Melanomas; lymphomas; H/N, colon carcinomas.
<i>TRAG-3</i>	A*0201	ILLRDAGLV	Zhu <i>et al.</i> , 2003 [218]	Melanomas; leukemias; NSCLC, prostate and breast carcinomas.

^a See also van der Bruggen *et al.* [191] for a more detailed tissue distribution.

^b These epitopes share different HLA, that is they are recognized by specific T cells when presented by different HLA alleles. This phenomenon is important as it allows an epitope to be employed for cancer immunotherapy in a larger number of patients.

^c Frequency of expression less than 10%.

Table 2 Class I HLA-restricted differentiation antigens. These TAA can only be expressed in normal and neoplastic cells of the same lineage. Those antigens which also present class II HLA-restricted epitopes are bolded.

Gene	HLA allele	Peptide epitope	Authors [ref.]	Normal tissue/tumor
CEA	A2	YLSGANLNL (CAP-1) ^a	Tsang <i>et al.</i> , 1995 [183]	Embryonic tissue; normal epithelia differentiation overexpressed in colon and other adenocarcinomas.
	A3	HLFGYSWYK	Kawashima <i>et al.</i> , 1999 [92]	
<i>Ep-CAM</i>	A2	GLKAGVIAV	Nagorsen <i>et al.</i> , 2000 [123]	Epithelia overexpressed in colon and other adenocarcinomas.
Gp100	A2	KTWGQYWQV	Bakker <i>et al.</i> , 1995 [11]	Melanocyte/melanoma.
	A2	AMLGHTTMEV	Tsai <i>et al.</i> , 1997 [182]	
	A2	MLGHTTMEV	Tsai <i>et al.</i> , 1997 [182]	
	A2	SLADTNSLAV	Tsai <i>et al.</i> , 1997 [182]	
	A2	ITDQVPFSV	Kawakami <i>et al.</i> , 1995 [86]	
	A2	LLDGTATLRL	Kawakami <i>et al.</i> , 1994 [85]	
	A2	YLEPGPVTA	Cox <i>et al.</i> , 1994 [38]	
	A2	VLYRYGSFSV	Kawakami <i>et al.</i> , 1995 [86]	
	A2	RLMKQDFSV	Kawakami <i>et al.</i> , 1998 [88]	
	A2	RLPRIFCSC	Kawakami <i>et al.</i> , 1998 [88]	
	A3	LIYRRRLMK	Kawakami <i>et al.</i> , 1998 [88]	
	A3	ALNFPQSQK	Kawashima <i>et al.</i> , 1998 [91]	
	A3	SLIYRRRLMK	Kawashima <i>et al.</i> , 1998 [91]	
	A3	ALLAVGATK	Skipper <i>et al.</i> , 1996 [165]	

	A24	VYFFLPDHL	Robbins <i>et al.</i> , 1997 [149]	
	A*6801	HTMEVTVYHR	Sensi <i>et al.</i> , 2002 [163]	
	B*3501	VPLDCVLYRY	Benlalam <i>et al.</i> , 2003 [14]	
	Cw8	SNDGPTLI	Castelli <i>et al.</i> , 1999 [27]	
<i>Mammaglobin-A</i>	A3	PLENVISK	Jaramillo <i>et al.</i> , 2002 [79]	Mammary gland/ breast cancer.
		KLLMVLMLA	Jaramillo <i>et al.</i> , 2002 [79]	
		TTNAIDELK	Jaramillo <i>et al.</i> , 2002 [79]	
		AIDELKECF	Jaramillo <i>et al.</i> , 2002 [79]	
<i>Melan-A/MART-1^b</i>	A2	AAGIGILTV	Coulie <i>et al.</i> , 1994 [36]	Melanocyte/melanoma.
			Kawakami <i>et al.</i> , 1994 [83]	
	A2	EAAGIGILTV	Schneider <i>et al.</i> , 1998 [162]	
	A2	ILTVILGVL	Castelli <i>et al.</i> , 1995 [26]	
	B*3501		Benlalam <i>et al.</i> , 2003 [14]	
	B45	AEEAAGIGIL	Schneider <i>et al.</i> , 1998 [162]	
	B45	AEEAAGIGILT	Schneider <i>et al.</i> , 1998 [162]	
<i>MC1R</i>	A2	TILLGIFFL	Salazar-Onfray <i>et al.</i> , 1997 [156]	Melanocyte/melanoma.
	A2	FLALIICNA	Salazar-Onfray <i>et al.</i> , 1997 [156]	
<i>OAI</i>	A*2402	LYSACFWWL	Touloukian <i>et al.</i> , 2003 [180]	Melanocyte/melanoma.
<i>P polypeptide</i>	A2	IMLCLIAAV	Touloukian <i>et al.</i> , 2001 [179]	Melanocyte/melanoma.
PSA	A1	VSHSFPHPLY	Corman <i>et al.</i> , 1998 [34]	Prostate gland/prostate carcinoma.
	A2	FLTPKKLQCV	Correale <i>et al.</i> , 1997 [36]	
	A2	VISNDVCAQV	Correale <i>et al.</i> , 1997 [36]	
<i>TRP-1 (or gp75)</i>	A31	MSLQRQFLR	Wang <i>et al.</i> , 1996 [202]	Melanocyte/melanoma.

<i>TRP-2</i>	A2	SVYDFFVWL ^c	Parkhurst <i>et al.</i> , 1998 [137]	Melanocyte/melanoma.
	A2	TLDSQVMSL	Noppen <i>et al.</i> , 2000 [125]	
	A31	LLGPGRPYR ^d	Wang <i>et al.</i> , 1996 [201]	
	A33	LLGPGRPYR ^d	Wang <i>et al.</i> , 1998 [203]	
	Cw8	ANDPIFVVL	Castelli <i>et al.</i> , 1999 [27]	
<i>Tyrosinase</i>	A1	KCDICTDEY	Kittlesen <i>et al.</i> , 1998 [99]	Melanocyte/melanoma.
	A1	SSDYVIPIGTY	Kawakami <i>et al.</i> , 1998 [88]	
	A2	YMDGTMSQV	Wölfel <i>et al.</i> , 1994 [208]	
	A2	MLLAVLYCL	Wölfel <i>et al.</i> , 1994 [208]	
	A24	AFLPWHRLF	Kang <i>et al.</i> , 1995 [81]	
	B44	SEIWRDIDF	Brichard <i>et al.</i> , 1996 [20]	
	B*3501	TPRLPSSADVEF	Benlalam <i>et al.</i> , 2003 [14]	

^a CAP-1 is an alternative name of this peptide.

^b Two different groups simultaneously discovered this gene and gave it two different names, MART-1 [84] and Melan-A [36] respectively.

^c This peptide was shown to be a CTL target also in glioblastoma multiforme restricted by HLA-A2 [111].

^d These epitopes share different HLA-A3 subtypes. This allows an epitope to be employed for cancer immunotherapy in a larger number of patients.

Table 3 Class I HLA-restricted widely occurring, overexpressed TAA. Underlined amino acids in the epitopes indicate splicing aberration. Those antigens which also present class II HLA-restricted epitopes are bolded.

Gene	HLA allele	Peptide epitope	Reference	Tissue distribution	
				Tumors	Normal tissues
<i>Adipophilin</i>	A2	SVASTITGV	Schmidt <i>et al.</i> , 2004 [159]	RCC, melanoma; breast, colon and ovarian carcinomas; CML, multiple myeloma.	Adipocytes, macrophages.
<i>AIM-2^a</i>	A1	<u>RSDSGQQARY</u>	Harada <i>et al.</i> , 2001 [66]	Melanoma; neuroblastoma; Ewing's sarcoma; breast, ovarian and colon carcinomas.	Weakly expressed in lung, brain, liver and testis.
<i>AFP</i>	A2	GVALQTMKQ	Butterfield <i>et al.</i> , 1999 [22]	Hepatocellular carcinoma, and yolk-sac tumors. Also detected in hilar bile duct carcinoma; pleomorphic adenoma of parotid gland; prostate, pancreatic, bladder, and thyroid papillary carcinomas [75].	Synthesized by the fetal liver and yolk sac. Low levels in adult brain, heart, skeletal muscle, prostate, stomach, pancreas, adrenal gland, salivary gland, liver, small intestine, and peripheral blood [75].
<i>ART-4</i>	A24	AFLRHAAL DYPSLSATDI	Kawano <i>et al.</i> , 2000 [90] Kawano <i>et al.</i> , 2000 [90]	Lung, esophageal, H/N, gastric, cervical, endometrial, ovarian, and breast cancers; leukemias.	High expression in fetal liver, adult pancreas, and ovary. Significant expression in heart, brain, placenta, liver, lung, kidney, spleen, thymus, prostate, testis, small intestine, colon and PBMC.
<i>CLCA2</i>	A2	LLGNCLPTV SLQALKVTV	Konopitzky <i>et al.</i> , 2002 [105] Konopitzky <i>et al.</i> , 2002 [105]	SCLC; pancreatic, and esophageal carcinomas.	Lung (very low levels by Northern blot), trachea, mammary gland.

<i>Cyp-B</i>	A24	KFHRVIKDF	Gomi <i>et al.</i> , 1999 [60]	NSCLC; T cell leukemia; lymphosarcoma;	Ubiquitously expressed in normal tissues.
		DFMIQGGDF	Gomi <i>et al.</i> , 1999 [60]	bladder, ovarian, uterine and esophageal carcinomas.	
<i>EphA2</i>	A*0201	IMNDMPIYM	Alves <i>et al.</i> , 2003 [2]	Overexpressed in breast, colon, lung,	Lung, kidney, skin, ovary, thymus.
		VLAGVGFFI		prostate, and gastric carcinomas; metastatic melanomas; tumor neovasculature.	
<i>FGF-5</i>	A3	NTYASPRFK ^b	Hanada <i>et al.</i> , 2004 [65]	RCC; prostate, and breast carcinomas.	Brain and kidney (low expression).
<i>G250</i>	A2	HLSTAFARV	Vissers <i>et al.</i> , 1999 [194]	RCC; colon, ovarian and cervical carcinomas.	Epithelial cells of gastric mucosa.
<i>GnT-V</i>	A2	<u>VLPDVFIRC(V)</u> ^c	Guilloux <i>et al.</i> , 1996 [63]	Melanoma; brain tumors; sarcoma	Breast and brain (low expression).
<i>HER2/neu</i>	A2	KIFGSLAFL	Fisk <i>et al.</i> , 1995 [50]	Melanoma, ovarian, gastric, pancreatic [141] ^d and breast carcinomas.	Epithelial cells.
	A2	IISAVVGIL	Peoples <i>et al.</i> , 1995 [142]		
	A2	RLLQETELV	Kono <i>et al.</i> , 1998 [104]		
	A2	VVLGVVFGI	Rongcun <i>et al.</i> , 1999 [151]		
		ILHNGAYSL	Rongcun <i>et al.</i> , 1999 [151]		
		YMIMVKCWMI	Rongcun <i>et al.</i> , 1999 [151]		
	A24	TYLPTNASL	Okugawa <i>et al.</i> , 2000 [134]		
	A3	VLRENTSPK	Kawashima <i>et al.</i> , 1999 [92]		
<i>HST-2 (FGF-6)</i>	A31	YSWMDISCWI	Suzuki <i>et al.</i> , 1999 [167]	Gastric signet cell carcinoma.	Not determined.
<i>hTERT</i>	A2	ILAKFLHWL	Vonderheide <i>et al.</i> , 1999 [195]	Lung, prostate and ovarian carcinomas; multiple myeloma; melanoma; sarcoma; acute leukemias; non-Hodgkin's	Hematopoietic stem cells and progenitors; germinal center cells; basal keratinocytes; gonadal cells; certain proliferating epithelial

				lymphomas.	cells.
	A2	ILAKFLHWL	Minev <i>et al.</i> , 2000 [119]		
		RLVDDFLLV	Minev <i>et al.</i> , 2000 [119]		
	A3	KLFGVLRK	Vonderheide <i>et al.</i> , 2001 [196]		
<i>iCE</i>	B7	SPRWWPTCL	Ronsin <i>et al.</i> , 1999 [152]	RCC.	Kidney, colon, small intestine, liver, heart, pituitary gland, adrenal gland, prostate, stomach.
<i>Livin (ML-IAP)</i>	A2	SLGSPVLGL RLASFYDWPL	Schmollinger <i>et al.</i> , 2003 [161]	High levels in melanoma [7, 197], colon and prostate carcinomas, B-cell lymphomas, erythroleukemia and promyelocytic leukemia. Lower expression in breast and cervical carcinomas, and AML [7]. Good expression in superficial bladder cancer (and not in normal tissue) [58].	Two isoforms. Expressed during normal fetal development. Detected in adult heart, testis, ovary, thymus, spleen, lymph node, PBL, and bone marrows. Low levels in prostate, small intestine, colon, brain, placenta, liver, skeletal muscle, kidney, and pancreas. Not detectable in other adult tissues, including melanocytes [197]. A different pattern of expression is given by other authors by mean of RT-PCR analyses: fetal kidney, heart and spleen. In adult tissues: high levels in heart, placenta, lung, spleen and ovary. Low levels in brain, skeletal muscle, kidney, and PBL [7].
<i>M-CSF</i>	B*3501	<u>LPAVVGLSPGEQEY</u> ^c	Probst-Kepper <i>et al.</i> , 2001 [145]	RCC.	Liver, kidney.
<i>MUC1</i>	A11	STAPPAHGV	Domenech <i>et al.</i> 1995 [45]	Aberrantly glycosylated forms in breast or ovarian cancer.	Ductal epithelial cells and activated T-cells.

	A2	STAPPVHNV	Brossart <i>et al.</i> , 1999 [21]		
<i>MUC2</i>	A2	LLNQLQVNL	Böhm <i>et al.</i> , 1998 [17]	Ovary, pancreas and breast mucinous	Colon, small intestine, bronchus, cervix and gall
		MLWGWREHV	Böhm <i>et al.</i> , 1998 [17]	tumors; colon carcinoma of non-mucinous	bladder.
				type.	
<i>PRAME</i>	A24	LYVDSLFFL	Ikeda <i>et al.</i> , 1997 [74]	Melanoma; H/N and lung SCC; NSCLC	Testis, endometrium, ovary, adrenals, kidney,
				[185]; RCC; sarcoma; leukemias [184].	brain, skin.
	A2	VLDGLDVLL	Kessler <i>et al.</i> , 2001 [93]		
		SLYSFPEPEA	Kessler <i>et al.</i> , 2001 [93]		
		ALYVDSLFFL	Kessler <i>et al.</i> , 2001 [93]		
		SLLQHLIGL	Kessler <i>et al.</i> , 2001 [93]		
<i>PSMA</i>	A1	HSTNGVTRIY	Corman <i>et al.</i> , 1998 [34]	Prostate cancer; tumor-associated	Prostate epithelium (cytosolic and PSMA-2
				neovasculature of several solid tumors.	isoform), ventral striatum and brain stem
					(PSMA-2 isoform), liver (PSMA-2 isoform),
					small intestine, kidney, spleen, colon.
	A24	LYSDPADYF	Horiguchi <i>et al.</i> , 2002 [72]		
		NYARTEDFF	Horiguchi <i>et al.</i> , 2002 [72]		
<i>P15</i>	A24	AYGLDFYIL	Robbins <i>et al.</i> , 1995 [147]	Melanoma.	Testis, spleen, thymus, liver, kidney, lung,
					retina.
<i>P53</i>	A24	AIYKQSQHM	Umano <i>et al.</i> , 2001 [184]	Esophageal, gastric, colon, pancreatic, and	Ubiquitous (low level).
				gall bladder carcinomas.	
	B46	SQKTYQGSY ^f	Azuma K <i>et al.</i> , 2003 [10]		
<i>RAGE</i>	B7	SPSSNRIRNT	Gaugler <i>et al.</i> , 1996 [57]	Melanoma; sarcomas; mesotheliomas; H/N	Retina only.
				tumors; bladder, renal, colon and mammary	

				carcinomas.	
<i>RUI</i>	B51	VPYGSFKHV	Morel <i>et al.</i> , 2000 [121]	Melanoma; renal and bladder carcinomas.	Testis, kidney, heart, skin, brain, ovary, liver, lung, lymphocytes, thymus, fibroblasts.
<i>RU2</i>	B7	LPRWPPPQL	Van den Eynde <i>et al.</i> , 1999 [187]	Melanoma; sarcomas; leukemia; brain, esophageal and H/N tumors; renal, colon, thyroid, mammary, bladder, prostatic and lung carcinomas.	Testis, kidney, liver, urinary bladder.
<i>SART-1</i>	A24	EYRGFTQDF	Kikuchi <i>et al.</i> , 1999 [97]	H/N SCC; esophageal SCC; NSCLC; uterine cancer.	Proliferating cells during the M phase. Fetal liver; adult testis, heart, placenta, skeletal muscle, pancreas, spleen, thymus, prostate, uterus, and small intestine [164].
	A*2601	KGSGKMKTE	Shichijo <i>et al.</i> , 1998 [164]		
<i>SART-2</i>	A24	DYSARWNEI	Nakao <i>et al.</i> , 2000 [124]	H/N SCC; esophageal SCC; lung	Although no significant expression was observed at protein level by Western blot in different tissues, high mRNA expression was observed by Northern blot in heart, placenta, spleen, and ovary. Whereas a lower mRNA expression was seen in lung, skeletal muscle, kidney, testis, small intestine and PBL.
		AYDFLYNYL	Nakao <i>et al.</i> , 2000 [124]	adenocarcinoma; melanoma; RCC; uterine	
		SYTRLFLIL	Nakao <i>et al.</i> , 2000 [124]	adenocarcinoma; brain tumors.	
<i>SART-3</i>	A24	VYDYNCHVDL	Yang <i>et al.</i> , 1999 [211]	The same as SART-2.	The same as SART-2.
		AYIDFEMKI	Yang <i>et al.</i> , 1999 [211]		
	A2	LLQAEAPRL	Ito <i>et al.</i> , 2000 [76]		
		RLAEYQAYI	Ito <i>et al.</i> , 2000 [76]		

<i>SOX10</i>	A2	SAWISKPPGV	Khong and Rosenberg, 2002 [95]	Overexpressed in melanomas.	Abundantly expressed in migratory neural crest during early stages of development. In adult, expression found in melanocytes, brain, heart, lungs, adrenal and salivary glands, colon, intestine, bladder, pancreas, prostate, and testis.
<i>Survivin</i>	A2	ELTLGEFLKL	Andersen <i>et al.</i> , 2000 [3] Schmitz <i>et al.</i> , 2000 [160] Andersen <i>et al.</i> , 2001 [4] Casati <i>et al.</i> , 2003 [25] Schmidt <i>et al.</i> , 2003 [158]	Abundantly expressed in carcinomas (NSCLC and SSC of the lung; esophagus, liver, pancreas, colon, breast, ovary, bladder and prostate); CLL and diffuse large B-cell lymphomas; melanoma and non-melanoma skin cancers; neuroblastoma.	Expressed during normal fetal development. High expression in testis, thymus, and placenta. Low expression in stomach, intestine, spleen, lung, kidney, prostate, pancreas, and heart. Transiently expressed in normal proliferating cells during the G2/M phase.
	A2	TLPPAWQPFL	Schmitz <i>et al.</i> , 2000 [160]		
<i>Survivin-2B^g</i>	A24	AYACNTSTL	Hirohashi <i>et al.</i> , 2002 [70]	The same as survivin.	Thymus.
<i>TRG</i>	B52	<u>YQLCLTNIF</u> ^h	Ohkouchi <i>et al.</i> , 2003 [128]	Breast, lung, colon, and prostate carcinomas.	Low expression in heart, liver and pancreas.
	B62				
<i>WT1</i>	A2	RMFPNAPYL	Oka <i>et al.</i> , 2000 [132]	Gastric, colon, lung, breast, ovary, uterine, thyroid and hepatocellular carcinomas; leukemia (including AML, ALL and CML).	Kidney, ovary, testis, spleen.
	A24	CMTWNQMNL RWPSCQKKF	Ohminami <i>et al.</i> , 2000 [130] Azuma <i>et al.</i> , 2002 [9]		
<i>707-APⁱ</i>	A2	RVAALARDA	Morioka <i>et al.</i> , 1995 [122]	Melanoma.	None.

^aUnspliced transcript containing intron 2. The immunogenic peptide is entirely comprised into the intronic sequence.

- ^b The peptide is generated by a post-translational protein splicing.
- ^c VLPDVFIRC(V) = nonamer and decamer peptides are both recognized by CTLs. The immunogenic peptide is entirely comprised into the intronic sequence.
- ^d Tissue distribution among tumors as described in the given references when different from the paper first reporting the sequence of the epitope.
- ^e The immunogenic peptide is encoded by an alternative ORF.
- ^f The epitope derives from mutated p53 protein, but does not contain the mutation.
- ^g This is a splicing variant of survivin, retaining a part of intron 2 as a cryptic exon.
- ^h The TRG gene is located in an intron of the putative tumor suppressor gene testin.
- ⁱ The immunogenic peptide sequence seems to be associated to an as yet unidentified antigen that is expressed in the majority of melanomas and in some tumors of other histological origin, but not in normal cells, as defined serologically [98]. However, as the tissue of the testis was not tested, it is not clear to which category the antigen may belong until more information is available.

Table 4 Class I HLA-restricted tumor-specific antigens, including both unique and shared antigens.^a Underlined amino acids in the epitopes indicate mutations or splicing aberration. Normal tissues never express these epitopes.

Gene	HLA allele	Peptide epitope	Tissue expression in tumors	Reference
UNIQUE				
<i>α-actinin-4</i>	A2	FIAS <u>N</u> GVKLV	Lung carcinoma	Echchakir <i>et al.</i> , 2001 [49]
<i>β-catenin</i>	A24	SYLDSGI <u>H</u> E	Melanoma	Robbins <i>et al.</i> , 1996 [148]
<i>Caspase-8</i>	B35	FPSDS <u>W</u> CYF	H/N tumor	Mandruzzato <i>et al.</i> , 1997 [116]
<i>CDK-4</i>	A2	A <u>C</u> DPHSGHFV	Melanoma	Wölfel <i>et al.</i> , 1995 [209]
<i>ELF2</i>	A68	ETVSE <u>Q</u> SNV	Lung SCC	Hogan <i>et al.</i> , 1998 [71]
<i>HLA-A*0201-R170I</i>	A2	CVEWLRI <u>Y</u> LENGK	RCC	Brändle <i>et al.</i> , 1996 [19]
<i>HSP70-2M</i>	A2	SLFEGID <u>I</u> Y	RCC	Gaudin <i>et al.</i> , 1999 [55]
<i>KIAA0205</i>	B44*03	AEPIN <u>I</u> QTV	Bladder cancer	Gueguen <i>et al.</i> , 1998 [62]
<i>Malic enzyme</i>	A2	FLDEFME <u>G</u> V	SCC of the lung	Karanikas <i>et al.</i> , 2001 [82]
<i>MART-2</i>	A1	FLE <u>G</u> NEVGKTY	Melanoma	Kawakami <i>et al.</i> , 2001 [89]
<i>MUM-1</i>	B44	EEKL <u>I</u> VVLF	Melanoma	Coulie <i>et al.</i> , 1995 [37]
<i>MUM-2</i>	B44	SELF <u>R</u> SGLDY	Melanoma	Chiari <i>et al.</i> , 1999 [31]
	Cw6	FRSG <u>L</u> DSYV		
<i>MUM-3</i>	A28	EAF <u>I</u> QPITR	Melanoma	Baurain <i>et al.</i> , 2000 [12]
<i>Myosin</i>	A3	<u>K</u> INKNPKYK	Melanoma	Zorn and Hercend, 1999 [219]

<i>OS-9</i>	B44	<u>KELEGILL</u>	Melanoma	Vigneron <i>et al.</i> , 2002 [192]
SHARED				
<i>BING-4</i>	A2	<u>MCQWGRLWQL</u> ^b	Melanoma	Rosenberg <i>et al.</i> , 2002 [153]
<i>K-RAS</i>	B35	VVVGA <u>Y</u> GVG	Pancreatic and colorectal adenocarcinomas	Gjertsen <i>et al.</i> , 1997 [59]
<i>N-RAS</i>	A1	ILDTA <u>G</u> REEY	Melanoma	Linard <i>et al.</i> , 2002 [109]
<i>OGT</i>	A2	<u>SLYKFSPFPL</u> ^c	Colon carcinomas (MSI ⁺)	Ripberger <i>et al.</i> , 2003 [146]
<i>TGFβRII</i>	A2	<u>RLSSCVPVA</u> ^c	Colon carcinomas (MSI ⁺)	Linnebacher <i>et al.</i> , 2001 [1110]
<i>TRP-2/INT2</i>	A68	<u>EVISCKLIK</u> ^d	Melanoma, glioblastoma multiforme [111]	Lupetti <i>et al.</i> , 1998 [114]
<i>TRP-2-6b</i>	A2	<u>ATTNILEHY</u> ^e	Melanoma, glioblastoma multiforme	Khong <i>et al.</i> , 2002 [94]

^a The table does not include other tumor-specific antigens such as fusion proteins, which are listed in Table 6.

^b The peptide derives from an alternative ORF.

^c The peptide derives from a translational frameshift.

^d The immunogenic peptide is entirely comprised into the intronic sequence.

^e The immunogenic peptide is encoded by exon 6b, one of the two novel exons alternatively spliced from intron 6.

Table 5 Class II HLA-restricted antigens.

Gene	HLA- allele	Peptide epitope	Tissue expression		Reference
			Tumors	Normal tissues	
A) EPITOPES FROM NON-MUTATED PROTEIN ANTIGENS					
Cancer-testis antigens					
<i>CAMEL</i>	DR11	PWKRWSWA	The same as NY-ESO 1	The same as NY-ESO 1	Slager <i>et al.</i> , 2003 [166]
	DR12		(see below).	(see below).	
<i>LAGE-1</i>	DRB1*1301	ILSRDAAPLPRPG ^a	The same as NY-ESO 1 (see below).	The same as NY-ESO 1 (see below).	Wang <i>et al.</i> , 2004 [200]
<i>MAGE-A1</i>	DRB1*1301, DRB1*1302	LLKYRAREPVTKAE ^b	Melanoma, myeloma (stage III), lung carcinoma, H/N SCC, esophageal SCC, superficial and infiltrating bladder carcinoma.	Testis, placenta.	Chaux <i>et al.</i> , 1999 [28]
<i>MAGE-A2</i>	DRB1*1301, DRB1*1302	LLKYRAREPVTKAE ^b	The same as <i>MAGE-A1</i> .	The same as <i>MAGE-A1</i> .	Chaux <i>et al.</i> , 1999 [28]
<i>MAGE-A3</i>	DRB1*1101	TSYVKVLHMHVKISG	The same as <i>MAGE-A1</i> .	The same as <i>MAGE-A1</i> .	Manici <i>et al.</i> , 1999 [117]
	DRB1*1301, DRB1*1302	LLKYRAREPVTKAE ^b			Chaux <i>et al.</i> , 1999 [28]
	DRB1*1301,	AELVHFLLLKYRAR ^b	Melanoma, lung and breast	Testis, placenta.	Chaux <i>et al.</i> , 1999 [29]

	DRB1*1302		carcinomas, H/N SCC.		
	DR1, DR4, DR11 ^c	RKVAELVHFLLLKYR ^b GDNQIMPKAGLLIIV TSYVKVLHHMVKISG	Melanoma, lung and breast carcinomas, H/N SCC.	Testis, placenta.	Consogno <i>et al.</i> , 2003 [33]
	DR1, DR4, DR7, DR11 ^c	FFPVIFSKASSSLQL ^b			Consogno <i>et al.</i> , 2003 [33]
<i>MAGE-A6</i>	DRB1*1301, DRB1*1302 DRB1*0401	LLKYRAREPVTKAE ^b ESEFQAALSRKVAKL, LLKYRAREPVTKAEMLGSVVGNWQ, VGNWQYFFPVIFSKASDSLQLVFGIELMEVD, IFSKASDSLQLVFGIE, LTQYFVQENYLEYRQVPG	The same as <i>MAGE-A1</i> .	The same as <i>MAGE-A1</i> .	Chaux <i>et al.</i> , 1999 [28] Tatsumi <i>et al.</i> , 2003 [172]
<i>NY-ESO-1</i>	DRB4*0101	VLLKEFTVSG	Melanoma; myeloma (stage III); lung carcinoma; H/N SCC; esophageal SCC; infiltrating bladder, prostate, and breast carcinomas.	Testis, placenta (very low levels).	Zeng <i>et al.</i> , 2000 [217]
	DRB4*0101-0103	PLPVPGVLLKEFTVSGNI VLLKEFTVSGNILTIRLT AADHRQLQLSISSCLQQL			Jäger <i>et al.</i> , 2000 [78]
Differentiation antigens					
<i>CEA</i>	DR9	YACFVSNLATGRNNS	Overexpressed in colon	Epithelial	Kobayashi <i>et al.</i> , 2002 [103]

carcinoma and other
adenocarcinomas.

differentiation antigen

DR*03, DR*0405,
DR*07, DR*1101,
DR*1104, DR*14^c

LWWVNNQSLPVSP

Campi *et al.*, 2003 [24]

<i>Gp100</i>	DRB1*0401	WNRQLYPEWTEAQRLD	Melanoma.	Melanocytes.	Li <i>et al.</i> , 1998 [108]
	DRB1*0701	TGRAMLGHTTMEVTVYH			Lapointe <i>et al.</i> , 2001 [106]
	DRB1*0401	IYRRRLMKQDFSVPQLPHS			Kierstead <i>et al.</i> , 2001 [96]
<i>MART-1/Melan-A</i>	DRB1*0401	RNGYRALMDKSLHVGTCALTRR	Melanoma.	Melanocytes.	Zarour <i>et al.</i> , 2000 [216]
<i>PSA</i>	DRB1*0401	ILLGRMSLFMPEDTG	Melanoma.	Melanocytes, prostate	Corman <i>et al.</i> , 1998 [34]
		SLFHPEDTGQVFQ		gland.	
		QVFQVSHSFPHPLYD			
		NDLMLLRLSEPAELT			
		KKLQCVQLHVISM			
		GVLQGITSMGSEPCA			
<i>Tyrosinase</i>	DRB1*0401	QNILLSNAPLGPQFP	Melanoma.	Melanocytes.	Topalian <i>et al.</i> , 1994 [176]
		DYSYLQSDPDSFQD			Topalian <i>et al.</i> , 1996 [177]
		SYLQSDPDSFQD			
	DRB1*1501	RHRPLQEVYPEANAPIGHNRE			Kobayashi <i>et al.</i> , 1998 [101]
	DRB1*0405	EIWRDIDFAHE			Kobayashi <i>et al.</i> , 1998 [102]
	DRB1*0401	YGQMKNGSTPMFNDINIYDL			Kierstead <i>et al.</i> , 2001 [96]
		ALHIYMDGTMSQVQGSA			

Widely expressed antigens

<i>Annexin II</i>	DRB1*0401	DVPKWISIMTERSVPH	Melanoma.	Endothelial, mesothelial and some epithelial cells; peripheral nerves; part of meninges [45].	Li <i>et al.</i> , 1998 [108]
<i>EphA3</i>	DRB1*1101	DVTFNIICKKCG	Overexpressed in melanoma, SC and NSCLC, sarcomas, and RCC.	High expression in retina, and in fetal brain. Significant expression in bladder, prostate, and colon. Low expression in several other normal tissues but hematopoietic cells. Melanocytes do not express the protein.	Chiari <i>et al.</i> , 2000 [32]
<i>HER2/neu</i>	DR11	GSYVSRLLGICL VPIKWMALESILRRRF	Melanoma; ovarian, gastric, pancreatic [141] and breast carcinomas.	Epithelial cells.	Anderson <i>et al.</i> , 2000 [5]
<i>MUC1</i>	DR3	PGSTAPPAHGVT	Breast and ovarian cancers; multiple myeloma; B-cell lymphoma.	None ^d .	Hiltbold <i>et al.</i> , 1998 [69]

<i>WTI</i>	DRB1*0401	PQQMGSDVRDLNALL	Gastric, colon, lung, breast, ovary, uterine, thyroid and hepatocellular carcinomas; leukemia (including AML, ALL and CML).	Kidney, ovary, testis, spleen.	Knights <i>et al.</i> , 2002 [100]
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B) EPITOPES FROM MUTATED PROTEIN ANTIGENS. Underlined are the mutated amino acids and the peptide sequences deriving from mutations or splicing aberration.

Unique

<i>CDC27</i>	DRB1*0401	FSWAMDLDPKGA ^e	Melanoma.	None.	Wang <i>et al.</i> , 1999 [205]
<i>FN</i>	DR2	MIFE <u>K</u> HGFRRTPP	Melanoma.	None.	Wang <i>et al.</i> , 2002 [199]
<i>Neo-PAP</i>	DR7	RVIKNSIRLTL ^e	Melanoma.	None.	Topalian <i>et al.</i> , 2002 [178]
<i>PTPRK</i>	DRB1*1001	PYYFAAELPP <u>R</u> NLPEP	Melanoma.	None.	Novellino <i>et al.</i> , 2003 [127]
<i>TPI</i>	DRB1*0101	GELIG <u>I</u> LNAAKVPAD	Melanoma.	None.	Pieper <i>et al.</i> , 1999 [143]

Shared

<i>TGFβRII</i>	DR (not identified)	<u>SLVRLSSCVPVALMSAMTTSSSQ</u> ^f	Colon carcinomas (MSI ⁺).	None.	Saeterdal <i>et al.</i> , 2001 [155]
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^a This epitope is specifically recognized by CD4⁺T regulatory cells that were cloned by limiting dilution from TILs deriving from a fresh melanoma sample. These cells significantly suppressed autologous effector CD4⁺T cells following a LAGE epitope ligand- specific activation.

^b These epitopes share different HLA-DR due to the known promiscuity of peptide binding to HLA-DR molecules. This allows an epitope to be potentially used for cancer immunotherapy in a larger number of patients.

^c In the paper, not all the HLA-DR alleles were completely sub-typed.

^d All epithelial tissues express highly glycosylated mucins whereas tumor cells often show hypoglycosylated mucins with a normal protein sequence.

^e The mutation is not located in the region encoding the peptide.

^f The peptide derives from a translational frameshift.

Table 6 Epitopes derived from chimeric proteins originated by gene translocation and fusion processes that do not normally occur in normal tissues. Therefore, these antigens are tumor-specific. Underlined are the sequences after the junction point.

Gene	HLA allele	Peptide epitope	Tissue distribution among tumors	Reference
HLA CLASS I RESTRICTED EPITOPES				
<i>abl- bcr alb-b3(b2a2)</i>	A*0201	FVEH <u>DDESPGL</u>	CML	Wagner <i>et al.</i> , 2003 [198]
<i>abl- bcr alb-b4(b3a2)</i>	A*0201	FVEH <u>DLYCTL</u>	CML	Wagner <i>et al.</i> , 2003 [198]
<i>bcr-abl^a</i>	A2	FMVELVEGA KLSEQESLL MLTNSCVKL	CML	Buzyn <i>et al.</i> , 1997 [23]
<i>bcr-abl p210(b3a2)</i>	A2	SSK <u>ALQRPV</u>	CML	Yotnda <i>et al.</i> , 1998 [213]
	A3	ATGFKQSS <u>K</u> KQSS <u>KALQR</u>		Greco <i>et al.</i> , 1996 [61]
	A3, A11	HSATGFKQSS <u>K</u>		Bocchia <i>et al.</i> , 1996 [15]
	A3	KQSS <u>KALQR</u>		Norbury <i>et al.</i> , 2000 [126]
	B8	GFKQSS <u>KAL</u>		Norbury <i>et al.</i> , 2000 [126]
<i>ETV6/AML</i>	A2	RIA <u>ECILGM</u>	ALL	Yotnda <i>et al.</i> , 1998 [214]
<i>NPM/ALK^b</i>	A2*0201	SLAMLDLLHV	NPM/ALK: in anaplastic large	Passoni <i>et al.</i> , 2002 [139]
		GVLLWEIFSL	cell lymphomas. ALK: in neuroblastomas.	

<i>SYT/SSX</i>	B7, B42	<u>QRPYGYDQIM</u>	Synovial sarcoma	Worley <i>et al.</i> , 2001 [210]
HLA CLASS II RESTRICTED EPITOPES				
<i>abl- bcr alb-b3(b2a2)</i>	DRB1*0701	<u>GPHCNVFEHDDDESPGLYG</u>	CML	Wagner <i>et al.</i> , 2003 [198]
<i>bcr-abl p190 (e1a2)</i>	DRB1*1501	<u>EGAFHGDAAEALQRPVAS</u>	ALL	Tanaka <i>et al.</i> , 2000 [170]
<i>bcr-abl p210 (b2a2)</i>	DRB5*0101	<u>IPLTINKEEALQRPVAS</u>	CML	ten Bosch <i>et al.</i> , 1999 [175]
<i>bcr-abl p210 (b3a2)</i>	DRB1*0401	<u>ATGFKQSSKALQRPVAS</u> ^c	CML	ten Bosch <i>et al.</i> , 1996 [174]
	DRB1*1501	<u>ATGFKQSSKALQRPVAS</u> ^c		ten Bosch <i>et al.</i> , 1995 [173]
	DRB1*0901	<u>ATGFKQSSKALQRPVAS</u> ^c		Yasukawa <i>et al.</i> , 1998 [212]
	DRB1*1101	<u>LIVVIVHSATGFKQSSKALQRPVA</u>		Pawelec <i>et al.</i> , 1996 [140]
	DR11	<u>IVHSATGFKQSSKALQRPVASFEP</u>		Bocchia <i>et al.</i> , 1996 [15]
<i>Dek-can</i>	DRB4*0103	<u>TMKQICKKEIRRLHOY</u>	AML	Ohminami <i>et al.</i> , 1999 [129]
<i>LDLR/FUT</i> ^d	DRB1*0101	<u>GGAPPVTWRRAPAPG</u>	Melanoma	Wang <i>et al.</i> , 1999 [206]
		<u>WRRAPAPGAKAMAPG</u>		
<i>Pml/RARα</i>	DR11	<u>NSNHVASGAGEAAIETQSSSSEEIV</u>	APL	Gambacorti-Passerini <i>et al.</i> , 1993 [54]
<i>TEL/AML1</i>	DP5, DP17	<u>IGRIAECILGMNPSR</u>	AML	Yun <i>et al.</i> , 1999 [215]

^a These bcr-abl epitopes derive from the BCR part of the chimeric protein and do not span the fusion junction. BCR is ubiquitously expressed in normal cells. From an immunotherapeutic point of view these peptides could be considered as widely/overexpressed epitopes rather than as tumor-specific fusion protein-derived epitopes.

^b The two epitopes occur entirely into the ALK region of the antigen, and do not span the fusion junction. CTLs directed against these two epitopes recognize both NPM/ALK⁺ lymphomas and ALK⁺ neuroblastomas. The ALK protein is normally expressed only in pericytes and scattered glial cells of selected regions of the CNS, such as the hypothalamus.

^c These epitopes share different HLA-DR alleles. This allows an epitope to be employed for cancer immunotherapy in a larger number of patients.

^d The antigen is unique to the examined melanoma patient, and the epitopes do not span the junction region. However, the fusion between the two proteins does generate the epitopes, as they derive from the antisense translation of the FUT sequence of the fusion protein.

Table 7 Frequency of epitopes recognized by a given HLA allele. In the case of cancer/testis and melanoma differentiation groups, the TAA most frequently used in clinical trials are outlined.

TAA	No. of epitopes	HLA-A	%	HLA-B	%	HLA-C	%	HLA-DR	%
Cancer/testis									
MAGE-1, -2, -3, -4, -6, -10, -12	42	14	33.3	9	21.4	4	9.5	15	35.7
GAGE-1, -2, -3, -4, -5, -6, -7B, -8	2	1	50	0		1	50	0	
NY-ESO-1	9	4	44.4	1	11.1	0		4	44.4
Other cancer/testis antigens	11	6	54.5	1	9.1	2	18.2	2	18.2
Melanoma differentiation									
Gp100	21	16	76.2	1	4.8	1	4.8	3	14.3
MART-1/Melan-A	7	3	42.8	3	42.8	0		1	14.3
Tyrosinase	14	5	35.7	2	14.3	0		7	50
Other melanoma and non-melanoma differentiation antigens	28	19	67.8	0		1	3.6	8	28.6
Widely expressed	71	59	83.1	7	9.8	0		5	7
Unique and shared tumor-specific	28	15	53.6	6	21.4	1	3.6	6	21.4
Fusion protein	28	13	46.4	2	7.2	0		13	46.4